Summary and conclusions

Chapter 1

The treatment outcome in patients with extremity sarcomas has improved considerably over the past 25 years due to advances in several disciplines. During this period limb-saving procedures have replaced amputation as the primary mode of surgical treatment. Pelvic sarcomas constitute a separate group of tumours due to the complex anatomy, the large size of these tumours and the technical difficulties often encountered at this anatomical site.

On the basis of 25 years of experience with the management of extremity sarcomas at the University Hospital Groningen, the Netherlands, this thesis aimed: to discuss the development and results of multidisciplinary treatment in extremity soft tissue sarcoma and osteosarcoma; to investigate the long-term results of the combined treatment of high-dose methotrexate-based neoadjuvant chemotherapy and surgery in malignant fibrous histiocytoma of bone; to assess the long-term oncological and functional outcome of endoprosthetic reconstructions after tumour resection of the lower extremity; to investigate the indications and oncological results of hindfoot amputation as a limb-sparing alternative to below-knee amputation; to inventorize the indications and oncological results of two major amputations in surgical oncology: interscapulothoracic amputation and hemipelvectomy; to analyse experience with Tikhoff-Linberg resection as an alternative to interscapulothoracic amputation, as well as internal hemipelvectomy with or without reconstruction and buttockectomy as alternatives to hemipelvectomy; to investigate the oncological outcome of pelvic osteosarcoma, which is a rare location for these tumours.

Chapter 2

Modern treatment strategies have resulted in improved local control and survival rates in patients with extremity soft tissue sarcomas. Several important factors, including improvements in imaging techniques, staging systems and the concept of centralised treatment by multidisciplinary teams, have contributed to this favourable outcome.

For local control of extremity soft tissue sarcoma, adequate surgical resection of the primary tumour with tumour-free margins remains essential. In the past, conservative local resection or shell-out procedures were associated with an unacceptable rate of local recurrence, ranging from 60 to 95%. The application of radiotherapy has had a major impact on the local control of soft tissue sarcomas and it is now being used routinely in combination with conservative function-preserving and limb-sparing

resection of the primary tumour. This treatment regimen of surgery and adjuvant radiotherapy prevents local recurrence in up to 90% of cases. However, local control after tumour resection is highly dependent on achieving negative surgical margins, even with the addition of radiotherapy. improved understanding of tumour and radiation biology has helped to determine the optimal radiation dose for the patient and to decrease serious local complications. More recently, impressive local control rates and an increasing number of limb-sparing resections were achieved in patients with locally advanced extremity soft tissue sarcoma after using hyperthermic isolated limb perfusion (HILP) including tumour necrosis factor-alpha (TNF-α) and melphalan. Local control might increase even further with adjuvant radiotherapy after HILP including TNF-α.

Chemotherapy has been disappointing in the management of soft tissue sarcoma. There has been no convincing evidence that single agent or combination chemotherapy has a positive effect on overall survival in patients with non-metastatic soft tissue sarcoma, although disease-free survival seems to have lengthened.

For extremity soft tissue sarcomas, the most important prognostic factors for the occurrence of local recurrence are surgical margins and tumour depth. Tumour grade, tumour size and tumour depth emerged as important prognostic factors for overall survival and the development of distant metastases. The causal relationship between local recurrence and subsequent metastases and survival remains one of the most controversial issues; this relationship has been questioned by several authors. Presently, cytogenetics and molecular biology are being studied to detect new prognostic markers with increasing impact.

Pulmonary metastases from soft tissue sarcoma are no longer considered to have a uniformly fatal outcome, although the prognosis remains poor. After complete resection of lung metastases, the 5-year post-thoracotomy survival rate ranged from 20 to 40%. The contribution of adjuvant chemotherapy is still limited.

Chapter 3

Over the past 25 years, the prognosis for osteosarcoma has improved significantly. Until the early seventies, the 5-year overall survival rates for patients with non-metastatic osteosarcoma of the extremities were approximately 15 to 20%. Most patients died of pulmonary metastases within 2 years of diagnosis. The observation that doxorubicin and high-dose methotrexate resulted in (partial) necrosis of metastasized osteosarcoma, led to the introduction of combination-chemotherapy for primary non-metastatic osteosarcoma. Chemotherapy to eradicate the micrometastases presumed to be present in 80% or more of patients at the time of

initial diagnosis and adequate surgical resection of the primary tumour soon had a major impact on the survival of patients with non-metastatic osteosarcoma. Due to this combined treatment regimen, 5-year disease-free survival and 5-year overall survival have increased to approximately 60% and 80%, respectively. The use of effective neoadjuvant chemotherapy regimens, the development of improved radiographic imaging techniques and advances in surgical procedures allowed tumour resection with closer margins than before. As a consequence, amputation has now been replaced by limb-saving procedures in most patients with extremity osteosarcoma. As most patients with osteosarcoma are young and can be expected to become long-term cancer survivors, the functional results and long-term integrity of the reconstructions are of increasing interest and concern.

Important prognostic factors for osteosarcoma include tumour size, tumour location and histological response to chemotherapy. Recently, new important biological factors have been identified with increasing impact. The influence of these factors, e.g., mutations in tumour-suppressor genes (p53, Rb) and overexpression of oncogenes (MDM2, c-erb B-2), growth factors and cytokines (IGF-1, TGF-β3), on prognosis is being studied extensively. Furthermore, the correlation of several mechanisms of multi-drug resistance (MDR), i.e., the phenomenon of simultaneous resistance to structurally unrelated natural chemotherapeutic agents, with outcome is being addressed in many recent trials. One of the most important mechanisms of MDR identified up to now is the overexpression of P-glycoprotein (P-gp), a transmembrane drug-efflux pump, that actively clears drugs from the cell. However, resistance-modifying agents to circumvent drug resistance caused by P-gp have not yet been successful in osteosarcoma.

If pulmonary metastases develop after initial treatment, aggressive metastasectomy, when feasible, is crucial to survival. Important prognostic factors are the number of metastases, the use of salvage chemotherapeutic regimens, complete resection of all metastases and the time to development of metasases.

Chapter 4

The value of high-dose methotrexate (HD-MTX)-based neoadjuvant chemotherapy was evaluated in patients with malignant fibrous histiocytoma (MFH) of bone. Since 1977, MFH of bone has been diagnosed in 17 patients. Ten patients (59%) completed treatment with 4 courses of neoadjuvant chemotherapy as follows: HD-MTX, vincristine, adriamycin, cyclophosphamide, bleomycin and dactinomycin, or HD-MTX, 4[1]-epidoxorubicin and carboplatin followed by local tumour resection (n=3), curettage-cryosurgery (n=2), amputation (n=2), or tumour resection-endoprosthetic

replacement or allograft (n=3). After recovery from surgery, an additional 6 courses of polychemotherapy, including HD-MTX in nine patients, were administered. One patient changed to cisplatin instead of HD-MTX-containing chemotherapy postoperatively. One additional patient received only adjuvant HD-MTX-containing polychemotherapy. Neoadjuvant MTX-containing chemotherapy was contraindicated in five patients (29%) due to age, cardiac insufficiency, or mental disorder. In one patient, neoadjuvant chemotherapy was stopped after 1 course due to renal failure. Treatment consisted of amputation (n=2), 1 course of chemotherapy and amputation (n=1), hyperthermic isolated limb perfussion (HILP; n=1), intra-arterial chemotherapy, radiotherapy and endoprosthetic replacement (n=1) and a combination of chemotherapy and radiotherapy (n=1). Five out of the six patients who did not receive HD-MTX based neoadjuvant chemotherapy developed metastatic disease (83%); the median time to the occurrence of metastatic disease was 17 months (range, 3 to 44). In contrast, in the 10 patients who completed treatment with HD-MTX-based neoadjuvant chemotherapy, with a mean follow-up of 9.8 years (range, 2.3 to 15.7) and a median follow-up of 10.8 years after diagnosis, no local recurrence or distant metastases were diagnosed (P<.005).
It was concluded that neoadjuvant HD-MTX-containing chemotherapy in addition to surgery dramatically improved the prognosis of patients with MFH of bone.

Chapter 5

Endoprosthetic replacement after resection of primary bone sarcomas of the lower extremity is well-established. However, little is known about the specific long-term consequences of these endoprosthetic reconstructions for the patients. Therefore, the oncological results and the survival of the endoprostheses were reviewed in 32 patients with primary bone sarcoma of the femur or proximal tibia. There were 26 high-grade sarcomas and six low-grade sarcomas. A proximal femoral endoprosthesis was used for reconstruction in four patients, a total or push-through femoral endoprosthesis in 11 patients, a distal femoral endoprosthesis in 15 patients and a proximal tibial endoprosthesis in two patients. Median survival was 10 years (range, 1.1 to 18.9) for patients with high-grade sarcoma and 8.1 years (range, 7.1 to 10) for patients with low-grade sarcomas. Distant metastases developed in seven patients (22%), all with stage IIB sarcoma, with concomitant local recurrence in three patients (9%). Five-year overall survival and 5-year disease-free survival for high-grade sarcomas were 81% and 73%, respectively. The overall endoprosthetic survival rate was 87% at 5 years, 80% at 10 years and 56% at 15 years. Median follow-up of the original endoprostheses was 8.3 years (range, 0.6 to 18.7).

Endoprosthesis-related complications occurred in 13 patients (41%); most complications were mechanical failures. The highest complication rate was found in distal femoral replacements (60%). Five endoprostheses (16%) were revised. Amputation of the involved limb was performed in four patients (13%): in two patients because of local recurrence and in the other two patients because of infection after implantation of a proximal tibial endoprosthesis. At follow-up, the median functional Enneking evaluation score was 22 points (range, 12 to 28), with the highest functional scores in patients with a distal femoral endoprosthesis and the lowest functional scores in patients with total or push-through femoral replacements.
It was concluded that endoprosthetic reconstructions gave satisfactory functional results in most long-term survivors. However, the proximal tibial and distal femoral endoprosthesis were at particular risk for long-term endoprosthetic complications requiring additional surgical procedures.

Chapter 6
The treatment for foot sarcomas is generally below-knee amputation. In selected sarcomas of the forefoot, however, transtarsal amputation according to Chopart, calcaneotibial arthrodesis according to Pirogoff, or supramalleolar amputation according to Syme can be considered. These approaches lead to an optimal functional outcome. Additional case histories are reported in this chapter.

Chapter 7
Nowadays, the majority of patients with bone or soft tissue sarcoma of the upper extremity can be treated with limb-saving procedures using combined modality therapies. However, in a small group of patients, interscapulothoracic amputation is the only surgical treatment option with either a curative or a palliative intent. From 1972 to 1991, interscapulothoracic amputation was performed on 12 patients, seven males and five females, median age 36 years (range, 13 to 82). In five patients this procedure was performed for bone sarcoma, in five for soft tissue sarcoma and in two for locoregional metastases. There were no postoperative complications. During a median follow-up of 8 years (range, 0.25 to 15), there were no local recurrences. The 5-year survival rate for soft tissue sarcoma was 80% and for bone sarcoma 30%.
It was concluded that interscapulothoracic amputation is a major ablative surgical procedure which can be performed with curative intent, but rarely with palliative intent.

Chapter 8

Combined modality therapies with limb-saving procedures can be used in the majority of patients with bone or soft tissue sarcoma of the upper extremity. In patients with a tumour in the shoulder area, interscapulothoracic amputation might be the only radical surgical treatment. However, in selected cases in which the tumour does not involve the neurovascular bundle, a limb-sparing alternative might be Tikhoff-Linberg resection. Normal function of the hand and forearm, with reasonable function of the elbow, can be maintained by this procedure. Four case histories are reported.

Chapter 9

The oncological and functional results after 11 external and 10 internal hemipelvectomies and the consequences of limb-saving treatment were studied in 21 consecutive patients with primary bone (19 patients) or soft tissue sarcoma (two patients) of the pelvic girdle. Following external hemipelvectomy, 10 patients (91%) died after a median follow-up of 1.6 years (range, 0.3 to 7.1). Isolated local recurrences occurred in three patients (27%), with concomitant distant metastasis in one (9%). Distant metastases without local recurrence developed in six patients (55%). The rates of flap necrosis and wound infection following external hemipelvectomy were both 25%. Following internal hemipelvectomy, nine patients (90%) were alive without evidence of disease after a median follow-up of 6.6 years (range, 2.3 to 16.0). Concomitant local and distant failures were found in one patient (10%). Reconstruction-related complications necessitated salvage procedures in five out of the seven patients (72%), and led to external hemipelvectomy in one.

Patients with a locally advanced pelvic girdle sarcoma who had to undergo external hemipelvectomy had a poorer prognosis than those treated by internal hemipelvectomy. Internal hemipelvectomy was not associated with an increased risk of local failure. However, long-term local complications occurred, requiring extensive surgical procedures.

Chapter 10

Reconstruction of the hip joint using a saddle prosthesis after excision of a malignant pelvic tumour is a relatively new method, which in the past has mainly been used for revision of infected hip arthroplasties. One patient with a metastatic cystosarcoma phyllodes and one patient with a chondrosarcoma of the pelvis were treated by local resection and reconstruction with a saddle prosthesis. Although the patient with the metastatic cystosarcoma phyllodes died 9 months after surgery from metastatic

disease, both patients had early recovery, with no difference in leg length and accomplished early painless complete weight-bearing with satisfactory functional results.

These two case reports illustrate the usefulness of the saddle prosthesis in limb-saving surgery for malignant tumours of the pelvis.

Chapter 11

Buttockectomy is an unusual surgical procedure for locally advanced soft tissue sarcoma in the buttock region. Nine buttockectomy procedures were performed in eight patients for primary (8) or recurrent (1) locally advanced soft tissue sarcoma of the buttocks. Adjuvant external beam radiotherapy was applied within six weeks of seven procedures. There were no postoperative complications, and no local recurrences in this series. However, distant metastases developed in five patients (63%) after a mean follow-up of 16 months (range, 6 to 25). Five-year overall survival and 5-year disease-free survival were 38% and 25%, respectively.

Buttockectomy with postoperative external beam radiotherapy may be an effective limb-saving treatment to achieve local tumour control in selected soft tissue sarcomas in the buttock region, without increased surgical and/or radiation-induced morbidity.

Chapter 12

We reviewed the oncological outcome of 40 consecutive patients with an osteosarcoma in the pelvic region registered in the files of the Netherlands Committee on Bone Tumours between 1978 and 1995. Six patients had distant metastases at initial presentation (Enneking stage IIIB), 33 patients had stage IIB osteosarcoma and one patient had stage IB osteosarcoma. Patients with metastases were treated with chemotherapy (4) or palliative procedures (2). Patients with non-metastatic osteosarcoma received surgery with (14) or without (4) (neo)adjuvant chemotherapy, chemotherapy without surgical resection (9), or palliative treatment (7). The median survival in stage IIB and IIIB osteosarcoma patients was 14 months (range, 2 to 175) and 7.5 months (range, 2 to 16), respectively ($P<.021$). Survival in patients with stage IIB osteosarcoma treated with curative intent was significantly better ($p<.0006$) than that in stage IIB patients treated with palliative intent. Two and 5-year survival rates in patients with curatively treated stage IIB osteosarcoma were 35% and 26%, respectively; distant metastases had developed in 65% of these patients. Univariate analysis revealed the following positive prognostic factors in patients with stage IIB osteosarcoma: complaints of 3 months duration or shorter

before initial presentation, tumour size of 8 cm or less, osteoblastic subtype and surgical resection of the primary tumour.

In conclusion, the prognosis of pelvic osteosarcoma remained poor despite modern multimodality treatment regimens, including neoadjuvant chemotherapy.