Future perspectives
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Radiotherapy in extremity soft tissue sarcoma

Surgical resection of the tumor combined with external beam radiotherapy (EBRT) is standard of care in most localized resectable extremity soft tissue sarcomas (ESTS) nowadays. EBRT is essential in most patients to obtain sufficient local tumor control, and can be administered either in the pre- or in the postoperative setting. The preoperative timing of EBRT is a known risk factor for the development of a major wound complication following surgical resection of the tumor remnant. Whereas postoperative EBRT induces more long-term fibrosis, edema and joint stiffness due to the larger radiation fields and higher doses, resulting in a detrimental functional outcome for these patients. Several advances in EBRT regimens and techniques in the treatment of ESTS are under current and ongoing investigation with the ultimate goal to achieve optimal oncological results while reducing treatment-induced short- and long-term morbidity.

Although data regarding hypofractionation of preoperative EBRT in ESTS is scarce, recent results seem to be promising. A 5x5 Gy hypofractionated preoperative EBRT regimen followed by surgical resection of the tumor within one week was found to be oncologically safe, while only 7% of these patients required a surgical intervention for the treatment of a wound complication in this series. Furthermore, the preliminary results of an ongoing phase II trial (NCT02701153) on preoperative hypofractionated EBRT were recently presented at the Connective Tissue Oncology Society Annual Meeting, showing a 17% major wound complication rate in the patients treated. These wound complications rates seem to be lower than the 30-35% major wound complication rate following conventional fractionated (25x2 Gy) preoperative EBRT. Therefore these new fractionation regimens might provide a useful alternative for the conventional EBRT treatment schemes.

Long-term morbidity resulting in a deteriorated functional outcome seems to be more pronounced in postoperative irradiated patients, although, the development of a major wound complication also is associated with an impairment of functional outcome. To reduce the long-term treatment-induced morbidity following postoperative EBRT, a randomized controlled trial was initiated in which patients are randomized into; Arm A, 25x2 Gy preoperative intensity modulated radiation therapy (IMRT), or Arm B, 25x2 Gy postoperative IMRT followed by a 8x2 Gy boost in case of positive surgical margins (NCT02565498). The conventionally used postoperative dose of 60-70 Gy
EBRT techniques are subject to advancements as well. The above mentioned randomized trial compares the use of pre- and postoperative IMRT. Considering the oncological outcome, IMRT was shown to be associated with a significantly reduced local recurrence risk when compared with the commonly used three-dimensional conformal radiotherapy (3D-CRT). Moreover, a phase II study tended to show a reduced wound complication risk following preoperative IMRT in comparison with 3D-CRT, as IMRT enables the radiation oncologist to deliver adequate radiation doses to the tumor volume, while it allows a dose reduction in tissues surrounding the tumor. This reduced wound complication risk following IMRT needs further validation in larger prospective trials. Besides the technical advancements in photon-based EBRT, proton beam radiotherapy (PBT) is used more commonly in soft tissue sarcoma (STS). In some cases PBT might be advantageous over photon-based EBRT owing to the unique energy absorption profile. The energy of the protons is delivered to a narrow range at the depth of the tumor, this peak in energy deposition is also known as the Bragg Peak. Beyond, or distally from the Bragg Peak, almost no energy is delivered, which allows for a significant reduction of the radiation dose delivered to the normal tissues surrounding the tumor. The selection of patients that might benefit from PBT over the commonly used photon-based EBRT is challenging and in the Netherlands a model-based approach has been developed, which was adopted by the Dutch Health Council. PBT is currently under ongoing investigation (NCT01561495) for ESTS, but its role might be limited as 3D-CRT and IMRT techniques seem to be sufficient for adequate radiotherapy planning and treatment in most ESTS patients, while PBT seems to be beneficial in paediatric and retroperitoneal sarcomas.

**Plastic surgical reconstructions and wound management**

Plastic surgical reconstructions have been used to obtain wound closure following extensive surgical resections in ESTS. In preoperatively irradiated patients, flap reconstructions permit the transposition from healthy tissue to the previously irradiated surgical area which results in an alteration in the risk for the development of a major wound complication. Although direct plastic surgical reconstructions may complicate the surgical procedure, they also seem to lower the major wound complication risk in preoperatively irradiated patients. Hence, in patients who underwent direct reconstructive surgery, the preoperative radiotherapy was not associated with major wound complication development. Further studies considering the appropriate patient selection for plastic surgical reconstructions, as well as studies investigating the ‘protective’ influence of direct flap reconstructions are necessary. Besides the advancements in EBRT techniques and plastic surgical reconstructions, several improvements in the postoperative wound care are currently under investigation to minimize the risk for the development of a major wound complication. The use of postoperative hyperbaric oxygen therapy (HBOT) is currently under investigation in a randomized trial (NCT03144206). This trial divides preoperatively irradiated patients into two groups. Patients in group I undergo the administration of HBOT directly following the surgical resection of the tumor, while patients in group II do not. HBOT comprises an intensive treatment commonly consisting of 20-40 daily sessions, during which the patient breathes 100% oxygen in a pressurized (2-3 atmosphere absolute pressure (ATA)) chamber. During this treatment the partial pressure of oxygen in the patients’ blood and accordingly in the damaged tissues is extremely increased, thereby it was shown to be beneficial for patients with ischemic wounds and late radiation-induced tissue injuries. Secondly, negative pressure wound therapy (NPWT) is investigated in preoperatively irradiated lower ESTS patients (NCT02638298). Patients are randomized into the use of NPWT or not. Accordingly, following the surgical resection of the tumor and closure of the wounds, NPWT is applied for half of the patients, while the other half of patients undergo traditional wound management with dry gauzes. NPWT provides gentle suction on the wound, and its influence on the development of postoperative wound complications is investigated.

**High risk localized extremity soft tissue sarcoma**

Patients’ oncological outcome following extremity soft tissue sarcoma treatment is mainly determined by the tumors potential to metastasize distantly, mainly to the lungs. Accordingly, several studies investigating the influence of (neo)adjuvant chemotherapy in high risk localized, non-metastatic, ESTS have been conducted during the last years. The data available is somewhat inconsistent and conflicting, making the implementation of standardized (neo)adjuvant chemotherapy in localized ESTS troublesome. An improvement in oncological outcome was found for a subgroup of localized ESTS patients treated with (neo)adjuvant chemotherapy, but further research is needed to correctly identify those patients who might benefit from the treatment.

**Locally advanced extremity soft tissue sarcoma**

The treatment of locally advanced ESTS is particularly demanding and multiple regional chemotherapy, i.e. hyperthermic isolated limb perfusion or isolated limb infusion, based regimens have been used to obtain limb-salvage to date. As recently presented in a large systematic review various chemotherapy agents, regimens and
Amputation in extremity soft tissue sarcoma

Nowadays, limb-salvage can be achieved in most ESTS patients, even in those patients with locally advanced tumors. However, when limb-salvage treatment fails, amputation of the affected limb is the only treatment option that remains. The level of amputation is mainly determined by the extensiveness of the tumor. However, also patients’ functional outcome following the amputation should be considered. The involvement of a rehabilitation specialist at an early stage in the amputation decision-process facilitates the determination of adequate amputation levels, a discussion regarding potential prosthesis use in the future and a patient-tailored postoperative rehabilitation program which all will improve the patients’ functional outcome following the amputation.

Limb-amputation in the metastatic setting should be reserved for patients suffering from severe symptoms of the local tumor, as survival following palliative amputation is generally poor, i.e. <8 months.

Histology based treatment

Approximately 50 histologic STS subtypes are identified in the latest World Health Organization classification, and therefore a histology based treatment seems to have a large potential for these patients. For instance, the proven radiosensitivity of myxoid liposarcomas led to the standardization of preoperative EBRT in these patients. Besides, a preoperative hypofractionated, 5x5 Gy, EBRT regimen followed by surgical resection of the tumor within one week was found to be effective in myxoid liposarcomas of the extremities. As a result of this, a radiotherapy dose reduction study in myxoid liposarcomas was initiated (DOREM-study, NCT02106312) and first results are awaited. The dose reduction of preoperative EBRT, to a total dose of 36 Gy, in these tumors must be proven to be oncologically safe, and alongside, this dose reduction might result in a decreased major wound complication risk in this specific subtype. As mentioned above, neoadjuvant chemotherapy is currently under ongoing investigation for high risk localized ESTS. In the metastatic setting the chemotherapy is patient-tailored and among others based on the histologic subtype. Subsequently a study was conducted randomizing high risk localized ESTS patients into a standardized neoadjuvant chemotherapy regimen (control arm) or into a histotype-tailored regimen. Surprisingly, no survival benefit for the histotype-tailored regimen was shown. Further studies regarding the sensitivity to (neo)adjuvant chemotherapy regimens for specific histologic subtypes are warranted.

Metabolic and histopathological responses in pretreated extremity soft tissue sarcoma

The evaluation of treatment efficacy through the measurement of treatment responses will take a larger part in the contemporary treatment of ESTS, as the use of neoadjuvant treatment regimens i.e. chemotherapy, hyperthermic isolated limb perfusion and/or radiotherapy is rising. This response evaluation either prior to surgical resection of the tumor through imaging modalities or following the surgical resection through the histopathological evaluation of resection specimens needs to be standardized and validated.

The validation of parameters to evaluate the metabolic tumor activity on fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography (18F-FDG PET-CT) scans needs to be accompanied by the validation of volume of interest (VOI) delineation techniques. The VOI used directly affects the values measured for the various parameters. The search for an robust and easy to implement VOI delineation technique for these heterogeneous tumors accompanied by the identification of the most predictive PET derived parameter within this VOI is needed. Alongside these advancements in PET imaging, also progression in magnetic resonance imaging (MRI) are expected. A recent feasibility study in 11 lower ESTS patients who underwent preoperative chemoradiotherapy showed that it might be possible to predict histopathological response using dynamic contrast-enhanced MRI.

The standardization of the histopathological examination of pretreated STS by the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG), including a 5-tier response score is a step forwards. However, further research needs to demonstrate the predictive value of this response score. Several studies including high risk localized ESTS patients whom are treated with neoadjuvant chemotherapy are currently ongoing. Hopefully, the results of the histopathological examination of these tumors will provide more insight in the response of these localized tumors including the relevance of the response induced by the neoadjuvant treatment. Hence, a good or excellent histopathological tumor response in a high risk localized tumor might result in a prolonged overall survival as micro metastases, not yet visible on the staging CT-chest scan, are treated as well. In contrast, a poor histopathological response of the primary tumor might be a reason to intensify the local treatment or to choose an alternative chemotherapy regimen in case of development of distant metastases during follow-up.
After the validation of both metabolic and histopathological responses in pretreated ESTS, it might be possible to alter the standardized treatment regimen into a patient-tailored approach based on treatment efficacy as measured at the response evaluation.

Centralization of ESTS treatment
The treatment of ESTS has changed significantly over the past decades, from ablative surgery in the mid-1980s to a multimodality limb-saving approach including, radiotherapy, hyperthermic isolated limb perfusion, neoadjuvant chemotherapy and extensive surgical resections combined with plastic surgical reconstructions. These advancements in ESTS treatment have complicated the decision making process and subsequently differences in treatment approaches and outcome have originated between high-volume and low-volume (<10 resections annually) hospitals. A recently published study showed less positive surgical margins and even an improvement in overall survival for STS patients treated in high-volume hospitals. Furthermore, adherence to clinical practice guidelines was found to be associated with an increase in progression-free and overall survival. In the future, further centralization of ESTS treatment will facilitate an evidence based patient-tailored treatment following discussion in a multidisciplinary tumor board. Consequently, this will contribute to a further improvement in the treatment and outcome of STS patients. Besides, further centralization of daily sarcoma care strengthens the opportunities to conduct further prospective research and to reduce treatment costs. In the Netherlands the treatment of STS patients can be further centralized into five specialized sarcoma-centers enabling clinicians to provide optimal sarcoma care.

References