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GENERAL REVIEW • TUMORS - MICROSURGERY

Microsurgery in musculoskeletal oncology

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Abstract

Sarcomas are rare mesenchymal bone and soft tissue tumors of the musculoskeletal system. In the past, the primary treatment modality was amputation of the involved limb and the 5-year survival was very low for high-grade tumors. During the last three decades, limb salvage has become the rule rather than the exception and the use of neoadjuvant and adjuvant therapies (radiation and chemotherapy) has dramatically increased disease-free survival. Reconstruction of large bone and soft tissue defects, though, still remains a significant challenge in sarcoma patients. In particular, vascularized tissue transfer has proved extremely helpful in dealing with complex bone and soft tissue or functional defects that are frequently encountered as a result of the tumor or as a complication of surgery and adjuvant therapies. The principles, indications and results of microsurgical reconstruction differ from trauma patients and are directly related not only to the underlying disease process, but also to the local and systemic therapeutic modalities applied to the individual patient. Although plastic reconstruction in the oncological patients is not free of complications, usually these complications are manageable and do not jeopardize oncological outcome. The overall treatment strategy should be tailored to the patient's and sarcoma profile.

Keywords Musculoskeletal oncology · Microsurgery · Flaps

Introduction

Sarcomas are rare malignant tumors of mesenchymal origin, constituting approximately 1.5% of all diagnosed malignancies [1]. Due to their rarity, available knowledge on the treatment of sarcomas was limited, with amputation being the traditional treatment of choice. During the last 30 years, however, there has been significant progress in the diagnosis, staging and therapeutic approach of patients with musculoskeletal neoplasms [2–4].

In the current decade, the treatment of a patient suffering from a musculoskeletal malignancy is highly individualized and requires a multidisciplinary approach. Currently, limb salvage is feasible in more than 90% for bone and soft tissue sarcomas. Primary extremity amputation for a limb sarcoma is indicated only when tumor resection to negative margins cannot be obtained, when the resulting tissue and functional defect cannot be reconstructed with available techniques, when functional loss will result in a dangerous limb function or when the expected complications rate would be very high. Although surgical resection remains the cornerstone of sarcoma treatment, adjuvant therapies are usually included for high-grade sarcomas. The combination of aggressive resection, limb preservation and the use of adjuvant therapies means that many of these patients require multidisciplinary reconstructive efforts to address tissue defects, functional defects and complications. In such a context, microsurgical reconstruction gains an increasingly prominent role in the field of musculoskeletal surgical oncology. Microsurgical reconstruction indications are directly related to patient survival, the biologic substrate for healing and rehabilitation, as well as the repercussions of chemotherapy and radiation on the patient's tissues.

Bone sarcoma reconstruction

Surgical resection of malignant, or certain benign-aggressive, pelvic or extremity bone tumors often results in large bone and soft tissue defects. Based on location and extent, such defects may be addressed with the use of a vascularized bone graft, an allograft, distraction osteogenesis or by

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the use of an endoprosthesis [4, 5]. The use of a vascularized fibula in the treatment of posttraumatic defects, infected nonunions or congenital pseudoarthrosis is well established [6–9]. The vascularized fibula flap has also been widely used for reconstruction of bone defects after tumor resection in the mandible and long bones (Fig. 1), for spinal stabilization after cortectomy and for pelvic reconstruction after internal hemipelvectomy [3, 9–13]. It can also be used in conjunction with muscle or a skin island, in order to achieve simultaneous soft tissue coverage [9]. Innocenti et al. based on a previous cadaveric study by Taylor et al. have described a vascularized transfer of the proximal epiphysis–diaphysis of the fibula, supplied by a branch of the anterior tibial artery [14, 15]. The transferred epiphysis maintains approximately 80% of its growth potential [14]. As it is covered by articular cartilage, the proximal fibular epiphysis can be used to reconstruct an articular surface (i.e., distal radius), aiding on the same time longitudinal growth [16]. A direct comparison of the use of a vascularized fibular graft either for posttraumatic or for tumor defects has yielded better results in the tumor group of patients. This has been attributed to the greater soft tissue damage (more scarring and tissue hypoxia) usually seen in the posttraumatic group [8].

The use of the vascularized fibula for reconstruction after bone sarcoma resection is undoubtedly associated with a complication rate reported to be as high as 33–55%. Most of these complications can be managed and do not typically lead to limb loss. The three most common complications are infection, nonunion and fracture [9, 17–20]. Despite the high biologic potential of the vascularized fibular graft, delayed union and nonunion do occur frequently, with the main contributing factor being inadequate fixation. In such a case, the fixation typically needs to be revised and occasionally augmented by bone graft [20]. Stress fractures usually occur within a year of achievement of union of the fibular graft to the recipient site. Conservative management typically results in abundant callous formation and fibular hypertrophy [9, 11, 17]. In the study performed by Sainsbury et al., there were 19 vascularized fibular grafts used to reconstruct lower limb bone defects after tumor resection in children [21]. Graft survival was reported to be 95%, union was achieved in a mean of 24 months, and the incidence of fibular fracture was 52.6%. Ninety percent of patients reported to be satisfied of the procedure.

During the 1980s and 1990s, the use of allografts was popularized. Defects with an intra-articular extension can be addressed with osteoarticular allografts, whereas diaphyseal defects can be reconstructed with diaphyseal structural allografts. However, after an early enthusiasm, it is observed that allograft use was associated with a significant amount of complications, especially in the case of distal femoral osteoarticular allografts, and for diaphyseal allografts exceeding 15 cm in length [22–24]. Similarly, the three main complications include infection, nonunion and allograft fracture [24–26]. Management of such complications is not as easy, though. Surgical debridement for infection and fixation revision and bone graft for fractures and nonunion often do not yield satisfactory outcomes [26–28]. However, the use of rotational or free vascularized flaps in conjunction with an allograft has been shown to reduce allograft failure and infection rates in the setting of oncologic defects [29]. The use of a vascularized fibular graft as a salvage procedure for existing allograft complications has also been shown to be effective [28, 30, 31]. Bae et al. [28]

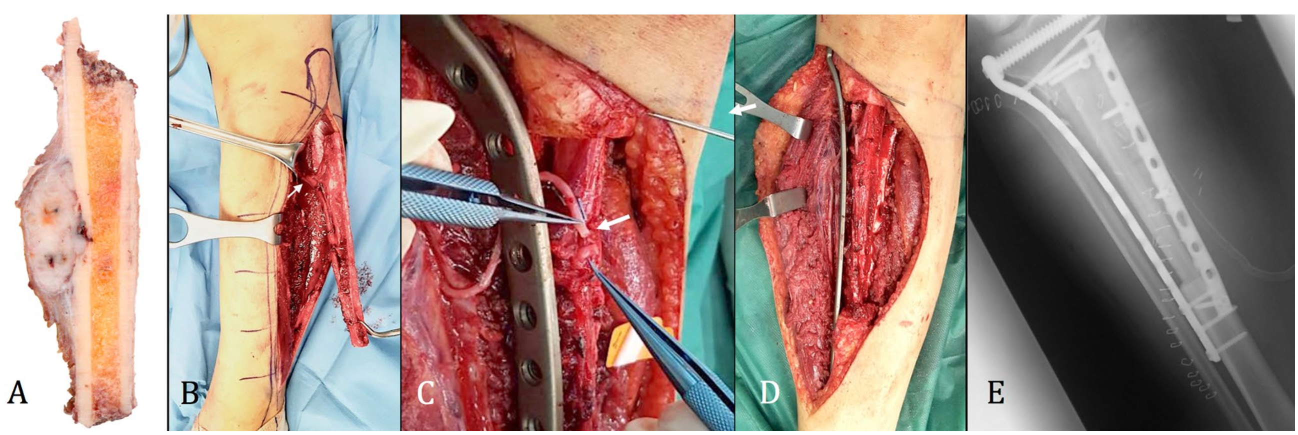

Fig. 1 A 24-year-old patient developed a high-grade surface osteosarcoma at the tibia diaphysis. The patient underwent pre-op chemotherapy. **a** Three months later, resection of the tumor was performed to negative margins. A diaphyseal bone defect of 14 cm was created. **b** The contralateral vascularized fibula graft was harvested (white arrow to peroneal artery). The bone tibia defect was reconstructed with a structural allograft and the harvested fibula (inlay). **c** Peroneal artery anastomosed to tibialis anterior artery (white arrow). **d** Intra-operative image of the reconstructed bone defect. Osteosynthesis with medial and lateral plates and screws. **e** Post-op X-ray. The patient had free weight bearing at 10-month post-op

employed a vascularized fibular graft in 8 patients with allograft nonunion, obtaining union in 7 patients (88%), as well as pain relief and limb preservation. Friedrich et al. used vascularized fibular transfer as a salvage procedure in 33 patients after development of allograft-related complications (25 nonunions, 6 infections, 2 fractures) [31]. Mean time to union was 7.7 months. Ten major complications arisen, five of which were related to infection. Twenty-three patients had a very good or good function result; five patients underwent limb amputation.

Capanna et al. [32] employed a hybrid reconstruction technique, involving the combined use of a structural allograft and a vascularized fibular graft. The allograft provided mechanical and structural support, until the vascularized fibula could hypertrophy and incorporate, thus reducing the chance of a stress fracture and facilitating patient rehabilitation and limb use. Moreover, it was theorized that the vascularized fibula biologic potential would reduce complications related to the presence of an avascular allograft, such as infection. Two different techniques have been described.

In the first of these techniques, the vascularized fibula is placed directly into the allograft lumen (inlay technique) [32, 33]. This can be achieved in one of two ways: (1) the fibula is dragged into the lumen of the allograft through one of the bone ends, with its vascular supply passing through a hole in the allograft cortex; (2) a longitudinal cortical defect is created in the desired level, wide enough to accommodate the harvested vascularized fibula. The graft is placed in the allograft cavity, so that its vascular supply is not compressed and can be easily anastomosed to the area's existing vascular network. The allograft bridges the bone defect and is secured in place with rigid fixation (plates and screws). The harvested fibula is usually 4–6 cm longer, so as to accommodate to the proximal and distal parts of the preexisting defect. This technique is particularly helpful in the case of tibial tumors, as diaphysial allografts are usually straight and can easily accommodate a relatively straight fibular graft. Depending on mechanical loads and degree of vascular supply, fibula may undergo either hypertrophy or atrophy [33].

In the second technique, the vascularized fibular graft is placed on the structural allograft (onlay technique) [34, 35]. This method is preferred for arthrodesis of the humerus to the scapula and in the case of large femoral defects, as anterior femoral bowing does not usually favor the employment of a straight fibular graft [9, 32, 34]. The allograft is then preferentially secured with a plate and screws construct, whereas the fibula is fixed in the femoral cortex with a proximal and a distal screw.

In a series published by Chang et al., a hybrid technique was used in 7 out of 8 patients. Union was achieved in a mean of 10 months [34]. Innocenti et al. [35] used this method in 10 patients with bone sarcomas of the tibia. Fibular graft survival was confirmed in 25 out of 27 patients. Mean time to union was 5.4 months for the fibular graft and 19.1 months for the allograft. Significant fibular hypertrophy (> 20%) occurred in 94.4% of cases. Stress fractures occurred in 3 patients, usually within 10 months of the procedure, which subsequently progressed to full union following 2 months of conservative treatment. Full weight bearing was achieved in a mean of 21.6 months (range, 15–36). 47.6% of patients developed a complication. Local recurrence rate was 9.5%, whereas metastatic disease occurred in 14.3% of patients.

Soft tissue sarcoma reconstruction

Amputation or radical resection (compartmental resection) used to be the main treatment modality for large high-grade soft tissue sarcomas. However, the prospective randomized trial performed by Rosenberg et al. [36] in 1982, as well as other studies, has clearly shown that tumor resection combined with local radiation delivery does not have a negative impact on survival, even though there was a higher rate of local recurrence, when compared with amputation. Although radical excisions are rarely used today, the aim of surgery remains excision with a negative margin, although the exact amount of surgical margin remains a matter of controversy [36–41]. Tumor resection with microscopically positive margins is associated with an increased rate of local recurrence and a reduction in long-term survival [38, 39]. Local radiation delivery, either pre- or postoperatively, reduces the rate of recurrence, regardless of margins, but may not improve survival [42, 43]. The role of chemotherapy in the treatment of soft tissue sarcomas still remains controversial and should individualized in a case-by-case basis [44]. Because limb salvage is feasible in more than 90% of cases, the large defects following successful tumor resection increase the need for subsequent local reconstruction [39, 41]. The use of soft tissue flaps is particularly helpful for wound closure, in the management of wound breakdown after radiation and for the reconstruction of functional defects. Local rotational, perforator and free soft tissue flaps can be utilized according to the anatomy, the size and the shape of the defect that has to be closed [45–47].

For small tumors, wound closure is relatively simple and is achieved either by simple sutures or by muscle approximation followed by split thickness skin grafting. When primary suture repair is impossible, use of a soft tissue flap becomes necessary for tissue coverage. Tensionless primary wound closure is usually not possible in case of large tumors or when wide resection of the surgical field is necessary (e.g., improper previous biopsy site resection or previous surgery with positive margins requiring re-excision), or in the case of resections for local recurrence (Fig. 2). Flap coverage is also

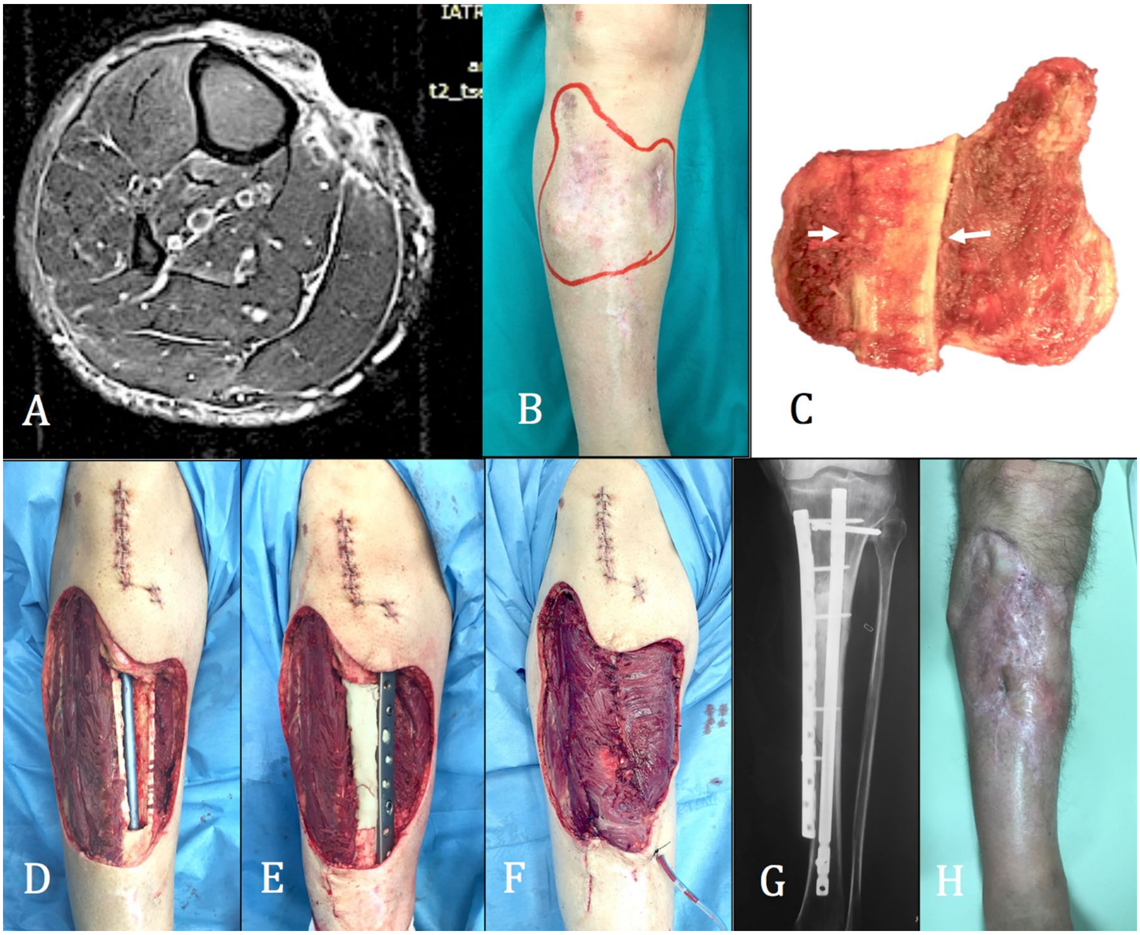

Fig. 2 A 70-year-old patient had an unplanned excision of a grade II soft tissue myxofibrosarcoma of the anterior tibia. Surgical margins were positive and post-op local radiation therapy 56G was delivered. **a** One year later, local recurrence was evident. MRI axial image. **b** Skin mark of the extent of tissue resection. **c** Local recurrence excision to negative margins. Tissue resection involved skin, muscle and anterior surface of tibia (white arrows). **d** An intramedullary nail was inserted. **e** Bone defect was filled with PMMA and a medial plate was applied. **f** Medial gastrocnemius rotational flap and soleus flap were transposed to cover the tissue defect. Split thickness skin graft was applied. **g** X-ray and **h** clinical appearance 12 months later. No local recurrence was evident

essential when the resection defect leaves exposed vessels, nerves or bone [48–53].

Flap utilization is also particularly important in the prevention or management of wound healing complications. The risk factors commonly associated with wound breakdown typically include diabetes, smoking, large tumor dimensions, location, surgical margins < 3 mm from the skin surface, and preoperative radiotherapy [53–56]. A prospective study comparing 190 patients that received either preoperative or postoperative radiotherapy demonstrated a wound healing complication rate (that needed surgical management) of 35% and 17%, respectively [57]. However, wound healing complications tend to occur more often in the lower limbs [48, 50, 53]. Barwick et al. [58] have shown that the use of plastic surgery principles after neoadjuvant radiotherapy/hyperthermia and subsequent tumor resection has reduced the rate of wound healing complications from 61 to 37%. Vasileios et al. [48] conducted a study on 57 patients with soft tissue undifferentiated pleomorphic sarcoma. A rotational or free flap was eventually needed in 28 patients. A major wound complication occurred in 17% of patients. All complications were related to preoperative radiotherapy, and 90% involved the lower limbs. Wound breakdown was associated with infection in 50% of cases. Morii et al. [59] have demonstrated that infection was strongly associated with the use of synthetic implants.

The use of vascularized flaps does not completely overcome the issue of wound healing problems after preoperative radiation, as the radiated field becomes devascularized and the molecular milieu of the field microenvironment is altered [48, 50, 60–62]. Major complications of microsurgical reconstruction after soft tissue tumor resection include anastomotic thrombosis, flap congestion, partial or complete necrosis and infection [48, 51, 59, 62]. Radiation locally induces cytokine expression in the vessel wall, as well as infiltration by inflammatory cells. Genetic expression modifications in the vessel wall as a result of radiation have been recently studied. An increase in NF-κB was observed, which was associated with persistence of vessel wall inflammation, even after several years [63]. In the long term, arterial wall damage has been found to be similar to that of atheromatosis, with lipid infiltration and intimal thickening [64, 65].

Experimental studies in rabbits in the 1980s have shown a high failure rate of microsurgical anastomoses in the irradiated field [66, 67]. In a large clinical series consisting of 493 flaps for coverage of defects of variable etiology, the failure rate was reported to be 4% [68]. Anastomotic thrombosis requiring revision occurred in 10% of cases. The use of preoperative radiotherapy was statistically correlated with the development of postoperative complications. Barwick et al. reported on the use of free flaps after preoperative radiotherapy in 36 patients with soft tissue sarcoma [58]. Major complications occurred in 14% of cases, with flap survival being approximately 94%. Morii et al. reported their results on the use of 55 rotational or free flaps [59]. Complication rate was 11% (5 flap congestions, 5 partial flap necroses, 1 complete flap necrosis), whereas infection rate was 20%. Benatar et al. studied 429 patients who required free flap reconstruction after tumor resection in the head and neck region [69]. Of these patients, 136 had received preoperative radiation. Preoperative radiation in a cumulative dose exceeding 60 Gy was associated with an increased risk of flap failure and an increased overall rate of complications. Halle et al. [70] have studied the results of 221 free flaps used for reconstruction after tumor resection in the head and neck region. Vascular complications (partial or complete necrosis) occurred in 30 out of 196 flaps placed in a previously irradiated field. Microsurgical reconstruction delayed until 6 months after the last radiotherapy session has been found to significantly reduce flap-related complications. Many authors suggest anastomosing flap-feeding vessels to vessels outside the irradiated field [59]. However, the feasibility of this depends on the length of the flap vessel and local anatomic considerations.

On the other side of this debate, Mulholland et al. conducted a large study on 334 flaps in the head and neck area [71]. They reported a similar failure for flaps placed in an irradiated and a non-irradiated area (3.5% vs. 2.9%). Townley et al. [72], in a study of 43 flaps, reported an arterial anastomosis revision rate of 9.4% (3/32) for flaps placed in an irradiated field versus a 7.1% (1/8) revision rate for flaps transposed in a pristine field ($p=0.63$). Chao et al. [73] conducted a study on 196 patients, comparing the effects of preoperative versus postoperative radiation in free flaps used for defects in the head and neck, trunk and limbs. Patients subjected to preoperative radiotherapy underwent surgical resection and flap coverage within 5.9 ± 1.9 weeks. They concluded that preoperative radiotherapy did not increase the incidence of microvascular complications, with a rate of vascular stump thrombosis of 5.5%, compared to 4.3% in the postoperative radiotherapy group.

The functional limb results after tumor resection and flap reconstruction are reported to be very good, with an Enneking score generally higher than 80% for most patients [51, 59, 74, 75]. Morii et al. [59] studied 55 patients operated for soft tissue sarcoma, with subsequent soft tissue coverage with a local or free flap. Mean functional result was 85.6% (88.2% for the lower limbs and 71.2% for the upper limbs). Infection was the main factor related to a poor functional result. Payne et al. reported their results with 113 flaps (37 free and 76 rotational) for reconstruction after tumor resection in the upper limb [76]. They found no difference in functional results between the two groups. For free flaps, the mean preoperative TESS score was 87.32, whereas the postoperative score was 87.68. For local flaps, the preoperative TESS score was 87.36 versus 86.28, postoperatively. One particular field of application of microsurgical techniques is the use of flaps for functional reconstruction, in order to restore joint mobility. Kobayashi et al. [77] have described four prerequisites necessary for flaps to succeed in joint mobility restoration:

(i) the joint in question must have retained a functional range of motion;
(ii) the joint must remain stable;
(iii) the dimensions, power and excursion of the transposed muscle must be similar to the resected muscle;
(iv) there must be local availability of functional arteries, veins and nerve motor branches.

Innocenti et al. [78] have used 11 latissimus dorsi free flaps in an attempt to restore knee extension after surgical resection of the quadriceps. The mean time to return of contraction in the transposed muscle was 8.3 months, whereas the MSTS score was very good or good in 73% of patients. Ihara et al. [79] have presented a series of 23 patients who underwent functional free muscle transfer. Mean reinnervation time was 6 months. Free latissimus dorsi transfer can be utilized when two or more heads of the quadriceps are resected [79, 80]. Markhede et al. [81] have concluded that removal of three heads of the quadriceps leads to a 55% decrease in isometric power of the muscle. However, as the weight of the latissimus dorsi is approximately 1/3 that of the entire quadriceps, such a transfer cannot completely restore previous function.

It has been hypothesized that the use of free flaps would lead to an increase in angiogenesis that would ultimately favor malignancy recurrence. Studies that followed attempted to compare the rate of local or systemic recurrence in patients who had a flap versus in those who did not have one. Multivariate analysis failed to demonstrate an increased local recurrence rate or a decrease in survival in patients who had a vascularized fibular graft or free soft tissue flap [20, 45, 48].

Conclusion

It can be deducted that vascularized flap use for reconstruction after tumor resection is a reliable, safe and necessary technique. As such, it can lead to a reduction in amputation rates, both when used primarily for wound closure and when employed as a salvage procedure after the development of complications. Use of flaps does not seem to compromise oncologic surgery principles. Even when complications arise, these are usually manageable and the limb can typically be salvaged. However, it must be emphasized that microsurgical indications in tumor surgery are not exactly the same as those relevant to posttraumatic defect management. Reconstruction in musculoskeletal oncology needs to be part of a wider management strategy, which must take into account not only tumor resection surgery, but also the need for adjuvant treatments, such as chemotherapy and radiation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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