Chapter 9

Future perspectives
Long-term research is important to gain genuine insights into the outcomes of cancer treatment. This is the case for sarcomas, as well as for other tumors, such as testicular cancer, breast cancer, colorectal tumors, tumors in children, and hematological malignancies. Long-term research has become an important component not just of clinical cancer research such as treatment induced morbidity but also of, for example, (genetic) epidemiological research.

Soft tissue sarcomas are a rare group of cancers accounting for circa 1% of all malignancies.\(^1\) The heterogeneity of sarcoma types and the rarity of cases have hampered evidence-based randomized double-blind studies concerning optimal treatment. In the mid-seventies, several important observations reshaped the approach to sarcoma treatment. Firstly, due to more insight in the growth pattern of sarcomas, the local recurrence rate after limb salvage treatment decreased to 10-15%.\(^2\) Secondly, histology, tumor type, grade, and size were defined as predictors of survival independent of the surgical therapy. Thirdly, local recurrence was not necessarily associated with poor outcome, as more than 30% of patients could be salvaged by additional surgery.\(^2\) Finally, a major change is the shift from surgical resection alone as the treatment of sarcomas to the use of multimodality treatment: surgery, radiation and/or chemotherapy.\(^3\)

This long-term research, into the value of regional perfusion as an induction treatment for primarily non-resectable soft-tissue sarcomas of the extremities, has also provided a lot of information that has already contributed to the improvement of this cancer treatment and will lead to further improvements in the future. The central issue should be the reduction of short-term and long-term complications caused by, on the one hand, extensive surgical resections and, on the other hand, the high radiation dosage. Tissue transposition and optimization of radiotherapy will be key elements in this endeavor. Years ago, we investigated the possibilities of intra-arterial chemotherapy in combination with radiotherapy.\(^4\) Although this treatment was highly effective, the complications were severe.\(^5\) Perfusion treatment in itself only causes minimal morbidity. Possibly, regional perfusion may be replaced by regional infusion, as is currently being developed for melanomas.\(^6,7\) Using this technique, groin catheters are inserted percutaneously into the blood vessels. After isolation of the lower limb with a tourniquet, the intra-arterial infused chemotherapy will be manually flushed without using an oxygenation system. The major advantage of the minimally invasive infusion treatment is the possibility to be repeated and to evaluate it non-invasively with Positron
Emission Tomography (PET). If necessary, pre-operative radiation followed by surgery may be preferred to surgery followed by radiotherapy.

There have been several breakthroughs in diagnostic imaging and treatment, resulting in improved limb salvage and survival rate, as summarized previously in this thesis. New technologies of high interest for the surgical oncologist are already available or will become available. Recently, spiral computed tomography (CT) was introduced, providing the surgeon with optimal three-dimensional images (3D-images) and further facilitating preoperative treatment planning. Computer-assisted navigation systems have become available, which are extremely useful in the intra-operative treatment planning of sarcomas located in or near the pelvic girdle or vertebral column. Improvements in the radiodiagnostics of soft tissue sarcoma have had a major impact on the staging and planning of surgical treatment. Imaging provides the clinician with crucial information in the diagnosis, staging, treatment planning, treatment evaluation, and post-treatment assessment of patients with soft tissue sarcoma. Magnetic Resonance Imaging (MRI), including contrast-enhanced sequences, is usually preferred for evaluating the primary site in extremity sarcomas and lesions of the head and neck. CT is generally preferred for imaging of the chest, abdomen, and pelvis, either in the evaluation of the primary site in those regions or for identifying metastatic disease. The experienced radiologist can often suggest a specific diagnosis or narrow the differential diagnosis from the imaging characteristics, particularly with MRI. It is imperative that imaging be performed in a manner specific for the evaluation of soft tissue masses, and before biopsy or surgery, to provide the most accurate preoperative assessment and treatment planning.

Although PET is not directly useful for diagnosing soft-tissue sarcomas, it may sometimes be helpful in the differential diagnosis of benign and malignant tumors. Its potential mainly lies in the area of therapy evaluation, and as such it is already being used with gastrointestinal stroma cell tumors. Other areas of application might include Ewing’s sarcoma and rhabdomyosarcoma and the evaluation of new induction chemotherapy treatments. PET-MRI provides a very good insight into local tumor growth processes, the presence of metastases and therapy evaluation. Figure 1. In patients with advanced solid tumors, phase I studies are being performed to measure the effect of oral angiogenesis inhibitors like AG-013736 with dynamic contrast-enhanced MRI as a pharmacodynamic measure of response. Using the biologic activity of tumors will optimize diagnostic as well as therapeutic options in the future.
Sentinel node biopsy has become a tool for the staging and treatment of breast cancer and will probably soon be used with melanoma also, while research is being conducted into its relevance with gastrointestinal tumors and lung cancer.\textsuperscript{11} Sentinel node biopsy may also be used for staging sarcomas that have a slightly higher risk of developing lymphogenic metastases, such as synovial sarcoma, epitheloid sarcoma, rhabdomyosarcoma, and clear cell sarcoma.

The transition from conventional radiotherapy to three-dimensional conformal radiation therapy (3D-CRT) means a reduction in the volume of healthy tissue receiving a high dose in favour of the radiation target volume. The technique that is already being used with breast cancer, the simultaneous integrated boost, may in future also be applied to sarcomas. It involves applying more radiation to a small area, which reduces the overall treatment time. By contrast, the move from 3D-CRT to intensity modulated radiation therapy (IMRT) involves more fields, while the dose-volume histograms show that, as a consequence, a larger volume of normal tissue is exposed to lower doses. In addition, the number of monitor units is increased by a factor of 2 or 3, increasing the total body exposure, due to leakage radiation. Altogether, a disadvantage of IMRT is likely to be the almost double incidence of second malignancies compared with conventional radiotherapy from about 1\% to 1.75\% for patients surviving 10 years.\textsuperscript{12}

The problem of radiotherapy has been, and will remain, a two-edged sword: although it is an important component of and for local tumor control, it may also induce secondary tumors and, in the long term, may also lead to fibrosis, with reduced limb function as the ultimate outcome.

What we have learnt by now is that reconstructive plastic surgery should be used on a much wider scale. Reconstructive plastic surgery procedures through tissue transfer and microvascular surgical techniques play a key role in coverage of major defects and prevention of wound-healing problems, and reduces the side effects of radiation treatment.

Sarcomas are an interesting tumor model. They give the word “radical” a new dimension. “Radical” from a purely surgical point of view, with “radical” excision of the root or source of a morbid process, appears to be highly important in the improvement of patient survival and the prevention of local recurrence. In the case of sarcomas, this has led to very extensive surgery, major amputations, and unique methods of reconstruction.
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An example of one of the first successful “radical” operations, a hemipelvectomy, was reported by Charles Girard in 1895, for a recurrent sarcoma. Pringle stated in 1916 that this procedure “entails the greatest mutilation for which surgery is responsible”. Nowadays these very extensive resections are preceded by more accurate preoperative assessment and followed by complex reconstructive procedures. This is shown in Figure 2.

Figure 1 PET-MRI provides a very good insight into local tumor growth processes and metastases as illustrated here in an upper leg with a locally advanced extremity sarcoma before and after isolated hyperthermic limb perfusion with TNFα and Melphalan. “Radical” also becomes a more abstract term referring to a fundamental shift in our paradigms on cancer biology and the outcome of the patient, both oncologic and functional.

Figure 2 En bloc breast and chest wall resection for a high grade sarcoma.
(A) Preoperative view of an angiosarcoma located in the left breast and thorax
(B) The surgical defect, including a major portion of the chest wall
(C) Reconstruction of the chest wall defect with polypropylene mesh, omental plasty and split skin graft.
A patient with a sarcoma located in the chest underwent chest wall resection with subsequent reconstruction. Without doubt, the most radical of all potential sarcoma surgeries is translumbar amputation or hemicorporectomy, which was performed for the first time in 1962.15

This leads us to the other reason why “radical” is an interesting model. Sarcomas are an interesting tumor model because they also cause radical changes in other areas than surgery, due to their remarkably aggressive growth and metastasis pattern. In these cases, “radical” means “departing markedly from the usual or customary”. The treatment of what used to be classified as leiomyosarcoma of the intestines but is now named gastrointestinal stroma tumor (GIST) in accordance with new insights into the condition, for example, made the cover of Time Magazine (volume 157, no 21, 2001). The selective tyrosine kinase inhibitor Imatinib, the new “target drug”, heralded the “new war against cancer”.

Angiogenesis inhibition remains a promising approach for new drug development in cancer therapy. In fact blocking vascular endothelial growth factor (VEGF) has already been shown to have potent antivascular effects and significant clinical activity as evidenced by an improvement in overall survival when combined with standard chemotherapy e.g. in colorectal cancer.16,17 Beside that, there are also trials with Ecteinascidin-743 (ET-743; also known as trabectedin and Yondelis), an isolated, purified, and synthesized extract of the Caribbean marine tunicate Ecteinascidia turbinata. ET-743 would inhibit cell proliferation and be potent against a variety of soft tissue sarcoma cell lines, even those resistant to many other cytotoxic agents.18

With the improved treatment of aggressive cancers such as soft tissue sarcomas, the number of cancer survivors is increasing gradually and they reach a higher age. This has several implications which may also lead to further insight into (genetic) cancer epidemiology. First, these patients often appear to be at increased risk of developing other malignancies later in life. This may either be due to chance occurrence thanks to increased life expectancy, or to environmental factors that also caused the first cancer or to long-term carcinogenicity of the therapy that was given for the first cancer. However, second malignancies might also occur due to the fact that the initial cancer arose as part of a genetic cancer predisposition. It can be expected that “new” hereditary cancer syndromes with only moderately increased cancer risks, will be delineated in the near future, if survivors of childhood cancer are monitored adequately. It will, however, need large datasets and long-term follow-up to establish these tentative cancer risk genes.
The second implication of improved cancer treatment and survival is that more patients will reach adulthood. Since in the treatment of cancer in children and young adults much attention is given to preserving fertility, these cancer survivors are now more often able to have children themselves. This may lead to a second way to recognize the possible genetic nature of their cancer (syndrome): if subsequently the same or related malignancies are diagnosed in their offspring. Long term follow-up data will be of great value here as well. The fact that increased life expectancy due to improved treatment enables the occurrence of subsequent cancers in the same patient, is most clear in cases with ‘early onset’ cancers, e.g. retinoblastoma and soft tissue sarcoma. These types of cancer are however relatively rare in the general population. The same effect of improved prognosis can be expected in common cancers that are diagnosed at later age, such as colon cancer or breast cancer. Since these types of cancer are much more frequent, the contribution of second and third cancers in this population to general cancer incidence may become substantial. It is through longevity that we will be able to recognize underlying genetic predispositions to late-onset types of cancer in this population. These may be “high risk” genes that come to clinical expression at later age, but they may also be “moderate risk” genes with an gradually increasing age-related penetrance. In the view of increasing life expectancy in the general population, the contribution of such genes to the total cancer incidence and the implications in general practice and health care are hard to predict and deserve further research. Since many high-grade tumors morphologically manifest themselves as undifferentiated tumors, the identification of chromosomal aberrations may be important for the final diagnosis and classification. With the help of micro-array analysis, which allows the simultaneous study of the expression of thousands of genes, it may be possible to realize a new classification, better diagnostics, and more effective therapies in the near future.

In essence, the new “radical” treatment for sarcomas involves radical resection, but also complex reconstruction and limb salvage techniques. Major contributions to this treatment approach include microvascular plastic surgery techniques, an increased emphasis on functionality, the development of prosthetic materials, neurovascular reconstruction, down-staging with isolated limb perfusion, and the concept of limb remodelling and replantation. The development of new kinase inhibitors and new angiogenese inhibitors might change in the near future the treatment approach and outcome of locally advanced and disseminated soft tissue sarcomas.
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References


