Referral patterns, prognostic models and treatment in soft tissue sarcomas

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Chapter 12

Future perspectives

Tumorgenesis and targeted therapy

The future of soft tissue sarcoma treatment relies in the increasing knowledge of sarcoma tumorgenesis. In the last few decades, advancement in technology has given us the opportunity to improve our understanding why cells start to grow uncontrollably. Different pathways and signaling factors that contribute to the development have been revealed. [1-3] Another important insight that has had a major impact on clinical practice is the discovery of new distinctive sarcoma subtypes based on genetic differences. Ten years ago, the classification of sarcoma subtypes existed out of 50 different soft tissue sarcomas [4], based on morphological characteristics, nowadays we know that there are additional subtypes, most of which have specific biologic behaviors and responsiveness or resistance to therapy, leading to an explicit need of individualized therapy.

A booming topic in sarcoma treatment is targeted therapy. Probably, one of the more famous discoveries was the c-kit mutation in gastrointestinal stromal tumors, and the spectacular responsiveness of these tumors to imatinib. [5, 6] Till than, only systemic chemotherapy was available, e.g. doxorubicin and paclitaxel, which were limited effective in only some sarcoma subtypes. The finding of targeted therapy like imatinib, which was really effective and at the same time less toxic on non-cancer cells, gave rise to an exploding start of innovative molecular science. Other pathways, leading to either loss of tumor suppression, e.g. p53 mutation, or tumor progress, e.g. up regulation of vascular endothelial growth factor (VEGF) regulating tumor angiogenesis, have been reported. [7, 8] This led to the identification of new targeted drugs such as pazopanib, which targets VEGF receptors, thereby inhibiting angiogenesis in for example leiomyosarcoma [9] and trabectedin in myxoid liposarcoma [10]. Some of these drugs have now also been approved in clinical setting. Although, these findings are helpful and promising in improving sarcoma treatment, it has to be noted that in terms of disease free and overall survival the results are sometimes limited to only a few months extra. [9] Therefore, new drugs have to be critically assessed, taking into consideration the real profit for patient survival, quality of life, and also taking financial costs into account.

Furthermore, as is the case with systemic chemotherapy, resistance also develops for targeted therapies and may be caused by secondary genetic alterations.

Resistance to imatinib in patients with GIST for example has become a new problem; therefore, the EORTC is currently performing phase II trials investigating cabozantinib in patients with metastatic disease and regorafenib as first line treatment. [11]

In collaboration with colleagues in Sweden the genetic differences and possible targeting pathways in angiosarcomas were explored, which are a particular difficult to treat subtype of sarcoma. Angiosarcomas can either develop as a primary tumor or secondary to earlier treatment, like radiotherapy, and are morphologically indistinguishable. A total of 26 primary and 29 secondary angiosarcomas were studied in this collaboration using whole genome analysis and validated with immunohistochemistry. [12] Although several years ago whole genome sequencing was costly and took years to give results, today, the technology is more efficient, and genome sequencing is executed in days and is financially more appealing for to be used in clinical practice. The asset of whole genome analysis is that previously unknown genes may be identified as contributing to sarcoma development. The above mentioned study showed that in total 103 genes were significantly deregulated between primary and secondary angiosarcomas. Secondary angiosarcomas showed upregulation of *MYC, KIT* and *RET* and downregulation of *CDKN2C*. Functional annotation analysis identified multiple target genes in the receptor protein tyrosine kinase pathway. This implies possibilities for diagnostic application and a mechanistic basis for therapeutic evaluation of RET-kinase-inhibitors. For future studies it would be relevant to investigate possible angiosarcoma treatment strategies.

Another challenge in precision medicine is the identification of markers predictive of response. Since treatment of sarcomas is associated with short and long term side effects, an optimized risk measure is central. This motivates sarcoma specialists to identify grading systems and prognostic models based on tumor characteristics using immunohistochemistry technique, leading to the well known grading systems proposed by the French Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) and the National Cancer Institute (NCI). Now that genetic profiling helped us defining distinctive tumor characteristics, it seems obvious that these will be incorporated in prognostic models to define patient categories benefiting from therapy. [13] And in addition to help predict patient survival. [3]

Improving quality of life of sarcoma patients and organization of health care

Sarcoma patients are willing to endure heavy treatment regimens in order to survive. Nevertheless, quality of life for cancer patients is becoming a more important topic in clinical practice discussing the different treatment options. Some side affects are under exposed, and sometimes due to their rare incidence a challenge to treat. Despite an usually thorough follow up after treatment, in which side effects are recognized and treated by the individual doctor, not much of this information is shared among them. Recording treatment related effects, its treatment and publishing the results are necessary to improve their treatment.

In the case of locally advanced soft tissue sarcoma of the extremities, in which surgery alone is not sufficient and a treatment schedule of hyperthermic isolated limb perfusion (HILP), surgery and usually in addition radiotherapy is given, patients are subjected to an exhausting long treatment schedule of several months. To improve this treatment schedule the University Medical Centre Groningen initiated several years ago a more efficient treatment schedule, starting with HILP, a short course of radiotherapy (12x3GY), shortly followed by surgical resection (IRB protocol review case-number 2010/299). The whole treatment time lasted no longer than 6 weeks. [14] These patients are now studied to compare outcome, in terms of disease free and overall survival and side effects, to patients treated with the more extensive schedule. This is an on going study, but intermediate analysis after ten patients has shown the same treatment outcome till now.

Another important subject in this analysis is how the different treatment modalities affect the tumor. After each modality an FDG-PET scan is performed and tumor necrosis is measured. In this way the additive value of high dose chemotherapy in the HILP setting and preoperative radiotherapy on diminishing tumor activity can be studied in a non-invasive manner and compared with the final pathology of the resected specimen.

Furthermore, final tumor response will be measured in the specimen after surgery. Recently, the EORTC-STBSG proposed a new classification to evaluate the histopathological tumor response. Instead of measuring tumor necrosis, vital

tumor cells are scored and related to treatment response. This proposal has to be validated, as is currently done by joined effort of the surgical and pathological department at the UMCG.

Organization of health care of sarcoma patients deserves also attention. Due to its rare entity, patients and physicians can cause delay in treatment, which eventually can lead to decreased chances of survival. In order to see where these problems arise, it is necessary to look into the time schedules of referrals. Analyzing published research about this problem, it is clear that this is a worldwide problem, and confined to several types of sarcomas. Recognizing the problem is a good first start, however, now we need to continue solving the problem by educating doctors about sarcomas, and determine clear referral requirements. In Sweden it has been spread throughout the country that all soft tissue tumors larger than 5cm or deep seated should be referred to a sarcoma centre before treatment is started [15]. This has not led to an overwhelming offer of patients with tumors to surgeons at sarcoma centres [16], but did lead till less 'whoops' procedures.

At the sarcoma centre itself, further improvement of efficient health care is equally important.

In 2012 a treatment model for sarcoma care in the Dutch medical society was developed by the Department of Surgical Oncology in close collaboration with the other team members of the UMCG Sarcoma working party. [17] The essence of this model was based on specialty transcending care. In the University Hospital in Groningen, sarcoma patients are treated by a sarcoma team consisting out of professionals with expertise in each necessary field; medical oncology, nuclear medicine, orthopaedic surgery, pathology, pediatric oncology, radiation oncology, radiology and surgery. Their aspiration of improving health care is limited by the fact that hospitals work with department-regulated care, in which surgery for example, is managed by a different team of people as is radiation oncology. It was proposed to make the sarcoma team in the lead and make the sarcoma team responsible for the delivered sarcoma care, the cost of diagnostic and treatment and the overall quality of care. In order to improve care efficiency, a template was made for referral of patients to the sarcoma centre and sarcoma meetings (Fig .1).

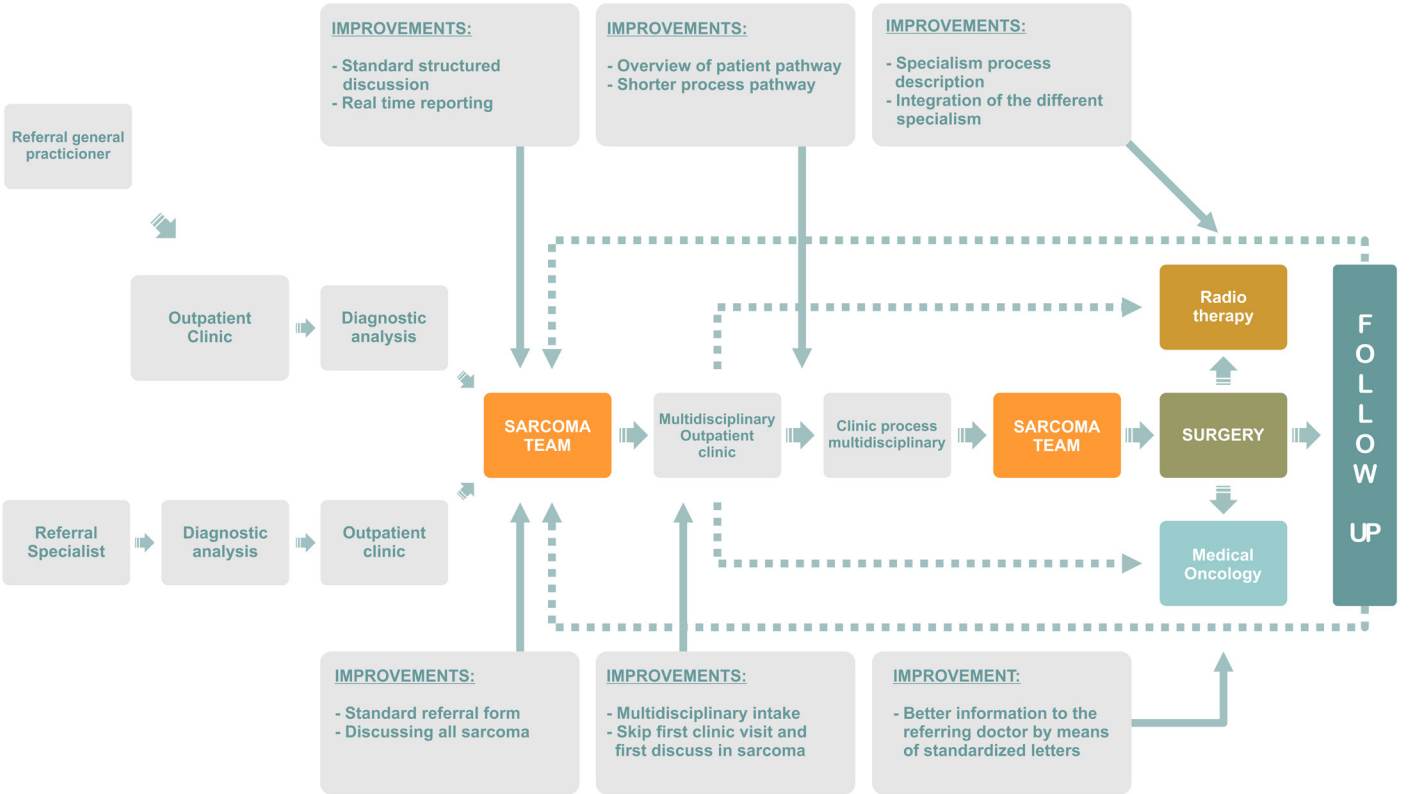

Figure 1. Flow diagram showing referrals and clinical process

Furthermore, to evaluate team efforts to improve sarcoma care, key performance indicators e.g. treatment outcome, patient and doctor satisfaction, were compiled, which in addition will enable the team to show results publically. Giving the professional the responsibility and autonomy for health care will not only improve quality of care but will also be cost effectively. Future research of the implementation of 'Resultaat Verantwoordelijke Eenheid' ('Result Responsible Unit') will determine whether or not this is the case.

A contributing aspect in the previously mentioned model is that professional autonomy leads to better job satisfaction for the professional. [18] In the last years worldwide, and more recently here in the Netherlands, 'fit to perform' became an important issue among medical professionals. It appeared that burn out or distressed feelings are high among medical trainees and professionals. [19-21] Moreover, there is a relationship between burn out and medical errors [21]. Therefore, it is not only in the interest of the medical professional but also from a point of view of patient safety, that medical professionals are enabled to be fit to perform. Many years, studies have focused on eliminating stressful factors, like diminishing working hours. However, more recent studies have linked improving work engagement with better job satisfaction, reporting professional autonomy as an important aspect. [22]
In concordance with previous findings the future should be with the medical professionals in the lead.

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