Centralization of soft tissue sarcoma

The southern Sweden experience

Anders RYDHOLM

Department of Orthopedics, University Hospital, S-221 85 Lund, Sweden. Tel +46-46-171510. Fax + 184454. e-mail anders.rydholm@ort.lu.se

It is generally agreed that patients with musculoskeletal sarcomas should be referred to a treatment center before surgery. Therefore physicians outside these centers, who are the first to see the patient, must know when to suspect a sarcoma. This is a simple matter in most cases of skeletal sarcomas; pain and/or a palpable tumor lead to a conventional radiographic examination which almost always arouses suspicion of a sarcoma. In contrast, most soft tissue sarcomas in the extremities or trunk wall present as a painless mass which causes no loss of function. The patient's general health is not affected and routine laboratory examinations are normal. Considering the fact that benign soft tissue lesions are 200 times commoner than sarcomas (Rydholm 1983), it is not surprising that sarcomas are misdiagnosed as benign lesions, such as lipomas or muscle ruptures. The clinician who classifies every soft tissue tumor as benign makes a correct diagnosis in well over 99% of his patients, an unprecedented diagnostic precision! A falsely benign diagnosis leads to one of two outcomes which may be disastrous: the patient is informed of a benign lesion that requires no treatment or else the tumor is shelled out.

To keep doctors aware of the existence of soft tissue sarcomas, and when to suspect one, requires continuous information to the medical community. Another problem is that surgeons may not know what is the optimal management of soft tissue sarcomas and perform an open biopsy when malignancy is suspected. This problem should be easier to avoid. In such a case the main problem is solved: the doctor suspects a sarcoma and the only thing that now is needed is that he realizes that it is best to refer the patient to a treatment center before biopsy. The disadvantages of open biopsies outside treatment centers have been clearly documented—mainly wrong diagnoses because of inexperienced surgeons (not representative tissue) or inexperienced pathologists (who do not seek second opinion) or wrongly located biopsies (requiring extension of the definitive surgery, in the worst case amputation). Mankin et al. (1982, 1996) found that errors, complications, and changes in the course and outcome were 2–12 times greater when the biopsy was done outside, instead of in a treatment center. Furthermore, in some centers, especially in Scandinavia, many patients are treated without open biopsy; the diagnosis is based on findings from the physical examination, radiological investigations, and fine needle aspiration to avoid local tumor spread (see pages 54–59 and Rydholm et al. 1991, Rydholm 1992). In the 1982 report by Mankin et al., one half of the sarcoma patients in the USA were referred only after open biopsy. This report was published in the American *Journal of Bone and Joint Surgery* and was accompanied by an Editorial written by a real authority, William F. Enneking (1982). The well substantiated message was simple: an open biopsy should be done only by the doctor also responsible for the definitive treatment, which implies that biopsies should not be performed outside treatment centers. The hope and intention was, of course, that these facts would change current trends. However, much to the surprise and disappointment of the authors, nothing changed. In the second investigation, 11 years later, one half of the sarcoma patients still had had an open biopsy before referral! This indicates something fundamentally wrong either in the education of surgeons or in the health care system, which does not encourage referral based on mere suspicion of a serious disease requiring special expertise. Another problem was that many patients with soft tissue sarcomas are not referred to treatment centers at all; in the reports by Mankin et al. (1982, 1996) 60% of the patients had bone tumors, although soft tissue sarcomas are twice as common as bone sarcomas. The same disproportion of soft versus bone sarcomas is evident in other publications from large international tumor centers.

All these international experiences and the inability to deal with the problem makes surprising reading for Scandinavian sarcoma specialists. During the last 10 years, most sarcoma patients in Sweden and Norway have been referred before surgery and most patients referred after surgery have had a small superficial

sarcoma marginally removed. Referrals after open biopsy have been exceptional. For this reason, it is of interest to report the experience with centralization of adult extremity and trunk wall soft tissue sarcoma, in Scandinavia and especially the pioneering work in Lund, southern Sweden.

A treatment center for musculoskeletal tumors started at the University Hospital in Lund in 1970. The primary uptake area is southern Sweden with its 1.5 million inhabitants. This means 25–30 new cases per year of soft tissue sarcoma in the extremities and trunk wall. The area is served by 16 hospitals outside Lund. Patients from other regions are also treated. However, all data given below refer to the primary uptake area. The data are population-based which means that also patients in our uptake area, but not referred to our center, are included. This is made possible by the Swedish Cancer Register which started in 1958. A double-reporting system requires every physician and pathologist to report all cases with a diagnosis of malignancy. Therefore almost all cases are reported (Mattsson 1984). Furthermore, all Swedish residents can be identified by their unique civic registration number. This allows the compilation of population-based patient series with complete follow-up. Our population-based series therefore covers all patients in the southern Sweden health care region with a soft tissue sarcoma, irrespective of where the treatment was given. Pertinent data concerning patients not treated at our center were obtained from the medical records at other hospitals, including a review of archival tumor tissue, which was available in almost all cases. A detailed description of our soft tissue sarcoma database has been given by Gustafson (1994). Before the center started only a few patients with soft tissue sarcomas were referred to our hospital. Patients were treated at their local hospitals in our region, as often by general surgeons as by orthopedic surgeons. They were commonly managed by a shelling-out excision for both diagnosis and treatment; in many cases malignancy was not suspected before surgery.

When the center started in 1970, all local hospitals were informed of our interest in sarcoma patients. Physicians were offered the possibility to refer patients to us and the advantages of referral before surgery were explained in lectures and mailed circulars. Physicians in local hospitals were also encouraged to send case histories and radiographs of suspected cases for discussion and evaluation at our weekly tumor conferences. Soon after the start, it became clear that orthopedic surgeons were more likely to suspect malignancy in extremity soft tissue lesions than general surgeons, who often diagnosed a lump not otherwise specified and shelled it out for diagnosis.

During the first 5 years, a consensus was reached among orthopedic surgeons in our region: patients with a musculoskeletal tumor should be treated at our center and they should preferably be referred before surgery. That this was a real consensus is proven by the referral pattern for patients with bone sarcomas, most of whom were seen by orthopedic surgeons. In the past 20 years all patients with bone sarcoma have been referred, with few exceptions before surgery. Today many of the bone sarcoma patients are referred by phone immediately after the first radiographic examination. However, during the first 5 years of our service only one third of all soft tissue sarcoma patients in our area were referred before surgery and one third were not referred at all. For patients referred after surgery, the reason in many cases was that the surgeon did not suspect a sarcoma. In patients not referred at all, the reason often was that they had been treated by general surgeons still not aware of our center. This latter problem was solved over the years by more information in letters and lectures at the local hospitals. In the past 15 years, almost all patients in our uptake area given a histologic diagnosis of soft tissue sarcoma have been referred to our center.

The first problem—when to suspect a soft tissue sarcoma—was more difficult to solve and it became increasingly evident that we had no simple and clearcut guideline indicating which patients with soft tissue lesions should be referred before surgery. *Suspicion of soft tissue sarcoma* was an empty phrase giving no help as to which tumors to select from the almost overwhelming numbers of benign lesions - so many that it was impossible to refer all patients with soft tissue lesions to our center. From our own experience, we soon learned that the clinical diagnosis of a soft tissue tumor is notoriously difficult. Slow growth over several years does not exclude a synovial sarcoma, a soft subcutaneous lesion does not exclude a myxoid malignant fibrous histiocytoma. The sudden appearance of a painful, tender, deep-seated mass simulating infection or thrombosis or a muscle rupture, may be be caused by bleeding in a necrotic, highly malignant sarcoma. Therefore we investigated whether differences in simple clinical variables, such as patient age, duration of symptoms, tumor location, tumor depth and size could be of value for the differential diagnosis between a sarcoma and a benign soft tissue tumor.

Since lipoma is the commonest soft tissue tumor, we analyzed its epidemiology (Rydholm and Berg 1983). During one year, 428 patients in a defined area (0.7 million inhabitants) had a histological diagnosis of lipoma, 61 of whom had multiple lipomas.

Solitary subcutaneous lipomas were found in 338

patients and 13 patients had deep-seated lipomas. Lipomas were almost nonexistent in children and were uncommon in the hand, thigh, lower leg and foot. The median size of solitary subcutaneous lipomas was 3 (1-20) cm; four fifths of the tumors were smaller than 5 cm, one fifth were between 5 and 10 cm, and only 4 lipomas were larger than 10 cm. The median size of deep-seated lipomas was 6 (4–28) cm. Notes concerning the duration of symptoms were available for one fourth of the patients and was 3 years in one third of them, less than 1 year in one half and less than 3 months in one fifth. On the basis of patient files from one health care center and one surgical department, we estimated the annual clinical incidence of lipoma at 1/1000 (number of patients consulting a doctor for a lipoma, even if not operated on).

We compared lipoma data with those concerning soft tissue sarcoma of the locomotor system from our population-based database and found that patient age and duration of symptoms (10 % of the sarcoma patients had had symptoms for more than one year) were of no value for the differential diagnosis. The median size of subcutaneous and deep-seated sarcomas was 4 (1–16) cm and 8 (1–30) cm, respectively. These figures are similar to those we found for lipoma. It seems that a certain tumor volume, smaller for superficial tumors, makes the patient aware of a lesion, either lipoma or sarcoma. One third of the soft tissue sarcomas and 3% of the solitary lipomas were located in the thigh. Considering only tumor size, the solitary lipoma/sarcoma ratio was 150/1 for tumors < 5 cm, 20/1 for tumors > 5cm and 6/1 for tumors > 10 cm. For deep-seated tumors, the lipoma/sarcoma ratio was 4/1.

We concluded that a tumor (1) larger than 5 cm, irrespective of depth and location, (2) located in the thigh, irrespective of depth and size or (3) deep-seated, irrespective of location and size, was more likely to be a sarcoma. Myhre-Jensen (1981) found in a large series of benign soft tissue tumors (one third lipomas) that only 1% were deep-seated and only 5% measured > 5 cm. These figures are smaller than those we found for lipomas, which implies an even higher ratio between malignant and benign lesions, other than lipoma, when they are deep-seated or > 5cm.

We then analyzed the clinical data for benign soft tissue tumors in general considering only size and depth; the rarity of lipomas in the thigh is not beeing shared by other benign tumors. We found that the annual clinical incidence of benign tumors is about 300/10^6 and that the corresponding figure for soft tissue sarcomas is 18/10^6, making benign tumors almost 200 times commoner than malignant tumors (Rydholm 1983).

On the basis of these observations, we formulated the following simple guidelines for referral of patients with soft tissue tumors:

Refer before surgery all patients with soft tissue lesions that fulfill any *of these criteria:*

1) larger than 5 cm,
2) deep-seated,
3) otherwise suspected of malignancy.

It may be argued that the 5 cm limit is unnecessary; all deep-seated tumors, irrespective of size should be referred before surgery and all subcutaneous tumors could be removed at local hospitals by a marginal excision, a histological diagnosis of sarcoma is followed by referral to the treatment center for a wide reexcision, including the deep fascia beneath the tumor. The local recurrence risk after wide reexcision of a subcutaneous sarcoma is low, even without adjuvant radiotherapy (see page x in this issue). However, for the inexperienced examiner—which means all physicians except the few who work full-time with tumors—it is sometimes difficult to determine tumor depth by physical examination; an intramuscular tumor eccentrically located in the outer part of a muscle may easily be misinterpreted as a subcutaneous tumor. Actually, 5 cm is a "safety boundary" as regards deep-seated sarcomas; four fifths of them are larger than 5 cm. By including both depth and size in the screening system, a safety margin is built in. The effect of misjudged tumor depth is thus minimized.

Otherwise suspected of malignancy refers to subcutaneous tumors less than 5 cm, but with other characteristics which mean they are probably not benign, i.e., rapid growth and firm consistency (which also applies to cases of nodular fasciitis, many of which are referred as suspected sarcomas!).

In view of our epidemiologic data for benign and malignant soft tissue tumors, we calculated that, if these guidelines were followed, about 10 patients with benign soft tissue lesions would be referred for every sarcoma patient and four fifths of the sarcoma patients would be referred before surgery. We considered this "over-referral" of 10/1 reasonable and it is the price that treatment centers have to pay in order to catch most soft tissue sarcomas, especially the deep-seated ones, before surgery.

These guidelines for referral were then sent to all hospitals in the region, with an in-depth explanation of the background to such recommendations and the reasons why patients with soft tissue sarcomas should be referred before surgery. The same information was given to all medical students during the course in pathology and, once again, during their education in general surgery and orthopedics. Furthermore, mem-

bers of our tumor group were asked to give postgraduate lectures in many of the local hospitals. We also started to give personal answers to all physicians who referred patients. I believe that a positive feedback is especially important; the physician who refers a sarcoma patient before surgery should be informed of the specific advantages for his patient. The other 10 doctors who have referred patients fulfilling the guidelines, but who turned out to have benign tumors, should be informed that their patients might well have had a sarcoma as judged by the physical examination, but that our further investigations revealed a benign tumor. The guidelines resulted in an increased referral of patients with benign tumors and sarcomas. Our calculations about over-referral were confirmed: more than 200 patients with benign tumors were referred every year.

The referral pattern stabilized about 10 years ago. During the 5-year period 1990–1994, 130 soft tissue sarcomas (41 subcutaneous, 89 deep-seated) were diagnosed in our region: 8 patients were not referred at all, 3 were referred after open biopsy and 2 were referred only after local recurrence. 29 patients were referred after marginal excision (20/41 subcutaneous tumors, 9/89 deep-seated) and 88 were referred before surgery (18/41 subcutaneous, 70/89 deep-seated). Thus, *four fifths of the patients having deep-seated soft tissue sarcomas were referred before surgery*—one third of them after fine-needle aspiration cytology. Note that this rate refers to *all* patients having a deep-seated soft tissue sarcoma diagnosed in our region. Data on referral pattern reported from other institutions are based only on the number of patients referred. One can safely assume that many patients are not referred at all and that the management of such patients is inferior to that given in treatment centers. Two thirds of the subcutaneous sarcomas had been shelled out before referral. This is not surprising and it accords with our guidelines—i.e. the risk of malignancy in small subcutaneous tumors is exceedingly small. One third of the subcutaneous sarcomas larger than 5 cm were referred after surgery. However, so long as a subcutaneous sarcoma is shelled out with no interruption of the deep fascia, a wide reexcision is easy to do. In our information to local hospitals we stress that a subcutaneous lesion when excised should be shelled out, and no attempts made to get a better margin. It is as easy to reoperate on a subcutaneous sarcoma after a marginal excision as it is difficult to treat a deep-seated soft tissue sarcoma after marginal excision. Therefore, it is most important to increase the respect for deep-seated lesions. *All* patients with deep-seated lesions should be referred to a treatment center before surgery.

When I have discussed this program with sarcoma specialists abroad I have met two objections: 1) This procedure can succeed only in a country with socialized medicine and (2) it is unreasonable to have patients travel a long distance for something that turns out to be a benign tumor. The first objection unfortunately is probably true; socialized medicine, as practiced in Scandinavia, is good for *all* patients with serious illnesses. With this system, doctors' prestige and economics do not prevent referral to institutions which give optimal treatment. In my opinion, open biopsy performed outside a treatment center because of suspicion of sarcoma is malpractice. The second objection is not correct; the longest distance a patient in our region have to travel to our center is 250 km (or in other words 3 hours). Most patients are diagnosed in a single ambulatory examination which includes fine-needle aspiration performed by cytopathologists in our team; most subcutaneous tumors are diagnosed by physical examination and fine-needle aspiration. These days, many patients with deep-seated tumors have already had a CT or MRI examination performed at the local hospital before referral. The diagnosis in such patients is based on the combined information from physical findings, radiological studies and the fine-needle aspirate. The diagnosis is formulated at a tumor conference in the afternoon which includes, among others, representatives from orthopedics, cytopathology, surgical pathology and diagnostic radiology. If all 3 examination modalities are not consistent with a specific benign or malignant diagnosis, additional examinations are done, most often the fine-needle aspiration is repeated for additional examinations (immunohistochemistry, electronmicroscopy, cytogenetics, see page 59). An open biopsy is used in less than 10% of the sarcomas and still fewer of the benign tumors.

Hitherto, no patient with a suspicion of a soft tissue sarcoma has felt that a return day-trip of a maximum of 500 km (the distance for most patients is considerably less) has been too much to confirm the presence of a sarcoma and meet the experts who are going to treat him, or better, have the suspicion refuted and return home with the diagnosis of a benign tumor. Many of the referred patients who prove to have a benign subcutaneous tumor are operated on at their local hospital or not operated on at all. Most patients with benign but deep-seated tumors are operated on at our center, if surgery is indicated. Such deep-seated, benign tumors are mainly lipomas (most of them are shelled out), hemangiomas (operated on if well demarcated and with severe pain on exertion), neurilemoma (not operated on in cases of only slight pain and no growth), aggressive fibromatosis (operated on

with a wide margin, if possible), and myxoma (shelled out).

We have examined the treatment of soft tissue sarcomas outside our center since 1964 (Gustafson et al. 1994). During 1964–1969, before our center had started, two thirds of the patients were treated by a marginal excision and no radiotherapy was given. These figures were the same for patients treated outside our center 1980–1989, although the number of patients treated outside diminished sharply because of increased referral. There is no reason to believe that treatment given outside centers in other countries should be better. In all large sarcoma series from international centers, a substantial number of the patients have been referred with a local recurrence.

During the last 15 years much money and effort have been spent on chemotherapy studies to improve the prognosis for soft tissue sarcoma patients, but the results have been disappointing: any effect is small. A complementary, but rapid and reliable, way to reduce the morbidity of soft tissue sarcoma would be to increase the number of patients referred to treatment centers before surgery.

References

Enneking W F(1982). The issue of the biopsy (editorial). J Bone and Joint Surg (Am) 64: 1119-20.

Gustafson P (1994). Soft tissue sarcoma. Epidemiology and prognosis in 508 patients. Acta Orthop Scand (Suppl 259) 65: 2-31.

Gustafson P, Dreinhöfer K, Rydholm A (1994). Soft tissue sarcoma should be treated at a tumor center. A comparison of quality of surgery in 375 patients. Acta Orthop Scand 65: 47-50.

Mankin H J, Lange T A, Spanier S S (1982). The hazards of biopsy in patients with malignant primary bone and soft-tissue tumors. J Bone Joint Surg (Am) 64: 1121-7.

Mankin H J, Mankin C J, Simon M A (1996). The hazards of the biopsy, revisited. J Bone Joint Surg (Am) 78: 656-63.

Mattson B (1984). Cancer registration in Sweden. Thesis, Karolinska Institute, Stockholm, Sweden.

Myhre-Jensen O (1981). A consecutive 7-year series of 1331 benign soft tissue tumors. Acta Orthop Scand 52: 287-93.

Rydholm A, Berg NO (1983). Size, site and clinical incidence of lipoma. Factors in the differential diagnosis of lipoma and sarcoma. Acta Orthop Scand 54: 929-34

Rydholm A (1983). Management of patients with soft-tissue tumors. Strategy developed at a regional oncology center. Acta Orthop Scand (Suppl 203) 54: 1-77

Rydholm A, Gustafson P, Rööser et al. (1991). Limb-sparing surgery without radiotherapy based on anatomic location of soft tissue sarcoma. J Clin Oncol 9: 1757-65.

Rydholm A (1992). Soft tissue lesions in adults: Biopsy—yes or no? Ann Oncol (Suppl 2); 3 : 57-8.