

**Scandinavian Sarcoma Group and
Oncologic Center, Lund, Sweden**

SSG XIX

Recommendations for treatment of metastatic soft-tissue sarcomas in adult patients



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Contents

Working group	3
1.0 Background	5
2.0 Choice of treatment intent	8
3.0 Proposals for decision of chemotherapy	9
3.1 With a curative treatment intent	9
3.2 With a palliative treatment intent	9
3.3 Chemotherapy regimens	10
3.4 Pre-treatment investigations	11
4.0 Radiotherapy	12
5.0 References	13
Table 1. Randomised studies on chemotherapy of metastatic or unresectable STS	17
Table 2. Levels of Evidence and Grade of Recommendation for various cytostatic regimens in metastatic STS	18
Table 3. Standard definitions: Levels of Evidence and Grade of Recommendation	18
Treatment chart for metastatic STS	19

1.0 Background

Soft-tissue sarcomas (STS) comprise a heterogeneous group of rare mesenchymal malignancies that vary largely according to the site, histology and grade. The overall five-year survival rate for STS is only about 50%. The most important prognostic factor is the histological grade, including features such as tumour necrosis and vascular invasion; high-grade tumours metastasize more often than low-grade tumours. Local recurrence is a poor prognostic factor (Lewis et al. 1997) and is more common in patients with distant metastases (Gustafson et al. 1991; Lewis et al. 1997; Trovik 2001). This association may be more statistical than causal; i.e. local recurrence indicates a highly malignant tumour with a propensity for both local and distant spread.

Most patients (80–90%) with STS have only localized disease diagnosed at presentation. Nevertheless, 40–60% of patients with high grade STS develop metastases despite curative local treatment. The median survival time after diagnosis of distant metastases is 1 year and most patients will die. The lungs are the most common (70%) site for distant metastases, others are the liver, bones and lymph nodes. Among patients with metastatic disease extrapulmonary metastases and histologies like leiomyosarcoma and malignant fibrous histiocytoma are poor prognostic factors for survival, while good performance status, absence of liver metastases, low histopathologic grade, long time since diagnosis of the primary tumour, few metastases, and young age are favourable (van Glabbeke et al. 1999).

A subset of patients with operable distant metastases and chemosensitive disease may have a long disease-free interval or even be cured. As concluded in two reviews (Alvegård and Sæter 1997; Sawyer and Bramwell 1999), long-term survival may be obtained for up to 40% of adult patients with STS after surgical removal of lung metastases. Favourable factors for long-term survival were complete metastasectomy, a metastasis-free interval longer than 12 months, and <2–4 identifiable metastases. Sometimes repeated thoracotomies for subsequent relapses were needed.

The role of chemotherapy combined with metastasectomy has been uncertain in metastatic and/or locally inoperable STS. In 1996 EORTC and SSG started a prospective trial (SSG XII) randomising operable patients to excisions of lung metastases with or without aggressive chemotherapy, but this study was closed in 2001 due to low inclusion rate. Enthusiasm for surgery combined with chemotherapy has previously been tempered by SSG (Alvegård and Sæter 1997; Wiklund et al. 1997). Promising results have been reported when effective chemotherapy has been combined with complete surgical removal of all metastatic disease. Good histopathological response to chemotherapy was associated with good prognosis and more relevant for outcome than a good radiological response (Sæter et al. 1995, Wiklund et al. 1997).

Chemotherapy in treatment of metastatic and/or unresectable STS is controversial (Benjamin et al. 1998; Sawyer and Bramwell 1999). Several chemotherapeutic agents have been evaluated, e.g. anthracyclines, ifosfamide, cyclophosphamide, trofosfamide, dacarbazine (DTIC), etoposide, and vincristine. Response rates for combination chemotherapy regimens have varied from 15% to over 50% at best and the rates for complete response from 0 to 22% (Santoro 1999). Three large randomised studies have been published in the 1990's (Table 1). These studies included only patients who had received no previous chemotherapy. The American Intergroup randomised doxorubicin/DTIC versus doxorubicin, ifosfamide/DTIC (MAID) (Antman et al. 1993), whereas the Eastern Cooperative Oncology Group (ECOG)

randomised doxorubicin versus doxorubicin and ifosfamide versus doxorubicin, mitomycin C and cisplatin (Edmonson et al. 1993). Higher response rates were found in the combination arms, but no significant differences in median survival times. Myelosuppression was significantly more intense in patients who received ifosfamide. In the largest study ever performed in STS the EORTC Soft Tissue and Bone Sarcoma Group (EORTC STBSG) group randomised 663 patients to receive either doxorubicin, or cyclophosphamide, vincristine, doxorubicin, and dacarbazine (CYVADIC) or ifosfamide + doxorubicin (Santoro et al. 1995). No statistically significant difference was found in response rates, remission duration, or overall survival, but myelosuppression and cardiotoxicity were more common in the combination of ifosfamide and doxorubicin than in the other two regimens. The group concluded that single-agent doxorubicin should be regarded as the standard regimen against which more intense or new drug treatments should be compared.

SSG performed a dose escalation study of etoposide and ifosfamide with G-CSF (VIG) in metastatic STS (SSG X). In 26 patients treated with VIG + complete surgery of metastases the relapse-free and overall survival at two years post-surgery were 39% and 74%, respectively (Sæter et al. 1997).

After many years of clinical research, doxorubicin and ifosfamide appear to be the most effective combination regimen against STS with regard to response rates, but no clear advantage has been demonstrated in survival. Moreover, a positive dose-response relationship has been shown for the both cytostatics and recently also for epirubicin (Reichardt et al. 1998, Patel et al. 1999, Spira and Ettinger 2002, Lopez et al. 2002). Response rates of 33–45% have been reported in phase II studies using high-dose ifosfamide in pretreated patients with metastatic or locoregionally unresectable STS (Le Cesne et al. 1995; Palumbo et al. 1997; Patel et al. 1997).

Reichardt et al. (1998) explored epirubicin 90 mg/m² given as a continuous infusion for 2 days with ifosfamide 12.5 g/m² for 5 days with G-CSF in 46 patients with locally advanced or metastatic STS. All patients experienced NCI grade 3 or 4 hematological toxicity, but there was no toxic death. Overall response rate was 52% with 22% complete responses. Patel and co-researchers at M.D. Anderson (1998, 2000) reported an overall response rate of 65% in 79 patients receiving doxorubicin 75 mg/m² or 90 mg/m² (as a 72h-infusion on day 1–3) along with ifosfamide 10 g/m² (2.5 g/m² over 3 h on day 1–4) with G-CSF. The Swiss Group for Clinical Research (Leyvraz et al. 1998) performed a dose escalation study of doxorubicin with two levels of ifosfamide. Ifosfamide was administered as a continuous infusion over 5 days and doxorubicin as divided doses over 3 days to 33 patients, escalating through five dose levels. Although the maximal tolerated dose was reached for the combination ifosfamide 12 g/m² and doxorubicin 60 mg/m², it was not reached for ifosfamide 10 g/m² and doxorubicin 90 mg/m². The investigators concluded that the latter regimen was acceptable with WHO grade 4 leucopenia 58%, thrombocytopenia 42%, and major mucositis 50%. Although it was a phase I study and response was not the primary endpoint, there was a trend toward increased response rates at higher dose levels. Results of the randomised phase II study by EORTC STBSG with two different ifosfamide regimens in first- and second-line chemotherapy were published recently (van Oosterom et al. 2002). They found that first-line treatment with ifosfamide 3 g/m² given over 4 hours on three consecutive days, every three weeks was more efficient than the 5 g/m² over 24 hours schedule, although survival times did not differ between the two regimens. Short infusion (2–4 hours) of ifosfamide seemed to show a higher response rate against soft-tissue sarcomas than did continuous infusion (74 hours) (45% versus 19%) (Patel et al. 1997). Investigators at the Dana-Farber Cancer Institute

found that the response rate to ifosfamide was 26% with a bolus schedule compared with 9% with a continuous infusion schedule (Antman et al. 1989).

EORTC STBSG recently published the results of the prognostic-factor analysis of 2185 patients with metastatic or unresectable STS who had been included in first-line chemotherapy protocols using anthracycline containing regimens between 1976 and 1990 in seven trials of the group. Performance status appeared to predict response, other favourable factors of response rate were absence of liver metastases, young age, high histopathologic grade, and liposarcoma (van Glabbeke et al. 1999). The group also found that long-term survivors, i.e. patients surviving at least 5 years, were observed in all prognostic subgroups of patients, even in those with high grade tumours, liver or bone metastasis, and poor performance status. In multivariate analysis independent parameters correlated to 5-year survival were performance status, female gender, grade I tumours, and the achievement of a complete response after first-line treatment, which was retained as the most powerful predictor for 5-year survival (Blay et al. 2003).

The same group (Blay et al. 2000) also tested high-dose chemotherapy with autologous hematopoietic stem-cell transplantation (HDCT) in 30 patients with advanced STS. They found that six of the eight patients with complete remission before HDCT were alive at 5 years. The studies on HDCT in STS (Pinkerton et al. 1991, Dumontet et al. 1992) include only small numbers of patients with histologic subtypes that are more chemosensitive than those usually found in adult patients with STS, and, hence, it is difficult to draw any definite conclusion of the role of HDCT.

Several newer agents like gemcitabine have been tested as treatment of locoregionally unresectable and/or metastatic STS in phase II trials including a limited number (25–34) of patients without any impressive results (Švancárová et al. 2002; Okuno et al. 2002 and 2003). Most patients had been pretreated with doxorubicin-containing regimens. However, objective responses have been reported in some small studies for gemcitabine (Spath-Schwalbe et al. 2000), combination of gemcitabine and docetaxel for leiomyosarcoma (Hensley et al. 2002), liposomal doxorubicin (Toma et al. 2000), ET-743 (Le Cesne et al. 2001), and paclitaxel especially for angiosarcoma (Fata et al. 1999).

The purpose of the current recommendations is to optimize the treatment of metastatic soft tissue sarcoma and provide principles that may guide the therapy. Because there are relatively few studies of sufficient standard (small studies, retrospective studies, limited randomized data, diversity of histological diagnosis etc) it is difficult to draw definite conclusions from the literature on the role of various treatment regimens. Therefore we have included definitions of “Levels of evidence” and “Grade of Recommendation” in order to show the degree of uncertainty of the current recommendations (See Table 2 and Table 3).

These recommendations do not concern gastrointestinal stromal tumours (GISTs), rhabdomyosarcoma or extraskeletal Ewing sarcoma. We have mainly focused on the use of chemotherapy. A small section on various techniques for radiotherapy that are used for locally advanced and metastatic sarcomas has been included.

2.0 Choice of treatment intent

Treatment of metastatic or locoregionally inoperable STS should be planned individually for each patient according to the age, performance status, symptoms, and other diseases that may influence e.g. tolerability. Tumour-related factors like size, histological type and grade, location of metastases, rate of tumour growth, and current status of the primary tumour have to be taken into account.

In principle, curative intention implies that surgery of the metastases is possible. The patients should be discussed early with the surgeon. The patients should be categorized in 1. Primary operable tumour and 2. Potentially operable disease. For *Category 2* a combination with intensive chemotherapy is recommended according to the guidelines below if tolerability is considered acceptable based on patient-related factors. If this is not the case e.g. in elderly patients, surgery may be performed without any chemotherapy. Excision of pulmonary metastases only may be considered, especially when there are few (≤ 4) metastases and the metastasis-free interval is longer than 12 months (Sawyer and Bramwell 1999).

Chemotherapy in patients without any probability of meaningful surgery is given with a palliative intention (*Category 3*). However, since long-time survivors can be found after chemotherapy even in non-operable patients, e.g., those with bone or liver metastases (Blay et al. 2003) the distinction between curative and palliative intent may be vague, especially in younger patients who have good performance status and will probably tolerate intensive treatment.

The treatment tradition has been divergent in Scandinavian countries with much more use of chemotherapy in Sweden (Wall and Starkhammar 2003) than in Norway. In Finland the combination of doxorubicin and ifosfamide with or without dacarbazine has often been used in the first line, whereas dose-intensive chemotherapy with growth factors has not. Chemotherapy may be considered as an effective palliation, since it occasionally results in long-time survival in selected cases. Therefore, these patients may be offered therapy as "curative treatment intent", i.e. as described as *Chemotherapy II*. However, in cases of treatment failure from the first line chemotherapy, some patients may be offered the same non-aggressive chemotherapy that is given in the first line as palliation to elderly patients or those with poor performance status. The use of a second line treatment should be avoided as a routine. In contrast, inclusion of these patients into prospective clinical trials for new drugs could be considered. Palliative radiotherapy or best supportive care might be an early option instead of chemotherapy when relief of symptoms is the goal for treatment (Sawyer and Bramwell 1999).

3.0 Proposals for decision of chemotherapy

3.1 With a curative treatment intent

Histologically proven soft tissue sarcoma of malignancy grades III and IV may be considered for treatment. Because there are no randomised trials showing that dose-intensified chemotherapy regimens will result in survival benefit, standard-dose chemotherapy should be the preferred treatment in metastatic or unresectable STS. The combination of doxorubicin and ifosfamide with or without dacarbazine is one of the options.

Nevertheless, dose-intensified chemotherapy (*chemotherapy I*, "dose-intensified") under prospective observation might be considered for those patients with metastases potentially amenable to radical surgery (Patel 2000, Spira and Ettinger 2002). Patient-related factors like good performance status, no significant comorbid conditions, chemosensitive histology (e.g. synovial sarcoma, liposarcoma), and age <65 years should be required. The toxicity is high, but usually manageable when treatment is given in conjunction with growth factors. Reporting of the patients receiving this treatment to the SSG register is essential to gain further knowledge of the role of dose-intensified treatment. If it is probable that the patient will not tolerate *chemotherapy I* ("dose-intensified"), *chemotherapy II* ("standard-dose") may be chosen. If the patient has a previous history of cardiovascular disease *chemotherapy III* should be preferred.

The patient is expected to complete three cycles before surgery of lung metastases. Surgery will usually be performed 2–3 weeks after the third cycle. Two postoperative cycles should be given unless there has been a clear progression by CT-scan. Histological reponse seems to be important for the prognosis, but there is not enough evidence to say that non-reponders will not benefit from further chemotherapy. Therefore all patients should have the same postoperative therapy independent of histological response.

Significant reduction of contrast enhancement by MRI imaging may indicate chemotherapy response in soft tissue tumour metastases. Surgery should be performed after three cycles and postoperative chemotherapy should be considered with similar criteria as for lung metastases. Unresectable localized metastases that respond to chemotherapy may be suitable for radiotherapy in order to increase the response.

3.2 With a palliative treatment intent

As discussed above, younger patients with good performance status may be offered treatment according to *Chemotherapy II or III* even if it is not possible to perform curative surgery of the metastases. When such approach is not judged to be meaningful or tolerable there may still be a need and a wish from the patient to try anti-tumour treatment. It is of importance that toxicity is low and that the quality of life will not be hampered during the rest of the disease course.

Low intensity chemotherapy

Single-agent doxorubicin 50–80 mg/m² every 3 weeks may be considered as suitable palliative therapy for elderly patients or those with impaired performance status (Santoro et al. 1995; Sawyer and Bramwell 1999). An alternative treatment with mild toxicity is low-dose doxorubicin with 20 mg i.v. weekly, which may be a good alternative especially for patients never treated with anthracyclines (Chlebowski et al. 1980).

Trofosfamide (Ixoten[®], 50 mg; ASTA Medica) is an oxazaphosphorine with ifosfamide as the predominant metabolite. It has been useful in patients with metastatic STS pre-treated with doxorubicin and ifosfamide, and response and/or disease stabilization has been achieved for up to 70% of patients in a German study (Kollmannsberger et al. 1999). The drug has also been used as maintenance therapy in patients pre-treated with aggressive chemotherapy resulting in partial remission or stable disease, and it seemed to prolong progression-free and overall survival (Reichardt et al. 2002). Trofosfamide is well-tolerated with a mild predominantly haematologic toxicity. A common total dose is 150 mg per day, e.g., one pill in the morning and two at night. Furthermore, the German Cooperative STS Study (CWS) recommended trofosfamide as maintenance therapy in combination with oral etoposide and idarubicin after aggressive chemotherapy in children with stage IV STS. The combination of trofosfamide and etoposide has been used in Scandinavia in palliation for patients who have failed on single agent trofosfamide (personal communication). The most common dosage has been trofosfamide 100 mg × 2 combined with etoposide 50 mg × 2 during 10 days, followed by 10 days pause before the next course. Shortening of treatment periods, e.g., to 7 days with 10 days pause, may be necessary due to haematologic toxicity.

3.3 Chemotherapy regimens

Chemotherapy I (Dose-intensified)

Doxorubicin 75 mg/m²- as a 4 hour infusion day 1

Ifosfamide 9 g/m² (3 g/m² as a 72 hour infusion, days 1–3) (with Mesna)

Alternatively as given in EURAMOS 1 (mandatory with double lumen CVK):

Doxorubicin 75 mg/m²- as a 48 hour infusion

Ifosfamide 3 g/m²/day × 3 days (with Mesna)

G-CSF 300 mikrogram s.c/daily day 6–14 (body weight <80 kg)

G-CSF 480 mikrogram s.c/daily day 6–14 (body weight >80 kg)

Or :

Neulasta (pegylated filgrastim) 6 mg 24 h following chemotherapy

Chemotherapy cycle repeated every 21 days

Chemotherapy II (Standard dose)

Doxorubicin: 75 mg/m²- as a 4 hour infusion day 1

Ifosfamide: 5 g/m² as a 24 hour infusion day 1 (with Mesna)

G-CSF 300 mikrogram s.c/daily day 3–11 (body weight <80 kg)

G-CSF 480 mikrogram s.c/daily day 3–11 (body weight >80 kg)

Or :

Neulasta (pegylated filgrastim) 6 mg 24 h following chemotherapy

Chemotherapy cycle repeated every 21 days

Chemotherapy III (VIG as described in SSG X)

Ifosfamide 1800 mg/m² as a 2 hour infusion (with Mesna) on 3 consecutive days

Etoposide (VP-16), total 720 mg/m² in 72 h infusion

G-CSF 300 mikrogram s.c/daily day 5–13 (body weight <80 kg)

G-CSF 480 mikrogram s.c/daily day 5–13 (body weight >80 kg)

Or :

Neulasta (pegylated filgrastim) 6 mg 24 h following chemotherapy

Chemotherapy cycle repeated every 21 days

Chemotherapy IV: In patients previously treated within SSG XIII or in a situation with failure on one of the other regimens, but still further treatment attempt seem to be motivated.

Ifosfamide 15 g/m² (3 g/m²/24 h on days 1–5) (with Mesna)

Given as ifosfamide treatment in SSG XIV

G-CSF 300 mikrogram s.c/daily day 7–15 (body weight <80 kg)

G-CSF 480 mikrogram s.c/daily day 7–15 (body weight >80 kg)

Or :

Neulasta (pegylated filgrastim) 6 mg 24 h following chemotherapy

Chemotherapy cycle repeated every 21 days

Chemotherapy V : IADIC

Doxorubicin 50 mg/m² as 30 minutes infusion day 1

Ifosfamide 1g/m² as a one hour infusion (with Mesna) days 1–5

Dacarbazine 250 mg/m² as a one hour infusion days 1–5

Repeated every 21 days

3.4 Pre-treatment investigations

1. Complete medical history and physical examination
2. Radiological evaluation of metastatic disease (CT of lungs, MRI of soft tissue tumours) (FNA if necessary)
3. Blood chemistry: blood counts, transaminases, electrolytes, creatinine, bicarbonate
4. Electrocardiogram (ECG)
5. Estimation of left ventricular ejection fraction (LVEF) either by cardiac ultrasound or MUGA scan
6. GFR

4.0 Radiotherapy

It is well documented that surgery combined with local radiotherapy decreases the local recurrence risk for soft tissue sarcomas of the extremities and trunk wall. The radiation is then delivered either preoperatively or postoperatively.

The use of radiotherapy alone is not nearly as well studied. Radiation therapy delivered with radical intent in soft tissue sarcomas gives a significant number of local controls and tumour sterilisation, although the number of local failures is unacceptably high (McGinn and Lawrence 1998).

Definitive radiotherapy requires high doses of 64–70 Gy given in 2 Gy fractions five days a week to have a chance for sustained local control. In palliative treatment shorter courses and higher daily fractions often have to be accepted e.g. 3 Gy × 10 or even single large fraction of 6–8 Gy depending on the site and size of metastases and the general condition of the patient. General principles for palliative radiotherapy can be applied bearing in mind that tumour regression often is a slow process in soft tissue sarcomas. Palliative radiotherapy is useful e.g. for ulcerative subcutaneous metastases, painful bone lesion, and mediastinal masses causing airway obstruction.

Fast growing tumours may be treated with hyperfractionated schedules. Clinical studies with hyperfractionation are few and most concerns childhood rhabdomyosarcoma. Examples of special techniques and beam qualities sometimes used for treatment of locally advanced and metastatic sarcomas are mentioned below:

Brachytherapy Besides from being used in combination with surgery, brachytherapy may also be used in selected recurrences after surgery. Brachytherapy may offer an advantage especially when soft tissue sarcomas recur in previously irradiated areas (Janjan et al. 2002).

Proton Beams Clinical benefit has been shown for protons in tumours located close to critical structures i.e. near the base of the skull or spinal cord. Chordomas and chondrosarcomas have been the most common tumor types (Hug and Slater 2000), but soft tissue sarcomas in the same region can be expected to benefit as well.

Neutrons Radiotherapy of locally advanced soft tissue sarcomas not suitable for surgery has been suggested as one clinical indication for fast neutrons. Positive results in the palliative setting have been reported due to a symptomatic response for gross disease with minimal serious late side effects (Schwartz et al. 2001). Neutrons are not available in Scandinavia.

Stereotactic Radiotherapy (SRT) Stereotactic radiotherapy is a highly conformal radiotherapy with a possibility to deliver high doses in few fractions to metastases in the lung, liver and abdomen (Blomgren et al. 1995, Wulf et al. 2001). The method is not validated for soft tissue sarcoma but hypofractionated treatment with large fractions (for example 15 Gy three times in one week) is possible to deliver to metastases of moderate size.

Intraoperative Radiotherapy (IORT) Intraoperative radiotherapy is an option used foremost in the treatment of retroperitoneal sarcomas. A large single dose of irradiation is delivered to a surgically defined area, while uninvolved and dose-limiting tissues are displaced, the final goal of IORT being enhanced local tumour control (Valentini et al. 2002). IORT is used in most modern protocol studies as a boost radiation component of multidisciplinary treatment approaches. Recurrences can also be boosted likewise (Lehnert et al. 2000).

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Table 1. Randomised studies on chemotherapy of metastatic or unresectable STS

Study	Number of patients	Response rate %	Overall survival
<i>Edmonson J (1993)</i> dox 80 mg/m ² vs. dox 60 mg/m ² + ifo 7.5 g/m ² vs. dox 40 mg/m ² + cis 60 mg/m ² + mit 8 mg/m ² - every 3 weeks	262	20 34 32	no difference
<i>Antman K et al. (1993)</i> dox 60 mg/m ² + DTIC 1 g/m ² vs. dox 60 mg/m ² + DTIC 1 g/m ² + ifo 7.5 g/m ² (ifo later decreased to 6 g/m ²) - every 3 weeks	339	17 32	no difference
<i>Santoro A et al. (1995)</i> dox 75 mg/m ² vs. dox 50 mg/m ² + ifo 5 g/m ² vs. CYVADIC - every 3 weeks	663	23 28 28	no difference

dox = doxorubicin
ifo = ifosfamide
mit = mitomycin C
cis = cisplatin

CYVADIC = cyclophosphamide 500 mg/m² + vincristine 1.5 mg/m² + doxorubicin 50 mg/m² + dacarbazine 750 mg/m²

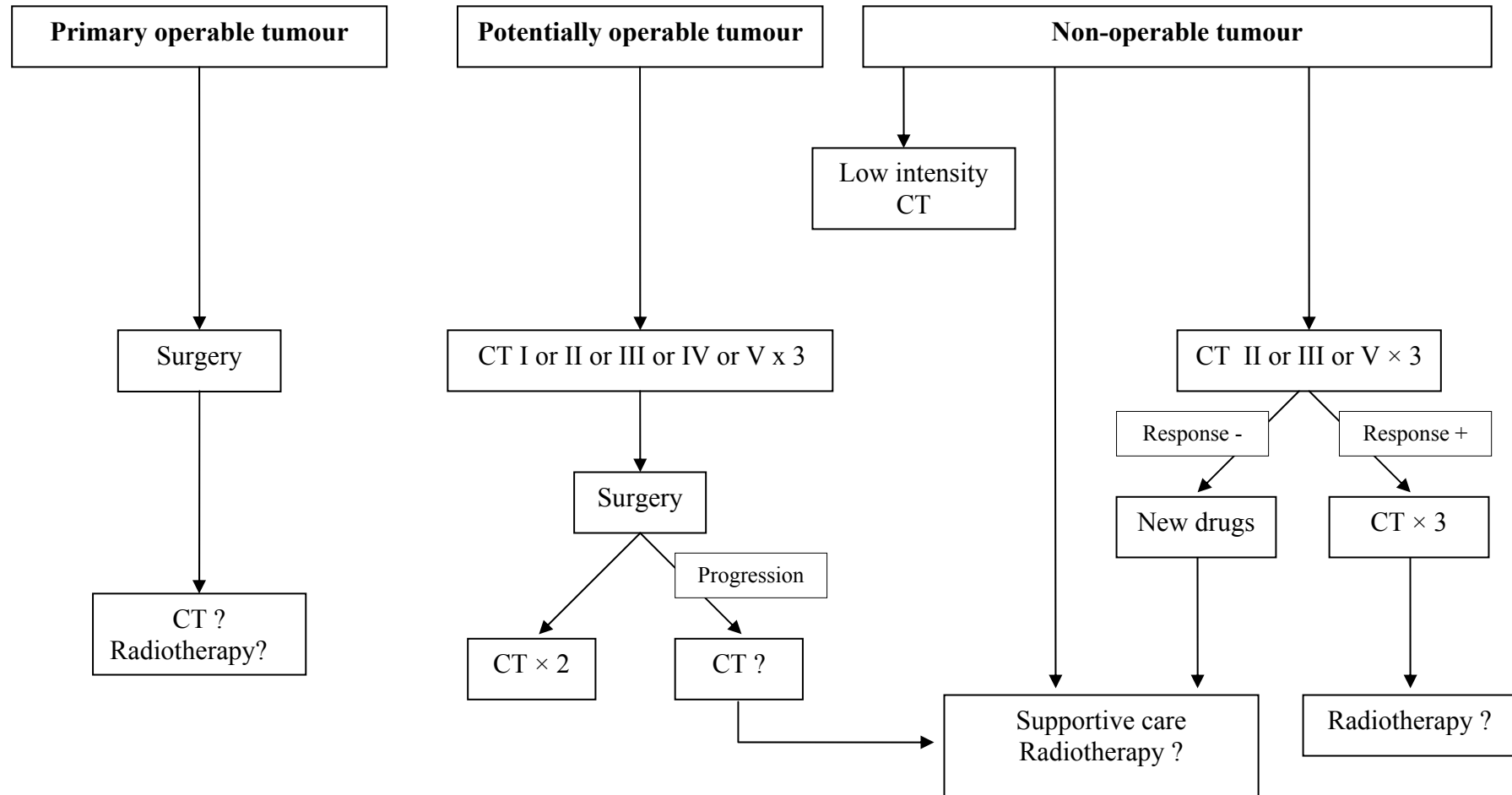
Table 2. Levels of Evidence and Grade of Recommendation for various cytostatic regimens in metastatic STS as based on standard definitions in Table 3

	Type of evidence (I–V)	Grade of recommendation (A–D)
Potentially operable tumours		
CT I (dox 75 mg/m ² + ifo 9 mg/m ²)	III	B
CT II (dox 75 mg/m ² + ifo 5 mg/m ²)	II	B
CT III (ifo 5,4 g/m ² + etoposide 720 mg/m ²)	III	B
CT IV(ifo 15 g/m ²)	II	B
CT V (dox 50 mg/m ² + ifo 5 g/m ² + dacarbazine 1250 mg/m ²)	II	B
Non-operable tumours		
“First line” chemotherapy	III	B
“Second line” chemotherapy	III	C

Table 3. Standard definitions: Levels of Evidence and Grade of Recommendation

Level	Type of Evidence
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomised trials with low false-positive and low false-negative errors (high-power)
II	Evidence obtained from at least one well-designed experimental study. Randomised trials with high false-positive and/or false-negative errors (low power)
III	Evidence obtained from well-designed, quasiexperimental studies such as non-randomised, controlled, single-group, pre-post, cohort, time, or matched case-control series
IV	Evidence from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples
Grade	Grade of Recommendation
A	There is evidence of type I or consistent findings from multiple studies of type II or III
B	There is evidence of type II, III or IV and findings are generally consistent
C	There is evidence of type II, III or IV but findings are inconsistent
D	There is little or no systematic empirical evidence

Treatment chart for metastatic STS



CT = chemotherapy. The regimens are described on page 9 and 10. Postoperative regimen should generally be the same as the preoperative regimen, but it should be adjusted to tolerability and general condition.

For Levels of Evidence and Grade of Recommendation, see Table 2