Comparative Effectiveness Research for Sarcoma

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Abstract

Modern multidisciplinary management of sarcoma represents several opportunities for comparative effectiveness research. Focusing on the outcomes of survival, quality of life and cost-effectiveness of care, the current state of the art is summarized. Specialized/regional care for sarcoma and the utility of tumor boards or multispecialty discussion is discussed. Issues related to treatment efficacy and sequencing in relation to chemotherapy, radiation, and surgery as well as margin reporting and surveillance are also discussed. Finally, future avenues of comparative effectiveness research for sarcoma are highlighted throughout the chapter.

Keywords

Extremity sarcoma · Retroperitoneal sarcoma · Comparative effectiveness research

Contents

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1 Introduction

Sarcoma represents the quintessential malignancy for a surgical oncologist. Whilst other cancers such as colon and breast may fall under the purview of the general surgeon, the rare incidence, heterogeneity in histology, and surgical challenges involved with sarcoma care call for specialized training. The multidisciplinary aspect of modern sarcoma care often requires consultation with other specialists prior to initiation of therapy, which may not be possible in practice settings not conducive to such co-ordination. The clinical challenges of sarcoma care make a ready recipe for the introduction of variation in delivery of care. Although some of this variation may be attributed to the co-ordination of complex care, lack of quality data to guide clinical management is also to blame. The focus of this chapter is to explore how this variation influences outcomes for patient with sarcoma, and to suggest future avenues for study to smooth out fluctuations in care by using the methodology of comparative effectiveness research.

Meaningful comparative effectiveness research should be linked to outcomes that are biologically relevant, measurable in an objective manner and comparable between studies. For oncologists of all stripes a scorched earth policy to maximize long-term outcomes is often justified by the primacy of long-term survival, or surrogates such as recurrence-free survival, as the arbiter of treatment efficacy. An increasing focus on patient-centered outcomes means that quality of life (QOL) among survivors is considered more often before embarking on potentially toxic therapy. In the context of the overall health care system cost can be regarded as a valid outcome measure for two treatments of equal efficacy, or one of marginal efficacy. The ideal therapy is one that combines maximal efficacy with minimal morbidity and is the most economical; this ‘goldilocks’ mix is seldom the case in the clinical world. In the ensuing discussion, the issues of multidisciplinary consultation and guideline-oriented care, regionalization, and treatment of soft tissue extremity and retroperitoneal sarcoma will be discussed while focusing on the three outcomes of survival, QOL, and cost.

2 Multidisciplinary Consultation and Guideline-Oriented Care

Current national comprehensive cancer network (NCCN) guidelines suggest that 'all patients be evaluated by a MD team with expertise and experience in sarcoma prior to initiation of therapy' [1]. The implication is that discussion in a multidisciplinary setting has the potential to improve patient outcomes for sarcoma. However, there is little data to support an improvement in survival, QOL, or cost of therapy with multidisciplinary consultation prior to initiation of therapy. Given the complexity of the disease and numerous patient and practice patterns involved in treatment, such a change may be hard to show in a direct comparison. Nevertheless, it does not invalidate the utility of such an approach. In a survey study of physicians involved in sarcoma care, 83 % had access to a multidisciplinary sarcoma tumor board and the usefulness in clinical decision-making was rated at a mean of 4.08 ± 0.05 on a Likert scale (where 1 = not helpful and 5 = always helpful) by the respondents [2].

Care outside of a multidisciplinary setting certainly has the potential to be fragmented and of potential detriment to the patient. Does this translate into worst outcomes? Although there is no direct confirmation, circumstantial evidence can be obtained from the same survey study of sarcoma specialists. When presented with an identical clinical scenario, each specialist was inclined to favor their respective treatment modality at the expense of others, suggesting a 'specialty bias' exists in treatment recommendations for soft tissue extremity sarcoma [3]. One would hope that in a multidisciplinary setting, consensus opinion would counteract the influence of individual bias on clinical decision-making. The role of multidisciplinary consultation on sarcoma survival, QOL, and cost outcomes remains an area ripe for comparative effectiveness research. Performing an observational cohort study of patients treated in a multidisciplinary setting versus those who are not, perhaps using the National Cancer Database (NCDB) to obtain the necessary information, could help demonstrate the effect of having a multidisciplinary team. Qualitative studies evaluating physicians' changes in plans before and after tumor board meetings may also help to illustrate the role of multidisciplinary care. This could both be done in an academic center as well as in community centers without multidisciplinary meetings, who would then begin to take part in academic tumor boards.

A central tenant of the NCCN guidelines is to provide providers with a set of recommendations as a reference point for the management of complex cancer patients. These guidelines are based on best available evidence with the tacit understanding that compliance with guideline-oriented care should improve outcomes. This approach is predicated on the quality of the evidence available to formulate the guidelines themselves, as well as access. The latter is usually not an issue as the guidelines are freely available on the web [1]. For sarcoma, many of the guidelines are derived not from randomized trials but Category 2 or below level evidence, leading to intentionally vague recommendations. Nevertheless, until better data becomes available, one can assume that adherence to current recommendations is not worse, and potentially better, than unstandardized care. Participation in

multidisciplinary care has been shown to improve compliance with guidelines, suggesting that discussion in a group setting improves conformity to best available evidence [4].

The discussion above begs the question—does care that is compliant with current sarcoma guidelines improve the quality of clinical care compared to care that is not? There is precious little data to inform this debate. Establishment of national guidelines for soft tissue sarcoma in the Netherlands led to improvements in preoperative diagnoses and pathology reporting for patients [5]. An analysis of the SEER database looking at the stage specific use of radiation therapy for soft tissue extremity sarcoma showed that omission of radiation therapy for Stage III patients led to worse survival outcomes, although selection bias could also explain these results. [6]. A cost-effectiveness analysis from two European regions showed that noncompliance to sarcoma guidelines resulted in a cost increase of 16 % compared to patients in whom guideline-oriented care was delivered [7]. These studies notwithstanding, an unambiguous association between multidisciplinary, guideline-oriented care, and an improvement in survival outcomes, QOL, or costs has yet to be demonstrated in the United States. Use of large databases to determine the outcomes of guideline-adherent practices should be undertaken.

3 Regionalization of Sarcoma Care

The majority of sarcoma care in the United States is performed by nonspecialists or 'part-time' sarcoma physicians. As with other complex cancers, there has been a call to regionalize care of sarcoma patients to high volume or specialized centers so that outcomes can be improved. Are there any grounds to justify these claims? Guiterrez et al. [8] looked at data from the Florida Cancer Data System (FCDS) to show that both survival and functional outcomes were indeed better at high volume centers. Although the majority of patients (68 %) received care at low-volume centers, 30-day mortality at high volume centers was lower (0.7 % vs. 1.5 %, $p = 0.028$). Long-term survival was also improved at high-volume centers, with a median survival of 40 months compared to 37 months at low-volume centers ($p = 0.002$). QOL may also be impacted by treatment at a low-volume center; the amputation rate was 13.8 % compared to 9.4 % for high volume centers ($p = 0.048$). Another study from the United Kingdom showed that only 21 % of patients were adequately worked up, and only 60 % received adequate treatment after an audit of sarcoma care [9]. The majority of these patients were treated by general surgeons and the authors called for treatment to be shunted toward specialists to improve care metrics. Several studies from Europe suggest that specialized care for sarcoma results in better compliance with guidelines and less variation in care [4, 9, 10]. The weight of the evidence currently available suggests that regionalization of sarcoma care results in improved survival outcomes and QOL. How this impacts cost and timeliness of care has yet to be determined, leaving the door open for well-designed cost-effectiveness analyses. Use of databases such as the NCDB or the Surveillance,

Epidemiology, and End Results (SEER)-Medicare datasets, which have been used by other regionalization studies, could also help to evaluate oncologic outcomes as a result of regionalization.

4 Soft Tissue Extremity Sarcoma

4.1 Neoadjuvant Chemotherapy

The use of neoadjuvant chemotherapy has several theoretical advantages, especially in high-risk extremity sarcoma. With visible disease an in vivo tumor response model is available. Shrinkage of a large tumor can potentially enhance limb salvage and decrease the morbidity associated with eventual surgery. Finally, early treatment of micrometastatic disease has the potential to improve long-term survival outcomes. Although an increase in perioperative morbidity due to myelosuppression and interference with optimal wound healing is a concern, this is not borne out by the data [11]. However, the evidence supporting the efficacy of chemotherapy alone in the neoadjuvant setting is underwhelming. Although an extensive review on the subject is beyond the purview of this chapter, some of the more pertinent studies are mentioned.

An EORTC randomized phase II trial compared neoadjuvant doxorubicin plus ifosfamide versus surgery alone in a high-risk population and failed to show better survival in the chemotherapy arm (5 years DFS 56 % vs. 52 %), and expansion into phase III study was abandoned [12]. Although a phase III study utilizing hyperthermia in combination with etoposide, ifosfamide, and doxorubicin (EIA) versus chemotherapy alone showed a relative hazard of 0.7 for the combination therapy, this approach is not currently used in the United States [13]. Besides the additional resources needed to establish hyperthermia, a major limitation of the study was that a comparison with surgery alone was not performed. The evidence to date suggests that there is no benefit to neoadjuvant chemotherapy plus surgery versus surgery alone for soft tissue sarcoma.

4.2 Neoadjuvant Chemoradiation

Although there are no randomized phase III studies on the topic of combination chemoradiation given in the neoadjuvant setting, some data suggest this may be an acceptable clinical choice. A RTOG phase II trial of the MAID regimen and interdigitated radiation therapy showed acceptable efficacy and toxicity [14]. Although no clear evidence of an improvement in cancer related survival was seen, preservation of QOL by acceptable morbidity with this approach was also confirmed in another study [11]. More data is needed with head-to-head comparisons between neoadjuvant chemoradiation versus surgery alone and neoadjuvant chemoradiation versus radiation alone.

4.3 Adjuvant Chemotherapy

There is a large body of literature on the use of adjuvant chemotherapy in soft tissue sarcoma which will not be reviewed in detail. Several meta-analyses of the published trials have been performed which are briefly discussed. In the initial study by the Sarcoma Meta-Analysis Collaboration (SMAC) group the addition of a doxorubicin-containing chemotherapeutic regimen following surgery compared to surgery alone showed a significantly longer local and distant recurrence-free survival, but not a statistically significant better overall survival (HR for death 0.89, 95 % CI 0.76–1.03). In the subset of patients with extremity and truncal sarcomas, a modest but significant benefit was seen for adjuvant chemotherapy, (HR 0.80, $p = 0.029$), which translates into a 7 % absolute benefit in overall survival at 10 years [15]. An updated meta-analysis conducted in 2008 showed an OR for local recurrence of 0.73 (95 % CI 0.56–0.94) and for distant recurrence of 0.67 (95 % CI 0.56–0.82) both in favor of chemotherapy. In contrast to the prior meta-analysis, the use of doxorubicin with ifosfamide was associated with a statistically significant overall survival benefit (HR 0.56, 95 % CI 0.36–0.85) [16]. Current consensus opinion is that adjuvant chemotherapy is not routinely recommended for patients with soft tissue sarcoma, but may be used in select cases for modest benefit [1].

4.4 Neoadjuvant Radiation

The advantages of using radiation in the neoadjuvant setting include downstaging of the tumor to increase chances of a margin negative resection, limitation of radiation dose to a smaller volume and minimizing long-term radiation-related morbidity. This has to be balanced against the risk of an increase in wound complications following surgery. What is the quality of the data to guide treatment sequencing for radiation use in extremity sarcoma? O'Sullivan et al. [20] conducted a randomized trial comparing preoperative with postoperative radiation in patients with extremity sarcoma with the primary endpoint being the rate of wound complications within 120 days of surgery. Wound complications occurred in 35 % of the preoperative group compared to 17 % in the postoperative group ($p = 0.01$). On follow up at 2 years after treatment, patients in the postoperative arm had greater rates of fibrosis, joint stiffness, and wound edema [21]. Generally, early complications were reversible with minimal impact on QOL while late radiation associated complications were not. Perhaps due to these findings an increase in the use of neoadjuvant radiation from 6.4 to 11.6 % from 2000 to 2009 was seen in a study of the National Cancer Database, with a corresponding decrease in postoperative radiation (34.3–29.2 %) during the same time period [22]. In a survey study of sarcoma specialists, we showed that radiation oncologists, physicians with >75 % of their practice devoted to sarcoma care, and those in practice <5 years had a preference for neoadjuvant radiation therapy [2]. Taken together, these data suggest that there is a trend toward an increasing use of neoadjuvant radiation for extremity

sarcoma due to equivalent local control and a decrease in irreversible late radiation associated morbidity. To date, no study on the cost-effectiveness of this approach has been conducted.

4.5 Adjuvant Radiation

The current standard of limb sparing surgery for the majority of extremity sarcomas is established based on evidence from randomized trials. The initial trials compared amputation alone versus limb sparing surgery plus adjuvant radiation therapy and showed equivalent rates of long-term survival [17]. Although there were no local recurrences in the amputation group compared to four in the limb sparing group, disease-free survival at 5 years was equivalent (71 % vs. 78 %, $p = 0.75$). This suggested that aggressive attempts at local control with amputation did not improve long-term survival and came at the expense of considerable physical limitation to the patient. Consequently, most modern series of extremity sarcoma have an amputation rate of <5 %.

Subsequent studies confirmed that limb sparing surgery alone had higher rates of local recurrence compared with limb sparing surgery plus radiation therapy. Yang et al. [18] randomized 91 patients with extremity sarcoma into two groups following surgery; external beam radiation versus no radiation. Following a median follow-up of 9.6 years, a significant decrease in the probability of a local recurrence but no difference in overall survival was seen. Although an improvement in local control was seen for both high-grade and low-grade tumors, the effect was more pronounced for high-grade tumors. A concurrent QOL study showed that patients who received radiation had significantly worse limb strength, edema, and range of motion. Although these deficits were mostly transient, further work is needed to identify a subset of patients at low risk for local recurrence who can undergo limb sparing surgery without adjuvant radiation therapy. A review of patients with T1 soft tissue sarcoma treated at the Memorial Sloan Kettering Cancer Center between 1996 and 2002 showed that in patients with a microscopically negative (R0) margin following surgery who did not receive radiation therapy, the cumulative incidence of local recurrence at 5 and 10 years was 7.9 and 10.6 % [19]. In this subset, surgery alone provided excellent local control rates without adjuvant radiation therapy, thus minimizing morbidity without compromising recurrence outcomes.

4.6 Brachytherapy

Advantages of brachytherapy over conventional external beam radiation include minimization of the radiation dose to the surrounding tissue and shorter treatment times. A phase III trial comparing the use of brachytherapy and surgery versus brachytherapy alone showed an improvement in local control with the use of brachytherapy [23]. After 76 months of median follow up, 5-year actuarial local

control rates were 82 % in the brachytherapy group and 69 % in the surgery alone group ($p = 0.04$). There was no difference in disease-specific survival rates. However, this improvement in local control was seen only for high-grade tumors and not for low-grade ones, with no improvement in long-term survival even in the high-grade subset [24]. To date there has not been a head-to-head comparison for brachytherapy versus external beam radiation in terms of local control, morbidity, or cost.

4.7 Surgery for Local Recurrence

Local failure in management of soft tissue extremity sarcoma manifests clinically as a local recurrence. Local recurrence is generally a poor prognostic sign and is associated with distant metastasis in a significant proportion of patients [25]. Once confirmed by physical exam or imaging subsequent management can be challenging. If resectable, then further surgery represents an attempt to re-establish local control. However, should aggressive re-resection be pursued in patients who are at high risk of dying from distant disease, especially in the absence of options for effective systemic control? Although there is no direct comparison between patients with local recurrence undergoing re-resection compared to those treated nonsurgically, we can use some published data to inform the debate. Ramanathan et al. [26] developed a prognostic index in patients developing a local recurrence to identify initial tumor size, histologic grade, and time to recurrence as the primary determinants of distant metastases and survival. This suggests that surgical re-resection for locally recurrent disease should be limited to patients at low risk for the development of synchronous or metachronous systemic metastases.

5 Retroperitoneal Sarcoma

5.1 Biopsy Versus No Biopsy

The question of a preoperative biopsy for a suspicious retroperitoneal mass is a vexing one for the nonspecialist. Often biopsies carried out target the wrong part of the tumor, violate oncological principles, and do not provide information that would result in a change in management. Generally agreed on indications for biopsy include presentation with metastatic disease and confirmation of the diagnosis in the neoadjuvant setting prior to initiation of chemotherapy [27]. Routine biopsy for a retroperitoneal mass felt to be a sarcoma after adequate work-up is not recommended. Some advocate performance of an intraoperative biopsy at the time of definitive surgery to confirm the diagnosis prior to radical surgery [27].

Open biopsy involves general anesthesia and a second operation for definitive treatment. CT-guided core biopsy is less invasive and costly but runs the risk of seeding of the needle tract [28]. An adequately performed core biopsy has been shown to be 95 % accurate for diagnostic purposes, but less so for detailed

information such as grade, and can be considered the modality of choice if a biopsy is indicated [29]. In general, if the information gained by a preoperative biopsy is not going to change management, then it is not routinely recommended.

5.2 Radical Compartment Surgery Versus Complete Resection

The basic principles of surgery for retroperitoneal sarcomas involve complete removal of the tumor with negative margins. Violation of the pseudocapsule often results in a marginal resection and is to be avoided. The best outcomes are obtained in series that have achieved an R0 or microscopically negative resection. Macroscopically incomplete resection (R2) does not result in better survival outcomes than biopsy alone [30]. These facts have led to increasingly radical surgery to improve margin negative rates and long-term survival. Multivisceral resections and vascular reconstruction are techniques used to accomplish this. Theoretically, this should also lead to increased morbidity, yet there is little data to show this, likely because of publication bias. Analysis of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) showed that multivisceral resection of contiguous organs in patients undergoing surgery for retroperitoneal sarcoma did not lead to an increase in 30-day or overall morbidity [31].

More recently radical compartment surgery has been proposed as a surgical technique to improve local control and possibly survival outcomes. This involves complete en bloc removal of organs present in the compartment of the abdomen containing the tumor, even if the organs themselves are not involved directly. Bonvalot et al. [30] reported a 93 % complete macroscopic resection rate when the median number of organs resected with the tumor was 2. At 5 years, overall survival was 65.4 % and local and distant recurrence cumulative incidences were 22.3 and 24.2 %, respectively. These results come at the expense of serious morbidity in 18 % and surgical reintervention in 12 % of patients. The same group has previously shown that compartmental resection predicted a 3.29-fold lower rate of abdominal recurrence compared with complete resection on multivariable analysis [32]. However, compartmental resection was not associated with an improvement in overall survival, which has led to criticism of this technique [33]. Until the role of selection bias can be eliminated by a head-to-head randomized comparison with complete resection, the jury is still out on whether compartment surgery can be considered as standard of care for improving local recurrence. The relative impact on QOL and cost of treatment will also need to be further studied.

5.3 Radiation Therapy

The utility of radiation to improve locoregional control as an adjunct therapy to surgery for retroperitoneal sarcoma is yet to be clearly defined, with no randomized trials to demonstrate efficacy. Nevertheless, local recurrence remains the main cause

of death even in patients with radical compartmental resection, suggesting that further improvement in local control will not be achieved by surgery alone. The American College of Surgeons Oncology Group (ACOSOG) attempted a phase III randomized trial (Z9031) to address the role of radiation in retroperitoneal sarcoma. Accrual to the trial was poor, leading to early closure [34]. Leaving asides issues of efficacy, treatment sequencing and modality of radiation delivery also need to be clarified for retroperitoneal sarcoma.

Retroperitoneal sarcomas present an unique challenge for radiation therapy, in which the area of the body to be covered may be quite large and potential benefit balanced against the morbidity of scatter damage to adjacent organs. Radiation has been used in the pre-, intra- and postoperative setting for these tumors. Potential advantages for preoperative radiation include shielding of adjacent organs by the tumor mass itself, better assessment of tumor volume, and a better response to radiation due to improved oxygenation. Resection of the tumor often results in displacement of normal tissue into the tumor bed, potentially increasing the dose of radiation delivered to tissue such as bowel in the postoperative setting [35]. The ideal sequence with surgery should be determined either by an improvement in local recurrence, overall survival or improvement in QOL as manifested by a reduction in complications.

Data on treatment sequencing to date is equivocal, although comparable survival and local recurrence results have been seen for preoperative radiotherapy when compared with 'traditional' postoperative therapy. Pawlik et al. [36] reported on the results from two prospective trials that showed a 5-year disease free survival rate of 46 %. This was even higher in patients who had a macroscopically negative resection after completing radiotherapy; 5-year local recurrence free survival of 60 %. Currently, preoperative radiotherapy is considered for intermediate or high-grade retroperitoneal sarcomas likely to have close or positive margins following resection. In most cases, a preoperative biopsy is needed to verify histology prior to initiation of therapy. Toxicity and impact on quality of QOL has been variable in the reported series but, in general, appear to be less with preoperative radiation [35, 37].

Modality of radiation delivery also remains unsettled. Attempts have been made to minimize toxicity by alternative targeting methods. Intensity modulated radiation therapy (IMRT) is an approach which has shown promise in minimizing delivery of high-dose radiation to regions of the body with low radiation tolerance, such as small bowel [38]. Intraoperative radiotherapy (IORT) can be delivered alone or in combination with pre- or postoperative external beam radiotherapy. This technique is limited by the need for a specialized operating room and equipment. Nevertheless, the use of IORT does appear to augment local control, albeit at the cost of additional toxicity. In one trial looking at long-term outcome in patients with retroperitoneal sarcoma treated by preoperative radiation, surgical resection and IORT, patients who underwent resection only had worse overall survival (30 % vs. 70 %) and local control (61 % vs. 83 %) compared to patients who had both resection and IORT [39]. Additional toxicity that has been reported with IORT is likely due to the exposure of tissue to the high doses employed and includes neuropathy, ureteral fistula, and bowel obstruction [40]. Brachytherapy is an alternative technique that has been looked at for

increasing the dose of radiation delivered to the tumor bed. Again, although the local control rates are promising, toxicity remains substantial, with reoperation rates of 21.5 % reported in one series in addition to long-term issues [41]. At this time, more prospective studies with long-term follow up are needed to establish the modality of choice to deliver radiotherapy for retroperitoneal sarcoma.

5.4 Margin Reporting

Current NCCN guidelines recommend that pathologists with expertise in STS should review pathological assessment of biopsies and resected specimens, especially to establish the initial diagnosis. Ancillary techniques such as cytogenetics, immunohistochemistry, electron microscopy, and molecular genetic testing should be available as needed. The report itself should include details about the primary, depth, size, histologic grade, presence or absence of necrosis, status of the excision margins, tumor, node, and metastases (TNM) stage. Additional features are mitotic rate, presence or absence of vascular invasion and the type and extent of inflammatory infiltration [1]. In particular, the margin status of the resected specimen should be clearly delineated, as this has direct bearing on the need for additional therapy and local recurrence.

No well-publicized study to date has looked at the completeness of pathology reporting for sarcoma following surgical resection. Audits of national registries in the Netherlands and in Scandinavia show considerable variability in reporting of margins following surgery for sarcoma [10, 42]. Margin status has direct bearing on decisions about adjuvant treatment and local recurrence, which in turn may influence long-term survival. How variability of margin reporting influences comparability of outcomes in the United States is essentially unknown.

5.5 Surveillance Imaging

Surveillance following multidisciplinary treatment of sarcoma is an issue with little research to guide management. A study conducted by Whooley et al. [43] of 141 patients with extremity sarcoma showed that 20 patients developed local recurrence on follow up, of which only one was detected by imaging and the rest by physical examination. Furthermore, 45 % of these recurrences were detected by the patient in between scheduled doctor visits. The conclusion was that a thorough history and physical combined with surveillance chest Xray was cost effective, whereas routine laboratory testing and imaging of the primary tumor site were not. Others have recommended a more intensive surveillance regimen for high-risk extremity sarcomas with more frequent chest imaging and abdominopelvic CT scan for retroperitoneal sarcoma [44]. Does more intense surveillance improve outcomes for patients with recurrent sarcomas? How does this influence QOL and cost of care? These questions are currently unanswered.

In sum, we have a smattering of data that makes it difficult to establish evidence-based treatment guidelines. In part, this is due to the nature of this disease; it is rare, with a considerable amount of histological variation, making timely accrual to large trial difficult. The time needed to enroll patients, test an intervention, and determine recurrence/survival would probably be largely outstripped by the evolution of medical advances. Instead, we need to mine large databases to get sufficient numbers; since trials have been so difficult to carry out in this disease, observation studies or decision analyses would be the best way to determine the best course of treatment for extremity and retroperitoneal sarcomas. Cost-effectiveness studies and meta-analyses also have a place in further developing the realm of sarcoma studies.

6 Conclusions and Future Directions

Sarcoma care involves multidisciplinary collaboration and the use of several treatment modalities. Questions about treatment efficacy and sequencing lead to varying approaches in clinical management. Further research is needed to identify ideal treatment sequencing for chemotherapy and radiation with surgery. For interventions that do not improve local recurrence or overall survival, additional outcomes such as quality of life and cost should be considered when considering clinical use. The table below summarizes the discussion in this chapter and highlights areas of further research needed on the subject.

	Outcome		
Clinical area	Local recurrence/overall survival	Quality of life	Cost
Multidisciplinary consultation	?	NA	?
Guideline oriented care	?	NA	Lower
Regionalization of sarcoma care	Improved	Improved	?
Soft tissue extremity sarcoma			
Neoadjuvant chemotherapy	Not improved	Similar	?
Neoadjuvant chemoradiation	Not improved	Similar	?
Adjuvant chemotherapy	Modest improvement in selected patients	?	?
Adjuvant radiation	Improved local control	Worse	Higher
Neoadjuvant radiation	Equivalent local control	Improved	?
Brachytherapy	Improved local control	?	?
Radiation modality	?	?	?
Surgery for local recurrence	Improved	?	?
Retroperitoneal sarcoma			
Preoperative biopsy	NA	NA	?

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	Outcome		
Radical compartment surgery	?	?	?
Radiation	?	?	?
Surveillance	?	?	?

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