

From DEPARTMENT OF MOLECULAR MEDICINE AND  
SURGERY  
Karolinska Institutet, Stockholm, Sweden

# CHEST WALL SARCOMAS

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# ABSTRACT

## Aim

To evaluate initial symptoms and clinical features, diagnosis and delay in osteosarcoma (OS), Ewing sarcoma (EWS) and chest wall chondrosarcoma (CS). To assess treatment and identify prognostic factors in chest wall CS.

## Patients

Initial symptoms and clinical features were analyzed from the records of the very first visit to a doctor often a general practitioner, for symptoms related to the bone sarcoma. **Study I** All patients (< 30 yrs) diagnosed in Sweden (1983-95) with OS or EWS, at all skeletal sites (149 patients). **Study II** All patients (< 30 yrs) diagnosed (1981-2000) with EWS of the chest wall (26 patients). **Study III and IV** All patients diagnosed in Sweden (1980-2002) with CS of the chest wall (106 patients).

## Clinical findings

The most common initial symptom in OS and EWS was pain related to strain, reported by 85 % of the OS and 64 % of the EWS. Pain at night was reported by approximately 20 % of the OS and EWS. In the chest wall, pain at night was reported by only 1/26 of the EWS and none of the CS. Only 32 % of the chest wall CS patients complained about pain. A palpable mass was the most important clinical finding noted in 34 to 69 % of the patients in the different series.

## Diagnosis

The initial symptoms in OS and EWS were non-specific and generated many differential diagnoses. A tumor was suspected in approximately 25 % of the cases at the first medical visit. In chest wall CS the doctor suspected a malignancy at the first visit in 83 %. Initial plain x-rays showed pathological findings in 91 % of the OS but only in 57 % of the EWS and 66 % of the chest wall CS. FNAB of CS gave a correct diagnosis for 26 % when done outside a sarcoma center but for 94 % at sarcoma centers.

## Treatment

23/26 of the EWS of the rib were treated surgically. Twelve had correct preoperative chemotherapy and only 9 were handled at a sarcoma center. 55/106 of the chest wall CS were treated at a sarcoma center, 42 at non-specialty hospitals and 9 had palliative treatment only. Chest wall CS treated at a sarcoma center resulted in 7 % intralesional resections compared to 52 % for those treated at non-specialty hospitals.

## Prognosis

The estimated 10-year survival rate for EWS of the rib was 0.54 and patients treated according to correct protocols had a better outcome ( $p < 0.05$ ). The 10-year survival rate was 0.67 for chest wall CS treated in a curative intend. Patients operated with wide surgical margins had a survival rate of 0.96 compared to 0.46 after an intralesional resection. The difference in surgical margins achieved at sarcoma centers and at non-specialty centers resulted in higher survival rates at sarcoma centers; 0.75 compared with 0.59 at non-specialty centers.

## Delay

Doctor's delay was longer in EWS than in OS (4 compared to 2 months). OS with metastasis at diagnosis had longer doctor's delay and also EWS with metastasis at diagnosis had longer delay but the difference was not significant. Chest wall CS were associated with a wide spread of both patient's and doctor's delay. A normal interpreted x-ray and falsely normal cytological diagnosis were associated with longer doctor's delay. Total delay was significantly longer in patients who died of the chest wall CS.

## Conclusions

The initial symptoms of sarcomas are often pain related to strain. A palpable mass was discovered in many patients already at the first visit. Plain x-rays often missed sarcomas of the rib, spine and pelvis. FNAB is unreliable when done outside a sarcoma center. Patients with chest wall sarcomas should be referred to sarcoma centers for diagnosis and treatment to improve outcome.



# LIST OF PUBLICATIONS

- I. Widhe, B. and T. Widhe, Initial symptoms and clinical features in osteosarcoma and Ewing sarcoma. *Journal of Bone and Joint Surgery-American Volume*, 2000. 82A(5): p. 667-674.
- II. Widhe B, T. Widhe and H.C.F. Bauer, Ewing sarcoma of the rib-initial symptoms and clinical features - Tumor missed at the first visit in 21 of 26 patients. *Acta Orthopaedica*, 2007. 78(6): p. 840-844.
- III. Widhe, B. and H. C. F. Bauer, Surgical treatment is decisive for outcome in chondrosarcoma of the chest wall: A population-based Scandinavian Sarcoma Group study of 106 patients. *Journal of Thoracic and Cardiovascular Surgery* 2009. 137(3): 610-614.
- IV. Widhe, B. and H. C.F. Bauer, Diagnostic difficulties and delays with chest wall chondrosarcoma: A population-based Scandinavian Sarcoma Group study of 106 patients. Manuscript.

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## LIST OF ABBREVIATIONS

CT	Computer tomography
CS	Chondrosarcoma
EWS	Ewing sarcoma
EWS-gene	Ewing sarcoma tumor related gene
ERG-gene	Ets Related Gene(oncogen)
FLI-1	Friend leukemia virus integration site 1
FNAB	Fine needle aspiration biopsy
Gy	Gray
ICD-7	International Classification of Diseases,7 <sup>th</sup> revision
ICD-7 (1962)	Vertebral column
ICD-7 (1963)	Rib, sternum and clavicle
ICD-7 (1964)	Upper limbs long bones
ICD-7 (1965)	Upper limbs short bones
ICD-7 (1966)	Pelvic bones, sacrum and coccyx
ICD-7 (1967)	Lower limbs, long bones
ICD-7 (1968)	Lower limbs, short bones
ICD-10	International Classification of Diseases, 10th revision
MWU-test	Mann-Whitney U test
MRI	Magnetic resonance imaging
OS	Osteosarcoma
PNET	Primitive neuroectodermal tumor.
SSG	Scandinavian Sarcoma Group

# THE THESIS AT A GLANCE

The common denominator for these studies was analysis of patient records before the diagnosis of skeletal sarcoma was made. Initially, osteosarcoma and Ewing sarcomas at all sites were included but later the scope was narrowed to one site, the chest wall, and came to focus on chondrosarcomas. Working backwards from the date of diagnosis acquired from the all-inclusive national Swedish Cancer Register, patient records could be traced back to the very first medical consultation for complaints related to the tumor. What were these complaints? How did the first doctor assess them? Referral to other medical services for diagnostic help? Referral to specialized or non-specialized centers for definite diagnosis and treatment? Delay by patient or by doctor? Possible significance for outcome?

## **STUDY I: OSTEOSARCOMAS AND EWING SARCOMAS AT ALL SITES**

*Aim and methods:* Initial complaints and presenting clinical features were culled from the records of all patients less than 30 years old diagnosed between 1983 and 1995, 102 with osteosarcoma and 47 with Ewing sarcoma.

*Findings and conclusions:* Local pain, often related to strain, sometimes with a palpable mass, dominated for both sarcoma types. Pain at night was unusual. A tumor was suspected in 30 % of the osteosarcomas and 20 % of the Ewing sarcomas at the first visit. Initial diagnoses for the remaining patients covered a wide range of skeletomuscular disorders, tendinitis being the most common. Plain radiographs showed pathological findings for 91 % of the osteosarcomas but for only 57 % of the Ewing sarcomas. Doctor's delay was influenced by tumor site (long for pelvis and spine), an initial normal or inconclusive radiograph interpretation and by reluctance to re-evaluate the original but incorrect diagnosis ("low back pain"). Patients with metastasis at diagnosis had a longer doctor's delay.

## **STUDY II: EWING SARCOMA OF THE RIB**

*Aim and methods:* Narrowing down the tumor site to the rib gave 26 patients diagnosed from 1981 through 2000. The clinical records back to the first visit could be recovered for all patients, radiographic interpretations for all but one.

*Findings and conclusions:* Most patients consulted a doctor for local thoracic pain, nearly half for a palpable mass and a few with dyspnea. The most common initial diagnosis was pleuritis. Most radiographs were pathological with pleural effusion dominating. A tumor was suspected for only 5 of the 26 patients. Doctor's delay tended to be shorter for patients with a palpable mass and/or fever but longer for patients who

proved to have metastases at the time of diagnosis. Early referral to a specialized sarcoma center increased the chances for a correct preoperative diagnosis and an adequate combination of chemotherapy and surgery.

### **STUDY III: CHEST WALL CHONDROSARCOMA - TREATMENT AND PROGNOSIS**

*Aim and methods:* Chondrosarcoma is the most common bone sarcoma of the chest wall and involves older patients than Ewing sarcoma. Surgery is the only treatment. Chondrosarcoma can suitably be compared with Ewing sarcoma in younger patients at the same site regarding the path to diagnosis (see Study IV) and the importance of adequate surgical treatment (this study). This study included all 106 patients diagnosed from 1980 through 2002 with a median follow up of 9 years (4-23) for survivors.

*Findings and conclusions:* Surgery with wide margins gave a 10-year survival rate of 0.96 compared to 0.46 for intralesional resections. Local recurrence rate was 4 % after wide resection but 73 % after intralesional procedures. Longer survival and fewer local recurrences could be attributed to referral to specialized sarcoma center for diagnosis and surgery. Ten-year survival rate was 0.75 at sarcoma centers and 0.59 for those treated at non-specialty centers.

### **STUDY IV: CHEST WALL CHONDROSARCOMA - CLINICAL FEATURES AND DELAYS**

*Aim and methods:* This study focuses on the initial symptoms and diagnostic problems for the 106 patients with chondrosarcoma and on factors contributing to doctor's delay and its consequences. The clinical records were searched as in studies I and II.

*Findings and conclusions:* Patients, most between 50 and 60 years old, most commonly presented with a palpable, painless mass. A tumor was initially suspected for 83 % of the patients at the first visit. Patient's and doctor's delay was generally within 3 to 4.5 months but could be extremely long, presumably because of the indolent nature of the tumor. An initial radiograph or fine needle aspiration biopsy interpreted as normal or inconclusive led to longer doctor's delay. Fine needle aspiration biopsies done at sarcoma centers gave a correct diagnosis in 94 % but for only 26 % when done at non-specialty centers. Long delay was related to outcome. Early referral to a sarcoma center gave more accurate diagnoses, better surgical results and higher survival rates.

# INTRODUCTION

Primary bone sarcomas are rare tumors accounting for less than 1 % of all cancer [1]. The three most common types are osteosarcoma, chondrosarcoma and Ewing sarcoma. Osteosarcoma and Ewing sarcoma are most frequent in children and adolescents whereas chondrosarcoma mostly affect adults. Osteosarcoma and Ewing sarcoma are locally aggressive tumors with a high risk of metastatic spread. On the other hand, most chondrosarcomas are slowly-growing tumors and only a small proportion are high-grade malignant.

Most patients with a bone tumor present with pain or an enlarging palpable mass [2, 3]. Unlike the other types, Ewing sarcoma patients often have systemic manifestations such as fever, malaise and weight loss [4]. Many osteosarcoma and Ewing sarcoma patients relate the onset of symptoms to a trauma occurring at the time that the symptoms began [5]. Chondrosarcoma patients usually have only mild discomfort such as pain on weight-bearing or a palpable mass.

Early recognition and treatment is important in all malignant disease. Numerous articles have focused on the treatment and prognosis of primary bone tumors but only a few have described the initial symptoms of the disease. Sweden like many other countries have centers specializing in the treatment of patients with bone tumors. The physicians at these sarcoma centers meet the patient when a tumor is already diagnosed or strongly suspected. On the other hand primary care doctors, have little or no experience with primary malignant bone tumors as they will only see one or two such patients in their life-time. However, they are the first doctors consulted when the patient seeks for symptoms of the disease. It may therefore be of interest to clarify the initial symptoms and physical findings in osteosarcoma, Ewing sarcoma and chondrosarcoma.

Only 10-15 % of chondrosarcomas and Ewing sarcomas are located in the thoracic wall [6-8]. Nevertheless chondrosarcoma and Ewing sarcoma are the two most frequent primary malignant bone tumors of the chest wall. Most chondrosarcomas arise *de novo* in normal bone but occasionally from a pre-existent benign cartilaginous tumor or many years after radiation therapy to the chest wall. The diagnosis and treatment of primary bone tumors in Sweden is centralized to 5 centers of which the Oncology Service at the Department of Orthopedics at the Karolinska Hospital is the largest with a referral population of 4 million.

In recent decades there has been a remarkable improvement in survival rates for osteosarcoma and Ewing sarcoma due to new adjuvant chemotherapy regimens. The survival for osteosarcoma and Ewing sarcoma patients is today 60 % in contrast to before the 1980:s when less than 20 % survived [3]. Advances in oncologic treatment have not similarly improved the survival for chondrosarcoma [9]. Adequate surgical excision remains the most important aspect of management of chondrosarcoma, since there is no effective chemotherapy. The prognosis in chondrosarcoma is highly

dependent on the histological grade. Low-grade tumors are associated with a survival rate of 90 % but high grade with only 20-30 % [10-12]. The histological grading system for chondrosarcoma is based on cellularity and cytologic atypia of the tumor [12]. The grading system is difficult to apply as there is no clear-cut distinction between different grades. In fact, the distinction between a benign chondromatous lesion and a low-grade chondrosarcoma is often unsure and is based not only on histological features but also on clinical symptoms and radiological appearance [13, 14].

The ultimate goal of surgery is to remove the tumor completely in order to avoid local recurrence and hopefully prevent metastatic spread. Nevertheless, there remains the problem of removing large tumors in difficult locations such as at the thoracic wall with a sufficient surgical margin without interfering with vital organs. Although treatment of malignant bone tumors is centralized to few institutions in Sweden, patients with chest wall tumors can be referred to either such centers or to thoracic surgery departments. It was therefore of interest to assess outcome at different types of treatment centers and also to assess to what extent the quality of the preoperative diagnosis affected outcome.



# AIM OF THE THESIS

- To conduct population-based epidemiological studies of osteosarcoma, Ewing sarcoma and chondrosarcoma with emphasis on tumors of the chest wall.
- To characterize the patients initial complaints from the very first medical consultation for symptoms related to the tumors.
- To follow the patients along the path to definitive diagnosis and treatment, to identify diagnostic pitfalls and to quantify the patient's and the doctor's delay and its consequences.

# PATIENTS AND METHODOLOGICAL CONSIDERATIONS

All studies (I-IV) were population-based. The Swedish Cancer Register is the basic tool for identifying patients with malignant disease. The double reporting system requiring every clinician and pathologist to report all diagnosed malignancies gives close to complete coverage [15]. Data for each patient included information about where and when the diagnosis was established, tumor site, pathological classification, and when applicable, date of death.

The first step after identifying the patient through the Cancer Register was to retrieve files from the reporting clinic. From these files, records from other medical services were collected to trail the patient through emergency departments, general practitioners, private practitioners, school and military doctors to find the very first medical visit for complaints that could be related to the tumor at study. Radiographic departments were also contacted to collect radiographic interpretations. Several patients had contacted more than one doctor before a tumor diagnosis was suspected.

Records from the first medical visit were culled for relevant clinical information such as pain, palpable mass, initial diagnosis etc. What was considered relevant for each tumor type is listed below under the heading for the particular tumor.

Patient's and doctor's delay were calculated from the records. Patient's delay was the period from when the patient first noted signs or symptoms to the first medical visit. Doctor's delay was the period from the first medical visit until the day of diagnosis as recorded in the Cancer Register.

Treatment, surgical and/or radio- or chemotherapy were noted in detail in studies II and III.

## Statistical methods

Statistical methods applied were chi-squared test, student's t-test, Kaplan-Meier method, log rank test, Mann-Whitney U-test (MWU). Patient survival was calculated with Kaplan Meier analysis and differences in prognostic factors with the log-rank test. Proportional hazard Cox ratio was used with stepwise forward procedure for multivariate analysis. Significance level was set to  $p < 0.05$ . All statistical analyses were made using statistical software package STATISTICA , 8 edition, Statsoft Inc.

A summary of the patients included in studies I-IV is presented in Figure 1.

## **STUDY I, OSTEOSARCOMA AND EWING SARCOMA**

The study covers the period from 1983 through 1995 and was limited to patients younger than 30 years, identified from the Swedish Cancer Register by tumor type code 766 for osteosarcoma and 756 for Ewing sarcoma and by site (ICD-7 codes 1962, 1964-1968). Skull, jaw, chest wall and tumors with multiple locations were excluded. Totally 109 patients with osteosarcoma and 54 with Ewing sarcoma could be identified according to the restrictions above. Three patients with osteosarcoma were excluded since the diagnosis was incorrect (2 osteoblastoma and 1 secondary osteosarcoma). Three of the Ewing sarcomas were extra-skeletal and excluded. Four of the osteosarcomas and 4 of the Ewing sarcomas were excluded because complete clinical information could not be traced.

Tracing back to the first medical consultation gave details about pain, pain at night, intermittent pain at rest, pain related to strain, duration, fever, history of trauma, physical activity and local swelling as well as physical findings such as palpable mass, tenderness, limping and muscle atrophy and any initial diagnostic procedure and finally the initial tentative diagnosis made at the first visit. Patient's and doctor's delay were calculated for each patient.

## **STUDY II, EWING SARCOMA OF THE RIB**

To concentrate on the chest wall, both the Swedish Cancer Register and the Scandinavian Sarcoma Group Register were consulted to find all patients younger than 30 years of age with tumor type code 756 for Ewing sarcoma and ICD-7 site code (1963 which includes the ribs and sternum but also the clavicle).

Twenty-seven patients were identified; one was excluded since the Ewing tumor was extra-skeletal. Medical records back to the first visit and treatment details for the remaining 26 were traced and analyzed as described above and patient's and doctor's delay were calculated. Complete follow-up was at least 5 years for survivors. Surgical margins were defined as wide, marginal or intralesional according to the pathology report. Treatment center was also registered. Chemotherapy regimens were T 11 (Rosen, 1981-1983), SSG IV (1984-1989) and SSG IX (1990-1999) [16, 17].

Records from the first medical visit gave details of pain, pleuritic pain, localized thoracic pain, pain at night, duration of pain, swelling, history of trauma, dyspnea, cough, periods of fever as well as physical signs such as palpable mass, tenderness and diminished breathing sounds. The tentative diagnosis at the first visit was recorded as well as the first chest radiograph interpretation.

## **STUDIES III AND IV, CHONDROSARCOMA OF THE CHEST WALL**

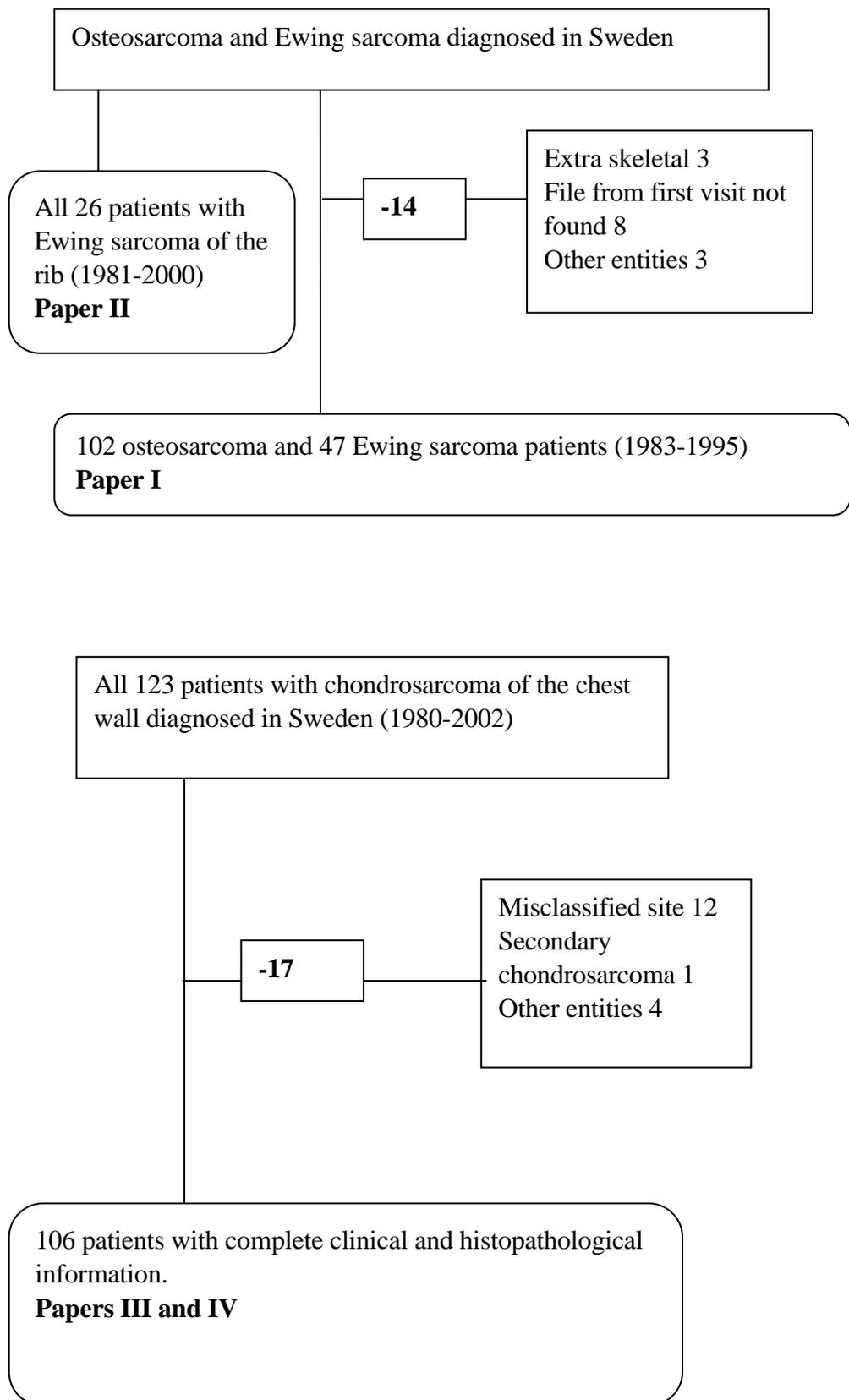
These studies concentrate on chondrosarcomas of the chest wall, i.e. the ribs and sternum. All patients diagnosed in Sweden from 1980 through 2002 at these sites were identified through the Swedish Cancer Register and the Scandinavian Sarcoma Group Register ([www.ssg-org.net](http://www.ssg-org.net)) and clinical records were traced back to the first consultation as described above. 123 patients with ICD-10 location code C413 (rib, sternum and clavicle) were identified. After exclusion of 9 patients with chondrosarcoma of the clavicle (not a flat bone and not part of the chest wall), 3 patients with misclassified tumor location (2 scapula and 1 spine), and 1 patient with radiation-induced chondrosarcoma 110 patients remained.

Tumor size was taken from the pathology reports. The histopathological slides were reviewed by the Pathology Board of the SSG (blinded as to outcome) and sub-classified as grade 1 to 4 where 4 was dedifferentiated and mesenchymal chondrosarcoma. This resulted in the exclusion of 4 patients for whom the diagnosis of chondrosarcoma was not supported. There remained 106 patients for analysis.

Surgical margins, taken from the pathology reports, were designated as wide, marginal or intralesional [18]. Applied to chest wall chondrosarcoma, a wide surgical margin required intact pleura internally, intact muscle fascia externally and transverse rib resection > 2 cm from the tumor on both sides. Less than 2 cm but otherwise as above was a marginal resection. Intralesional resections refer to tumors taken out in pieces or to microscopic positive margins.

Case records were traced back to the first visit as described above for initial complaints and findings. Pain, palpable mass, dyspnea and fever were registered. Delay could be calculated. In this study, however, doctor's delay was the period from the first medical visit to the first day of treatment. Other details such as tumor characteristics, diagnostic procedures, treatment at a sarcoma center or non-specialty hospital and outcome were extracted from the appropriate records. For survivors there was complete follow-up for a median of 9 (4-23) years.

**Figure 1.** Patient selection from the Swedish Cancer Register for studies I-IV.



# EPIDEMIOLOGY AND CLINICAL FEATURES

In Sweden with a population of 9 million there are approximately 25 new chondrosarcoma cases, 20 osteosarcoma and 10 Ewing sarcoma cases per year. Osteosarcoma and Ewing sarcoma have the highest incidence in the young population with the incidence peak in the second decade of life. On the other hand chondrosarcoma have the highest incidence between 40 and 60 years of age. For all three types of bone sarcoma there is a slight male predilection. Potentially, every single bone of the body can harbor a bone sarcoma. Osteosarcomas are most frequently located in the distal femur, proximal tibia and the humerus. The chest wall is an extremely uncommon location for osteosarcoma, accounting for 2 % of all osteosarcomas [3, 19].

The two most common primary bone sarcomas of the chest wall are chondrosarcoma and Ewing sarcoma making up 10-15 % of all Ewing sarcomas and chondrosarcomas, respectively [6-8, 20].

## *Etiology and risk factors for bone sarcomas*

Although most bone sarcomas arise spontaneously, several risk factors have been identified. Prior radiation and Paget's disease, Li Fraumeni syndrome and hereditary retinoblastoma are all associated with increased incidence of osteosarcoma [21, 22].

No hereditary or congenital syndromes have been associated with the occurrence of Ewing sarcoma. Several risk factors have been proposed; residence on a farm or parental farming, pesticide exposure and hernias [23, 24]. Ewing sarcoma has ethnical differences and the tumor is less frequently diagnosed in the Afro-Caribbean and Chinese populations than in the white population in the United States [25].

Chondrosarcomas may arise in preexisting conditions such as enchondromas and cartilaginous exostoses. Congenital syndromes such as Ollier's disease (multiple enchondromas), Maffucci's syndrome (multiple enchondromas in combination with cavernous hemangiomas) and multiple exostoses are all associated with an increased risk for development of chondrosarcoma [26, 27]. How many of the chondrosarcoma arise *de novo* and how many develop in a benign cartilage abnormality is controversial. The real incidence of secondary chondrosarcoma is not known since reports in the literature range from 1 to 40 % [10, 28, 29].

## *Symptoms and clinical features of bone sarcoma*

The symptoms and signs of primary bone malignancies are frequently similar to much more common and less serious condition. The most common symptoms are pain and a swelling. Descriptions of the clinical picture of primary bone sarcomas are based on reports from sarcoma centers. Doctors at sarcoma centers meet the patient when the

sarcoma diagnosis is established or strongly suspected. There has often been a considerable delay from the time the patient first noted symptoms until the first visit at a sarcoma center. The patient's recollection of when and under what circumstances the disease started may at that time be influenced both by the threat of a cancer diagnosis and also by long delay. To investigate the initial symptoms and clinical picture of primary bone malignancies and particularly in chest wall sarcomas we have conducted three different studies all based on information from the first medical visit for symptoms that could be related to the bone sarcoma.

## **PATIENTS**

There were 149 patients with osteosarcoma or Ewing sarcoma (study I), 26 patients with Ewing sarcoma of the chest wall (study II) and 106 with chondrosarcoma of the chest wall (study IV).

## **RESULTS**

Patient age and sex distribution are illustrated in Figures 2-5. Initial complaints at the time of the first medical visit and the clinical findings at this visit are summarized in Table 1.

There were 102 patients with osteosarcoma, male predilection of 1.5:1. Mean age at diagnosis for males was 16 (5-26) years and for females 15 (5-29) years (Figure 2).

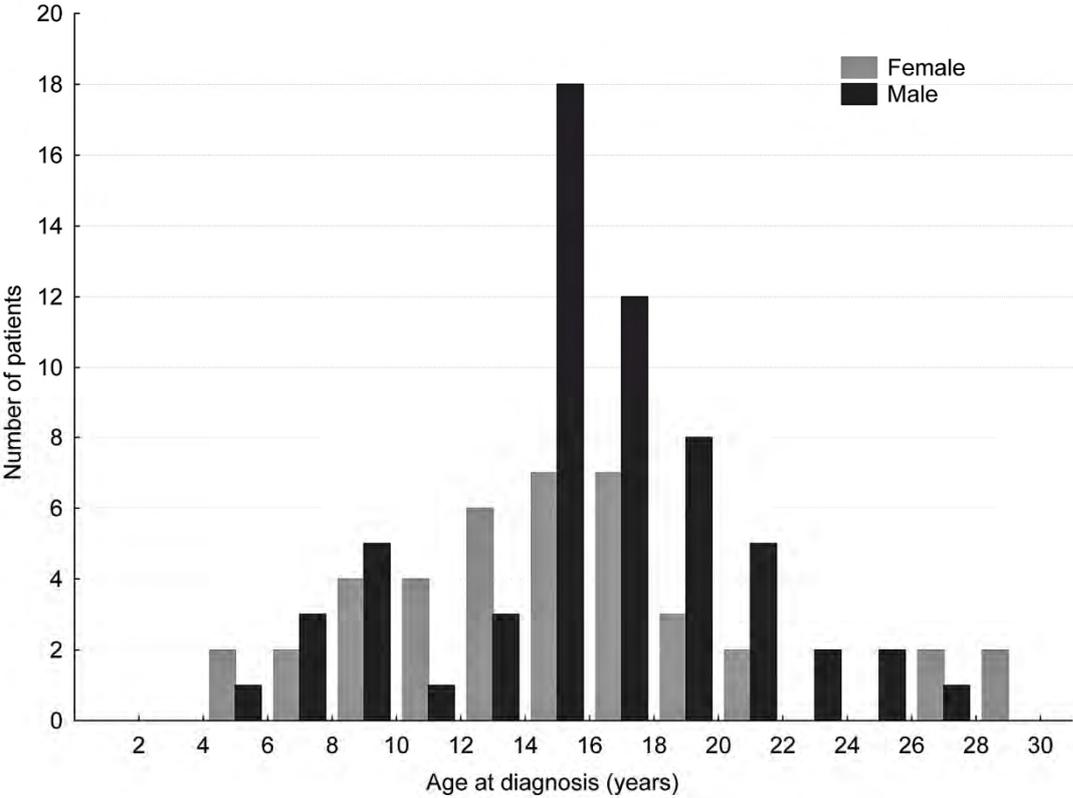
There were 47 patients with Ewing sarcoma, 28 were male and 19 were female. Mean age at diagnosis was 15 (2-26) years, almost equal in both sexes (Figure 3).

There were 26 Ewing sarcoma of the rib (16 males and 10 females) and mean age at diagnosis was 16 (6-26) years.

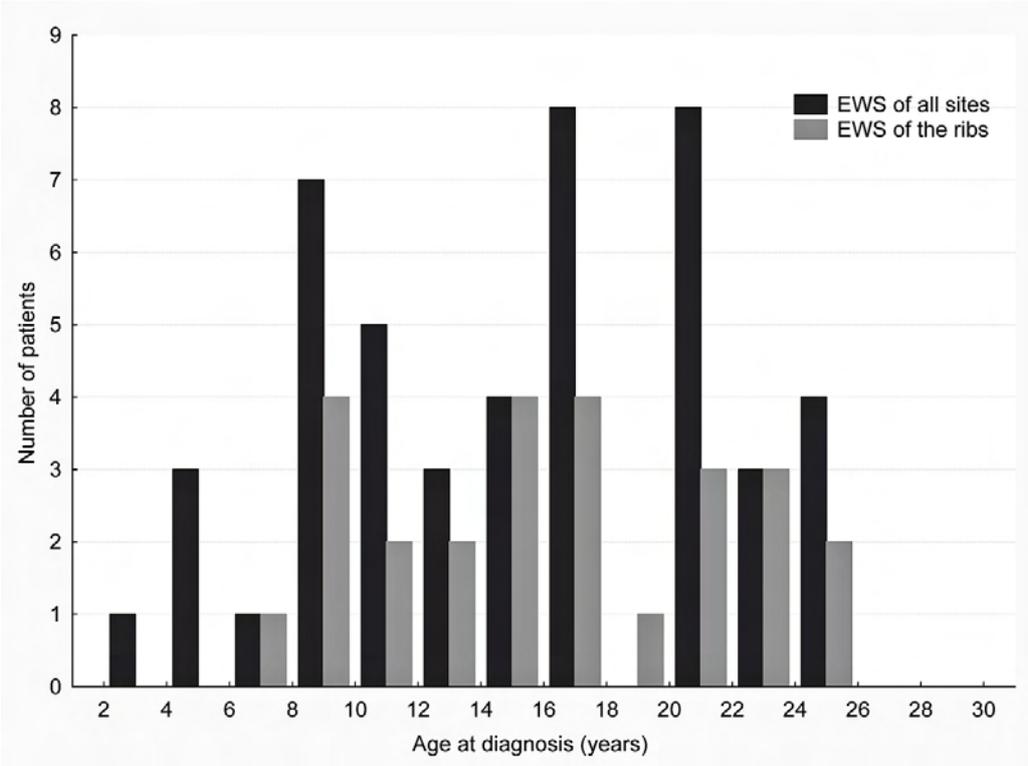
Chondrosarcoma of the chest wall had some unique features. Not only were the patients older but also the yearly frequency varied (Figure 5). Another unique feature was that 14 % were diagnosed incidentally from a plain chest radiograph done for other reasons in conjunction with the first visit. Three of the 106 patients were secondary chondrosarcoma (1 Ollier's disease, 2 multiple hereditary exostoses).

There were 106 consecutive patients with chest wall chondrosarcoma (Figure 4), 59 males and 47 females. Mean age was 57 (13-85) years, equal for both sexes. 89 were located in the ribs and 17 in the sternum.

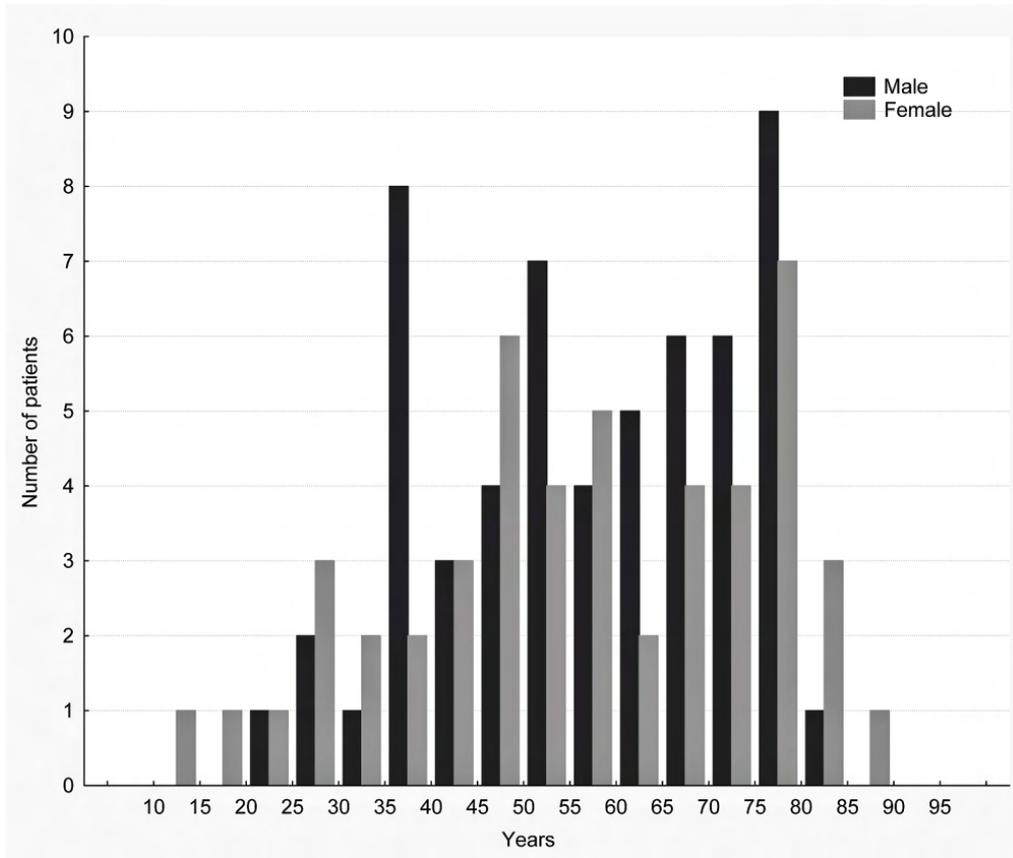
**Figure 2.** Osteosarcoma, sex and age at diagnosis.



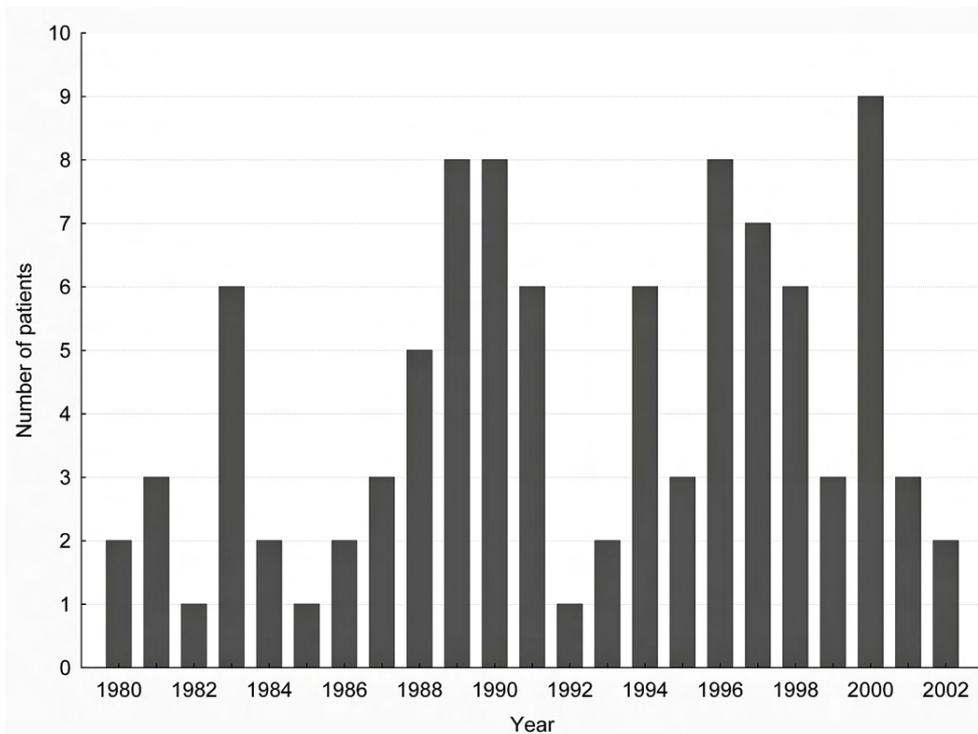
**Figure 3.** Ewing sarcoma at all sites and the ribs. Age at diagnosis.



**Figure 4.** Chondrosarcoma of the chest wall, sex and age at diagnosis.



**Figure 5.** Chondrosarcoma of the chest wall, number of patients diagnosed each year (1980-2002).



**Table 1.** Initial complaints and findings at the first visit.

	osteosarcoma (all sites)* N=102	Ewing sarcoma (all sites)* N=47	Ewing sarcoma (rib) N=26	chondrosarcoma (chest wall) N=106
<b><i>Initial complaints at the first visit</i></b>				
Pain on strain	85 %	64 %	-	-
Pain at night	21 %	19 %	4 %	0
Pain at rest	56 %	57 %	-	-
Localized thoracic pain	-	-	85 %	32 %
Pleuritic pain	-	-	38 %	0
Previous trauma	47 %	26 %	19 %	18 %
Dyspnea	-	-	19 %	0
No symptoms	0	0	0	13 %
<b><i>Findings at the first visit</i></b>				
Local tenderness	92 %	70 %	42 %	30 %
Palpable mass	39 %	34 %	42 %	69 %
Diminished breath sound	-	-	23 %	5 %
Limping (only lower extremity)	31 %	40 %	-	-

\*all locations (chest wall, jaw and skull excluded)

## COMMENTS

We have conducted three different research projects to study the initial symptoms and clinical features of bone sarcoma. All studies were population-based and included all patients over a long study period. This study design was unique in two major ways. First, it was population-based and included all patients diagnosed in Sweden and not like many other studies based on the experience at individual sarcoma centers, where referral bias would affect the results. Secondly, we investigated the initial symptoms and clinical features by analyzing the records from the first visit to a doctor for

symptoms that could be related to the bone sarcoma. We believe this method is the most accurate to explore initial symptoms and clinical features.

The Swedish Cancer Register includes all patients with a malignant tumor diagnosed since 1958. It is based on a double reporting system; both the clinician and the pathologist must report every new patient diagnosed with a malignant tumor. The Cancer Register is widely used not only as an important tool to monitor cancer incidence and survival but also for research purposes. The overall completeness of the Swedish Cancer Registry is high and 99 % of all cases are morphologically verified [15]. A recent report concerning completeness of the Swedish Cancer registry showed underreporting of certain specific tumors such as leukemia, lymphoma and tumors of the central nervous system [15]. For rare malignancies like osteosarcoma errors occur in the Swedish Cancer Register, but taken together they make up a low percentage [30, 31].

Study I included osteosarcoma patients diagnosed in Sweden from 1983 to 1995. Unlike Ewing sarcomas, osteosarcomas have a second peak incidence at around 60 years, and approximately 30 % of osteosarcoma patients are older than 40 years [19, 30]. We were interested in describing and comparing the clinical picture of bone sarcomas in children and adolescents. Therefore, only patients < 30 years at the time of diagnosis were included.

In our study of chest wall Ewing sarcoma over a 20-year period we could identify 26 patients, a yearly incidence of 0.15/ million.

The 106 patients with verified chondrosarcoma of the thoracic cage, is the largest population-based series published to date [32]. These 106 cases collected over a 22-year period in a population of around 9 million gives an expected yearly incidence corresponding well with the 0.5 cases per million reported by others [8]. We noted a variation in the yearly frequency of chest wall chondrosarcoma, ranging between one and 9 cases per year. A similar variation in annual incidence has previously been reported for osteosarcoma [30].

The initial clinical picture of primary bone malignancies is similar to many more common and less serious conditions. Pain at night is considered to be a hallmark for bone sarcomas [33-35]. However, this contention was not supported in any of the three bone sarcoma entities studied here. Instead, we noted that in the initial phase of the disease pain related to activity was the most common symptom both in osteosarcoma and in Ewing sarcoma outside the chest wall. Pain related to strain is a very common symptom in a young population and a reason why patients consult a doctor. It is therefore not surprising that many patients were not diagnosed at the first visit.

Chest wall Ewing sarcoma, unlike osteosarcoma and chondrosarcoma, typically presented with localized chest pain in combination with systemic symptoms such as fever, malaise and weight loss. Dyspnea was reported by 23 % of Ewing sarcoma patients of the rib. The findings are comparable with previous reports [36]. The combination of local and systemic symptoms reported by patients with Ewing sarcoma could mislead a clinician into considering other diagnoses.

None of the chest wall chondrosarcoma patients, one of the 26 Ewing of the rib and 20 % of the osteosarcoma and Ewing sarcoma at all sites reported suffering from pain at night. Pain at night does not appear to be a typical initial symptom in contradiction to other reports [34, 35, 37].

Chondrosarcoma of the chest wall, more usually than not, presented as a painless palpable mass. While 69 % of the patients had a palpable mass at the first visit, pain was reported only by one-third. We believe that this painlessness is an important finding. The possibility of a chondrosarcoma, regardless of pain, has to be considered in the differential diagnosis of a mass in the chest wall. One reason why chondrosarcoma of the chest wall does not give pain might be that this tumor does engage a weight-bearing bone [38]. Other reports, based on referred patients, regard pain as a dominating symptom for malignancy and the absence of pain as an indicator of a benign mass. [35, 39] The absence of pain might be one important reason accounting for long patient's and doctor's delay.

The presence of a lump, which was found at the first visit for 34-69 % of the patients in our studies, emphasizes the importance of a physical examination. A bone-hard lump is a physical finding that needs to be investigated properly.

# DIAGNOSIS

Symptoms and clinical findings can suggest the possibility of a bone tumor. The next step in the clinical investigation is radiography. For long bones, conventional radiographs are still the most important modality for diagnosing bone lesions. MRI and CT add important information for the surgical treatment but are seldom diagnostic. Even large lesions in the pelvis, spine and ribs can easily be missed on plain films and here CT or MRI is safer for diagnosis.

## **Osteosarcoma**

Osteosarcoma can be subclassified according to the predominant cell type (osteoblastic, chondroblastic, fibroblastic, or teleangiatic) but malignant bone formation is a prerequisite for the diagnosis. Osteosarcoma most often is located in the metaphysis of a long bone, and a plain radiograph is often indicative of the lesion [40]. Typical radiological features of osteosarcomas are a combination of bone destruction, irregular, spiculated periosteal reaction and a soft tissue mass [41]. Laboratory screening may show increased alkaline phosphates or lactic dehydrogenase activity. These increases may correlate with poorer prognosis [42, 43].

The definitive diagnosis is established by needle or incisional biopsy. This procedure must be carried out by a person with special knowledge of musculoskeletal oncology since the biopsy tract should be placed so that it can be excised en-bloc during the surgical procedure [44, 45].

## **Ewing sarcoma**

Classical Ewing sarcoma of bone belongs to a family of tumors, including also extra skeletal Ewing sarcoma [46], Askin tumor [47] and primitive neuroectodermal tumors [48]. Immunohistochemical, cytogenic and molecular studies have proven that these tumors originate from mesenchymal stem cells, although the exact cell of origin is unknown [49]. About 95 % of Ewing sarcomas have a balanced chromosome translocation, t(11;22) or t(21;22), which results in a fusion of the EWS gene on chromosome 22 with the FLI1 gene on chromosome 11 or ERG gene on chromosome 21 [49, 50]. Identification of the chromosomal rearrangement is now almost mandatory for diagnosis. Other small-cell tumors such as rhabdomyosarcoma, non-Hodgkin's lymphoma, neuroblastoma can be very similar histologically but they do not express this chromosomal rearrangement.

Unlike osteosarcoma, found mostly in the metaphysis of long bones, Ewing sarcoma can arise in any bone although the pelvis is the most common site. When Ewing sarcoma is found in long bones they will be more often diaphyseal than metaphyseal [51]. The radiological appearance is more often lytic than sclerotic and is associated

with an aggressive lamellated periosteal reaction, onion-skinning [52]. MRI and CT will reveal a soft tissue component which in Ewing sarcoma is often much larger than the bony lesion [53]. Laboratory tests may show an increased sedimentation rate and/or increased lactic dehydrogenase activity, both associated with a poorer prognosis [54].

## **Chondrosarcoma**

Chondrosarcoma of bone is a malignant cartilaginous tumor with wide variations in morphology, behavior and clinical outcome. Chondrosarcoma derives from malignant cartilage cells of various stages of maturity. Chondrosarcoma can be divided into primary (without evidence of a pre-existing benign lesion such as enchondroma or osteochondroma) or secondary (with evidence of a pre-existing lesion). The varying histological appearance of chondrosarcoma and the fact that the diagnosis is also based on clinical and radiological features makes diagnosis especially difficult [10, 14]. Low-grade chondrosarcomas may be difficult to distinguish from enchondroma and high-grade from osteosarcoma and fibrosarcoma [55].

Conventional plain x-ray often detect the majority of the cases of chondrosarcomas. The radiological lesion, though seldom specific, often shows a fusiform, lytic defect with scalloping of the inner cortex and stippled calcification. Extension into the soft tissues suggests higher grade malignancy [35].

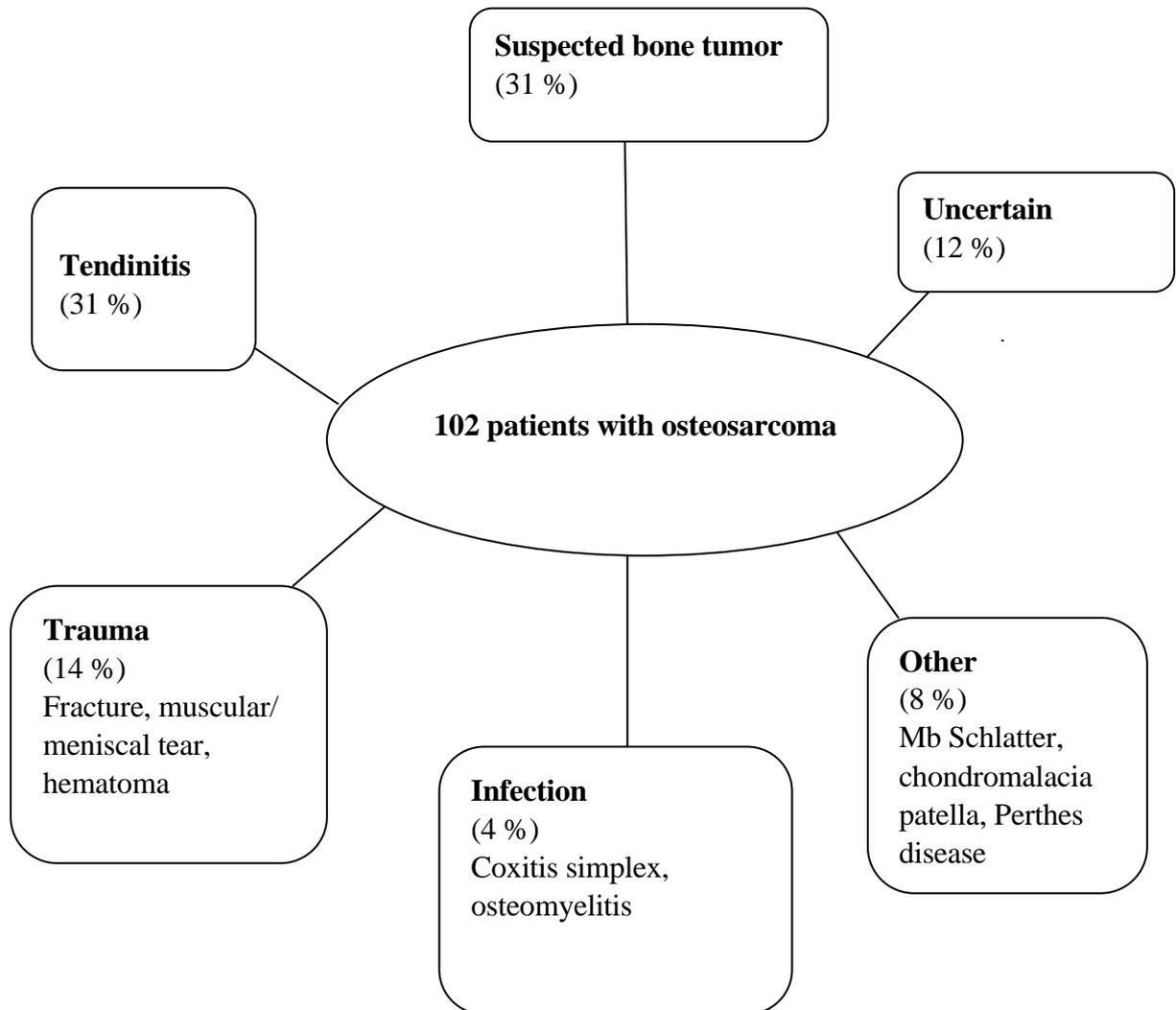
## **PATIENTS AND RESULTS**

### **Osteosarcoma and Ewing sarcoma at all sites (study I)**

The initial diagnoses from the first medical consultation for the 102 patients with osteosarcoma are illustrated in Figure 6. For the 47 patients with Ewing sarcoma at all sites (the ribs are dealt separately) the first visit aroused a suspicion of a tumor for 19 %. Tendinitis was the most common misdiagnosis for 21 %.

Plain radiographs were ordered at the first medical visit for 67 % of the osteosarcoma patients and for 60 % of the Ewing sarcoma patients. The initial radiological interpretation described pathological findings for 91 % of the osteosarcomas, but for only 57 % of the Ewing sarcomas.

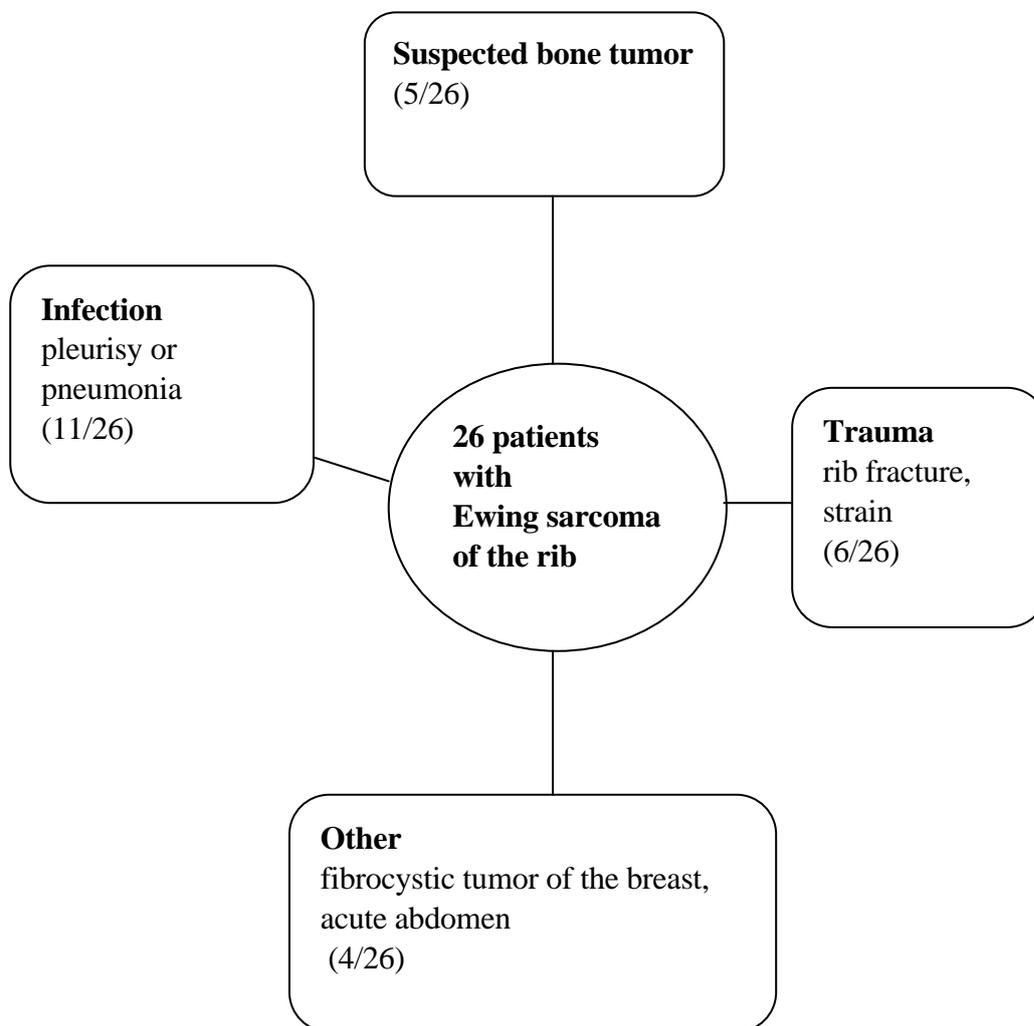
**Figure 6.** The initial diagnosis at the first visit for 102 osteosarcoma patients.



### **Ewing sarcoma of the rib (study II)**

There were 26 patients with Ewing sarcoma of the rib in study II. A tumor was suspected in 19 % (5/26) at the first medical consultation. The other initial diagnoses are illustrated in Figure 7. The initial chest radiographs showed pathological findings in 21/25 (radiographic interpretation not found for 1 patient). A pleural effusion was detected in 17 cases. The amount of fluid varied from 2 cm in supine position to almost complete obliteration of the lung.

**Figure 7:** The initial diagnosis at the first visit for 26 Ewing sarcoma of the rib patients.



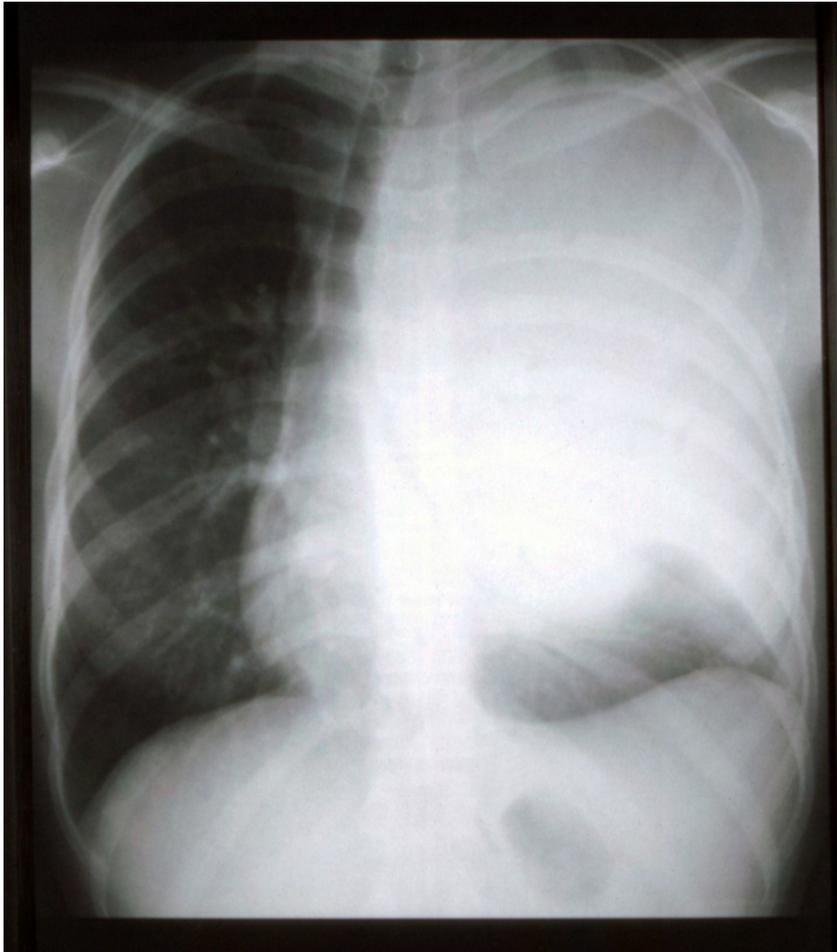
Case a young man

A 20-year-old male consulted a general practitioner for low back pain. Before the first medical visit he had had intermittent low back pain for one year. The patient was prescribed analgesics. After one month he returned with more or less the same complaints. At the third consultation the patient complained not only about low back pain but also of weakness in the left leg and periods of fever. He was referred to an orthopedic surgeon who ordered a plain x-ray and myelography which were normal. The orthopedic surgeon referred the patient back to the general practitioner. Since symptoms of severe pain and fever persisted, the patient was again admitted to a local hospital. Laboratory analysis showed SR 80, CRP 96 and also increased levels of alkaline phosphates. A scintigraphy detected pathological uptake in the left pelvis. He was treated with antibiotics on the suspicion of osteomyelitis. After further delay a biopsy was finally done showing Ewing sarcoma. At this point the patient had disseminated disease and he died within 6 months.

### Case Ewing sarcoma of the rib

A 12-year-old girl consulted a general practitioner for fever and dyspnea. She had had a period of fatigue over the last month but no other symptoms or signs. She was admitted to a local hospital and chest radiograph, computer tomography and fine needle aspiration biopsy were performed. Severe osteolysis of the 4<sup>th</sup> rib and an adjacent soft tissue mass were noted and as well as complete compression of the left lung due to pleural effusion (Figure 8). Cytology indicated a Ewing sarcoma, confirmed by open biopsy. After preoperative T11 chemotherapy, the 4<sup>th</sup> rib was resected. Histopathological analysis detected no viable tumor cells. The patient had further postoperative chemotherapy and she is today, more than 10 years after treatment healthy.

**Figure 8.** Plain chest radiograph showed large pleura effusion of the left hemithorax.



## Chest wall chondrosarcoma (study IV)

There were 106 patients with chondrosarcoma of the chest wall in study IV.

At the first visit, a tumor was suspected in 88 of the 106 patients, including the 14 discovered incidentally. Pleuritis/infection was the initial diagnosis for 4, rib fracture/muscle strain for 10, and other diagnoses for 4.

A palpable mass was noted at the first visit for 69 % (73/106) of the patients. Patients with a lump were either referred for a chest radiograph, FNAB at the local hospital, or to sarcoma centers for further investigations, or were asked to wait and see.

The results from the initial chest radiographs could be traced for 104 patients. For 34 % (35/104) the radiographs were interpreted as normal. In the remaining 69 there were pathological findings, not always, however, leading to the correct diagnosis.

FNAB was performed at a local hospital in 39 cases and at a sarcoma center in 34. Only 26 % (10/39) of the FNAB done at local hospitals showed chondrosarcoma, in 13 % (5/39) they were designated benign and in the remaining as inconclusive. On the other hand, when FNAB technique was applied at a sarcoma center with specialized cytopathologists a correct diagnosis of chondrosarcoma was made in 94 % (32/34) and only 6 % (2/34) were inconclusive (Table 2).

**Table 2.** Fine needle aspiration biopsy (cases).

Hospital	Chondrosarcoma	Benign	Inconclusive
Sarcoma center	32	0	2
Non-specialty center	10	5	24
Totally	42	5	26

## COMMENTS

Our results show that initial symptoms from osteosarcoma and Ewing sarcoma are not specific but lead to a wide spread of differential diagnoses. A history of minor trauma, pain related to strain and local tenderness generated many possible explanations. Tendinitis was the most common misdiagnosis in this study but tendinitis is actually a quite uncommon condition [56].

Malignant diseases are generally considered to have a steadily progressive clinical course. However, Ewing sarcoma in particular often has periods of fever and pain followed by periods of no or only minor symptoms. This intermittent clinical course often misled both the doctor and patient into believing that the condition would resolve spontaneously. The systemic symptoms and local pain often guided the doctor into considering inflammatory conditions such as pleuritis, osteomyelitis and coxitis simplex [57, 58].

Plain radiographs remain the most important tool for diagnosing bone lesions. Pathological findings at the initial x-ray were found for 91 % of the osteosarcomas, but for only 57 % of the Ewing sarcomas. A normal x-ray will be misleading and result in longer delay to correct diagnosis and treatment [59, 60]. When the clinical picture diverges from the expected renewed clinical examination and further radiological studies are indicated.

Ewing sarcomas of the chest wall were more often associated with pathological findings on chest x-rays. However, the findings were not specific and the correct diagnosis was delayed due to misinterpretations. Large pleural effusions were drained surgically and treated as infections with antibiotics and a malignant diagnosis was never considered. A tumor was suspected in only 5 of 26 patients at the first visit. Delayed diagnosis may be a lesser problem today as computer tomography and MRI are readily available. However, correct diagnosis still requires that the examining doctor includes a primary malignant chest wall tumor among the differential diagnoses.

Unlike the case for osteosarcomas and Ewing sarcomas, a malignant tumor was suspected in 88 % of the chest wall chondrosarcoma patients at the first visit. Why doctors suspected a cancer in these patients immediately and not in the osteosarcoma and Ewing sarcoma patients might have two main explanations. First, chest wall chondrosarcoma patients were much older and malignant diagnoses are more common in older populations. Secondly, a bone hard palpable mass was noted in 69 % of the chest wall chondrosarcoma compared with 34 % of the Ewing sarcoma. A bone hard mass in the chest wall is certainly a physical finding that arouses suspicion of malignancy.

In chest wall chondrosarcoma, the first doctor to be consulted for most of the patients, usually a general practitioner, suspected malignancy at the first visit. Nonetheless the diagnosis was often delayed. Chest x-rays were reported either as normal or not suggestive of malignancy and the cytological diagnosis was correct for only 26 %, when done at a local hospital. These normal results and minimal discomfort from the tumor resulted in a long delay. At sarcoma centers, inconclusive or benign FNAB results for a thoracic mass are not readily accepted and a repeat FNAB or open biopsy is performed [61]. Delay will be dealt with in more detail in section DELAY.

FNAB of chondrosarcoma is challenging, particularly in inexperienced hands because of large amounts of extra cellular matrix and few cells [61, 62]. Non-center cytologists also missed high-grade chondrosarcoma which emphasizes that this procedure is not suitable for hospitals with limited experience of bone sarcomas.

The lesson from this is that all patients with a suspected bone tumor should be referred, untouched, to a sarcoma center and that all biopsies, whether FNAB, true-cut or open, should be done at sarcoma centers with a multidisciplinary group for diagnosis and treatment [45]. The difficulties in diagnosing chondroid tumors by FNAB are known among sarcoma specialists, but probably not among doctors not handling sarcomas [61, 63-66]. Non-specialists tend to rely on conventional x-ray and FNAB but neither of these procedures are specific enough to exclude a bone sarcoma.

The consequences for patients with a chest wall sarcoma not referred to a sarcoma center were dire. At non-specialized centers, with an inconclusive or benign FNAB result and with general or thoracic surgeons without experience of sarcoma surgery, many patients were treated inappropriately with tumor spillage and early local recurrence.

# TREATMENT

The path from initial patient complaints through diagnostic procedures leads sooner or later to treatment decisions. Pre-operative histological diagnosis is a governing factor in planning treatment. For osteosarcomas, treatment is dealt with in innumerable publications and textbooks and follows well-established guidelines. Nearly all patients with this diagnosis in Sweden are treated by a multidisciplinary approach at specialized orthopedic sarcoma centers.

This chapter focuses on Ewing sarcoma and chondrosarcoma of the chest wall with emphasis on the problems that this site poses for referral pattern, diagnosis and treatment.

## TREATMENT OF EWING SARCOMA OF THE CHEST WALL

Ewing sarcomas are sensitive for both radiation and chemotherapy. With the advent of multi-agent chemotherapy, there have been significant improvements in the overall survival of these patients over the last 30 years [6, 67, 68]. Local therapy alone is not enough. Even seemingly localized Ewing sarcomas will metastasize and lead to death without chemotherapy. Chemotherapy is by far the most important part of the multidisciplinary treatment.

Ewing sarcoma of the chest wall is treated similarly to Ewing tumors elsewhere. Neo-adjuvant induction chemotherapy is given to shrink the tumor in order to increase the possibility of achieving adequate surgical margins. Distant microscopic metastases are the other targets of the neo-adjuvant chemotherapy regimens.

Surgery and/or radiotherapy are used as an adjunct to chemotherapy to increase the chances of local tumor control. Most Ewing sarcomas of the chest wall are amenable to surgical treatment after preoperative chemotherapy. The chest wall defect is patched by a prosthesis (Mesh or Gore-Tex) and muscular flaps are often used to obtain soft tissue coverage. Indications for postoperative radiotherapy dependent on surgical margin and the effects of preoperative chemotherapy [69]. The exact indications differ between different treatments protocols. Radiotherapy alone directed to the chest wall is planned for patients with tumors that are unresectable. Sometimes surgery becomes possible after both preoperative chemo- and radiotherapy. Additional chemotherapy regimens are given after removal of the Ewing sarcoma tissue. The duration of treatment is 8-12 months.

Several late effects of the treatment are well known. Resection of several ribs, especially in the posterior part of the thoracic cage may result in a scoliosis, which occasionally will need operative treatment. Late effects of the chemo- and radiotherapy are lung damage, heart toxicity, chest wall deformities and secondary malignancies [69-72].

## PATIENTS AND RESULTS

### Ewing sarcoma of the rib (study II)

There were 26 patients diagnosed in Sweden with Ewing sarcoma of the rib during 1981-2000, and all included in this study.

Most patients (88 %; 23/26) were treated surgically. In 6 patients the Ewing sarcoma was not suspected prior to surgery and operations were planned for surgical drainage of a presumed pleura empyema. These procedures resulted in an incisional biopsy or intralesional surgical excision. Only 14 of the operated patients had preoperative chemotherapy. For two of these, the regimens were inappropriate due to a wrong preoperative diagnosis (lymphoma). Surgical margins were classified as wide, marginal and intralesional (Table 3). Treatment of Ewing sarcoma was spread over as many as 11 hospitals. Three patients received only radiation or chemotherapy. The chemotherapy regimens used were: T11 (1980-1983), SSG-IV (1984-1989) and SSG-IX (1990-1999) [16, 17]. Only 9 of the 26 were referred to a sarcoma center for operation.

**Table 3.** Surgical margins (Ewing sarcoma of the rib).

Hospital	Wide	Marginal	Intralesional
Sarcoma center	4	4	1
Non-specialty center	2	6	6
Totally	6	10	7

The survival rate of Ewing sarcoma of the rib was 0.54. Five patients had metastases at the time of diagnosis; 4 of these died from the Ewing sarcoma. The survival rate for non-metastatic Ewing sarcoma was 0.61. Fourteen of the 26 patients developed local recurrence or metastases or both and only three of them survived.

## **TREATMENT OF CHEST WALL CHONDROSARCOMA**

Unlike Ewing sarcoma, chondrosarcoma is treated strictly surgically [11, 12, 73-76]. The surgical procedure is the same as for Ewing sarcoma at the same site. There are no chemotherapy protocols for chondrosarcoma and the tumor is relatively insensitive to radiation therapy. In clinical practice radiotherapy is considered in two situations, after a surgical procedure with insufficient surgical margins, or as a palliative measure. Radiation doses > 60 Gy are required and the close proximity of the tumor to vital structures such as heart, lung, and spinal cord often makes these high doses unfeasible [10, 29, 77].

In Sweden, bone sarcomas in general are handled by a multidisciplinary approach at special sarcoma centers. This is strictly adhered to for sarcomas of the pelvis and long bones. The referral pattern and surgical treatment was analyzed for this series of chondrosarcoma of the chest wall.

## **PATIENTS AND RESULTS**

### **Chest wall chondrosarcoma (study III)**

There were 106 patients with chondrosarcoma of the chest wall diagnosed 1980-2002, all included in this study III.

Surgery was the only treatment for 90 patients. One received preoperative and 6 had postoperative radiotherapy. The remaining 9 were not treated with a curative intent. Four were given radio and/or chemotherapy, one was operated to reduce tumor bulk and four had no treatment. The reasons for abstaining from curative surgery were high age, unresectable tumors and poor general condition.

The surgery was conducted at 19 different hospitals, the majority at orthopedic sarcoma centers (55 patients) and the remaining 42 at 16 different hospitals in either thoracic or general surgery departments. The surgical margins achieved were classified into wide, marginal or intralesional (Table 4). The median tumor size was 8 (2-23) cm. There was no difference in tumor size between patients treated at a sarcoma center and those treated at a local hospital. At sarcoma centers, a median 3 (1-6) ribs were resected compared with 2 (0-4) ribs at non specialty hospitals  $P=0.002$  (MWU-test). In 60 of 97 operations the defect was replaced by a net, Mesh or Gore-tex. There were no per- or postoperative deaths.

**Table 4.** Surgical margins (chondrosarcoma of the chest wall).

<b>Hospital</b>	<b>Wide</b>	<b>Marginal</b>	<b>Intralesional</b>
Sarcoma center	25	26	4
Non-specialty center	2	18	22
Totally	27	44	26

The 10-year-survival rate for the whole series of 106 chondrosarcoma patients was 0.64. Among the 97 patients treated in a curative intent, the 10-year survival rate was 0.67.

Survival rates were the same for the first (1980-1991) and for the second period (1992-2002) of study, 0.66 and 0.64 respectively.

Local recurrence rate was 0.34 and mean time to local recurrence was 3.5 (0.1-14) years but 4 recurred after 10 years.

## **COMMENTS**

The haphazard referral pattern for Ewing sarcoma of the chest wall is a striking feature of this small but population-based series collected over a 20-year period. Most patients were operated outside a sarcoma center and often without appropriate neo-adjuvant chemotherapy. The major reason for treatment outside a sarcoma center was an incorrect preoperative diagnosis.

Our study of chest wall chondrosarcoma is the first population based study comprising more than 100 patients. Previous reports have been center based and included only a small number of patients [8, 78, 79].

There is general consensus that sarcoma surgery should be conducted at special sarcoma centers. In spite of these recommendations, nearly half of the chest wall chondrosarcoma patients and the majority of those with Ewing sarcoma of the rib were treated outside a sarcoma center. The treatment was spread among as many as 19 different hospitals for chest wall chondrosarcoma and 11 for Ewing sarcoma of the rib. We have clearly shown that surgical margins achieved at the operations were much better at sarcoma centers than when the patients were treated elsewhere. These poor margins resulted in both local failure and ultimately in patient death.

One reason for the difference in outcome between sarcoma centers and non-specialty hospitals was the accuracy of the preoperative diagnosis. Outside of centers, a sarcoma was either not suspected or a FNAB was interpreted as benign or inconclusive. A wide surgical margin is feasible only if the diagnosis is clear and the treatment is planned conjointly by the sarcoma, thoracic and plastic surgeons.

The evidence for any benefit of chemotherapy or radiotherapy for chest wall chondrosarcoma treatment is limited [8, 11, 80]. Chemotherapy might be indicated for mesenchymal and dedifferentiated chondrosarcoma and radiotherapy as palliation but the benefits remain uncertain at best [10, 29, 80, 81]. New radiotherapy modalities might become an option in the treatment of chest wall chondrosarcoma [82]. Proton radiation therapy has the advantage of minimal exit dose after energy deposition in the tumor and hence better sparing of surrounding vital organs but studies are still limited.

Treatment methods are different for chondrosarcoma involving the axial skeleton and the long bones. A low-grade chondrosarcoma situated in a long bone can be treated by intralesional curettage of the tumor, with a good prognosis and less morbidity than after a wide excision [83-85]. Curettage is not an option for chondrosarcoma of the pelvis or chest wall, even for low grade tumors [10, 83].

Nine of the chest wall chondrosarcoma patients were not treated with intent to cure. All but one of them died from the tumor. These patients suffered for a long time with a steadily progressive expansion of the tumor mass. The mass was not only heavy but grew to dimensions difficult to cover with ordinary clothes and when ulcerated, smelled badly. There were no preoperative deaths in our series and several of these patients considered inoperable might have been helped with a surgical procedure.

# PROGNOSIS

Conventional prognostic estimates for malignant disease are generally based on WHO and national grading, staging and treatment protocols. These, in turn, represent the cumulative experience from a multitude of centers and, usually, referred patients with a known or suspected malignancy.

The basic approach for studies I-IV was to begin at the beginning with the first medical consultation for complaints which could be related to the skeletal tumors. Is there anything of prognostic value to be gleaned from these first visits?

The initially localized and often palpable tumors of the chest wall, Ewing sarcoma and chondrosarcoma (II-IV), could be expected a priori to be suitable for a search of prognostic features than the more heterogeneous osteosarcomas and all-site Ewing sarcomas in study I.

## PATIENTS AND RESULTS

### **Ewing sarcoma of the rib (study II)**

The fate of the 26 patients identified during a 20-year period has been followed through the previous sections dealing with initial complaints, diagnosis and treatment. For many of these patients, delay, misdiagnosis and inappropriate treatment clouded the issue making detailed analysis of specific prognostic factors uncertain at best.

Study II, however, gives an indication that referral pattern can be related to a more or less favorable outcome (Table 3).

Referral to a center using SSG protocols gave longer survival. Whether or not the classic surgical marker, free margins at primary excision, was relevant for the survival of these patients cannot be quantified from the material available but the treatment at a sarcoma center undoubtedly gave the patients a better chance.

### **Chondrosarcoma of the chest wall (study III)**

Factors associated with survival were tested using univariate and multivariate analysis (Table 5 and Table 6). The 10-year survival rate was .64 for all 106 patients, and .67 for the 97 patients treated in a curative intent. Survival in relation to surgical margin, local recurrence and treatment center is displayed in Figures 9-12.

**Table 5.** Chest wall chondrosarcoma. Univariate analyses of factors predicting survival.

<b>Variable</b>		<b>Number of patients</b>	<b>10-year survival rate</b>	<b>p-value (log rank)</b>
<b>Sex</b>	Male	54	.59	NS
	Female	43	.73	
<b>Surgical Margin</b>	Wide	27	.96	0.005*
	Marginal	44	.69	
	Intralesional	26	.46	
<b>Histological grade</b>	Grade 1	19	1	0.0001^
	Grade 2	39	.71	
	Grade 3	31	.66	
	Grade 4	8	0	
<b>Size (missing data 7)</b>	<7 cm	49	.85	.01
	>7 cm	41	.43	
<b>Tumor location</b>	Rib	82	.70	0.04
	Sternum	15	.57	
<b>Local recurrence</b>	Yes	33	.37	<0.0001
	No	64	.94	
<b>Metastasis</b>	Yes	19	.04	<0.0001
	No	78	.87	
<b>Micronecrosis</b>	Yes	42	.52	0.03
	No	31	.85	
<b>Sarcoma center</b>	Yes	55	.75	0.04
	No	42	.59	

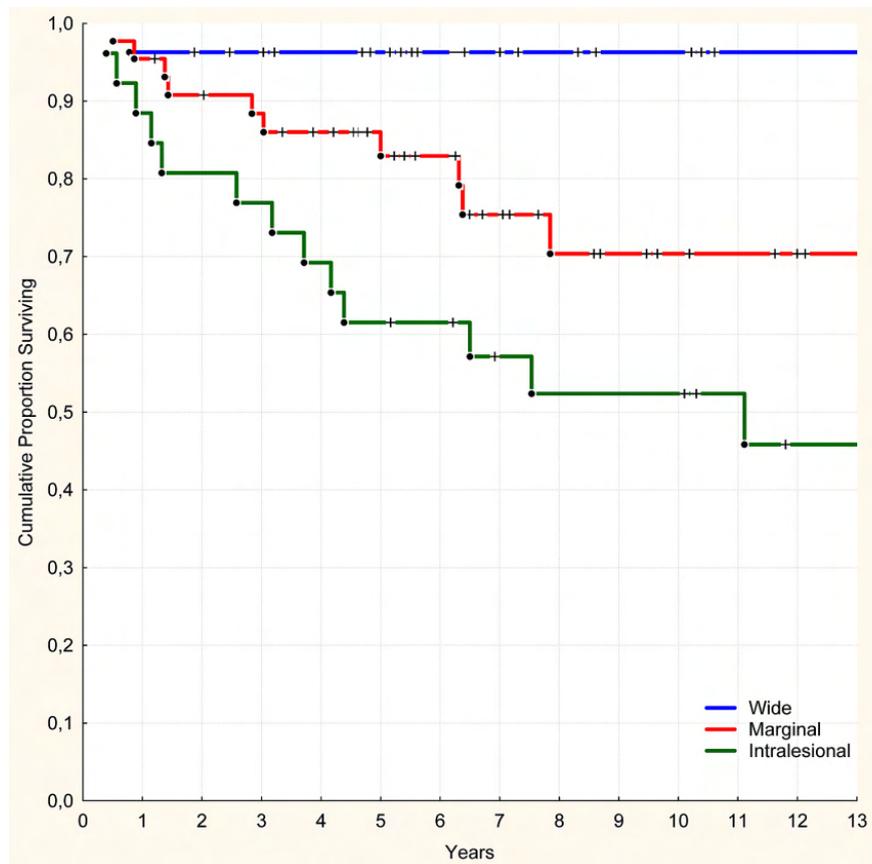
\*chi-square test

^ Fischer exact test

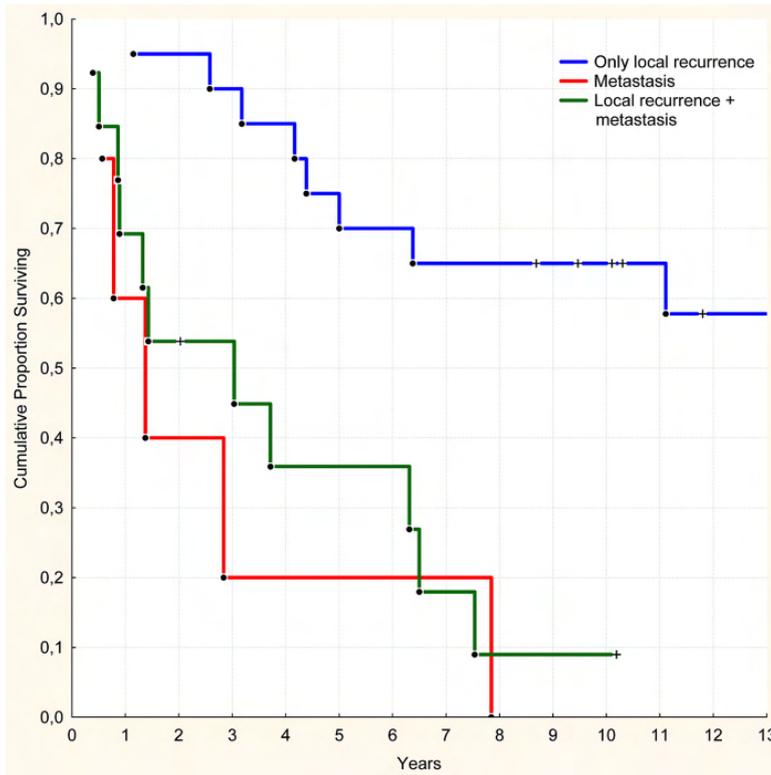
**Table 6.** Chest wall chondrosarcoma. Multivariate analysis of factors predicting survival.

Variable		Hazard ratio Conf. Inter (95 %)	p-value
Surgical margin	Wide	1	<0.01
	Intralesional	2.4 (1.1-5.4)	
Histological grade	Low grade (1+2)	1	<0.05
	High grade (3+4)	3.2 (1.3-8.1)	
Metastasis	No	1	<0.0001
	Yes	9.1 (3.8-22.1)	

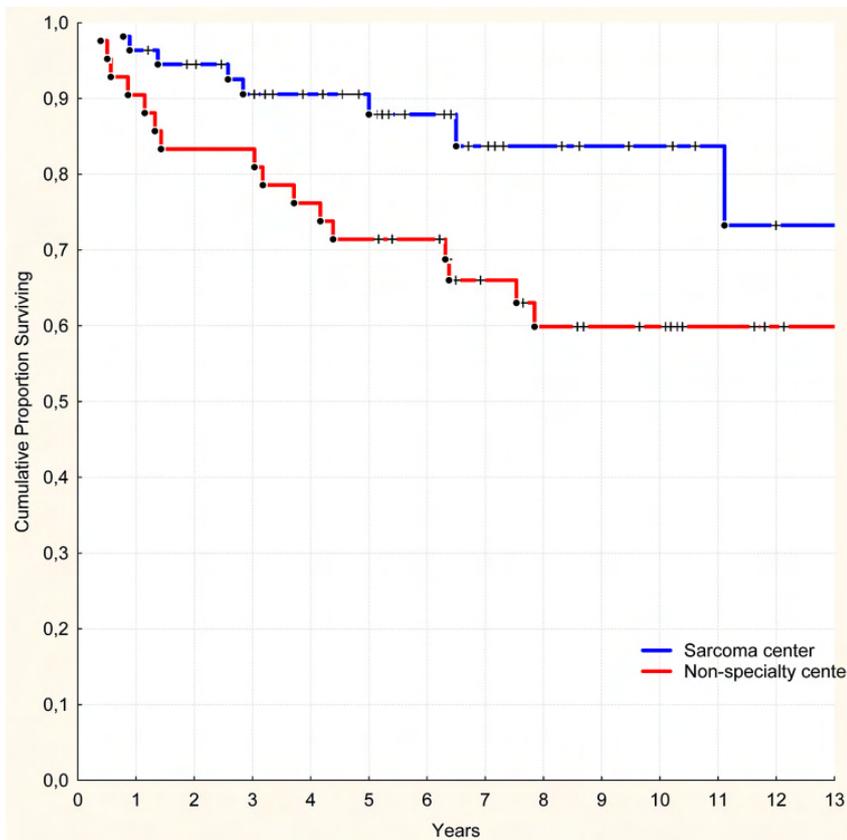
**Figure 9.** Kaplan-Meier analysis of surgical margins and survival (chest wall chondrosarcoma).



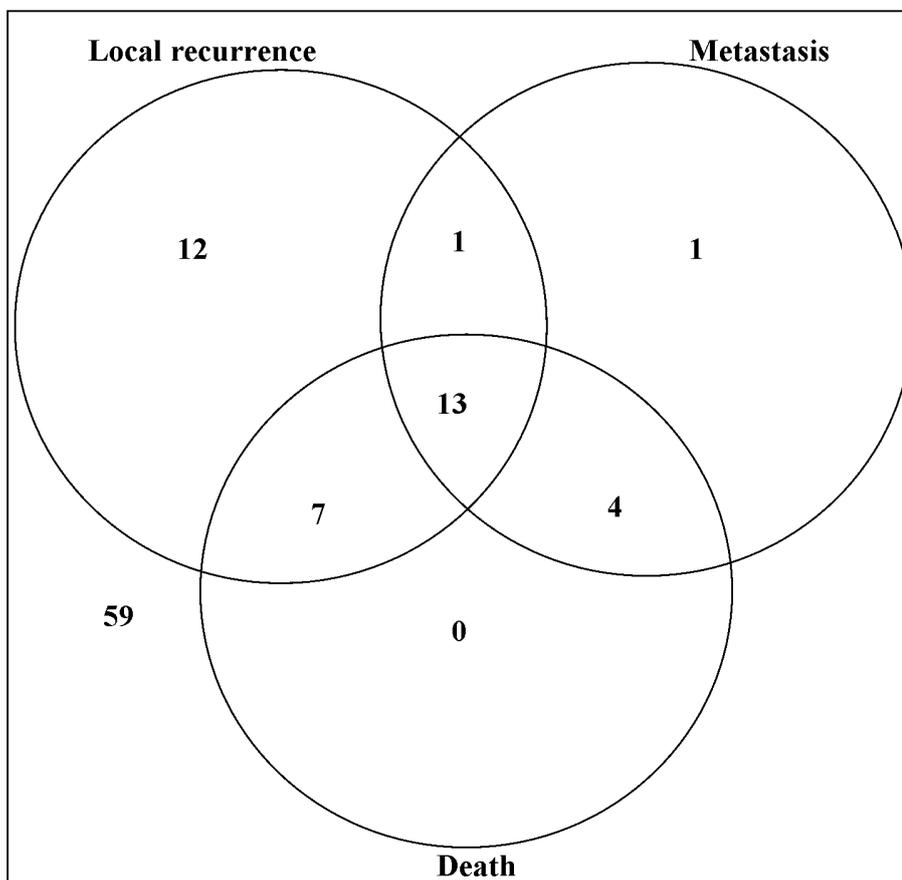
**Figure 10.** Kaplan-Meier analysis of local recurrence and metastasis and survival (chest wall chondrosarcoma).



**Figure 11.** Kaplan-Meier analysis, of survival after surgery at a sarcoma center or at a non-specialty center (chest wall chondrosarcoma).



**Figure 12.** Venn diagram illustrating the distribution of local recurrence, metastasis and death for 97 chest wall chondrosarcoma patients treated with curative intent.



## COMMENTS

Several prognostic factors have been identified for Ewing sarcoma; one of the most important is metastasis at time of diagnosis [50, 51, 86]. Ewing sarcomas with metastasis still have a dismal prognosis despite chemotherapy regimens. Non-metastatic disease at presentation has a 5-year disease free survival rate of 70 % compared with 25 % for patients with metastatic disease [86]. Other prognostic factors are tumor volume, tumor location, chemotherapy response and age at diagnosis [54, 68, 87]. Ewing sarcoma of the pelvic region and older patients are both associated with a worse outcome. Since there were only 26 patients no meaningful prognostic analysis

could be performed. However, the survival rate of .61 was similar to non-metastatic Ewing sarcoma in other sites. Poor preoperative diagnosis and inadequate multimodal treatment were associated with a poor outcome.

Our results from the study of the chondrosarcoma of the chest wall showed an overall 10-year survival rate of .64, for all 106 patients. Nine patients were not treated in a curative intent and all except one of them died from the chondrosarcoma. The 10-year survival rate was .67 among the 97 patients treated with a curative intent.

Studies of chondrosarcoma require a long follow-up period since patients can develop local recurrences up to even a decade after operation. This study had a median follow-up of 9 (4-23) years for survivors. In other series of chondrosarcomas at all sites the 5-year survival was around 70 % [20, 73, 88]. Previous reports of chest wall chondrosarcoma have reported a 5-year survival rate of 64 % and 10-year survival of 60 % [8, 78]. Our results are comparable with these two studies and to survival for chondrosarcoma in all sites.

Chondrosarcomas are heterogeneous tumors and sampling is therefore important to establish correct histological grade. However, correct grade can often be established only after surgery when the whole tumor can be assessed. However, this is of no practical consequence as the surgical procedures for low and high-grade chondrosarcoma of the thoracic cage are the same. Grade is accepted to be one of the most important prognostic factors [11, 12, 75]. Many studies have been conducted to find molecular markers for better prediction of outcome. Unfortunately, most of these markers have not been independent of tumor grade and they therefore have little additional prognostic value [77, 89].

Chondrosarcomas of the pelvis are associated with survival rates inferior to the chest wall [9, 11]. As there are no new treatment modalities the outcome in chondrosarcoma has remained largely unchanged for the last two decades [9, 20]. Our study shows that the overall outcome in chest wall chondrosarcoma can be increased with better referral patterns.

We classified the surgical treatment into 3 categories - wide, marginal and intralesional. The 10-year survival rate was 0.96 for those treated with wide resection compared with 0.46 after intralesional treatment. Most previous studies have reported more wide and less intralesional procedures but with similar local recurrence rates [8, 11, 38]. The local recurrence rate was highly dependent on the surgical margin, 0.04 after a wide resection and 0.73 after an intralesional. This confirms that our classification of surgical margins was valid. The other independent factor related to local recurrence was histological grade.

A previous study reported that local recurrence in chondrosarcoma (in all locations) is only relevant to survival if the patient has metastases at the time of detection of the local recurrence [73]. However, we noted that in chest wall chondrosarcoma, local recurrence *per se* reduces survival, even without metastases. The local recurrences could grow to an enormous size leading to respiratory insufficiency and death; nearly

half of the patients in our study with a local recurrence but no metastasis died due to progressive disease.

Metastasis is a highly negative prognostic factor [88, 90, 91]. In our study 20 % of the patients developed metastasis. We found two factors related to metastasis, local recurrence and histological grade. The metastases rate was 0.42 in patients with a local recurrence and 0.08 without. No patient with histological grade 1 developed metastasis but 7/ 8 of the patients with grade 4 did so.

By multivariate analysis we found 3 independent factors for survival - grade, intralesional procedure, and metastasis. The findings are consistent with previous reports. Both grade and metastasis are well-known predictors of outcome [13, 73, 78]. Surgical margins are more difficult to compare because in most reports definitions are unclear. However, applying a strict definition of surgical margin, intralesional procedures were independently associated with a high risk of tumor related death.

Treatment at the sarcoma centers (55 patients) gave 7 % intralesional procedures compared with 52 % when the patient was treated at a non-specialty center. The higher survival rate at sarcoma centers compared with that for non-specialty centers can be ascribed to the difference in surgical margins.

## DELAY

A general practitioner, confronted by a patient seeking advice for symptoms mimicking much more common and much less serious conditions, would hardly entertain the possibility of a skeletal sarcoma as a first choice among differential diagnoses. Some delay in arriving at a definite diagnosis is inevitable. Some of this delay, however, can be coupled to clinical practices and judgments amenable to improvement.

### PATIENTS AND RESULTS

The medical records for all 281 patients in studies I-IV were scrutinized to calculate patient's and doctor's delay as described in section patients and methodological considerations.

#### Osteosarcoma and Ewing sarcoma of all locations (study I)

Mean doctor's delay for osteosarcoma patients was 2 month and for Ewing sarcoma 4 months. Both patient's and doctor's delay were longer in Ewing sarcoma patients than in osteosarcoma patients (Table 7). Distribution of doctor's delay in osteosarcoma patients is illustrated in Figure 13.

Two factors related to shorter doctor's delay were identified. First, patients with a palpable mass at the first visit had shorter doctor's delay than those without a mass (1 compared with 4 months,  $p < 0.001$ ). Secondly, patients who were referred to x-ray at the first visit had also shorter doctor's delay than those not ordered an x-ray (2 compared with 4 months,  $p < 0.01$ ).

Osteosarcoma patients with metastases at the time of diagnosis had longer doctor's delay compared to those without metastasis (Figure 14). Ewing sarcoma patients with metastases at diagnosis also had longer doctor's delay but the difference was not significant (Figure 15).

**Table 7.** Patient's, doctor's, and total delay, for osteosarcoma and Ewing sarcoma (all sites<sup>^</sup>).

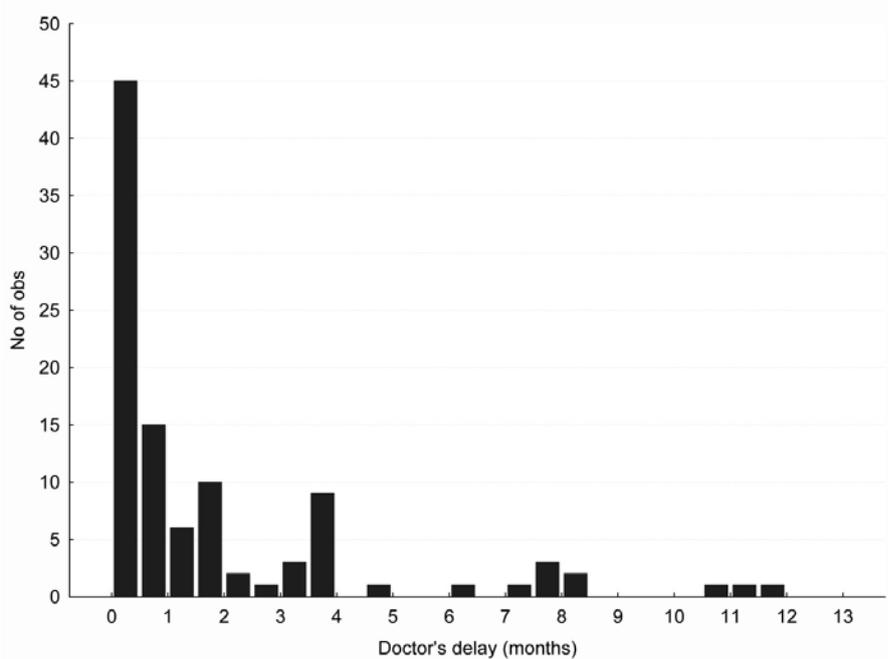
	Osteosarcoma	Ewing sarcoma	P-value
Patient's delay	1 (0.2-6; median 1)	3 (0.1-22; median 1)	<0.001
Doctor's delay	2 (0.1-12; median 1)	4 (0.1-16; median 3)	<0.001
Total delay	3 (0.4-17; median 2)	7.5 (0.7-33; median 5)	<0.01

*Values are given as the mean number of months, with range and median in parentheses.*

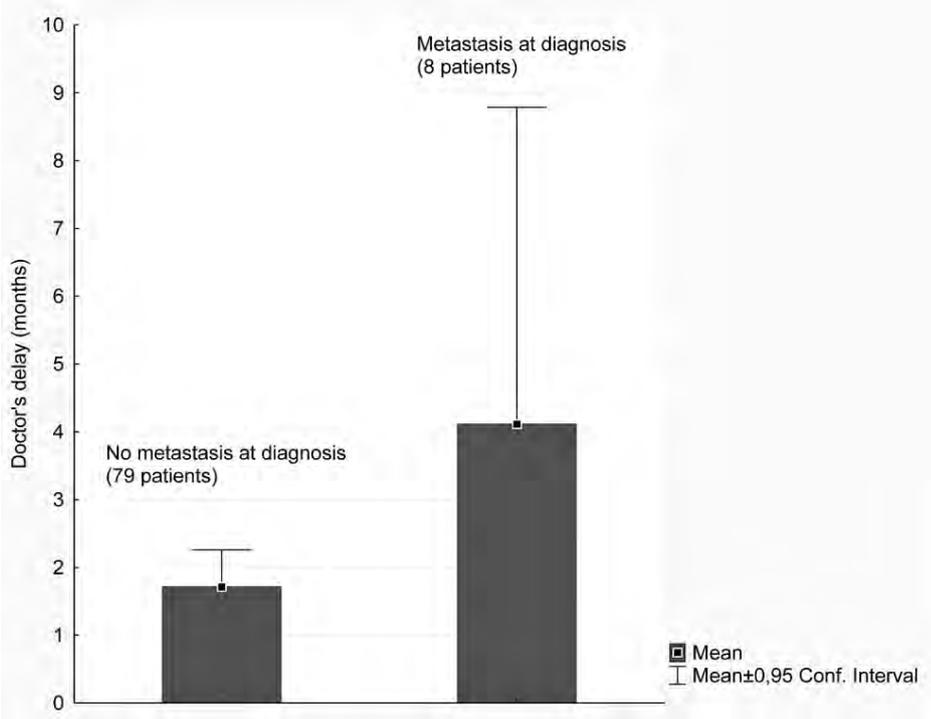
<sup>^</sup> Chest wall, skull and jaw excluded.

**Figure 13.** Doctor's delay for all 102 osteosarcoma patients.

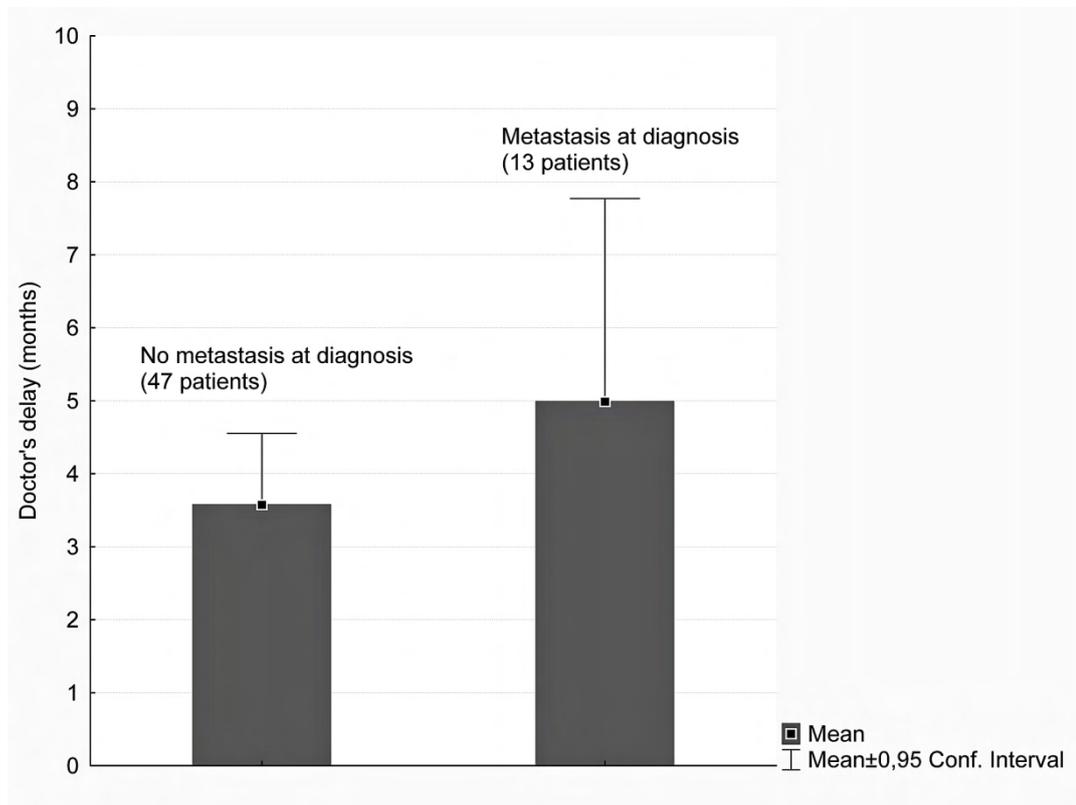
Purpose of this graph is to illustrate that most patients with osteosarcoma are diagnosed within a few months, and that only a minority have a doctor's delay longer than 6 months.



**Figure 14.** Doctor's delay for osteosarcoma patients without or with metastasis at diagnosis. MWU-test  $p < 0.05$  (for 15 patient data missing).



**Figure 15.** Doctor's delay for Ewing sarcoma patients without or with metastasis at diagnosis. MWU-test,  $p=0.09$  (for 13 patients data missing).



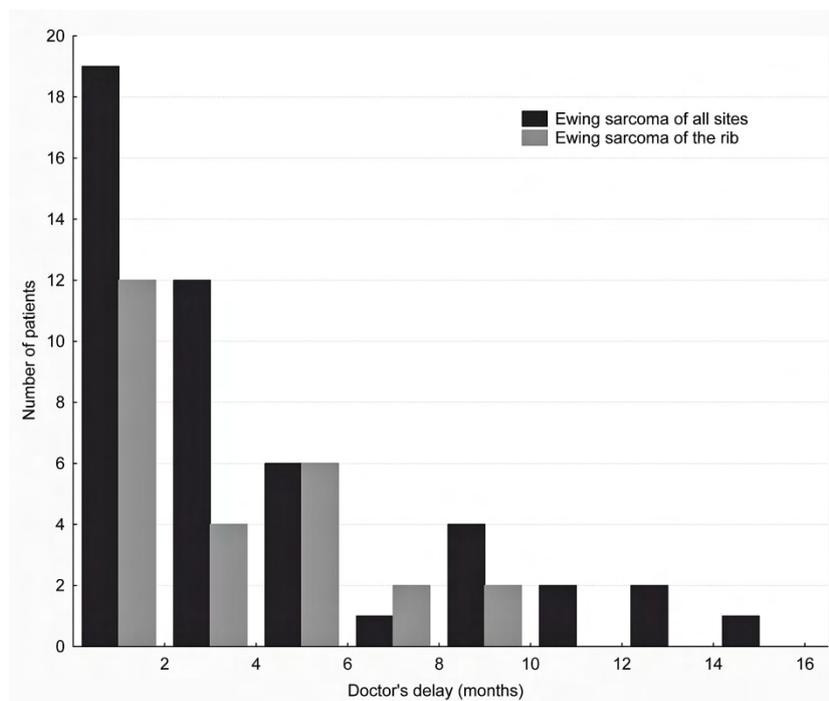
### Ewing sarcoma of the rib (study II)

Patient's delay averaged 3 months (0-10, median 2) and doctor's delay 3 months (0-10, median 2). Ewing sarcoma of the chest wall was associated with shorter doctor's delay than for other sites. Patients who noted a palpable mass or had fever had a shorter doctor's delay (Table 8). Patients who presented with metastases at diagnosis had a mean doctor's delay of 5 months compared to 3 months but the difference was not significant (MWU-test  $p=0.09$ ). Four patients had doctor's delay exceeding 7 months and all of them had metastases at diagnosis or relapsed after primary treatment. Distribution of doctor's delay in Ewing sarcoma patients is illustrated in Figure 16.

**Table 8.** Doctor's delay in diagnosis for Ewing sarcoma of the rib.

Symptom		Number of patients	Doctor's delay (months)	p-value MWU-test
Fever	yes	11	2	0.05
	no	15	4	
Palpable mass	yes	11	1.5	0.06
	no	15	3	

**Figure 16.** Doctor's delay for Ewing sarcoma patients.



### Chondrosarcoma of the chest wall (study IV)

Patients with chondrosarcoma of the chest wall had long patient's and doctor's delay (Table 9). One-quarter of the patients consulted a physician within 2 weeks from first noticing a mass and one quarter waited more than 6 months. Doctor's delay for 20 % of the cases was between 6 months and one year and in another 20 % it exceeded one year. Long total delay was related to outcome (Figure 17). Patients who had an x-ray interpreted as normal had longer doctor's delay MWU-test, ( $p < 0.05$ ) (Figure 18).

**Table 9.** Patient's, doctor's and total delay for chest wall chondrosarcoma.

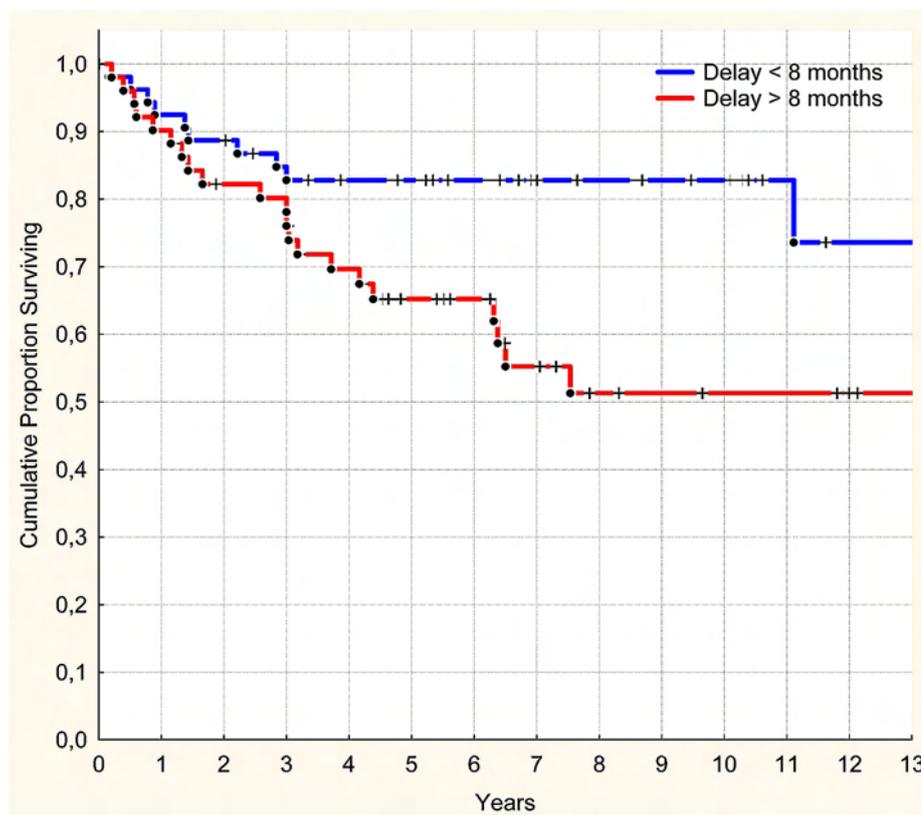
	Patient's delay	Doctor's delay	Total delay
<b>Chest wall chondrosarcoma</b>	<b>8 (0-118; 3)</b>	<b>12 (0.1-197; 4)</b>	<b>19 (1-199; 8)</b>

*Values are given as the mean number of months, with range and median in parentheses.*

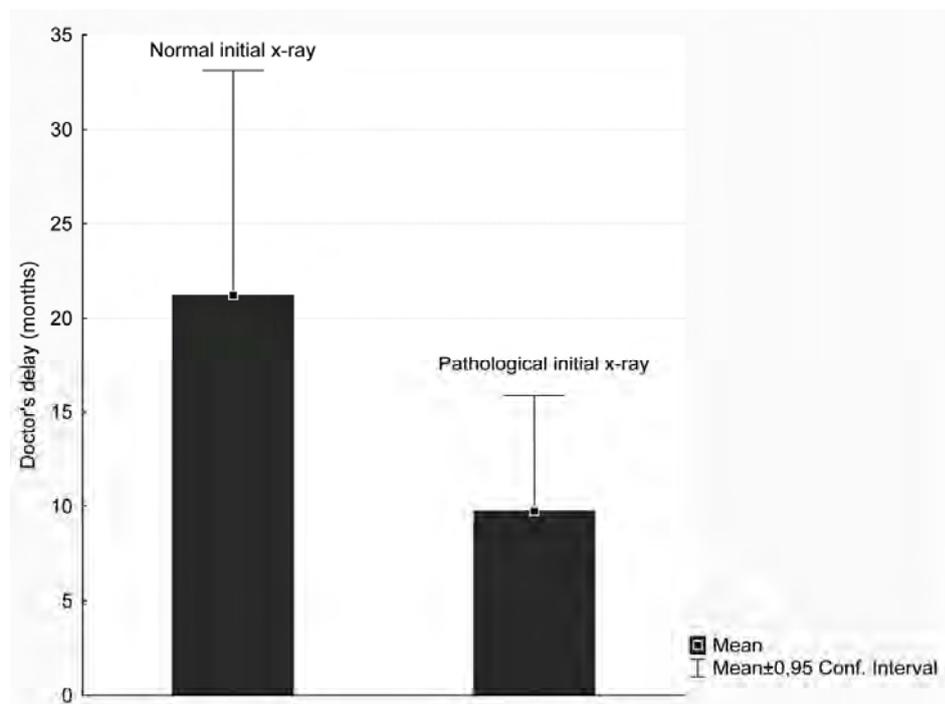
Case 70 year old woman

A 70-year-old female consulted her general practitioner for a lump in the right anterior chest wall. Chest radiograph detected a 40 x 26 mm tumor in the 5<sup>th</sup> rib in the costo chondral junction. The patient was admitted to the surgery department at a local hospital. The surgeon believed the tumor process was slowly growing and ordered a new chest radiograph after one year. The tumor had only increased to 48 x 33 mm by then. Since the patient had no discomfort, the decision was watchful waiting and a yearly chest radiograph. No biopsy was performed. Further yearly examinations were done and the tumor increased slowly for 8 years. At this time the tumor started to expand rapidly to a 200 x 230 mm. Surgery was no longer an option and the patient was sent for palliative radiotherapy. The patient died soon after due to the large chest wall chondrosarcoma.

**Figure 17.** Kaplan-Meier analysis, of survival and total delay. Median total delay was 8 months. (chest wall chondrosarcoma).



**Figure 18.** Doctor's delay was longer for chest wall chondrosarcoma patients with an initial x-ray interpreted as normal. MWU-test  $p < 0.05$ .



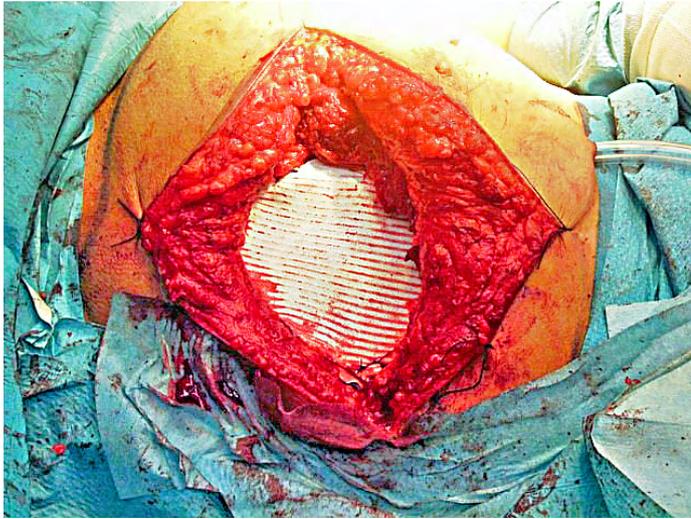
Case 50 year old man

A previously healthy man noted a bone hard lump in his sternum. He consulted a general practitioner and a computer tomography showed a chondroid tumor in the lower part of the sternum (Figure 19). At the sarcoma center the diagnosis was confirmed by FNAB. The tumor was resected and the defect was patched with a Gore-tex graft and muscular flap. The surgical margins according to the pathology report were wide, and maximum diameter of the tumor was 80 mm (Figure 20 and 21).

**Figure 19.** CT of the sternal chondrosarcoma.



**Figure 20.** The surgical field. After resection of the chondrosarcoma, the defect was patched with Gore-Tex.



**Figure 21.** The resected sternal chondrosarcoma.



## **COMMENTS**

The common basis for these studies were analysis of clinical records from the first consultation to definite diagnosis generating information on delay and the factors contributing to shorter or longer delay on the part of both patients and doctors.

Patient's delay is a subjective and individual phenomenon to some extent influenced by the accessibility of medical services. Statistically, patient's delay turned out to be shorter than doctor's delay for all tumor types. The extremely long patient's delay, noted for some patients with chondrosarcoma of the chest wall, can probably be accounted for by the lack of pain and indolent growth of this particular tumor. In practice, the only way to shorten the time from first symptoms to diagnosis is to shorten doctor's delay.

The delay we found for osteosarcoma and Ewing sarcoma of all sites was slightly shorter than that reported by Sneppen but comparable with that cited with others [92-96].

For osteosarcoma and Ewing sarcoma at all sites (study I) the decisive factor for shorter doctor's delay were the presence of a palpable mass and/or the decision to refer the patient for radiography at the time of the first visit. A worrisome feature is the finding that doctor's delay was longer for the 10 % of the patients who had metastases at diagnosis. The question implicit in this is whether or not the delay for these patients affected outcome. The answer is important medico-legally at least the patient claims an answer for late diagnosis.

To give an answer would require detailed analysis of all other prognostic factors such as tumor volume and include chemotherapy response. Since the chemotherapy regimens were changed during the period covered by the study no detailed analysis was made. Metastases at the time of diagnosis, however, are known to be strongly negatively predictive and such patients have poor survival rates even with the most recent chemotherapy regimens [6, 97-99].

Delay for Ewing sarcoma of the rib was slightly shorter than for Ewing sarcoma at all sites. The presence of a palpable mass and fever episodes contributed to shorter doctor's delay. For patients with metastases at diagnosis doctor's delay was somewhat longer than for those without, 5 months versus 3, but the difference was not significant ( $p=0.09$ ). Our results contradict previous studies, claiming that Ewing sarcoma patients with a short delay have a worse prognosis [54, 100].

Unlike Ewing sarcoma, chondrosarcoma of the chest wall was associated with a much longer doctor's delay. In most previous reports dealing with doctor's delay for bone sarcomas, the main explanation for the delay was the rareness of the disease [101, 102]. In our series, however, a tumor was suspected in 88 of the 106 patients at the first consultation. Still, doctor's delay, from suspicion to treatment, exceeded 6 months for 40 per cent of the patients. We have identified several factors contributing to doctor's delay.

In the first place, a painless mass as noted by two-thirds of the patients at their initial consultation did not incite diagnostic celerity. We believe that this painlessness is an important finding. The possibility of a chondrosarcoma, especially in the absence of pain, has to be considered in the differential diagnosis of a mass in the chest wall. Other reports, based on referred patients, reported pain as a dominating symptom for malignancy and the absence of pain as an indicator of a benign mass [35, 39, 103]. Their findings could not be confirmed in this study based on an analysis of symptoms at the first medical consultation.

The absence of pain at the time of the very first medical examination of our chondrosarcoma patients undoubtedly contributed to both patient's and doctor's delay. A possible explanation for the absence of pain is that the ribs and sternum are not weight-bearing bones [38].

Secondly, a radiograph first interpreted as normal, as was the case for 34 per cent of the patients, led to a significantly prolonged doctor's delay. Both patient and doctor tended to regard the mass as harmless, although still without a clear diagnosis. Assured by the report of a normal x-ray, both doctor and patient waited while the tumor slowly continued to grow – as for one 72-year-old woman who did not return until after 2 years with a 17 cm larger tumor.

Thirdly, the results of FNAB, when inconclusive or benign, contributed to doctor's delay. An inconclusive or a benign FNAB result at non-specialty centers lulled both patient and doctor into accepting the mass as harmless and prolonged the time to treatment. At non-specialty centers, only 26 % of the chondrosarcomas sampled were correctly diagnosed as malignant. At sarcoma centers, 94 % were correctly diagnosed by the same procedure. Furthermore, at sarcoma centers, inconclusive or benign FNAB results are not readily accepted; the FNAB is repeated or an open biopsy is done [61].

This study of initial symptoms and diagnostic procedures provide support for the referral of all patients with a suspected bone lesion, untouched, to a sarcoma center. All biopsies, whether FNAB, true-cut or open, should be done at sarcoma centers and by a multidisciplinary group for diagnosis and treatment [45]. It is not difficult to perform a needle or open biopsy, but it requires vast experience to get relevant samples and to make a diagnosis on the biopsy material.

Although there is general agreement that early diagnosis and treatment are of benefit in malignant disease, there is no apparent correlation between delay in diagnosis and outcome in sarcoma in general [104, 105]. Rougraff et al included large number of patients (624) with either bone or soft tissue sarcomas [104]. The duration of symptoms was assessed by questioning the patient at the sarcoma center. They could not detect any adverse effect of prolonged symptom intervals before treatment. However, the material was based on a heterogeneous group of diagnoses and they did not specifically assess doctor's delay. Assessing delay based on records of the first medical visit should be a more accurate means of establishing the lag time.

The significance of lag time has been debated for a long time. For several malignancies reports have demonstrated an impact on survival [106-110]. In other non screened cancers no correlation between survival and delay has been reported [111, 112]. Our findings, based on three different series of patients, are compelling evidence for an adverse effect of a long delay for the tumor types studied.

Patient perception of delay as possibly life-threatening in itself, regardless of statistics, is an unnecessary burden in the process of accepting the existential realities of a malignant diagnosis. The lessons to be learned about delay as documented in studies I-IV are that malignancies do occur in young people, that palpable masses require an explanation and that normal or inconclusive radiological or pathological reports cannot be accepted in the face of clinical suspicion to the contrary and that referral practices can be decisive for outcome.



# GENERAL CONCLUSIONS

Primary bone sarcomas are so rare that most physicians will never meet a single patient with an undiagnosed bone sarcoma during their working-career. Early diagnosis and correct treatment is important for good outcome. Our results show that symptoms from osteosarcoma and Ewing sarcoma are not specific but lead to a wide range of differential diagnoses. A history of minor trauma, pain related to strain and local tenderness generated many possible explanations. The presence of a lump, which was found in 34-69 % of the patients in our studies already at the first visit, emphasizes the importance of a physical examination. A bone hard lump is a physical finding that needs to be investigated properly.

Malignant diseases are generally believed to have a steadily progressive clinical course. However, especially Ewing sarcoma often had periods of relapsing fever and pain that were followed by periods of no or only minor symptoms. This intermittent clinical course often misled both the doctor and patient to believe that the condition would resolve spontaneously. The systemic symptoms and local pain often misled the doctor to infectious explanations such as pleurisy, osteomyelitis and coxitis simplex [57, 58].

We have in this thesis concluded that conventional plain radiograph often detects osteosarcomas but not chondrosarcomas of the chest wall or Ewing sarcomas. When the clinical picture diverges from the expected it is important to challenge the diagnosis. Osteosarcomas in general had shorter doctor's delay than Ewing sarcoma and chondrosarcoma. Most of the osteosarcomas were diagnosed within 3 months from the first visit. As opposed to osteosarcoma, Ewing sarcomas had longer doctor's delay and the initial plain radiograph missed the tumor in half of the patients which significantly delayed correct treatment. This knowledge might not be new to sarcoma specialists, but to the medical community in general.

FNAB of chondrosarcoma was in inexperienced hands unsafe probably because of large amounts of extra cellular matrix and few cells. Even high grade chondrosarcoma were missed by non-center cytologists, which emphasizes that this procedure is not suitable at hospitals with limited experience of bone sarcomas.

The lesson from this is that all patients with a suspected bone tumor should be referred, untouched, to a sarcoma centre and that all biopsies, whether FNAB, true-cut or open, should be done at sarcoma centers with a multidisciplinary group for diagnosis and treatment [45].

We found that in chest wall chondrosarcoma, local recurrence *per se* reduces survival, even without metastases. The local recurrence expanded enormously and resulted in respiratory insufficiency and death; nearly half of the patients in our study with a local recurrence but no metastasis died due to progressive disease.

There is consensus that sarcoma surgery should be conducted at special sarcoma centers. In contrast to these recommendations, nearly half of the chest wall chondrosarcoma patients and the majority of the Ewing sarcoma of the rib were treated outside a sarcoma center. The treatment was performed in as many as 19 different hospitals in chest wall chondrosarcoma and 11 in Ewing sarcoma of the rib. We have clearly shown that surgical margins achieved at the operations were much better at sarcoma centers than when the patients were treated elsewhere. These poor margins resulted in both local failure and patient death.

In the multivariate analysis of chondrosarcoma we found 3 independent factors for survival, grade, intralesional procedure, and metastasis. The findings are consistent with previous reports. Both grade and metastasis are well known predictors of outcome [13, 73, 78]. Surgical margin is more difficult to compare with other series since in most reports the definition is unclear. However, applying a strict definition of surgical margin, intralesional procedures were independently associated with a high risk of tumor related death.

Treatment at the sarcoma centers (55 patients) gave 4 % intralesional procedures compared to 52 % when the patient was treated at non-specialty center. The higher survival rate at sarcoma centers compared to non-specialty centers was due to this difference in surgical margins.

Doctor's delay as a negative prognostic factor is not as readily amenable to detailed analysis. Yet for osteosarcoma, doctor's delay was significantly longer for patients with metastases at diagnosis, a strongly negative factor. A similar tendency was evident for Ewing sarcoma. Total delay was significantly longer for patients who died from the chest wall chondrosarcoma. Patient perception of delay as life-threatening in itself, regardless of statistics, is an unnecessary burden in the process of accepting the existential realities of a malignant diagnosis.

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