SARCOMA

Systemic Therapy in Sarcomas: Integrating the Old with the New

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Do Our Current Clinical Trial Designs Help to Guide Clinical Practice?

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OVERVIEW

There is a markedly increasing contrast between the current refinement of nosologic classification of sarcoma integrating molecular typing with a growing number of subtypes and the usually standardized approach proposed in clinical practice guidelines for both local and systemic treatment. Although gastrointestinal stromal tumor (GIST), dermatofibrosarcoma protuberans, and a few other subtypes now have specific therapeutic strategies, the majority of sarcomas are still lumped together in clinical trials investigating novel therapeutic options. These trials may not provide sufficient information to guide routine clinical practice. Proof-of-concept trials exploring a targeted agent in a selected molecular subtype, randomized phase II trials, and trials focusing on histologic subtypes—all integrating translational research and aiming to identify the mechanisms of sensitivity and resistance to the treatment—are needed. This paper discusses the limitations of previous clinical trial designs to guide clinical practice in this complex context.

Soft tissue and visceral sarcomas (STSs) constitute a heterogeneous group of neoplasms originating from mesenchymal tissues, accounting for approximately 2% of all cancers, with an incidence close to 5.9/100,000/year.1,2 The histologic classification is complex, gathering more than 50 different histotypes and even more subtypes. Another layer of heterogeneity is represented by the presence of recurrent cytogenetic abnormalities such as translocations, amplifications, and tumor suppressor gene losses.1 These molecular alterations further fragment the already complex world of sarcoma histotypes into a myriad of different entities, whose clinical behavior after local treatment and response to treatment can be notably different. GIST with platelet-derived growth factor receptor alpha (PDGFRA) D842V mutations has a usually indolent disease course but, when metastatic, exhibits a complete resistance to imatinib.3,4 In 2013, molecular biology is an essential tool to classify the disease, prognosticate its outcome, and to predict its sensitivity to cytotoxic treatment and targeted therapies.

Despite this heterogeneity, most STSs are still treated according to clinical practice guidelines, which often propose a similar approach across histotype.5–8 The emergence of novel targeted therapies has led to rationally based, personalized approach to management for a minority of sarcomas.9 It can be expected that this situation will rapidly evolve, with the rapid emergence of novel molecular signatures of several sarcoma types.10

For sarcoma management, the physician is facing the following challenge: although the clinical practice guidelines most often propose a one-size-fits-all approach for all sarcomas, there is emerging evidence that treatment should be adapted to the histologic subtype and guided by the presence of a driver mutation. Future clinical research must address these challenges of defining standard treatments in a myriad of very rare histologic and diverse molecular entities. This paper will discuss whether previous clinical trial designs help to inform clinical practice in this complex context.

PHASE III CLINICAL TRIALS IN AN UNSELECTED POPULATION OF PATIENTS WITH SARCOMA

Are large, phase III trials that randomize all sarcoma subsets still useful to inform clinical practice? The European Organisation for Research and Treatment of Cancer (EORTC) 62012 trial is the last and largests trial of a series comparing single-agent doxorubicin to the combination with ifosfamide in first-line treatment for patients younger than age 60. The primary endpoint was overall survival (OS), and the trial was negative in this perspective (median 12.8 to 14.3 months, p = 0.07). However, a significant improvement of progression-free survival (PFS) and response rate was observed (p = 0.003), at the expense of an increase in hematologic toxicity.11 The interpretation of this clinical trial is the topic of intense debates, but most experts would agree that this trial demonstrates that combination treatment is not the standard treatment for all patients. Subsets of young patients with advanced disease may benefit from this approach when rapid response or volumetric response is the therapeutic goal.
trial is therefore very informative in this perspective but is not sufficient to identify precisely the candidates for a combination treatment approach.

Gemcitabine had not been recognized as a highly active treatment in phase II trials in unselected populations of patients, possibly because of a suboptimal schedule used in some early studies. Despite this, the combination of gemcitabine and docetaxel given in the first- or second-line metastatic setting was found to improve PFS and also OS compared with gemcitabine alone in patients with all sarcoma subtypes. This study used a Bayesian adaptive design, which is unusual in clinical research, and the interpretation of its results has for this reason been debated. A subsequent small, randomized, phase II trial also comparing gemcitabine with gemcitabine/docetaxel but performed in only leiomyosarcoma (LMS; uterine and non-uterine) failed to demonstrate an improvement of PFS or OS. Finally, the demonstration of the utility of gemcitabine came from the GEIS study comparing gemcitabine and dacarbazine with the standard dacarbazine regimen. This study demonstrated an improvement in OS and PFS with the combination. Altogether, these studies are informative in that they demonstrate the utility of gemcitabine in advanced sarcoma. Whether the agent should be given alone or in combination may depend on the histologic subtype. The selection of the agent to combine with gemcitabine, docetaxel, or dacarbazine varies across countries, but no precise guidance can be provided for selected histologic subsets or for the non-LMS group of sarcomas.

The utility of the mTOR inhibitor ridaforolimus has been explored in a very large randomized trial compared with placebo in the maintenance setting after achievement of at least stable disease or better with cytotoxic chemotherapy in first-, second-, or third-line treatment. Most histologic subtypes of STS and selected subsets of bone sarcoma were also included. The study was positive for its primary endpoint, showing an improvement in PFS in all subsets of patients but no improvement in OS. Although significant, the improvement of PFS was considered of limited clinical significance by health authorities, and the drug is currently not approved (hazard ratio = 0.72, p = 0.0001, median PFS 14.6 vs. 17.7 weeks. Ridaforolimus previously showed antitumor activity in sarcoma when tested in an uncontrolled, phase II trial, but no reliable predictive biomarker of response was identified. Biomarkers could have been used for selection purposes and may have helped to identify the sensitive patient group, possibly spanning a variety of histologic subtypes sharing common key biologic alterations.

In the Palette study, pazopanib was compared with placebo and had no crossover in patients with advanced sarcoma progressing after doxorubicin treatment. The only nosologic selection applied was the exclusion of liposarcoma (LPS). The trial was positive for its primary endpoint, PFS. No biomarker could be investigated in this study. Whether all patients benefit from pazopanib to the same extent, however, remains unclear. This will be an important issue to be explored if pazopanib is studied in an earlier setting. In view of the results obtained with other targeted agents for vascular endothelial growth factor receptor 2 (VEGFR2), selected subtypes of sarcoma—such as solitary fibrous tumors or alveolar soft part sarcomas—may have a specific sensitivity to this class of compounds.

Altogether, large, phase III trials in unselected populations of patients with sarcoma are still useful to demonstrate the utility of a novel treatment if the magnitude of the effect is felt to be relatively homogenous and sufficiently large across histologic subtypes. As mentioned above, such trials have recently been able to demonstrate the lack of utility of high-dose doxorubicin and ifosfamide for all patients and the utility of gemcitabine and pazopanib in patients with advanced stage sarcoma. However, the analysis of biomarkers predictive of response in these trials has been suboptimal, and the adaptation of their use for selected subgroups remains a challenge. Large phase II trials still have a role to play but will need a careful selection of stratification criteria and an extensive analysis of biomarkers to more efficiently guide future clinical use.

### PHASE II OR PHASE III CLINICAL TRIAL IN SELECTED HISTOTYPES

The STS201 trial is a unique randomized trial exploring two modalities of administration of trabectedin in patients with advanced sarcoma progressing on doxorubicin and ifosfamide. Trabectedin given every 21 days was found to be superior to the weekly administration in terms of centrally reviewed time to tumor progression (the primary endpoint). This trial was conducted only in LMS and LPS—two major histologic subtypes of sarcoma—because these were felt at the time to be the most sensitive histotypes to this agent. Although myxoid LPS indeed exhibits a specific sensitivity to trabectedin, it became clear that the majority of sarcoma histotypes actually exhibits sensitivity to this agent. The selection of these two histotypes enabled investigators to obtain a more homogenous group for the clinical trial. However, the analysis of the utility of the agent in other histologic subtypes has been rendered more complex, based mostly on phase II and IV studies, where it has been reported that most other

### KEY POINTS

- Molecular characterization further fragments the complex world of sarcomas in a variety of histologic and molecular subtypes.
- Most clinical trials in sarcoma were performed with broad inclusion criteria.
- A growing number of sarcomas now require a tailored approach for systemic therapy.
- Novel strategies of clinical trials are now needed to face the challenges of rarity of many molecular subtypes of sarcomas.
- Translational research and biomarker research must be an integral part of all sarcoma trials.
sarcoma histotypes do achieve a relatively similar tumor control and response. The phase III trial of eribulin uses similar criteria based on the activity of the drug in the phase II trial. Molecular subtyping will most likely be used increasingly to identify the subset in which to explore the activity of novel agents in this setting as described here.

In GIST, this process has already started. The GRID trial demonstrated the utility of regorafenib in patients with advanced GIST, with a similar magnitude of benefit found in all molecular subtypes. Although patients with high- and intermediate-risk tumors achieve relapse-free survival from adjuvant imatinib, it is becoming clear that some molecular subsets should be spared this treatment, such as PDGFRA D842V and nuclear factor 1 mutants. In this setting, subset analysis is limited by its lack of power to demonstrate differences in small molecular subgroups. Experts are therefore debating whether adjuvant imatinib should be given to patients with wild-type KIT/PDGFR and or if the dose of adjuvant imatinib used in patients with exon 9 KIT mutant tumors should be increased to 800 mg/d.

In recent years, it has been demonstrated that randomized trials in selected histologic and molecular subsets of sarcomas are feasible and informative for clinical practice. However, molecular subgroup analysis may lack power and will require additional confirmatory studies. Also, because of the small number of patients, a worldwide collaborative study may be needed. A new generation of trials is currently being performed, comparing, for example, preoperative radiotherapy in retroperitoneal sarcoma with immediate operation (STRASS study by EORTC), and preoperative tailored with standard chemotherapy in localized sarcoma within the ISG, FSG, and GEIS trials (both trials supported by the EuroSARC FP7-278472 project).

### PHASE II AND PROOF-OF-CONCEPT STUDIES

There is a need to develop trials evaluating novel therapies in a single nosologic entity. This approach is feasible, and phase II studies identified paclitaxel and sorafenib as an active treatment for angiosarcoma, cediranib for alveolar soft part sarcoma, temozolomide and bevacizumab for solitary fibrous tumors, and imatinib for desmoid tumor and chondroma. This approach is more efficient than the phase II studies performed in the 1980s that gathered all histologic subtypes. However, the median PFS in these trials is in the range of 4 to 6 months (with the exception of desmoids), and a significant proportion of patients still do not benefit from these treatments. This screening of a new agent in a selected histologic subtype without a more in-depth understanding of the disease’s biology is valuable and can help to guide clinical practice. Translational research exploring the mechanisms of resistance in these patients is needed in forthcoming trials.

Several recent proof-of-concept studies explore this direction further. These recently reported studies were analyzing a targeted agent on a selected population of tumors bearing the driver molecular alteration. Among several examples, the targeting of MDM2 with Nutlin in MDM2-amplified, well-differentiated LPS, the targeting of macrophage colony-stimulating factor receptor (MCSFR) in pigmented villonodular synovitis (PVNS), and the targeting of RANKL with denosumab in Giant cell tumor of bone (GCTB). The Nutlin trial was a neoadjuvant study where patients were exposed to 3 months of RG7112 before definitive surgery. In this study, the functional reactivation of p53 was demonstrated, with the induction of a cytostatic and proapoptotic effect. Whether the treatment has an effect on tumor progression in these tumors needs to be further explored.

With MCSFR inhibitors in PVNS and denosumab in GCTB, the treatment targeted the driver biologic factor for these specific tumors. In both cases, phase II trials demonstrated control in tumor progression in the majority of patients. With denosumab in GCTB, the tumor control rate is above 98% in non-transformed GCTB, while tumor control rates in PVNS may be slightly lower with the MCSFR inhibitors tested so far. In both cases, these results are in marked contrast with the results achieved within the phase II trials described previously and designed on a more limited biologic rationale. This approach also enables helps determine the inefficiency of an agent, as shown in synovial/sarcoma with gefitinib. When only a small subgroup of patients seems to benefit from an agent—as observed with insulin-like growth factor 1 receptor (IGF1R) Ab in Ewing sarcoma—it becomes again essential to explore the pharmacodynamic response to the treatment to avoid dimissing an efficient treatment.

This latter approach of a proof-of-concept study based on a strong biologic rationale is feasible and efficient to demonstrate the biologic activity of an agent. It is sometimes sufficient to demonstrate the activity of the drug if with exceptional activity. When the activity is less dramatic, it must be complemented by a randomized trial compared with the standard treatment. In this case, the feasibility of such trial may require a large global collaborative effort.
• Proof-of-concept clinical trials testing the pharmacodynamic response to a targeted agent in a tumor with an identified driver mutation may be small trials with innovative statistical designs (Bayesian) and a primary biologic endpoint.
• A phase II study—ideally randomized compared with standard treatment if feasible—should be performed, possibly in intergroup studies at the global scale. Innovative statistical designs are also needed here, refining the surrogate endpoints and, as much as possible, reducing the number of patients needed. This study also calls for a centralized management of these rare tumors in a small number of reference centers in each country to facilitate diagnosis and proper accrual in trials.
• Finally, large phase III trials remain relevant for less rare subtypes or when the treatment is thought to have a global effect on most sarcoma subtypes. This strategy can efficiently explore new generations of cytotoxics. To better guide clinical practice, a careful selection of stratification factors and an integrated translational research program must accompany all trials.

Because of their rarity and the opportunities revealed by molecular characterization, sarcomas are models to explore novel agents. When common tumors are characterized and subdivided by molecular classification, the lessons and mistakes learned in clinical research for these diseases should inform clinical practice and research beyond their examples and be useful to other fields of oncology.

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References


16. Chawla SP, Blay J, Ray-Coquard IL, et al. Results of the phase III, placebo-controlled trial (SUCCEED) evaluating the mTOR inhibitor ridaforolimus (R) as maintenance therapy in advanced sarcoma patients (pts) following clinical benefit from prior standard cytotoxic chemotherapy (CT). *J Clin Oncol*. 2011;29;(suppl; abstr 10005).


The Past, Present, and Future of Cytotoxic Chemotherapy and Pathway-Directed Targeted Agents for Soft Tissue Sarcoma

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OVERVIEW

The individual rarity of the many subtypes of soft tissue sarcomas has historically mandated an empiric approach to systemic therapy. Doxorubicin, first reported to have activity in sarcomas 40 years ago, remains the generalizable first-line treatment of choice for many subtypes, with no other drug or combination having shown an overall-survival advantage. Other cytotoxic agents, such as paclitaxel for angiosarcoma or gemcitabine with docetaxel for leiomyosarcoma, are commonly used for certain histologic subtypes based on relatively small studies. Trabectedin, particularly active against leiomyosarcoma and myxoid liposarcoma, is approved in many countries worldwide but not yet in the United States or Australia. Newer cytotoxic agents, including ifosfamide derivatives, are in current phase III testing. Although advances in systemic therapy of soft-tissue sarcomas have been hampered by their biologic heterogeneity, this diversity also serves as fertile ground for discovery and validation of targetable molecular drivers. The most notable success in this regard has been the development of small molecule therapies for gastrointestinal stromal tumors. Other targets of recent interest include mouse double minute 2 homolog (MDM2) in dedifferentiated liposarcoma and anaplastic lymphoma kinase (ALK) in inflammatory myofibroblastic tumor. Molecular therapies that have shown activity in diverse sarcoma populations include mammalian target of rapamycin (mTOR) inhibitors and vascular endothelial growth factor (VEGF-R) inhibitors. Among the latter, pazopanib demonstrated a progression-free survival over placebo in prior-treated patients with advanced sarcoma, and is now approved for use in the sarcomas in many countries. Efforts to understand the key molecular aberrations in any particular tumor continue towards a goal of individualized sarcoma therapy.

Sarcomas are a broad group of mesenchymal neoplasms, now subclassified into over 50 subtypes, representing approximately 2% of adult and 15% of pediatric cancers. These subtypes, many of which are quite distinct, are still generally classified using traditional morphological and immunohistochemical criteria. In the last 2 decades, the identification of translocations, many of which lead to the development of fusion proteins, have provided opportunities to further characterize them, at least for diagnostic and prognostic purposes. The argument of whether being a “lumper” or “splitter” really matters in determining patient care, particularly in advanced soft tissue sarcomas, has now been clearly overtaken by a desire to develop predictive molecular markers that may allow for a rational selection of targeted systemic agent.

The profound heterogeneity of sarcoma subtypes complicates the conduct and interpretation of clinical trials. Although therapeutic choices for many solid tumors have expanded over the last decade, systemic options for soft tissue sarcomas remain relatively limited. Select sarcomas, including gastrointestinal stromal tumors, Ewing’s Family of Tumors, and embryonal and alveolar rhabdomyosarcomas are exceptions that are effectively treated with specific therapies, with management strategies having evolved independently from other soft tissue sarcomas. For most soft tissue sarcomas the use of cytotoxic agents remains more or less empiric, some drugs having been in use for over 30 years despite lack of proven overall survival advantage. In some ways, the use of nonspecific cytotoxic agents seems appropriate for generalized treatment of soft tissue sarcomas, a histologically, genetically, and clinically diverse group of malignancies of profound individual rarity. Even in the case of so-called molecularly-targeted therapies, we remain limited in being able to prospectively predict a high likelihood of success with that agent. Until further progress is made toward identifying particular patient subsets based on a targetable molecular driver, we must rely on the arsenal of chemotherapies, and take a somewhat pragmatic approach to the use of these targeted agents in broader patient groups.

This review will focus on the progress that has been made in the development of systemic therapies, both cytotoxic and targeted, and the challenges we face in trying to optimize the use of these agents on an individualized basis.


**CYTOTOXIC CHEMOTHERAPY**

**Doxorubicin**

Doxorubicin remains the most active agent for the generalized treatment of soft tissue sarcomas. The first studies evaluating doxorubicin in cancer were published 40 years ago. Significant activity in soft tissue sarcomas was noted in these early studies, with reported response rates of up to 50%. In interpreting these results, it must be remembered that such studies predated modern imaging technology and did not employ current objective response criteria; interpretation is further complicated by the heterogeneity of sarcomas included in these early studies (e.g., both bone and soft tissue tumors, probable inclusion of unrecognized gastrointestinal stromal tumors). Modern studies of doxorubicin in unselected soft tissue sarcomas have reported response rates of less than 15%, and likely represent a more realistic measure of response activity in current practice. Although doxorubicin results in meaningful responses in some patients, its effect on overall survival is less clear, with median survival approximating 1 year in most studies. Despite its shortcomings, doxorubicin is generally accepted as standard first-line therapy for advanced soft tissue sarcomas.

Studies have suggested a dose-response relationship for doxorubicin. Modern dosing for sarcoma is typically up to 75 mg/m². One drawback to doxorubicin is that cumulative dosing is limited by cardiotoxicity. Because of this, the treatment course of doxorubicin is necessarily curtailed, and those patients who benefit from treatment are without safe option for chronic therapy. Alternative agents have been looked at in hopes of circumventing the dose-limiting cardiotoxicity. Epirubicin was initially considered to have less cardiotoxicity, but with equimolar dosing, epirubicin has shown similar toxicity (and activity) as doxorubicin. Liposomal doxorubicin has been embraced by some as a lower-toxicity alternative to standard doxorubicin for treatment of soft tissue sarcomas. Although an initial study of liposomal doxorubicin in second line sarcoma treatment did not show activity, subsequent studies have reported activity similar to doxorubicin. Formal phase III testing has not been performed to test noninferiority to standard doxorubicin.

### Table 1. Doxorubicin versus Doxorubicin/Ifosfamide Randomized Trials

<table>
<thead>
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<th>Treatment</th>
<th>RR %</th>
<th>OS</th>
<th>Author</th>
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<tbody>
<tr>
<td>Dox versus</td>
<td>23</td>
<td>52 wk</td>
<td>Santoro⁴⁴</td>
</tr>
<tr>
<td>Dox/Ifos versus</td>
<td>28</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>CYVADIC</td>
<td>28</td>
<td>51</td>
<td></td>
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<tr>
<td>Dox/DTIC versus</td>
<td>17</td>
<td>12 mo</td>
<td>Antman⁵⁵</td>
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<tr>
<td>Dox/DTIC/Ifos</td>
<td>32</td>
<td>13</td>
<td></td>
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<tr>
<td>Dox versus</td>
<td>20</td>
<td>NR</td>
<td>Edmonson⁶⁶</td>
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<tr>
<td>Dox/Ifos versus</td>
<td>34</td>
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<tr>
<td>Dox/Mit C/Cis</td>
<td>32</td>
<td></td>
<td></td>
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<tr>
<td>Dox versus</td>
<td>13</td>
<td>51% (1 yr OS, NS)</td>
<td>van der Graaf⁴⁹</td>
</tr>
<tr>
<td>Dox/Ifos</td>
<td>25</td>
<td>60%</td>
<td></td>
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Abbreviations: Dox, doxorubicin; Ifos, ifosfamide; CYVADIC, cyclophosphamide, vincristine, doxorubicin, dacarbazine; DTIC, dacarbazine; Mit C, mitomycin C; Cis, cisplatin.

**Ifosfamide**

Ifosfamide is an alkylation agent that requires biotransformation in the liver for activation. Some of the metabolites of ifosfamide are associated with serious side effects including encephalopathy and hemorrhagic cystitis. Ifosfamide’s use in clinical practice was limited for many years because of the associated hemorrhagic cystitis until the availability of mesna in 1979. Numerous studies have been performed with ifosfamide in soft tissue sarcomas, with response rates comparable to those seen with doxorubicin. Although some reports suggested a dose-response relationship justifying high doses of ifosfamide of 12 to 18 g/m², subsequent studies have not validated a benefit to such high doses and have confirmed excess toxicity with such dosing. A randomized trial exploring 2 different schedules of ifosfamide 9 g/m² in comparison to doxorubicin did not demonstrate any advantage over doxorubicin. Along with doxorubicin, ifosfamide is currently considered one of the most active agents against soft tissue sarcomas.

**Dacarbazine**

The activity of dacarbazine in soft tissue sarcomas was first reported in the 1970s. Although its activity is generally considered less than that of doxorubicin or ifosfamide, dacarbazine has activity as second-line therapy. There has been resurgence in the use of dacarbazine for pretreated soft tissue sarcoma in recent years. Dacarbazine currently serves as the control arm in 2 large phase III trials in pretreated leiomysarcoma and liposarcoma. The combination of dacarbazine and gemcitabine has shown improved overall survival (OS) and progression-free survival (PFS) over dacarbazine alone in a randomized phase II trial, and showed limited efficacy of single-agent dacarbazine with only a 2-month median PFS.

**Doxorubicin-Based Combination Therapies**

Numerous chemotherapies have been studied in combination with doxorubicin, including dacarbazine, cyclophosphamide, vincristine, and ifosfamide. Among these,
doxorubicin and ifosfamide containing regimens have been considered the most active. The combination of doxorubicin, ifosfamide, and dacarbazine (MAID) was reported to have a 47% response rate in a cooperative group phase II trial. Several studies of doxorubicin or epirubicin combined with ifosfamide reported response rates in excess of 50%.35,36

The advent of growth factor support permitted dose intensity in combination regimens, and reports suggested that higher doses of doxorubicin and ifosfamide were associated with better outcome.14,23,25,26 However, subsequent studies have questioned the importance of dose-intensity in treatment of sarcomas and randomized trials have failed to show survival benefit to such strategies.15,27

The high response rates of combined doxorubicin and ifosfamide eventually led to evaluation in clinical trials compared to single-agent doxorubicin (Table 1). Although doxorubicin and ifosfamide regimens were often found to have higher response rates, no significant difference in overall survival compared with single-agent doxorubicin has been observed. Based on these data, single-agent doxorubicin has been the accepted standard in Europe for a number of years. In the United States, many centers have continued to view combined doxorubicin and ifosfamide as standard treatment for advanced soft tissue sarcomas. In 2012, results from EORTC 62012 were reported, a large phase III trial comparing doxorubicin and ifosfamide with single-agent doxorubicin, and using growth factor support to promote modern dose intensity in the combination arm.3 This trial, long awaited as the definitive answer to the question of single-agent or combination therapy, showed improved response rate and progression-free survival with doxorubicin and ifosfamide, but no significant overall survival advantage compared to doxorubicin alone. However, given the PFS and response advantage reported in the EORTC 62012 trial, it remains unknown whether the potentially more “active” combination regimen might have meaningful benefit to any individual patient with soft-tissue sarcoma.

It seems that in 2013, we have come full circle to the recognition of single-agent doxorubicin as the standard therapy for advanced soft tissue sarcomas. Doxorubicin is the recognized first line chemotherapy for general soft tissue sarcoma use, with no other single-agent or combination showing significant overall survival superiority:2 The use of doublet therapy in patients whom aggressive downsizing or subsequent metastasectomy is of clinical relevancy remains a valid consideration.

**Other Chemotherapy Strategies**

The nucleoside analog gemcitabine has shown modest activity against soft tissue sarcomas in a number of phase II studies.30-34 Subsequently, the combination of gemcitabine plus docetaxel was found to have activity that suggested possible synergy between the agents, despite the general lack of activity of single-agent docetaxel in soft tissue sarcomas.35-39 The activity of gemcitabine and docetaxel is considered to be most pertinent to leiomyosarcoma, in particular uterine leiomyosarcoma.38 A randomized trial including a variety of histologies showed an advantage of the combination over single-agent gemcitabine, while another randomized trial specifically in leiomyosarcoma did not show a difference in response rates, questioning the utility of the combination.40

Despite a lack of comparative efficacy data with doxorubicin, the gemcitabine and docetaxel combination is sometimes used as a first-line regimen in the United States. The toxicity of this regimen is often underestimated, and it should not be assumed to have a better tolerability than single-agent doxorubicin. A phase III trial comparing gemcitabine and docetaxel with doxorubicin in the first-line setting is currently ongoing in the United Kingdom.41

In recent years, we have seen an increased trend of selecting chemotherapy based on histologic subtype. Included among the types of sarcoma for which alternate chemotherapy choices are often considered are synovial sarcoma (high-dose ifosfamide42), angiosarcoma (taxanes,43 liposomal doxorubicin44), leiomyosarcoma (gemcitabine and docetaxel,38 trabectedin45), and myxoid liposarcoma (trabectedin45). Most of these associations are based on small series or phase II trials, and randomized trials validating such choices are either lacking or ongoing.

**New Cytotoxics**

Trabectedin is a marine alkaloid initially isolated from an invertebrate sea squirt, *Ecteinascidin turbinate*. Its cytotoxic mechanism of action is not fully defined, but is thought to exhibit its activity through binding to the minor groove of DNA.46 Based on many phase II data demonstrating activity in pretreated soft tissues sarcomas, especially leiomyosarcoma and liposarcomas, trabectedin has been approved in numerous countries worldwide, with notable exceptions being the United States and Australia.45,47 Trabectedin is currently in phase III testing versus dacarbazine in leiomyosarcoma and liposarcoma, the results of which may serve to support registration in other countries.20

Eribulin is a synthetic analog of halichondrin B, derived from marine sponges, that works through inhibition of microtubule function in a mechanism of action distinct from those of other antitubulin drugs. A phase II study by the EORTC showed favorable progression-free survival, most notably in liposarcoma and leiomyosarcoma, and a phase III trial versus dacarbazine is currently accruing in pretreated patients with these histologies.19,48

Several compounds related to ifosfamide metabolites are in current phase III testing and hold promise to circumvent some of the toxicities of ifosfamide while maintaining activity. Palifosfamide, the DNA-alkylating metabolite of ifosfamide, does not generate acrolein and chloracetaldehyde as toxic byproducts of metabolism and bypasses potential resistance mechanisms mediated by aldehyde dehydrogenase enzymes.49 A randomized phase II trial showed improved progression-free survival of doxorubicin with palifosfamide compared with doxorubicin alone.50 TH-302 is a hypoxia-activated prodrgn composed of 2-nitroimidazole conjugated to a bromo-substituted analog of isophosphoramide mustard, an active metabolite of ifosfamide.51 A phase I trial of
doxorubicin + TH-302 in patients with soft tissue sarcoma showed promising activity with modest side effects. Two current phase III trials are comparing single-agent doxorubicin to doxorubicin with TH-302 or palifosfamide, respectively. If positive, these trials will force examination of the role of ifosfamide in sarcoma treatment, warranting careful consideration of issues such as quality of life and cost.

**Future Directions**

Although select chemotherapy agents have activity against soft tissue sarcoma, their overall effect against these diseases remains minimal. In the clinic, it is clear that select patients benefit from these drugs, with occasional profound responses seen, and therefore cytotoxics are still the primary treatment of choice for most patients with metastatic disease. Single-agent doxorubicin, 40 years after its first reports of activity, remains the standard to which new agents should be compared in randomized trials.

**MOLEULARLY TARGETED AGENTS**

Sarcomas such as GIST and DFSP have helped pave the way for direct bench to bedside translation and have provided important insights into treating other solid tumors with molecularly-directed therapies. In the case of GIST, a confluence of key events have enabled a dramatic improvement in outcomes for patients including the discovery of activating mutations in KIT, the development of a reliable and broadly applicable diagnostic test (CD117 expression), and the availability of a reasonably selective and potent kinase inhibitor (imatinib) that targets the most common driver mutations in GIST. Following on from these initial proof of principle studies, progress has continued at a steady rate, and we now have three approved agents for the treatment of metastatic GIST, an approved adjuvant systemic therapy, and continued refinements of treatment algorithms focused on personalizing treatments for each patient’s unique disease characteristics. These advances have largely come about because of ongoing efforts to develop and share GIST laboratory models that have allowed for rapid and reasonably robust translation of new agents into the clinic, proof of concept trials with a strong translational focus, and outstanding international collaborative efforts focused on conducting adequately powered definitive clinical trials.

**mTOR Inhibitors**

The phosphotidylinositol 3-kinase (PI3K)/Akt/mTOR pathway is a cell signaling pathway which plays a central role in the control of cell proliferation, survival, mobility and angiogenesis. The mTOR pathway is abnormally activated in a number of sarcomas, providing a rationale for the formal evaluation of mTOR inhibitors as therapeutic agents. The largest trials of mTOR inhibition in sarcomas conducted to date have been with the mTOR inhibitor ridaforolimus. In a phase I dose escalation trial of ridaforolimus administered to patients with advanced malignancies, seven patients with sarcoma were enrolled; with all of these patients noted to have a partial response (two patients), minor response or stable disease for more than three months. This led to the conduct of a phase II study of ridaforolimus in patients with advanced soft tissue or bone sarcoma, with a primary endpoint of clinical benefit response, defined as complete or partial response or stable disease for 16 weeks. Of the 212 patients enrolled on this trial, 61 patients (29%) had a clinical benefit response, including five partial responses.

In light of what was considered to be promising clinical activity and an acceptable safety profile in this phase II trial, this agent was evaluated in a large, international randomized phase III double-blind placebo-controlled trial: ‘Ridaforolimus in Treatment of Sarcoma—SUCCEED (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Ridaforolimus)’. Results of the SUCCEED trial were initially presented at the ASCO Annual Meeting in Chicago 2011, and have recently been published. 711 patients with bone or soft tissue sarcoma who had achieved a favorable response to chemotherapy (objective response or stable disease) were randomized to receive ridaforolimus or placebo on a 1:1 basis as a maintenance therapy. The study’s primary endpoint PFS was met, with a statistically significant difference between the two arms; median PFS: 17.7 versus 14.6 weeks for ridaforolimus versus placebo (hazard ratio = 0.72; 95% confidence interval: 0.61, 0.85; p = 0.0001). Median OS was not significantly different: ridaforolimus 90.6 versus 85.3 weeks with placebo (HR = 0.93; 95% CI: 0.78, 1.12; p = 0.46). There were other clear signals of biologic activity of ridaforolimus in these patients, as evidenced by a significantly higher clinical benefit rate, 40% compared with 29%; and a mean decrease of 1.3% as the best response in target lesions in the ridaforolimus group compared to a 10.3% increase in the placebo group.

The key issue relates to whether the magnitude of the benefit seen would be considered large enough to transform clinical practice. Early indications, at least as far as regulatory approval goes, suggests this may not be the case with a rejection by the United States Food and Drug Administration (FDA) and other agencies, as has been discussed in the accompanying manuscript by Blay et al. Given clear hints of biologic activity, the challenge is to be able to better define subpopulations of patients with tumors that are more (or less) dependent on signaling through mTOR. The investigators from this study have collected tumor samples from treated patients, with analyses ongoing to identify potential predictive markers of mTOR inhibition. These results will be eagerly awaited, but it remains to be seen whether the molecular tools available to us at this stage are sophisticated enough to allow us to determine this with any confidence.

**ANGIOGENESIS INHIBITORS**

A number of angiogenesis inhibitors have been trialed in sarcomas, initially based on a rationale that increased VEGF expression correlates with higher-grade soft tissue sarcomas (STS) and a poorer outcome. The best studied of these is pazopanib, the agent now approved by several regulatory
authorities for the treatment of refractory soft tissue sarcoma. Pazopanib is an oral kinase inhibitor targeting VEGF-R, PDGFR and c-KIT that showed promising activity in a large multiarm phase II trial of soft tissue sarcomas conducted by the EORTC. In an effort to differentiate activity across a spectrum of STS, and take a pragmatic approach in being able to predict what tumor types would not benefit from pazopanib, this trial stratified patients into four different arms based on traditional anatomic pathology criteria. Activity, defined as progression free rate at 12 weeks (PFR12 weeks) was seen in three (synovial sarcoma, leiomyosarcoma and other STS subtypes) of the groups; but not in the adipocytic group, although the limited number of patients studied did not fully explore potential activity of pazopanib in this subgroup. These results provided the rationale for the conduct of an international randomized phase III (the PALLETTE, or Pazopanib Explored in Soft Tissue Sarcoma) trial in patients with STS refractory to conventional chemotherapy. In this trial, 369 patients who had received up to 4 lines of prior chemotherapy were randomized to pazopanib (800 mg/d) or placebo. Although the primary endpoint of the study, OS was not found to be statistically significant on an interim analysis (p = 0.18, 11.9 versus 10.4 months); there was a significant improvement in PFS seen (p < 0.0001, HR: 0.31; 4.6 versus 1.5 months). The lack of translation of translation from a PFS to an OS benefit was surprising, given that cross-over from placebo to pazopanib was not allowed; and that this trial was really designed to enrol patients who were refractory to chemotherapy, i.e., for whom this would be the last treatment. However, there was a high rate of use post-trial systemic therapy with other agents, potentially impacting on the ultimate effect of pazopanib.

Many other angiogenesis inhibitors have also shown some level of activity in specific subtypes of soft tissue sarcomas, particularly in angiosarcomas and alveolar soft part sarcomas (ASPS). With angiosarcomas, activity has been noted with a number of agents including sorafenib (5 of 37 patients treated showed a partial response) and bevacizumab (17% objective response rate with 50% stable disease from 30 evaluable patients). ASPS is an essentially chemoresistant disease. In a case series of 10 patients with unresectable progressive ASPS, treated with sunitinib 37.5 mg daily continuously via a compassionate access scheme, five of eight (63%) assessable patients demonstrated a partial response with a further patient exhibiting stable disease for >6 months. Cediranib, a multitargeted kinase inhibitor with potent VEGF-inhibition is currently being tested in international collaborative efforts in two phase II trials; a single-arm and a randomized, placebo-controlled study. Initial results of the single-arm study, based on data from the first 28 of a total of 60 planned patients treated showed 12 (43%) PRs and a further 10 (36%) patients with stable disease.

Considerable efforts are underway to explore potential underlying mechanisms of response to cediranib in these trials. However, it still remain unclear on how we can potentially identify what the molecular drivers are in these individual tumors that confers such a high degree of sensitivity to these particular kinase inhibitors. The dynamic interplay between tumor cells, and their surrounding stroma has made it difficult to determine what angiogenic pathways are activated at the time of treatment. The approach to developing angiogenesis inhibitors in sarcomas has therefore needed to be pragmatic, relying on clinical observations in patient populations defined by traditional anatomic pathology criteria rather than being (predictive) biomarker driven, as is the current desire for drug development in many solid tumors.

Other Pathway-Directed Agents

Several other pathways are being actively investigated as new agents become available for clinical evaluation. Some of these are pathways that have been well described for years, but thought to be too difficult to target in vivo. For example, dysregulation of the p53 pathway via mutation of p53 is commonly seen in pleomorphic sarcomas. In the case of well-differentiated/dedifferentiated liposarcoma, p53 is dysregulated via amplification of MDM2, a key modulator of p53; along with amplification of CDK4. A number of first and second-generation p53/MDM2 inhibitors along with inhibitors of CDK4 are now in early clinical development. A key focus for the development of these molecules, both at the proof of concept stage and beyond, will be on understanding how complex the modulation of p53 really is in an in vivo setting, and therefore not only how “drugable” it is but also on whether a single target such as p53/MDM2 can act as a critical gateway to a protein such as p53.

An alternate approach that has been adopted with success on a number of occasions has involved taking a proactive role in rapidly translating emerging data on newly identified molecular drivers into small proof of concept trials. These have often been in rare sarcomas, that interestingly have also been resistant to conventional cytotoxics; perhaps adding further weight to the argument that these tumors were dependent on a single molecular pathway. An early example of this approach was with the development of imatinib in dermatofibrosarcoma protuberans (DFSP). In DFSP, a characteristic translocation (t17:22) results in the creating of a fusion oncogene between COL1A1 and PDGFB, which functionally switches on PDGFB resulting in a constitutively activated pathway. Imatinib’s PDGF inhibition has been exploited successfully with confirmed clinical activity in this disease, leading to its expanded regulatory approval for this indication.

Other successes have been noted through taking similar opportunistic approaches. These might be through the use of an existing drug to rationally treat a newly discovered target, such as with DFSP; or by efforts to identify patients for participation in a trial of a new therapeutic targeting a previously identified pathway. A recent example of this has been with the recruitment of two patients with Inflammatory myofibroblastic tumor (IMTs) on the phase I trial of the MET inhibitor crizotinib. Dysregulation of ALK can occur in approximately half of patients with IMT. One of these two patients treated on the crizotinib trial, who had an ALK-translocated IMT had a sustained response, while the other patient who did not have an ALK translocation did not.
respond.81 As was seen with crizotinib’s development in non-small cell lung cancer, the high rates of response in ALK-translocated tumors82 may suggest similar results in the subset of translocated-IMT.

**CONCLUSION**

The systemic management of sarcomas continues to evolve. With regards to cytotoxic chemotherapy, doxorubicin remains at the core of conventional management of patients with most sarcoma subsets. As is now the case with most solid tumors, much of the current focus on improving outcomes in sarcoma revolves around the ability to better understand what the key molecular drivers are in an individual’s tumor, thus enabling a more tailored treatment approach. Parallel to this, efforts will continue to improve clinical outcomes using a more empiric approach, by either combining cytotoxic agents with targeted therapeutics or by combining cytotoxics.

**Disclosures of Potential Conflicts of Interest**

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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**References**


68. Chawla SP, Blay J, Ray-Coquard I, et al. Results of the phase III, placebo-controlled trial (SUCCEED) evaluating the mTOR inhibitor ridaforolimus (R) as maintenance therapy in advanced sarcoma patients (pts) following clinical benefit from prior standard cytotoxic chemotherapy (CT). J Clin Oncol. 2011;29(suppl; abstr 10005).


SARCOMA

The Use of Local Modalities in the Treatment of Patients with Metastatic Sarcoma: State of the Art

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Surgical Management and Minimally Invasive Approaches for the Treatment of Metastatic Sarcoma

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OVERVIEW

Soft tissue sarcomas describe a very heterogeneous group of soft tissue tumors mainly arising in the lower extremities. If diagnosed at an early stage and a complete resection of the primary tumor is achieved, the patients’ prognosis is excellent. However, metastatic tumor spread is common with only limited treatment possibilities. Despite an improved insight into tumor biology of sarcomas, no notable improvement has been gained in the last 20 years regarding prognosis of patients. Metastatic lung disease has long been the preserve of systemic treatments, local treatments being considered in a purely palliative intention. Several studies have objectified benefit to the local treatment of metastases, especially in an oligometastatic state. The development of techniques for stereotactic radiotherapy on the one hand and the refusal or contraindication for surgery on the other hand inaugurated studies in this direction.

Besides surgery and radiotherapy, other local modalities have been investigated in the last few years such as thermal therapy (radiofrequency and laser ablation) or combined modalities (isolated limb perfusion and deep-wave hyperthermia plus chemotherapy) to help patients with metastatic soft tissue sarcoma. Minimally invasive, image-guided therapies such as thermal ablation should be considered particularly in patients who are not suitable surgical candidates or may have exhausted all other viable surgical options. Some of these techniques will be reviewed in this article, and their value for the patients will be evaluated in the light of indication from tumor biology and technical feasibility. These highly selected and specific procedures should only be performed after decision making in an interdisciplinary sarcoma-board.

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may occur later in the clinical course, sometimes even beyond 5 years.

Most of the patients with pulmonary metastases of soft tissue sarcomas are asymptomatic and the tumors are detected during follow-up visits. The metastases are located mainly within the parenchyma or subpleurally. In consequence, symptoms related to invasion to the vascular or bronchial structure, such as hemoptysis, cough, or shortness of breath, are uncommon. Pain in relationship to pulmonary metastases is only expected in cases with localized chest wall invasion or a spontaneous pneumothorax because of rupture of the pleural surface covering the metastasis. There are no data showing that metachronous metastases behave differently compared with those being present at the initial diagnosis of the primary tumor, however, the time interval between primary tumor and detection of metastases is a prognostic factor.6,7

Other sites of metastases might depend to some extent from the histologic subtype of the sarcoma. Clear cell sarcoma, epithelioid sarcoma, and synovial sarcoma show lymph node metastases in up to 10% of the cases.7,8 Brain metastases are relatively uncommon in adult soft tissue sarcoma; in a prospective series the incidence was 1%,9 however, children with Ewing’s sarcoma or osteosarcoma are more often affected.10 Given the rarity of the subtype, alveolar soft part sarcoma metastasizing to the central nervous system has been reported more often recently. In principle, all sites of the body can be targets of metastases from sarcoma, and leiomyosarcoma tend to show a higher rate of metastases to the liver and soft tissues.11 Metastases to the skeleton are more often detected in myxoid-round cell and metastatic dedifferentiated liposarcoma.12

**THE CONCEPT OF OLIGOMETASTASES AND THE INDICATION FOR LOCAL TREATMENT**

If metastatic sarcoma typically presents with multiple bilateral lung metastases, systemic chemotherapy is the treatment of choice. However, a considerable proportion of patients might have disseminated cancer with only a limited number of metastases—each, per se, accessible to local therapy. This subset of patients was called “oligometastatic” by Hellman and Weichselbaum in 1995.13,14 Their tumor biologic concept adopts the “seed and soil” theory and forms the basis to render those patients eligible for local treatment measures of their M1 disease. Recently, this has been particularly applied to lung tumors and the development of stereotactic radiation therapy15 or colorectal cancer with isolated liver and/or lung metastases.

The concept of oligometastases is related to the observation that patients with 1 to 5 metastatic or recurrent lesions that could be treated by local therapy might achieve long-term survival or cure. Those lesions could be in different organs and then are called oligo-recurrent but have had curative therapy for the primary tumor (Fig. 1). Long-term survival with oligometastatic or oligo-recurrent metastases is clearly dependent from the type of cancer and the sites involved. The concept has found also critical comments in the light of
overestimating the results of resection of single lung metastases in the absence of prospective randomized trials. The typical criterion to call a state "oligometastatic" is less than 5 metastases, but a more pragmatic approach would be to call an oligometastatic state when metastases are limited in number and are amenable local (surgical) or regional treatment. Oligo-recurrence is considered to have a better prognosis than oligometastases. Treatment of the "oligo-lesion" is loco-regional therapy and includes surgery, radiation therapy, and radiofrequency ablative therapy.

PRETHERAPEUTIC WORK-UP
Typically, sarcoma metastatic sites at the lungs are staged by computed tomography. Before assuming that there are single metastases offering the option of a local treatment with some curative intent, whole-body magnetic resonance imaging or abdomino-thoracic computed tomography scan should be performed to rule out further tumor deposits. Adding \(^{18}\text{F}\)FDG-PET to conventional staging could result in detecting additional tumorous lesions. Although lung metastases are the most common site of metastases in patients with high-grade tumors, these are often small and are not visualized on \(^{18}\text{F}\)FDG PET. For this reason, a complete staging examination for both soft tissue and bony sarcomas also consists of a high-resolution contrast-enhanced CT scan of the chest. Metastases outside of the lung might be detected easier by PET. However, in a series of 109 patients with predominantly intermediate and high-grade sarcoma, a change in treatment because of new findings in \(^{18}\text{F}\)FDG-PET scan resulted in only 6% of the patients. Therefore, PET scanning is not recommended outside of trials or specific situations as a measure to support the indication for local therapy of M+ sarcoma disease.

SINGLE MODALITY TREATMENT
Surgery
Pulmonary metastasectomy is a well-accepted cornerstone in the treatment of sarcoma. The standard approach commonly used in pulmonary metastases for unilateral disease or as a staged thoracotomy for bilateral lesions is anterior thoracotomy. Despite that sternotomy may offer less postoperative discomfort, it has exposure problems of the posterior areas of the lung and in case of larger metastases involving the posterior lung hilus. However, sternotomy may be preferred if bilateral metastatic resections need to be performed with resecting multiple nodules on both sides. Moreover, it has always to be taken into account that— even today—finger palpation detects more pulmonary nodules than computer tomography scans.

There is sometimes debate on the advantages and the necessity of adding a mediastinal lymph node dissection in parallel to lung metastasis resections. The data in favor of lymphadenectomy mainly is based from its use in resecting pulmonary metastases from kidney cancer and germ cell tumors. However, both tumor types have their metastatic spread alongside the vena cava and aorta, and lymph node metastases in the mediastinum might represent the disease on its metastatic way from the primary tumor to the lungs. In contrast, data on lymph node involvement of mediastinal nodes in conjunction to lung metastases in soft tissue sarcomas are very rare and question the need for systemic mediastinal lymph node dissection patients undergoing metastasectomy.

Less invasive and therefore better tolerable approaches have been evaluated in the last years. Surgery by a video-assisted thoracoscopic (VATS) approach has proven over more than a decade to provide good access with a minimum of postoperative pain and very short in-hospital duration with a complete resection rate of 97%, No doubt, these circumstances positively affect patients’ quality of life in comparison to any open procedure. However, the inability to perform a manual palpation of the lung and limitations to detect even single metastasis growing below the pleural surface makes the indication of a VATS approach sometimes problematic. Prospective studies of VATS followed by open thoracotomy and manual exploring of the lungs showed that metastases are often missed.

Regarding surgical results, completeness of resecting all metastases is the decisive point. Whether this is reached by thoracotomy, sternotomy, or VATS does not influence recurrence-free survival or overall survival, but it clearly affects patients’ quality of life. There are no randomized data on this topic as the only scheduled trial by the Cancer and Leukemia Group B (CALGB) had to be closed in the late 1990s because of poor accrual. Patients were not willing to be randomly assigned between a formal opening of the chest and a minimally invasive procedure.

There are three major factors having prognostic importance after pulmonary metastasectomy: (1) the time interval between initial diagnosis of the primary tumor and onset of metastasis (disease-free survival) better or less than 36 months; (2) the number of metastases (solitary, 2–3, 4 and more), (3) and the completeness of resection R0 compared with R1 compared with debulking surgery. The Registry of Lung Metastases collected data on the outcome of patients undergoing pulmonary metastasectomy for different tumor types and found out that germ cell tumors do best because of their sensitivity to systemic chemotherapy. Between all other subtypes, soft tissue sarcomas showed a slightly worse outcome compared with bone sarcomas and colorectal cancer. Taking into account the three major prognostic factors, patients with solitary metastasis that has developed late after primary resection and where a complete R0 excision could be achieved did best even at 10 years follow-up.

According to literature, surgical resection of pulmonary and extrapulmonary sarcomatous metastases is associated with improved survival in appropriately selected patients. The 5-year survival rate is around 30% in larger series. In the absence of any randomized trial, a recent systematic review of reported outcomes of pulmonary metastasectomy for sarcoma analyzed 18 publications (five bone, six soft tissue,
four mixed series) from 1990 to 2009 reporting at least 20 patients. Interest-ingly, the survival rates were higher than what had been reported in the single publications. After 1,357 pulmonary metastasectomy operations, 34% of the patients were alive 5 years after the first metastasectomy. The review confirmed that better survival was achieved for patients with fewer metastases and longer interval between diagnosis of the primary tumor and appearance of lung metastases. The authors also concluded that 5-year survival does not equate to cure because there were survivors with metastatic disease. However, the series also demonstrated that after repeated resections a subset of patients could be cured. Therefore, pulmonary metastasectomy remains the only potentially curative treatment for soft tissue sarcoma lung metastases if all known disease can be removed with clear margins. If the sarcoma recurs in the lungs, again in an oligo-metastatic setting, after a reasonable (12 months?) time interval, the patient is still a candidate for resection if technically feasible as an R0 resection with adequate pulmonary function post-operatively to be expected.

ATTITUDE TOWARD EXTENSIVE RESECTIONS OF METASTASES (PNEUMONECTOMY, MULTIVISCERAL RESECTIONS)

Although sublobar and lobar resections are accepted operations for pulmonary metastases, pneumonectomy is viewed as a major incursion on stage IV patients. Post-pneumonectomy survival is often hampered by limited ventilation and oxygenation capacity of the patient and might significantly compromise quality of life. Thorough examination of the expected postoperative lung function is mandatory, and the planned postoperative FEV1 (forced expiratory ventilation capacity) should not be less than 1,000 mL. Koong and colleagues reported an analysis of the results of pneumonectomy survival is 4% and a 5-year survival rate of 20% was achieved following complete resection (R0). In contrast, the 21 incompletely resected patients had an operative mortality rate of 19%. The majority did not survive beyond 2 years (p = 0.02), and this was the only prognostic factor with significance. In the 38 completion pneumonectomy patients, 35 were operated for recurrent disease and three for residual disease, and sarcoma patients predominated (n = 28). Complete resection was achieved in 82%. The operative mortality rate was 3%, and the 5-year survival rate was 30%.

An interesting survey has been performed to analyze the current clinical practice among European thoracic surgeons to lung metastasectomy. For 68% of the respondents, lung metastasectomy represents a minor proportion (0% to 10%) of their clinical volume. Approximately 90% of respondents usually review their lung metastasectomy cases within a multidisciplinary meeting. Palpation of the lung (thus scheduling the patient for an open procedure) is considered necessary by 65%, and 40% use a thorascoscopic approach with therapeutic intent. Responses demonstrated a remarkable consistency of practice patterns, although certain areas of potential controversy showed greater variance.

MINIMALLY INVASIVE MANAGEMENT OF METASTATIC TUMORS

However, despite a complete resection of lung metastases, 40% to 80% of patients develop recurrent metastases in the lungs. Redo pulmonary operations are possible and may lead to improved survival in a subset of patients, but less invasive approaches are associated with fewer morbidities, require shorter hospital stay, and are certainly more desirable. To this end, image-guided interventions provide a broad scope of percutaneous and transcatheter endovascular cancer therapies, which complement the more traditional medical, surgical, and radiation oncology treatment options. Percutaneous tumor ablation techniques include chemical, thermal, and nonthermal technologies. Percutaneous ethanol injection, a form of chemical ablation, has been used for treatment of small primary liver tumors. Chemical ablation has mostly been replaced by more powerful thermal ablative technologies such as radiofrequency (RF) or microwave ablation. Transcatheter therapies include embolotherapy techniques where chemotherapeutic agents or radionuclides may be infused directly into the tumor via the nutrient artery followed by an embolic agent. The end result is higher intratumoral concentration of chemotherapeutic agents or radionuclides with longer dwell time. In patients who may not be fit for surgery or have exhausted all other surgical treatment options, one or more of these minimally-invasive interventional techniques may be used to achieve local tumor control.

Percutaneous Image-Guided Thermal Ablation of Tumors: An Overview

Thermal ablative therapies that are currently available include RF, microwave, laser, and cryo ablation technologies. At most centers in the United States, these treatments are provided in an interventional radiology suite equipped with an appropriate imaging modality, as an outpatient or with an overnight hospital stay. Using computed tomography, ultrasoundography, or even magnetic resonance imaging for guidance, one or more needle-like applicators are inserted into the tumor for delivery of the thermal energy within the intended volume of ablation. The goal for this treatment is to cause necrosis of the tumor along with an approximately 1 cm margin around the tumor to achieve a complete ablation. This is analogous to the concept of R0 resection in surgical oncology. In general, two important predictors of success are tumor size and tumor location. For most thermal ablative techniques, tumors up to 4 cm in size can be easily treated with adequate margin, provided that they are not abutting a large blood vessel, the heart, or any other vital organ that could not be safely included in the ablation zone.
RF ablation is currently the most widely used technology throughout the world. In this technique, an alternating electrical current (480 KHz) induces ionic agitation immediately next to the electrode, which in turn causes resistive heating in a finite volume of tissue. Sufficient heating (usually greater than 60°C) induces immediate cell death and leads to coagulation necrosis within the ablation zone. In microwave ablation, an oscillating electromagnetic field (up to 2.45 GHz) causes frictional heating by repeatedly realigning polar water molecules within the tissue. Microwaves propagate freely within the tissue and are not affected by low electrical conductivity and high tissue impedance which limit the effectiveness of RF ablation. As such, microwave ablation will likely surpass RF ablation in clinical effectiveness. But at the present time, most of our experience is based on RF ablation devices that have been available during the last 15 to 20 years.

Thermal Ablation for Lung Metastases
Radiofrequency (RF) ablation has evolved as a safe and effective therapeutic option for selected patients with unresectable non-small cell lung cancer and lung metastases from colorectal cancer (Fig. 2). A few of the earlier studies included small cohorts of patients with metastatic sarcoma, establishing the safety and feasibility of RF ablation in these patients. More recently, two small series were published outlining the outcomes and survival rates for patients with lung metastases from sarcoma.

Nakamura and colleagues reported their experience with radiofrequency ablation of lung metastases from musculoskeletal sarcomas in 20 patients. The number of tumors ranged from one to 18 (mean, 7) and tumors measured 5 mm to 40 mm in diameter (mean, 14 mm). A total of 89 lung tumors were treated in 63 RF sessions. There were no procedural mortalities. Complications were limited to pneumothoraces that were successfully managed by observation or chest tube placement. In 11 of 20 patients (55%) all of the lung metastases were treated. In the other nine patients (45%), complete ablation of all tumors was not feasible. After a mean follow-up of 18 months (range, 7 to 54 months), 9 of 20 patients died of lung tumor progression. The 1- and 3-year survival rates from the time of RF ablation were 58% and 29%, respectively, for all patients with a median survival of 12.9 months. In a multivariate analysis, complete ablation of all lung tumors emerged as the only independent predictor of outcome. The 1- and 3-year survival rates were 88.9% and 59.2%, respectively, in 11 patients who underwent complete ablation of all their lung metastases. In contrast, the 1- and 3-year survival rates were 29.6% and 0% in 9 patients with incomplete tumor ablation. This study highlights the importance of patient selection. The goal of ablation must be eradication of all pulmonary metastases. Only then, survival

FIG 2. A 17-year-old boy with recurrent osteosarcoma was referred for thermal ablation of a 3 cm metastasis in the left lower lobe. An axial PET/CT image of the chest (a) shows intense metabolic activity within the tumor (SUV, 12.2). He underwent CT-guided radiofrequency ablation. Axial CT image of the chest (b) during the ablation shows 2 of the 3 electrodes placed within the tumor. There were no complications. He was discharged after an overnight hospital stay. Follow-up axial PET/CT image of the chest (c) performed 18 months after ablation shows a necrotic tumor with no metabolic activity.
benefit from RF ablation may be comparable with that achieved by metastasectomy.

More recently, Palussiere and colleagues published the results of a single-center study in 29 patients with sarcoma lung metastases treated with percutaneous RF ablation. Selection criteria included a maximum of five lung tumors, no extrapulmonary metastases, tumors located greater than 1 cm from the hilum, and tumor size smaller than 4 cm in diameter. Nineteen of 29 patients (65.5) had been previously treated with surgery for lung metastases. All patients were treated with a curative intent. For three patients with bilateral disease, surgery was performed on one side and RF on the other. Overall, 47 metastases were treated in this study. There were no major complications. During the follow-up period, 19 patients developed extrapulmonary metastasis. Eighteen patients received chemotherapy initiated on average 20 months (range, 1 to 42 months) after RF ablation. Median follow-up time was 50 months. The 1- and 3-year survival rates were 92.2% and 65.2%, respectively.

**Thermal Ablation of Liver Metastases**

For patients with small, solitary, early-stage hepatocellular carcinoma, RF ablation can achieve excellent results that are comparable with surgical resection. For patients with colorectal liver metastases, long-term survival after RF ablation of solitary, small metastasis (less than 4 cm) compares favorably to surgical resection. The role of thermal ablation in the management of noncolorectal and non-neuroendocrine liver metastases is not well defined. Surgical resection of sarcoma liver metastases results in 5-year survival rates of 27% to 51%. Thermal ablation of sarcoma liver metastases in appropriately selected patients is likely to yield similar results.

Yamanaka and colleagues treated 21 gastrointestinal stromal tumor liver metastases in seven patients with RF ablation. Six patients had received imatinib as first-line therapy with limited success. Mean follow-up was 30.6 months (range, 5.9 to 76.4 months). The 1-, 3-, and 5-year local tumor progression rates were 0%, 0%, and 12.5%, respectively. One local recurrence was treated with repeat RF ablation. The overall and cancer-specific 5-year survival was reported as 85.7% and 100%, respectively.

Berber and colleagues reported on ablation of liver metastases from unusual primaries (noncolorectal and non-neuroendocrine) in 53 patients who had liver only disease. Eighteen patients had sarcoma liver metastases. The overall median survival was 33 months for the whole group, and 25 months for patients with metastatic sarcoma. The authors concluded that the type of liver tumor has little or no influence on whether effective local control can be achieved with RF ablation.

In conclusion, percutaneous thermal ablation of lung and liver sarcoma metastases should be considered in patients who may not be good surgical candidates. In carefully selected patients with oligometastatic disease, one may achieve complete response with thermal ablation. Furthermore, percutaneous image-guided ablation can be repeated multiple times in these patients who are at high risk of developing recurrent metastases.

**COMBINED MODALITY TREATMENT**

Historically, surgical removal of sarcoma metastases has been the only way to make sure that metastases do not grow any further. In recent years, different other techniques have been developed and evaluated to control metastases.

Isolated limb perfusion (ILP) is an approach for limb-saving treatment of primary sarcoma of the extremity. It has also been adopted to allow for control of in-transit metastases of malignant melanoma but also could be used to control soft tissue metastases within a limb (Fig. 3). In case of sarcoma metastases tumor necrosis factor-α (rhTNFα) and melphalan provide local tumor control and enable limb-preserving surgery in a majority of cases. This procedure has mainly been performed in advanced but localized extremity soft tissue sarcomas and meanwhile has gained a permanent place in the multimodality treatment of soft tissue sarcomas. Especially in patients with metastatic spread of sarcoma to the extremity soft tissues it might be a helpful procedure to control tumor growth. Grunhagen et al. report that out of 339 ILP procedures between 1991 and 2003, 37 patients with stage IV soft tissue sarcoma have been identified. Eighteen patients underwent resection of the tumor after its shrinkage A complete response was observed in 16% of patients, a partial response occurred in another 68%. Median survival of patients after ILP was 12 months. Limb salvage was achieved in 36 of 37 patients, with only one patient undergoing amputation as a result of treatment toxicity. Taken together, ILP serves as excellent treatment approach providing tumor control and limb salvage for the sometimes short survival time of patients with metastasized, bulky tumors of the extremity.

**FIG 3. Metastasis of high-grade osteosarcoma in a 28-year-old male to the left lower limb concomitant to brain metastasis, not R0 resectable without a major procedure and function loss. Isolated limb perfusion with rhTNFalpha, melphalan and cisplatinum destroyed the metastasis to a cystic lesion with persistent limb function and was able to control the lesion for 14 months until death.**
Deep-wave hyperthermia plus chemotherapy might be an individual option in solitary deeply located tumors not amenable to R0 resection. Regional hyperthermia has been shown to act synergistically with radiotherapy or chemotherapy. The technique has been proven effective in a randomized phase III study in the neoadjuvant setting. It is mainly used in localized high-risk soft tissue sarcomas—per definition, size ≥ 5 cm, grade 2 or 3, deep to fascia. Regional hyperthermia is aiming for tumor temperatures of 42°C for 60 minutes given on days during chemotherapy cycles, usually consisting of doxorubicin and ifosfamide. Adding regional hyperthermia to chemotherapy resulted in a significantly better local progression-free survival and disease-free survival compared with chemotherapy alone. It could be a new effective treatment strategy for patients with sarcoma metastases of borderline resectability, including those with locoregional lymph node metastases and an abdominal or retroperitoneal location. However, hyperthermia plus chemotherapy has only been performed in selected cases of soft tissue sarcomas with oligo-metastatic pulmonary disease.

**LEVEL OF EVIDENCE AVAILABLE**

An important question is whether there are any data from randomized comparison not only of the different technical approaches but also of the indication for local surgical treatment at all. Unfortunately, there is not a better level of evidence than level IIIa (systematic review with homogeneity of case-control studies). One interesting question would be whether there is any benefit from adding “adjuvant” chemotherapy to pulmonary metastasectomy, either before or after surgery, and on data on this subject are all anecdotal. The last randomized trial that tried to answer this question (three cycles of DOX/IFOS before and two cycles postsurgery) of the European Organization for Research and Treatment of Cancer, Eastern Cooperative Oncology Group (ECOG) and Scandinavian Sarcoma Group (SSG) had to be closed because of poor accrual in the year 2000, and the data of this study have never been reported. A retrospective analysis on the effect of perioperative chemotherapy did show convincing data that chemotherapy would improve postmetastasis disease-specific survival and in one analysis patients with combination treatment did even worse.

Available data do not favor or form the basis for any phase III-study. However, the data reported on surgical resection therapy should not be taken for granted. As could be shown from a thorough analysis of the published data on resection of colorectal lung metastases there is a selective citation network in favor of lung resection and papers expressing an opposing viewpoint are rarely cited.

**Disclosures of Potential Conflicts of Interest**

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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**References**


