CENTER FOR CLINICAL GUIDELINES | CANCER

Radiotherapy of bone sarcomas

– Ewing's tumours

Version 2.0

APPROVED
Content
January 11th 2023 (DSG)
Form
January 13th 2023 (Center for Clinical Practice Guidelines | Cancer)

REVISION
Planned: January 1st 2026

INDEXING
Sarcomas, Radiotherapy, Ewing's sarcoma

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/en/

Development of this clinical practice guideline has been funded by The Danish Health Authority (National Cancer Plan IV) and the Danish Clinical Registries (RKKP).

Nyt siden sidst - DA (ændringslog)

Nyt siden version 1.1

Retningslinjeafsnit	**Beskrivelse af ændring**
Anbefalinger	Anbefaling nr. 5 er ændret til: "Hel lunge bestråling bør gives til patienter med lunge eller pleural metastasis. Der skal udvises forsigtighed hos patienter der blev behandlet med høj dosis kemoterapi og stem cell transplantation (B)" Anbefaling nr. 7 er ændret til: "Radikal, præoperativ og postoperativ strålebehandling bør starte så tidligt som muligt efter induktionskemoterapi undtagen hos patienter, der får højdosis kemoterapi og stem cell transplantation , i hvilke strålebehandling bør starte 10 uger efter høj dosis kemoterapi (B)" Anbefaling nr. 10 er ændret til: "Dosis til definitiv strålebehandling bør være 54,0 Gy i fraktioner på 1,8 Gy, leveret. For tumorer ≥8 cm og/eller <50% regression på induktionskemoterapi bør et boost til en total dosis mellem 60 – 70,2 Gy overvejes. (Styrke B)" Anbefaling nr. 11 er ændret til: "Dosis til hel lunge bestråling skulle være 15 Gy i 10 fraktioner for patienter <14 år eller 18 Gy i 12 fraktioner for patienter ≥14 år. Til patienter der er behandlet med høj dosis kemoterapi og stem cell transplantation given kun 15 Gy i 10 fraktioner (Styrke B)"

Litteratur og evidensgennemgang	Følgende afsnit er tilføjet under afsnittet om Indikationer: "A recent literature review on lung toxicities in Ewing sarcoma patients treated with whole lung irradiation following different modes of high dose chemotherapy and bone marrow or stem cell transplantation has examined 9 reports with a total of 227 patients (18). They showed that the risk of adverse lung effects after whole lung irradiation depends on: the cumulative radiation dose, the dose per fraction, the high dose chemotherapy regimen, and interval between the high dose therapy and whole lung irradiation. A cumulative dose of 15 Gy and a time interval of at least 60 days can potentially lead to a reduced risk of toxicities. [2b]" Følgende afsnit er tilføjet til afsnittet om Dosis og fraktionering: "A recent phase III dose escalation study randomized 95 unresectable Ewing sarcoma patients between standard 55.8 Gy vs 70.2 Gy (30). Their results showed statistically significant superior 5-Y local control rate in the dose escalation arm compared to the standard arm (76.4% vs. 49.4% respectively) [A]." "A recent literature review on lung toxicities in Ewing sarcoma patients treated with whole lung irradiation following different modes of high dose chemotherapy and bone marrow or stem cell transplantation has examined 9 reports with a total of 227 patients (18). They showed that the risk of adverse lung effects after whole lung irradiation depends on: the cumulative radiation dose, the dose per fraction, the high dose chemotherapy regimen, and interval between the high dose therapy and whole lung irradiation. A cumulative dose of 15 Gy and a time interval of at least 60 days can potentially lead to a reduced risk of toxicities. [2b]"
Referencer	Referenceliste er opdateret.
Litteratursøgning	Tidsafgrænsningen er udvidet fra 1990-2019 til 1990-2022.
Bilag	Opdateret.

Revisions to previous version - ENG (changelog)

Revisions to version 1.1

Guideline chapter	Description of revisions or additions
Recommendations	Recommendation 5 is changed to: "Whole lung radiotherapy should be given to patients with pulmonary or pleural metastatic disease. Caution should be adopted in patients that received high dose chemotherapy and stem cell transplantation (B)" Recommendation 7 is changed to: "Radical, preoperative and postoperative radiotherapy should start as early as possible after the induction chemotherapy except in patients receiving high dose chemotherapy and stem cell transplantation in whom radiotherapy should start 10 weeks after high dose chemnotherapy treatment (B)" Recommendation 10 is changed to: "The total dose for definitive radiotherapy should be 54.0 Gy in 1.8 Gy fractions, delivered as a single phase. For tumours ≥8cm, and/or <50% regression on induction chemotherapy a boost to a total dose between 60 – 70.2 Gy ought to be considered. (Strength B)" Recommendation 11 is changed to: "The dose for whole lung radiotherapyshould be 15 Gy in 10 fractions for patients <14 years, or 18 Gy in 12 fractions for patients ≥14 years. To patients treated with high dose chemotherapy and stem cell transplantation only 15 Gy in 10 fractions is given (Strength B)"

Literature and evidence review	Section added to Indications: "A recent literature review on lung toxicities in Ewing sarcoma patients treated with whole lung irradiation following different modes of high dose chemotherapy and bone marrow or stem cell transplantation has examined 9 reports with a total of 227 patients (18). They showed that the risk of adverse lung effects after whole lung irradiation depends on: the cumulative radiation dose, the dose per fraction, the high dose chemotherapy regimen, and interval between the high dose therapy and whole lung irradiation. A cumulative dose of 15 Gy and a time interval of at least 60 days can potentially lead to a reduced risk of toxicities. [2b]" Sections added to Dose and fractionation: "A recent phase III dose escalation study randomized 95 unresectable Ewing sarcoma patients between standard 55.8 Gy vs 70.2 Gy (30). Their results showed statistically significant superior 5-Y local control rate in the dose escalation arm compared to the standard arm (76.4% vs. 49.4% respectively) [A]." "A recent literature review on lung toxicities in Ewing sarcoma patients treated with whole lung irradiation following different modes of high dose chemotherapy and bone marrow or stem cell transplantation has examined 9 reports with a total of 227 patients (18). They showed that the risk of adverse lung effects after whole lung irradiation depends on: the cumulative radiation dose, the dose per fraction, the high dose chemotherapy regimen, and interval between the high dose therapy and whole lung irradiation. A cumulative dose of 15 Gy and a time interval of at least 60 days can potentially lead to a reduced risk of toxicities. [2b]"
References	Updated.
Literature search	The search period has been extended from 1990-2019 to 1990-2022.
Appendices	Updated.

1. Anbefalinger - DA (Quick Guide)

Indikationer

1. **Kirurgi bør overvejes til lokal terapi, når det er muligt, mens definitiv strålebehandling kun tilrådes til patienter med inoperable læsioner (B)**

2. **Postoperativ strålebehandling bør gives til alle patienter, bortset fra dem med negative resektions margener på mindst 1 mm, samt fjernelse af alt væv, der oprindeligt var involveret i den præ-kemoterapi tumorvolumen, og en god histologisk respons (> 90% nekrose) til præoperativ kemoterapi (B)**

3. **Forventet marginal resektion bør betragtes som en indikation for planlagt præoperativ strålebehandling (B)**

4. **Hemithorax bestråling bør gives til patienter med tumorer ved thorax væggen og pleural invastion (effusion) (B)**

5. **Hel lunge bestråling bør gives til patienter med lunge eller pleural metastasis. Der skal udvises forsigtighed hos patienter der blev behandlet med høj dosis kemoterapi og stem cell transplantation (B)**

6. **Begrænset metastatisk sygdom kunne behandles med radikal dosis af strålebehandling, hvis det er teknisk muligt (C)**

Tid til bestråling

7. **Radikal, præoperativ og postoperativ strålebehandling bør starte så tidligt som muligt efter induktionskemoterapi undtagen hos patienter, der får højdosis kemoterapi og stem cell transplantation , i hvilke strålebehandling bør starte 10 uger efter høj dosis kemoterapi (B)**

Dosis og fraktionering

8. **Dosis til præoperativ bestråling bør være 50,4 Gy i 28 fraktioner til PTV. Hvis der er bekymring for organtolerance eller sårheling, kan denne dosis reduceres til 45 Gy i 25 Gy-fraktioner. (B)**

9. **Dosis til postoperativ strålebehandling bør være 54 Gy i 30 fraktioner, leveret som 45 Gy i 25 fraktioner til PTV1 og 9 Gy i 5 fraktioner til PTV2. (Styrke B)**

10. **Dosis til definitiv strålebehandling bør være 54,0 Gy i fraktioner på 1,8 Gy, leveret. For tumorer ≥8 cm og/eller <50% regression på induktionskemoterapi bør et boost til en total dosis mellem 60 – 70,2 Gy overvejes. (Styrke B)**

11. **Dosis til hel lunge bestråling skulle være 15 Gy i 10 fraktioner for patienter <14 år eller 18 Gy i 12 fraktioner for patienter ≥14 år. Til patienter der er behandlet med høj dosis kemoterapi og stem cell transplantation given kun 15 Gy i 10 fraktioner (Styrke B)**

Recommendations - ENG (Quick Guide)

Indications

1. **Surgery should be considered for local therapy whenever feasible, while definitive radiotherapy is advised only in inoperable lesions (B)**

2. **Postoperative radiotherapy should be given to all patients except for cases with wide local excision (negative resection margins of at least 1mm) with removal of all tissues originally involved by the pre-chemotherapy tumour volume, and a good histological response (>90% necrosis) to pre-operative chemotherapy (B)**

3. **Expected marginal resection should be considered an indication for planned preoperative radiotherapy (B)**

4. **Hemithorax irradiation should be given to patients with chest wall tumours and pleural invastion (effusion) (B)**

5. **Whole lung radiotherapy should be given to patients with pulmonary or pleural metastatic disease. Caution should be adopted in patients that received high dose chemotherapy and stem cell transplantation (B)**

6. **Limited metastatic disease could be treated with radical dose of radiotherapy if technically feasible (C)**

Timing

7. **Radical, preoperative and postoperative radiotherapy should start as early as possible after the induction chemotherapy except in patients receiving high dose chemotherapy and stem cell transplantation in whom radiotherapy should start 10 weeks after high dose chemnotherapy treatment (B)**

Dose and fractionation

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

9. **The total dose for postoperative radiotherapy should be 54 Gy in 30 fractions, delivered as 45 Gy in 25 fractions to PTV1, and 9 Gy in 5 fractions to PTV2. (Strength B)**

10. **The total dose for definitive radiotherapy should be 54.0 Gy in 1.8 Gy fractions, delivered as a single phase. For tumours ≥8cm, and/or <50% regression on induction chemotherapy a boost to a total dose between 60 – 70.2 Gy ought to be considered. (Strength B)**

11. **The dose for whole lung radiotherapyshould be 15 Gy in 10 fractions for patients <14 years, or 18 Gy in 12 fractions for patients ≥14 years. To patients treated with high dose chemotherapy and stem cell transplantation only 15 Gy in 10 fractions is given (Strength B)**

2. Introduction

Ewing's sarcoma is the second most common primary sarcoma of bone in children and adolescents. While the survival benefit provided by multi-agent chemotherapy has been clearly demonstrated, the optimal approach for local tumor control remains a topic of debate. Compared to other bone sarcomas, Ewing's sarcoma is considered radiosensitive, and radiotherapy has therefore always played an important role in the multimodality treatment protocols, either in combination with surgery, or as definitive local treatment usually in unresectable cases.
The challenge in Ewing's sarcomas is their rarity, and distribution between various anatomical localizations. Most of the studies and randomized trials in Ewing's sarcomas are being done in Children. The experiences gained in these pediatric cases are being extrapolated for treating sarcomas in adults. This guideline examines the evidence that has been accumulated regarding the role of external beam radiotherapy in treating Ewing's sarcomas. The recommendations are based on the expected effect on local control rate as well as 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 or metastatic Ewing's sarcomas. These details include: indications, and timing as well as dose and fractionation. The guideline is also concerned with specifying the various subgroups in which radiotherapy could/should be omitted.

Target population

All adult and pediatric patients with localized or metastatic Ewing's sarcoma regardless of 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. **Surgery should be considered for local therapy whenever feasible, while definitive radiotherapy is advised only in inoperable lesions (B)**

2. **Postoperative radiotherapy should be given to all patients except for cases with wide local excision (negative resection margins of at least 1mm) with removal of all tissues originally involved by the pre-chemotherapy tumour volume, and a good histological response (>90% necrosis) to pre-operative chemotherapy (B)**

3. **Expected marginal resection should be considered an indication for planned preoperative radiotherapy (B)**

4. **Hemithorax irradiation should be given to patients with chest wall tumours and pleural invastion (effusion) (B)**

5. **Whole lung radiotherapy should be given to patients with pulmonary or pleural metastatic disease. Caution should be adopted Caution should be adopted in patients that received high dose chemotherapy and stem cell transplantation (B)**

6. **Limited metastatic disease could be treated with radical dose of radiotherapy if technically feasible (C)**

Literature review and evidence description

Achieving local control is an essential goal of Ewing's sarcoma treatment. Surgery has mainly been used for dispensable bones whereas radiotherapy is often used for central inoperable lesions. Though most of the current practice in treating Ewing's sarcoma is based on strong evidence from large randomized studies conducted by collaborative groups such as CESS, SSG, and EURO-EWING, there has never been a randomized trial comparing radiotherapy with surgery and the majority of these trials didn't have a specific radiotherapy-related question. A great deal of the current radiotherapy practices is derived from a later retrospective analysis of the (prospectively collected) data in these trials. This evidence is the base for the current recommendations in SSG (1), NCCN (2) and ESMO (3) guidelines as well as in the radiotherapy guidelines of the most recent EURO-EWING protocol (appendix 3).

The evidence for the superiority of surgery comes from retrospective studies from major single institutions showing superior local control rates after radical surgical resection than that after radiotherapy alone (4,5) [2b]. It should be noted however that these results may suffer from statistical bias because of selection criteria for the local treatment modalities that may have led to imbalances in the prognostic factors between the 2 subgroups. It is also to be noted that tumour site is of importance as a large retrospective study of 965 patients showed that local tumor control is excellent and similar between surgery and RT for axial non-spine, spine,

and extraskeletal tumors but not for pelvis and extremities where radical radiotherapy is associated with the highest risk of local failure (6) [2a].
The strongest evidence of the superiority of surgery comes from a large database study by Miller et al. (7) [2a]. In this study the authors have analyzed the data of 1031 Ewing's sarcoma patients in National Cancer Data Base (NCDB), maintained by the American College of Surgeons and the American Cancer Society. The results of this investigation showed a statistically significant better local control at 5 years for patients treated with surgery alone (77.2%) compared to those receiving radiotherapy alone (52.5%). This result was still valid after multivariate analysis.

Based on (4,5) [2b], and (6) [2a] as well as the Scandinavian Sarcoma Group (SSG) Guidelines (1), National comprehensive cancer network (NCCN) clinical practice guidelines (2) and the most recent European School of Medical Oncology (ESMO) guidelines (3), and other reviews (8-10), the strength of **recommendation 1** is evaluated to be strength **B**.

There are no randomized studies on the question of whether combined local treatment (surgery plus radiotherapy) offers an advantage over surgery alone. However, combined local treatment was used in various studies, for patients with high risk of local recurrence because of inadequate margin. The data from major retrospective studies were summarized and analyzed in 2 reviews and demonstrate that the local control rate after surgery plus radiotherapy was identical or better that after surgery alone despite a poorer selection of patients for the combined modality approach (8,9) [2a].

The strongest evidence for the indication of radical radiotherapy or the use of combined surgery and radiotherapy (preoperative or postoperative] comes from a large study analyzing the data of 1058 patients with localized Ewing tumors treated in the CESS 81, CESS 86, and EICESS 92 trials (11) [2a].
In these trials a surgical local therapy approach was used. In patients with a poor histologic response or with intralesional and marginal resections, this was to be followed by radiotherapy (RT).
In EICESS 92, preoperative RT was introduced for patients with expected close resection margins. Definitive RT was used in cases in which surgical resection seemed impossible.
The rate of local failure was 7.5% after surgery with or without postoperative RT, and was 5.3% after preoperative and 26.3% after definitive RT ($p = 0.001$). Event-free survival was reduced after definitive RT ($p = 0.0001$). The authors concluded that with preoperative RT, local control was comparable to surgery. After intralesional or marginal resections and after a poor histologic response and wide resection, postoperative radiotherapy would improve local control [1b].

Based on (11) [2a], as well as the Scandinavian Sarcoma Group (SSG) Guidelines (1), National comprehensive cancer network (NCCN) clinical practice guidelines (2) and the most recent European School of Medical Oncology (ESMO) guidelines (3), and other reviews (8-10), the strengths of **recommendation 2 & 3** are evaluated to be strength **B**.

In the European (EI) CESS-studies, post-operative hemithorax irradiation was recommended for tumors of the chest wall that presented with extensive pleural invasion and large intrathoracic masses. This treatment

concept was based on an analysis of the first CESS-study in which patients with chest wall tumors had high risk of local failures within the ipsilateral thorax, probably due to pleural dissemination (12) [2b].

A recent retrospective analysis clearly indicates that radiotherapy reduces the risk of recurrences in the ipsilateral thorax (13) [2b]. The 7-year event-free survival was 63% in 42 patients with surgery plus hemithorax irradiation versus 46% in 86 patients with surgery alone. The better survival outcome was due mainly to a reduction in lung metastases after hemithorax irradiation (7% vs. 21%). Hemithorax irradiation after surgery for chest wall primaries, became a standard in all recent Ewing's sarcoma protocols including EURO-EWING 99, and EURO-EWING 2012 (appendix 3).

Based on (12,13) [2b], as well as the Scandinavian Sarcoma Group (SSG) Guidelines (1), National comprehensive cancer network (NCCN) clinical practice guidelines (2) and the most recent European School of Medical Oncology (ESMO) guidelines (3), and other reviews (8-10), the strength of **recommendation 4** is evaluated to be strength **B**.

There is no randomized trial testing the role of whole lung irradiation in Ewing's sarcoma patients with pulmonary metastasis. Whole lung irradiation was, however, used as treatment option in the CESS-studies for patients with lung metastases at diagnosis who achieved a complete clinical response to chemotherapy. A first retrospective analysis of these studies suggested a dose-dependent increase in survival with additional lung radiotherapy (14) [2b]. In a later separate analysis using multivariate analysis, lung irradiation was associated with improved survival in patients with primary lung metastases at diagnosis (15) [2b]. A recent retrospective study of 136 patients showed that when analyzing the entire group of pulmonary relapsed patients the 3 years overall survival outcome was 47% in the patients receiving whole lung irradiation compared to 33% for those who didn't ($p = 0.007$) (16) [2b]. Bilateral lung irradiation with 15–20 Gy (depending on age) was tested against high-dose chemotherapy with busulfan in the EURO-EWING-99-study (17). The results showed no benefit from high dose chemotherapy [A].

A recent literature review on lung toxicities in Ewing sarcoma patients treated with whole lung irradiation following different modes of high dose chemotherapy and bone marrow or stem cell transplantation has examined 9 reports with a total of 227 patients (18). They showed that the risk of adverse lung effects after whole lung irradiation depends on: the cumulative radiation dose, the dose per fraction, the high dose chemotherapy regimen, and interval between the high dose therapy and whole lung irradiation. A cumulative dose of 15 Gy and a time interval of at least 60 days can potentially lead to a reduced risk of toxicities. [2b]

Based on (14-18) [2b], as well as the Scandinavian Sarcoma Group (SSG) Guidelines (1), National comprehensive cancer network (NCCN) clinical practice guidelines (2) and the most recent European School of Medical Oncology (ESMO) guidelines (3), and other reviews (8-10) , the strength of **recommendation 5** is evaluated to be strength **B**.

There is no evidence from randomized trials or large retrospective studies that radical radiotherapy to limited metastatic disease improve local control or survival. There is indirect evidence in the form of a study in which an aggressive approach of high-dose chemotherapy and local irradiation to most or all clinically involved sites resulted in long-term remissions in about 40–50% of patients (19) [3b]. Recent US-studies suggest, however,

that high-dose chemotherapy alone did not improve survival in these patients as compared to standard intensive chemotherapy, suggesting that the previously reported improved survival is the result of the radiotherapy part of the treatment (20) [3b]. In a small study of 13 children with metastatic Ewing and Rhabdomyosarcoma receiving radical Rth dose to metastatic sites, at a median follow-up of 18 months, a single local failure was seen (21) [3b].
Although the benefit of irradiation to metastatic lesions is not yet clearly proven, this treatment approach has become standard practice in recent protocols such as EURO-EWING 2012 (appendix-3) and usually recommended in various guidelines (1-3).

Based on (19-21) [3b for all 2 trials], as well as the Scandinavian Sarcoma Group (SSG) Guidelines (1), National comprehensive cancer network (NCCN) clinical practice guidelines (1) and the most recent European School of Medical Oncology (ESMO) guidelines (3), and other reviews (8-10), the strength of **recommendation 6** is evaluated to be strength **C**.

Patient values and preferences

The value of these indications is improved local control and overall survival. Not following the guidelines means either amputation (in case of extremety Ewing's sarcoma) or accepting higher risk of local recurrence and eventually death from the metastasis.

Rationale

The outcome that forms the basis of the recommendation is local control, as well as limb or organ preservation, and a good quality of life. This is balanced against amputation (in case of extremity sarcoma) or major mutilating surgery in case of sarcoma to other sites as well as a higher risk of recurrence and metastasis. From organizational point of view, the decision is taken in multidisciplinary conference.

Comments and considerations

There are no barriers to the application of the guidelines. Further research in the area is ongoing.

Timing

7. Radical, preoperative and postoperative radiotherapy should start as early as possible after the induction chemotherapy except in patients receiving high dose chemotherapy and stem cell transplantation in whom radiotherapy should start 10 weeks after high dose chemotherapy treatment (B)

Literature review and evidence description

The timing of radiation after surgery is still an issue to be resolved. In an analysis of 153 patients receiving post operative in the CESS 86 and EICESS trials, Schuck et al. (22) reported that patients with early onset of postoperative irradiation (9 weeks of chemotherapy) showed a trend (though not statistically significant) for improved local control compared to patients with a later onset radiotherapy (12-18 weeks of chemotherapy) [2b].
Burgers et al. (23) retrospectively analyzed the outcome after radiotherapy in pelvic tumors and found (in univariate analysis) that the duration of chemotherapy prior to the start of XRT was the only significant prognostic factor [2b].
Dunst and Chuck (8) analyzed the data from various published large multicenter trials and showed that when the duration of upfront chemotherapy is plotted against the overall survival after radiotherapy, a significant association between delayed start of radiotherapy and reduced survival was revealed [2a].

Based on (22,23) [2b], as well as the retrospective analysis or trial data in (8) [2a], Scandinavian Sarcoma Group (SSG) Guidelines (1), National comprehensive cancer network (NCCN) clinical practice guidelines (2) and the most recent European School of Medical Oncology (ESMO) guidelines (3) , and other reviews (9,10), the strength of **recommendation 7** is evaluated to be strength **B**.

Patient values and preferences

In case of radical or preoperative radiotherapy, early application of radiotherapy could mean faster relief of local symptoms which will be preferable for patients. For postoperative radiotherapy, there the question of timing of radiotherapy has no immediate effect and causes no extra discomfort for the patients.

Rationale

The basis of the current recommendation is better local control and survival which is the ultimate goal of therapy. Considerations are given to factors that increases complication risk and extended times are allowed in case, for example, of using biological grafts.

Comments and considerations

There are no barriers to the application of the guidelines. Patients are seen in MDT and radiation times are coordinated with surgeons and booked good time in advance.

Dose and fractionation

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

9. **The total dose for postoperative radiotherapy should be 54 Gy in 30 fractions, delivered as 45 Gy in 25 fractions to PTV1, and 9 Gy in 5 fractions to PTV2. (Strength B)**

10. **The total dose for definitive radiotherapy should be 54.0 Gy in 1.8 Gy fractions, delivered as a single phase. For tumours ≥8cm, and <50% regression on induction chemotherapy a boost to a total dose between 60 – 70.2 Gy ought to be considered. (Strength B)**

11. **The dose for whole lung radiotherapyshould be 15 Gy in 10 fractions for patients <14 years, or 18 Gy in 12 fractions for patients ≥14 years. To patients treated with high dose chemotherapy and stem cell transplantation only 15 Gy in 10 fractions is given (Strength B)**

Literature review and evidence description

3 retrospective publications suggest that a minimal dose of 45 Gy is needed to control microscopic disease of Ewings sarcoma while a minimum of 54 Gy is needed for macroscopic disease, while an intermediate dose of 50 Gy is sufficient for preoperative radiotherapy (24-29) [2b],
Schuck et al (11) performed a retrospective review of previous intergroup trials to assess the optimal dose and to use in patients with Ewing sarcoma and confirmed the above mentioned results [2a]. Their results were confirmed on year later by another analytical review by Donaldson S (10) [2a]. Donaldson S (10) also suggested that tumours larger than 8 cm may have better tumour control with doses of 60 Gy or more [1c] which is confirmed later by another retrospective study in 40 patients by Paulino et al. 2007 [2b]. A recent phase III dose escalation study randomized 95 unresectable Ewing sarcoma patients between standard 55.8 Gy vs 70.2 Gy (30). Their results showed statistically significant superior 5-Y local control rate in the dose escalation arm compared to the standard arm (76.4% vs. 49.4% respectively) [A].
The current good local control achieved in recent trials with these doses lead to its adoption in the most recent EURO-EWING protocol (appendix-3)

Based on (10,11) [2a for both trials], as well as the retrospective studies (24-30) [2b], Scandinavian Sarcoma Group (SSG) Guidelines (1), National comprehensive cancer network (NCCN) clinical practice guidelines (2) and the most recent European School of Medical Oncology (ESMO) guidelines (3), and other reviews (9,10), the strengths of **recommendations 8, 9 & 10** are evaluated to be strength **B**.

A recent literature review on lung toxicities in Ewing sarcoma patients treated with whole lung irradiation following different modes of high dose chemotherapy and bone marrow or stem cell transplantation has examined 9 reports with a total of 227 patients (18). They showed that the risk of adverse lung effects after

whole lung irradiation depends on: the cumulative radiation dose, the dose per fraction, the high dose chemotherapy regimen, and interval between the high dose therapy and whole lung irradiation. A cumulative dose of 15 Gy and a time interval of at least 60 days can potentially lead to a reduced risk of toxicities. [2b]

The dose of whole lung irradiation is limited by possible lung toxicity (31) [2a] and is therefore kept under lung tolerance and no unexpected toxicities were reported using the recommended dose (14,15) [2b].

Based on (18, 31) [2a], as well as other retrospective studies (14,15) [2b], Scandinavian Sarcoma Group (SSG) Guidelines (1), National comprehensive cancer network (NCCN) clinical practice guidelines (2) and the most recent European School of Medical Oncology (ESMO) guidelines (3), and other reviews (9,10), the strength of **recommendation 11** is evaluated to be strength **B**.

Patient values and preferences

The value for the patients of the current recommendations is providing maximum local control and acceptable risk of complications and side effects.

Rationale

The basis of the current guidelines is providing an optimal balance between probability of local control and the risk of severe complications to the minimum. Current doses and fractionation provide excellent chance of local control while the risks of severe late complications are dependent on factors such as tumour size, anatomical site and the patient's age.

Comments and considerations

There are no barriers for the application of the current guidelines.

4. Reference list

(1) Scandinavian Sarcoma group. Recommendations for Radiotherapy in Bone- and Soft Tissue Sarcoma. 2015:http://www.ssg-org.net/wp-content/uploads/2011/05/SSG-RT-Guidelines-December-2015.pdf.
(2) National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. 2018:https://www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf.
(3) Casali PG, Bielack S, Abecassis N, Aro HT, Bauer S, Biagini R, et al. Bone sarcomas: ESMO-PaedCan-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018 Oct 1;29(Suppl 4):iv79-iv95.
(4) Bacci G, Palmerini E, Staals EL, Longhi A, Barbieri E, Alberghini M, et al. Ewing's sarcoma family tumors of the humerus: outcome of patients treated with radiotherapy, surgery or surgery and adjuvant radiotherapy. Radiother Oncol 2009 Nov;93(2):383-387.
(5) Bacci G, Ferrari S, Longhi A, Versari M, Forni C, Donati D, et al. Local and systemic control in Ewing's sarcoma of the femur treated with chemotherapy, and locally by radiotherapy and/or surgery. J Bone Joint Surg Br 2003 Jan;85(1):107-114.
(6) Ahmed SK, Randall RL, DuBois SG, Harmsen WS, Krailo M, Marcus KJ, et al. Identification of Patients With Localized Ewing Sarcoma at Higher Risk for Local Failure: A Report From the Children's Oncology Group. Int J Radiat Oncol Biol Phys 2017 Dec 1;99(5):1286-1294.
(7) Miller BJ, Gao Y, Duchman KR. Does surgery or radiation provide the best overall survival in Ewing's sarcoma? A review of the National Cancer Data Base. J Surg Oncol 2017 Sep;116(3):384-390.
(8) Dunst J, Schuck A. Role of radiotherapy in Ewing tumors. Pediatr Blood Cancer 2004 May;42(5):465-470.
(9) Laskar S, Mallick I, Gupta T, Muckaden MA. Post-operative radiotherapy for Ewing sarcoma: when, how and how much? Pediatr Blood Cancer 2008 Nov;51(5):575-580.
(10) Donaldson SS. Ewing sarcoma: radiation dose and target volume. Pediatr Blood Cancer 2004 May;42(5):471-476.
(11) Schuck A, Ahrens S, Paulussen M, Kuhlen M, Konemann S, Rube C, et al. Local therapy in localized Ewing tumors: results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. Int J Radiat Oncol Biol Phys 2003 Jan 1;55(1):168-177.
(12) Schuck A, Hofmann J, Rube C, Hillmann A, Ahrens S, Paulussen M, et al. Radiotherapy in Ewing's sarcoma and PNET of the chest wall: results of the trials CESS 81, CESS 86 and EICESS 92. Int J Radiat Oncol Biol Phys 1998 Dec 1;42(5):1001-1006.
(13) Schuck A, Ahrens S, Konarzewska A, Paulussen M, Frohlich B, Konemann S, et al. Hemithorax irradiation for Ewing tumors of the chest wall. Int J Radiat Oncol Biol Phys 2002 Nov 1;54(3):830-838.
(14) Dunst J, Paulussen M, Jurgens H. Lung irradiation for Ewing's sarcoma with pulmonary metastases at diagnosis: results of the CESS-studies. Strahlenther Onkol 1993 Oct;169(10):621-623.
(15) Paulussen M, Ahrens S, Craft AW, Dunst J, Frohlich B, Jabar S, et al. Ewing's tumors with primary lung metastases: survival analysis of 114 (European Intergroup) Cooperative Ewing's Sarcoma Studies patients. J Clin Oncol 1998 Sep;16(9):3044-3052.
(16) Scobioala S, Ranft A, Wolters H, Jabar S, Paulussen M, Timmermann B, et al. Impact of Whole Lung Irradiation on Survival Outcome in Patients With Lung Relapsed Ewing Sarcoma. Int J Radiat Oncol Biol Phys 2018 Nov 1;102(3):584-592.
(17) Dirksen U, Brennan B, Le Deley MC, Cozic N, van den Berg H, Bhadri V, Brichard B, Claude L, Craft A, Amler S, Gaspar N, Gelderblom H, Goldsby R, Gorlick R, Grier HE, Guinbretiere JM, Hauser P, Hjorth L, Janeway K, Juergens H, Judson I, Krailo M, Kruseova J, Kuehne T, Ladenstein R, Lervat C, Lessnick SL, Lewis I, Linassier C, Marec-Berard P, Marina N, Morland B, Pacquement H, Paulussen M, Randall RL, Ranft A, Le Teuff G, Wheatley K, Whelan J, Womer R, Oberlin O, Hawkins DS; Euro-E.W.I.N.G. 99 and Ewing 2008 Investigators. High-Dose Chemotherapy Compared With Standard Chemotherapy and Lung Radiation in Ewing Sarcoma With Pulmonary Metastases: Results of the European Ewing Tumour

Working Initiative of National Groups, 99 Trial and EWING 2008. J Clin Oncol. 2019 Dec 1;37(34):3192-3202.

(18) Scobioala S, Eich HT. Risk stratification of pulmonary toxicities in the combination of whole lung irradiation and high-dose chemotherapy for Ewing sarcoma patients with lung metastases: a review. Strahlenther Onkol. 2020 Jun;196(6):495-504.
(19) Burdach S, van Kaick B, Laws HJ, Ahrens S, Haase R, Korholz D, et al. Allogeneic and autologous stem-cell transplantation in advanced Ewing tumors. An update after long-term follow-up from two centers of the European Intergroup study EICESS. Stem-Cell Transplant Programs at Dusseldorf University Medical Center, Germany and St. Anna Kinderspital, Vienna, Austria. Ann Oncol 2000 Nov;11(11):1451-1462.
(20) Meyers PA, Krailo MD, Ladanyi M, Chan KW, Sailer SL, Dickman PS, et al. High-dose melphalan, etoposide, total-body irradiation, and autologous stem-cell reconstitution as consolidation therapy for high-risk Ewing's sarcoma does not improve prognosis. J Clin Oncol 2001 Jun 1;19(11):2812-2820.
(21) Liu AK, Stinauer M, Albano E, Greffe B, Tello T, Maloney K. Local control of metastatic sites with radiation therapy in metastatic Ewing sarcoma and rhabdomyosarcoma. Pediatr Blood Cancer 2011 Jul 15;57(1):169-171.
(22) Schuck A, Rube C, Konemann S, Rube CE, Ahrens S, Paulussen M, et al. Postoperative radiotherapy in the treatment of Ewing tumors: influence of the interval between surgery and radiotherapy. Strahlenther Onkol 2002 Jan;178(1):25-31.
(23) Burgers JM, Oldenburger F, de Kraker J, van Bunningen BN, van der Eijken JW, Delemarre JF, et al. Ewing's sarcoma of the pelvis: changes over 25 years in treatment and results. Eur J Cancer 1997 Dec;33(14):2360-2367.
(24) Marcus Jr RB, Berrey BH, Graham-Pole J, Mendenhall NP, Scarborough MT. The treatment of Ewing's sarcoma of bone at the University of Florida: 1969 to 1998. Clin Orthop Relat Res 2002 Apr;(397):290-7. doi(397):290-297.
(25) Ahrens S, Hoffmann C, Jabar S, Braun-Munzinger G, Paulussen M, Dunst J, et al. Evaluation of prognostic factors in a tumor volume-adapted treatment strategy for localized Ewing sarcoma of bone: the CESS 86 experience. Cooperative Ewing Sarcoma Study. Med Pediatr Oncol 1999 Mar;32(3):186-195.
(26) Nesbit ME,Jr, Gehan EA, Burgert EO,Jr, Vietti TJ, Cangir A, Tefft M, et al. Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: a long-term follow-up of the First Intergroup study. J Clin Oncol 1990 Oct;8(10):1664-1674.
(27) Dunst J, Jurgens H, Sauer R, Pape H, Paulussen M, Winkelmann W, et al. Radiation therapy in Ewing's sarcoma: an update of the CESS 86 trial. Int J Radiat Oncol Biol Phys 1995 Jul 15;32(4):919-930.
(28) Arai Y, Kun LE, Brooks MT, Fairclough DL, Fontanesi J, Meyer WH, et al. Ewing's sarcoma: local tumor control and patterns of failure following limited-volume radiation therapy. Int J Radiat Oncol Biol Phys 1991 Nov;21(6):1501-1508.
(29) Paulino AC, Nguyen TX, Mai WY, Teh BS, Wen BC. Dose response and local control using radiotherapy in non-metastatic Ewing sarcoma. Pediatr Blood Cancer 2007 Aug;49(2):145-148.
(30) Siddhartha Laskar [1], Shwetabh Sinha [2], Abhishek Chatterjee [2], Nehal Khanna [2], Jifmi Jose Manjali [2], Ajay Puri [3], Ashish Gulia [3], Prakash Nayak [3], Tushar Vora [4], Girish Chinnaswamy [4], Maya Prasad [4], Jyoti Bajpai [5], Shashikant Juvekar [6], Subhash Desai [6], Amit Janu [6], Venkatesh Rangarajan [7], Nilendu Purandare [7], Sneha Shah [7], Bharat Rekhi [8], Nirmala Jambhekar [8], Mary Ann Muckaden [2], Purna Kurkure Radiation Therapy Dose Escalation in Unresectable Ewing Sarcoma: Final Results of a Phase 3 Randomized Controlled Trial. Int J Radiat Oncol Biol Phys. 2022 Aug 1;113(5):996-1002
(31) Ronchi L, Buwenge M, Cortesi A, Ammendolia I, Frakulli R, Abate ME, et al. Whole Lung Irradiation in Patients with Osteosarcoma and Ewing Sarcoma. Anticancer Res 2018 Sep;38(9):4977-4985.

5. Methods

Literature search

Evidence was looked for in Medline database using “Ewing Sarcoma” and “Radiotherapy” as a MESH terms. Details of the search terms are in appendix -1. The search was restricted to English language human studies between 1990- 2022. The following studies were excluded:

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

The search terms results included reviews, so we didn’t make specific search for reviews or meta-analysis. 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.
When no direct evidence is found we formulated recommendations in accordance with the radiotherapy guidelines in EURO-EWING 1999 and EURO-EWING 2012 international protocols as well as in the Scandinavian sarcoma group radiotherapy guidelines as they are describing the best standard radiotherapy practice (see flow chart, appendix 3).

Literature review

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 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 4).

Wording of the recommendations

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

Stakeholder engagement

It was not considered relevant given the nature of the subject to involve patients in the current guidelines.

External review and guideline approval

The RKKP secretariat got the first draft during preparation of the guidelines for comments. Feedback from secretariat will be included and the guideline will be modified accordingly. Members from DSG representing both oncologists and orthopedic surgeons in the 2 national sarcoma centers received the first draft of the guidelines and their comments will be incorporated in the final version.

Recommendations that entail additional costs

No additional cost is estimated.

Need for further research

The next EURO-EWING protocol will include specific relevant radiotherapy questions.

Authors and conflicts of interest

Akmal Safwat, Consultant Clinical Oncology and Associate Prof. Aarhus University Hospital, the Department of Oncology and the Danish Centre for Particle Therapy (DCPT). No conflict of interest.

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 will be revised by members from the 2 national sarcoma centers. It will be presented to the remaining members of the DSG during the next meeting on January 8th, 2020. 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, Ewing/radiotherapy"[Majr] AND (("1990/01/01"[PDAT] : "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])

Appendix 2 – Radiotherapy guidelines of EURO-EWING 2012 protocol

EE2012 PROTOCOL RADIOTHERAPY GUIDELINES

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

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

Some patients with localised disease (R2loc poor responders) may be treated with high dose buslphan-melphelan (Bu-Mel) chemotherapy. For these patients, there are special considerations regarding radiotherapy as local therapy, because of interactions with the high dose chemotherapy agents, potentially resulting in significant toxicity after delivery of high radiotherapy doses to spinal cord/cauda equina, lung, or bowel. This may compromise the ability to deliver an effective radiotherapy dose to central axial sites (spine, sacrum, pelvis), or when lung or bowel are within the radiotherapy treatment fields. Careful consideration will therefore be needed to balance up the competing needs for Bu-Mel as part of systemic therapy, and radiotherapy for local therapy, and individualised decision making should made for patients in the setting of an MDT meeting.

1. Indications for radiotherapy

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

1.1. Pre-operative radiotherapy

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

1.2. Postoperative radiotherapy

Postoperative radiotherapy is considered for all patients except for:

- those who have had a wide local excision, defined as negative resection margins of at least 1mm;
- and a good histological response (>90% necrosis) to pre-operative chemotherapy;
- and with removal of all tissues originally involved by the pre-chemotherapy tumour volume;

- or for those in whom the anticipated adverse side effects of radiotherapy are sufficiently high to outweigh the additional benefit of radiotherapy for local control (anticipated to be an improvement of approximately 10%) for an individual patient. Reasons for deciding against radiotherapy may include:

Concerns about impaired wound healing following surgery and radiotherapy:

- Concerns about morbidity of giving radiotherapy to young patients
- Concerns about the increased risk of infection of a metallic prosthesis following radiotherapy
- Concerns about the risk of a 2nd radiation-induced malignancy
- Patients who have received high dose Bu-Mel (R2 loc poor responders), if RT dose constraints cannot be achieved for critical organs (see section 7.3).

Specific indications for post-operative radiotherapy include:

- For positive surgical margins with microscopic residual disease (R1 excision; <1mm or tumour up to edge of resection specimen) if further surgery to achieve negative margins is not possible
- For positive surgical margins with macroscopic residual disease (R2 excision), if further surgery to achieve negative margins is not possible (this should be an unusual situation)
- For negative surgical margins if all tissues involved by the original pre-chemotherapy tumour volume have not been excised
- For negative surgical margins if poor histological response (≤ 90% necrosis) to pre-operative chemotherapy
- Displaced pathological fracture of bone at primary site (unless it is possible to excise all contaminated tissue)

For certain tumour sites, where local control is judged to be more difficult to achieve:

- Spine and paraspinal sites - because in these sites excision is rarely complete, and is often intra-lesional

Pelvis and sacrum – because in these sites it is frequently difficult or impossible to be sure that the entire pre-chemotherapy tumour volume has been excised

- Rib tumours when presenting with a pleural effusion

1.3. Definitive radiotherapy

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

1.4. Whole lung radiotherapy

Whole lung radiotherapy is indicated in patients with pulmonary or pleural metastatic disease (R2 VAI and R2 IEVC) in both arms A and B. Whole lung radiotherapy should never be delivered after high dose Bu-Mel.

1.5. Radiotherapy in R3 metastatic patients

Patients with metastatic disease will still need to be considered for local therapy to their primary tumour. The requirement for local therapy will be dependent on the extent of the metastatic disease, and the primary site, and decisions should be made on an individual patient basis. For example, for a patient with limited metastatic disease, local therapy to the primary tumour may be felt to be high priority, whereas for a patient with very widespread metastatic disease, local therapy may be felt to be a less important part of their overall management.

1.5.1. Radiotherapy to the primary tumour in limited metastatic disease

Local therapy should be considered for these patients, and if radiotherapy, this may be delivered either pre-operatively, post-operatively or as definitive local therapy, as discussed above. Consideration should be given to additionally giving definitive radiotherapy to sites of metastatic disease if this is technically feasible in terms of number and sites of metastases.

1.5.2. Radiotherapy to the primary tumour in extensive metastatic disease

Local therapy to the primary tumour may be considered for this group of patients on an individual patient basis, and is more likely to be radiotherapy than surgery, as this modality is more likely to achieve local tumour control with acceptable morbidity than surgery. Examples of when local therapy may be indicated include when a primary tumour is symptomatic, or when progression of the primary tumour could result in significant morbidity, e.g. spinal tumours. The dose and fractionation used may be as for definitive radiotherapy for non-metastatic patients, although for some patients a shorter fractionation may be more clinically appropriate.

1.5.3. Palliative radiotherapy for metastatic disease

Any patient with metastatic disease may require palliative radiotherapy to metastatic sites for symptomatic relief. Precise doses and fractionations will be decided on an individual patient basis, as clinically appropriate.

2. Timing of radiotherapy

2.1. Radiotherapy to primary tumour

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

Patients who are to receive postoperative radiotherapy following surgery should continue with chemotherapy to allow recovery from surgery, wound healing and planning of radiotherapy. Radiotherapy should be aimed to start during the 2nd to 4th cycles of post-operative consolidation chemotherapy. For patients receiving high dose Bu-Mel (R2loc poor responders), radiotherapy should start 10 weeks after Bu-Mel treatment. Delays in starting RT should be avoided. Actinomycin D (arm A) or doxorubicin (arm B) should to be omitted during radiotherapy, and re-introduced after completion of radiotherapy after acute reactions have resolved (see

section 7). For patients who have had a biological reconstruction as part of their surgery, it may be desirable to delay post-operative radiotherapy in order to allow time for the bone graft to unite.
For R2 VAI and R2 IEVC patients with pulmonary and/or pleural metastatic disease, whole lung radiotherapy is given on completion of consolidation chemotherapy.

3. Radiotherapy techniques and delivery
Patients will be treated with CT-planned conformal 3D radiotherapy using dose volume histograms to assess doses to organs at risk. Intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), or tomotherapy can be used at centres with access to this technique, and should be particularly considered for head and neck, pelvic and paraspinal tumours in order to achieve optimal dose distributions and dose delivery. Proton beam radiotherapy is also permitted as long as this does not compromise delivery of chemotherapy. Patients should be immobilised using customised immobilisation devices for limb, and head and neck, tumours. Image guided radiotherapy (IGRT) should be used, according to institutional protocols. Dose specification is according to the ICRU 50 and 62 reports.

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

4.1. Pre-operative and definitive radiotherapy

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

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

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

4.2. Post-operative radiotherapy

4.2.1. GTV

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

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

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

4.2.2. Clinical target volume 1 (CTV1)

CTV1 should encompass any sites of potential microscopic extension of GTV, or of contamination by GTV, including metallic prostheses, drain sites and surgical scars (if feasible), and should be at least GTV + 1.5 – 2cm radially (depending on exact anatomical location). It should also take into account anatomical barriers to tumour spread such as fascial boundaries and bone. It may not be necessary to treat the entire prosthesis, depending on its structure and size; this should be decided on an individual patient basis, balancing the need to include the prosthesis, and the resulting additional normal tissue that must be treated to achieve this. Similarly, it may not be necessary or possible to treat the entire scar, particularly if its inclusion results in a significant increase in treatment volumes with a resultant anticipated increase in the morbidity of radiotherapy.

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

4.2.3. Clinical target volume 2 (CTV2)

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

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

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

4.3. Whole lung radiotherapy

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

5. Radiotherapy dose and fractionation

5.1. Pre-operative radiotherapy

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

5.2. Post-operative radiotherapy

The total dose for postoperative radiotherapy is 54 Gy in 30 fractions, delivered as 45 Gy in 25 fractions to PTV1, and 9 Gy in 5 fractions to PTV2. For patients who have had an R0 resection and a good response (>90% necrosis) to chemotherapy, a dose of 45Gy in 25 fractions to PTV1 may be used especially if the resection did not include the pre-treatment tumour volume. For patients who have received high dose Bu-Mel (R2loc poor responders), specific dose constraints must be adhered to, to avoid organ-specific toxicities (see section 7.3).

5.3. Definitive radiotherapy

The total dose for definitive radiotherapy is 54.0 Gy in 1.8 Gy fractions, delivered as a single phase. There is some limited evidence that local tumour control is poorer for tumours ≥8cm, and those that have exhibited <50% regression on induction chemotherapy, and that dose escalation may improve local tumour control. For such patients a boost of 5.4 Gy in 3 fractions may be considered.

5.4. Whole lung radiotherapy

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

5.5. Fractionation

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

6. Considerations for specific tumour locations

6.1. Extremity tumours

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

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

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

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

6.5. Spinal/paraspinal tumours
GTV should be treated with an appropriate margin around any soft tissue extension, and should receive a maximum dose of no more than 50.4 Gy in 28 fractions. CTV should normally include one unaffected vertebra above and below the affected vertebra, and should also include the scar and any metallic stabilisation rods and cages if the patient has had surgery (as long inclusion of these does not increase the CTV to an unreasonably large size); a smaller CTV2 can be used if appropriate, that does not completely encompass scars, and rods and cages. PTV1 should be treated to a dose of 45 Gy in 25 fractions, and PTV2 to a dose of 5.4 Gy in 3 fractions. Otherwise, PTV is treated in a single phase to a total dose of 50.4 Gy in 28 fractions. Spinal and paraspinal tumours may benefit from an IMRT/VMAT/tomotherapy plan, in order to achieve optimal doses to PTV while keeping the spinal cord dose within tolerance. However, the presence of metal rods and cages may produce dosimetric uncertainties when using IMRT/VMAT/tomotherapy techniques, which should therefore be used with caution.

7. Chemotherapy during radiotherapy

7.1. Actinomycin D
Actinomycin D given during VAC and VAI consolidation chemotherapy (arm A) should be omitted during radiotherapy, or where there are concerns for acute toxicity that may be exacerbated by actinomycin D. It can

be re-introduced again on completion of radiotherapy. Radiotherapy should start no sooner than 1 week after the last dose of actinomycin, and actinomycin should be re-introduced no sooner than 1 week after completion of radiotherapy.

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

7.3. Radiotherapy and high dose busulfan and melphelan (Bu-Mel) chemotherapy
Some patients with localised disease (R2loc poor responders) may be treated with high dose Bu-Mel chemotherapy. For these patients, there are special considerations regarding radiotherapy as local therapy, because of interactions with the high dose chemotherapy agents, potentially resulting in significant toxicity after delivery of high radiotherapy doses to spinal cord/cauda equina, lung, or bowel. This may compromise the ability to deliver an effective radiotherapy dose to central axial sites (spine, sacrum, pelvis), or when lung or bowel are within the radiotherapy treatment fields. Careful consideration will be needed to balance up the competing needs for Bu-Mel as part of systemic therapy, and radiotherapy for local therapy, and individualised decision making should made for patients in the setting of an MDT meeting.
Bu-Mel high-dose chemotherapy is contra-indicated for primary tumours for which the following dose constraints cannot be met:

- ≤ 45 Gy to gastrointestinal tract (stomach, small bowel, large bowel, rectum)
- ≤ 45 Gy to bladder
- ≤ 30 Gy to spinal cord
- ≤ 36 Gy to cauda equnia (including sacrum)
- V20Gy <30% or V30Gy <20% for a single lung

Whole lung radiotherapy is contraindicated following Bu-Mel high dose chemotherapy.
Consideration should be given to use techniques that can minimise dose to normal tissues or exclude normal tissues from radiotherapy treatment fields:

- Spacer devices can be used in the pelvis to displace bowel away from treatment volumes
- Intensity modulated radiotherapy [IMRT] techniques (fixed field IMRT, volumetric modulated arc therapy, tomotherapy)
- Proton beam therapy or carbon ion therapy (if available).

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

9. Long term monitoring

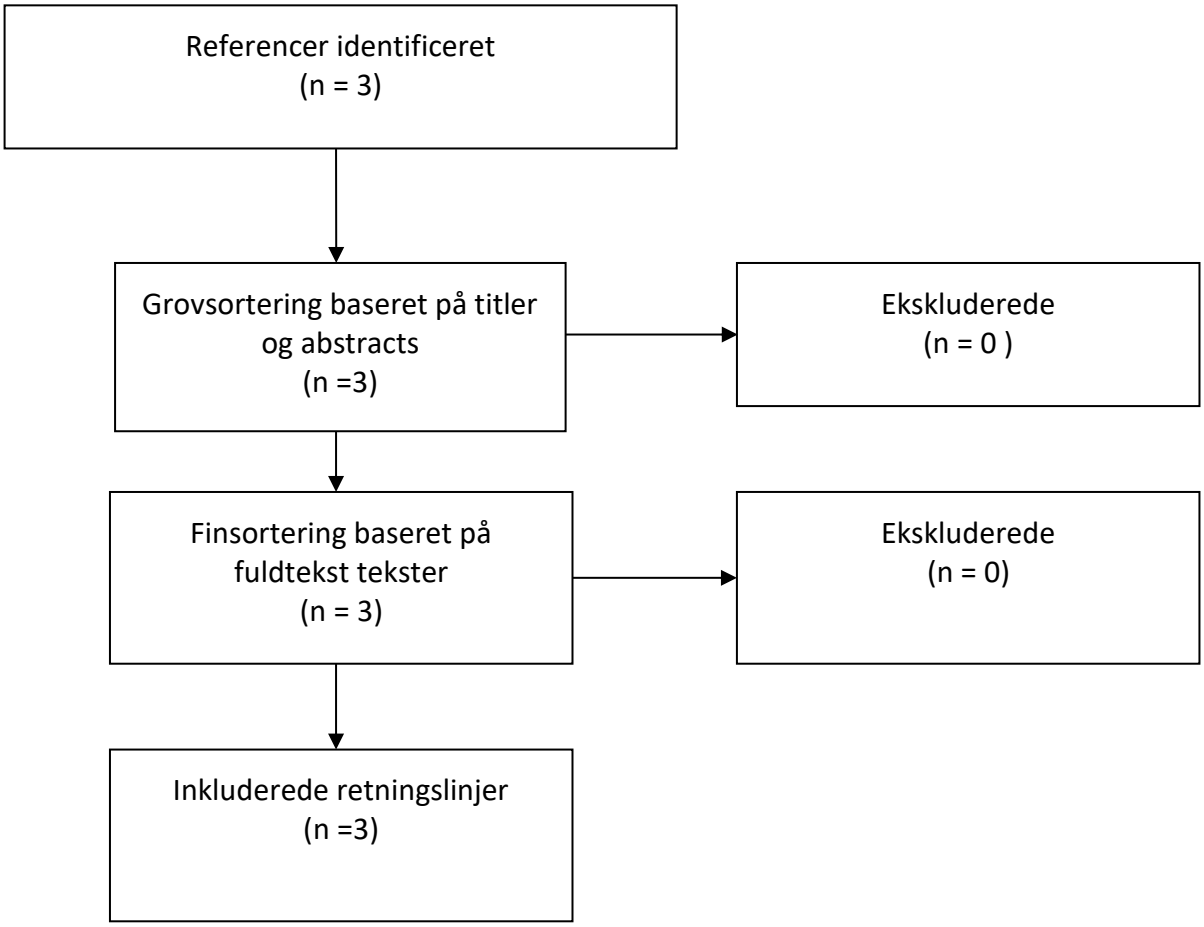
It is recommended to follow national guidance for each country with regard to long term monitoring for late effects following radiotherapy, specifically the monitoring for girls receiving radiotherapy to the lung involving breast tissue, and hence screening for breast cancer.

References

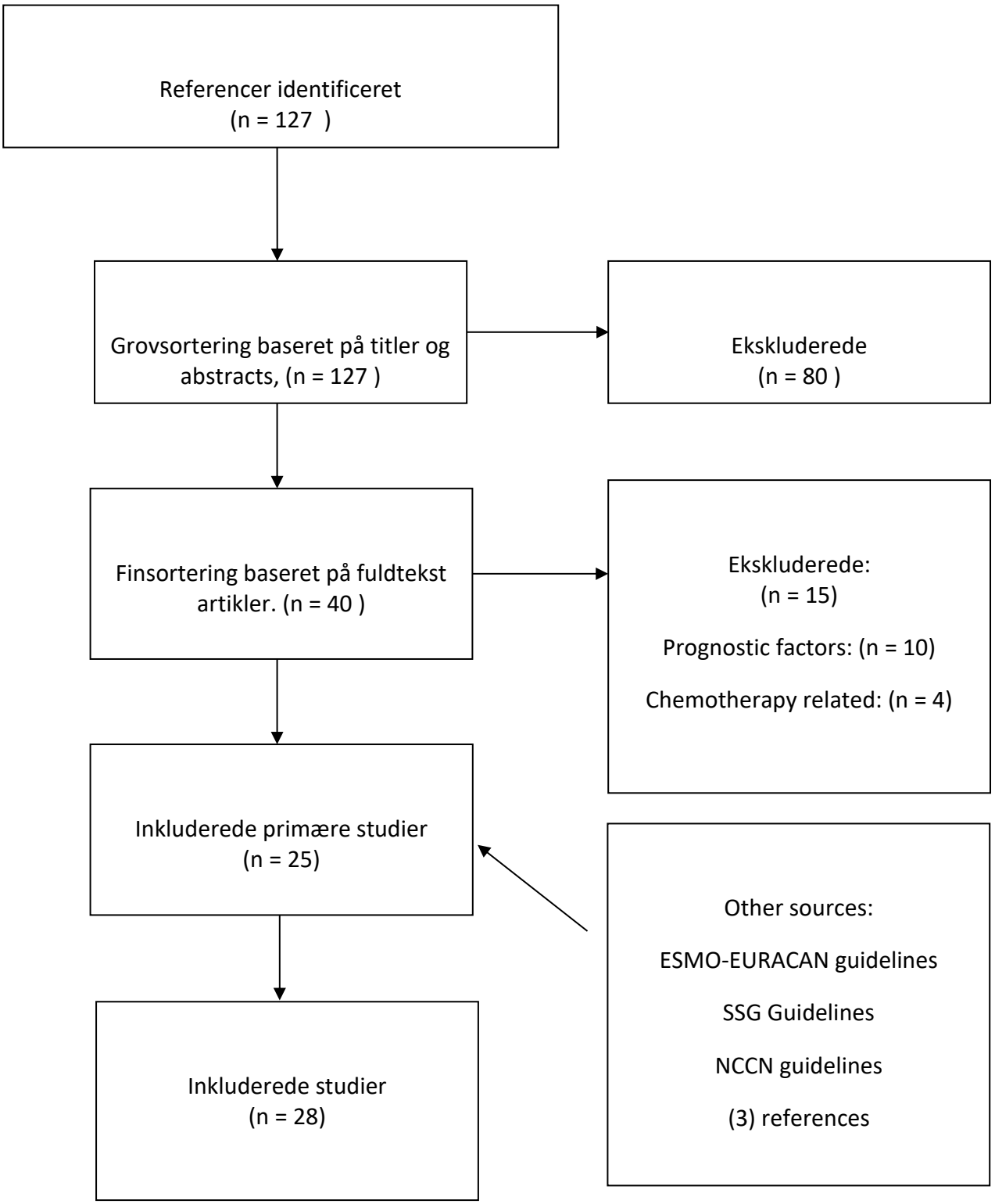
1. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S10-9.

Appendix 3 – Flow chart

Flowchart – Guidelines



Flowchart – Primære studier



Appendix 4 – Evidenstabel

Dette arbejdspapir kan anvendes til kritisk gennemgang af den litteratur, der skal danne grundlag for retningslinjens anbefalinger.

	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 (nr. of pts.)***
1	SSG s	2015	Guidelines	2a	None	None	All sites, Ped. & adults	Radiotherapy details are described	
2	NCCN	2018	Guidelines	2a	None	None	All sites, Ped. & adults	Radiotherapy details are described	
3	ESMO	2018	Guidelines	2a	None	None	All sites, Ped. & adults	Radiotherapy details are described	
4	Bacci G. et al.	2009	retro	2b	Combined treatment	Surger vs Rth	Humerus	Surgery is the best treatment for small tumors. Postop Rth is mandatory when margins are inadequate.	55

5	Bacci G. et al.	2003	retro	2b	Combined treatment	Surger vs Rth	Femur	Better local control is achieved by surgical treatment ± Rth) compared with Rth alone.	91
6	Ahmed SK et al..	2017	retro	2a	Surgery or radiotherapy	Surgery vs Rth.	spine	The LC in spine after Rth is the same as surgery	965
7	Miller BJ. et al.	2017	database	2a	Combined treatment	Surger vs Rth	All sites	Surgery alone resulted in the best overall survival.	103
8	Dunst J, & Schuck A	2004	review	2a	None	None	All sites, Ped. & adults	Radiotherapy details are described	
9	Laskar S. et al.	2008	review	2a	None	None	All sites, Ped. & adults	Radiotherapy details are described	
10	Schuck A. et al.	2003	retro	2a	Combined treatment in trials	Definitive Rth vs postoperative Rth	All sites	Definitive RT showed comparable local control to that of postoperative RT after	1058

								intralesional resection.	
11	Schuck A. et al.	1998	retro	2b	Combined ttt in trials	Surger vs surgery + rth	Chest wall	Better control of chest wall Ewing after hemithorax Rth	114
12	Schuck A. et al.	2002	retro	2b	Combined ttt in trials	Surger vs surgery + rth	Chest wall	Better control of chest wall Ewing after hemithorax Rth	138
13	Dunst J	1993	retro	2b	Radiotherapy	Chemotherapy or no ttt	Lung mets.	WLI improves outcome	42
14	Paulussen M	1998	retro	2b	Radiotherapy	Chemotherapy or no ttt	Lung mets.	WLI improves outcome	114
15	Scobioala S	2018	retro	2b	Radiotherapy	Chemotherapy or no ttt	Lung mets.	WLI improves outcome	136
16	Burdach S	2000	retro	2b	Combined ttt	Rth to mets sites + cth	Bone mets	High dose cth and local rth to mets. gives superior results	36
17	Driksen U et al.	2019	Prospective phase III	A	High dose chemotherapy	Whole lung irradiations	Lung metastasis	No benefit of high dose chemotherapy	543
18	Scobioala S & Eich H.T.	2020	Review	2a	Whole lung irradiation	High dose chemotherapy	High risk patients	15 Gy and 60 fays interval reduced the risk	227

19	Meyers PA	2001	retro	2b	High dose cth only	Compared to pts received rth	Bone mets	High dose cth alone is not effective in mets cases	32
20	Schuck A	2002	retro	2b	Combined ttt in trials	Short interval vs long interval to rth	Localized Ewing	Short interval to irradiation gives better outcome	138
21	Schuck A	2002	retro	2b	Combined ttt in trials	Short interval vs long interval to rth	Localized Ewing	Short interval to irradiation gives better outcome	153
22	Burgers JM	1997	retro	2b	Combined ttt in trials	Short interval vs long interval to rth	Localized Ewing	duration of chemotherapy prior to the start of XRT was the only significant prognostic factor	35
23	Donaldson SS	2004	review	2a	None	None	All sites, Ped. & adults	Radiotherapy details are described	
24	Marcus RB, Jr.,	2002	retro	2b	Combined ttt in trials	Low vs high dose	All sites	Minimum dose of 45 is needed	144
25	Ahrens S	1999	retro	2b	Combined ttt	Small vs. large tumurs	All sites	Despite risk-adapted treatment intensity, tumor volume retained its	177

								prognostic significance	
26	Nesbit ME	1990	retro	2b	Combined ttt in various trials	Different ttt strategies	All sites	there was no evidence that local recurrence rate differed by treatment	342
27	Dunst J et al.	1995	retro	2b	Combined ttt in various trials	Different ttt strategies	All sites	Rth yielded relapse-free and overall survival figures comparable to radical surgery.	177
28	Arai Y	1991	retro	2b	Combined ttt in trials	Low vs high dose	All sites	The overall local tumor control rate following the tested dose level of 35 Gy appears to be inadequate	60
29	Paulino AC	2007	retro	2b	Combined ttt in trials	Low vs high dose	All sites	Radiotherapy dose was found to influence local control in ES. In particular, patients who received RT doses >or=49	40

								Gy for tumor size <or=8 cm and >or=54 Gy for tumor size >8 cm had improved local control.	
30	Laskar S. et al.	2022	Phase III trial	A	Radiotherapy dose escalation	Standard dose vs. dose escalation	Unresectable	Better local control with 70.2 Gy	95
31	Ronchi L	2018	review	2a	Whole lung irradiation	Lung irradiation vs. control	Lung mets	The real impact of WLI on patients' outcomes remains unproven	