The role of pulmonary metastasectomy for soft tissue sarcoma

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A number of studies which included highly selected series of patients have reported long-term survival of 10–40% for adults soft tissue sarcoma patients after surgical removal of lung metastases, without the addition of other treatment modalities (Roth et al. 1985, Potter et al. 1985, Beattie 1984, Jablons et al. 1989, Creagan et al. 1979, Casson et al. 1992, Gadd et al. 1993, Rizzoni et al. 1986). A few small studies have failed to suggest improvement in survival with a surgery/chemotherapy combination compared with surgery alone (Edmonson et al. 1984, Zalupski et al. 1991, Elias et al. 1989, Weh et al. 1992), whereas other have found some support for the multimodality approach (Kawai et al. 1995, Pastorino et al. 1990, Mentzer et al. 1993).

Favorable factors for survival include the accomplishment of complete metastasectomy, a metastasis-free interval longer than 18 months, and < 2–4 identifiable metastases (Roth et al. 1985, Potter et al. 1985, Beattie 1984, Jablons et al. 1989, Creagan et al. 1979, Casson et al. 1992, Gadd et al. 1993, Rizzoni et al. 1986). In addition, further thoracotomies for subsequent relapses appear to be of major importance for long-term survival (Kawai et al. 1995, Pastorino et al. 1990, Mentzer et al. 1993, Choong et al. 1995, Lanza et al. 1991).

In a recent study by Choong et al. 1995, a prognostic system for patient with pulmonary metastases from soft tissue sarcoma is described. The number of metastases > 1, metastases-free period ≤ 18 months, and size > 2 cm were regarded as high risk factors. A 4-level prognostic system based on the number of high risk factors (0, 1, 2, or 3) was constructed. The best survival rate was seen in patients who had no high risk factors, while the incremental addition of these factors was accompanied by a decrease in survival (Figure 1).

Interestingly, no survival benefit after metastasectomy has been demonstrated for radiological responders compared with non-responders to pre-operative chemotherapy, which at first glance weakens the case for the addition of aggressive chemotherapy to surgery for patients with metastastic disease (Sæter et al. 1996). Recent preliminary results from the SSG X study, where complete surgery for advanced/metastatic soft tissue sarcoma was preceded by aggressive chemotherapy in 26 patients, indicate a relapse-free and overall survival at two years post-surgery of 39% and 74%, respectively (Sæter et al. 1996), which may be superior to results of previous reports. The study appears to substantiate the lack of correlation between survival and radiological response to pre-operative treatment (Figure 2). However, if histological response to treatment is considered, there is a significant advantage in relapse-free survival for good responders.

The lack of good correlation between radiological and histological response to treatment was further illustrated in the SSG X study (Figure 2, Sæter et al. 1996). In 11/26 patients who showed a discrepancy between radiological and histological response evalu-

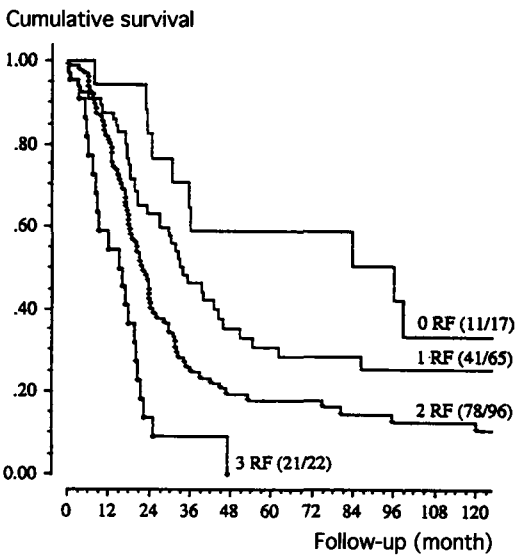

Figure 1. Postthoracotomy survival based on the number of risk factors (RF) present: number of metastasis >1, size of metastasis >2cm, MFP ≤18 months, P <0.001. Numbers in parentheses represent events/patients. Adapted from Choong et al. (1995).

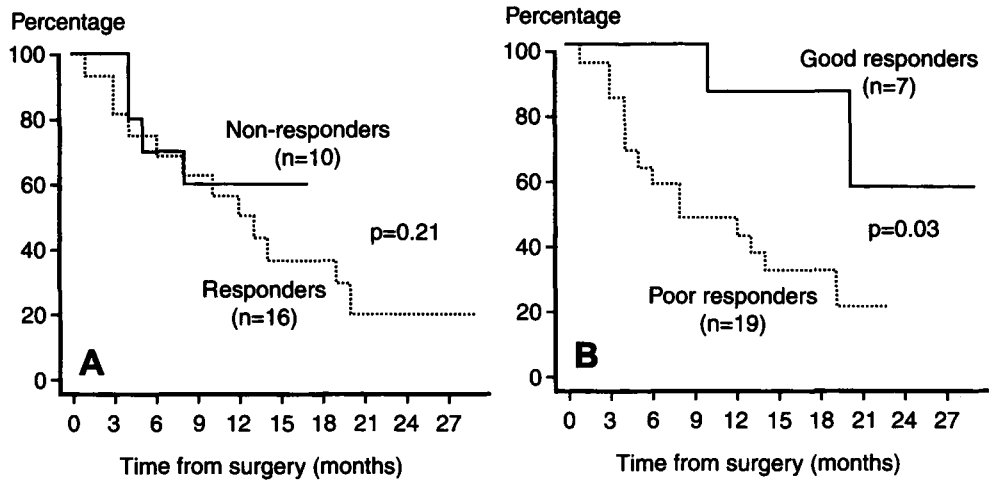

Figure 2. Relapse-free survival following pre-operative chemotherapy and surgery in 26 patients with advanced adults STS, with (A) radiological or (B) histological response to chemotherapy as prognostic indicators. Adapted from Sæter et al. (1996).

ations, all but one had a radiological response, although large areas of viable tumor tissue were present on post-surgical histological examination. In conclusion, a good histological response is a considerably rarer event than a good radiological response, and the former is a significantly better prognostic indicator.

The results of the SSG study indicate that chemotherapy contributes to long-term survival in at least some metastasectomized patients, which is analogous at least to the SSG experience in osteosarcoma (Sæter et al. 1996). This however, should be examined in a prospective and controlled trial, randomizing operable patients to metastasectomy alone or metastasectomy in combination with aggressive chemotherapy.

Metastasectomy and chemotherapy for lung metastases from soft tissue sarcoma—a randomized phase III study (SSG XII)

During the 1995, the EORTC (Soft Tissue and Bone Sarcoma Group) and the Scandinavian Sarcoma Group agreed on an intergroup prospective, randomized, phase III study for metastasectomy and chemotherapy for lung metastases from soft tissue sarcoma. Patients with lung metastases (≤ 5) planned for radical resection of metastases will be randomized to receive pre-metastasectomy chemotherapy (treatment arm 1) or no chemotherapy (treatment arm 2). Patients with treatment arm 1 will receive 3 pre-operative chemotherapy cycles and will continue chemotherapy (2 cycles) after metastasectomy if there is either a clinical complete or partial response on CT scan or if there is a histological response grade III or IV, regardless of clinical response. If no necrosis at all, the patient does not continue to post-operative chemotherapy.

For SSG institutions, chemotherapy will consist of:

- Doxorubicin 75 mg/m^2 bolus i.v., day 1
- Ifosfamide 5 gr/m^2 24-hour infusion, day 1
- G-CSF (Neupogen Roche) 1.0 ml, (0.3 mg) s.c./ daily day 3-13.
- Cycles to be repeated every 21 days

Inclusion criteria: Patient must have histological evidence of soft tissue sarcoma and the following histiotypes are included: malignant fibrous histiocytoma, liposarcoma, synovial sarcoma, malignant paraganglioma, fibrosarcoma, leiomyosarcoma, angiosarcoma including haemangiopericytoma, neurogenic sarcoma, unclassified sarcoma, and miscellaneous sarcoma including mixed mesodermal tumors of the uterus.

Exclusion criteria: Patient less than 15, or more than 70 years of age, performance status of ≥ 2 (WHO criteria), other severe medical illness, other distant metastases and/or local recurrence, previous chemotherapy for metastatic disease, second primary cancer, and patients for whom regular follow-up attendences are unpractical or not feasable. The SSG institution started to randomize patients from July 1996.

Conclusions

A number of studies which included a highly selected series of patients have reported long-term survival of 10–40% for adult soft tissue sarcoma patients after surgical removal of lung metastases, without the addi-

tion of other treatment modalities. Favourable factors for survival include the accomplishment of complete metastasectomy, a metastasis-free interval longer than 12 months, and 2–4 identifiable metastases. In addition, further thoracotomies for subsequent relapses appear to be of major importance for long-term survival. A prognostic system has been described by Choong et al. (1995). Sæter et al. (1996) found histological response to chemotherapy to be of prognostic importance. The role of chemotherapy is still uncertain and therefore a prospective, controlled trial, randomizing operable patients to metastasectomy alone or metastastectomy in combination with aggressive chemotherapy has been initiated by the EORTC and SSG.

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