

Neoadjuvant Treatment Facilitating Surgery

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49.1 Basic Clinical History

A 72-year-old male presented with a spontaneous soft tissue mass in his left arm. Initially, he was diagnosed with a hematoma from a possible rupture of the long head of the biceps brachii muscle by initial MRI.

Four months later, due to a rapid growth of the mass, the patient came to our sarcoma center. A new MRI was indicated, describing a tumor in the middle third of the anterior medial part of the left arm, with a size of $57 \times 37 \times 81$ mm. After appropriate work-up of the mass, in which detectable metastases were ruled out, by thoracic CT and PET-CT, a percutaneous core Tru-Cut biopsy CNB performed under ultrasound guidance, and the final pathologic report was a high-grade undifferentiated pleomorphic sarcoma (UPS) grade 2 by Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) and IIIA (G3 T2 N0 M0) by American Joint Committee on Cancer (AJCC).

49.2 Pretreatment Clinical and Radiological Images

See Figs. 49.1, 49.2, and 49.3.

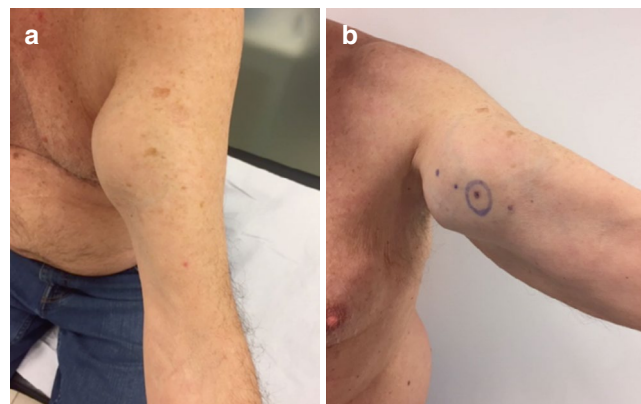


Fig. 49.1 Pretreatment clinical image of the mass at the time of diagnosis. (a) Soft tissue mass in the medial part of the left arm. (b) Planned incision and planned site of biopsy

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Fig. 49.2 Pretreatment MRI of the left arm showed a relatively well-circumscribed bilobated mass located in the biceps brachii muscle, with a signal isointense with the muscle on T1-weighted sequences (a) and heterogeneous, high signal intensity in fat-suppressed T2-weighted sequences, exerting a positive mass effect on surrounding structures due to their large size. It measured about $9 \times 8.7 \times 5.2$ cm. No signs of invasion of the humerus (b). After the administration of paramagnetic contrast, the mass showed prominent enhancement of solid components and non-enhancing necrotic areas (c). Sagittal T1-weighted MRI and paramagnetic contrast: enhancing tail of tumor extending along the remaining portion of the muscle (d)

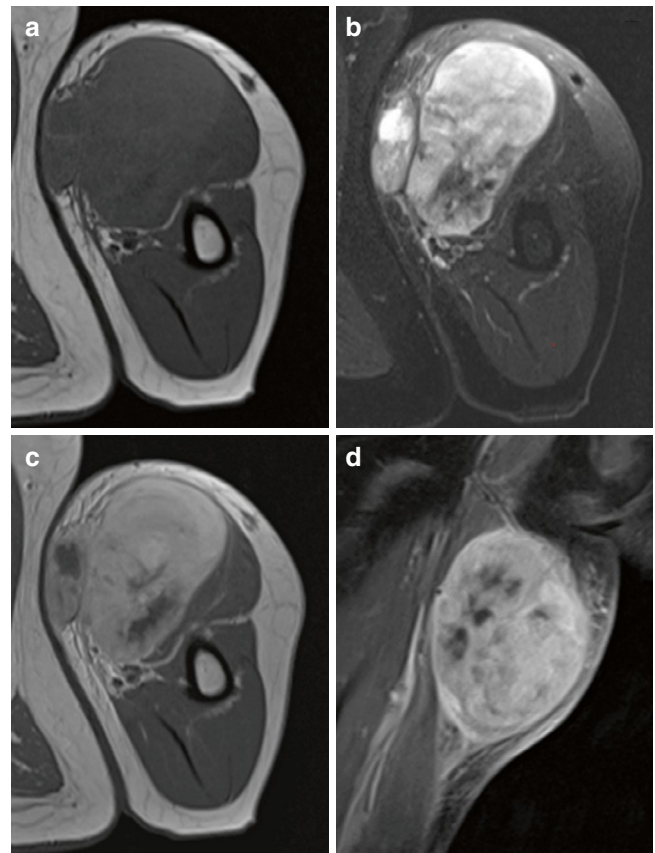
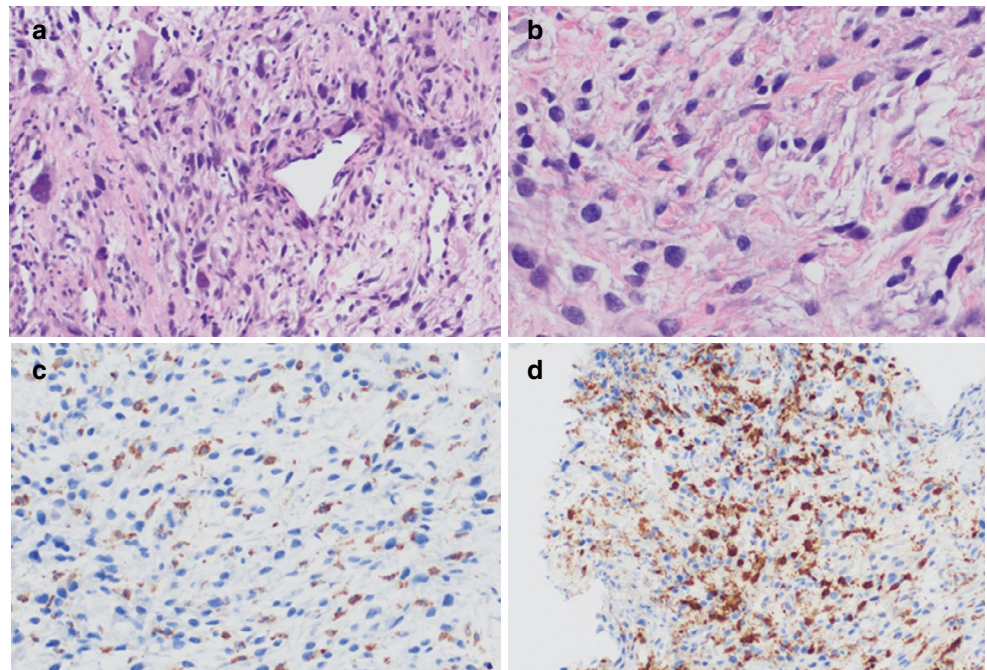


Fig. 49.3 Microscopic images of the percutaneous biopsy. There is a malignant fusocellular mesenchymal proliferation, high-grade pleomorphic, with evident cytologic atypia, presence of hyperchromatic variable in shape and size nuclei, occasional macronucleoli, and evident mitotic activity. Maximum cell proliferation index (Ki67) was 30%. (a) H&E staining, $\times 200$. (b) H&E staining, $\times 400$. Cells were immunoreactive to CD68 (c) and XIIIa factor (d), and negative to smooth muscle actine, desmin, caldesmon, S-100 protein, CD34, and STAT6



49.3 Problem List

- (a) A soft tissue mass that can be clinically misdiagnosed as a benign pathology without an adequate medical history and a perfect physical exam.
- (b) Attribute the radiological abnormality to a benign process (hematoma, traumatic, or orthopedic problem).
- (c) Once diagnosed as a soft tissue sarcoma (STS), sometimes the surgeon needs to reduce the mass with neoadjuvant therapy to achieve oncological wide surgical margins with less functional impairment, or postoperative therapies that may imply complications in the follow-up.

49.4 Treatment Strategy

- (a) Appropriate preoperative work-up (with history, physical exam, plain X-rays, ultrasound, CT, MRI, and bone scan, followed by percutaneous biopsy)
- (b) Precise staging of the tumor and multidisciplinary committee decision about preoperative therapies
- (c) Preoperative neoadjuvant treatment (radiotherapy and/or chemotherapy) prior to wide tumor resection surgery.
- (d) Neoadjuvant chemotherapy with the regimen epirubicin + ifosfamide (x3 cycles). The last cycle was synchronous with the first sessions of radiotherapy
- (e) Neoadjuvant radiotherapy included a radiation dose of 50 Gy (2 Gy/day) with 6 MV beam energy, for 5 weeks, with IMRT technique (intensity-modulated radiation therapy)
- (f) Surgical oncological resection 6 weeks after the end of radiotherapy
- (g) More functional resection with wide safe margins of the reduced mass and subsequent soft tissue reconstruction with local or free flaps

49.5 Basic Principles

1. Basic warning signs to make a referral to a sarcoma center:
 - (a) Mass greater than 4 cm (subcutaneous or deeper)
 - (b) Mass that has experienced recent growth
 - (c) Pain is not a straightforward symptom of a soft tissue sarcoma, but together with any of the previous signs may reinforce the presumption of malignancy
 - (d) Maintain appropriate level of suspicion
2. If the patient is going to be referred
 - (a) Do not biopsy and, if necessary, avoid excisional biopsies
 - (b) The biopsy tract must be planned with the surgeon.
 - (c) Planning the biopsy site is essential and should be in the area of the incision.

- (d) The biopsy should be done after imaging studies are performed. It is the final part of the staging process.
3. Document every step with clinical and radiological images to assess the effect of therapies and the recurrence.
4. Neo/adjuvant chemotherapy has demonstrated to improve overall survival in patients with a high-grade STS of the extremities >5 cm (except in chemoresistant histotypes).
5. Radiotherapy in extremities STS increases local control and survival:
 - (a) Advantages of preoperative radiotherapy compared to postoperative: lower radiation dose, smaller treatment volume, improved resectability, margin-negative resections, better oxygenation of tumor cells, fewer long-term toxicities.
 - (b) Collaboration between surgeon and radiation oncologist is essential for the integration of local treatments and includes recurrence risk assessment, defining areas of concern for close or positive margins.
6. Surgery
 - (a) Basic surgical principles
 - Safe wide oncological margin.
 - Resection overcomes reconstruction when defining surgical resection.
 - Adjuvant radiotherapy or chemotherapy does not compensate for an improper surgery.
 - Adequate soft tissue reconstruction.
 - (b) Approach:
 - The scar and the biopsy track must be included en-bloc in the surgical procedure.
 - The incision must always be longitudinal in the extremities.
 - Careful oncologic dissection.
 - (c) Resection
 - Resection overcomes reconstruction when defining surgical resection.
 - Ascertain safe oncological margins.
 - Make an intraoperative biopsy.
 - After resection of the tumor:
 - Change gloves and surgical instruments.
 - Very careful hemostasis must be ensured.
 - Bring personally the mass to the pathology laboratory.
 - The drains—if needed—should be placed in line with the scar.
 - Put clips in the surgical bed if postoperative radiotherapy is needed.
 - (d) Adequate soft tissue reconstruction

49.6 Photos and Imaging During Treatment

See Figs. 49.4, 49.5, 49.6, 49.7, 49.8, 49.9, 49.10, and 49.11.

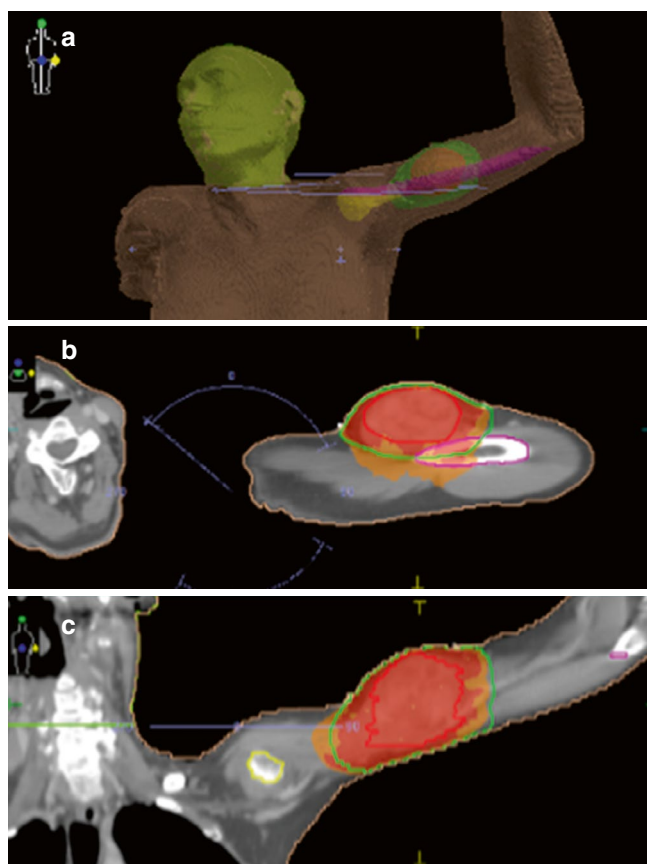


Fig. 49.4 Clinical and dosimetric images of the neoadjuvant radiotherapy. (a) 3D plan. (b) Axial section. (c) Coronal section

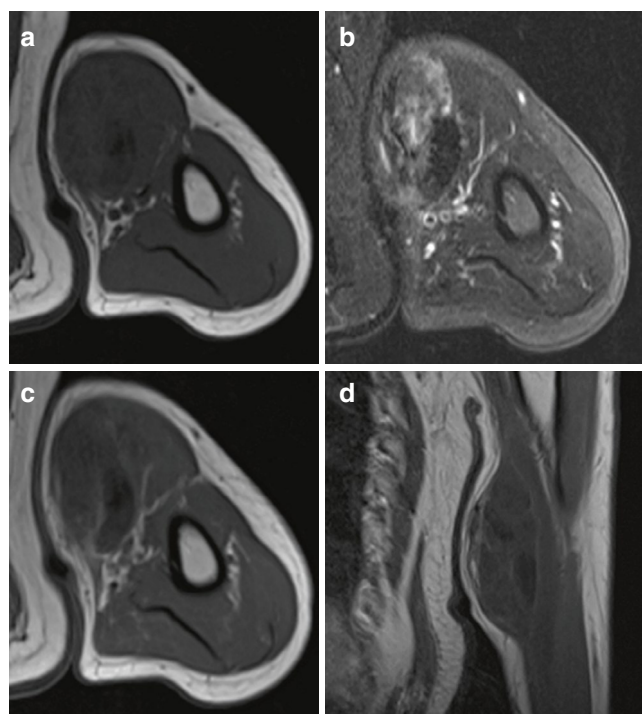


Fig. 49.6 MRI images after neoadjuvant treatment showed a clear reduction in the size—measured $7 \times 5 \times 2.1$ cm—and a change in the characteristics of the mass with a hypointense foci on T1-weighted sequences (a) and fat-suppressed T2-weighted sequences corresponding to hemosiderin deposits secondary to bleeding. In these sequences, a decrease in the cellular component is also observed, which leads to a decrease in the mass signal (b). After the administration of paramagnetic contrast, the mass showed discrete enhancement (c). Sagittal T1-weighted MRI and paramagnetic contrast: the enhancing tails have disappeared (d). According to RECIST criteria, there was a partial response: $>30\%$ decrease in longest axis measurement, no new lesions

Fig. 49.5 Clinical images (a: frontal view with the patient standing and b: with the patient supine) at the end of the neoadjuvant treatment. A reduction of the size (and palpated consistency) can be observed in compared with Fig. 49.1

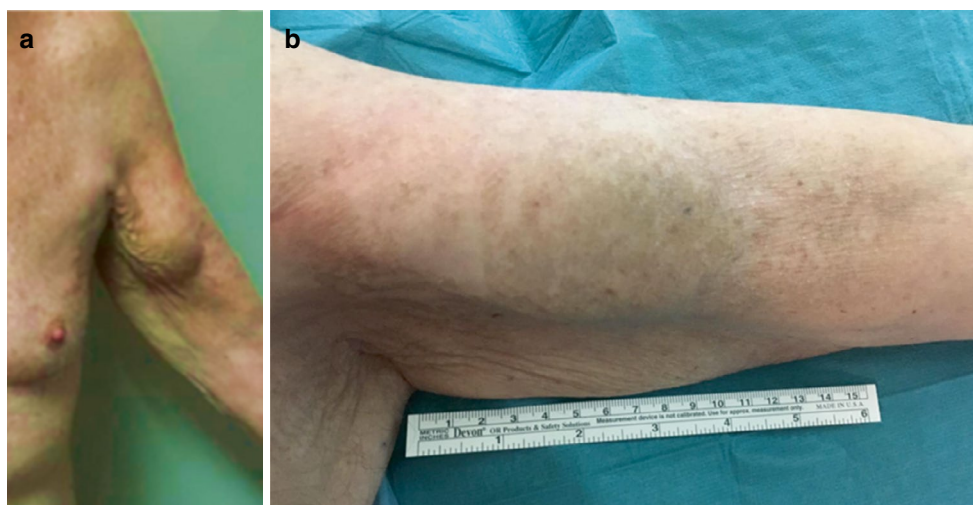




Fig. 49.7 Surgical approach. (a) Clinical picture before surgery. (b) Planned cutaneous resection along with the mass

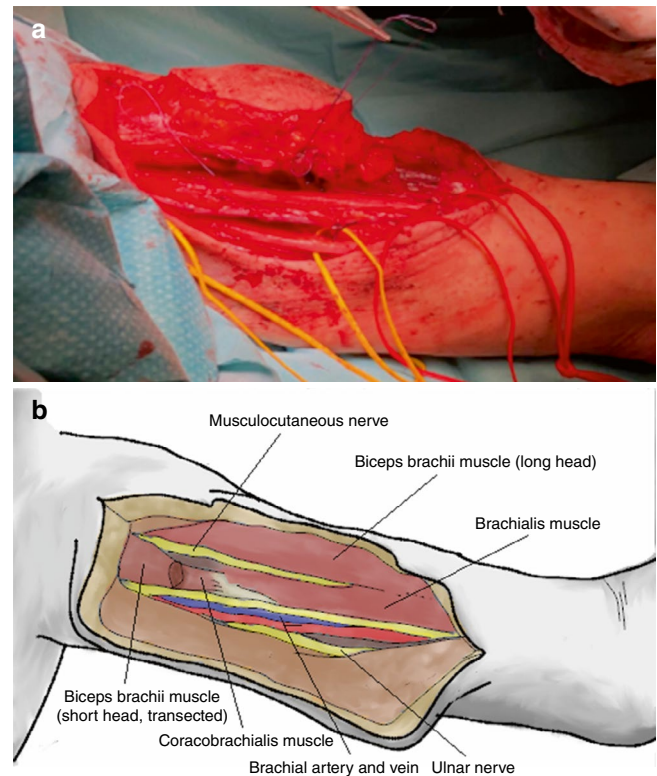


Fig. 49.8 Oncological surgical resection. (a) Mass dissected and elevated from its surgical bed. (b) Scheme of the surgical bed after the resection. (c) Photograph of the surgical bed after the resection

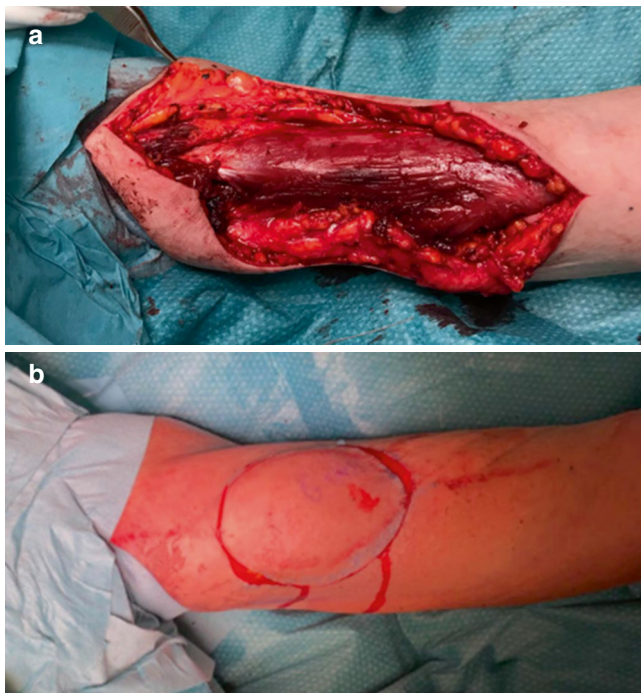


Fig. 49.9 Soft tissue reconstruction. (a) Biceps brachii is repositioned anteriorly, leaving the neurovascular bundle medial to its muscular mass. (b) The cutaneous defect is closed with a local flap

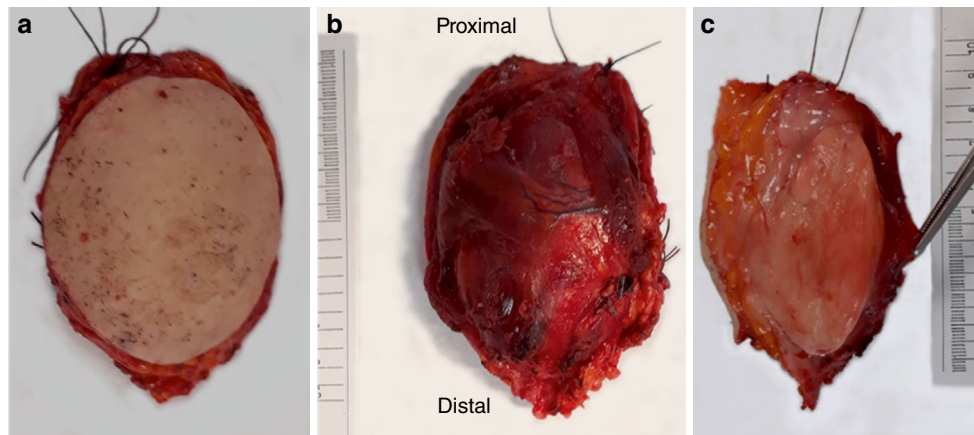


Fig. 49.10 Macroscopic images of the specimen. Size of the resected tissue was $7 \times 4 \times 3.2$ cm. (a) Anterior superficial view. (b) Posterior deep view (with muscular belly of the short biceps brachii). (c) Longitudinal section. When sectioned, a well-delimited,

oval-shaped, clear pink mass is seen, surrounded by skin in the surface and striated skeletal muscle in the depth. In both proximal and distal ends, there is lax grayish tissue that matches the tails in the MRI

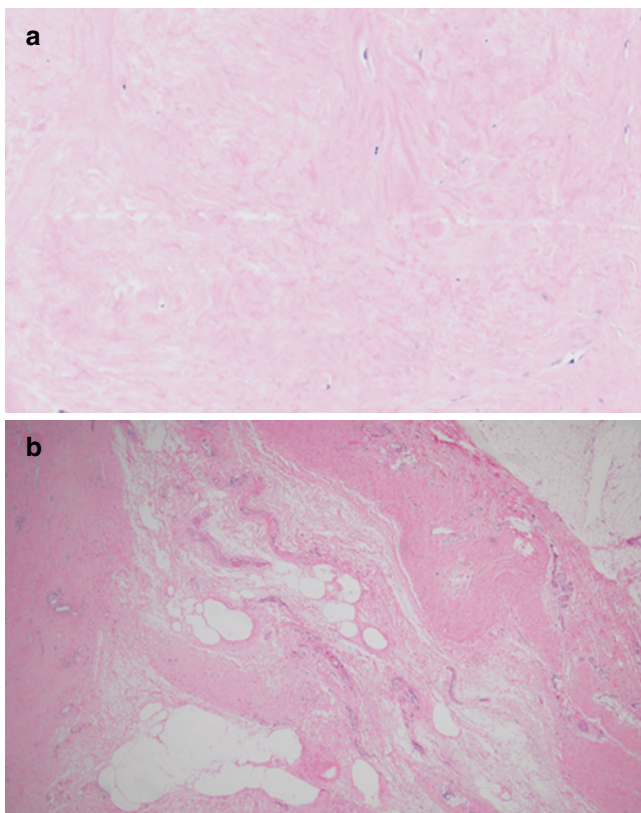


Fig. 49.11 Microscopic images of the specimen. H&E staining. The residual tumoral mass shows hyalinization and no signs of viability after chemotherapy and radiotherapy. (a) Fragment of the center of the mass, $\times 200$. (b) Fragment of one of the tails, observing, from left to right: hyalinized no viable tumor, lax connective tissue of the tail, fascia, and subcutaneous cellular tissue

49.7 Technical Pearls

1. Neoadjuvant therapy

- Chemotherapy according to first line protocols for UPS.
- Radiotherapy focused on the size and grade of the tumor, thus avoiding extended postoperative irradiation of the surgical bed.
- IMRT is better than 3D conformal radiotherapy because of the normal tissue sparing and increased local control.

2. Surgical resection

- An adequate margin should consider:
 - Quantity margin width.
 - Quality margin—type of anatomical barrier
 - Close to nerves: Epineurium resection. In this case, no major nerves or branches were resected or transected, only medial cutaneous brachial nerve in the approach.
 - Close to vessels: Adventitia resection or vessels resection and by-pass. Adventitia was preserved (Fig. 49.6).
 - Close to bone (increased bone uptake or by MRI): Periosteum resection or bone resection. Although periosteum was seen after the resection of the short head of the biceps brachii muscle, it was not affected.
 - Close or adjacent skin: resection of the affected skin with wide margins, and skin graft, or free or local muscular flap.

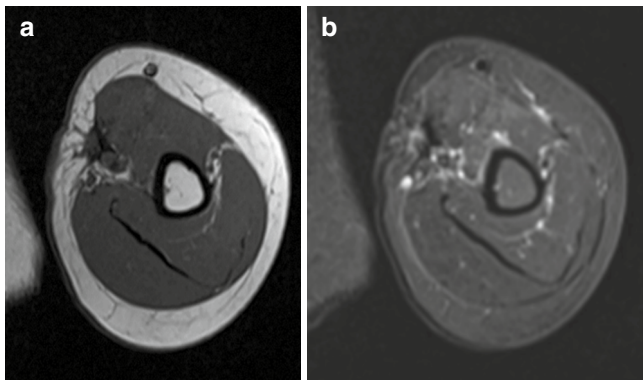


Fig. 49.12 MRI 3 years after surgery. Axial sections (a) T1 sequence. (b) T2 sequence. No signs of local recurrence are observed

- (b) The quality of the surgery will be defined by its worst margin.
- (c) Every attempt should be made to avoid positive microscopic surgical margins.
- (d) A positive margin over an anatomical barrier was the worst surgical prognostic factor for local recurrence. This issue did not happen in the case presented.

49.8 Outcome Clinical and Radiological Images

From a clinical point of view, the patient is asymptomatic, with no signs of local recurrence, and no functional deficit.

MRI obtained 3 years after resection: no tumor or signal alterations are visualized, only areas of low signal in all the sequences that correspond to fibrosis. No distant disease is observed either (Fig. 49.12).

49.9 Avoiding and Managing Complications

- (a) Drains should be placed at the incision line.
- (b) Drains should be maintained, mainly in patients with preoperative radiotherapy, until the debit is less than 30–50 cc/24 h.
- (c) Do not remove staples or stitches until the third week postoperative.
- (d) Antibiotic therapy, while maintaining drainage or bladder catheter.
- (e) Radiation is an adjunct, not a substitute, for poor surgical technique.
- (f) Surgery preferably takes place 4–6 weeks after completion neoadjuvant radiotherapy in order to decrease the risk of wound complications.
- (g) The surgeon must take the resected specimen to the pathology laboratory, to show the pathologist its

orientation, and to assess high-risk areas with a positive or close margin.

- (h) In case of doubt, an intraoperative biopsy should be performed.
- (i) Soft tissue reconstruction should not be started until the intraoperative biopsy is reported to the surgical team.
- (j) Processing may affect the difference between the margin reported and the margin you thought you delivered.
 1. Communicate with your pathologist.

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Suggested Readings

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