European Journal of Surgical Oncology 45 (2019) 1762–1769

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Resuscitating extremities after soft tissue sarcoma resections: Are functional reconstructions an overlooked option in limb salvage? A systematic review

Enrico Martin [a], Max J. Dullaart [a], Michiel A.J. van de Sande [b, c], Winan J. van Houdt [d], Pascal P.A. Schellekens [a], J. Henk Coert [a, *]

[a] Department of Plastic and Reconstructive Surgery, University Medical Center Utrecht, the Netherlands
[b] Department of Orthepedic Surgery, Leiden University Medical Center, the Netherlands
[c] Department of Pediatric Orthopedic Surgery, Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands
[d] Department of Surgical Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 29 March 2019
Received in revised form
7 May 2019
Accepted 20 May 2019
Available online 31 May 2019

Keywords:
Soft tissue sarcoma
Functional reconstruction
Nerve
Functionality
Systematic review

ABSTRACT

Background: Although resection of extremity soft tissue sarcomas can occasionally lead to large disabilities, literature regarding the necessity and outcome of functional reconstructions are scarce. The goal of this review is to assess outcomes and usage of functional reconstructions in light of multimodal treatment.
Methods: A systematic search was performed in July 2018 in PubMed and Embase databases according to the PRISMA guidelines. Search terms related to 'soft tissue sarcoma' and 'functional reconstruction' were used. Case series evaluating outcomes of functional reconstructions after STS resection were included. Functional reconstructions were limited to free functioning muscle transfers, tendon reconstructions, and nerve reconstructions. Qualitative synthesis was performed on all studies. Tumor grade, multimodal treatment, reconstruction, outcomes, and complications were collected from individual patient data. Results were summarized by tumor site.
Results: Fourteen studies were included after full-text screening. A total of 134 patients were described, of which the majority (74.9%) had functional reconstructions in the lower extremity. Radiotherapy and chemotherapy were administered in 60.3% and 49.4% respectively. Free functioning muscle transfers were used in 41.0% of all cases, tendon reconstructions in 58.2%, and nerve reconstructions in only 12.7%. A wide variety of outcome measures were used. Most patients regained good functionality, also after multimodal treatment. Unfavorable outcomes were often related to flap failure or allograft tendon rupture.
Conclusion: Functional reconstructions in extremity STS are rarely described, but generally result in good functionality in spite of multimodal treatment. Early participation of reconstructive surgeons may help achieve ideal functional and oncological outcomes.

Introduction

With an annual incidence of approximately 4 cases per 100,000, soft-tissue sarcomas (STS) comprise 1% of adult cancers [1]. Around 15% and 35% of all STS arise in upper and lower extremities respectively [2]. Resection with clear margins remains key to improve survival and diminish local and distant recurrences [3,4]. While amputation was not uncommon in the past, limb-sparing surgery (LSS) has become standard of care as it improves functionality providing it does not decrease local control [5,6]. Radiotherapy is often part of limb-sparing treatment for local control and many centers are increasingly preferring preoperative to postoperative radiotherapy because it has lower long-term toxicities, albeit its higher postoperative complication rates [7–12].

The rise of limb-salvage surgery has partly been due to a combination of improved local control using radiotherapy and an

* Corresponding author. Department of Plastic and Reconstructive Surgery G04.126, University Medical Center Utrecht, PO Box 85060, 3508 AB, Utrecht, the Netherlands.
E-mail address: j.h.coert@umcutrecht.nl (J.H. Coert).

https://doi.org/10.1016/j.ejso.2019.05.024
0748-7983/© 2019 Published by Elsevier Ltd.

increase in reconstructive possibilities, but the main goal of plastic surgery has traditionally been soft tissue coverage [13]. Functional reconstructions, the replacement of lost functions due to complete muscle, tendon, or nerve resections, are gaining popularity in trauma cases but still little can be found in STS literature [13–15]. This is in contrast with the reconstruction of major arteries, and to a lesser extend veins, which are more common practice in centrally located sarcoma, especially in leiomyosarcoma where the tumor derives from a vein. Several reasons may underlie the latter. Firstly, in most cases where muscles are resected, the remaining muscles are able to hypertrophy after resection and partially replace the function of the resected muscle [16]. Secondly, about a quarter of STS grow superficially, obviating the need for large muscle resection [17]. Thirdly, the focus of treatment is obtaining adequate margins and improving oncological outcome, as well as preventing major complications or wound healing problems. Therefore, research has not focused on the potential role of functional reconstructions so far. Finally, the rather poor prognosis of some STS patients and limited knowledge of rehabilitation may withhold surgeons to consider such reconstructions. As a result functional reconstructions are often not implemented as common practice [13,14,18]. It should be noted that not only motor deficits are regarded as functional deficits; sensory loss may also be present after resection of sensory or mixed nerves.

Achieving clear margins in LSS may often be compromised by involvement of critical structures such as nerves, bones, or arteries [19]. Resection of aforementioned structures can result in large functional deficits [19–24]. Techniques as preoperative limb perfusion, preoperative radiotherapy, and epineural dissection are several ways that have shown to diminish the need for resection of such critical structures [8,25–27]. However, their resection is sometimes inevitable, especially when the tumors are encasing major structures or are deriving from major structures such as MPNSTs which may originate from large nerves. Frequently, such involvement is considered an indication for amputation because of its anticipated functional deficit [19,28,29]. However, since STS has a relatively high incidence at a younger age, and treatment options are slowly improving, more STS patients will become long-term survivors [30], resulting in an increased amount of patients with lifelong disabilities.

The purpose of this review is to summarize current literature on functional reconstructions used in extremity STS and assess their feasibility and outcomes in light of multimodal treatment. This may help sarcoma teams to improve selection of future candidates for such reconstructions before initial treatment.

Methods

Literature search

A systematic search was performed in both PubMed and Embase databases according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines, in order to identify all potentially relevant articles as of July 2018. The search string was built with the help of a professional librarian using search terms related to “soft tissue sarcoma” and “functional reconstruction”. The exact search syntaxes for PubMed and Embase are shown in Supplementary Table S1. Studies were included that evaluated outcomes of functional reconstructions after soft tissue sarcoma resection. Only free functioning muscle transfers, tendon reconstruction using transfers or allografts, or any nerve reconstruction were considered a functional reconstruction. Replantation of tendons or muscles after tumor excision was not regarded as such. Exclusion criteria included lack of full text, outcomes not stratified for soft tissue sarcomas, case reports, no use of functional outcome measures, no human studies, and languages other than English, Dutch, French, or German. The initial review was conducted by two independent authors (E.M. and M.J.D.). Disagreements were solved through discussion, in which one additional author was involved (J.H.C.).

Data extraction and synthesis

All data was extracted at an individual patient level and included tumor grade (high/low), tumor site, treatment with radiotherapy or chemotherapy, reconstruction(s) performed, oncologic (survival, local recurrence, metastasis) and functional outcomes, and duration of follow-up. Patients with bone sarcomas or non-extremity sites were excluded from qualitative synthesis, as well as patients with incomplete outcome data. Patients were also excluded in case of soft tissue coverage only, or in case individual patient data in tables and article text did not clarify if functional reconstruction was performed. Results were summarized and stratified per anatomical site: shoulder, upper arm, forearm, hand/wrist, upper leg, and lower leg. In each study the mean of each functional outcome was calculated per muscle group.

Results

After removal of duplicates, a total of 2902 citations were identified in PubMed and Embase databases. 736 potentially relevant articles were selected through title/abstract screening, of which 14 studies remained for qualitative synthesis after full-text screening (Fig. 1).

Study characteristics and multimodal treatment

All studies were small retrospective cohort studies or case series describing a total of 134 patients with any form of functional reconstruction after extremity STS resection (Table 1). Of all reconstructions 26% were performed in the upper extremity and 74.9% in the lower extremity, which is in line with the anatomical distribution of sarcomas. Reconstructions were generally performed if loss of a major muscle was anticipated or present due to large or complete muscle group resection, tendon resection, or major nerve resection. Free functioning muscle transfers were used in 41.0% of all cases, tendon reconstructions in 58.2%, and nerve reconstructions in 12.7%. Most studies included patients with high grade sarcomas, which resulted in 60.3% (range: 0–100%) of all cases using radiotherapy, and 49.4% (range: 0–70%) chemotherapy. A wide variety of functional outcome measures were used, of which the Musculoskeletal Tumor Society scoring system (MSTS) and Medical Research Council muscle grade (MRC) were most commonly used.

Shoulder and upper arm

Four different studies included reconstructions of shoulder and upper arm functions in 13 patients (Table 2). The deltoid muscle was most commonly reconstructed with a pedicled innervated latissimus dorsi flap (LD), but a free functioning tensor fascia lata (TFL) flap was also described. Both operations yielded good muscle grades (M4), good range of motion in shoulder abduction, and high MSTS scores (both >90%). Loss of elbow flexion was commonly reconstructed with the use of a pedicled LD [13,31], but a free functioning gracilis transfer has also been performed [31]. Although relatively low MSTS scores were seen on average in one study (63.3%), patients did regain M4 elbow flexion [31]. Toronto Extremity Salvage Scores (TESS) were however excellent in another study (98.7%) [13]. The latter

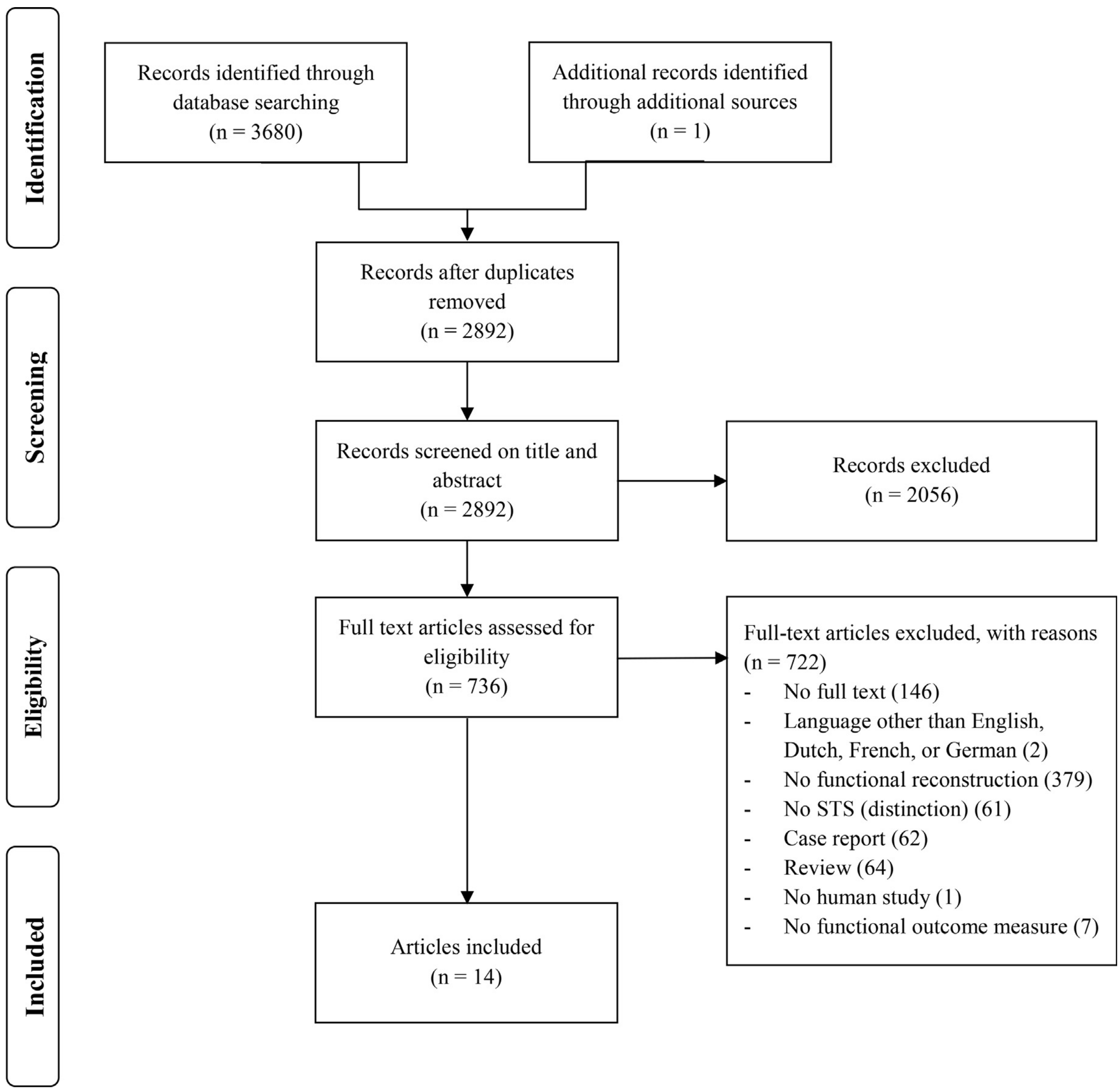

Fig. 1. Flowchart depicting study selection.

study also presented one patient with loss of elbow extension reconstructed with the use of a pedicled LD as well yielding good results (TESS = 100%) [13]. All studies that evaluated muscle grade, showed that all patients regained at least M3 muscle power, regardless of multimodal therapy.

Forearm

Functional reconstructions in forearm compartments are described in four studies in nine patients. Loss of function in the flexor compartment was either reconstructed by tendon transfers [13] or a free LD flap [32]. Lost extensor compartment function, leading to either loss of wrist extension, finger extension, or a combination, was reconstructed with a free gracilis flap [32,33], a free LD flap [32], or a composite anterolateral thigh flap (ALT) [34]. A composite ALT may contain part of the vastus lateralis, TFL, and iliotibial band. All patients regained reasonable muscle grade (M3-4) and reasonable to excellent MSTS scores (66.7–100%) and TESS (61.3–92.6%) [34]. No nerve reconstructions have been described in these studies.

Hand and wrist

Defects after STS in hand and wrist area are diverse and according to each specific deficit three different studies describe their reconstructions performed in 13 patients [13,35,36]. One study specifically reported on thumb reconstructions after STS [35]. These were commonly reconstructed with tendon transfers, but a successful toe-to-thumb reconstruction has also been described. On average, high MSTS scores were yielded (95.2%). Other deficits of the hand occurred after tendon resections or resection of digital nerves. Tendon defects of other fingers could often be reconstructed with the use of allografts or tendon transfers [13,36]. Functional results were variable, but of the three unfavorable outcomes, one was related to tendon rupture [13]. Digital nerve defects and median nerve defects were reconstructed with the use of sural nerve grafts or lateral antebrachial cutaneous nerve grafts [35,36]. In one study, no neuropathic pain was observed after nerve reconstruction [36]. No other sensibility outcome measures were described. No study reported cases of nerve transfers used to restore sensation in the hand.

Table 1
Study characteristics.

Study, year	Patients			Reconstructions			High grade tumors	Other treatment		Functional outcome measure	F–U (mo)
	Total	UE	LE	FFMT	Tendon	Nerve		Rx	Cx		
Doi et al., 1999	17	11.8%	88.2%	100%	29.4%	5.9%	Yes	0%	64.7%	MSTS, MRC, ROM lag, walking aid	60 (27–106)
Fischer et al., 2015	43	0%	100%	0%	100%	0%	*NA*	51.2%	27.9%	ROM, strength, Karnofsky, QoL, satisfaction, walking aid	66 (22–107)
Grinsell et al., 2012	18	16.7%	82.3%	100%	0%	11.1%	Yes	100%	0%	MSTS, MRC, LEFS, DASH	18 (6–42)
Gunterberg et al., 1980	2	0%	100%	0%	100%	0%	No	NA	NA	ROM, strength	40 (36–44)
Innocenti et al., 2009	10	0%	100%	100%	40%	0%	Yes	80%	70%	MSTS, MRC	69 (21–136)
Mehrara et al., 2008	7	100%	0%	0%	71.4%	57.1%	*NA*	28.6%	0%	MSTS	47 (*NA*)
Melendez et al., 2001	6	0%	100%	0%	0%	100%	*NA*	83.3%	50%	MRC, S	12 (5–42)
Mirous et al., 2016	3	100%	0%	0%	100%	66.7%	Yes	33.3%	66.7%	MSTS, DASH, VAS	54 (12–156)
Mundinger et al., 2014	12	100%	0%	0%	100%	0%	Yes	83.3%	*NA*	TESS	43 (*NA*)
Muramatsu et al., 2009	4	100%	0%	100%	0%	0%	Yes	0%	*NA*	MSTS	69 (12–173)
Muramatsu et al., 2014	4	100%	0%	0%	100%	0%	Yes	*NA*	*NA*	MSTS, MRC, ROM	50 (12–106)
Stranix et al., 2017	4	0%	100%	100%	0%	0%	Yes	*NA*	*NA*	MSTS	22 (20–36)
Tokumoto et al., 2018	2	0%	100%	0%	0%	100%	Yes	*NA*	*NA*	MRC, S	12 (3–24)
Walley et al., 2017	2	0%	100%	100%	0%	0%	Yes	100%	50%	MSTS, KSS, ROM, MRC, walking aid	19 (17–21)
Total	134	26.1%	74.9%	41.0%	58.2%	12.7%		60.3%	49.4%		

DASH: disability of arm, shoulder, and hand, FFMT: free functioning muscle transfer, F–U: follow-up, KSS: knee society score, LE: lower extremity, mo: months, MRC: medical research council muscle grade, MSTS: musculoskeletal tumor society rating scale, N: number of, NA: not available, No. pt: number of patients, QoL: quality of life, ROM: range of motion, S: sensibility, TESS: Toronto extremity salvage score, UE: upper extremity, VAS: visual analog scale.

Table 2
Average functional outcomes in upper extremity reconstructions.

	Study	Flaps (N)	Objective measures[a]		Subjective measures[a]			
			MRC	ROM	MSTS	DASH	TESS	VAS
Shoulder& upper arm	*Deltoid*							
	Doi et al.	TFL (1)	4.0	0° lag	93.3%			
	Muramatsu et al.	Pedicled LD (4)	3.8	164°	91.5%			
	Trapezius							
	Grinsell et al.	Pedicled LD (1)	5.0		100%	0		
	Biceps							
	Grinsell et al.	Pedicled LD (1), gracilis (1)	4.0		63.3%	22.5		
	Mundinger et al.	Pedicled LD (3)					98.7%	
	Triceps							
	Mundinger et al.	Pedicled LD (1)					100%	
Forearm	*Flexor compartment*							
	Mundinger et al.	TT: FDS to FCR (1), PL to FPL (1)					77.0%	
	Muramatsu et al.	LD (1)			83.3%			
	Extensor compartment							
	Doi et al.	Gracilis + PL (1)	3.0	30°	93.3%			
	Muramatsu et al.	Gracilis (2), LD (1)	4.0[b]		88.9%			
	Stranix et al.	Composite ALT (1)			80%			
Hand & wrist	*Hand*							
	Mehrara et al.	Toe-to-thumb (1)			95.2%			
	Mirous et al.	TT: FDS to FPL (2), ECR to EPL (1), FPL to P1 (1) LABCN (2), sural nerve (1) Allografts: finger flexion (2)TT: PL to ECRL and ECRB (1), EIP to EPL (1), hemiFCR to APL (1)Sural nerve (2)			75.3%	21.3		0
	Mundinger et al.	Allografts: finger flexion (1), finger extension (1), wrist extension (1)					65.1	

APL: abductor pollicis longus DN: digital nerve, ECRB: extensor carpi radialis brevis, ECRL: extensor carpi radialis longus, EIP: extensor indicis proprius, EPL: extensor policis longus, FCR: flexor carpi radialis, FDS: flexor digitorum superficialis, FPL: flexor pollicis longus, LABCN: lateral antebrachial cutaneous nerve, LD: latissimus dorsi flap, P1: first phalanx, PL: palmaris longus, TFL: tensor fascia lata flap, TT: tendon transfer.

[a] DASH: disability of the arm, shoulder, and hand questionnaire (0–100 points, higher score correlates to larger disability), MRC/MMT: medical research council muscle grade/manual muscle testing (0–5), MSTS: musculoskeletal tumor society scale (0–30 points, higher score correlates to higher function), ROM: range of motion (degrees), TESS: Toronto extremity salvage score (0–150 points, high score correlates to higher function), VAS: visual analog scale (0–10).

[b] MRC outcome only given in one case.

Upper leg and hip

Eight studies reported a total of 89 patients with reconstructions of upper leg and hip functions (Table 3). After resection of the complete hamstrings, knee flexion was regained with the use of free innervated LD flaps, resulting in good functional outcomes (M3-4, MSTS 63.3–86.7%) [31,33]. One patient did not regain active knee flexion (M2) which resulted in the use of a static knee brace and the lowest MSTS score (63.3%) [33]. Loss of knee extension function was most commonly reconstructed with a free LD flap as well, but a gracilis or sartorius tendon transfer was concomitantly performed in cases with complete quadriceps resection [33,37]. Outcomes were variable ranging from M2-5. A total of 3/17 patients did not regain more than M2 muscle power, most of which resulted

Table 3
Average functional outcomes in lower extremity reconstructions.

	Study	Flaps (N)	Objective measures[a]			Subjective measures[a]				
			MRC	ROM	S	MSTS	KSS	LEFS	SF-36	Karnofsky
Upper leg & hip	*Hamstrings*									
	Doi et al.	LD (5)	3.2	20° lag		82.7%				
	Grinsell et al.	LD (4)	4.0			91.2%		63.5		
	Quadriceps									
	Doi et al.	LD (6) + gracilis (3), RF + gracilis (1)	3.7	9° lag		90.5%				
	Fischer et al.	BF (17) +/− gracilis or semitendinosus (6)	4.0	66%					78%	82
	Grinsell et al.	Gracilis (1), TRAM (2)	5.0			100%		72.3		
	Innocenti et al.	LD (10) + sartorius (4)	2.8			Good[b]				
	Stranix et al.	Composite ALT (1)				76.7%				
	Walley et al.	Composite ALT (2)	4.5	5–75°		71.7%	77			
	Adductors									
	Doi et al.	LD (1)	3.0	0°		96.7%				
	Grinsell et al.	Gracilis (1), RA (1)	4.5			86.7%		69.0		
	Gluteus									
	Grinsell et al.	LD (1), TRAM (1)	5.0			100%		80.0		
	Sciatic nerve									
	Melendez et al.	Peroneal nerve (5) +/− sural nerve (3)	Knee: 5.0 Ankle: 2.0		Protective					
	Tokumoto et al.	Vascularized sural nerve (2)	Knee: 4.0 Ankle: 1.0		Protective					
Lower leg	*Anterior compartment*									
	Doi et al.	Gracilis (2)	3.5	0° lag		95.0%				
	Grinsell et al.	Gracilis (1)	5.0			100%		78.0		
	Gunterberg et al.	TT: TP to EDL and PT (2)		0–5°						
	Stranix et al.	Composite ALT (2)				85.0%				
	Posterior compartment									
	Grinsell et al.	LD (1), gracilis (1), parascapular + sural nerve(1)	4.0			91.1%		55.0		

ALT: anterolateral thigh flap, BF: biceps femoris muscle transfer, EDL: extensor digitorum longus, KSS: knee society score, LD: free functioning latissimus dorsi muscle flap, LEFS: lower extremity functional scale, MRC: medical research council muscle grade, MSTS: musculoskeletal tumor society rating scale, N: number of, PT: peroneus tertius, ROM: range of motion, RA: rectus abdominis muscle flap, RF: free functioning rectus femoris muscle flap, SF-36: short-form 36, TESS: Toronto extremity salvage score, TFL: tensor fascia lata flap, TP: tibialis posterior muscle, TRAM: transverse abdominal muscle flap, TT: tendon transfer.

[a] = DASH: disability of the arm, shoulder, and hand questionnaire (0–100 points, higher score correlates to higher disability), Karnofsky: Karnofsky performance status scale (0–100, higher score correlates to higher function), KSS: knee society score (0–100 points, higher score correlates to higher function), LEFS: lower extremity functional scale (0–80 points, higher score correlates to higher function), (0–5), MRC/MMT: medical research council muscle grade/manual muscle testing (0–5), MSTS: musculoskeletal tumor society scale (0–30 points, higher score correlates to higher function), ROM: range of motion (degrees), SF-36: short-form 36 (8 subdomains, total: 0–100%, higher score correlates higher well-being).

[b] no specified percentages.

in a fair MSTS score. In one patient with flap failure, knee extension was completely absent and a poor MSTS score was observed [37]. Two studies evaluated the effect of a contralateral composite ALT flap, which showed good muscle grade (M4-5) and reasonable MSTS scores (63.3–80%) [34,38]. A free rectus femoris flap, transverse abdominal muscle flap (TRAM), and free gracilis flap have also been described all of which yielded high functional outcomes (M4-5, MSTS 100%) [31]. Tendon transfers using the biceps femoris tendon for reconstruction of knee extension have been described in one study which resulted in an M4 muscle grade on average [39]. These tendon transfers sometimes included a gracilis or semitendinosus tendon as well, depending on surgeon preference. However, such additional tendons did neither increase power nor functionality, but did increase wound dehiscence and lymph edema rates [39]. Adductor muscles of the leg were reconstructed using either a free LD, free gracilis, or a free rectus abdominis flap [31,33]. All of which regained reasonable to excellent muscle power (M3-5) and good MSTS scores (86.7–96.7%). Reconstruction of the gluteal muscle after STS resection has also been described in one study [31]. Either a free LD flap or TRAM was used, both resulting in M5 hip extension and 100% MSTS scores. Sciatic nerve reconstruction after STS resection was described in two studies [40,41]. Gaps of 11–19 cm were reconstructed using peroneal nerves or (vascularized) sural nerves. Both studies combined, more than half of all patients regained protective sensation of the foot sole, but all patients regained some protective sensation in any part of the foot at least one year postoperatively [40,41]. Also, while motor function of the lower leg commonly sustained, knee flexion was often unharmed. In one study, only two patients regained M3-4 dorsiflexion and plantar flexion [40].

Lower leg

Functional deficits of the lower leg were reconstructed in four studies describing 10 patients. The anterior compartment of the lower leg mainly provides foot and hallux dorsiflexion and has been reconstructed in seven patients. Both free flaps and tendon transfers were performed. Two studies described a free gracilis transfer resulting in good muscle power (M3-5), and excellent MSTS scores (90–100%) [31,33]. Composite ALTs also resulted in good results in one study [34]. A tendon transfer of the tibialis posterior to the extensor digitorum longus and peroneus tertius showed that the foot could remain in neutral position, but dorsiflexion beyond that point was minimal [42]. The posterior compartment's primary function is plantar flexion. One study describes reconstructions of this compartment using either a free LD, gracilis or parascapular flap and sural nerve [31]. These reconstructions generally provided good motor function (M3-5) and high MSTS score (83.3–100%).

Surgical complications

A total of 31 patients (23.8%) had postoperative complications. Most of these complications (67.7%) were wound-related, such as superficial infections, wound dehiscence, and seroma. Other complications that occurred were lymph edema (n = 5), venous thrombosis (n = 2), fistula (n = 1), hematoma (n = 1), and femoral fracture (n = 1). Most complications (51.6%) were reported by a single study using different biceps femoris transfer for the restoration of knee extension [39]. Overall, flap failure occurred in two patients [31,37]. One patient had a pedicled LD for reconstruction of arm flexion which was replaced with a free gracilis flap after which an M4 muscle grade was obtained [31]. The other patient ended up with poor functional outcomes [37]. Tendon rupture after reconstruction of the hand occurred in one patient as well, which also resulted in a poor MSTS score [13]. Both patients did not receive radiotherapy or chemotherapy in any modality, but do show that failed reconstructions give poor functional outcomes.

Discussion

Functional reconstructions in extremity STS are uncommon, yet good muscle grades and high functional outcome scores can be expected when performed even if radiotherapy and chemotherapy are used. Poor outcomes are seen after flap failure, which are not restricted to patients with multimodal therapy. Reconstructions are most commonly used after resection of a complete muscle group. The type of reconstruction depends mainly on the defect size and location. While large muscles in proximal extremities will need larger muscle transfers to restore function, more distal defects often require tendon repair by transfer or grafting. Nerve reconstructions using grafts or transfers are also possible in selected cases, yet have rarely been described. Such reconstructions are especially of interest in distal extremities to restore both motor and sensory function.

Reconstructions in STS

As limb salvage surgery has emerged as standard of care over the past decades and reconstructive possibilities have increased, an increasing amount of extremity STS patients survive with salvaged limbs. However, in a few cases resection of neurovascular bundles and/or complete muscle compartments is inevitable [19]. Depending on location and extent of muscle resection different degrees of disability will arise. Unfortunately, almost no studies report on the difference in functionality between patients undergoing a resection for STS only and patients that undergo functional reconstruction alongside resection. One study showed that in lower extremity STS receiving functional reconstructions had improved function [18]. Moreover, it was shown that albeit slightly longer operative times and length of hospital stay, functional reconstructions added up to be cost-effective [18]. Selection of ideal candidates is however important when considering functional reconstructions preoperatively. Resection of many muscles and tendons and even some nerves do not result in significant functional deficits. For instance in upper leg STS, only resection of three or four heads of the quadriceps muscle or the complete hamstring compartment will result in a considerable impairment as remaining muscles are not able to fully compensate for the resected muscle [16,33]. However, few cases in this study that have poor muscle function because of a 'failed' reconstruction, do show that MSTS scores are lower compared to their 'successful' counterparts and more commonly require postoperative use of braces.

Reconstruction of the sciatic nerve also remains a topic of debate. Whereas some authors do not advocate restoring it [43,44], others do recommend it [40,41,45]. Indeed, recovery of motor function should not be anticipated, especially of the peroneal compartments [46], but studies included in this review do show that protective sensation of the foot can be acquired within little over a year [40,41]. Sural nerve grafts are commonly used because of their length, easy harvest, and low donor site morbidity as they generally only supply sensation to a part of the lateral foot and lower leg. [47] However in nerve reconstructions of large gaps, higher patient age should be considered as a contraindication because of its notorious negative effect on nerve regeneration [48]. The use of postoperative radiotherapy should on the other hand not necessarily be considered as a hard contraindication for nerve reconstruction, as it may not significantly affect functional outcomes [49]. However, nerve reconstruction itself may be complicated by preoperative radiotherapy which should be considered when planning a treatment plan. Timing of functional reconstructions is difficult, but direct reconstruction (within 2–3 weeks) seems to be preferred over a delayed surgical reconstruction [50–53]. This ensures an early start of rehabilitation, which is even more important to obtain good results after such reconstructions [51–53]. Additionally, less complications occur and fibrosis is not yet present which complicates delayed reconstructions since adequate vessels and nerves may be difficult to find [50–53]. In high-grade STS achieving clear margins may be essential before performing any type of reconstruction. Also, one must consider that nerve regeneration in FFMT and nerve reconstructions can take several months before reaching its target [33]. In contrast, tendon transfers result in immediate function restoration and could be considered in cases where early recovery is needed [54]. Nerve transfers are also increasingly used in traumatic nerve injuries and are becoming standard of care in brachial plexus surgery [55,56]. These reconstructions provide the opportunity to restore nerve function distal to the defect, thus decreasing the time to recovery. In extremity STS this may also imply reconstructing outside of possible radiation fields.

Multimodal treatment and reconstruction in STS

Although LSS is performed for functionality purposes, in STS oncologic treatment should of course have priority in almost any case. This means that clear margins are essential, especially in high grade STS. Studies have however shown that the early participation of a plastic surgeon can yield higher rates of clear margins if free flaps are considered at an early stage [57,58]. The effect of chemotherapy and radiotherapy in functional reconstructions has not been thoroughly investigated. Studies included in this review however showed that all but one flap survived, and generally only minor complications occurred. One study did report radiotherapy induced fractures which ultimately affected functional outcomes [37]. Another series showed no negative effect of radiotherapy on functional outcomes after biceps femoris transfer for the reconstruction of knee extension [39]. In LSS generally, multiple studies have shown that preoperative radiotherapy does not increase complications when flaps are used [59–63]. These studies are however in contrast to the trial by O'Sullivan et al. [11] and other LSS studies [7–10]. In case postoperative radiotherapy is administered, free flap surgery can facilitate early start of treatment [64]. Also, complications may possibly be diminished when flaps are used compared to no flap usage [61,63–65]. Besides, restoration of function may alleviate the need for orthoses [33], which are difficult to wear on irradiated skin. Overall, the use of functional reconstructions does not seem to impede the use of either pre- or postoperative radiotherapy. The effects of chemotherapy are less frequently addressed in literature, but its use in LSS does not seem to increase complications regardless of sequence [66,67].

Strengths and limitations

Main limitations to our study include the large heterogeneity among studies and their patients, as well as the low amount of patients treated with functional reconstructions. Direct comparison between studies and flaps used is complicated due to the different defects being reconstructed and the diversity in outcome measures used. Also, with only a small amount of cases with differing tumor grades, location, and indications for multimodal treatment may have differed. As such, investigating the correlation of multimodal treatment to functional outcomes is impaired. Nonetheless, this study shows encouraging outcomes for the use of functional reconstructions. These results may stimulate sarcoma teams to incorporate early participation of experienced reconstructive plastic surgeons and rehabilitation teams. Such cooperation may result in facilitating wider tumor excision as well as planned preservation of certain structures needed for reconstruction. In order to increase our understanding of outcomes, future studies on limb salvage in STS patients should preferably differentiate functional reconstructions from soft-tissue coverage only. Additionally, when investigating outcomes of functional reconstructions, future studies are to be stimulated using both objective outcome measures assessing true muscle or sensory function and subjective outcome measures. This may further help elucidate expected outcomes and select ideal candidates. As such, sarcoma teams will increasingly be capable to incorporate functional reconstructions as part of their treatment strategy in extremity STS.

Conclusion

Functional reconstructions in extremity STS are uncommon in literature. However, resection of major nerves or complete muscle groups can lead to loss of specific functions. Reconstructions of nerves, muscles, and tendons can potentially improve function. As numerous options exist, the choice of reconstruction depends mainly on patient and tumor characteristics, such as size and location. Multimodal treatment does however not preclude successful restoration of function. A patient-tailored approach is needed to balance appropriate oncological resections with optimal functional outcome.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.05.024.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics. Ca - Cancer J Clin 2016;66:7–30. https://doi.org/10.3322/caac.21332. 2016.

[2] Yasko A, Patel R, Pollack A, Pollack R. Sarcomas of soft tissue and bone. In: Lehnhard RE, Osteen RT, Gansler T, editors. Clin. Oncol. Atlanta: American Cancer Society; 2001. p. 611–32.

[3] Byerly S, Chopra S, Nassif NA, Chen P, Sener SF, Eisenberg BL, et al. The role of margins in extremity soft tissue sarcoma. J Surg Oncol 2016;113:333–8. https://doi.org/10.1002/jso.24112.

[4] von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Conrad 3rd EU, et al. Soft tissue sarcoma, version 2.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 2016;14:758–86.

[5] Rosenberg SA, Tepper J, Glatstein E, Costa J, Baker A, Brennan M, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 1982;196:305–15.

[6] Johansen R, Nielsen OS, Keller J. Functional outcome in sarcomas treated with limb-salvage surgery or amputation. Sarcoma 1998;2:19–23. https://doi.org/10.1080/13577149878118.

[7] Davis A, O'Sullivan B, Turcotte R, Bell R, Catton C, Chabot P, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol 2005;75:48–53. https://doi.org/10.1016/j.radonc.2004.12.020.

[8] Haas RL, Gronchi A, van de Sande MAJ, Baldini EH, Gelderblom H, Messiou C, et al. Perioperative management of extremity soft tissue sarcomas. J Clin Oncol 2018;36:118–24. https://doi.org/10.1200/JCO.2017.74.7527.

[9] van Praag VM, Rueten-Budde AJ, Jeys LM, Laitinen MK, Pollock R, Aston W, et al. A prediction model for treatment decisions in high-grade extremity soft-tissue sarcomas: personalised sarcoma care (PERSARC). Eur J Cancer 2017;83:313–23. https://doi.org/10.1016/j.ejca.2017.06.032.

[10] Lansu J, Groenewegen J, van Coevorden F, van Houdt W, van Akkooi ACJ, van Boven H, et al. Time dependent dynamics of wound complications after preoperative radiotherapy in Extremity Soft Tissue Sarcomas. Eur J Surg Oncol 2018. https://doi.org/10.1016/j.ejso.2018.09.001.

[11] O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet (London, England) 2002;359:2235–41. https://doi.org/10.1016/S0140-6736(02)09292-9.

[12] Haas RLM, Delaney TF, O'Sullivan B, Keus RB, Le Pechoux C, Olmi P, et al. Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? Int J Radiat Oncol Biol Phys 2012;84:572–80. https://doi.org/10.1016/j.ijrobp.2012.01.062.

[13] Mundinger GS, Prucz RB, Frassica FJ, Deune EG. Concomitant upper extremity soft tissue sarcoma limb-sparing resection and functional reconstruction: assessment of outcomes and costs of surgery. Hand (N Y) 2014;9:196–204. https://doi.org/10.1007/s11552-013-9567-9.

[14] Saint-Cyr M, Langstein HN. Reconstruction of the hand and upper extremity after tumor resection. J Surg Oncol 2006;94:490–503. https://doi.org/10.1002/jso.20486.

[15] Momoh AO, Kumaran S, Lyons D, Venkatramani H, Ramkumar S, Chung KC, et al. An argument for salvage in severe lower extremity trauma with posterior tibial nerve injury: the Ganga hospital experience. Plast Reconstr Surg 2015;136:1337–52. https://doi.org/10.1097/PRS.0000000000001814.

[16] Markhede G, Stener B. Function after removal of various hip and thigh muscles for extirpation of tumors. Acta Orthop Scand 1981;52:373–95.

[17] Ogura K, Higashi T, Kawai A. Statistics of soft-tissue sarcoma in Japan: report from the bone and soft tissue tumor registry in Japan. J Orthop Sci 2017;22:755–64. https://doi.org/10.1016/j.jos.2017.03.017.

[18] Nelson AA, Frassica FJ, Gordon TA, Deune EG. Cost analysis of functional restoration surgery for extremity soft-tissue sarcoma. Plast Reconstr Surg 2006;117:277–83.

[19] Jones KB, Ferguson PC, Deheshi B, Riad S, Griffin A, Bell RS, et al. Complete femoral nerve resection with soft tissue sarcoma: functional outcomes. Ann Surg Oncol 2010;17:401–6. https://doi.org/10.1245/s10434-009-0745-5.

[20] Davis AM, Sennik S, Griffin AM, Wunder JS, O'Sullivan B, Catton CN, et al. Predictors of functional outcomes following limb salvage surgery for lower-extremity soft tissue sarcoma. J Surg Oncol 2000;73:206–11.

[21] Bell RS, O'Sullivan B, Nguyen C, Mahoney J, Langer F, Cummings B, et al. Fractures following limb-salvage surgery and adjuvant irradiation for soft-tissue sarcoma. Clin Orthop Relat Res 1991:265–71.

[22] Brooks AD, Gold JS, Graham D, Boland P, Lewis JJ, Brennan MF, et al. Resection of the sciatic, peroneal, or tibial nerves: assessment of functional status. Ann Surg Oncol 2002;9:41–7.

[23] Payne CE, Hofer SOP, Zhong T, Griffin AC, Ferguson PC, Wunder JS. Functional outcome following upper limb soft tissue sarcoma resection with flap reconstruction. J Plast Reconstr Aesthet Surg 2013;66:601–7. https://doi.org/10.1016/j.bjps.2013.01.034.

[24] Davidge KM, Wunder J, Tomlinson G, Wong R, Lipa J, Davis AM. Function and health status outcomes following soft tissue reconstruction for limb preservation in extremity soft tissue sarcoma. Ann Surg Oncol 2010;17:1052–62. https://doi.org/10.1245/s10434-010-0915-5.

[25] Clarkson PW, Griffin AM, Catton CN, O'Sullivan B, Ferguson PC, Wunder JS, et al. Epineural dissection is a safe technique that facilitates limb salvage surgery. Clin Orthop Relat Res 2005;438:92–6.

[26] Grunhagen DJG, de Wilt JHW, van Geel AN, Verhoef C, Eggermont AMM. Isolated limb perfusion with TNF-alpha and melphalan in locally advanced soft tissue sarcomas of the extremities. Recent Results Cancer Res Fortschritte Der Krebsforsch Prog Dans Les Rech Sur Le Cancer 2009;179:257–70.

[27] Gerrand CH, Wunder JS, Kandel RA, O'Sullivan B, Catton CN, Bell RS, et al. Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. J Bone Joint Surg Br 2001;83:1149–55.

[28] Alamanda VK, Crosby SN, Archer KR, Song Y, Schwartz HS, Holt GE. Amputation for extremity soft tissue sarcoma does not increase overall survival: a retrospective cohort study. Eur J Surg Oncol 2012;38:1178–83. https://doi.org/10.1016/j.ejso.2012.08.024.

[29] Ghert MA, Abudu A, Driver N, Davis AM, Griffin AM, Pearce D, et al. The indications for and the prognostic significance of amputation as the primary surgical procedure for localized soft tissue sarcoma of the extremity. Ann Surg Oncol 2005;12:10–7. https://doi.org/10.1007/s10434-004-1171-3.

[30] Gronchi A, Miceli R, Colombo C, Collini P, Stacchiotti S, Olmi P, et al. Primary extremity soft tissue sarcomas: outcome improvement over time at a single institution. Ann Oncol Off J Eur Soc Med Oncol 2011;22:1675–81. https://doi.org/10.1093/annonc/mdq643.

[31] Grinsell D, Di Bella C, Choong PFM. Functional reconstruction of sarcoma defects utilising innervated free flaps. Sarcoma 2012;2012:315190. https://doi.org/10.1155/2012/315190.

[32] Muramatsu K, Ihara K, Doi K, Hashimoto T, Taguchi T. Sarcoma in the forearm and hand: clinical outcomes and microsurgical reconstruction for limb salvage. Ann Plast Surg 2009;62:28–33. https://doi.org/10.1097/SAP.0b013e3181743a11.

[33] Doi K, Kuwata N, Kawakami F, Hattori Y, Otsuka K, Ihara K. Limb-sparing surgery with reinnervated free-muscle transfer following radical excision of soft-tissue sarcoma in the extremity. Plast Reconstr Surg 1999;104:1679–87.

[34] Stranix JT, Lee Z-H, Lam G, Mirrer J, Rapp T, Saadeh PB. Limb-sparing sarcoma reconstruction with functional composite thigh flaps. Microsurgery 2017. https://doi.org/10.1002/micr.30254.
[35] Mehrara BJ, Abood AA, Disa JJ, Pusic AL, Halvorson E, Cordeiro PG, et al. Thumb reconstruction following resection for malignant tumors. Plast Reconstr Surg 2008;121:1279–87. https://doi.org/10.1097/01.prs.0000304590.09003.1b.
[36] Mirous MP, Coulet B, Chammas M, Cupissol D, Lazerges C. Extensive limb-sparing surgery with reconstruction for sarcoma of the hand and wrist. Orthop Traumatol Surg Res 2016;102:467–72. https://doi.org/10.1016/j.otsr.2016.01.026.
[37] Innocenti M, Abed YY, Beltrami G, Delcroix L, Balatri A, Capanna R. Quadriceps muscle reconstruction with free functioning latissimus dorsi muscle flap after oncological resection. Microsurgery 2009;29:189–98. https://doi.org/10.1002/micr.20607.
[38] Walley KC, Taylor EM, Anderson M, Lozano-Calderon S, Iorio ML. Reconstruction of quadriceps function with composite free tissue transfers following sarcoma resection. J Surg Oncol 2017;115:878–82. https://doi.org/10.1002/jso.24594.
[39] Fischer S, Soimaru S, Hirsch T, Kueckelhaus M, Seitz C, Lehnhardt M, et al. Local tendon transfer for knee extensor mechanism reconstruction after soft tissue sarcoma resection. J Plast Reconstr Aesthet Surg 2015;68:729–35. https://doi.org/10.1016/j.bjps.2015.01.002.
[40] Melendez M, Brandt K, Evans GR. Sciatic nerve reconstruction: limb preservation after sarcoma resection. Ann Plast Surg 2001;46:375–81.
[41] Tokumoto H, Akita S, Kubota Y, Kuriyama M, Mitsukawa N. Use of vascularized sural nerve grafts for sciatic nerve reconstruction after malignant bone and soft tissue tumor resection in the lower legs. Ann Plast Surg 2018;80:379–83. https://doi.org/10.1097/SAP.0000000000001315.
[42] Gunterberg B, Markhede G, Stener B. Function after anterolateral resection of the lower leg for extirpation of tumors. Extension and pronation of the foot restored by transfer of the tibialis posterior muscle. Acta Orthop Scand 1981;52:95–8.
[43] Fuchs B, Davis AM, Wunder JS, Bell RS, Masri BA, Isler M, et al. Sciatic nerve resection in the thigh: a functional evaluation. Clin Orthop Relat Res 2001;34–41.
[44] Sweiti H, Tamimi N, Bormann F, Divo M, Schulz-Ertner D, Ahrens M, et al. Limb-salvage surgery of soft tissue sarcoma with sciatic nerve involvement. Sarcoma 2018:6483579. https://doi.org/10.1155/2018/6483579. 2018.
[45] Nambisan RN, Rao U, Moore R, Karakousis CP. Malignant soft tissue tumors of nerve sheath origin. J Surg Oncol 1984;25:268–72.
[46] Kim DH, Murovic JA, Tiel R, Kline DG. Management and outcomes in 353 surgically treated sciatic nerve lesions. J Neurosurg 2004;101:8–17. https://doi.org/10.3171/jns.2004.101.1.0008.
[47] Hallgren A, Bjorkman A, Chemnitz A, Dahlin LB. Subjective outcome related to donor site morbidity after sural nerve graft harvesting: a survey in 41 patients. BMC Surg 2013;13:39. https://doi.org/10.1186/1471-2482-13-39.
[48] Terzis JK, Barbitsioti A. Primary restoration of elbow flexion in adult post-traumatic plexopathy patients. J Plast Reconstr Aesthet Surg 2012;65:72–84.
[49] Evans GRD, Brandt K. Peripheral nerve regeneration: the effects of post-operative irradiation. Plast Reconstr Surg 2003;111:2023–4. https://doi.org/10.1097/01.PRS.0000056837.37545.58.
[50] Usui M, Ishii S, Naito T, Yamashita M, Yamamura M. Microsurgical reconstruction in limb-salvage procedures: comparison between primary and secondary reconstruction. J Reconstr Microsurg 1993;9:91–101. https://doi.org/10.1055/s-2007-1006657.
[51] Reece GP, Schusterman MA, Pollock RE, Kroll SS, Miller MJ, Baldwin BJ, et al. Immediate versus delayed free-tissue transfer salvage of the lower extremity in soft tissue sarcoma patients. Ann Surg Oncol 1994;1:11–7.
[52] Sanniec KJ, Velazco CS, Bryant LA, Zhang N, Casey WJIII, Mahabir RC, et al. Immediate versus delayed sarcoma reconstruction: impact on outcomes. Sarcoma 2016;2016:7972318. https://doi.org/10.1155/2016/7972318.
[53] Marre D, Buendia J, Hontanilla B. Complications following reconstruction of soft-tissue sarcoma: importance of early participation of the plastic surgeon. Ann Plast Surg 2012;69:73–8. https://doi.org/10.1097/SAP.0b013e31821ee497.
[54] Goertz O, Langer S, Uthoff D, Ring A, Stricker I, Tannapfel A, et al. Diagnosis, treatment and survival of 65 patients with malignant peripheral nerve sheath tumors. Anticancer Res 2014;34:777–84.
[55] Boyd KU, Nimigan AS, Mackinnon SE. Nerve reconstruction in the hand and upper extremity. Clin Plast Surg 2011;38:643–60. https://doi.org/10.1016/j.cps.2011.07.008.
[56] Maldonado AA, Bishop AT, Spinner RJ, Shin AY. Five operations that give the best results after brachial plexus injury. Plast Reconstr Surg 2017;140:545–56. https://doi.org/10.1097/PRS.0000000000003620.
[57] Kim JY, Subramanian V, Yousef A, Rogers BA, Robb GL, Chang DW. Upper extremity limb salvage with microvascular reconstruction in patients with advanced sarcoma. Plast Reconstr Surg 2004;114:400–10.
[58] Lohman RF, Nabawi AS, Reece GP, Pollock RE, Evans GRD. Soft tissue sarcoma of the upper extremity: a 5-year experience at two institutions emphasizing the role of soft tissue flap reconstruction. Cancer 2002;94:2256–64. https://doi.org/10.1002/cncr.10419.
[59] Chao AH, Chang DW, Shuaib SW, Hanasono MM. The effect of neoadjuvant versus adjuvant irradiation on microvascular free flap reconstruction in sarcoma patients. Plast Reconstr Surg 2012;129:675–82. https://doi.org/10.1097/PRS.0b013e3182412a39.
[60] Barwick WJ, Goldberg JA, Scully SP, Harrelson JM. Vascularized tissue transfer for closure of irradiated wounds after soft tissue sarcoma resection. Ann Surg 1992;216:591–5.
[61] Slump J, Hofer SOP, Ferguson PC, Wunder JS, Griffin AM, Hoekstra HJ, et al. Flap reconstruction does not increase complication rates following surgical resection of extremity soft tissue sarcoma. Eur J Surg Oncol 2018;44:251–9. https://doi.org/10.1016/j.ejso.2017.11.015.
[62] Townley WA, Mah E, O'Neill AC, Wunder JS, Ferguson PC, Zhong T, et al. Reconstruction of sarcoma defects following pre-operative radiation: free tissue transfer is safe and reliable. J Plast Reconstr Aesthet Surg 2013;66:1575–9. https://doi.org/10.1016/j.bjps.2013.06.029.
[63] Kapalschinski N, Goertz O, Harati K, Kueckelhaus M, Kolbenschlag J, Lehnhardt M, et al. Plastic surgery in the multimodal treatment concept of soft tissue sarcoma: influence of radiation, chemotherapy, and isolated limb perfusion on plastic surgery Techniques. Front Oncol 2015;5:268. https://doi.org/10.3389/fonc.2015.00268.
[64] Tseng JF, Ballo MT, Langstein HN, Wayne JD, Cormier JN, Hunt KK, et al. The effect of preoperative radiotherapy and reconstructive surgery on wound complications after resection of extremity soft-tissue sarcomas. Ann Surg Oncol 2006;13:1209–15. https://doi.org/10.1245/s10434-006-9028-6.
[65] Spierer MM, Alektiar KM, Zelefsky MJ, Brennan MF, Cordiero PG. Tolerance of tissue transfers to adjuvant radiation therapy in primary soft tissue sarcoma of the extremity. Int J Radiat Oncol Biol Phys 2003;56:1112–6.
[66] Evans GR, Black JJ, Robb GL, Baldwin BJ, Kroll SS, Miller MJ, et al. Adjuvant therapy: the effects on microvascular lower extremity reconstruction. Ann Plast Surg 1997;39:141–4.
[67] Meric F, Milas M, Hunt KK, Hess KR, Pisters PW, Hildebrandt G, et al. Impact of neoadjuvant chemotherapy on postoperative morbidity in soft tissue sarcomas. J Clin Oncol 2000;18:3378–83. https://doi.org/10.1200/JCO.2000.18.19.3378.