Vascular Surgery in Oncology

Antonio Eduardo Zerati
Kenji Nishinari
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Editors

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Foreword

Managing the Vascular Phase of Cancers

From a biological perspective, the vascular phase of cancers is critical for tumor progression, as pioneering studies by Judah Folkman and his alumni demonstrated. The interaction of tumor cells with the vascular system, either through cooption of already-formed vascular structures or the ability of both tumor and microenvironmental cells to induce angiogenesis, allows the integration of cancer with virtually all systems of the organism – for good or for bad.

While it is through a functional vascular system that drugs or immune cells can target tumors, it is through dysfunctional vascularization that cancer cells are exposed to an intermittent state of hypoxia followed by reoxygenation, favoring DNA damage, mutations, and increased cancer cell genomic instability. Tumors represent barriers to regular blood flow and interfere with lymph circulation, often releasing cell debris which stimulates thrombotic phenomena. Different particles released by tumor cells into circulation subvert the immune system and allow the formation of premetastatic niches. These processes culminate in the metastatic spread which ultimately is responsible for three out of four cancer patients' death. Maintaining a functional or normalized vascular system is not a simple task. However, it is a most needed one. This is just one of the challenges that our colleagues in vascular surgery embrace when applying their expertise in the management of a cancer patient.

Integration and collaboration are key for the successful management of cancer patients. For that, a constant dialogue needs to be maintained among those who provide patient care. Zerati, Nishinari, and Wolosker coordinated this dialogue with a number of colleagues in this complete book on vascular surgery in oncology. First, they promote a discussion with experts from every major specialty in oncology, who delineate the problems faced in their areas and then the editors bring the perspective of their integrative specialty. The readers are invited to take part in this interesting conversation and learn not only the state of the art on vascular surgery but also

identify the gaps in the field, which will require the attention of medical research in the future.

This is a book to read and to keep as a reference. Hopefully, other books like this will come along and provide the reader with the multidisciplinary dialogue which is essential for the best practices in oncology.

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Part I
Surgical Oncology

Chapter 1
Head and Neck Surgery

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1.1 Upper Aerodigestive Tract Cancer

The upper aerodigestive tract (UAT) includes the oral cavity, pharynx, larynx, nose and paranasal sinuses, and salivary glands. Cancers of the UAT are the sixth most frequent worldwide [1] and, in great majority, are squamous cell carcinoma (SCC). The main risk factors are tobacco and alcohol consumption, although the importance of human papillomavirus (HPV)-associated cancer is growing, especially in oral cavity and oropharynx [2].

The main clinical manifestation is the presence of a chronic ulcerated lesion or lymph node enlargement, especially in smoking patients. But other symptoms may occur, such as persistent hoarseness, dysphagia or odynophagia, pain, or dyspnea. Biopsy is mandatory, generally under local anesthesia, and enlarged lymph nodes may be evaluated by a fine-needle aspiration, if necessary.

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Approximately 90% of all cases are squamous cell carcinoma (SCC) that originates from initial dysplasia until the invasive carcinoma, some of them HPV-related. Other tumors are verrucous carcinoma, spindle cell carcinoma, salivary malignant tumors, sarcomas, lymphoepithelioma, and melanomas, among other rare conditions.

After initial diagnosis, the next step is the proper staging of the lesion, always according to the AJCC/UICC (International Union Against Cancer) staging system. Factors such as histologic diagnosis, site and stage of primary tumor, as well as biological tumor behavior define the initial treatment. The therapeutic options are surgical resection or radiotherapy, sometimes associated with chemotherapy. In advanced cases, a combination of them is required, always in a context of a multidisciplinary team. Because of the rich lymphatic drainage of the region, besides the resection of the primary lesion, we must always discuss the proper management of the cervical lymph nodes, in performing a neck dissection, the term used for the approach for lymphatic chain, with many variations.

The head and neck region is an anatomic site very rich in vascular structures. Due to proximity with them, especially the carotid artery and jugular vein in neck dissection, but also the maxillary artery or the brachiocephalic trunk in the resection of the primary lesions, the approach of a vascular surgeon is sometimes required, mainly in more recent years, when there was a massive increment in surgical rescue planning after initial approach in a nonsurgical therapy and its consequences.

1.1.1 Oral Cavity/Lip

1.1.1.1 Epidemiology

The lips are the entrance to the alimentary tract and are essential to maintain the oral competency, but they are also important in articulation of speech and facial expression. The most important risk factor in sun exposure, especially in the lower lip, and approximately 95% are SCC, with a clinical behavior similar to skin cancer counterparts.

The oral cavity begins at the lips, includes the hard palate and upper dentition and, inferiorly, the mandibular dentoalveolar structure and the oral tongue, floor of the mouth, and jugal mucosa. It is continuously exposed to inhaled and ingested carcinogens, such as tobacco, alcohol, and betel and, by this reason, it is the most common site for cancers in the head and neck region.

1.1.1.2 Clinic Evaluation

Lip tumors use to be exophytic or ulcerated, sometimes preceded by hyperkeratosis and leukoplakia and usually have a lower incidence of lymph node metastasis. In the oral cavity, the tumors present as an ulcerative, exophytic, or endophytic lesion.

Leukoplakia and erythroplakia are precancerous lesions that have a varying risk of progression to malignancy. Different from the lips, oral cavity tumors are at a high risk of regional metastasis.

1.1.1.3 Histology

SCCs have a typical histologic progression from in situ to invasive carcinoma, still ranging from well-differentiated to poorly differentiated and sarcomatoid types. A great histologic feature is its Depth of Invasion (DOI), related to the risk of lymph node metastasis and worse survival rates.

1.1.1.4 Staging

The most recent revision (eighth edition of the AJCC Staging Manual) included the depth of invasion (DOI), added to the surface dimensions and local extent for primary tumor staging (Table 1.1).

1.1.1.5 Treatment

Surgery is the treatment of choice and the surgical planning must include reconstruction, using local, regional, or distant flaps. Neck dissection is indicated in positive cases or, electively, in advanced primary tumors. Interoperate negative margins have to always be confirmed by the frozen section.

Surgery is also the modality of choice for oral cavity, with complete tumor resection (on frozen sections), neck dissection, and reconstruction. Surgical approaches may be "per os," via cheek or visor flap approach, combined or not with mandibulectomy (marginal or segmental) or even mandibulotomy for adequate access. Reconstruction varies from primary closure to local or regional flaps, such as the pectoralis major, or free microvascularized flap that may include the fibula for bone reconstruction, usually based on facial artery and vein.

Table 1.1 TNM staging system for carcinoma of the lip and oral cavity (T)

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm, DOI ≤5 mm
T2	Tumor ≤2 cm, DOI >5 mm and ≤10 mm or tumor >2 cm but ≤4 cm, and ≤10 mm DOI
T3	Tumor >4 cm or any tumor >10 mm DOI
T4a	Invasion of adjacent structures (cortical bone of the mandible or maxilla, maxillary sinus, or skin)
T4b	Invasion of masticator space, pterygoid plates, or skull base and internal carotid artery

Adapted from AJCC Staging Manual

Advanced cases classified as T4b because of internal carotid artery invasion are generally not candidates for surgical treatment. But sometimes this involvement is not so clear, especially in recurrent postradiation therapy cases, where images may not be so clear. Radical resections including carotid artery resection are being increasingly performed, with many options as tumor peeling in the artery wall, ligation, or resection with reconstruction. Outcomes in morbidity or mortality varies, but this approach requires a proper case selection and has to be weighed against the risks of complications, eventually very impactants [3]. These more radical interventions usually do not alter survival, but can improve the quality of life for very selected cases [4].

1.1.2 Pharynx

The pharynx is a tubiform organ that connects the airway from the nasal cavity to the larynx and the digestive way from oral cavity to the cervical esophagus. It is divided into three contiguous anatomic regions: the nasopharynx, oropharynx, and hypopharynx, of which one of them is divided into distinct anatomic features, with specific physiologic functions and particular tumor behavior. The most frequently malignant neoplasm in the pharynx is SCC and, although tobacco and alcohol consumption remain the most important etiologic factors, viral exposure such as Epstein-Barr virus (EBV) for the nasopharynx and human papillomavirus (HPV) for the oropharynx are frequently and increasingly associated with these tumors.

1.1.2.1 Subsites

Oropharynx

Anatomy

Posteriorly to the oral cavity, it includes the soft palate in the superior and median portion and, on each side, the tonsillar fossae, lateral wall and, inferiorly, the posterior third of the tongue, called “base of tongue” that continues with the lingual aspect of the epiglottis, and it ends in the posterior wall.

Clinic Evaluation

The base of the tongue and tonsils is the most frequent site of primary tumors, largely because there is a significant rise in the tonsils and soft palate, attributed to the incidence of HPV-associated SCCs. Cervical lymph node metastases occur very often, sometimes bulky even with small primary tumors, and cystic in HPV-positive cases. From an epidemiological point of view, HPV-related cancers are seen in a younger population, without a history of heavy smoking or alcohol consumption.

Histology

Most lesions are still SCC related to tobacco and alcohol consumption, but there are some particularities in HPV-associated tumors, which have a basaloid morphological appearance and are less undifferentiated and non-keratotic. Immunohistochemistry is used to detect the p-16 protein, a surrogate marker for HPV infection.

Staging

The eighth edition of the AJCC/UICC staging system has separated the oropharynx cancer in "HPV (p16) negative" and "HPV (p16) positive," due to the importance of p16 protein as a marker for HPV+ cases and great differences in prognosis for them (Tables 1.2 and 1.3).

The T classification, based on surface dimensions, remains the same, except for the inexistence of in situ cases, but nodal metastasis differs for HPV-positive cases. Laterality and size of metastatic nodes keep being included, but not extra nodal extension.

Treatment

The major recent aspect for the oropharynx is the responsivity to radiotherapy, even in advanced tumors, eventually associated with chemotherapy, with the great advantage of not manipulating the mandible. For this reason, the nonsurgical treatment has turned the first therapeutic choice, especially in HPV+ cases. But small lesions may be treated with surgical resection or, eventually, radiotherapy, always in a single-therapy context.

Table 1.2 TNM staging system for carcinoma of the oropharynx (p16 negative, p16−)

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor <2 cm in greatest dimension
T2	Tumor >2 cm but ≤4 cm in greatest dimension
T3	Tumor >4 cm or extension to lingual surface of epiglottis
T4a	Invasion of the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T4b	Invasion of lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base, or encases carotid artery

Adapted from AJCC Staging Manual

Table 1.3 cN for HPV-positive, p16+ oropharynx carcinoma

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, <6 cm
N2	Contralateral or bilateral lymph nodes, <6 cm
N3	Lymph node(s) >6 cm

Adapted from AJCC Staging Manual

In more recent years, new advances in transoral endoscopic or robotic approaches have been used, especially in recurrent disease or other histology neoplasms. The greater open approaches, via mandibulotomy or mandibulectomy, have been reserved for recurrent disease advanced tumors with bone involvement. Neck lymph nodes must be always evaluated, according to N status, in surgical planning or even in the radiation field, due to the high frequency of nodal metastasis.

In the particular situation of carotid involvement, usually in recurrent diseases, a series from Baylor University Medical Center reported a 5-year overall survival of 10% for patients submitted to carotid resection *en bloc* with the primary tumor, with six cancer-related deaths and three deaths due to other causes [5].

An early series of 12 patients including both primary treatment and salvage reported one postoperative death and two cancer-related deaths, but several patients had a very short time of follow-up. Due to improved patency at low-flow rates and resistance to infections, the authors consider the saphenous vein graft as the treatment of choice [6], as shown in another example in Fig. 1.1. These findings were challenged by a report of seven patients published in 1994. The authors report a mortality of 29% with no long-term survivors [7].

Hypopharynx

Anatomy

The inferior part of the pharynx begins at the level of the tip of the epiglottis and ends at the border of the cricoid cartilage, when the UAT continues to the cervical esophagus. It is still divided in three parts: pyriform sinuses on each side, posterior wall, and post cricoid region.

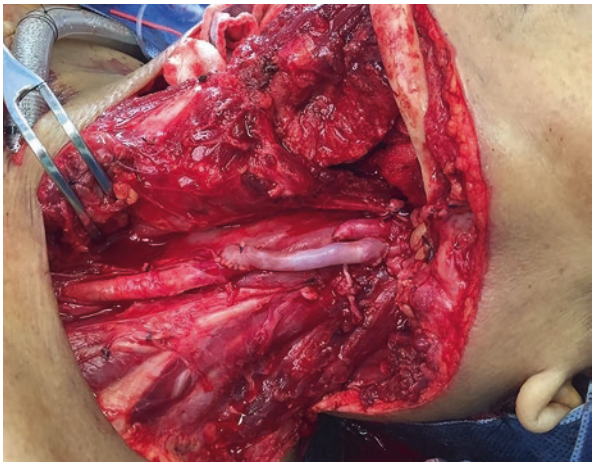

Fig. 1.1 Saphenous vein graft for carotid reconstruction

Clinic Evaluation

The usual symptoms are dysphagia, odynophagia, otalgia, hoarseness, or dyspnea, many times accompanied by palpable cervical lymph nodes, especially in patients with a heavy history of tobacco and alcohol consumption. Flexible fiber-optic examination provides adequate initial clinical assessment.

Histology

Histologically, these tumors are moderate to poorly differentiated SCCs with a poor prognosis, in part because of a great tendency for submucosal spread.

Staging

Staging of hypopharynx tumors is related to local extent and invasion of various sites within the hypopharynx, oropharynx, or larynx. Laryngeal function is closely related to the staging system, and local dissemination occurs often and early (Table 1.4).

Treatment

Early lesions, quite rare, can be managed by external radiation therapy or endoscopic resection as definitive treatment. In the last two decades, hypopharyngeal cancers that would require total laryngectomy are being treated with chemoradiotherapy, in a larynx preservation treatment context. But most patients require surgical treatment, a pharyngolaryngectomy with neck dissection, followed by postoperative radiation therapy, with or without chemotherapy. The submucosal spreading often implies the necessity for circumferential pharyngectomy or even a pharyngolaryngoesophagectomy. Reconstruction may be performed with local or regional flaps, myocutaneous flaps, or distant free flaps, like the anterolateral thigh free flap. Gastric transposition or a jejunum graft may also be used.

Table 1.4 TNM staging system for carcinoma of the hypopharynx

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	One subsite of hypopharynx and/or 2 cm or smaller in greatest dimension
T2	Tumor >2 cm but ≤4 cm, invasion of more than one subsite of hypopharynx or an adjacent site, without fixation of hemilarynx
T3	Tumor >4 cm, fixation of hemilarynx or extension to esophagus mucosa
T4a	Invasion of thyroid/cricoid cartilage, hyoid bone, thyroid gland, central compartment soft tissue, or infiltration muscle of esophagus
T4b	Invasions of prevertebral fascia, mediastinal structures, or encases carotid artery

Adapted from AJCC Staging Manual

Because of the aggressiveness of hypopharyngeal malignant tumors, carotid involvement is considered an absolute contraindication for surgical treatment, due to the very poor outcomes.

Nasopharynx

Anatomy

Nasopharynx begins at the posterior border of the nasal cavity and extends to the level of the free edge of the soft palate and contains some subsites as the vault, lateral walls (that includes the Rosenmuller fossetas and the opening of the eustachian tube), and the posterior wall.

Clinic Evaluation

Usual initial symptoms are nasal obstruction, epistaxis, otalgia, unilateral or bilateral middle-ear effusion, or cranial neuropathy, depending on the location and extent of the lesion, although the initial manifestation may be the cervical lymph node metastases. Clinical evaluation includes flexible or rigid nasal endoscopy and cervical status.

Histology

Many primary neoplasms may occur, like SCCs, minor salivary gland tumors, chordomas, soft tissue tumors, bone tumors, and lymphomas of the Waldeyer's ring. But the most important primary tumor is the EBV-associated carcinoma (Epstein-Barr Virus), that, from a histopathologic point of view, is undifferentiated carcinoma surrounded by lymphocytic infiltrate, and historically called "lymphoepitheliomas." The World Health Organization divides these carcinomas into keratinizing, nonkeratinizing, and undifferentiated types.

Staging

Local extension to the adjacent soft tissues (parapharyngeal space) and bone (skull base) defines the T staging, although the invasion of adjacent muscles occurs at early stages in staging, as long as cervical metastasis also occurs at early stages, according to AJCC/UICC staging system (Table 1.5).

Finally, SCCs of the nasopharynx have a different classification, based on specific clinical behavior

Treatment

Nasopharyngeal carcinomas are highly responsive to radiation therapy that, combined with chemotherapy, form the initial therapeutic choice. Surgical approach is reserved for localized, residual, or recurrent disease, as well as for treatment of recurrent neck nodal disease.

Table 1.5 N staging for nasopharyngeal carcinoma

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral lymph node(s) and/ or retropharyngeal lymph node(s), <6 cm, above the caudal border of cricoid cartilage
N2	Bilateral lymph node(s), <6 cm, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral lymph node(s), >6 cm, and/or extension below the caudal border of cricoid cartilage

Adapted from AJCC Staging Manual

Small and localized lesions may be managed endoscopically. When open access is required, there are many options based on anatomic localization of the lesion: transpalatal, via medial maxillectomy, or maxillary swing, sometimes associated with mandibulotomy for infratemporal fossa approach.

When a major vascular structure is compromised, the surgery is not indicated. The maxillary artery is the final branch of the external carotid artery and a bleeding in the maxillary plexus is often serious. A particular situation on the radiation therapy for nasopharyngeal carcinoma is the carotid blowout syndrome, that must be treated with an endovascular treatment [8].

1.1.3 Larynx

1.1.3.1 Anatomy

The larynx divides the upper aerodigestive tract into respiratory and digestive and, by this reason, has a role importance in breathing, swallowing, and speaking. It is divided into supraglottic, glottic, and subglottic regions, based on embryologic development with profound clinical implications by the difference among lymphatic drainage, symptoms, and therapeutic management. It is the second most common site for SCC in UAT, which is causally related to tobacco and alcohol exposure.

1.1.3.2 Clinic Evaluation

The glottic region is by far the most commonly affected and the main symptom is the persistent hoarseness, while the supraglottic region causes dysphagia and the subglottic region causes early dyspnea. In advanced cases, it causes respiratory obstruction, with a necessity for tracheostomy. The supraglottic region is very rich in terms of lymphatic drainage and, by this reason, the nodal metastasis is very common, many times the initial presentation. The opposite occurs in glottic cancer, with poor lymphatic drainage.

1.1.3.3 Histology

The great majority of tumors is the SCCs tobacco-related, but other histologies may occur, like sarcomas (chondrosarcomas) or small salivary glands neoplasms.

1.1.3.4 Staging (Table 1.6)

1.1.3.5 Treatment

The therapeutic options are radiation therapy, surgery, or a combination of both, based on equivalent efficacy in survival outcomes, and depending on the following parameters: location and extent of the primary tumor and lymph node status, as well as patient and physician factors.

Early glottic SCCs may be treated by endoscopic resection or isolated radiotherapy, with a particular concern about the anterior comissura. As long as the tumor grows, endoscopic resection may not be feasible and we consider open partial laryngectomies that can be vertical, like the anterolateral or hemilaryngectomy if the arytenoid is resected; or horizontal, like the supracricoid laryngectomy with cricohyoidoepiglottopexy or a supraglottic laryngectomy. The larger the resection, the greater the dysfunction in speech and deglutition, and the greater possibility to use a tracheostomy.

For larger tumors that require a total laryngectomy, it indicated the larynx preservation treatment program, with radiotherapy or chemoradiotherapy. But if an initial nonsurgical treatment fails, or if there is a massive cartilage or extra laryngeal involvement, the total laryngectomy would be the only therapeutic option. Complementary treatment is indicated for more advanced cases.

In head and neck, the larynx is the organ which first had a protocol for the concept of "organ preservation," in an attempt to avoid a total laryngectomy and try to manage it with a scheme of chemotherapy and radiotherapy with good outcome results, especially in glottic cancer, which has a better outcome. But when this

Table 1.6 TNM staging system for carcinoma of the larynx

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor in one subsite of supraglottis or glottis (T1a for one vocal cord, T1b for both vocal cords) with normal vocal cord mobility or one site of subglottis
T2	Invasion of more than one supraglottic subsite without fixation of the larynx, extension to supraglottis or subglottis or with impaired vocal cord mobility or glottic extension for subglottis
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/ or inner cortex of thyroid cartilage
T4a	Invasion of the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx
T4b	Invasion of prevertebral space, carotid artery, or mediastinal structures

Adapted from AJCC Staging Manual

initial approach fails, we still have the option for a surgical rescue, with all the implications of a surgery in an irradiated neck. One of the paradigms is the potential involvement of the carotid artery that, in specific cases, may not be a contraindication for the surgical procedure and should include an en bloc carotid artery resection and reconstruction with a prosthesis or a saphenous vein graft. The functional results are generally good in terms of carotid patency and the outcomes are better in absence of nodal metastasis and with the primary in larynx, compared to other types of tumors [9].

In terms of carotid resection, some series shows a 5-year survival rate of 49% (95% CI: 39–59%) after resection *en bloc* involving the internal carotid artery with no postoperative mortality. Unlike the other series, the reconstruction was performed with polytetrafluoroethylene (PTFE) grafts. Analyzing quality of life for patients with carotid resection and those submitted to nonoperative treatment, the authors record a benefit of 3.12 quality of life-adjusted life years for patients treated by surgery. They consider that this approach leads to good local control with acceptable morbidity and an improvement in quality of life [10] and may bring some benefices in cases where no other conservative management offers any hope for cure or palliation [11]. One particular situation is the surgical treatment of a stomal recurrence after laryngectomy, a situation of very poor outcome. In the rare condition when a surgical rescue procedure in indicated, the manubrium is commonly resected for the maturation of the new tracheostomy in the anterior thoracic wall, at the mediastinal level and, for this purpose, the great vessels of the superior mediastinum are dissected for an eventual passage of the new stoma below the brachiocephalic trunk, and a large flap, usually the pectoral myocutaneous island flap, is used for mediastinal (and artery) coverage [12].

1.1.4 Nasal Sinus/Skull Base

1.1.4.1 Epidemiology

Malignant neoplasms of the sinonasal tract are rare and, frequently, with involvement of more than on site at initial diagnosis.

1.1.4.2 Clinic Evaluation

They are usually asymptomatic and may develop largely in an air-filled cavity prior to having symptoms, which use to be: nasal obstruction (especially unilateral in older patients without history of allergic processes), epistaxis or swelling or masses in the hard palate, upper gum, or soft tissues of the face. More advanced cases may develop loose teeth, local or regional anesthesia, diplopia or proptosis, trismus, or commitment of cranial nerves. Primary evaluation is performed with nasal endoscopy and radiographic imaging: computed tomography and magnetic resonance imaging scans.

1.1.4.3 Histology

The most common malignancy is the SCC, followed by salivary glands carcinomas, melanomas, sarcomas, and esthesioneuroblastomas. Benign lesions and mesenchymal tumors may also occur.

1.1.4.4 Staging (Table 1.7)

1.1.4.5 Treatment

Historically, surgical resection with or without postoperative radiation or chemoradiotherapy is the standard treatment but, in recent years, other options are considered like induction chemotherapy, systemic, or intra-arterial, followed by surgery or radiation therapy.

There are several possible surgical approaches, and the blood supply is always a great concern. Branches of the external carotid artery, especially the sphenopalatine branches of the internal maxillary artery, and internal carotid arteries (ophthalmic artery), as long as the venous drainage, that forms a dense plexus, may be a potential source of important bleeding.

A very important factor is the potential involvement of the skull base, divided in three parts. The anterior cranial fossa is commonly affected by nasal cavity tumors that involve the ethmoid region, via cribriform plate, like the esthesioneuroblastoma, or tumors that involve the orbit and lacrimal apparatus, like advanced skin malignancies. The middle cranial fossa may be affected by neurogenic tumors like schwannomas and neurofibromas, or by a perineural extension of other tumors, like salivary adenoid cystic carcinomas, or even sarcomas and paragangliomas. The posterior fossa may be affected by glomus tumors and chordomas of the clivus. These cases are complex and treated by a craniofacial resection, in a multidisciplinary team and, in most cases, complementary treatment is indicated with radiation therapy, many times associated with systemic chemotherapy.

Table 1.7 TNM staging system for carcinoma of the nasal cavity and paranasal sinuses (T)

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor limited to maxillary sinus mucosa, no bone erosion
T2	Bone erosion, extension into the hard palate and/or middle nasal meatus
T3	Invasion of the posterior wall of maxillary sinus, subcutaneous tissues, floor of medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Invasion of anterior orbital, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid, or frontal sinuses
T4b	Invasion of orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus

Adapted from AJCC Staging Manual

In patients with carotid artery resection at the skull base, a postoperative mortality of 11.1% with morbidity of 16.7% has been reported. All patients died due to cancer progression or further treatment complications, with no long-term survivors. The immediate risks and long-terms results make the authors consider this option as inadequate [13].

1.1.5 Unknown Primary and Neck Management

1.1.5.1 Epidemiology

Approximately 10% of patients with metastatic SCCs in the neck do not have an identifiable primary tumor, and the UAT must be totally evaluated, especially the oropharynx (tonsils and base of tongue), larynx (supraglottic region), nasopharynx, and hypopharynx.

1.1.5.2 Clinic Evaluation

Investigation of the primary includes physical examination and endoscopy under general anesthesia to search for the primary tumor. The diagnosis is performed by a fine-needle aspiration biopsy, followed by a p16 staining and complementary exams, particularly a PET-SCAN.

1.1.5.3 Nodal Staging

According to AJCC/UICC, the nodal staging takes into account the site, number, size, and extranodal extension (ENE) for classification. The clinical N stage from SCCs of the UAT is the same for oral cavity, HPV-negative oropharynx, hypopharynx, larynx, paranasal sinuses, salivary glands, and nonmelanoma skin cancers (Table 1.8).

Table 1.8 TNM staging system for metastatic carcinoma of the cervical lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2a	Single ipsilateral or contralateral node 3–6 cm, ENE(−)
N2b	Multiple ipsilateral nodes, <6 cm, ENE(−)
N2c	Bilateral/contralateral lymph nodes, <6 cm, ENE(−)
N3a	Lymph node >6 cm, ENE(−)
N3b	Metastasis with ENE(+)

Adapted from AJCC Staging Manual

Clinical staging (cN) for squamous cell carcinoma of the head and neck

For the HPV-positive cancers in oropharynx, due to a better overall prognosis, the N staging has changed in the eighth edition, as previously shown in the Oropharynx section.

1.1.5.4 Treatment

Management of the neck is part of an overall treatment of choice, and nodal status influences decision. If radiation or chemoradiation therapy is indicated, the neck should be included and a surgical approach must be indicated for salvage or regional recurrence. But, in the case of initial surgical approach, the cervical lymph nodes should be always considered, based on characteristics of the primary tumor.

In N0 cases, the sentinel node mapping procedure may be indicated, especially in the floor of the oral cavity cases. But the relatively high incidence of occult metastasis justifies the selective neck dissection, which usually encompasses the first cervical levels of lymphatic drainage as, for example, the supraomohyoid, the jugular node, or the posterolateral neck dissections.

In N+ cases, the neck dissection must be radical, including the five cervical levels, which contain the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve. Several possibilities exist, taking into account the nodal status and the affected structures.

According to the AJCC Cancer Staging Manual [14], encasement of the internal carotid artery corresponds to stage T4b, if it occurs by direct extension of the primary tumor, or to unresectable nodal disease or very advanced head and neck cancer. These patients are not considered candidates for surgical treatment due to the morbidity of the operation and dismal oncologic prognosis. These considerations contribute to internal or common carotid artery resection being considered an exceptional procedure and limit the reported experience in the literature with this approach.

Resection of the carotid artery due to encasement by cervical lymph node metastasis was addressed specifically by a series of 58 patients with 41 submitted to simultaneous reconstruction. In this subgroup, the rate of postoperative stroke was 20%. Both disease-specific and overall survival rates were 50% after a 12-month follow-up [15].

Aggressive surgical approach for patients with advanced squamous cell head and neck carcinoma with carotid invasion can lead to cure in a select group of patients. Saphenous vein grafts demonstrated favorable outcomes with low infection and high patency rates, suggesting a valid alternative for arterial reconstruction in these cases. Five-year survival is 12.9% and the saphenous vein graft was used in all patients and it was considered, due to high patency rates and resistance to infections, superior to PTFE grafts [16].

The largest reported series in the literature includes 51 consecutive patients. Perioperative mortality was low with one death (2%) and two cases of stroke (3.9%). Overall survival at 2 years was 82% with five patients dying from disease progression [17].

A different approach is reported by Zhang et al. They performed carotid resection without vascular reconstruction in a series of 31 patients, most with carotid body tumors after previous evaluation with cerebral blood flow tests. They propose that such an approach may have fewer complications than reconstructive surgery due to lack of concern with graft patency [18].

A recent meta-analysis accrued 357 patients from 24 articles submitted to internal or common carotid artery resection and reconstruction. The favored reconstruction technique was autologous grafts in 274 patients (77%) with 13 articles stating selective use of shunts during clamp time and three never using it. The overall 30-day mortality was 3.6%. In 20 articles, 1-year overall survival data could be extracted, and it was 52.4% with significant difference according to publication period. In the articles published from 1981 to 1999, it was 37.0% and in those from 2001 to 2016, it was 65.4% [19].

Carotid artery resection carries a high risk of postoperative morbidity with variable 5-year survival rate. Patient selection is essential for success with discussion in multidisciplinary tumor boards mandatory.

1.2 Thyroid Cancer

More than 90% of neoplasms of follicular origin, papillary and follicular carcinomas, are considered well-differentiated, and its global incidence is growing worldwide, although the numbers of attributed deaths have not changed. That is due to more early detection in routine exams and the indolent behavior of these neoplasms. On the other hand, the medullary carcinoma of the thyroid, a more undifferentiated and aggressive tumor, accounts for less than 5% of all cases and may be related to an inherited cancer syndrome in approximately 20% of cases. The more undifferentiated cancer is the anaplastic carcinoma, much rarer but, by far, the most aggressive neoplasm of the thyroid gland.

1.2.1 Differentiated Thyroid Cancer

Papillary and follicular carcinomas are very indolent diseases, common in young people and usually asymptomatic. Initial proper evaluation occurs with physical examination focused in the thyroid gland and cervical lymph nodes. Measurement of thyroid function (specially TSH—thyroid-stimulating hormone) and neck ultrasonography, with fine-needle aspiration of thyroid nodules and suspect lymph nodes, are the next steps to complete diagnosis and therapeutic planning.

Staging is based on The American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC), published in the eighth edition in 2016. The most important factors are the age of the patient, better if less than 55 years, gross extrathyroid extension, and positive lateral neck nodes. Initial

radiological assessment begins with ultrasonography, but a CT scan or MRI may be necessary in suspicion of extension to retropharyngeal lymph nodes, larynx, trachea, cervical esophagus, or carotid artery.

1.2.1.1 Treatment

Surgery, sometimes associated with RadioActive Iodine (RAI-131), is the recommended therapy. There are many surgical possibilities that must be considered for each patient, according to risk group stratification based on prognostic factors related to patient and tumor characteristics. Unilateral lobectomy may be performed for early situations, but total thyroidectomy is indicated for bilateral involvement, gross extrathyroidal extension, high-risk cases, history of radiation exposure or family's thyroid cancer, or extensive regional nodal metastases.

The lymph nodes of the central compartment (levels VI and VI, the space between the hyoid bone and suprasternal notch) must be intraoperatively evaluated and, if positive nodes or a gross extrathyroidal extension are present, a central compartment dissection must be performed.

In more recent years, endoscopic or video-assisted, even remote access robotic, techniques have been proposed for aesthetic reasons (basically, not to have a cervical scar), but they must always respect criteria for not to compromise an oncologic result.

Locally advanced thyroid cancer may extend to superior mediastinal and parapharyngeal lymph nodes. Involvement of the recurrent laryngeal nerve, larynx, trachea, or esophagus generally is resectable and staged as T4a. Invasion of the prevertebral fascia or encasement of the carotid artery or mediastinal large vessels are staged T4b. In theory, these cases are considered surgically unresectable, but, in some situations, a limited invasion of the common carotid artery can be a candidate for resection and reconstruction, in general after a balloon occlusion testing [20].

The treatment must be completed with RAI-131 according to a risk stratification that takes into account variables such as age at diagnosis, presence of distant metastasis, gross extrathyroidal extension, tumor size, and nodal status.

1.2.2 Undifferentiated Carcinomas

1.2.2.1 Treatment

For the medullary thyroid carcinoma, total thyroidectomy with central compartment lymph node dissection is the recommended surgical procedure. Lateral neck dissection is performed in N+ cases, but may be also indicated in more advanced tumors or a high preoperative calcitonin level. If the superior mediastinum is involved, with encasement of the common carotid artery or mediastinal vessels, the surgery is contraindicated.

The extremely aggressive undifferentiated thyroid carcinoma, most common in older patients, has a very poor prognosis and, habitually, has no surgical indication, except for eventual palliative tracheostomy.

1.3 Salivary Glands

Salivary glands are divided into major (parotid, submandibular, and sublingual) and minor, about 400–600 of them, localized submucosally throughout the UAT, from lips down to the esophagus and trachea. Salivary glands tumors are rare, accounting for approximately 5% of all tumors of the head and neck. Most of them are benign.

1.3.1 Clinic Evaluation

Parotid and submandibular tumors present as an asymptomatic nodular mass, without facial compromise, while minor salivary glands tumors present as a submucosal mass, sometimes ulcerated. Diagnosis, or suspicion of malignancy, is performed by fine-needle biopsy aspiration. Diagnostic imaging studies, like ultrasonography or computerized tomography, are used for surgical planning.

1.3.2 Histology

The most common is the pleomorphic adenoma, which occurs mainly in the parotid gland. Oncocytomas, Warthin's tumor, and myoepithelioma are other benign lesions, but many other types may occur and, not infrequently, the final diagnosis is made with immunohistochemistry study. The most frequent malignant neoplasms are the mucoepidermoid carcinoma and the adenoid cystic carcinoma. In general, they are low-grade malignant tumors and tend to have an indolent course. But the high-grade tumors are very aggressive, with risk for regional and distant metastasis and a poor prognosis.

1.3.3 Staging (Table 1.9)

1.3.4 Treatment

Treatment of benign or malignant salivary tumors is surgical, with complete primary excision and eventual neck dissection. For parotid tumors, preservation of the facial nerve is mandatory but, in cases of nerve involvement and sacrifice,

Table 1.9 TNM staging system for carcinoma of the major salivary glands

T0	Primary tumor cannot be assessed
Tis	No evidence of primary tumor
T1	Carcinoma in situ
T2	Tumor <2 cm, without extraparenchymal extension
T3	Tumor >4 cm and/or extraparenchymal extension
T4a	Invasion of the skin, mandible, ear canal, and/or facial nerve
T4b	Invasion of skull base and/or pterygoid plates and/or encases carotid artery

Adapted from AJCC Staging Manual

reconstruction may be primarily performed by nerve grafting. In the submandibular gland, a regional neck dissection may be adequate to improve local control. High-grade and high-stage tumors have a high risk of nodal metastases, and neck dissection must be considered. For parotid advanced high-grade neoplasms, resection of the auditory canal and mastoidectomy may be performed. Radiotherapy may be indicated for adjuvant treatment for local and regional control in advanced cases.

Carotid invasion is usually a contraindication for surgical excision, due to the proximity with the skull base and an inaccessibility to the distal control that should be necessary for an eventual reconstruction.

1.4 Vascular Anomalies: Vascular Tumors and Vascular Malformations

Management of vascular anomalies involves a multidisciplinary approach to treat a diverse group of congenital and acquired diseases. Vascular anomalies are a group of diseases that involve proliferation of vessel-forming cellular structures or the abnormal development of vascular structures. Benign or malignant vascular tumors and malformations of the vascular system are considered in the broad spectrum of vascular anomalies [21, 22, 27].

Terminology and classification of vascular anomalies have always been major problems, and this is one of the causes of the rate of diagnostic errors and misinformation provided to patients about prognosis and treatment [23, 24].

The pioneering studies by Mulliken and Glowacki started the current era of understanding of vascular anomalies and "The International Society for the Study of Vascular Anomalies (ISSVA)" Classification is currently the most widely used (Table 1.10) [24]. In an international effort over decades of discussions and improvements, this classification was consolidated by all professionals involved in the treatment of vascular anomalies, including surgeons, pediatricians, hematologists, dermatologists, radiologists, pathologists, geneticists, and researchers [25].

The current classification of vascular anomalies divides them into two main groups: vascular tumors and vascular malformations. Vascular tumors include benign tumors, such as infantile hemangioma, congenital hemangiomas, and

Table 1.10 International Society for the Study of Vascular Anomalies (ISSVA) Classification (2018)

Vascular Tumors	Vascular Malformations			
	Simple	Combined	of Major Named Vessels	Associated with other anomalies
Benign Infantile Hemangioma Congenital hemangioma	Capillary (C)	CVM, CLM	Anomalies of Origin Course	Klippel- Trenaunay
Locally aggressive or borderline Kaposiform hemangioendothelioma	Lymphatic (L)	LVM, CLVM	Length Diameter Valves Communication Persistence	Parkes-Weber Sturge-Weber Mafucci
Malignant Angiosarcoma Epithelioid hemangioendothelioma	Venous (V)	CAVM		CLOVES CLAPO FAVA,
	Arteriovenous (A)	CLAVM others		Etc.

pyogenic granulomas, borderline tumors as hemangioendothelioma, tufted angioma, and also malignant tumors, such as angiosarcoma and epithelioid hemangioendothelioma [21, 22, 24, 26, 27]. The term hemangioma refers, therefore, to a true benign neoplasm, triggered by disorders of angiogenesis.

Vascular malformations are considered congenital malformations of the vascular system and include arterial, venous, lymphatic, or capillary malformations and their combinations. Also, they can be subdivided into high-flow and low-flow lesions, and many are associated with known genetic mutations and complex syndromes.

1.4.1 Vascular Tumors

1.4.1.1 Infantile Hemangioma

Infantile hemangioma (HI) is the most common benign vascular tumor in children. The incidence is about 5% in Caucasian newborns and there is a predominance of females, by 3–5 times. About 80% are noticed during the first month of life and the preferred location is cervicofacial, occurring in about 60% [25, 27].

Low birth weight, prematurity multiparity, and advanced maternal age are risk factors [28]. The cutaneous (non-visceral) form of infantile hemangioma can affect soft tissues in depth and extension. They can be superficial (cutaneous only), deep (involvement of the soft tissues, deep to the skin), or mixed. They can be localized or segmental, when affecting an anatomical unit or a large area. Segmental HI and multiple cutaneous hemangiomas (more than 5) have a greater association with visceral hemangiomas, increasing morbidity and mortality [28]. In addition, segmental IH has an increased correlation with complications, other structural anomalies, and the need for treatment.

Infantile hemangioma has a typical triphasic presentation [29]. In the proliferative phase (usually up to 12 months of life), there is a fast growth, able to assume considerable dimensions in proportion to the child's size, potentially causing functional and aesthetic impairment. Clinically, it is characterized as a solid, compressible, warm, and well-defined lesion. In 20% of cases, growth can cause functional impairment due to its dimensions or location and ulceration may occur leading to pain, bleeding, and secondary infection. In the involutive phase, volume reduction and color changes occur with endothelial cell reduction and replacement by fibroadipose tissue, in a process biologically characterized by induction of cell apoptosis [30, 31]. The end of the proliferative phase and the beginning of involution vary individually, as well as the size that a lesion can reach. When spontaneous regression ceases, involuted hemangioma is considered. At the injury site, sequelae may remain, such as a residual mass, cutaneous atrophy, and telangectasias [32]. MRI imaging findings vary according to each phase. In the proliferative phase, at T1, IH shows an isointense or hypointense signal in relation to muscle tissue. Contrast injection shows uniform intensification. In T2 sequences, they present hypersignal, as a lobulated mass. In the involutive phase, in sequences T1 and T2, variable fat content is observed. In the involuted phase, HI behaves like an avascular lesion. T1 shows a lesion with hypersignal (similar to fat), without intensification after contrast injection. In T2, it presents hyposignal (similar to fat), with no signs of blood flow in gradient studies.

Infantile hemangioma can affect the airways and are usually superficial, unilateral, and subglottic. Symptoms usually appear between 6 and 12 months of life. The typical clinical picture is hoarseness and stridor with progressive obstructive respiratory failure, which may require tracheostomy, according to the studies by Drolet et al. and Metry [21, 27]. There is a relationship between the distribution of hemangiomas in the cheeks, lips, mandibular region, and neck—called the "beard region"—and a higher incidence of concomitant injuries in the upper airways. Studies formalized the indication for fibroscopy of the upper airways when diagnosing cutaneous hemangiomas located in the "beard region" [33, 34].

In some syndromes, IH is present, the most significant being "PHACES" syndrome, due to its severity, since malformations of the posterior cerebral cortex, cervicofacial hemangioma, arterial anomalies, cardiac anomalies, ocular anomalies, and sternal anomalies coexist.

1.4.1.2 Other Vascular Tumors

Congenital Hemangiomas

Congenital hemangiomas, benign, are present and fully developed at birth. According to their postnatal evolution, they are subdivided into three types, namely, rapidly involutive (RICH), partially involutive (PICH), and non-involutive (NICH). Unlike IH, congenital hemangioma does not express the GLUT1 marker [35].

Kaposiform Hemangioendothelioma and Tufted Angioma

Considered locally aggressive or with borderline behavior, it may be associated with the Kasabach-Merrit phenomenon (hemolytic anemia, thrombocytopenia, and coagulopathies). Histology is typical, with proliferation of spindle cells and positivity for markers such as podoplanin [36].

1.4.1.3 Treatment

The vast majority of IH have a favorable evolution towards complete regression. In these cases, the recommended conduct is conservative and must include clinical monitoring, photographic documentation, and psychological support. The indication for active treatment can be divided into emergency indication and elective indication. Treatment modalities include clinical drug treatment and surgery. Emergency treatment is indicated for benign tumors in specific situations (functional impairment, such as obstruction of the visual axis, airway obstruction, and congestive heart failure) and for borderline and malignant tumors (to treat the lesion itself and systemic complications like the Kassabach-Merrit phenomenon). Relative indications occur in cases with potential for deformity due to the growth of the lesion, in order to reduce potential future complications.

The current clinical treatment of infantile hemangioma is based on the use of systemic oral beta-blockers. The therapeutic efficacy associated with the low side effects consolidated its indication [37]. Systemic corticosteroid administered orally is now considered as the second line of treatment. Corticosteroids for intralesional injectable use have been less used, as well as other medications such as alpha-interferon. In the case of kaposiform hemangioendothelioma, the use of mTOR inhibitors, such as sirolimus (rapamycin), has been shown to be effective as shown by recent studies.

Surgical treatment of hemangiomas must respect strict technical guidelines: removal of the lesion should not result in a sequel greater than that possibly left by the spontaneous involution; partial resections can be performed, solving the problem that motivated the indication for treatment and allowing, with the subsequent involution of the lesion, a definitive solution. Early treatment is proposed in emergency cases due to the risk of death or functional impairment in risk areas and also in elective cases in hemangiomas with low involutive potential [38, 39] or in growing areas with disfiguring potential such as nose, lips, and ear, with preference for intralesional accesses for superficial injuries or accesses resulting in reduced or hidden scars, often taking advantage of the classic approaches already used in aesthetic facial surgery [31]. The use of beta-blockers on a larger scale changed the profile of surgical indication, causing an impact on the total number of surgeries and its complexity, allowing a new perspective on the surgical and clinical management of infantile hemangiomas considering medical treatment as a neoadjuvant indication reducing the lesion to facilitate resection or postpone surgery.

1.4.2 Vascular Malformations

Recent advances in the studies of molecular biology and genetics have provided new explanations for development of vascular malformations. Several somatic and germline genetic mutations, as well as changes in the genetic coding of anomalous protein products, have been described and implicated in the development of specific vascular lesions [40–42].

The clinical picture is variable and dependent on the components of a specific malformation (Fig. 1.2). Regarding radiological findings, ultrasonography is the

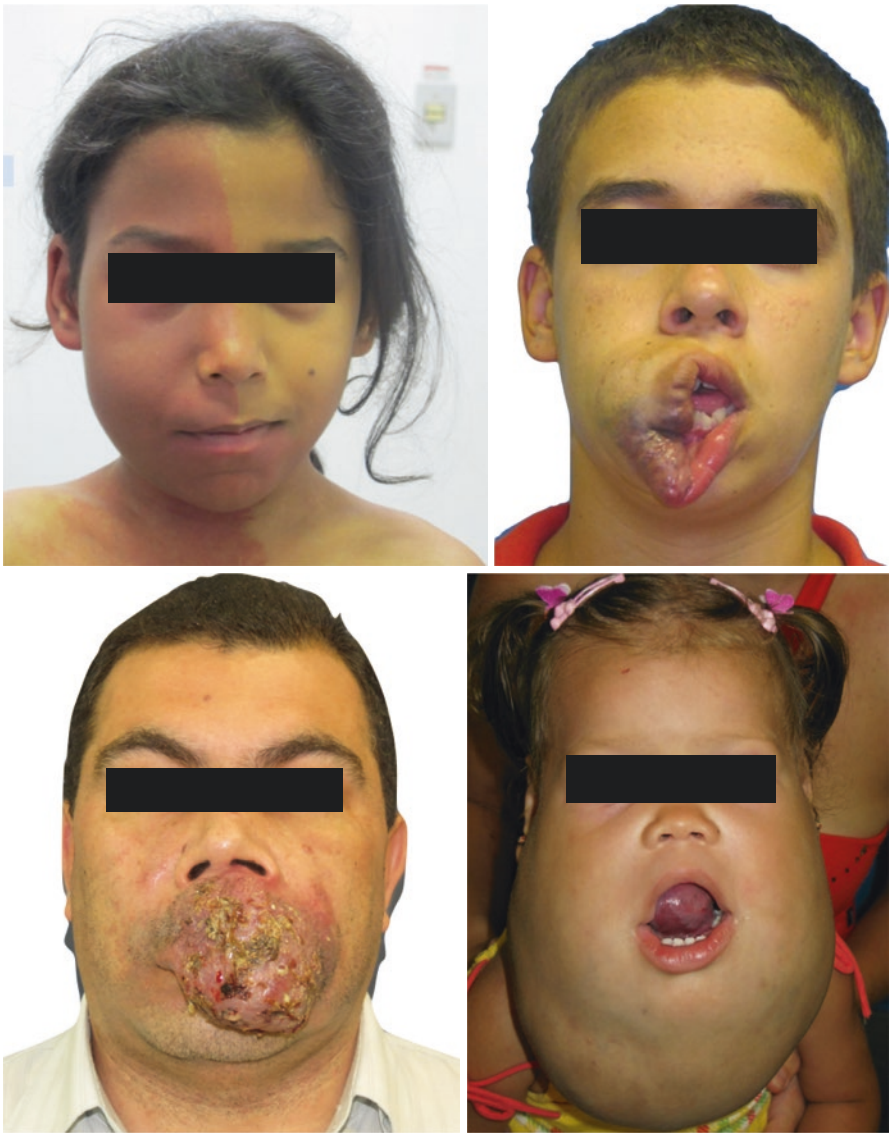

Fig. 1.2 Types of vascular malformations: capillary, venous, arteriovenous, and lymphatic

simplest method and the least invasive. When associated with Doppler, it provides important information regarding the flow of the lesion. However, it is less specific and operator-dependent. Computed tomography and angio-CT are much more specific. Magnetic resonance imaging is the diagnostic test with the greatest sensitivity and specificity. It allows to differentiate tumors and vascular malformations very accurately, as well as vascular malformations subtypes. In MRI studies, venous malformations are usually isointense to muscle tissue in T1, with hypersignal in T2. Phlebolites can be seen as flow voids images in T1 and T2. The use of contrast (gadolinium) allows the differentiation between venous and lymphatic lesions. In the diagnosis of high-flow malformations, angioresonance provides images similar to those obtained by conventional angiographic methods, with the advantage of reduced morbidity.

The more widespread use and the improvement of the techniques of noninvasive methods reduced the indication of arteriography and phlebography, as an initial purely diagnostic method. However, its value has become greater and more relevant as a therapeutic method for performing superselective embolization procedures and sclerotherapy.

1.4.2.1 Low-Flow Malformations

Capillary Malformations (CMs)

Capillary malformation is characterized by presence of ecstatic vascular channels, with diameters of arterioles and venules, between the papillary and upper reticular dermis, with thin walls and composed of mature endothelium. Historically, they were called “Port wine stains.” They are congenital, have an equivalent sexual distribution, and there is no involution over time. They are flat and well-defined patches, presenting growth proportional to the patient’s development. Its color can vary from pale pink to dark red, becoming darker and thicker over the years. They can be localized or extensive and generally follow distribution by dermatomes.

CMs are associated with some syndromes. Sturge-Weber syndrome (GNAQ mutation) is characterized by CM in the face, respecting the dermatomes of the trigeminal nerve in its ophthalmic and maxillary subdivisions, intracranial vascular malformations (choroid plexus), and ipsilateral eye. It may present neurological symptoms, such as seizures, hemiplegia, and delayed neuropsychomotor development, and ocular symptoms such as glaucoma and blindness, resulting from hemorrhages and retinal detachments. In the treatment of CM, surgical excision of the lesion is a possible method, but with the risk of definitive sequelae. Currently, the method of choice for treating this malformation is the laser [43].

The selective absorption of LASER by hemoglobin inside the dermal vessels is responsible for the beneficial whitening effect, while the energy absorbed by melanin is responsible for the undesirable effects of altering the texture and pigmentation of the skin. The pumped pulsed dye-laser flash—FPPDL, with a wavelength of 577-585nanometers, is currently one of the most used LASERs for the treatment of MCs.

Venous Malformations (VMs)

Depending on their dimensions, they may or may not be visible at birth. The clinical picture varies according to the location and extent of the involvement. They can be composed of multiple intercommunicating venous lakes (PIK3CA mutation) or large venous dilations (TEK / TIE2 mutations) [44]. They are generally compressible and have slow refilling and postural volume variation. The Valsalva maneuver tends to increase significantly in size. Often solid nodules are palpable, corresponding to phlebolites.

On the face, they are often seen affecting the lips and periorbital region. There may be communication with the intracranial vasculature and consequent complications resulting from this fact can be observed. When it affects the oral region, the growth of lesions can cause anatomical distortions and changes in dental occlusion. More extensive lesions can lead to consumption coagulopathy due to blood stasis. Recent studies have pointed to a situation of localized intravascular coagulation, with intralesional changes in markers of thrombotic phenomena (D-dimer and fibrinogen). VMs are present in some syndromes, such as Bean syndrome (blue rubber bleb nevus) and Klippel-Trenaunay syndrome (in association with lymphatic malformations and capillary malformations) [45].

The treatment of localized lesions can be surgical resection or intraluminal sclerosis procedures. Interventional radiology procedures with sclerosis are usually performed by phlebography or venography by direct puncture for topographic identification of the lesion and its collateral circulation. The sclerosing agents most used today are absolute alcohol, polidocanol (associated with bleomycin), and sotradecol. These procedures must be performed carefully, and the procedure is performed by a highly specialized professional, since extravascular injections can develop with massive tissue necrosis. Multiple procedures may be necessary.

Surgical procedures can be performed primarily or follow a previous sclerosis procedure. In the presence of pure MV, in which blood flow is slow and the regimen is low pressure, piecemeal resection is a technique that can be performed. Therefore, an accurate diagnosis is essential to allow this type of surgical procedure [46].

Arteriovenous Malformations (AVMs)

Arteriovenous vascular malformations are relatively rare if compared to other vascular anomalies [47]. Every AVM is singular in clinical presentation what makes particularly difficult to establish a strict treatment protocol. It implies some individualization on approach, more evident in outsized lesions [48]. There is a

consensus, however, that treatment precludes a multidisciplinary effort with collaboration of surgeons and interventional radiologists, at least [30, 48–51].

Arteriovenous vascular malformation (AVM) grows gradually, may harm the patient unless treated, and can be even considered life-threatening secondary to hemorrhagic problems. Data regarding lesion location, associated facial compromise, previous histories of bleeding, functional impairment, or esthetic compromise need to be assessed. Patients must be treated over a multidisciplinary approach and the team was composed of plastic surgeons, head and neck surgeons, interventional radiologists, anesthesiologists, pathologists, and psychologists. Routine treatment involves embolization and surgical resection. Surgical approach without embolization is frequently hazardous and endovascular embolization alone usually does not reach lifelong control. Therefore, multidisciplinary approach combining superselective embolization (SSE) and surgical resection is the most accepted method, performed under a planned and detailed strategy. Superselective embolization regularly uses permanent agents, including glue (histoacrylate glue), metallic coils, Onyx® (Ethylene vinyl alcohol + dimethyl sulfoxide + tantalum powder), or ethanol and is applied as distal as possible and inside the nidus, to promote intralesional vascular obliteration [52–54].

During the natural history of complex AVMs, consecutive TE procedures may be necessary, to acutely control hemorrhagic episodes or reduce disease progression, waiting for the best moment for surgery. When resection is planned, performing superselective presurgical embolization (PE) up to 72 hours before is a useful tool to control bleeding during the procedure [30].

PE is usually performed with resorbable particles placed more proximally than superselective embolization (intranidal). The objective of PE is to reduce intraoperative bleeding. Surgery is planned as an elective procedure, whenever possible. As a protocol, surgical resection is always planned to obtain a complete resection. The use of exclusive endovascular approach may be effective in small extracranial lesions. In large AVMs, it can only temporarily control growth and bleeding. Even in well-defined lesions when TE initially appears successful, definitive nidus obliteration may not occur and an increase in vascularity over time may occur. Compromise of non-affected areas and recruitment of contralateral components may also occur, worsening curative perspectives. Moreover, to be efficient in some cases, aggressive embolization procedures are needed and it may cause tissue ischemia and necrosis, demanding surgical approach. Regrowth after surgical resection is always a problem, and even in cases when an apparent radical resection is performed, there is a risk. Usually, regrowth originates from the external limits and probably derives from marginal vascular remnants. It may occur any time after surgical resection. New pharmacologic agents based on the association with genetic mutations are a promising alternative to surgical resection and clinical control in selected cases [55, 56].

Lymphatic Malformations (LMs)

Histologically, they are characterized by cysts of different sizes, lined by endothelial cells and filled with lymphatic fluid [57]. They are clinically classified into microcystic, macrocystic, and mixed. The clinical picture is related to the

dimensions of the lesion and may be noticeable at birth or grow during the first years of life. When there is bleeding inside the lesion, clinical translation is characterized by the violet aspect of the skin in microcystic lesions and a heterogeneous aspect of the content in macrocystic lesions. LM occurs most commonly in the head and neck, representing 60–75% of cases, a fact that may be related to the presence of a rich lymphatic system in these areas, followed by the axilla and mediastinum [58–60].

LMs are most often found at the base of the neck. The most commonly affected site is the lower face (lips, oral mucosa, tongue, ears, etc.) and often causes hypertrophy and deformities such as macroglossia and macrocheilia and may be associated with mandibular hypertrophy [61]. Extensive lesions involving the floor of the mouth, oropharynx, and neck usually compromise the airways. Cervical malformations can compress the pharynx, mediastinum, and trachea, causing breathing difficulties [58]. On the face, they can cause airway obstructions and significant anatomical distortions. Close to skeletal structures, they cause hypertrophy of these structures and can lead to malocclusions and joint disorders. Ultrasonography and MRI are important diagnostic approaches to identify the location, size, and extent of the lesions. Images are always indicated if therapeutic consequences are expected. If the ML does not appear to be superficial and the extent of the lesion needs to be determined. MRI is the method of choice. The signal strength is intermediate in T1-weighted images, hypersignal in T2 without improvement with contrast injection. Sometimes, macrocystic malformations with hemorrhage exhibit hyposignal in T2-weighted image due to hemoglobin degradation [60].

Historically, the first-line treatment for ML was surgical excision. Although this treatment is reasonably effective, extensive resections must respect the regional anatomy and anesthetic-surgical risk. The high rates of recurrence and the risks of complications gave incentive for the development of a less invasive approach. During the past few years, sclerotherapy has emerged as a promising alternative [62]. This therapy has advantages over surgery, as it can overcome complications that may occur from this, such as damage to the surrounding structures, including nerves and vessels, scarring, and recurrence due to incomplete excision [61]. In macrocystic lesions, aspiration of the content and injection of sclerosing agents, such as bleomycin and doxycycline, have shown encouraging results in macrocystic lesions.

1.4.3 Juvenile Nasoangiofibroma

Although nasal tumors in teenagers have been described by Hippocrates in the fifth century B.C, only in 1940, these tumors came to be called as vascular fibroids or angiofibromas. Currently, they are known as juvenile nasoangiofibroma (JNA) and represent 0.05–0.5% of all tumors in the head and neck, with an incidence of 1:150,000 people [63–66]. A Danish study identified the incidence of JNA in 0.4 cases per million inhabitants/year with a median diagnosis at 15 years of age.

However, when only the at-risk population (male adolescents aged 10–24 years) was considered, the incidence increased to 3.7 cases per million inhabitants/year [67].

They are rare tumors before 10 years of age, with the majority predominating at puberty, mainly between 10 and 25 years. The JNA are exclusive or predominantly affect adolescent boys [65–67], since there are rare case reports in women, especially in adults after menopause [68]. Cases of teenage girls or even pregnant women have also been reported [69, 70]. The cases of JNA described in women or adult men, as well as lesions originating in different locations, such as nasal septum or paranasal sinuses, must be carefully evaluated, histologically and genetically, since they may actually be angiomatous polyps, fibrous anthrochoanal polyps, or hemangiomas. These atypical JNA cases generally have a clinical behavior that is distinct from classic cases, even with less bleeding during the operation [71, 72].

The etiology of JNA has been discussed for more than 150 years, and until now, there is no consensus on it, despite changes in understanding over the years. In the nineteenth century, theories suggested a fibrous origin for the tumor, while in the twentieth century the focus was on a vascular origin. Other explanations involve origin in paraganglia present in the terminal portion of the internal maxillary artery, growth of ectopic vascular tissue, or hamartomas [73]. Histological and electron microscopic studies suggest that JNAs are not a true neoplasm; rather, a vascular malformation, of unknown etiology [74]. These vascular malformations are related to the involution of the artery of the first branchial arch, which would be located in the vidian canal and may explain the location of these tumors [73]. However, none of these theories explain all the characteristics or cases of JNA, nor would it explain the predominance in boys in the pubertal phase.

Several genetic studies have identified androgen receptors in JNA and immunohistochemical studies confirm that these tumors are androgen-dependent, which could be the key to explain the predominance in male adolescents. However, the same studies have conflicting results, since most confirm the high expression of androgen receptors in JNA [67, 72, 73, 75], but are discrepant in relation to the search for estrogen and progesterone receptors, probably due to the use of different monoclonal antibodies in the investigation [75]. Investigation of the expression of androgen receptors in JNA, together with research of changes in the Y and X chromosomes, identified a significant loss of the Y chromosome, and at the same time, a gain of the X chromosome. This combination suggests that JNA are really androgen-dependent tumors, favoring the findings of overexpression of ß-catenin, which would act as a coactivator of androgen receptors in these tumors [73].

Other data that suggest the participation of androgenic receptors in these tumors are the therapeutic effects, with tumor reduction, with the use of some antiandrogenic drugs and estrogens in their treatment. Although estrogen receptors are not always found in these tumors, the effect of this medication would be explained by their antiandrogenic action [76].

JNA is histologically an abundantly vascular tumor within a fibrous stroma, without a capsule. According to some observations, they may originate in the nasopharynx, region of the sphenopalatine foramen, and medial pterygoid plaque or

pterygopalatine fossa near the opening of the vidian canal [65, 66]. Analysis of computed tomography scans of 72 patients with JNA proposes that their origin occurs, precisely, in the recess behind the sphenopalatine ganglion that is formed by the sphenoid process of the palatal bone and the medial plate of the pterygoid, next to the opening of the vidian canal. When growing medially towards the nasal cavity, the posterior margin of the sphenopalatine foramen, which is the sphenoidal process of the palatal bone, forms the medial border of this recess. At this point, the tumor is already visible on computed tomography. Therefore, despite some controversy, the JNA seems to really originate in the vicinity of the sphenopalatine foramen and from there it extends medially to the nasal cavity, laterally to the pterygopalatine and infratemporal fossa, superiorly to the lower orbital fissure and later to the sphenoid sinus [77]. The submucosal growth pattern of the tumor promotes local bone destruction in some patients and can even invade the skull, especially the middle fossa [63, 64].

The classic symptoms of JNA are unilateral nasal obstruction, usually associated with recurrent nosebleeds in a population of male adolescents. Advanced tumors, with involvement of the infratemporal fossa or orbit, can cause edema and facial deformity, trismus, proptosis, and diplopia [64]. Rhinoscopy or nasal endoscopy identifies a lesion in the posterior region of the nasal fossa with extension to the nasopharynx.

Due to the vascular nature of these tumors, biopsy is contraindicated due to the risk of massive bleeding and the diagnosis is made through a detailed history and clinical examination, nasal endoscopy, and image examinations such as computed tomography or magnetic resonance imaging [77].

Imaging exams make it possible to identify the lesion, its extent, and the involvement of adjacent structures with precision. Computed tomography shows a heterogeneous lesion, centered on the sphenopalatine foramen and avid for contrast. The growth of the tumor in the pterygopalatine fossa causes its enlargement, which may project or push on the posterior wall of the maxillary sinus previously, a sign known as “antral sign” or Holman-Miller sign (Fig. 1.3a). The tumor can grow laterally inside the pterygopalatine fossa, passing through the pterygomaxillary fissure, reaching the infratemporal fossa, lower orbital fissure, involving V2 and invading the orbital apex (Fig. 1.3b). From there, it can extend into the middle fossa, through the upper orbital fissure. The posterior growth of the tumor, from the pterygopalatine fossa, occurs along the vidian canal (Fig. 1.3c) or by the direct invasion of the base of the pterygoid bone and the larger sphenoid wing, which allows the invasion of the cavernous sinus and middle fossa [77, 78].

Magnetic resonance imaging shows a lesion that varies from hypointense to isointense in T1, from isointense to hyperintense with heterogeneity in T2, and enhancement with the presence of flow voids in T1 with contrast [79] (Fig. 1.3d). It is superior to tomography to assess intracranial extension and postoperative recurrences [78]. The main differential diagnoses are inflammatory polyps, angiomatous polyps, hemangiopericytomas, lymphomas, and rhabdomyosarcoma, among others.

JNA staging is based on imaging tests and there is no consensus on the best classification. In this way, several staging systems have been proposed and the most

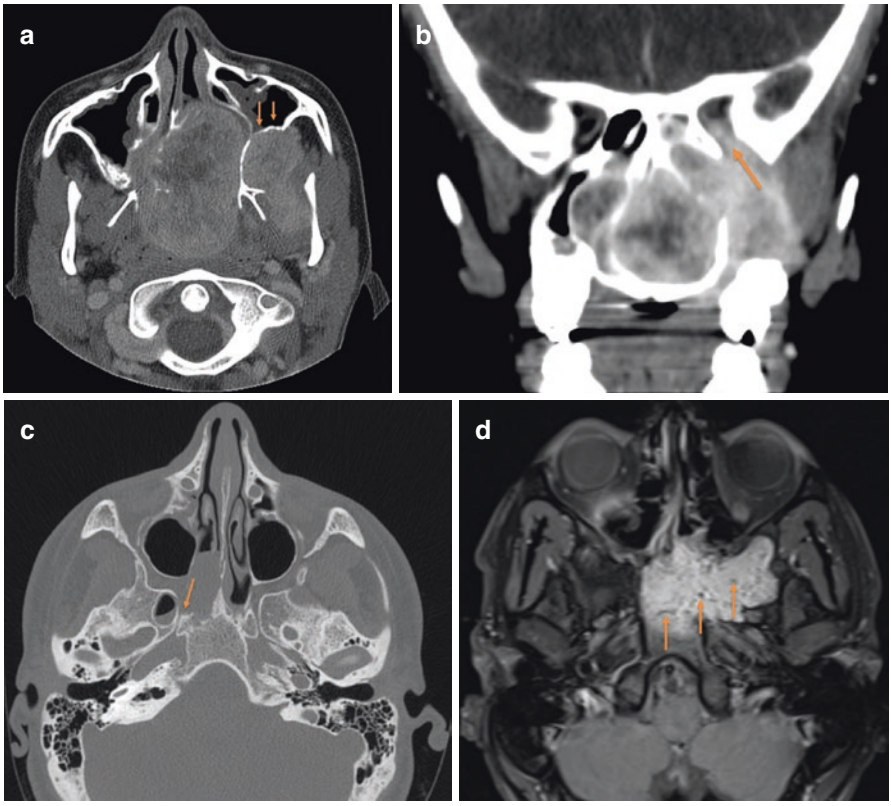

Fig. 1.3 (**a**) JNA (axial) tomography with Holman-Miller sign (arrows). (**b**) Tomography (coronal) with JNA invading the lower orbital fissure (arrow). (**c**) Tomography (axial) showing the vidian canal involved by the lesion. (**d**) T1 resonance with contrast with hypercapture lesion and presence of sign flow-void areas (arrows)

used are those by Chandler et al. [80, 81]. The Pittsburgh group proposed a staging system; in addition to imaging tests, the result of preoperative embolization should be considered. This staging has a strong correlation with the estimate of intraoperative blood loss, partial resections, and tumor recurrences, being a good predictor of surgical difficulties [82]. Arteriography can be used to aid in the diagnosis, but it is more used to study the vessels that supply the tumor and to perform preoperative embolization [82]. The main vascularization of JNA is given by the internal maxillary artery and its terminal branches, although vascularization from the vidian artery, ascending pharyngeal artery, and the contralateral external carotid system can occur, depending on the size of the tumor [64]. Small tumors are usually irrigated only by the internal maxillary artery, mainly through the sphenopalatine, descending palatine, and upper alveolar branches [66, 79]. However, with tumor growth and involvement of the sphenoid sinus, parapharyngeal space, or intracranial extension, other arteries start to contribute to tumor vascularization, such as the

ascending pharyngeal artery, middle, and facial meningeal artery. The participation of the internal carotid artery can be found, mainly with its vidian branch, as well as the contralateral external carotid artery [83], which can occur in up to 40% of cases [84].

Surgical treatment is globally accepted as the best treatment option for JNA and can be performed through exclusive endoscopic surgery, open or combined surgery. The greatest surgical difficulties are related to intraoperative hemorrhage, surgical access, recurrence rate, and biological tumor behavior [65]. Due to the vascular nature of these tumors, massive bleeding in the intraoperative with life-threatening has already been reported [85].

External transpalatal, midfacial degloving, lateral rhinotomy, Le Fort I maxillectomy, transantral, and infratemporal accesses have been widely used in the past, but today they have been gradually replaced by endoscopic accesses, which have become popular and widely used in the last 2 decades, even in tumors with extension to the infratemporal or intracranial fossa [86]. In comparison to endoscopic surgeries, open surgeries present more paresthesia in the V2 and infraorbital region, serous otitis media, trismus, and nasolacrimal duct stenosis, in addition to facial scar [64]. The surgical team's learning curve has a significant impact on the results, with the most recently operated cases evolving with fewer complications and lower rates of recurrences or incomplete resections when compared to the initial cases [78].

Surgical results have improved over the years not only because of the improved surgical techniques, but also because of the advance in diagnosis with the development of imaging tests and a better understanding of the anatomy of the skull base. In relation to endoscopic surgery, the development of specific instruments, cameras, and surgical strategies increased the indication for endoscopic removal of the JNA, since this access has better results in terms of blood loss, length of hospitalization, postoperative sequelae, and rates of similar or even lower recurrences than open accesses [87].

Most authors agree that preoperative embolization substantially reduces intraoperative bleeding and should be performed 24 to 48 hours before surgery [63, 64, 67, 78]. There has already been some controversy regarding preoperative embolization to increase the rate of recurrence of the JNA, which would be due to the difficulty in differentiating between the embolized tumor and the surrounding tissues [88]. However, there seems to be a consensus today that embolization actually facilitates resection and reduces the risk of tumor recurrences, especially after the introduction of endoscopic surgery [65].

Recurrence rates vary widely in the literature, reaching in some series above 50% [88]. Retrospective series publications show that recurrences are related to advanced tumors, greater transoperative bleeding, open surgery, and the surgical team's learning curve. Most recurrences are detected in the first 2 years of postoperative follow-up and surveillance should preferably be done with magnetic resonance imaging [64, 67]. Recurrences can only be followed up with periodic examinations, since small tumor residues can regress spontaneously or remain asymptomatic [77, 88]. When recurrences grow or become symptomatic, they must be treated, surgery being the first option.

The main reason for recurrence is the incomplete resection associated with the biological behavior of the tumor [89]. Several studies call attention to the importance of the base of the pterygoid bone and the vidian canal in the genesis of recurrences [65, 77, 82, 89]. The presence of spongy bone in this region can facilitate recurrences, due to the presence of residual disease inside, even if microscopic. Currently, imaging tests allow assessing, even preoperatively, the involvement of the vidian canal in the JNA (Fig. 1.3c), and even in cases without radiological involvement, the presence of the tumor can be confirmed through histological studies of biopsies performed during surgical procedures. In 20% of cases, there was a tumor in the vidian canal even when the surgical team's judgment was that the lesion had been completely removed [89]. Therefore, draining the vidian canal after tumor resection is recommended for all cases, regardless of its radiological involvement in the preoperative evaluation. This surgical time reduces or completely avoids tumor recurrences, as long as the removal of the vidian canal is done properly [89, 90]. Endoscopic surgery has lower recurrence rates, even in advanced tumors [64] and the ease of draining this region with endoscopic vision can explain these results.

The use of radiotherapy in JNA has limited application, but it can stabilize or even reduce the tumor volume in selected cases. A dose of 30–35 Gy was sufficient to control 80% of cases in a series of 55 irradiated patients [91]. Large tumors with symptomatic tumor residue benefit from radiotherapy, especially Gamma knife, with improvement of symptoms and its use should be considered when there is involvement of vital structures such as the cavernous sinus, optic nerve, or major intracranial invasion where surgery can be performed. High-risk patients with multiple recurrences and tumor growth should also be considered candidates for radiotherapy [64, 77, 78].

Although JNA is not considered a systemic disease, there are several reports of the use of chemotherapy in recurrent, symptomatic tumors and without the possibility of surgical or radiotherapy treatment. Combining vincristine with dactinomycin or doxorubicin with dacarbazine has been used in a few cases in the past, but with success [78]. There are reports of other drugs such as bevacizumab, sirolimus, etoposide, celecoxib, and thalidomide, with variable responses [92].

Hormonal therapies have shown some effectiveness in postpubertal patients with JNA without surgical possibilities or in the preoperative period as a neoadjuvant to reduce tumor volume. Among these options, medications with antiandrogenic actions such as flutamide have already been tested and had promising results, but still have limited use due to side effects [79, 89].

Finally, there are many reports of spontaneous reduction of JNA, including tumors with an intracranial component [77, 83]. Observations show that the fibrous component of the tumor increases with the patient's age, favoring the tumor's involution over the years [77].

The posttreatment surveillance of these lesions should be performed with nasal endoscopy and magnetic resonance for 6/6 months in the first 2 years and then annually, at least until completing 5 years of follow-up [66, 67].

1.4.4 Head and Neck Paragangliomas

Paraganglia are structures made up of nonneural cells derived from the neural crest and which are widely distributed throughout the human body associated with the autonomic nervous system. Sympathetic paraganglia are related to the adrenal medulla and sympathetic nerves in the pelvis, retroperitoneum, vertebral, and prevertebral chains. Tumors of these structures usually produce catecholamines, and when present in the adrenal medulla, they are called pheochromocytomas. Those related to sympathetic chains are called extra-adrenal pheochromocytomas or sympathetic paragangliomas [The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer, 2010]. Parasympathetic paraganglia are distributed mainly in the cephalic and trunk segment, generally along the vagus and glossopharyngeal parasympathetic nerves, in addition to the carotid body at the bifurcation of the common carotid artery. Tumors from parasympathetic paraganglia rarely produce vasoactive substances and are classified as cervical and temporal bone paragangliomas.

Head and neck paragangliomas (HNPGs) have an estimated incidence of 1–30/100,000 per year, accounting for 3% of head and neck tumors. They are embryologically derived from neural crests cells that jointly migrate with the autonomic nervous system [93]. They are named for their original topography, with carotid body paragangliomas (CBPG) being the most common [94]. Other primary sites in the head and neck are the tympanic, jugular, and vagal paragangliomas [95], with other locations as larynx, thyroid, and esophagus being very rare [96, 97].

1.4.4.1 Clinical and Radiological Evaluation of Carotid Body Paragangliomas

Clinical presentation of HNPG is highly variable. Patients may be diagnosed incidentally during head and neck imaging exams for other purposes [98] or may present with clinical symptoms. The most common clinical symptoms for CBPGs are a pulsatile tumor below the mandibular angle, hypoacusis, dysphonia, dysphagia, and cranial nerve palsy. An interesting feature in clinical examination is the so-called Fontaine sign, the mass is mobile in the horizontal plane, but not in the vertical plane. Hormonally active HNPG produce noradrenaline and normetanephrine, unlike pheochromocytomas, and may present with headache, irregular heart beatings, and sweating associated with arterial hypertension. Although highly specific, this presentation is very rare in HNPG [99].

Several imaging methods are available for HNPG evaluation, including computerized tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), angiography, and nuclear medicine techniques.

CBPGs present on CT scan as a solid mass in the infrahyoid neck within the carotid space. The tumor occupies a location between the two branches of the carotid artery causing lateral separation of the internal and external carotid branches,

what is considered the most characteristic radiological sign of this tumor. They typically show intense enhancement after intravenous contrast injection due to its hypervascularity and are homogeneous, except for large tumors where areas of necrose and hemorrhage may be detected [100]. CBPGs have a low to intermediate signal intensity on T1-weighted images and high signal intensity in T2-weighted MRI images. The characteristic finding on MRI is the presence of multiple serpentine and punctate areas of signal void within the tumor matrix. These findings correspond to high-velocity flow of intratumoral vessels. The adjacent areas of high- and low-signal intensity are called "salt and pepper" pattern. The salt component represents high-signal regions because of slow flow or hemorrhage and the pepper component represents the multiple signal voids of tumor vessels on both T1 and T2-weighted images [101].

Although once an essential part of diagnosis of CBPG, angiography is nowadays restricted to preoperative embolization or palliative treatment. The main findings for this exam are marked hypervascularity, multiple enlarged feeding arteries, dense tumor blushing, and rapidly draining veins [102].

The use of Doppler US can help in the diagnosis of CBPG by demonstrating a typical pattern, but it is not commonly used for surgical planning like CT and/or MRI, although it is usually the primary diagnostic intervention [103].

A significant finding must be reported in all patients submitted to preoperative radiological imaging in the Shamblin classification. It was originally established based on surgical notes and demonstrates a clear relationship to the risk of surgical interventions:

- Type I tumors are localized within the carotid space.
- Type II partially surround the carotid arteries.
- Type III tumors completely surround at least one carotid artery [104].

This classification can be accurately predicted in the preoperative setting by MRI imaging using the maximum degree of circumferential contact of the tumor with the internal carotid artery. Type I tumors have a maximum contact circumference of 180 degrees, type II tumors between 180 and 270 degrees, and type III over 270 degrees of contact [105].

Vagal paragangliomas arise usually from the ganglium nodosum, the inferior one of the two vagal ganglia, but may occur anywhere along the nerve course of its branches. Clinically, it is usually present as a neck mass behind the mandibular angle without further symptoms. Nerve dysfunction occurs late in the evolution and may prompt investigation for malignancy. Unlike CBPG, these tumors dislocate the carotid bulb and its branches anteriorly, not causing splaying of the vessels. The aspects on CT and MRI are the same of CBPGs. These tumors may extend superiorly through the jugular foramen into the posterior cranial fossa. Therefore, the imaging method should include these structures [106].

Nuclear imaging methods have no role in preoperative planning of HNPGs, their main usefulness being the detection of multifocal or metastatic disease. Their use is indicated in patients with genetic mutations with a high-risk of malignancy or, if genetic testing is not available, in young patients [107].

The most frequently used nuclear imaging methods are 131I/123I-metaiodobenzylguanidine (MIBG) scintigraphy and 111In-diethylenetriaminepentaacetic acid (DTPA)-pentetreotide scintigraphy. With parasympathetic paragangliomas, 111In-DTPA-pentetreotide has shown superiority over I131-MIBG with sensitivities of 89–100% and 18–50%, respectively [108], and is currently the scintigraphy of choice for patients with HNPGs [European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of pheochromocytoma and paraganglioma]. The use of positron emission tomography has increased in patients with paragangliomas. The most used tracers are 18F-FDG and 18F-FDOPA. Interestingly, the tracer of choice may be influenced by the genetic mutation underlying the tumor. Paraganglioma syndromes type 1, 2, and 3 are ideally scanned with 18F-FDOPA while those with type 4 by 18F-FDG [109]. Other tracers, Ga-68DOTATATE/Ga-68DOTATOC PET, are indicated in the preoperative setting for patients with germline SDHB mutations [110].

Although most patients will present with hormonally inactive HNPGs, missing a hormonally active tumor will be detrimental to the patient. Therefore, biochemical testing should be performed in all patients with HNPGs. They can secrete any combination of catecholamines based on their profile, but it's episodic and a single test may be misleading in up to 30% of patients. Therefore, their metabolites, which are constantly released in circulation, should be tested. Several studies demonstrate that measurement of fractionated metanephrine is superior to dosage of parent catecholamines [111]. The USA Endocrine Society recommends plasma-free metanephrine or urinary fractionated metanephrine as initial screening tests [Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. 126] that may be complemented by dopamine and plasma 3-methoxytyramine (3-MT) to establish the biochemical phenotype of a tumor [112].

There is no role for preoperative biopsy in patients with suspected HNPGs. The imaging exams are considered diagnostic, and invasive procedures carry risks of tumoral hemorrhage with expansive effects in the neck and are formally contraindicated in patients with hormonally active tumors. In the suspect of metastatic disease, functional imaging techniques with 123-I-MIBG or Ga-68DOTATATE/Ga-68DOTATOC PET are also considered diagnostic and histologic diagnosis is unnecessary [113].

1.4.4.2 Management of Carotid Body Paragangliomas

The management options of HNPGs must take into account the availability of resources in the treatment setting, the morbidity and risks of the proposed, and the patient desire. Generally, three options are available as first-line treatments: observation, surgery, and radiotherapy.

Observation may be used in patients with significant comorbidities to avoid high-risk surgeries or if the patient is unwilling to be submitted to a surgical procedure. HNPGs have a tendency for slow growth with doubling times ranging from 0.6 to 21.5 years (median, 4.2 years) in a retrospective series and around 40% of

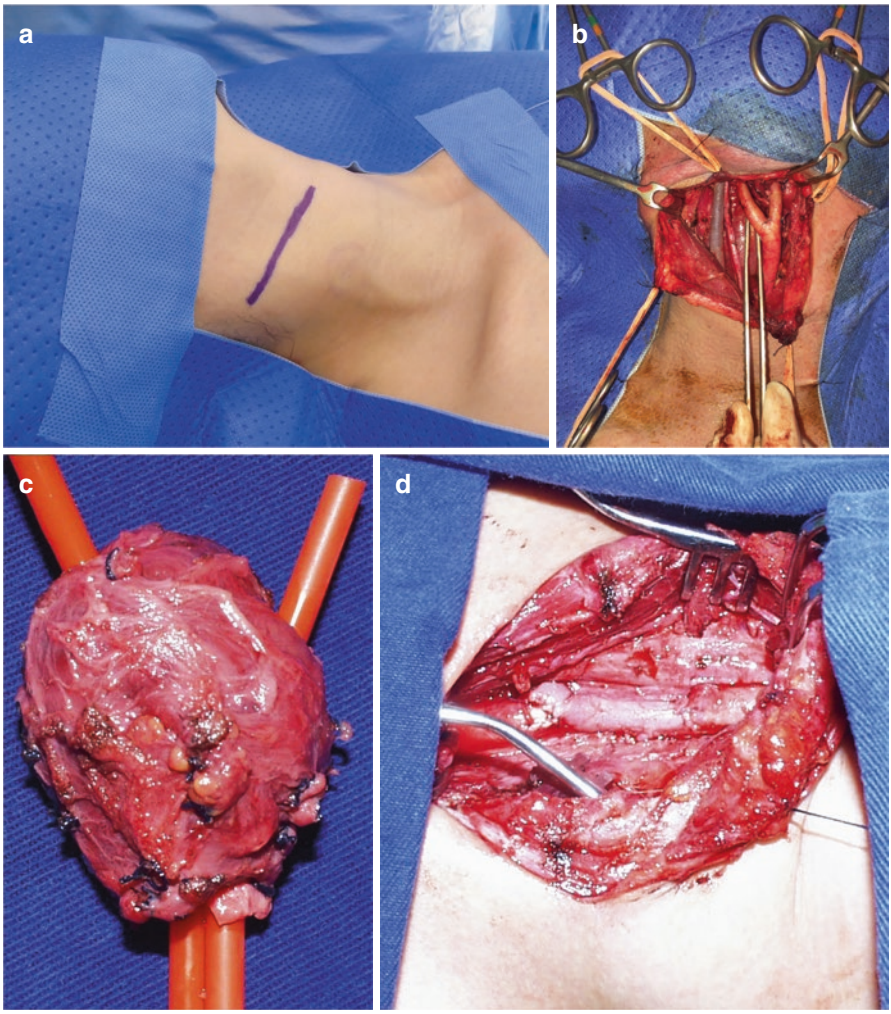

Fig. 1.4 Different aspects of carotid body tumor surgery: (**a**) Incision planning using a cervical skin fold. (**b**) Local aspect after tumor removal with preservation of significant neurovascular structures. (**c**) Shamblin III tumor with encasement of the carotid bulb.; (**d**) Reconstruction of the internal carotid artery with saphenous graft after removal of a carotid body tumor

patients had a growth of less than 20% in sequential exams [114]. Some authors contend that early surgery may help decrease the risk of postsurgical complications and therefore observation should be avoided in patients who fit for surgery [115]. Finally, other authors contend that only tumors with maximum diameter less than 3 cm and classified as Shamblin I and II should be considered for observation.

Surgery is the mainstay of treatment and is based on complete tumor resection with careful dissection. The incision may run along the anterior border of the sternocleidomastoid muscle or horizontally along the cervical skin folds, the latter being our preference based on esthetical considerations (Fig. 1.4a). Afterwards, the

common carotid artery and its branches are dissected and repaired below and above the tumor. Finally, dissection of the tumor itself from the vascular walls is performed on the subadventitial plane. Ideally, neural and vascular structures in the vicinity of the tumor are dissected free and remain undamaged (Fig. 1.4b). Ligation and traction of the external carotid artery may improve exposure of the internal carotid artery and facilitate dissection, but these procedures are not mandatory and may be avoided with a little patience. Vascular repair or reconstruction may be necessary, especially in patients with Shamblin III tumors (Fig. 1.4c). This may be accomplished by the interposition of vein or synthetic grafts. The use of saphenous grafts may be done without the use of temporary shunts if good collateral circulation was demonstrated on preoperative angiography and with shunts if otherwise (Fig. 1.4d).

Considering that the neck lymph nodes are the most common site of metastasis, several authors recommend an elective neck dissection when operating carotid body or vagal paragangliomas. Most of the reports are on small surgical series and the literature lacks evidence to support this therapeutic course over therapeutic neck dissection when metastasis occurs. Just for illustration, the embryologic origin of CBPG is the third branchial arch that correlates with neck lymphatic levels II and III. Most surgeons remove suspicious lymph nodes or when necessary to expose the tumor and carotid vessels. A systematic neck dissection in not usually performed [116].

In patients with biochemically active HNPGs, antihypertensive medications should be used prior to embolization and surgery. The first therapeutic choice should be an a-blocker, followed by an b-blocker that may be used for control of arrythmias, tachycardia, or angina. Calcium channel blockers may be added afterwards if blood pressure control was inadequate or the side effects of a-blockers were intolerable. The main objective of preoperative treatment is preventing a hypertensive crisis during surgery and providing volume expansion to reverse volume contraction induced by catecholamines, avoiding hypotension after tumor resection. Patients with hormonally silent tumors do not need preoperative block [117].

As any surgery, removal of HNPGs has risks of complications. In a series of 183 CBPG treated by surgery, postoperative complications occurred in 36 patients (19.7%). The most common was cranial nerve deficit in 16 patients (8.7%) with long-term sequelae in 10 patients (5.5%), followed by injury to other head and neck nerves in 12 patients (6.5%), hematoma in 3 patients (1.6%), and stroke in two patients (2.0%) and no postoperative mortality [20]. A Japanese multi-institutional survey demonstrated postoperative complications in 55 out of 94 patients with one case of stroke. The most common complication was paralysis of the X cranial nerve [118]. Another multi-institutional series from England showed a complication rate of 33% with 1% mortality. The main complication was cranial nerve paralysis, occurring in 19% of all patients [103].

An important discussion regarding surgery is the need for preoperative embolization (PE). Evidence from the literature is contradictory on its effects on the

outcome of surgery. PE carries a risk of stroke by itself of less than 1–2% in different series [119] and its main intended effects are blood loss and operative time reduction. Several reports have not shown any of these beneficial effects [120, 121], while others have shown a significant decrease in operative blood loss [122, 123], but these reports are restricted to patients with tumors over 3 centimeters in diameter [124]. In a cohort of 133 patients, PE decreased blood loss, but had no impact on operative time or postoperative complications [125]. A Japanese series demonstrated a nonsignificant increase in operative bleeding in patients with Shamblin I and II submitted to PE and the opposite effect in Shamblin III patients [118]. In other series, no significant difference in blood loss or operative time was observed based on realization of PE [126]. A systematic review and meta-analysis including 25 published papers on the topic demonstrated that PE caused a significant reduction in operative blood loss and time, but the risk in this analysis bias was considered high. Postoperative outcomes, like cranial nerve paralysis, stroke, and length of hospital stay, were unaffected by PE [127].

Another option for local control of HNPGs is radiotherapy (RT). The objective of RT is to prevent tumor growth and stability defines "cure." Both external beam and stereotaxic RT are used for HNPG, with the gross tumor volume defined by pretreatment imaging studies. In a series of 131 patients with 156 tumors, local recurrence defined by tumor growth after treatment occurred in 3.2% [128]. The main risks of RT for HNPGs are mucositis, skin toxicity in the radiation field, middle-ear effusions, long-term hearing loss, hypopituitarism, xerostomia, and carotid stenosis.

Nuclear medicine methods may be used not only for diagnosis, but also for treatment. A series of 30 patients with metastatic paragangliomas and pheochromocytomas showed partial response in seven patients with stable disease in 20 patients and median progression-free survival of 91 months in parasympathetic paragangliomas [129]. A phase I trial enrolling 20 patients evaluated the efficacy of I131-MIBG in patients with metastatic disease and showed complete response in 10% of cases, stable disease in 65% of cases, and progressive disease in 15% of cases. There were no dose-limiting toxicities, indicating good tolerability and safety of the technique [130].

Another option is peptide receptor radionucleotide therapy that uses an analog of somatostatin linked to a radioisotope, usually 177-Luthecium, with symptom improvement and lack of tumor progression in up to 50–70% of patients [131].

The management of bilateral tumors is usually done in stages. For bilateral CBPGs, one side is operated first and the second after verification of vagal function in the postoperative setting. Bilateral synchronous removal may cause paralysis of both vocal cords and baroflex reflex with severe, constant hypotension in the first 72 hours followed by sporadic hypertension and headaches. Bilateral vagal paragangliomas require nonoperative approach to one side due to the anticipated sequela of bilateral paralysis of the larynx [132].

1.4.4.3 Malignant Carotid Body Paragangliomas

Malignant head and neck paragangliomas represent a challenge in multiple ways to the attending physician. The most frequent location of metastases are the cervical lymph nodes, lung, axial skeleton, and liver [213], but there is no consensus on the need to evaluate systemic metastasis in patients with head and neck paragangliomas or the methods that should be employed for this.

Malignant paragangliomas are defined by the presence of metastases and not by their radiological or pathological aspect. Therefore, no paraganglioma can be unquestionably defined as benign [133]. The use of pathological criteria to differentiate benign from malignant disease has met little success. The Armed Forces Institute of Pathology considers as malignant those with "extensive local invasion or documentation of metastases" in disagreement with a previous statement by the World health Organization that only the presence of metastases to non-paraganglia organs constitutes evidence of malignancy [134]. Scores based on pathological features like architectural patterns, cellular or nuclear atypia, presence of necrosis, vascular or neural invasion, and Ki-67 staining were developed, but proved unreliable for patients with head and neck paragangliomas, as they were originally based in pheochromocytoma specimens [135].

From a clinical standpoint, several variables affect the risk of malignancy and should be assessed in the preoperative setting. The risk of malignancy is related to the primary site. In a literature review, the malignant rate was, in decreasing order, higher for sinonasal paragangliomas (24%), vagal (10%), jugulo-tympanic (5.1%), carotid body (1.4%), and laryngeal primary sites (1.4%) [136]. Also, pain and age at onset less than 45 years were significantly associated with malignancy in a clinical series of 84 tumors [137]. As discussed in the section on hereditary syndromes, several mutations are associated with an increased risk of malignancy and should be assessed as part of preoperative evaluation, especially in younger patients.

The use of postoperative radiotherapy in patients with malignant HNPGs is based on retrospective series that lack strong statistical power. In an analysis of 26 patients with PG and 15 with pheochromocytoma, postoperative or palliative RT improved symptoms in 95% of patients and provided a median survival after treatment of 11.4 years [214]. In the National Cancer Database series, the use of adjuvant RT provides patients with a longer median survival (45 months) than those treated by surgery alone (12 months). The 5-year survival rate for the whole series was 59.5%, with a significantly better prognosis for those with neck metastasis (5-year survival rate of 76.8%) versus distant metastasis (5-year survival rate of 11.8%) [138].

Although described for metastatic pheochromocytoma ablation, radiofrequency ablation may provide relief of symptoms, including those related to metabolic active products. Special care should be taken in these patients to adequately control hypertension [138].

Finally, we must consider all patients with paragangliomas for long-term follow-up since the median interval from treatment of the primary tumor to metastasis development is 8 years [139], but a 32-year disease-free interval has been reported

[140]. There is no consensus in the literature, however, on how this follow-up should be done. For patients with hormonally active tumors, annual dosage of metanephrines and chromogranin A is indicated. And it should be considered in patients with SDHx mutations. Chromogranin A should be routinely used in nonfunctioning HNPGs. Imaging cross-sectional exams of the head and neck area are indicated in an annual basis [141].

1.4.4.4 Temporal Bone Paragangliomas

In the temporal bone, the most common paraganglioma location is next to the jugular foramen, close to the adventitia of the internal jugular vein, followed by the middle ear, next to the Arnold or Jacobson nerves on the promontory [142]. Although benign tumors are considered histologically, they can be locally invasive, with involvement of nerves and / or vascular structures, causing in these cases multiple dysfunctions, such as impact on speech, swallowing, hearing, and facial motricity. Paragangliomas can rarely be characterized as malignant tumors, which is not defined by histopathological findings, but by the occurrence of metastases to non-neuroendocrine tissues, mainly lymph nodes, lung, skull, jaw, column, or skin [142].

In the temporal bone, jugular paraganglioma is more common than tympanic, but the latter is the most common neoplasm of the middle ear [143]. In some cases, it is not possible to define its exact origin, being called jugulo-tympanic. The most used classification for these tumors is the one proposed by Moe et al. [144], for having a correlation with the surgical indication. They are divided into the following classes:

A. Tympanic
B. Tympanic with extension to mastoid or hypotympanum
C. Lesions of the jugular foramen (subdivided into C1 to C4, depending on the relationship with the petrous internal carotid artery)
D. Tumors with intracranial component (can be subdivided into De—extradural or Di—intradural)

The clinical presentation of paragangliomas is closely linked to their size and location. In general, it presents with pulsatile tinnitus and dysacusis. When the bulbar nerves are affected, there may be dysphagia, dysphonia, altered motility and atrophy of the tongue, and cervical atrophy. Progressive facial paralysis occurs when the facial nerve is involved. On physical examination, in addition to peer research that tends to prove fruitful, otoscopy may show a reddish tumor, often pulsatile, retrotympanic or occupying the external auditory canal [142].

The diagnosis of paragangliomas is made through a suggestive clinical history associated with the findings on imaging studies. The preoperative biopsy procedure is contraindicated, its occurrence being incidental in some cases when the tumor is externalized by the external auditory canal and is confused with other tumors [142].

Both magnetic resonance imaging and computed tomography can be used in the diagnosis of paragangliomas, and in most cases, they are complementary exams. Computed tomography allows an excellent bone evaluation of the middle-ear and

jugular foramen [142, 145]. The tumor presents itself on tomography as a homogeneous, well-defined lesion with intense contrast gain. In the jugular foramen, it may present the classic sign of erosion of the jugular spine, and it also presents bone erosion characteristic of the bone permeation type that can be seen as a rarefaction of the bony contours of the jugular foramen [143] (Fig. 1.5a).

Magnetic resonance imaging has as main area of interest the assessment of soft tissues adjacent to the tumor and neurovascular structures of the skull base [143]. T2 images are hyperintense and, in larger lesions, there is the classic "salt and

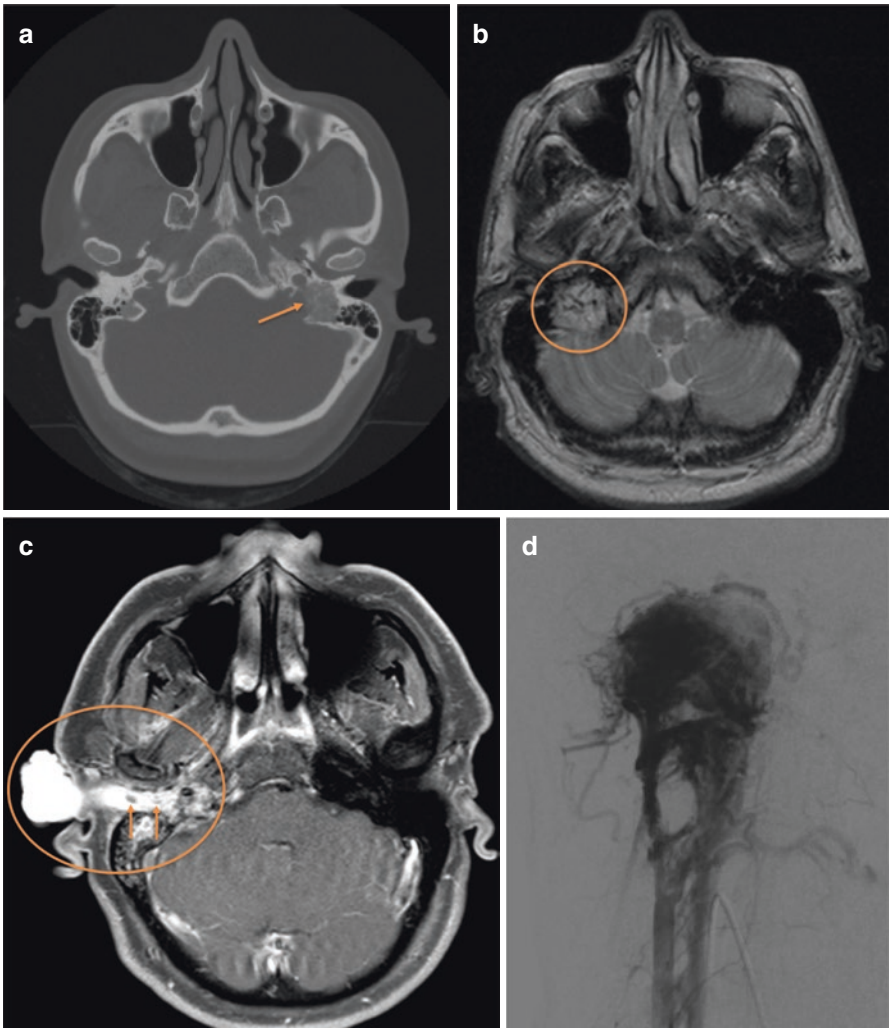

Fig. 1.5 (**a**) Tomography with erosion of the jugular spine and presence of bone permeation in the left jugular foramen. (**b**) T2 resonance with hyperintense lesion and salt and pepper appearance. (**c**) T1-weighted contrast resonance showing a lesion in the jugular foramen that extends to the external auditory canal and presents sign flow-void areas. (**d**) Digital angiography of the paraganglioma vascularization

pepper" aspect, with hypo- and hyperintense areas permeated, representing regions of low and high vascular flow (Fig. 1.5b). In T1 images, the lesion is hypointense and with great enhancement after the use of gadolinium, with areas of "signal flow-void," and the use of paramagnetic contrast is very useful to define the limits between the tumor and the surrounding tissues (Fig. 1.5c). However, this sign is not pathognomonic of the paraganglioma because it can be present in other hypervascularized tumors, such as metastases of thyroid and kidney carcinoma. The performance of angioresonance allows a good evaluation of arterial (carotid) and venous structures (internal jugular and sigmoid and sinus sinuses transverse). It is considered more sensitive and specific than tomography in the assessment of neurovascular structures and also for differentiating between tumor, inflammatory tissue, and fluid accumulation [143].

Digital angiography (Fig. 1.5d) is more sensitive than angioresonance for the diagnosis of tumors smaller than 10 mm and, in addition, it is considered essential to perform preoperative embolization, a procedure that aims to facilitate surgery with a significant reduction in transoperative bleeding [142, 143].

The differential diagnosis should be established with schwannomas, meningiomas, chondrosarcomas, chondromas, carcinomas, chordomas, aneurysmatic bone cysts, cholesteatomas, lymphangiomas, inflammatory granulomas, metastases, rhabdomyosarcoma, histiocytosis, vascular malformations, carcinoid tumor, and melanoma.

In the treatment of paragangliomas, the patient's age, growth rate, associated diseases, and neurovascular structures involved must be considered. The primary objective of treatment varies from case to case, ranging from complete resection with the aim of curing the patient or controlling tumor growth with radiotherapy, or even partial resection followed or not by radiotherapy to reduce complications associated with surgical treatment [146]. Observation and follow-up with imaging tests can also be used in selected cases.

Surgical treatment is still considered as the first therapeutic option for the treatment of paragangliomas, with a chance of curing the patient, as long as the tumor resection is complete. The surgical approach for tympanic or tympanomastoid paragangliomas is relatively simple and can be performed through an endoaural access, usually associated with a canaloplasty and sometimes a mastoidectomy. Complete and curative resection is usually achieved with low risk of bleeding, hearing loss (conductive and / or sensorineural), and facial paralysis, by manipulating the tumor adhered to the promontory. Transoperative bleeding is usually limited and easily controlled through local hemostatic measures, with preoperative embolization being considered unnecessary [147].

Surgery for jugular paragangliomas is more challenging, with real potential for massive bleeding due to its extensive tumor vascularization. For this reason, preoperative embolization is practically mandatory in these cases and must be performed between 2 and 5 days before surgery.

Even for experienced teams and the systematic use of preoperative embolization, surgery for jugular paragangliomas still has a high morbidity rate associated with lesions of neurovascular structures at the base of the skull, which can aggregate

severe neural lesions, mainly of the facial and bulbar nerve nerves. Partial injuries to at least one bulbar nerve in the preoperative period significantly increase the chance of injuries to other bulbar nerves during surgery [148]. Likewise, the presence of an intracranial tumor has a significant increase in the risk of injury to the bulbar nerves during the surgical procedure [149]. Postoperative CSF fistula is a feared complication, mainly due to the risk of meningitis and its sequelae. Therefore, it must be identified early and adequately treated; in some cases, it can be with external lumbar drainage, reinforcement in the suture with surgical glue and compressive dressings, or in other situations, mainly in fistula with high output, the surgical reapproach is necessary. Dehiscence and infection of the surgical wound occur to a lesser extent and should be managed with dressings and the use of antibiotics.

The preferred surgical technique is Fisch's type A infratemporal [150]. This access allows a wide exposure of the mastoid and upper cervical region, allowing the dissection of the dura mater pre and post sigmoid, the lateral and sigmoid sinus, the jugular foramen, and the ascending petrous segment of the internal carotid artery, in addition to the neurovascular bundles in the cervical region. In particular situations, it is possible to expand the approach, as in cases where there is intracranial invasion, which occurs more frequently in the posterior fossa, with the opening of the dura mater through the existing surgical incision itself.

The choice for surgical treatment gains support in cases of aggressive and rapidly growing tumors, a risk situation for cranial nerve involvement and/or cerebral invasion, especially in young patients (less than 50 years of age). Partial resections scheduled to decrease tumor volume and subject the patient to postoperative adjuvant radiotherapy are currently accepted for the chance of controlling tumor growth and reducing the risk of complications, mainly related to bulbar nerves. Elderly patients or those without adequate clinical conditions and who are symptomatic in relation to the tumor may also be candidates for partial resections and adjuvant radiotherapy. However, the indications for radiotherapy in paragangliomas is still controversial, remaining an open question to be answered in the future by comparative analysis of long-term results [151, 152].

Radiotherapy aims to control tumor growth and not to cure it and can be performed with conventional fractional external radiotherapy or stereotactic radiosurgery, especially the gamma knife. Still in a debatable way, it is believed that the main role of radiotherapy in limiting tumor growth would not be the direct action of radiation on tumor cells, which in fact are not very sensitive. The mechanism of the therapy apparently focuses on fibrosis caused by blood vessels, with limited flow of nutrients to the tumor. The greatest advantage of radiotherapy is related to the low morbidity rate after the procedure, due to a better definition of the irradiated area, with less exposure of neighboring tissues to ionizing radiation [151, 152]. Even today, tumors with indication for exclusive radiotherapy are those that are inoperable or in elderly patients and without clinical conditions for surgical treatment.

Elderly patients or those without clinical conditions and with asymptomatic lesions can only be followed up with periodic imaging exams. If tumor growth is identified, or the patient becomes symptomatic, then another treatment is proposed,

which in these cases is usually radiation therapy. Imaging, tomography, or resonance exams must be performed annually or every 2 years [142].

1.4.4.5 Hereditary Paragangliomas

Hereditary paragangliomas should be suspected in patients with early age at presentation, multiple primary tumors, and familial history. It is estimated that around 35% of all HNPG are associated with germline mutations in one of several genes associated with the disease [142].

The increase in knowledge about the genetic pathways of paragangliomas and pheochromocytomas led to the definition of several subtypes with their division by unsupervised analysis in two clusters: cluster 1 (further subdivided in 1A and 1B) and cluster 2 [153–155]. Cluster 1 genes represent the pseudo-hypoxic pathway of tumoral development and include PHD2, VHL, SDH variants, IDh, HIF2A, MDH2, and FH. Tumors within this cluster show increased angiogenesis and expression of VEGF and its receptors. Cluster 1 is divided in cluster 1A containing tumors related to SHDx, while cluster 1B includes tumors related to HIF2A and VHL. Cluster 2 tumors are related to mutations in associated with abnormal activation of the kinase signaling pathway. They are divided in 2A, 2B, 2C, and 2D. Cluster 2A comprehends tumors with mutations in RET, MAX, NF1, and TMEM127, while clusters 2B and 2C are sporadic tumors and cluster 2D are those tumors without any known PGL-related mutation [156].

According to gene profile cluster and mutations involved, several syndromes related to hereditary paragangliomas have been described:

- Paraganglioma syndrome type 1 (SDHD—cluster 1): this syndrome exhibits an interesting "parent-of-origin dependent effect", with maternal gene transmission only rarely associated with tumor development [Founder effect at PGL1 in hereditary head and neck paraganglioma families from the Netherlands. American Journal of Human Genetics 1998 179]. The most prominent feature is the high risk of multiple primary tumors, either simultaneously or metachronously, in up to 79% of affected individuals and an incidence of HNPG between 91% and 98% [157].
- Paraganglioma syndrome type 2 (SDHAF2—cluster 1): the incidence of HNPG approaches 100% in these patients, but no other primary sites or malignant tumors were reported [136].
- Paraganglioma syndrome type 3 (SDHC—cluster 1): these patients usually present with a single tumor, with an incidence of multiple primaries ranging from 19% to 31%, but the risk of developing HNPG in carriers of SDHC mutations is almost 100% [158]. The presence of positive family history is very low compared to other syndromes, ranging from 12% to 25% [159].
- Paraganglioma syndrome type 4 (SDHB—cluster 1): the risk of developing HNPG ranges from 27% to 31% with a multifocality risk of 8% [142]. Mutations in SDHB were associated with malignant tumors in 20.6–41% of cases [160]

and, in these patients, were significantly associated with worse disease-specific survival than other mutations [161].
– Paraganglioma syndrome type 5 (SDHA—cluster 1): this mutation accounts for less than 3% of paragangliomas with uncommon familial history [162].

FH and MDH2: FH mutations are present in about 1% of patients with paragangliomas, but the incidence of malignant transformation in patients with germline FH mutation is around 40%. MDH2 mutation has not been identified in patients with HNPG [154].

– von Hippel-Lindau syndrome: the incidence of HNPG is 0.5% [163].
– Neurofibromatosis type 1: usually associated with non-head and neck paragangliomas, but hormonally active tumors [164].

The characteristics of the familial paraganglioma syndromes are resumed in Table 1.11.

Functioning extra-adrenal paragangliomas are also part of the Carney triad together with gastric sarcomas and pulmonary chondroma [165].

Unsurprisingly, HNPG genotype correlates with biochemical phenotype. The noradrenergic phenotype includes HNPG that predominantly produce noradrenalin and are characterized by elevated norepinephrine and normetanephrine levels. They include patients with cluster 1 mutations. It is suggested that all patients with noradrenergic phenotype should be screened for mutations in cluster 1 genes [166]. The adrenergic phenotype has cluster 2 mutations that are usually well-differentiated and localized in the adrenal medulla, but may be found in extra-adrenal sites in patients with TMEM127 mutations [167]. The dopaminergic phenotype is common in patients with head and neck paragangliomas and secretes dopamine with or without an increase in norepinephrine (normetanephrine). The dosage of 3-MT is an important diagnostic measure and the most common mutations related to this phenotype are SDHB and SDHD [168].

Table 1.11 Summary of clinical characteristics of patients with familial paraganglioma syndromes

	Mutation	Frequency	Age at diagnosis (years)	Head and neck site	Penetrance	Renal cell carcinoma	Other neoplasms
PGL1	SDHD	35%	35	85%	75% (40 years)	8%	GIST/ Hypophysis
PGL2	SDHAF2	1%	30	100%	75–100% (45 years)	–	–
PGL3	SDHC	10%	38	Close to 100%	Unknown	Rare	GIST
PGL4	SDHB	52%	30	20–25%	40% (40 years)	14%	GIST/ Hypophysis
PGL5	SDHA	2%	Variable	30–60%	14%	–	GIST/ Hypophysis

Asymptomatic carriers of SDHB, SDHC, and SDHD mutations should have cross-sectional exams of the head and neck, thorax, abdomen, and pelvis on a regular basis, probably every 3 years, although shorter intervals are proposed for SDHB and SDHD. SDHC and SDHAF2 mutation carriers may have only head and neck cross-sectional exams [169].

1.5 Other Conditions

1.5.1 Epistaxis

Epistaxis or nosebleeds are common clinical entities, but in most cases, they are self-limiting and do not require specialized medical care. Data from the National Center for Health Statistics report that 1 in 200 emergency room visits is due to epistaxis and that 60% of the population have at least 1 episode of epistaxis in their lifetime; however, only 6% of epistaxis cases require hospitalization [170].

Some studies suggest that there is a correlation between the circadian cycle and epistaxis, with a large concentration of cases in the early morning and another, smaller peak, in the early evening. Other hemorrhagic events have the same biphasic pattern as subarachnoid hemorrhage and rupture of aortic aneurysms, which are related to the physiological circadian rhythm of blood pressure [171].

Epistaxis has a bimodal incidence with a peak between 5 and 15 years and then another between 65 and 85 years [172]. During childhood and adolescence, the distribution is equal between the sexes; however, after 20 years of age, there is a predominance of cases in men, with twice the incidence in relation to women. After the age of 50, there is still a predominance of cases among men, but this difference is much smaller, perhaps due to the presence of some hormonal protection of the woman before the climacteric begins [172]. Although bimodal, most cases of epistaxis in young people are mild and few require hospitalization or more specialized treatment, differing from cases that occur in older patients [170].

Epistaxis can be classified as anterior or posterior, 90% of the cases being anterior and only 10% posterior. Anterior epistaxis occurs in the anterior part of the nasal cavity and is usually associated with a retrocolumellar vein or the Kiesselbach plexus in Little's area, which is in the lower and anterior third of the nasal septum. This region is responsible for almost all previous cases of epistaxis and is related to minor nasal trauma, sneezing, blowing or scratching the nose, or dryness of the nasal mucosa, especially during the winter [170, 173].

Most young patients have previous epistaxis, and sometimes recurrent symptoms, with several episodes per year that can be triggered by physical exertion, heat, or inflammatory conditions such as sinusitis or allergic rhinitis [173, 174]. Deviated septum in this region favors the exposure of the septum to trauma or swirling airflow and sometimes needs to be corrected to control recurrent epistaxis [175].

Anterior epistaxis is easily controlled with bidigital external pressure on the nose, use of topical vasoconstrictors, anterior nasal plug, and chemical cauterization with silver nitrate or with trichloroacetic acid or with electrical cauterization, usually with bipolar [175].

Posterior epistaxis usually occurs in adult or elderly patients and the bleeding is much more massive than the bleeding previously located. Aging promotes degeneration of the middle layer of medium-sized arteries, making them more fragile, in addition to a higher incidence of comorbidities such as arterial hypertension, arteriosclerosis, and coagulopathies that facilitate the onset of epistaxis [172]. Subsequent epistaxis is more difficult to control and treat, and it is often challenging to find the bleeding point, which commonly has an arterial origin and represents a risk for blood aspiration and swallowing. The posterior bleeding is related to the territory of the sphenopalatine artery and its branches, which are distributed to the posterior septal region and mainly to the lateral nasal wall, next to the inferior, middle turbinates, and the region close to the sphenopalatine foramen [176].

Epistaxis can also be divided in terms of etiology into primary and secondary. The primary ones are idiopathic, appear spontaneously, and represent about 85% of all cases of epistaxis. Although it is idiopathic, there is a relationship between these conditions and environmental factors such as dry weather, winter, and the use of heaters leading to dehydration of the nasal mucosa, predisposing to dryness, and epistaxis. Secondary cases have a defined etiology and may have a traumatic, iatrogenic, metabolic origin, vascular abnormalities, acquired or genetic coagulopathies, use of anticoagulants, and inflammatory or neoplasm diseases [176]. Another additional risk factor for epistaxis is congestive heart failure due to venous hypertension, especially in recurrent cases of previous epistaxis [177].

The management of patients with epistaxis varies widely between different services and depends more on personal experience than on widely accepted protocols. In general terms, the effectiveness of the treatment depends on the correct identification of the bleeding point. However, in the initial care of a patient with epistaxis, it is important to identify severe cases, initially following the ABC of emergency care: free airways, breathing, and circulation [178].

During the initial assessment of epistaxis with a large volume of bleeding, it is necessary to have a venous access, check and correct coagulation changes, and request blood reserves. After this initial stage, local anesthesia of the nasal cavity is associated with the use of topical vasoconstrictors in an attempt to identify the bleeding point. If the bleeding is anterior, it can usually be treated with cauterization or anterior nasal packing. In subsequent bleeding, the use of nasal endoscopes associated with a vacuum cleaner for aspiration of blood and clots can help in identifying the bleeding site. If it is in the posterior nasal septum, you can try to cauterize with a bipolar. If it is not possible to identify or cauterize the vessel, a nasal packing is usually chosen, which can be permanent or only temporary until the patient is taken to the operating room. When nasal packing is the definitive treatment, the packing should remain between 2 and 3 days [178].

Nasal tamponade has always been used as the first option for the treatment of posterior epistaxis and for cases not subject to cauterization, leaving surgical

treatment only for situations where there is a failure of nasal tamponade [178–180]. However, it is observed that currently there is greater flexibility in the surgical indication, mainly after the disclosure of endoscopic surgical techniques [181]. Many services have reduced the indication for nasal packing due to failure in up to 50% of cases, great discomfort for the patient due to pain and difficulty in swallowing, risk of local and systemic infections, nasal complications such as septum perforation, synechia, ethmoid and skull base, nasal wing necrosis, and need for hospitalization and use of antibiotics.

Surgery to treat epistaxis has been used for nearly 100 years, the first report from 1925 described the ligation of the external carotid artery. After that, there were some reports of ligation of the internal maxillary artery through a transantral access, but this technique was standardized and popularized only in 1965 by Chandler et al. [182] In the late 1970s, Prades publicized the use of the microscope in nasal surgeries, including for ligation of the sphenopalatine artery. However, the use of the surgical microscope, via transnasal, with the objective of dissecting and cauterizing the branches of the sphenopalatine artery within the nasal cavity in the treatment of epistaxis was reported shortly afterwards by Neto and Stamm [183].

Endoscopic surgery to treat epistaxis was described in 1992 [184], and since then, it has been used with great efficiency in the treatment of them [175, 179, 185]. In fact, the use of the microscope in nasal surgeries has been practically abandoned and today, when referring to surgery, it is implied that it is endoscopic surgery. When comparisons are made between different treatment methods, surgeries are clearly superior to nasal packing. Surgery is between 90% and 100% effective and tamponades reach a maximum of 80% bleeding control [175, 179, 185]. A review of epistaxis treated with endoscopic surgery shows a quick procedure, with an average duration of less than 1 hour, and confirms the high success rates, with values above 90% of cases. Most services use bipolar cauterization of the sphenopalatine branches, but some use clips to control bleeding. Few publications report complications related to the procedure, the majority being minor complications such as the presence of nasal crusts, palate paresthesia, septal perforation asymptomatic, alteration of tearing, and postoperative sinusitis [175, 181].

Among the reasons for failure of surgical treatment after ligation of the sphenopalatine artery are bleeding from the anterior ethmoidal artery. Most surgical revisions for bleeding recurrence address the anterior ethmoidal artery, with external or intranasal ligation, usually with control of the epistaxis [179, 181, 184]. The role of the anterior ethmoidal artery in bulky, posterior epistaxis has been studied more recently and is probably far greater than previously imagined. The use of the endoscope in the care room facilitated the identification of the bleeding point in these patients, and surprisingly, many cases are due to branches of the anterior ethmoidal artery located in the nasal septum [185, 186]. The most frequent site of bleeding related to the anterior ethmoidal artery is in the upper nasal septum next to the projection of the middle turbinate axilla, called the S-point, which easily mimics bleeding from the lateral nasal wall, as blood flows through the lateral nasal wall [186]. Despite descriptions of initial success above 90% in exclusive sphenopalatine artery surgeries, when these patients are followed for a long term, the number of relapses

increases and many of these patients need new clinical or surgical treatments [187]. Possibly, these relapses can be explained by the incorrect identification of the bleeding point, including those related to the anterior ethmoidal artery.

The use of embolization in cases of epistaxis has increased in recent years and has similar efficacy to surgery [188–190]. Most series show control of epistaxis between 90% and 100% of cases using percutaneous embolization, with the advantage that it can be performed without general anesthesia [181, 188, 189]. However, this procedure is related to some serious complications such as stroke, visual loss, ophthalmoplegia, skin necrosis, and facial paralysis [191].

Another aspect to be considered between surgery and embolization is that surgery is the rule and embolization is performed in a few cases [191]. Most patients who are treated with embolization have already been treated with surgery and either bleed again or are severe cases without anesthetic conditions [178, 180, 191]. Embolization is also the first option for cases of vascular malformations such as pseudoaneurysms and vascularized tumors [191, 192].

Patients treated for epistaxis should be instructed to avoid, in the 2 weeks following treatment, care such as blowing their nose, removing dry scabs from their nostrils, or participating in vigorous physical activities such as contact sports. They should also open their mouths when sneezing to avoid increasing pressure in the nasal cavity. Patients using anticoagulants should evaluate the possibility of temporary suspension with a medical doctor and hypertensive patients should strictly control blood pressure. In the event of another bleeding, the patient should be instructed on local measures such as sitting down and leaning forward, avoiding swallowing blood, placing ice on the nasal dorsum, and making compression of the nostrils. If the bleeding is massive or does not improve with these maneuvers, you should seek emergency services immediately [180].

1.5.2 Carotid Blowout Syndrome

The carotid blowout syndrome (CBS) is a rare but potentially fatal complication of head and neck cancer and its treatment and may occur in up to 5% of all patients [193]. Major risk factors include advanced tumor stage, previous oncologic treatment, alcohol abuse, intraoperative bleeding above 700 milliliters (ml), free flap reconstruction, and fluid overload (above 4000 ml in 24 hours). These patients have a five-fold increase in their risk of postoperative death [194]. Also, 58% of patients with advanced stage head and neck cancer may present acute tumoral bleeding with invasion of cervical or mediastinal vessels as the major cause. But even in patients under palliative care, bleeding control may prolong survival and improve quality of life [195]. Other significant causes of CBS are soft tissue necrosis, especially after radiotherapy, neck lymph node metastasis, local complications after neck dissection, and pharyngocutaneous fistulae. The most common clinical presentation is acute bleeding that may be preceded by a limited, sentinel bleeding in half the patients [196].

The recent improvements in endovascular surgery have made these approaches the first therapeutic choice in patients with head and neck cancer, replacing surgical ligature [215]. In a cohort of 37 consecutive patients with CBS due to head and neck cancer, 51% of the episodes were from the common carotid artery, 29% from the external carotid artery, and 19% from the internal carotid artery. All patients were submitted to interventions, with endovascular embolization in 38%, endovascular stent placement in 30%, surgical ligature in 22% and primary reconstruction in 10%. The incidence of perioperative cerebral ischemia was 10.8% with a new bleeding episode occurring in 29.7% of patients after a median interval of 7 days (range, 6–49 days) [197].

The CBS represents an acute, life-threatening event and demands immediate management. The initial approach to a patient presenting with acute head and neck bleeding should follow these steps:

- Dorsal position with elevated decubitus
- Continuous compression over the bleeding point
- Secure airway, with orotracheal tube placement or a surgical/percutaneous cricothyroidotomy
- Oxygen supplementation
- Venous access for blood typing and exams collection followed by IV fluid infusion
- Tomography with IV contrast for bleeding source localization if patient stable
- Immediate transfer for the surgical center/hemodynamics center for intervention

Angiography is considered the exam of choice to identify the bleeding source. The most common findings are contrast spill or pseudoaneurysm formation in 66% of patients and contrast impregnation, suggesting a hypervascular tumor or mucosa. In up to 6% of all patients, no abnormal finding is reported [198].

The management of CBS is challenging, and its surgical approach is associated with a risk of neurological sequelae around 40% and postoperative death around 60% [199]. In this setting, the recent advances in endovascular surgery have been a welcome addition and improved outcomes [200]. Endovascular embolization is a safe and effective method for acute hemorrhage control in patients with head and neck cancer. In a cohort of 51 patients, a 91% success rate has been reported in the first 24 hours. Bleeding recurrence occurred in 12 patients (23.5%) after a mean interval of 127.5 days. The mean hospitalization time was 7.4 days with a mortality of 66.6% and the mean time from embolization to death was 132.5 days [201].

New techniques like coil embolization and balloon occlusion brought a significant reduction in the complications rate compared to surgical ligature. But 15% of patients treated for CBS with balloon occlusion will present immediate or late neurologic sequelae due to non-patent Willis polygon or embolic dislocation due to acute carotid occlusion [202]. This prompted the development and use of drug-coated stents for CBS. These are implanted in an atraumatic technique and capable of self-expansion to bypass the ruptured vascular wall and reestablish cerebral blood flow. This action simultaneously controls the acute bleeding and limits the incidence of ischemic complications. Although an improvement, complication rates as

high as 27% with this procedure have been reported [203]. Stents are the preferred approach in patients who failed the balloon occlusion test as an alternative to minimize the risk of neurologic sequelae [204, 205]. Stents are not complication-free procedures with short-term morbidity like stroke and delayed risks like rebleeding, thrombosis, and infection [206–208].

A systematic review including 266 patients comparing embolization and stent placement demonstrated the former has a lower risk of new bleeding episodes (9.1% vs. 31.9%, $p < 0.001$), but higher stroke rates (10.3% vs. 2.5%, $p < 0.002$) [209].

Another treatment possibility is simultaneous transcutaneous arterial embolization (TAE) with angiography that presents a low complication rate [210]. Patients considered to TAE are those with previous vessel ligature, anatomical variation, and vessel tortuosity, making an endovascular approach challenging [211].

Vascular interventions in patients with head and neck cancer are a marker of dismal prognosis. Overall survival rate for patients with emergency treatment of head and neck cancer bleeding is 38% in 1 year, also significantly related to advanced disease stage [212].

Editor's Comments

Cerebral venous drainage is essential in maintaining cerebral perfusion homeostasis and intracranial pressure. This drainage occurs through the veins of the superficial and deep systems with preferential flow through the internal jugulars and other secondary routes such as the vertebral, pterygoid, and orbital venous plexuses [216].

Among all the veins in the deep venous system, the internal jugular vein is undoubtedly one of the most sacrificed without being reconstructed, either as part of the surgical margin in an oncological procedure or as a substitute for another venous site [217, 218].

Bilateral resection of the internal jugular veins, sometimes necessary in bilateral radical neck dissection, even as a stepped procedure, can significantly compromise brain and face drainage with increased intracranial pressure, possibly causing significant clinical repercussions such as facial edema, pharyngeal or laryngeal, blindness, stroke, and death [219].

Some authors recommend the unilateral or bilateral reconstruction of the internal jugular vein using various techniques and substitutes to minimize these effects.

In 1984, Takeichi et al [220]. performed bilateral reconstruction in two patients with thyroid carcinoma. A bypass was performed with the great saphenous vein in a patient undergoing unilateral *cervical emptying*, evolving with perioperative occlusion leading to facial edema and dyspnea with subsequent need for tracheostomy. After 18 months, he underwent contralateral emptying and reconstruction with PTFE prosthesis, evolving with occlusion after 6 months. Face edema present in the preoperative period disappeared after 1 month.

In another patient who underwent bilateral radical cervical emptying, reconstruction was performed with a PTFE prosthesis on one side and the anastomosis between the external jugular and the distal stump of the internal jugular on the other side. There was perioperative occlusion of the prosthetic bypass with mild facial edema that disappeared after 1 month.

The spiral graft made with the great saphenous vein was described by Leafstedt et al. in 1985 [221]. The saphenous vein initially removed is incised longitudinally and then sutured continuously and spiraled over a rigid structure, generating a more calibrated conduit. There was an immediate drop in the high intraoperative levels of cranial venous pressure in the three patients who underwent unilateral reconstruction of the internal jugular vein, evolving without symptoms in the postoperative period.

In 2000, Katsuno et al. [222] described unilateral jugular reconstruction in four patients, all of whom progressed without venous drainage complications. The reconstructions were of three types: type A, consisting of anastomosis between the distal stump of the internal jugular vein and the external jugular vein; type B, consisting of the interposition of the great saphenous vein between the stumps of the internal jugular vein, and type C, consisting of the interposition of the great saphenous vein between the distal stump of the internal jugular vein and the external jugular vein.

Another type of reconstruction was described by Kamizono et al. [223], consisting of an end-to-end anastomosis between the internal jugular vein and the anterior jugular vein in a patient who evolved without facial edema, possibly due to the patency of the reconstruction associated with preservation of the external jugular vein.

Recently, Daurade et al. [224] described bilateral reconstruction at the same surgical time, using the ipsilateral external jugular vein as a substitute, with a patch on the right and a graft by interposition on the left. The patient evolved without complications, and the control tomography after 1 month showed patent internal jugular veins.

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Chapter 2
Thoracic Surgery

Ricardo Mingarini Terra and Eserval Rocha Júnior

2.1 Lung Cancer

Lung cancer is the most lethal malignancy. It is responsible for over 2 million deaths per year and almost 20% of all cancer deaths [1]. The high mortality is related to the low diagnostic rate for the early stages. Just 16% of cases present as an initial disease at diagnosing. Most of them appear with distant metastasis when the 5-year survival rate is around 5% [2]. When diagnosed early, curative surgical treatment is possible, and 5-year survival is around 70–90% [3, 4].

The key risk factor for lung cancer developing is smoking. It is related to 80% of all lung cancer deaths, and the tobacco is a familiar pathogen for vascular surgeons, because of its relationship with vasculopathy and circulatory disorders [5, 6]. Other conditions such as occupational exposure to carcinogens (arsenic, asbestos, cadmium), pollution from burning fossil fuels, preexisting respiratory diseases (COPD, tuberculosis), and family history are being studied as predictive factors with less influence [7, 8]. It is estimated that 10 to 15% of lung cancer deaths occur in patients with no history of tobacco exposure. This population is made up mainly of middle-aged women with a higher incidence on the Asian continent [1, 9].

2.1.1 Diagnosis

The lack of typical symptoms in the early form of the disease is one of the major reasons for delayed diagnosis. When present, the symptoms are related to the advanced disease progression resulting in intrathoracic organs and chest wall

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invasion. Cough, hemoptysis, and dyspnea may correspond to tracheobronchial tree invasion and pleural effusion secondary to metastatic pleural disease. Mediastinal structures invasion can be responsible for superior vena cava syndrome leading to facial and upper limb plethora. Central and superior sulcus tumors (Pancoast tumors) can cause the invasion of the recurrent laryngeal nerve and other neural structures of the upper chest, leading to hoarseness and Horner syndrome. More frequently present on small cell lung cancer (SCLC) patients, the paraneoplastic syndromes may indicate for hidden lung cancer, for example, neurologic syndromes such as Lambert-Eaton myasthenic syndrome [10].

Without typical symptoms in the early phase, a considerable number of cases are diagnosed accidentally during routine examinations, investigation of infectious pulmonary conditions, or in the preoperative assessment of elective surgeries. Population screening using a periodic low dose CT scan showed a reduction of up to 20% in mortality in the population over 55 years old, smoker, or with significant exposure to tobacco. As we can see, the populations indicated to screening has a familiar profile with vascular surgery patients, and they should require attention during the preoperative evaluation of these patients by the vascular surgeon [11, 12].

A frequent finding in clinical practice is the solitary pulmonary nodule. Often accidentally found, its presence raises doubts for the doctor whose routine does not involve the care of thoracic malignancies. Depending on the population incidence of inflammatory diseases, the diagnostic probability between malignant and benign disease varies. The key factors to be evaluated in front of this finding are the patient's risk profile, the lesion size, and its radiological characteristics. Lesions larger than 8 mm, spiculate edges, located in upper lobes, with a ground-glass opacity component in patients with significant risk factors for lung cancer are highly indicative of malignancy, and we should refer the patient for evaluation by a thoracic surgeon [13].

Nodules smaller than 1 cm in patients at low risk for lung cancer can be followed with chest tomography within variable intervals reported in the literature. However, the average recommendation is 3–6 months of interval between a new CT scan. In case of growth or solidification of the ground-glass component, it indicates the biopsy [13].

2.1.2 Diagnostic Techniques

There are three options available to get a tissue sample in front of a suspected pulmonary nodule: bronchoscopy, percutaneous image-guided biopsy, and surgical biopsy. The sensitivity of the method should guide the choice of the best strategy in front of the lesion characteristics. Less invasive procedures are the first choice, but an adequate tissue sample capacity should be considered because of the actual importance of immunohistochemistry and cytogenetics to the therapeutic strategy.

Bronchoscopy is recommended in the presence of centrally located tumors that have an endobronchial neoplastic component. Chest tomography may show neoplastic projection into the airway, and when associated with a centrally located

lesions with more than 2 cm, the biopsy by this method has a diagnostic rate of almost 80% [14]. For lesions without an endoluminal component, simple transbronchial biopsy with a forceps or using the endobronchial ultrasound (EBUS-TBNA) can be used. Simple transbronchial biopsy is performed without direct visualization of the lesion, and because of that, the diagnostic accuracy is lower. EBUS-TBNA locates the lesion by ultrasound and performs a cytological sample of the lesion getting more precise results, but it is not capable of providing tissue analysis and requires trained pathologists in cytological evaluation [15]. Endoscopic procedures are performed more often with the patient under mild sedation on an outpatient basis and have a low complication rate.

With peripheral lesion greater than 1 cm, image-guided thoracic biopsy is the preferred diagnostic option in patients suspected of having lung cancer. The imaging method could be a CT scan or a simple USG and is used to get tissue by core needle biopsy or fine-needle aspiration. With a high sensitivity rate (90%), it also has excellent specificity (97%) since when core needle biopsy is used, a considerable amount of tissue is obtained [16]. Complications include pneumothorax (10–15%) and bleeding (1%), and patients with significant emphysema and complete ground-glass opacity require attention since they have a greater incidence of pneumothorax and less diagnostic accuracy [17]. The procedure also has low morbidity and mortality, with excellent tolerance been performed with local anesthesia, allowing discharge after 30 minutes [18].

Surgery is the last resort for obtaining a diagnosis. As the most invasive procedure, it requires general anesthesia, a thoracic incision, and a chest tube. With the possibility of video-assisted thoracoscopic surgery, high-quality visualization of the pleura cavity and the lung could be achieved by small incisions with lower postoperative pain. Surgery allows the simultaneous staging, resectability assessment, and lesion biopsy but should be reserved for cases where less invasive procedures could not be performed [16].

2.1.3 Histology

Lung cancer is divided into two major groups according to their histological characteristics, prognosis, and therapeutic options: non-small cell lung cancer (NSCLC) (approximately 85% of cases) and small cell lung cancer (SCLC). Other rarer subtypes such as carcinoid tumor, primary lung sarcoma, and primitive neuroectodermal lung tumors (PNET) represent a minimal fraction of cases [19].

Non-small cell lung cancer is subdivided into adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell carcinoma, and sarcomatoid carcinoma. The most frequent subtype is adenocarcinoma, responsible for about 38.5% of all cases. Its incidence is increasing and is directly related to cases in nonsmoking patients [19, 20]. Its primitive lesion is the atypical adenomatoid hyperplasia that grows to adenocarcinoma in situ, progressing to the minimally invasive adenocarcinoma until reaching its invasive form. This evolutionary history has radiological

correspondence where the ground-glass lesion corresponds to the preinvasive form and the solid pulmonary nodule the invasive one. The prevalent subtype will influence the invasive capacity of adenocarcinoma. The lepidic adenocarcinoma is the most indolent, with a low invasive capacity and only a 7% chance of lymph node metastasis. On the other hand, the micropapillary adenocarcinoma is the most aggressive, with a high invasive capacity and a probability of lymph node spread of 76% [13, 19].

Squamous cell carcinoma is the second most common subtype of NSCLC, and its occurrence has a great relation to the chronic airway inflammation caused by cigarettes. The relation between tobacco usage and squamous cell carcinoma is so close that smoke-free policies decrease its incidence drastically and adenocarcinoma becomes the most prevalent NSCLC [21].

Lung cancer morphological analysis performed by microscopy must be complemented with the immunohistochemical evaluation to define, with precision, the tumor subtype. Adenocarcinoma is marked by thyroid transcription factor 1 (TTF1) and Napsin A, while P64, cytokeratin 5, and cytokeratin 6 mark squamous cell carcinoma. Genetic research by molecular tests is also recommended since specific mutations can lead to specific target therapies when in the presence of genetic mutations such as the two most frequent: EGFR and KRAS genes [19, 21].

Small cell lung cancer is aggressive lung neoplasia originating from neuroendocrine lung cells. It is responsible for almost 15% of all lung cancer cases and has an association with smoking as well. The great majority of cases are diagnosed with metastatic disease because of the rapid progression of this tumor. With elevated tumor growth rate, it tends to infiltrate mediastinal lymph nodes, originating great mediastinal bulks. The histopathological evaluation is compatible with a neuroendocrine tumor showing expression of chromogranin A, synaptophysin, neural cell adhesion molecule (NCAM), and high grade of KI67 [19, 22].

2.1.4 Staging

After diagnoses, staging is the next step. When performed correctly, it helps to define the appropriate treatment, increasing not only survival but also the quality of life. A large international database provides information to create a prognostic profile according to the characteristics of the lesion based on the TNM system (Table 2.1) [3, 23]. This database is maintained and actualized by The American Joint Commission on Cancer, The Union for International Cancer Control, and The International Association for the Study of Lung Cancer.

Evaluating the tumor extension (T), lymph node metastases (N), and distant lesions (M) is necessary to correctly stage the disease. The spread of lung cancer occurs essentially through the lymphatic and hematogenous routes. The hilar and mediastinal lymph nodes are the first site of lymphatic spread, while the adrenal, brain, liver, and bones represent the principal foci of hematogenous dissemination.

Table 2.1 TNM staging system for lung cancer

Tis	In situ (adenocarcinoma or squamous cell carcinoma)
T1	Tumor up to 3 cm without invasion of visceral pleura or main bronchus
T1min	Tumor up to 5 mm of the invasive component
T1a	Tumor up to 1 cm
T1b	Greater than 1 cm and less or equal to 2 cm.
T1c	Greater than 2 cm and less or equal to 3 cm
T2	Tumors up to 5 cm or with visceral pleura or main bronchus invasion; or causing obstructive atelectasis.
T2a	Greater than 3 cm and less or equal to 4 cm
T2b	Greater than 4 cm and less or equal to 5 cm
T3	Tumor up to 7 cm or with satellite nodule in the same lobe, or invading: chest wall, phrenic nerve, or parietal pleura
T4	Tumor larger than 7 cm or with a nodule in another lobe of the same lung or invading: large vessels, diaphragm, esophagus, recurrent laryngeal nerve, trachea, carina, or mediastinum.
N0	Absence of lymph node metastasis
N1	Ipsilateral hilar or intrapulmonary lymph nodes
N2	Ipsilateral mediastinal lymph nodes or subcarinal lymph node
N3	Contralateral mediastinal lymph nodes or in cervical or supraclavicular sites
M0	Absence of distant metastasis
M1	Presence of distant metastasis
M1a	Malignant pleural or pericardial effusion; contralateral lung tumor
M1b	Single metastasis in a single extrathoracic organ
M1c	Multiple extrathoracic metastases

Adapted from IASLC—Lung Cancer Staging System 8°Ed [23]

Chest tomography can preview mediastinal involvement and lesions affecting the adrenals. However, the first proper step is to perform a PET scan. The presence of mediastinal lymph nodes larger than 1 cm on CT scan generates clinical suspicion for malignant involvement with sensitivity around 51%. The combination with the positron emission raises the sensitivity to around 74% by measuring tissue uptake by the FDG, and a full-body exam is indicated for evaluation whenever there is a suspicion by simple tomography, central lesions, or tumors greater than 3 centimeters. It should perform brain MRI in the presence of neurological symptoms or lesions larger than 2 centimeters [24, 25].

Despite the high negative predictive value, mediastinal uptake at PET-CT should not define lymph node involvement. For confirmation, it is essential to perform an invasive staging procedure to get a cytological or tissue sample capable of elucidating the presence of malignant cells.

The procedure of choice for performing invasive staging is the endobronchial ultrasound-guided transbronchial needle aspirate (EBUS-TBNA). Despite obtaining only a cytological sample and being an examiner-dependent procedure, it has sensitivity and specificity (94.6% and 96.3%, respectively) close to

mediastinoscopy, the gold standard procedure for lymph node sampling. EBUS-TBNA is a bronchoscopy exam that can be performed on an outpatient basis with mild sedation. Its biggest problem is the need for expert staff and the availability of a trained pathology team in the cytological evaluation of this procedure [25, 26].

The gold standard for mediastinal evaluation is mediastinoscopy, an invasive surgical procedure performed under general anesthesia by introducing the mediastinoscope through a small cervical incision. From there, it extracts lymph nodes from the mediastinal chains, enabling tissue sampling with greater representation for anatomicopathological analysis. It is a procedure with a complication rate of less than 0.5%, but with the need for a surgical incision, hospitalization, and more complex anesthetic procedure [27]. Both mediastinoscopy and EBUS-TBNA cannot safely assess all mediastinal lymph node chains, and the pre-vascular (6) and aortopulmonary window (5) chains are inaccessible by such methods. When necessary, a left videothoracoscopy (VATS) or an extended videomediastinoscopy (VMLA) can be performed to access these chains.

It is worth mentioning that staging is not a guide for defining treatment, but a unified way of estimating the patient's prognosis. Patients with localized disease and early-stage tumors have 5-year survival ranging from 77% to 92%, while mediastinal lymph node involvement reduces these numbers to 13–56% [3, 23].

2.1.5 Treatment for NSCLC

The curative treatment of non-small cell lung cancer with better long-term results is surgical resection. The 5-year survival for early stages NSCLC is close to 80% after lung resection [3] The presence of metastatic disease in the mediastinal lymph nodes will be the defining point regarding the benefit of the procedure. Patients with N2 disease have no benefit in disease-free survival when treated surgically, and they are considered locally advanced disease. Sometimes with a low volume of mediastinal disease, only one lymph node station committed, surgery can be performed preceded by neoadjuvant chemotherapy or followed by adjuvant treatment. In locally advanced cases with a high volume of mediastinal disease, the indicated treatment comprises chemotherapy and radiotherapy [28–30].

Gold standard surgery is lobectomy with mediastinal lymphadenectomy. It may indicate anatomical sub-lobar resections in initial cases of a pure ground-glass lesion and without lymph node involvement (N0). The procedure can be performed by conventional thoracotomy or by minimally invasive surgery (videothoracoscopy or robotic) with equivalent oncological results [31, 32]. Lymphadenectomy plays an important role in complementing staging and defining the need for adjuvant treatment. In the presence of compromised lymph nodes after surgical resection or tumors larger than 4 cm, it indicates systemic treatment with adjuvant chemotherapy based on cisplatin doublet, leading to a 4–5% increase in 5-year survival [28, 30].

Initial tumors, however not amenable to surgical resection because of lack of clinical condition or patient disagreement regarding the procedure, can benefit from performing stereotactic ablative radiotherapy (SABR), presenting, in this situation, results similar to surgical resection [30, 33].

Patients with advanced non-resectable disease should undergo cancer treatment with concurrent chemotherapy and radiotherapy for better results in survival. Elderly or debilitated patients may undergo sequential treatment with chemotherapy, followed by radiation therapy with similar results. The indicated chemotherapy regimen is based on cisplatin doublet and radiotherapy with 60–66 Gy in 30–33 daily doses [30].

Immunotherapy is a promising treatment for locally advanced disease. Randomized studies initially showed an increase in survival after the administration of Durvalumab as consolidation therapy after chemotherapy. This drug acts as an inhibitor of PD-L1, a ligand present in the tumor cell that inactivates the natural immune response against the tumor. Later, other drugs were studied, and Nivolumab, Pembrolizumab, and Atezolizumab are approved for use by the FDA. Pembrolizumab is already used as a first-line drug for treatment-naïve metastatic patients with PDL-1 expression greater than or equal to 50% [34, 35].

2.1.6 Treatment for SCLC

Given the aggressiveness of this histological type, only 5% of cases are diagnosed in early stages, with an average 2-year survival of only 20–40%. Patients in the earliest stages (T1.2 N0) have the best prognosis, with a 5-year survival rate of around 50% [19, 22].

Surgical treatment is reserved for T1 or T2 lesions without the involvement of mediastinal lymph nodes proven by the invasive staging of the mediastinum. In this group of patients, surgical resection may benefit survival, but it should be followed by adjuvant chemotherapy comprising four platinum-based cycles. If the pathological staging is an unexpected N1 or N2, the adjuvant therapy must also be composed of radiotherapy aiming at adequate local disease control. Patients at high surgical risk should undergo chemotherapy and concomitant radiotherapy as a curative treatment. Both patients submitted to curative trimodal or bimodal treatment should receive prophylactic cranial irradiation if they have a good response to the initial treatment [23, 30, 36].

Patients with N2 or N3 disease still without evidence of distant metastasis have a recommendation to receive treatment with a curative intent composed of concomitant chemotherapy and radiotherapy. If they get a positive response to the initial therapy, they must also undergo prophylactic cranial irradiation [23, 25, 30, 36].

In the presence of metastatic disease, local treatment, whether with radiotherapy or surgery, is not indicated. Here, palliative chemotherapy should be performed, and in case of a positive response to treatment, it also indicates prophylactic cranial irradiation as well [23, 30, 36].

2.2 Lung Cancer and Venous Thrombosis

The incidence of venous thromboembolism (VTE) in patients with lung cancer is between 3% and 13.8%, being among the group of neoplasms considered at high risk for thromboembolic events [37]. A population study involving 91,933 patients found that the probability of developing a thromboembolic event after 1 year of diagnosis is 3%, and after 2 years, 3.4%. Major thromboembolic events such as pulmonary embolism (PE) occur in 3.4% of cases [38]. White et al., in a database analysis of 528,693 patients, observed that the occurrence of VTE significantly preceded the diagnosis of lung cancer, especially in the 4 months before the diagnosis; this finding was even more relevant in patients with advanced disease. Incidental findings of venous thromboembolism can be seen in staging exams, being present in up to 1.4% of PET-CT exams [39].

The pathogenesis of thromboembolic events related to lung cancer is associated with the presence of tissue factor (TF) expressed by neoplastic cells. TF is a physiological trigger of coagulation that is commonly overexpressed in a variety of neoplasms at different intensities. Overexpression of TF in neoplastic cells leads to the formation of so-called microparticles in the systemic circulation, contributing to a hypercoagulability environment. The exaggerated presence of TF in patients with lung cancer has already been reported in previous studies that observed even higher rates in patients with metastatic disease [37, 40].

Some risk factors make lung cancer patients even more prone to thromboembolic events. The thrombocytosis observed sometimes is related to a higher probability of thromboembolic events with an OR of 3.66 (2.25–5.96) and a lower 5-year survival rate [41]. The histological subtype and staging are major risk factors as well. Patients with adenocarcinoma have almost twice the incidence of VTE than squamous cell carcinoma cases, and patients with metastatic disease have an incidence almost four times higher than those with localized disease, being a significant predictor for the development of VTE within 1 year after diagnosis [39, 42].

During the treatment, patients are exposed to an even higher risk. Patients undergoing chemotherapy have a hazard ratio of 5.7 compared to patients who do not receive, and the peak incidence is in the first 6 months [41]. Patients undergoing thoracic surgery rarely stay bed-restricted, and early physiotherapies, usually instituted to optimize pulmonary reexpansion, are protective factors for VTE. However, studies indicate that patients undergoing pneumonectomy are at high risk for VTE, and patients undergoing surgery for lung resection because of neoplasia have a greater probability in present VTE comparing to those undergoing the same procedure for benign disease. Pneumonectomy is the surgery with the highest ratio, and squamous cell carcinoma is the subtype most related to VTE in the postoperative period [43].

2.3 Lung Cancer and Arterial Embolic Event

Acute arterial occlusion due to tumor embolization is a rare event more related to atrial myxomas. However, lung cancer is the second most frequent cause of tumoral arterial embolism. In a review carried out with 104 patients affected by tumoral arterial embolism, with no evidence of atrial myxoma, almost 76% of the patients had lung cancer, 58% of which were primary lung cancer. With primary lung cancer, adenocarcinoma is the most associated subtype, while on metastatic lung disease, sarcomas are the most frequent [44].

Two mechanisms are proposed to explain tumor embolization related to lung cancer: the pulmonary veins invasion resulting in embolization of tumoral particles, and the direct invasion of the aorta by tumors in the left lung. They describe both situations in the literature, and pulmonary vein invasion is present in up to 92% of cases [44]. The occurrence could be spontaneous (54%), but a significant portion (46%) is related to tumor manipulation during surgery. Several case reports show the thromboembolic process during surgery for lung resection or a few hours after the procedure. In this situation, the presence of epidural anesthesia, frequent in open thoracic surgery, can mask the initial symptoms, delaying the diagnosis [45].

Chest tomography with venous contrast is not always used in the preoperative evaluation of lung neoplasms. It should evaluate its indication on suspicion of vascular structures invasion, but sometimes, additional tests are necessary. Transthoracic ultrasound (USG), often performed as a preoperative assessment for pulmonary resections, has low sensitivity for assessing tumor invasion to the pulmonary veins as well. Only in 71% of cases, transthoracic ultrasound can assess only two of the four pulmonary veins. On the other side, transesophageal USG has a high capacity for assessing all pulmonary veins, being extremely sensitive for diagnosing; however, it is a more invasive and not widely available procedure [46, 47].

The primary embolization points are the aortic bifurcation for the iliac arteries (50%) and the cerebral arterial field (30%) [47]. The most frequent symptoms vary from neurological signals because of cerebral ischemia or symptoms in the lower limbs resulting from acute arterial obstruction: pallor, pain, and absence of a pulse. Emergency embolectomy and even subclavian-bi-femoral shunt have been described, but the outcome is usually negative, especially when in early postoperative cases. Some intraoperative techniques are recommended to prevent this event occurrence: reduced manipulation of the lung, early pulmonary vein ligation, and even installation of extracorporeal circulation to perform cardiotomy and tumor resection when that is projecting into the atrium. However, given the low incidence of these events and the lack of a high degree evidence, preventing protocols are not developed yet.

2.4 Superior Sulcus Tumor—Pancoast Syndrome

Tumors originating from the pulmonary apex that invade the parietal pleura, musculature, vessels, and nerves from the upper thoracic narrow are called Pancoast tumors. Formally described for the first time in 1924 by the radiologist Henry Pancoast, these lesions are difficult to treat and represent a challenge for the thoracic surgeon who often needs multidisciplinary help with a vascular surgery and neurosurgery team. They represent 3%–5% of lung neoplasms, with a predilection for males and patients in the sixth decade of life. Its most common cause is NSCLC, with squamous cell carcinoma being the most frequent subtype, which explains its close relationship with smoking [48, 49].

Tumors of the upper sulcus are not an entity with a specific anatomical origin. They are a peculiar neoplasms disease that develops in the apical region of the thoracic cavity, the costovertebral gutter, and that typically invade structures in the region such as the first rib, parietal pleura, endothoracic fascia, vertebral bodies, brachial plexus, stellate ganglion, and subclavian vessels, leading to a characteristic symptom constellation defined as Pancoast-Tobias Syndrome.

2.4.1 Diagnosis

Pancoast-Tobias syndrome is characterized by severe pain radiating to the upper limb in the territory of the eighth cervical trunk (C8) and the first and second thoracic nerves (T1 and T2), atrophy of the superior limb muscles, and Horner syndrome characterized by eyelid ptosis, miosis, and facial anhidrosis ipsilateral to the lesion. These symptoms are secondary to the invasion or compression of the brachial plexus branches and the stellate ganglion. In the early stages, most of the patients are asymptomatic and respiratory symptoms such as cough, hemoptysis, and dyspnea are uncommon since the tumor is peripheral and does not directly affect central structures of the tracheobronchial tree. Therefore, such lesions are often diagnosed in advanced stages, which further reduces the prognosis and hinder treatment [50].

The diagnosis is difficult to achieve using simple chest X-rays since the incidences commonly performed can superimpose soft-tissue images on the lesion. With clinical examination, a CT scan is most often the first complimentary radiologic exam to be performed. Able to provide important information regarding size, extension, the involvement of adjacent structures, and mediastinal lymph nodes clinical status, chest tomography should be performed with intravenous contrast injection to characterize better the vessels of the upper strait and the mediastinal structures. Although important, its accuracy in identifying invasion of the adjacent structures of the upper strait is only 63%, and MRI should be frequently used to precisely define the extent of the lesion. Capable of better-characterizing structures

of the brachial plexus, invasion of the vertebral foramen, and subclavian vessels, chest MRI has an accuracy of 94%, being the exam of choice to define the extent and resectability of Pancoast tumors [51].

2.4.2 Staging

The histological definition is mandatory for adequate treatment institutions. It can establish the diagnosis in most cases through percutaneous biopsy guided by CT scan or USG with sensitivity around 95%. Invasive mediastinal staging is always recommended even in the absence of mediastinal uptake on PET-CT, given the poor prognosis for NSCLC associated with Pancoast syndrome and mediastinal lymph nodes involvement (N2 disease). Therefore, such patients should always be submitted to EBUS-TBNA or mediastinoscopy. Besides PET-CT of the entire body, brain MRI is also routinely indicated for the investigation of metastasis to the central nervous system [3, 23].

According to TNM (Table 2.1), Pancoast tumors are classified as T3 because of the invasion of the chest wall or T4 when they involve vessels of the upper strait or vertebral bodies. The involvement of mediastinal lymph nodes, even in the presence of a negative PET-CT, is around 20%. Although the invasion of supraclavicular lymph nodes is classified as an N3 disease, some reports suggest that this involvement related to the Pancoast tumor behaves like an N1 disease because of a locoregional involvement given to the proximity of the tumor to the lymph node chain. The 5-year survival rate for patients with exclusive ipsilateral N3 involvement reaches 14%, while for patients with N2 involvement, they report it as 0%. The involvement of subclavian vessels also defines a poor prognosis with a reported survival of around 30% even when unrelated to the mediastinal lymph nodes involvement [3, 23].

2.4.3 Treatment

The standard treatment for Pancoast tumors comprises chemotherapy cisplatin-based combined with concomitant radiotherapy as induction therapy followed by radical surgery in case of stability or local regression of the disease. This treatment was standardized after studies of great relevance published by the Southwest Oncology Group (SWOG 9416) and by the Japan Clinical Oncology Group (JCO 9806) that showed improvement in the rates of complete resection and the 5-year survival when the surgery was preceded by chemotherapy plus radiotherapy. The 5-year survival rate of patients who complete this treatment is around 54%, for T3N0 and T4N0 patients, and disease recurrence in most cases is because of the appearance of distant lesions [52, 53].

The possibility of complete resection is usually the limiting factor for surgical treatment. The involvement of subclavian vases is a relative contraindication and depends on the expertise of the surgical team. Subclavian vein can be resected and ligated without major functional impairments or the need for reconstruction. Subclavian artery, when possible, can be resected and reconstructed using synthetic prostheses or allogeneic grafts. Even the common carotid artery can be resected and reconstructed. For that, when this type of resection is possible, the surgical team must anticipate the strategies by studying the carotid field performing US-Doppler to assess the permeability of the contralateral arterial system and to investigate the presence of atherosclerotic disease. Lesions invading the brachial plexus above the T1 root are usually considered unresectable since their resection leads to functional loss of the superior limb [28].

2.5 Primary Pulmonary Artery Sarcoma

Primary pulmonary artery sarcoma (PPAS) is a rare entity with only about 400 cases described in the literature, but its clinical similarity to pulmonary embolism makes it an important differential diagnosis. The clinical and radiological similarity can lead to delayed diagnosis and underdiagnosis, with 3–4% of the cases dismissed with a diagnosis of chronic pulmonary embolism being, in fact, lost diagnoses of PPAS [54].

2.5.1 Etiology

Most of these tumors originate on the dorsal face of the pulmonary artery trunk. Its origin is in the totipotent mesenchymal cells of the intima and subintimal layer. Characteristically, significant intraluminal growth occurs before any extraluminal component is noticed. The presence of the tumor inside the vessel promotes the occurrence of distal pulmonary embolism both by thromboembolic and tumoral processes, causing peripheral pulmonary metastases and infarction. They describe 12 different histological types of sarcoma related to PPAS, with the most frequently described leiomyosarcoma (20%). Although the gender has not shown a relationship with the histological subtype, younger patients appear to be more prone to the myofibroblastic and undifferentiated subtype, while older patients have a higher incidence of rhabdomyosarcoma and liposarcoma [54, 55].

2.5.2 Diagnosis

The age ranges from 43 to 67 years, with an average age of around 52 years old. There is no gender predilection, and specific risk factors are unknown. The average duration of symptoms until the diagnosis is about 100 days, and the most frequent

clinical symptom is dyspnea, present in 74% of patients. Cough, chest pain, fever, weight loss, and signs of right heart failure are part of the clinical picture. The diagnosis of PPAS is often preceded by a misdiagnosis of PE, and the patient is treated with anticoagulant therapy and even underwent embolectomy in 22% of cases. Therefore, in the presence of constitutional symptoms, refractoriness to anticoagulant treatment, and the prolonged duration of symptoms, the clinical suspicion for PPAS should be raised [54].

The radiological findings are usually similar, and patients are frequently submitted to contrast CT scans, MRI, and transesophageal echocardiograms. Differently from what they observe in PE, the CT scan with PPAS may present with vascular distension due to expansive tumor growth, presence of extravascular tumoral component, heterogeneous lesions with hemorrhagic attenuation, and distal lung lesions that may correspond to metastasis [56]. MRI with gadolinium is more sensitive since the tumor has a different signal than that observed in a patient with PE. Transesophageal USG can evidence invasion of the vascular wall and quantify the involvement of the right cardiac chambers. At the same time, PET-CT can complement the evaluation of CT scans since the tumor lesion usually presents greater FDG uptake than the thromboembolic lesion [56, 57].

2.5.3 Treatment

The median survival reported is 528 days. The main prognostic factor is the interval between the onset of symptoms and the correct diagnosis. When the time between diagnosis and the onset of symptoms doubles, mortality increases by 46% [54]. Another factor that influences the prognosis is the diagnosis strategy and the invasive procedures performed before correct treatment. Patients who underwent exploratory surgery or embolectomy without suspicion for PPAS diagnosis had shorter survival after treatment. Despite, sometimes, delaying the oncological diagnosis, the anticoagulant treatment introduced in a PE suspicious did not negatively interfere in global survival as a single prognostic factor.

Because it is a rare etiology with few reports, well-structured treatment guidelines are not available. Some centers that report the largest case series suggest induction chemotherapy with two doses of doxorubicin and isophosphamide for stable patients who tolerate treatment. Radical surgical resection has shown benefit in disease-free survival and can be achieved in 44% of patients reported in the literature. Of the patients who underwent radical surgical resection, 56% required pneumonectomy and 22% lobar resection, which show the need for careful preoperative preparation and adequate planning about pulmonary resection. For radical resections of central tumors, close to the main trunk of the contralateral pulmonary artery, endovascular stent placement in the contralateral pulmonary artery may prevent massive bleeding, facilitate radical resection, and avoid extracorporeal circulation [54, 55, 58].

Local recurrence occurred in only 9% of patients undergoing complete resection, while progression to distant metastatic disease could be seen in 23% of cases. It indicates adjuvant chemotherapy, based on a scheme composed of anthracycline and some alkylating agent, and although it does not show any benefit in preventing local recurrence, it had a positive effect on overall survival by preventing distance progression [58].

2.5.4 Palliative Treatment

Debulking surgery is sometimes recommended as it has also been shown to prolong survival, and it is preferably performed preceded by induction chemotherapy. For cases with local recurrence, some reports have shown positive results with the use of radiotherapy, but its use is not routinely recommended [58]. Endovascular treatment with stent placement in the pulmonary artery can relieve symptoms of vascular obstruction and control pulmonary hypertension, but the long-term results are poor [59].

2.6 Mediastinal Tumors

Mediastinal tumors encompass a wide range of malignancies with different histological subsets and clinical manifestations. Given the proximity to the great vessels and noble structures, the growth of these tumors leads to a constellation of symptoms such as superior vena cava syndrome and Horner syndrome. Complex surgical resections requiring a multidisciplinary approach because of reconstructions or vascular resections are not uncommon.

Almost two-thirds of mediastinal tumors are benign lesions, which include bronchogenic cysts, esophageal duplication cysts, pericardial cyst, goiter, and others. Malignant lesions are more frequent in the anterior mediastinum (56%) given the incidence of lymphomas, thymomas, and teratomas in that compartment [60].

At this point, we will address the most frequent malignant lesions with surgical intent that affect the anterior and middle mediastinum, with potential vascular involvement and the need for a multidisciplinary approach.

2.6.1 Thymic Tumors

Thymic tumors represent 50% of all tumors of the anterior mediastinum. They represent 20% of all mediastinal tumors. Despite this, it is a rare neoplasm, responsible for almost 1.5% of all malignancies and with an incidence of 0.15/100,000pop [61].

The histopathological spectrum of thymic tumors involves two types of epithelial neoplasia of thymus: thymoma and thymic carcinoma. The most used histological classification is from 1999, proposed by the World Health Organization (WHO). It recognizes six types of thymic epithelial tumors divided by the predominance of lymphocytes and the degree of atypia present in the epithelial cells. The classification divides between A, AB, B1, B2, B3, and C, with subtype A being the one with the lowest degree of atypia and the best prognosis. Subtype C represents the thymic carcinoma, the lesion with high cell atypia, and significant invasion capacity of adjacent tissues, resulting in a worse prognosis [62].

2.6.1.1 Thymomas

Thymoma is the most frequent thymic tumor. Its incidence is similar between the sexes, being prevalent after the age of 30, with a peak around 70. As a neoplasm of sluggish development, its symptoms are vague and most often related to advanced disease or secondary paraneoplastic syndrome. Symptoms associated with growing mass are present in 40% of patients, and almost 30% present systemic symptoms. The most frequent presentation is chest pain, cough, and dyspnea [63, 64].

The most common differential diagnosis is lymphoma, and it should employ effort to perform the correct differential diagnosis, considering that opposite to thymoma, lymphoma is a nonsurgical condition. Sometimes with a similar radiological presentation, differentiating between the two diseases is based on clinical suspicion taken by typical symptoms and associated conditions, also called parathymic syndromes. Frequently related to auto-immunologic response, the most typical example is myasthenia gravis (MG) that is present in approximately 30% of cases [65]. Other common associations are pure red cell aplasia and hypogammaglobulinemia [66]. However, the diagnosis in some cases is incidental, with the identification of an anterior mediastinal lesion during the investigation of a bronchopneumonic disease by chest tomography or even in preoperative assessment for elective surgeries where finding is mediastinal enlargement.

The preferable exam for radiological evaluation is the CT scan with endovenous contrast. Anterior mediastinum well-defined rounded mass with homogeneous soft-tissue attenuation that enhances homogeneously after IV contrast injection is almost pathognomonic of a thymoma. Large masses could present focal calcifications, areas of necrosis, and hemorrhage due to its growth, making difficult the differentiation between thymic carcinoma. CT scan is usually superior or equivalent to MRI, besides being an exam easier to perform, more accessible, and cheaper. The use of MRI is reserved for the assessment of supposedly cystic lesions on CT or for further clarification regarding vascular and cardiac tissue invasion [67].

The classic dissemination pattern of thymoma is locoregional with a spread to adjacent structures and “drop metastasis” for the pleural cavity, but they still can metastasize to lymph nodes and for distant sites at approximately 10% of cases. The locoregional spread is significant to do the disease staging since complete surgical

resection of the tumor is the most remarkable prognostic factor. The most used classification for the locoregional spread and disease staging is the Masoka Classification [68, 69]. It tests the microscopic and macroscopic invasion of the adjacent structures, and since its creation in 1981, it has undergone some modifications, without losing its basic concept (Table 2.2) [70].

Unlike other thoracic neoplasms, the most used thymoma staging classification, as seen, is non-preoperative and does not evaluate the nodal status, its primary characteristic focus on an intraoperative and anatomicopathological evaluation.

Classification according to the TNM molds has been proposed and adds to staging a preoperative assessment with tomographic criteria that may suggest a higher risk of tumor invasion or incomplete surgical resection and test the nodal status as well (Table 2.3). This classification aims at a better preoperative staging, facilitating the multidisciplinary decision regarding up-front surgery or nonsurgical treatment with chemotherapy and radiotherapy [71–73].

Table 2.2 Masaoka-Koga staging system for thymic malignancy

I	Completely encapsulated tumor
IIa	Microscopic transcapsular invasion
IIB	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion into a neighboring organ (i.e., pericardium, great vessel, lung, phrenic nerve)
IVa	Pleural or pericardial metastases (separate lesions from the primary tumor)
IVb	Lymphatic or hematogenous metastasis (nodal involvement)

Masaoka staging system [70]

Table 2.3 TNM staging for epithelial thymic tumors

T1	Encapsulated tumor or with mediastinal fat invasion. Maximum extension to the mediastinal pleura
T1a	Negative mediastinal pleura invasion
T1b	Positive mediastinal pleura invasion
T2	Pericardial invasion
T3	Invasion of: extrapericardial pulmonary vessels, vena cava, brachycephalic vein, chest wall, lung, or phrenic nerve
T4	Invasion of: aorta, myocardium, trachea, intrapericardial pulmonary vessels
N0	No lymph node metastasis
N1	Metastasis in perithymic lymph nodes—lymph nodes in the anterior mediastinum
N2	Deep mediastinal lymph nodes or cervical lymph nodes metastasis
M0	No distant metastasis
M1	Distant metastasis (hematogenous or drop metastasis)
M1a	Drop metastasis for pleural or pericardial sites
M1b	Distant metastasis (hematogenous)

Tx, Nx: when the variable could not be accessed or evaluated
Adapted from IASLC Staging Handbook in Thoracic Oncology [73]

The radiologic aspects that could suggest incomplete resection are as follows: tumor size greater than 8 cm, lobulated or ill-defined contour, calcification, mediastinal fat infiltration, the involvement of pulmonary parenchyma, and invasion or circumvention of great vessels.

The curative treatment of thymoma is surgical resection, and the evaluation of complete resectability depends on the expertise of the surgical team involved. As the main prognostic defining factor of the disease, complete resection should always be desired, even in the face of extreme cases leading to vascular and adjacent organ resections. However, given the high surgical risk, such cases should be discussed in multidisciplinary meetings involving the thoracic surgery team, additional surgical specialties (vascular surgery, cardiovascular surgery, plastic surgery), radiology, and clinical oncology team.

For unresectable tumors, up-front surgery should be avoided, and induction with anthracycline-based chemotherapy should be started after performing a transthoracic biopsy of the lesion to define the histological type. If the neoadjuvant treatment presents an adequate response, and the lesion becomes amenable to resection, surgery with adjuvant radiotherapy and chemotherapy is indicated. If resection is not possible, definitive treatment with radiotherapy and chemotherapy should be instituted [74].

The access route must provide adequate visualization of the intrathoracic structures to be addressed, facilitating vascular control, minimizing tumor manipulation, and the possibility of intrathoracic dissemination. For initial stages (Masaoka I and II), minimally invasive resection by videothoracoscopy or robotic-assisted surgery can be performed, as long as the surgical team has expertise. The conventional surgical access is the median sternotomy, which can be complete or partial. It provides a broad view of the anterior mediastinum, allowing vascular control to the great vessels and cardiac area. With pulmonary hilum invasion or more lateral mediastinal structures, combined incisions such as sterno-thoracotomy (Masaoka approach or Hemi-Clamshell incision) or even bilateral thoracotomy (Clamshell incision) are indicated (Fig. 2.1) [74–76].

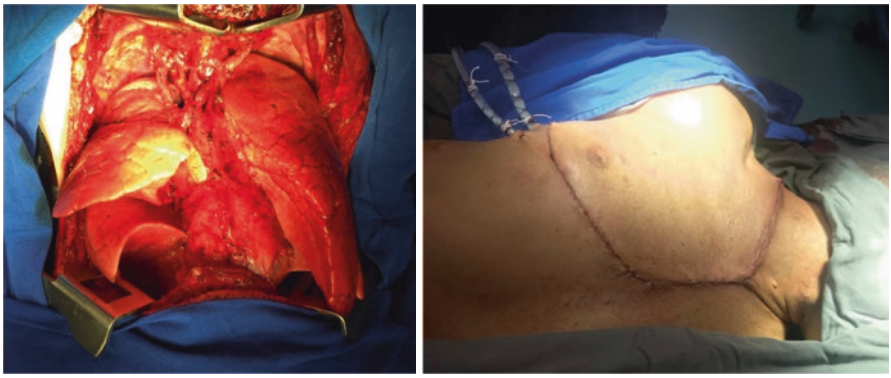

Fig. 2.1 Clamshell incision with excellent exposure to the mediastinal vessels. Final surgery aspect of a Masaoka approach

Vascular resection and reconstructions have been reported, even when involving the aortic arch [77]. The superior vena cava is a vascular structure that can be easily affected because of its proximity and thin vascular wall. In this case, we should proceed with *en bloc* resection to get a satisfactory oncological result. The circumferential vessel wall involvement will define the vascular resection, and we should perform a complete resection followed by reconstruction if the tumor commits over 30% of the vessel wall. For the reconstruction, the polytetrafluoroethylene (PTFE) prosthesis is an option, but biological materials such as bovine or porcine pericardium can be used. Some specialized centers have reported reconstruction using cryopreserved cadaveric aortic allograft with the supposed advantage of greater robustness, lower infection rate, more biological compatibility, and less possibility of kinking [75].

At the end of the resection, the margins should be marked with metal clips to guide possible postoperative radiotherapy. Frozen section biopsy of surgical margins is related to a high rate of false negatives and should not be routinely performed [76].

The adjuvant treatment is based on radiotherapy, which is reserved for selected cases taking into account the main factors for relapse-free survival: staging, complete resection of the lesion, and the histological subtype. Its applicability is aimed at R1 and R2 resection or advanced stages (Masaoka III and IVA) even when R0 resection is achieved. Clinical studies have shown no benefit regarding its performance in patients with Masaoka I stage. In cases of Masaoka II, it can be considered when there is a gross transcapsular invasion (stage IIB) or aggressive histology (B2 and B3). For R0 or R1 resections, adjuvant chemotherapy is not indicated [74].

2.6.1.2 Thymic Carcinoma

Thymic carcinomas are heterogeneous neoplasms of the thymic epithelial tissue currently classified into seven different histological types: Basaloid, squamous cell, mucoepidermoid, sarcomatoid, small cell, clear cell, and lymphoepithelial. They represent a minor percentage within the thymus epithelial malignancies (15%), and given their rarity, retrospective studies and case series are the best basis for prognostic and therapeutic evaluation [62].

Its epidemiology is similar to thymoma with a peak incidence between 40 and 60 years. Its most frequent anatomical site is the anterior mediastinum, and its relationship with parathymic syndrome is also frequent. Given the great aggressiveness of those tumors, patients are often diagnosed in advanced stages of the disease, and the symptoms are most frequently due to invasion of mediastinal structures.

The staging used is the same for thymomas, but it reports a predilection for the use of the TNM system, given the greater incidence of lymph node involvement in cases of thymic carcinoma. There is evidence in the literature that Masaoka-Koga staging is not sufficient for an accurate prognostic definition and that the only isolated factor with a worse prognosis would be a great vessel invasion [69, 71].

Surgical treatment with complete resection is also the gold standard treatment, but given the high rate of lymph node dissemination (20%), systematic lymphadenectomy is routinely recommended. Adjuvant radiation therapy can be performed from Masaoka stage I and is recommended in stages III and IV or at any stage when the anatomopathological evaluation shows R1 or R2 resection. Adjuvant chemotherapy should be considered from stage II, even with complete resection and especially when there was no induction chemotherapy treatment [78].

2.6.2 Mediastinal Germ Cell Tumors

Extragonadal germ cell tumors are rare entities, corresponding to less than 5% of all germ cell tumors. The main extragonadal sites are the mediastinum and the retroperitoneum, given the theory that its origin is from incomplete migration of germ cells through the midline during the embryonic period. Primary mediastinal germ cell tumors are responsible for only 10%–15% of all primary mediastinal tumors, while the prevalence of the malignant forms is around 4% [79]. They usually affect the anterior mediastinum and can be divided into benign mature teratoma, seminomatous, and non-seminomatous tumors. Despite its histology similar to gonadal tumors, its prognosis and treatment are peculiar and should be studied separately [80].

2.6.2.1 Teratoma

This tumor is composed of cells from at least two or more of the embryonic cell layers: endoderm, mesoderm, and ectoderm. Most of the time, its tissues are well-differentiated, and in this case, it is called a mature teratoma, a benign slow-growing lesion with little potential for malignancy. There is a similar incidence between the genders when it is in its benign form, but malignant teratoma predominates in males. It could be present at any age, but the incidence is higher in young adults. Despite its low incidence, it is the second most frequent cause of tumor at the anterior mediastinum, behind only the thymoma [80, 81].

Frequently, the diagnosis is an accidental finding since most cases are asymptomatic. Symptoms when present are because of the lesion growth and the compression of the mediastinal structures: cough, dyspnea, and chest pain are the most frequent. More specific and rare symptoms such as trichoptysis (the act of expelling hair by coughing) or fever related to pleural empyema are related to the tumor rupture and leakage of its contents into the pleural, pericardial cavity, or tracheobronchial tree.

Chest radiography shows mediastinal enlargement and is usually complemented with a CT scan. Chest tomography is the exam of choice for radiological diagnosis and can show a heterogeneous lesion with fatty content, soft-tissue attenuation,

calcifications, and fluids. When the radiological image is very suggestive, and the lesion does not have a great dimension, a biopsy can be dispensed, and complete surgical resection should be performed.

Complete surgical resection is the recommended treatment. The potential of adjacent structures invasion is low and vascular reconstructions are not usually necessary. When the anatomopathological finding suggests malignant transformation or immature teratoma, chemotherapy and adjuvant radiotherapy can be performed [82].

2.6.2.2 Seminomatous Tumors

Half of the malignant germ cell tumors are seminomas. The primary mediastinal seminomas are histologically identical to their gonadal counterparts, but given their location, their behavior and prognosis are peculiar. They are usually located in the anterior compartment of the mediastinum and originate from sperm germ cells. They can gain large volumes, infiltrate the middle mediastinum, and spread via the lymphatic system to mediastinal lymph nodes and hematogenous to the lung, liver, and bone. Symptoms will result from mediastinal compression, with the superior vena cava syndrome present in up to 20% of cases [79, 81].

The diagnosis is commonly made through transthoracic biopsy and anatomopathological evaluation. This tumor rarely alters alpha-fetoprotein or B-HCG unless it has a non-seminomatous component. LDH may be elevated, but has no diagnostic capacity. Sometimes immunohistochemical evaluation is necessary to confirm the diagnosis through positive placental alkaline phosphatase labeling (PAPL). Radiologically, it presents as a relatively homogeneous mass with soft-tissue attenuation, with rare calcifications and slow contrast enhancement (Fig. 2.2). It is worth mentioning that, because of the low incidence of the primary mediastinal form, it is recommended to perform a physical testicular examination or USG of the scrotum.

Seminomas have a good prognosis given their positive response to radiotherapy and chemotherapy, with long-term survival of around 60–80% of treated patients. Therefore, the initial treatment should comprise chemotherapy based on cisplatin

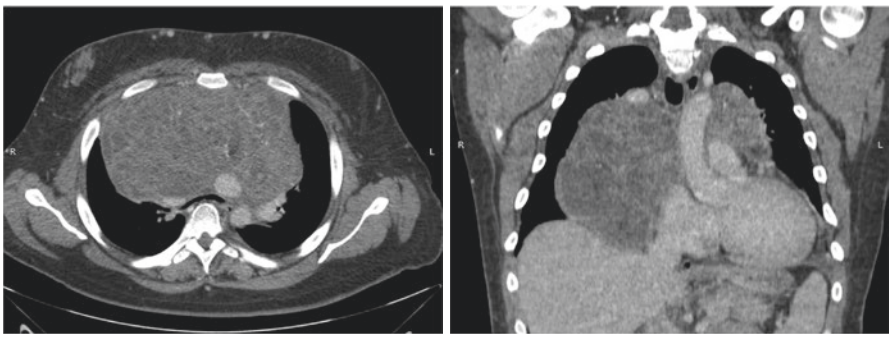

Fig. 2.2 Large primary seminomatous tumor

associated with radiotherapy. After this treatment, in the case of residual disease, radical resection is indicated for better control of the disease and long-term survival [79, 83].

2.6.2.3 Non-seminomatous Tumors

It comprises a group of malignant tumors derived from primitive germ cells. Tumors of the yolk sac, embryonal carcinoma, teratocarcinoma, and choriocarcinoma are included. They are almost exclusive from young male patients and have a worse prognosis when compared to seminomatous tumors, with an average long-term survival of 45% [79].

The clinical features are similar to that of seminomatous tumors; however, about 80% of patients present with metastatic disease at diagnosis, which can cause a higher incidence of respiratory symptoms. The association with paraneoplastic syndromes is around 6%, and the most frequent are malignant hematological diseases such as leukemia or myelodysplastic syndrome. Its association with Klinefelter syndrome has already been reported, with an incidence of approximately 18% in this population [83].

The diagnosis can be made with no lesion biopsy since an anterior mediastinal tumor associated with an increase in alpha-fetoprotein and B-HCG has a high-grade diagnostic specificity for a non-seminomatous germinal tumor. In radiological assessment, it appears as a bulky mass in the anterior mediastinum, heterogeneous, with ill-defined constraints because of the invasion capacity of adjacent structures. The performance of a chest MRI is indicated when suspected of vascular structures' invasion or the cardiac muscle [84].

The standard treatment is cisplatin-based chemotherapy with favorable results, but less efficient than in patients with seminomatous tumors. Approximately 30% of patients do not respond to chemotherapy and may be submitted to high-dose carboplatin and etoposide as a second-line therapy associated with bone marrow transplantation, which increases the response rate. For patients who remain with residual disease, adjuvant surgery is indicated. Surgical results are better for patients with negative serological markers, which shows the destruction of the malignant component by chemotherapy. Surgical resection is often difficult given the invasion of mediastinal structures and the occasional need for complex vascular reconstructions and pulmonary resections, with a mortality rate of around 4% being reported mainly related to respiratory complications [85, 86].

2.7 Editor's Comments

Thoracic neoplasms and the peripheral vascular system have an important link in smoking. Smoking is the most critical risk factor for the most common chest cancer—lung cancer—and atherosclerosis, responsible for the vast majority of arterial

diseases, most notably obstructive diseases. Thus, atherosclerotic arterial disease's coexistence in a patient with lung cancer is not a rare event.

The intersection between thoracic oncology and circulatory events occurs in the venous territory, classically through venous thrombosis. The association between cancer and venous thromboembolism (VTE) is well known. About 20% of new cases of deep vein thrombosis occur in patients with neoplasia [87, 88]. In a retrospective study with 63,000 cancer patients at VTE diagnosis, the highest prevalence was lung cancer, present in 17% of these individuals, followed by the pancreas (10%) [89]. In addition to the higher risk of VTE, lung cancer patients also have a higher risk of recurrence of venous thromboembolic episode, a risk that can reach almost seven times that of an individual without cancer and almost four times of a patient with breast cancer, for example [90]. Also, the risk of bleeding during drug therapy practically doubles in a patient with lung cancer compared to a patient with breast cancer [90].

The growth of the tumor due to early diagnosis difficulty can have repercussions on other intrathoracic structures. One of the most frequent events in locally advanced mediastinal tumors is the superior vena cava syndrome from the circulatory point of view. In this syndrome, VCS drainage is impaired by external compression, venous thrombosis, or both. SVC thrombosis can be caused by tumor invasion or other conditions related to cancer, such as a state of hypercoagulability and the presence of venous catheters. If the local effect of the tumor (external compression, invasion) has always been the major cause of SVCS, the association of this event with venous catheters has increased its frequency, currently corresponding to 20% to 40% of cases [91].

SVCS is secondary to an intrathoracic neoplastic process in 60% to 85% of cases, of which non-small cell lung cancer (NSCLC) is the most common (50%), followed by small cell cancer (NSCLC) (25%–35%) and non-Hodgkin's lymphoma (NHL) (10%–15%) [91–93]. The risk of developing SVCS is more significant in patients with CPPC, in whom SVCS occurs in up to 10% of patients. Cases; individuals with NSCLC have SVCS in about 2% of cases, but this is a more frequent histological type than CPPC [94–96]. Other tumors, much less frequently, can also cause SVCS, such as tumors of the thymus, cell tumors mediastinal germinatives, mesotheliomas, and metastases from other solid tumors (Fig. 2.3) [97–100].

Clinical presentation—the intensity of symptoms may vary with the rate of progression of the obstruction. Collateral veins develop over weeks to allow blood to drain into the right atrium, reducing thoracic venous hypertension. The main routes of collateral circulation come from the azygos, internal mammary, lateral thoracic, paraspinal, and esophageal systems. An acute thrombotic event can accentuate the symptoms of a patient with compression that was previously well-compensated.

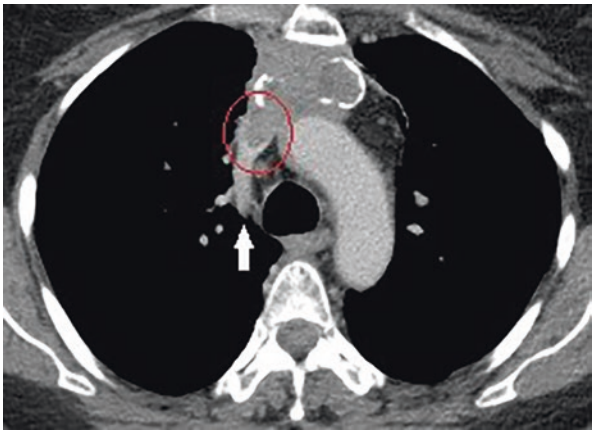

Fig. 2.3 Thymus tumor with invasion of the superior vena cava (red circle). Dilated azygos vein (white arrow)

The main signs and symptoms are edema of the face and/or upper limbs. Dyspnea, as well as facial edema, can be accentuated with the patient lying down. Swelling of the pharynx and larynx can accentuate dyspnea, in addition to causing cough, hoarseness, stridor, and dysphagia. Dyspnea may not be secondary to venous obstruction, but a result of airway compression. Headache, mental confusion, and visual changes may indicate cerebral edema. The physical examination can reveal, in addition to edema of the face and upper limbs, facial plethora and engorgement of the cervical and collateral veins in the chest wall.

The severity of clinical repercussions secondary to SVC obstruction can be graded according to the proposal shown in Fig. 2.4.

Grading	Findings	Estimated incidence (%)
0	Asymptomatic—radiographic superior vena cava obstruction in the absence of symptoms	10
1	Mild—edema in head or neck (vascular distension), cyanosis, plethora	25
2	Moderate—edema in head or neck with functional impairment (mild dysphagia, cough, mild or moderate impairment of head, jaw, or eyelid movements, visual disturbances caused by ocular edema)	50
3	Severe—mild or moderate cerebral edema (headache, dizziness), mild/moderate laryngeal edema, or diminished cardiac reserve (syncope after bending)	10
4	Life-threatening—significant cerebral edema (confusion, obtundation), significant laryngeal edema (stridor), or significant hemodynamic compromise (syncope without precipitating factors, hypotension, renal insufficiency)	5
5	Fatal—death	<1

Grading	Findings	Estimated incidence (%)
0	Asymptomatic – radiographic superior vena cava obstruction in the absence of symptoms	10
1	Mild – edema in head or neck (vascular distension), cyanosis, plethora	25
2	Moderate – edema in head or neck with functional impairment (mild dysphagia, cough, mild or moderate impairment of head, jaw, or eyelid movements, visual disturbances caused by ocular edema)	50
3	Severe – mild or moderate cerebral edema (headache, dizziness), mild/moderate laryngeal edema, or diminished cardiac reserve (syncope after bending)	10
4	Life-threatening – significant cerebral edema (confusion, obtundation), significant laryngeal edema (stridor), or significant hemodynamic compromisse (syncope without precipitating factors, hypotension, renal insufficiency)	5
5	Fatal – death	<1

Fig. 2.4 Grading the severity of malignant superior vena cava syndrome. (It is reproduced from Yu et al. [124])

Diagnosis

- Chest radiography: mediastinal enlargement and pleural effusion are the most frequent changes.
- Computed tomography / angio-tomography: useful to assess the level and extent of the obstruction, in addition to the degree of development of the collateral circulation. It can also be important in investigating the cause of SVCS.
- Nuclear magnetic resonance / nuclear magnetic resonance: more extended, more expensive, and less available examination than tomography, can be an alternative to this, providing similar information.
- Venography: in patients at imminent risk of life, it allows for immediate treatment of venous obstruction.

Treatment

The therapeutic option depends on the severity of the symptoms and the cause of the compressive syndrome (the histological type of the tumor, extent, prognosis). Survival after the diagnosis of SVCS of the neoplastic cause was 6 months on average, according to some studies, with higher mortality in individuals with solid tumors when compared to those with hematological neoplasms [101–103].

General measures: decubitus elevation, systemic anticoagulation if there is associated venous thrombosis, and no other contraindication. The use of corticosteroids may be useful in patients undergoing radiotherapy treatment to prevent or reduce airway edema or in individuals with corticosteroid-responsive tumors, such as lymphoma and thymoma. If the histological diagnosis of lymphoma has not yet been confirmed, the use of corticosteroids may mask this diagnosis, jeopardizing future research.

Marked edema of the larynx and coma due to cerebral edema are emergencies and require immediate treatment with recanalization by endovascular route. In patients with exclusive compression (without thrombosis), stent angioplasty can lead to more immediate symptom relief. If thrombosis is associated, mechanical and/or pharmacological thrombolysis can help with recanalization and better exposure of a segment liable to angioplasty with a stent [104]. The technical success of angioplasty with a stent is greater than 95%, with the relief of symptoms in about 90% of patients [102, 105–108]. Recurrence is reported between 0 and40% (average 13%) [109]. There does not seem to be any difference in the results obtained with the use of balloon-expandable, self-expanding, or tissue-covered stents (endoprostheses) [102, 104, 106, 110–115]. Some studies have shown greater patency with the use of coated stents, but without increasing the rate of technical success or patient survival [105, 116]. Complications of stent angioplasties occur in up to 7% of cases and, among the most feared are pulmonary embolism, rupture of the SVC, and stent migration [117]. The maintenance of antithrombotic therapy after stent implantation in patients without associated thrombosis is not yet well-defined. We suggest dual antiplatelet therapy with aspirin and clopidogrel for 3 months, maintaining the first after that period.

In patients outside of emergencies, chemotherapy is the first alternative in responsive tumors, such as CCPC, NHL, and germ cell cancer, in which symptom relief occurs after 1 to 2 weeks of treatment [118]. In neoplasms less responsive to chemotherapy, radiotherapy is the alternative in radio-sensitive histological types in patients who have not previously been irradiated. Radiotherapy usually leads to improved symptoms in up to 72 hours, but this period can reach up to 4 weeks. A literature review comparing therapeutic options exclusively in patients with lung cancer (CPPC, CPNPC) showed symptom relief in 95% of patients treated by stent angioplasty [95]. Among patients diagnosed with CPPC and SVCS treated with chemotherapy, chemo/radiotherapy, and radiotherapy, clinical improvement occurred in 84%, 94%, and 78%, respectively [95]. As for those with NSCLC, 60% evolved with symptom improvement when treated with chemo or radiotherapy [95]. As for the recurrence of SVCS symptoms, the rates were 11% in patients treated with a stent and 17%–19% among those treated with chemo or radiotherapy [95].

Surgical en bloc resection of the tumor with a reconstruction of the SVC with an autologous or synthetic substitute is an operation with high morbidity and mortality, and patients in these conditions generally have a more reserved prognosis [119]. Thus, this procedure is rarely recommended in patients with tumors that are unresponsive to chemo and radiotherapies, such as thymomas or thymic carcinomas, or even in patients undergoing germ cell tumor resection [119–123].

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Chapter 3
Gastrointestinal Surgery

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3.1 Esophagus/Stomach

3.1.1 Esophagus

The anatomy of the esophagus is especially distinctive since its topography is related to both vascular and airway organs, from the cervical to the abdominal part. Esophageal cancer is one of the most difficult to treat surgically due to the relationship of the esophagus to another organ [1, 2]. Esophageal carcinoma is usually confirmed by an upper endoscopy with biopsy, and it has two main histological types: squamous cell carcinoma (SCC) and adenocarcinoma (adenocarcinoma of the esophagogastric junction – AEGJ) [3]. Alcohol, smoking, achalasia, esophageal caustic stricture, and synchronic head and neck tumors are the main factors related to SCC, and gastroesophageal reflux disease and obesity are related to adenocarcinoma of the esophagus [4, 5]. Unfortunately, in the University of Sao Paulo (ICESP/Hospital das Clínicas da Faculdade de Medicina da Universidade de Sao Paulo), only one third of SCC cases and half of all followed cases in the Institution are curable esophageal tumors. From those cases, the resectable rate is less than half [6].

The anatomy of the esophagus is divided into the upper, middle, and distal third. The upper third is near the trachea, subclavian and brachiocephalic arteries, and veins; the middle third is close to the distal trachea, carina, left bronchus, and descending thoracic aorta; and finally, the distal third is close to the descending thoracic aorta [7].

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After diagnosis, esophageal cancer is staged as follows: (1) cervical, thoracic, and abdominal computerized tomography (to evaluate extension of the tumor and lymph nodes status); (2) bronchoscopy (only in SCC cases); (3) 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) has the potential to improve the lymph nodal staging; and, (4) Echoendoscopy to evaluate potential early resectable lesions by submucosal resections and to analyze suspicious lymph nodes [8].

After staging, for tumors higher than T2 and/or positive lymph nodes, neoadjuvant multimodal treatment is indicated [9]. After CROSS trial, both locally advanced SCC and adenocarcinoma are indicated to cisplatin with paclitaxel and a total radiation dose of 41.4 Gy (daily dose of 1.8 Gy) and weekly chemotherapy [10]. However, after FLOT trial, adenocarcinoma of the esophagogastric junction advanced tumor is treated with four cycles of perioperative chemotherapy with scheme of fluorouracil plus leucovorin, oxaliplatin, and docetaxel. Prospective randomized trials are needed to determinate which group of patients may benefit from chemo or radio chemotherapy, such as Neo-AEGIS and ESOPEC trials [11].

3.1.1.1 Surgical Treatment

Transhiatal

According to recent consensus, a radical transmediastinal en bloc esophagectomy (Fig. 3.1) associated with extended lymphadenectomy and resection of proximal stomach with gastroplasty reconstruction is the preferred surgical procedure for AEGJ type I (adenocarcinoma of the distal esophagus) [12]. This approach promotes an extended lymph node resection in the lower posterior mediastinum and upper abdominal compartment (for example, in Long Barrett's esophagus). However, it does not perform an adequate infra-carinal, greater curvature, and parapyloric lymphadenectomy [13]. Transhiatal resection of the distal esophagus with an extended total gastrectomy and Y-Roux reconstruction is performed in patients with type III tumors (subcardial gastric carcinoma). Nevertheless, the success of this technique is related to an intraoperative frozen section analysis, which can have

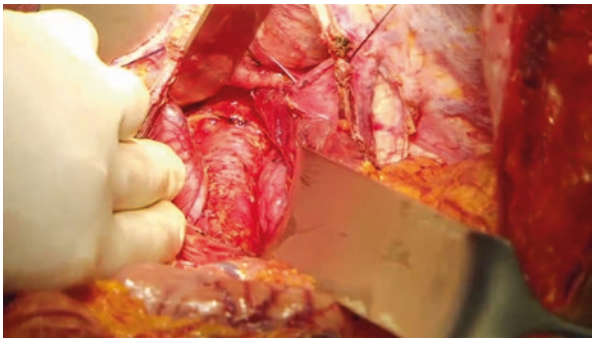

Fig. 3.1 Final aspect after esophageal and lymph node resection of the lower mediastinum by transhiatal esophagectomy approach for patients with esophagogastric junction adenocarcinoma

a false negative conclusion from 10% to 21% [14, 15]. Therefore, the high incidence of the intrathoracic anastomosis leakage in the subtotal esophagectomy is another problem which contributes to mortality rates [16]. In patients with type II tumors (carcinoma of cardia), some groups tend to execute an extended gastrectomy with transhiatal resection of the distal esophagus; however, in our Institution these cases are treated by an esophagectomy with proximal gastric resection through a transdiaphragmatic approach [17].

Thoracoscopy

After selective intubation of the left bronchus, the patient is placed in a prone position. Dissection of the esophagus is performed from the lower part of the mediastinum towards the upper one. The esophageal and lower periesophageal lymph node, including periaortic, supradiaphragmatic, and pericardial, are dissected. Following dissection, the right and left infra-carinal lymph nodes are removed, exposing the right and left bronchi to their origin in the carina (Fig. 3.2).

The thoracoscopic approach is indicated to extended thoracic and recurrent nerve lymphadenectomy. In this way, SCC is a preferred access regarding clinical conditions (such as pulmonary disease and cardiopulmonary comorbidities). For AEGJ, comparatives studies have shown higher number of retrieved lymph nodes in thoracoscopic esophagectomy, however without a clear improvement in the overall survival and disease-free survival. In addition, the pulmonary complications, such as, atelectasis and pneumonia, in this group of patients are higher than transhiatal (extrapleural route) approach [12].

Recent study has discussed supercharged cervical microanastomosis for esophagectomy (SAFE procedure) in the cervical esophagogastric anastomosis, improving perfusion area of the cervical anastomosis and potentially reducing anastomotic leakage rates [18]. Since the perfusion, assessment of the esophagogastric

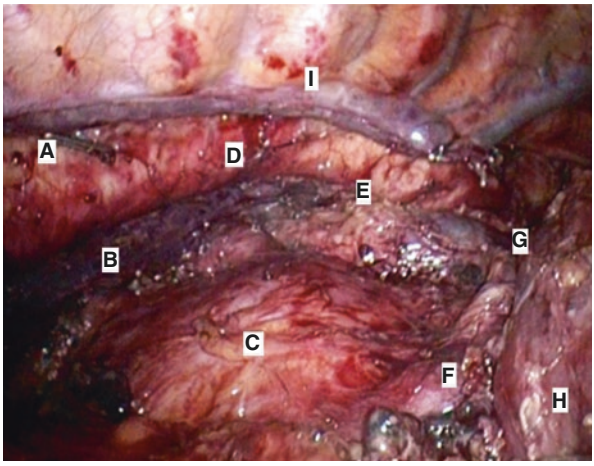

Fig. 3.2 Final mediastinal aspect after esophagectomy with lymphadenectomy by thoracoscopic transthoracic esophagectomy technique for patients with esophagogastric junction adenocarcinoma. A Clipped thoracic duct. B left parietal pleura, C left atrium, D descending aorta, E left bronchus, F right bronchus, G carina, H esophagus, I azygous vein

anastomotic has been extensive using the indocyanine dye and fluoroscopy. This issue represents a new perspective reducing complications after esophagectomy, mainly anastomotic leakage.

3.1.1.2 Unresectable Tumors

In this way, locally advanced esophageal tumors are more likely to invade those anatomical structures according to the level and extension of the tumor in the esophagus. However, if the esophageal tumor invades adjacent organs, even in multimodal therapy, it is considered a palliative treatment. One of the most frequent organs is the descending aorta/thoracic aorta (Fig. 3.3), and it may cause esophagoaortic fistula with an intense hemoptysis. In this unique situation, thoracic endovascular aortic repair (TEVAR) is under discussion: first, to control the potential bleeding, and secondly, to prove the efficacy modality to prolong the survival of patients [19].

3.1.2 Stomach

Adenocarcinoma is the more frequent type of malignant neoplasia of the stomach, accounting for around 94% of all cases. Preoperative staging consists of clinical observations and the use of imaging methods. The presence of hepatomegaly, ascites, enlargement of the Virchow lymph node (in the left supraclavicular location), umbilical nodules, and enlargement of the left axillary lymph node examination are indicative of advanced disease [20].

The computerized tomography examination of the total abdomen and thorax is the method of choice for staging gastric cancer because it is more sensitive for the evaluation of peritoneal, liver, and pulmonary metastases [21]. Preoperative

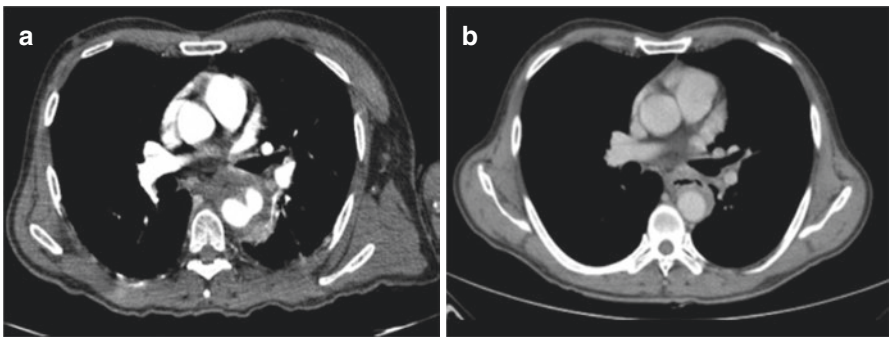

Fig. 3.3 Thoracic computed tomography staging in esophageal carcinoma. (**a**) Thoracic esophageal carcinoma involving thoracic aorta and causing aortic dissection. (**b**) Esophageal carcinoma involving thoracic aorta more than 180°

assessment of the level of invasion of the gastric wall is essential when there is an intention to adopt a therapeutic approach other than gastrectomy with type D2 lymph node dissection, a gold standard technique with proven success in the treatment of gastric cancer [22]. For this, it is essential to rely on highly reliable staging methods to avoid treatment that is less than necessary, which could be extremely harmful to the patient. Eco-endoscopy is a highly efficient method for this purpose [23].

Positron emission tomography (PET CT) has not yet proved its usefulness in patients with gastric cancer and should only be performed in cases where there are doubts about the presence of distant metastases. In patients with gastric cancer of the undifferentiated type, the usefulness of PET CT is even lower [22].

Diagnostic laparoscopy allows the visualization of the surface of the parietal and visceral peritoneum in search of metastatic lesions smaller than 5 mm that are usually not detected by tomographic examination [22]. The method also allows the performance of peritoneal lavage, which is important for the analysis of the patient's prognosis, as well as the performance of an associated ultrasound examination to increase sensitivity in the search for liver metastases [24].

Gastric cancer staging can be performed following the rules of the UICC (International Union for Combating Cancer) and AJCC (American Cancer Committee). Since 2010, the JGCA (Japanese Association of Gastric Cancer) has followed the same AJCC classification in an attempt to standardize the language of gastric cancer in the west and east [22]. Figure 3.6 shows the Staging seventh edition classification. It should be noted that in the eighth edition published in December 2016, there was no change in parameters T, N, and M, but there was a conceptual change in the stage of cancer of the AJEG. Previously, all Siewert I, II, and III tumors followed esophageal cancer staging (when the tumor's epicenter was up to 5 cm from JEG), now Siewert III tumors, with epicenter >2 cm from JEG, follow cancer stage gastric, even if the esophagus is involved.

There is agreement in the medical literature that radical gastric resection is still the best treatment for stomach adenocarcinoma. The surgical technique and the extent of gastrectomy and lymphadenectomy depend on the following factors: tumor location, penetration into the gastric wall, and histological type. The complete tumor resection with free margins in adequate extension, as well as its lymphatic drainage, is the objective of the radical operation. The level of tumor invasion in the gastric wall, the presence of lymph node metastases, and the occurrence of distant metastases are the most important prognostic factors for patients with gastric cancer.

Usually gastrectomy with D2 lymphadenectomy is the method of choice in the treatment of gastric cancer with adequate rates of morbidity and mortality and favorable and well-known oncological results (Fig. 3.4) [25]. However, aiming at improving the quality of life, several techniques, including minimally invasive or function preserving procedures, have been developed in the last decades.

The algorithm in Fig. 3.5 shows the current recommendations of the JCGA – 2014 for the treatment of gastric cancer in the various forms of clinical presentation [26].

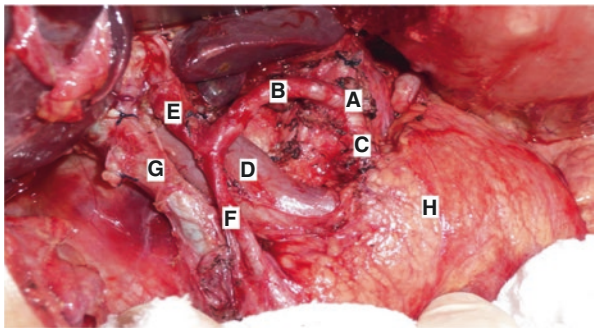

Fig. 3.4 Final aspect after total gastrectomy with D2 lymphadenectomy. A Left gastric artery, B common hepatic artery, C splenic artery, D portal vein, E proper hepatic artery, F pancreas, G choledochal, H pancreas

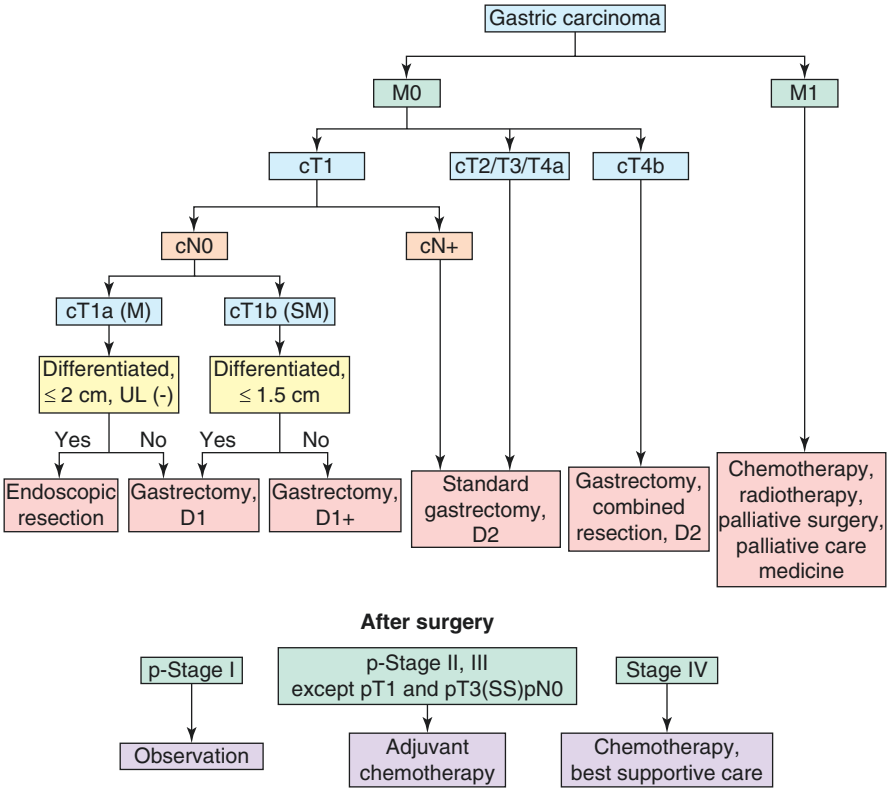

Fig. 3.5 Recommendations of the Japanese Gastric Cancer Association (JCGA) – 2014 for the treatment of gastric cancer

3.1.2.1 Endoscopic Treatment

The absolute indications for endoscopic treatment by mucosectomy or submucosal dissection are differentiated histological tumor, without ulceration, cT1a, and ≤2 cm. Patients undergoing endoscopic resection (EMR or ESD) should be

followed up with special care. Resection is considered curative when all the following criteria are met: en bloc resection, tumor smaller than 2 cm, differentiated histological type, invasion to the mucosa, negative horizontal and vertical margins, and absence of lymphovascular invasion [27].

3.1.2.2 Surgical Treatment

Since 2010, the Japanese guideline has been revised for simplification and international use. The definition of lymphadenectomy was simplified: the lymph node stations (D1, D2, and D3) were defined for the type of gastrectomy (total or subtotal), regardless of the anatomical location of the tumor. D3 was no longer defined by the failure to recommend D3 lymphadenectomy. The lymph nodes station was included as lymphadenectomy D1 and those in lymph nodes 14 were excluded from lymphadenectomy D2. The current recommendation is as follows: [22]

- Gastrectomy + D2 lymphadenectomy for non-early tumors (cT2–4 or cN +).
- D1 or D1 + are options for T1 tumors.
- D1: T1a without criteria for EMR/ESD or different type cT1bN0 ≤1.5 cm.
- D1 +: other CT1N0 tumors or can be an option for patients with low performance status, without conditions for D2.

D2 lymphadenectomy is considered the gold standard in the treatment of gastric cancer. When the surgeon has doubts about the preoperative characterization or when he does not have access to echo-endoscopy or the appropriate anatomopathological examination, this should be the adopted approach. D2 lymphadenectomy is indicated in cases of potentially curable T2-T4 tumors, as well as in T1N + lesions.

3.1.2.3 Multimodal Treatment

Western Trials

In the late 1990s, two randomized studies of paramount importance were published. The first, INT 0116, compared exclusive surgery with chemo (leucovorin and 5-fluoracil) and adjuvant radiotherapy and showed a tendency towards greater survival in the group with QT/Adjuvant RDT, despite the insufficient number of patients with D2 lymphadenectomy [28]. The other, MAGIC, trial compared exclusive surgery with a group of patients undergoing perioperative chemotherapy (epirubicin, cisplatin, and 5-fluoracil) showing a 13% survival gain in the group undergoing preoperative chemotherapy [29].

In 2012, the CROSS trial was published by a Dutch group, showing an increase in resectability of 23%, an increase in overall survival by 13%, and a complete pathological response of 29% when chemotherapy (carboplatin and paclitaxel) and preoperative radiotherapy were performed [9].

Eastern Trials

In contrast, in the East, two randomized studies were published with more than 1000 patients in each study. The first Japanese ACTS-GC trial used adjuvant chemotherapy with S1 after gastrectomy or esophagectomy with D2 lymphadenectomy and showed a 10.6% survival gain [30]. The other published study is the CLASSIC trial, which showed a 15% gain in 3 years in patients undergoing adjuvant treatment with capecitabine and oxaliplatin for 6 months after surgery with adequate D2 lymphadenectomy [31]. However, as previously discussed, the incidence of Siewert III tumors is much greater than II and I in the east.

A controlled randomized study carried out in the Korea ARTIST trial was unable to demonstrate the benefit of the combination of radiotherapy and chemotherapy in both its adjuvant and neoadjuvant forms [32]. As lymphadenectomy in the east is more extended, there seems to be no need for complementation with radiotherapy after surgery.

The prognosis in Japan is estimated at 40–60% in 5 years, better than the 20% in Western countries, but this fact is explained by the high number (65%) of T3/T4 cases seen at diagnosis in the West [33]. Still in the west, the profile is of tumors of a more proximal location, of the esophagogastric junction, mostly of the undifferentiated signet ring type. In the east, most tumors are mid-distal with intestinal type and with earlier treatment (consistent with the time of diagnosis), so from a technical point of view, more favorable to surgical treatment both in relation to cancer staging and comorbidities.

3.2 Pancreas/Liver

3.2.1 Introduction

Surgical treatment remains the gold standard in most oncological diseases of the digestive tract, however, depending on the location of some neoplasms, the relationship with vascular structures may appear as an impediment to resections for curative purposes. In some situations, small tumors may be in close contact with noble vascular structures and, to preserve these structures, the oncological margins may be small or even compromised, leading to early local recurrences. An example are cholangiocarcinomas that develop in the hepatic hilar region (Klatskin's tumor), and often have an intimate relationship with main trunks of the portal vein and/or hepatic artery. Another example is pancreatic adenocarcinomas, which, depending on their locations, can lead to involvement by contiguous superior mesenteric vein, portal vein, superior mesenteric artery, hepatic artery, and even the celiac trunk and aorta. Primary or secondary liver tumors also may present with vascular invasion that may require resection and reconstruction.

Technological developments associated with new systemic (chemotherapy) and local (radiosurgery) treatment schemes have allowed for an advance in the treatment of locally advanced oncological diseases with vascular impairment. Modern chemotherapy schemes, due to their ability to control cancer residues, allowed a change in the criteria for surgical indication: from free margins to coincident margins, that is, technically resectable tumors. Even so, expanded resections, with free surgical margins, allow the best oncological results, however, they may depend on complex vascular reconstructions and with increased morbidity and mortality.

In this chapter we will address the applicability of vascular surgery within the context of surgical treatment of hepato-pancreatic-biliary neoplasms, as follows:

3.2.2 Pancreas

Pancreatic cancer is the 14th most common cancer and the 7th leading cause of cancer mortality in the world. It occurs more frequently in developed countries and its worldwide incidence is increasing [34–36]. In the United States, it is the fourth leading cause of cancer-related death; however, this proportion continues to increase. This tumor is more frequent after the 6th decade of life and the main associated risk factors are smoking, obesity, type 2 diabetes, alcoholism, and family history [37].

Adenocarcinoma and its subtypes represent 90% of all pancreatic carcinomas, presenting high lethality, with low probability of cure, that is, low rates of disease-free survival and overall survival. In contrast to what happened with most malignant tumors, the 5-year survival of pancreatic cancer has improved somewhat in the past 40 years. Even so, surgical resection is the only treatment that offers the potential to cure this tumor, and the addition of adjuvant chemotherapy has been shown to improve survival rates [38–41].

Unfortunately, in a significant number of patients, the diagnosis is made at a late stage of the disease, with locally advanced or metastatic disease. Pancreatic cancer staging classification is shown in Table 3.1. It is estimated that about 50–80% of patients present this condition at the time of diagnosis, when the 5-year survival is only 3% [37]. This fact is due to the presentation of nonspecific initial symptoms, delaying the diagnosis, and the intimate anatomical location with main blood vessels, allowing their early involvement.

More recent data suggest benefit through strategies with the administration of chemoradiotherapy in the neoadjuvant scenario, with additional improvement in survival, but more robust studies are needed to identify which group of patients will have better results [42, 43].

Even among patients receiving neoadjuvant therapy and surgical resection, the overall 5-year survival rate is approximately 28% [44]. Since surgical resection offers the best chance of survival for patients with pancreatic cancer, aggressive removal of loco disease, regionally advanced, is increasingly recommended; however, less than 30% of patients with newly diagnosed pancreatic cancer are eligible for surgical resection [45].

Table 3.1 Pancreatic cancer staging classification according to AJCC 8th edition

Stage	TNM	
0	Tis N0 M0	The cancer is confined to the top layers of pancreatic duct cells and has not invaded deeper tissues. It has not spread outside of the pancreas. These tumors are sometimes referred to as carcinoma in situ (Tis). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IA	T1 N0 M0	The cancer is confined to the pancreas and is no bigger than 2 cm across (T1). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IB	T2 N0 M0	The cancer is confined to the pancreas and is larger than 2 cm but no more than 4 cm across (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIA	T3 N0 M0	The cancer is confined to the pancreas and is bigger than 4 cm across (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIB	T1 N1 M0	The cancer is confined to the pancreas and is no bigger than 2 cm across (T1) *AND* it has spread to no more than 3 nearby lymph nodes (N1). It has not spread to distant sites (M0).
	T2 N1 M0	The cancer is confined to the pancreas and is larger than 2 cm but no more than 4 cm across (T2) *AND* it has spread to no more than 3 nearby lymph nodes (N1). It has not spread to distant sites (M0).
	T3 N1 M0	The cancer is confined to the pancreas and is bigger than 4 cm across (T3) *AND* it has spread to no more than 3 nearby lymph nodes (N1). It has not spread to distant sites (M0).
III	T1 N2 M0	The cancer is confined to the pancreas and is no bigger than 2 cm across (T1) *AND* it has spread to 4 or more nearby lymph nodes (N2). It has not spread to distant sites (M0).
	OR	
	T2 N2 M0	The cancer is confined to the pancreas and is larger than 2 cm but no more than 4 cm across (T2) *AND* it has spread to 4 or more nearby lymph nodes (N2). It has not spread to distant sites (M0).
	OR	
	T3 N2 M0	The cancer is confined to the pancreas and is bigger than 4 cm across (T3) *AND* it has spread to 4 or more nearby lymph nodes (N2). It has not spread to distant sites (M0).
	OR	
	T4 Any N M0	The cancer is growing outside the pancreas and into nearby major blood vessels (T4). The cancer may or may not have spread to nearby lymph nodes (Any N). It has not spread to distant sites (M0).
IV	Any T Any N M1	The cancer has spread to distant sites such as the liver, peritoneum (the lining of the abdominal cavity), lungs or bones (M1). It can be of any size (Any T) and might or might not have spread to nearby lymph nodes (Any N).

Initially adopted by the National Comprehensive Cancer Network (NCCN) in 2006, the definition of borderline pancreatic ductal adenocarcinoma for resection emerged, based on anatomical criteria and, more specifically, on the extent of

venous and arterial involvement of the tumor. Although the concept has been widely used for recruitment in clinical trials and for the selection of treatment modalities, the definition is variable; it has been published by different societies, without a clear internationally agreed consensus. Thus, it is understood that the definition of borderline disease for resection is often subjective and influenced by the experience of the surgeon and the service. More recently, during the 20th meeting of the International Association of Pancreatology, in Sendai (2016), a consensus was sought for this definition, considering anatomical and biological aspects related to the tumor, and clinical aspects of the patient. For the anatomical definition of adenocarcinoma of the borderline pancreas for resection, it is understood as a tumor that presents a high risk of positive oncological margin (R1, R2) when surgery is used as an initial treatment strategy. The biological definition of borderline pancreatic adenocarcinoma for resection is when there are findings or evidence that increase the possibility (but not certainty) of extra-pancreatic metastatic disease, taking into account the tumor marker CA19.9 (>500 units/ml) and the presence of affected lymph nodes assessed by biopsy or PET-CT. The conditional definition is when the patient has a high risk of morbidity and mortality after surgery due to factors related to the host, including performance status and comorbidities [46]. Therefore, many services have started to adopt neoadjuvant chemotherapy as a strategy in these borderline pancreatic tumors. These patients, after neoadjuvant treatment, are considered for pancreatic resection when there is no anatomical contraindication to resection; there was no development of metastatic disease and the patients have acceptable performance status [47–49].

Another interesting aspect analyzed was whether the vascular involvement in pancreatic tumors was the result of more aggressive cancer behavior? When comparing patients undergoing PD with and without the need for portal mesenteric vascular resection, no difference was demonstrated in the average size of the tumors, degree of differentiation, and number of lymph nodes affecting between patients. There was also no longer hospital stay, postoperative morbidity and mortality, and survival. These facts suggest that vascular involvement is mainly related to the location of the tumor and not to biological behavior [50–52].

Although debatable, several centers have started offering neoadjuvant therapy even for initially resectable pancreatic cancer, representing a change in the treatment paradigm by the significantly improved survival recognition reported with this approach [48]. The best response rate to current chemotherapy regimens (FOLFIRINOX, gemcitabine-abraxane, GTX) made patients, initially considered unresectable, candidates for resection. There are an increasing number of reports disclosing the positive effect of neoadjuvant therapy on the status of the margin, lymph node positivity, and tumor response. Neoadjuvant therapy allows the selection of patients with biologically responsive tumors to be considered for resection, especially in patients bordering on resection and who require complex vascular reconstruction with curative intent.

3.2.2.1 Tumors Located in the Head and Uncinate Process of the Pancreas

For tumors located in the head and uncinate process of the pancreas, the recommended surgery is pancreaticoduodenectomy (PD). Different technical modalities have been proposed and can be used to reconstruct the alimentary, biliary, and pancreatic pathways after this resection; however, this is not the focus of attention in this chapter. The main vascular structures potentially affected by head adenocarcinoma or uncinate process of the pancreas are the superior and/or superior mesenteric veins and the superior mesenteric artery.

Currently, vascular resections are performed to obtain a free margin (R0) during PD, when the only area that prevents a complete resection of the tumor is related to vascular involvement. Vascular resection can be performed if vascular reconstruction is feasible or, if alternative vascular pathways allow compensation for the anatomical structures involved.

Some pancreatic surgeons consider the involvement of the superior mesenteric vein as a contraindication for the resection of pancreatic cancer. In the context of vascular neoplastic involvement, when resection of the affected vascular segment is not performed, the retroperitoneal margin will be affected. Patients submitted to resection with a positive surgical margin have a similar survival rate to patients treated nonsurgically with exclusive radiotherapy. The resection of locally advanced disease, with isolated venous involvement, allows a gain of survival in up to 2 years. In 2009, after the American Hepato-Pancreato-Biliary Association/Society of Surgical Oncology consensus, portal vein resection with primary reconstruction became the standard of treatment for pancreatic adenocarcinoma with splenic-mesenteric-portal venous invasion. Some retrospective studies have shown that in properly selected patients who have undergone an R0 resection, the rates of morbidity, mortality, and survival for those with portal vein resection are similar to those of patients who do not require resection for surgical treatment of cancer of pancreas [53–55]. A meta-analysis of 22 retrospective cohort studies found no difference in perioperative morbidity and survival of one or three years in those submitted to portal or superior mesenteric vein resection when compared to those in which no vascular intervention was necessary. As expected, there was an increase in operative time and blood loss recorded in the venous resection group [56]. Unfortunately, the lack of randomization leaves these studies at risk of selection bias. However, pancreatectomy combined with venous resection can play a role in a select group of patients and must be performed to obtain free oncological margins.

Arterial resection and reconstruction during PD were also part of the regional approach to pancreatectomy; however, enthusiasm for these procedures was reduced due to the technical difficulties of the operation and its high morbidity and mortality [57]. A meta-analysis of studies involving patients undergoing PD procedure with or without arterial resection found higher rates of perioperative mortality and worse results in the first and third years in the group with arterial reconstruction. For this reason, invasion of the superior mesenteric artery or the celiac trunk remains a contraindication for resection in many centers [58]. Another aspect to be considered is

that the celiac trunk and the superior mesenteric artery, mainly in its proximal portion, are surrounded by a dense plexus of autonomic nerves. Thus, when these vessels are involved in the tumor, extensive perineural invasion usually prevents successful margin-negative resection.

With improved surgical techniques and new surgical technology, available in specialized centers, arterial resections in appropriately selected patients were again adopted, with better results [59]. In addition to technical advances in surgery, advances in systemic chemotherapy have also resulted in better response rates and increased survival.

The main indication for vascular resection in pancreatic tumors is based on the prospect of radical surgery with free margins in a patient with locally advanced disease, that is, in the absence of metastatic disease. Positive surgical oncological margin is associated with worse prognosis, therefore, resection of invaded peripancreatic vessels may be necessary to obtain a negative surgical margin during PD in patients with pancreatic head cancer [60]. The anatomical study and the extent of oncological involvement vascular are fundamental for clinical and surgical therapeutic planning since it is an important criterion in the definition of resectability and has significant prognostic value [61, 62]. Therefore, the resectability of pancreatic cancer is mainly determined by the degree of tumor-vascular contact, assessed on computed tomography or magnetic resonance imaging with venous contrast. The protocols for these tests must include the arterial and portal phases. Among the various criteria for assessing pancreatic cancer image resectability, those proposed by the National Comprehensive Cancer Network (NCCN) are the most widely used and serve to classify pancreatic cancer as resectable, borderline for resectability, or unresectable [63]. Currently, computed tomography with multidetectors and venous contrast (angiotomography of the abdomen) is the most accepted and used test to assess resectability. Magnetic resonance and PET-CT scans are most used for the evaluation of extra-pancreatic disease, mainly hepatica and lifonodal.

Pancreatic head tumors are considered anatomically resectable when they do not have contact with the superior mesenteric vein (SMV), portal vein (PV), superior mesenteric artery (SMA), celiac trunk (CT), and common hepatic artery (CHA) or when present unilateral contact of PV or VMS.

The anatomical factors that define borderline tumors for resection are subclassified according to SMV/PV involvement alone or in association with arterial invasion. Tumor contact with the superior mesenteric artery and/or celiac trunk below 180° is considered, without presenting stenosis or deformity; tumor contact with the common hepatic artery without tumor contact with the common hepatic artery and/or celiac trunk; and tumor contact with the superior mesenteric vein and/or portal vein, including bilateral narrowing or occlusion without extending beyond the lower border of the duodenum.

Locally advanced tumors are considered irresistible, those that present bilateral SMV/PV narrowing/occlusion, exceeding the lower border of the duodenum; tumor contact/invasion of 180o or more with SMA, CA; tumor contact/invasion of the CHA, together with tumor contact/invasion of the own hepatic artery (PHA) and/or CA; contact or tumor invasion of the aorta.

It is important to note that about 50% of tumors with suspected intravenous invasion were later evaluated histologically as presenting only inflammatory adhesions to the portal vein [51, 64, 65].

Mesenteric-Portal Vein Involvement

As previously mentioned, partial resection of the superior mesenteric and portal vein, within established limits, is accepted and encouraged for the radical resection of locally advanced pancreatic head tumors, with oncological involvement of these vessels. Despite the oncological results supporting this approach, some studies show an increase in the rate of postoperative complications such as infection, bleeding, cardiopulmonary complications, as well as, longer surgical time and the need for perioperative transfusion and mortality [66–69]. Despite this, these findings are not consensual and many authors have demonstrated similar mortality between groups with and without portal vein resection [64, 70–74].

The best modality of mesenteric-portal vein reconstruction depends on the extent of resection required to achieve free margins. There are three options: lateral resection with primary venorrhaphy [75] with or without the use of a patch; end-to-end anastomosis [76]; or graft interposition (Fig. 3.6) [77]. It is important to note that a lateral venorrhaphy should not be attempted in cases where more than 30º of the circumference is involved. In such cases, a patch or even end-to-end anastomosis should be the procedure of choice.

All types of venous reconstruction may have problems such as partial or complete thrombosis that may lead to severe complications. Therefore, care is needed to avoid hemodynamically significant stenosis of the mesenterial drainage. The splenic vein ligation can be performed however, whenever possible, it should be avoided due to the possibility of left portal hypertension.

Superior Mesenteric Artery

The most relevant arterial involvement that occurs in adenocarcinoma of the head and uncinate process of the pancreas is related to the superior mesenteric artery. Tumor detachment from adventitia of the artery is associated with local recurrence because it has an inadequate tumor margin, not allowing survival gain. Thus, arterial resection may be necessary to achieve surgical radicality; however, arterial resection remains a controversial topic in pancreatic resection. Past data suggest high morbidity and mortality when resection and reconstruction of the superior mesenteric artery are applied. Although these past data have not supported the use of this aggressive approach to pancreatic tumor, more recent data suggest benefits of arterial resection in well-selected groups [58, 78–80]. Indeed, we are also including this modality of treatment in selected patients (Fig. 3.7). Data from the past 5 years examining arterial resection for curative surgical intent for adenocarcinoma of the pancreas have changed compared to the last 20 years ago. Interestingly, many

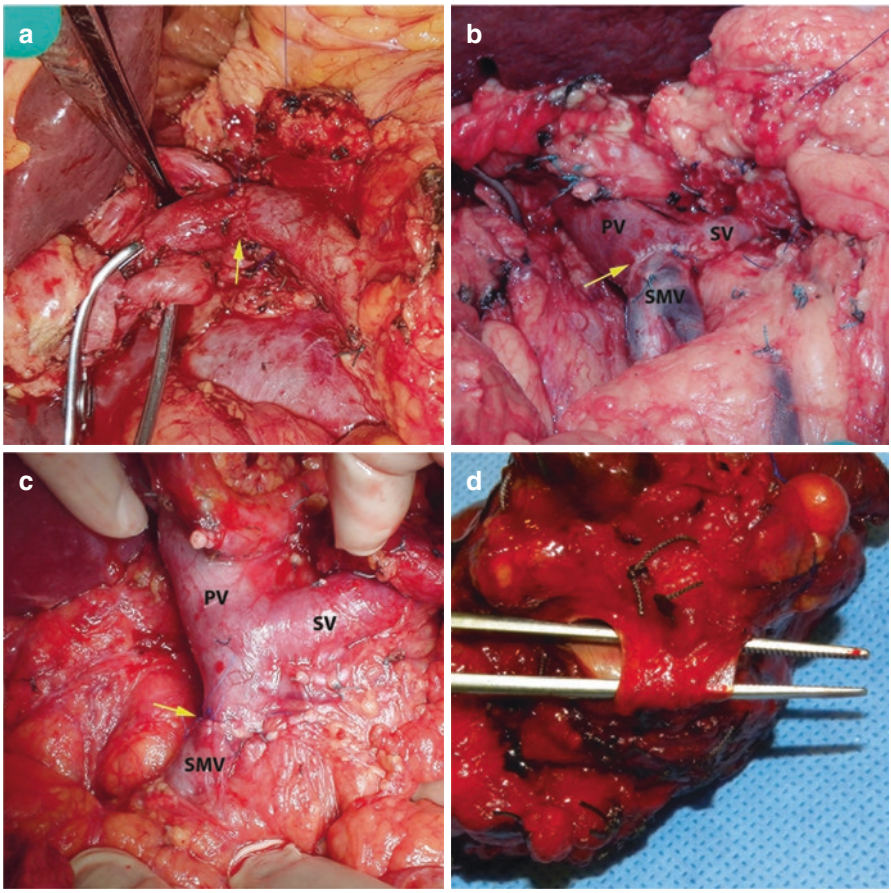

Fig. 3.6 Portal vein (PV) resection during pancreaticoduodenectomy. (**a**) Partial vein resection with primary venorrhaphy (arrow). (**b**) Resection at the level of mesenteric-splenic-portal confluence with end-to-end reconstruction (arrow). SV splenic vein. (**c**) Superior mesenteric vein (SMV) resection with end-to-end primary reconstruction (arrow). (**d**) Surgical specimen showing *en bloc* portal vein resection

centers are reporting 20% 5-year survival for patients undergoing arterial resection, which is improved over previous results, reaching, in selected cases and after neoadjuvant treatment, 53 months of median survival [81].

Hepatic Artery Involvement

When the pancreatic head tumor is in its superior border, the hepatic artery may be involved. In this situation, the hepatic arterial flow should be reestablished. This can be carried out with primary end-to-end anastomosis (Fig. 3.8) or using any available artery such as middle colic artery or splenic [82].

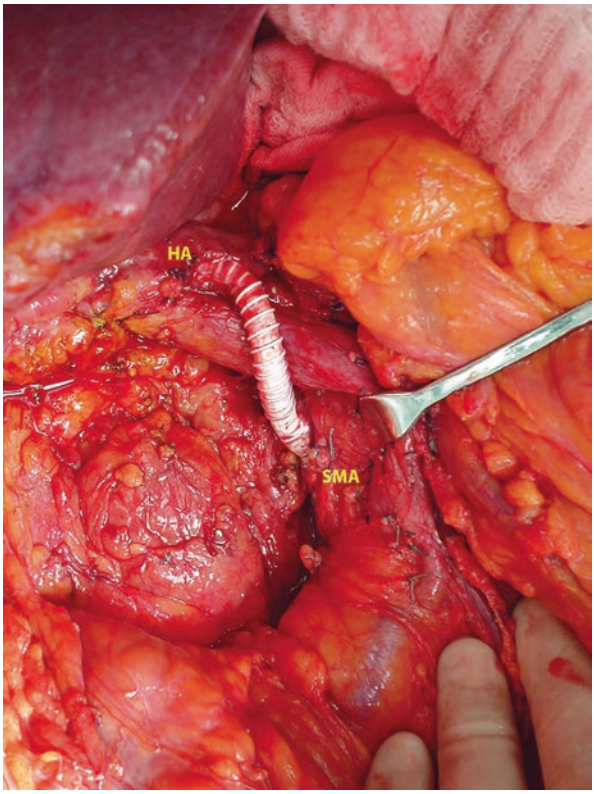

Fig. 3.7 PTFE graft interposition between hepatic artery (HA) and superior mesenteric artery (SMA)

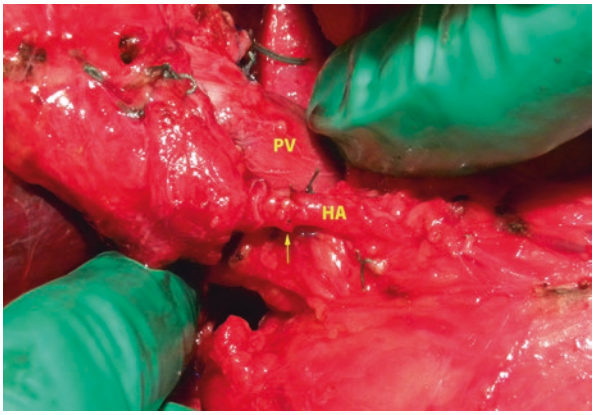

Fig. 3.8 End-to-end reconstruction (arrow) of the hepatic artery (HA); PV portal vein

3.2.2.2 Tumors Located in the Neck and Body of the Pancreas

Pancreatic tumors located distally, from the neck of the pancreas, are usually treated with distal pancreatectomies accompanied by splenectomy, without the need for reconstructions of the alimentary pathway or derivation of the pancreatic stump.

Thus, it is a less complex procedure when compared to pancreaticoduodenectomy (proximal pancreatectomy).

Venous neoplastic involvement in distal pancreatic tumors usually involves the splenic vein and/or the splenic artery, whose resection is usually feasible and free from major complications. The resection of the splenic vein, as well as the splenic artery, is routine in these tumors, both for enlarging the oncological margin and for adequate lymphadenectomy, regardless of the tumor-vascular involvement. Thus, splenectomy must also be adopted together. The main exceptions occur when there is an involvement of the splenic-mesenteric-portal venous junction and involvement of the celiac trunk.

In view of the involvement of the splenic-mesenteric-portal junction, mesenteric-portal reconstruction is necessary and can often be achieved through primary left lateral reconstruction, similar to the technique described above for proximal pancreatectomies.

A subset of patients has a locally advanced tumor, with no evidence of metastatic disease, with arterial involvement of the celiac trunk, while other major vessels such as Aorta, superior mesenteric artery, and gastroduodenal are free. According to most international guidelines, the neoplastic involvement of the celiac trunk in locally advanced pancreatic tumors is a contraindication for surgery; however, a select group of patients could benefit from a distal pancreatectomy with resection of the celiac trunk (DP-CAR) [83–85]. This procedure is similar to the procedure previously described for the resection of a locally advanced gastric tumor and was formerly known as modified Appleby. Evidence of the benefit of the indications and results of distal pancreatectomy with resection of the celiac trunk are still scarce, and controlled multicenter studies are lacking. A multicenter European study evaluated the short-term and oncological results in 68 patients undergoing this procedure, observing 16% mortality in 90 days and an average survival of 18 months [84]. Most patients who experienced early mortality (90 days) had complications in ischemic reactions related to the procedure. The 90-day mortality from distal pancreatectomy with resection of the celiac trunk is, as expected, higher in low-volume centers (18% versus 5.5%) [85]. Considering these data, the author believes that strategies should be taken to reduce the high mortality compared to the modest survival benefit, considering 4 main aspects: selection of clinically more fit patients; limit this procedure to experience centers with a high volume of pancreatic surgery; oncological disease with more favorable biological behavior, which presents at least stability through adjuvant therapy, to avoid futile surgeries; and research into strategies to reduce the physiological and ischemic impact caused by resection of the celiac axis [85].

Conceptually, after distal pancreatectomy with resection of the celiac trunk (modified Appleby), the liver maintains its arterial perfusion through a retrograde flow from the superior mesenteric artery through the arch of the pancreas head to the gastroduodenal artery. Several modifications have been proposed in order to increase safety and improve the results of this procedure: preoperative embolization of the hepatic artery [86, 87]; embolization of the left gastric artery [88]; preservation of

the left gastric artery [89, 90]; reconstruction of the left gastric artery by the middle colic artery [91]; and reconstruction of the hepatic artery with graft interposition [92, 93]. Despite these technical proposals, mortality remains high in 90 days after DP-CAR, reaching up to 17% [84, 85, 94, 95]. The surgical treatment of pancreatic adenocarcinoma with involvement of the celiac trunk should be understood as an exceptional conduct and applied to selected patients, with adequate clinical conditions, in the absence of distant disease and in tumors that present favorable biological behavior. Neoadjuvant chemotherapy should always be considered, both for local tumor reduction and to exclude patients with rapid tumor progression in more aggressive tumors. The progression of local or distant disease during neoadjuvant treatment avoids a complex surgery with high morbidity and mortality that would not bring oncological benefit. In preparation for the resection of the celiac trunk, angiographic arterial embolization with springs from the left gastric and common hepatic arteries can be considered, with the purpose of developing collateral arterial compensation networks for the liver and stomach. The presence of hepatic artery from the superior mesenteric favors the resection of the celiac trunk without the need for reconstruction.

Celiac Trunk Involvement: Establishment of Hepatic Artery Flow

Whenever celiac trunk needs to be divided, hepatic arterial flow should be assured. Usually, liver arterial perfusion is maintained through a retrograde flow from the superior mesenteric artery through the gastroduodenal artery. However, when this flow is inadequate, hepatic artery flow should be reestablished. There are several techniques to accomplish it. A direct end-to-end anastomosis can be performed between hepatic artery and the stump of the celiac trunk (Fig. 3.9) or graft can be used between hepatic artery and another arterial vessel (Fig. 3.10) [92].

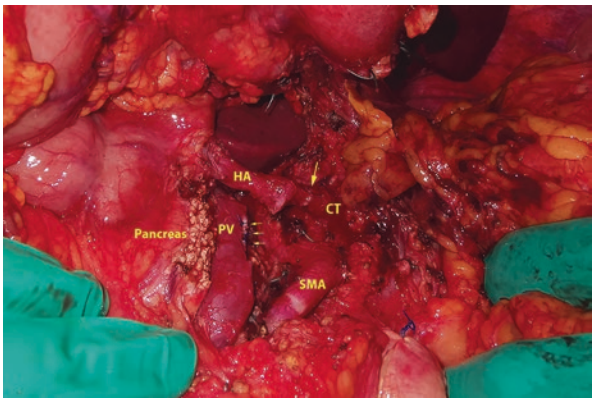

Fig. 3.9 End-to-end (arrow) reestablishment of the hepatic artery (HA), using stump of the celiac trunk (CT). Portal vein (PV) was partially resected with lateral venorrhaphy. SMA superior mesenteric artery

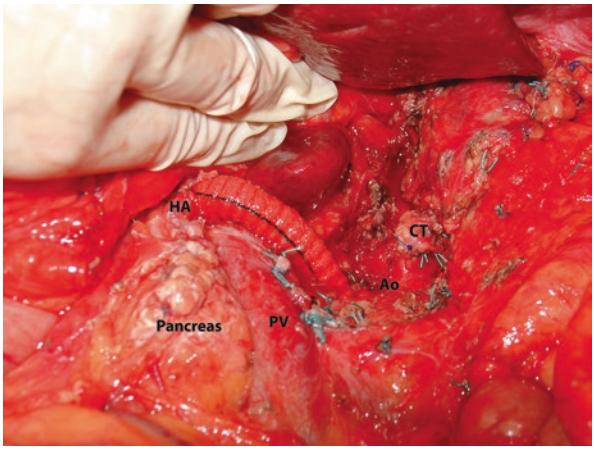

Fig. 3.10 Reestablishment of the hepatic artery (HA) flow using PTFE graft interposition from aorta (Ao). PV portal vein, CT celiac trunk

3.2.3 Liver

3.2.3.1 Hilar Cholangiocarcinoma

Hilar cholangiocarcinoma or Klatskin tumor is a carcinoma that originates in the bile ducts and affects the main right and/or left and/or common hepatic ducts. These tumors can be classified according to the site of biliary involvement according to the Bismuth-Corlette classification in types I, II, IIIa, IIIb, and IV (Fig. 3.11) [96]. The purpose of this classification is to direct surgical treatment (Table 3.2).

Due to their location in the hepatic hilar or peri-hilar region, these tumors are closely related to the main hepatic vascular structures (hepatic artery and portal vein). Thus, the Bismuth classification, although widely used today, is simplistic in relation to the proposal for surgical treatment, as it does not consider vascular involvement and oncological extension of the disease. Hilar cholangiocarcinoma staging classification according to AJCC 8th edition considers vascular involvement (Table 3.3).

Surgical resection is the only therapeutic modality that allows a chance of cure; however, it is usually a challenging operation, even in initial tumors. Surgery must always be performed with a radical purpose (R0) and, for this, the preoperative surgical planning must be careful.

In most hilar cholangiocarcinomas, the tumor infiltrates and proliferates along the extrahepatic bile duct, which is thickened in most cases. The formation of liver mass can be minimal, with preferential intraductal growth, until the formation of a large tumor mass. The hepatic extension usually presents an infiltrative characteristic, often making it difficult to clearly define margins in imaging exams. Another characteristic of these neoplasms is the frequent lymphatic and perineural involvement. Therefore, the preoperative evaluation must consider the longitudinal and radial extension of the neoplasms, the presence of lymph node involvement, vascular infiltration, and possible anatomical variations.

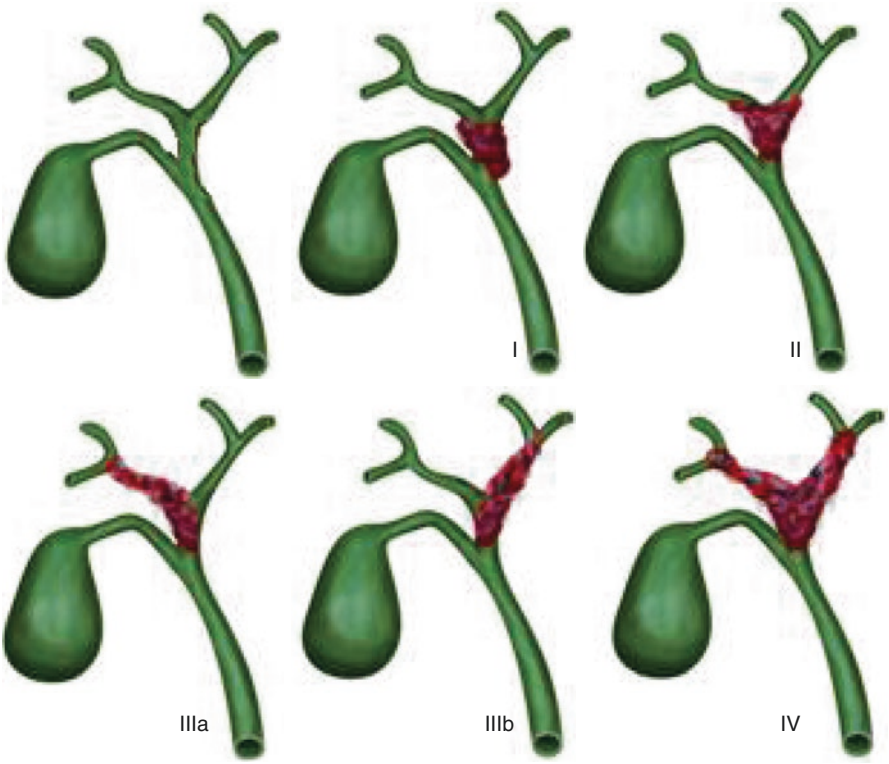

Fig. 3.11 Bismuth-Corlette classification of hilar cholangiocarcinoma [65]

Table 3.2 Bismuth-Corlette Classification

Type I: limited to the common hepatic duct, below the level of the confluence of the right and left hepatic ducts
Type II: involves the confluence of the right and left hepatic ducts
Type IIIa: type II and extends to the bifurcation of the right hepatic duct
Type IIIb: type II and extends to the bifurcation of the left hepatic duct
Type IV: extending to the bifurcations of both right and left hepatic ducts

It is the oncological characteristics of hilar cholangiocarcinoma that determine the basis for surgical treatment. These characteristics imply excision of the biliary tract, usually associated with liver resection including the caudate lobe, and complete regional lymphadenectomy, always looking for free margins. Bile duct frozen-section biopsy is mandatory to check negative margin. Thus, surgical resection should aim at neoplastic resection with free oncological margins, allowing maintenance of the liver parenchyma in sufficient volume and with adequate arterial perfusion and portal so that the patient does not develop postoperative failure. The biliary tract reconstruction is done with Roux-en-Y hepatico-jejunostomy.

Table 3.3 Hilar cholangiocarcinoma staging classification according to AJCC eighth edition

Primary tumor (pT)
TX: primary tumor cannot be assessed
T0: no evidence of primary tumor
Tis: carcinoma in situ/high grade dysplasia
T1: tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2: tumor invades beyond the wall of the bile duct to surrounding adipose tissue or tumor invades adjacent hepatic parenchyma
T2a: tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b: tumor invades adjacent hepatic parenchyma
T3: tumor invades unilateral branches of the portal vein or hepatic artery
T4: tumor invades the main portal vein or its branches bilaterally or the common hepatic artery; or unilateral second-order biliary radicles with contralateral portal vein or hepatic artery involvement
Regional lymph nodes (pN)
NX: regional lymph nodes cannot be assessed
N0: no regional lymph node metastasis
N1: one to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct (choledochal), hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes
N2: four or more positive lymph nodes from the sites described for N1
Notes: regional lymph nodes are listed above, in the N1 criteria
Distant metastasis (pM)
M0: no distant metastasis
M1: distant metastasis
Stage grouping
Stage 0: Tis N0 M0
Stage I: T1 N0 M0
Stage II: T2a-b N0 M0
Stage IIIA: T3 N0 M0
Stage IIIB: T4 N0 M0
Stage IIIC: any T N1 M0
Stage IVA: any T N2 M0
Stage IVB: any T any N M1

The close relationship and possible neoplastic invasion of the portal vein trunk and/or the contralateral arterial and portal branch may indicate resection and vascular reconstruction to obtain free margins with maintenance of the perfusion of the contralateral hepatic remnant.

Studies have shown that exclusive resection of the extrahepatic biliary tract has been associated with an increased risk of positive surgical margins and inadequate lymphadenectomy. Thus, hepatectomy should be considered the standard treatment for hilar cholangiocarcinoma and resection of the portal vein should be indicated when necessary for radical resection. Expanded hepatectomy combined with resection of the extrahepatic biliary tract, lymphadenectomy, and resection of the

contralateral portal vein with primary reconstruction may offer long-term survival in some patients with advanced hilar cholangiocarcinoma [97].

Imaging exams are essential for assessing resectability. The resectability decision must be made before the surgery, as it is unlikely that the surgeon will have the perception of unresectability, or even the impossibility of surgical radicality, before the extrahepatic bile duct section is performed, which is an irreversible step in the surgery. Currently, MRI and computerized tomography exams with venous contrast allow an adequate assessment of the extent of the disease in the bile duct and vascular involvement. Invasion of the portal vein or hepatic artery are important findings, as they can be an indicator of unresectability.

Computed tomography is an excellent method for assessing oncological extension, the relationship with anatomical structures, and surgical planning. This method provides an adequate assessment of relationships with vascular structures and the neoplastic involvement of vessels in the hepatic hilar region. Magnetic resonance cholangiopancreatography imaging is also useful to evaluate the intrahepatic biliary tree. Staging may be completed with PET/CT whenever hidden metastases must be ruled out. Laparoscopy is another method to evaluate peritoneal disease and is usually performed immediately before surgery. Small peritoneal implants contraindicate resection and are often not diagnosed by diagnostic imaging methods.

The main contraindications for surgical treatment of hilar cholangiocarcinoma are distant metastases, including non-regional lymph nodes; liver metastases; neoplastic involvement to second-order biliary branches bilaterally; invasion of the hepatic artery trunk and/or hepatic arteries bilaterally and/or the right and left portal vein and/or portal vein; invasion of the hepatic artery or portal vein with biliary involvement up to second-order contralateral branches; and invasion of the hepatic artery or portal vein with contralateral hepatic atrophy. In well-selected patients, vascular resection, with primary reconstruction, can be considered to achieve surgical radicality.

Decompressive biliary drainage in the preoperative period can be indicated in the face of obstructive jaundice; however, several points are controversial and cause for debate. The need for preoperative biliary drainage is not consensual, but in hilar tumors that require massive liver resection, drainage of the future liver remnant is widely accepted. This can be accomplished by either endoscopic or percutaneous drainage [98]. The main indications for biliary drainage in patients who are candidates for resection are treatment of cholangitis and prediction of extensive hepatectomy with perspective of residual hepatic volume less than 40%, in patients with significant cholestasis (bilirubin greater than 10 mg/dl) for a prolonged period (>2–3 weeks). In these situations, the side to be drained should preferably include the future remaining liver, as prolonged cholestasis is unfavorable to liver regeneration.

Preoperative embolization of the hepatic lobe portal vein to be resected is used to induce compensatory hepatic hypertrophy of the future liver remnant in patients with an insufficient volume. As previously mentioned, surgical resection of hilar cholangiocarcinoma must include negative margins and, for this, extensive hepatectomies are often necessary. Preoperative portal vein embolization may allow

resection with a negative margin in a patient who would be considered unresectable due to concerns about insufficient residual liver volume in the postoperative period. The concern with the residual liver volume is even more important in the presence of cholestasis.

For Bismuth 1 type tumors, surgical procedure includes *en bloc* resection of the extrahepatic bile ducts and gallbladder with free bile margins, along with regional lymphadenectomy, followed by biliary reconstruction with Roux-en-Y hepaticojejunostomy. In types 2, 3, and 4 lesions, the caudate branches are frequently involved, and for this reason, caudate lobe resection is to be included in surgical patients. For the surgical treatment of type 3 tumors, larger liver resections on the right or left are necessary to achieve a free oncological margin. Type 3 and type 4 tumors may be subject to potentially curative resection in centers with experience in these procedures and in selected patients. Complex techniques, such as extensive liver resections and *en bloc* vascular resections, therefore, should not be an absolute contraindication for the treatment of hilar cholangiocarcinoma. To obtain free margins, avoiding tumor exposure, extensive liver resection, with principle portal resection, followed by primary venous reconstruction, was advocated by some authors (Fig. 3.12) [99, 100].

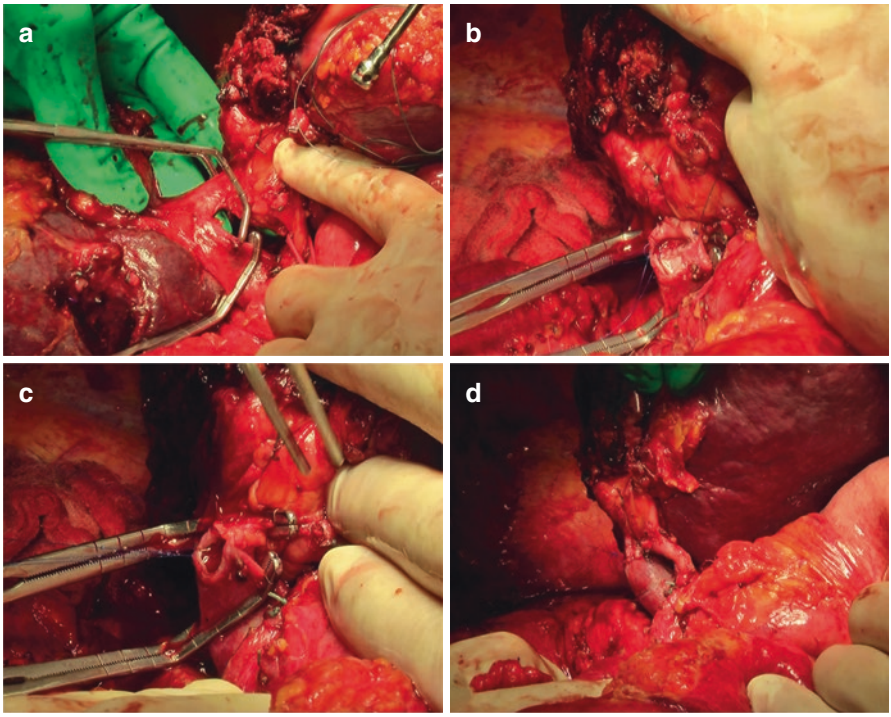

Fig. 3.12 Portal vein (PV) resection and reconstruction during right trisectionectomy for hilar cholangiocarcinoma. No-touch technique. (Neuhaus et al. [68]). (**a**) Proximal (main trunk) and distal (left) portal vein clamping. (**b**) End-to-end anastomosis between main trunk and left portal vein. Posterior layer with running suture. (**c**) End-to-end anastomosis between main trunk and left portal vein. Anterior layer with running suture. (**d**) Final view after portal vein reconstruction

Types 3 and 4 tumors are susceptible to potentially curative resection in centers with experience in these procedures. Aggressive techniques, such as resection of multiple liver segments with resection of portal veins (hilar block resection) to obtain negative margins, should not be a contraindication for resection.

Tumor involvement, requiring resection and vascular reconstruction, was considered a contraindication for the surgical treatment of hilar cholangiocarcinoma. However, technical and perioperative care improvements allowed for more extensive and complex surgeries, associated with vascular resections, with acceptable results. Possible resections with vascular reconstruction in hilar cholangiocarcinoma include resection of the portal vein, resection of the hepatic artery, and combined resection of the portal vein and hepatic artery. The resection of the portal vein with primary reconstruction is adopted in some centers to obtain surgical radicality and portal venous revascularization of the hepatic remnant [99, 100]. Some authors defend the principle resection of the portal vein with primary reconstruction to avoid portal dissection with possible tumor exposure, what became known as the "no-touch technique" [99–104].

3.2.3.2 Portal Vein Involvement

When resection of the portal vein responsible for the perfusion of the hepatic remnant is necessary, end-to-end reconstruction is often possible (Fig. 3.12). This anastomosis must remain wide and tension-free. As the hepato-duodenal ligament lymphadenectomy is performed routinely, the portal vein remains largely dissected from the pancreatic plane, allowing a tension-free anastomosis. The use of a patch or graft interposition may be necessary when tension-free anastomosis cannot be achieved.

3.2.3.3 Hepatic Artery Involvement

Due to the usual anatomical situation of the right and left hepatic arteries, cholangiocarcinomas with preferential extension on the right (Bismuth 3A) rarely lead to involvement of the left hepatic artery. Thus, when hepatectomies enlarged on the right are proposed, neoplastic involvement of the left hepatic artery is uncommon. However, when an enlarged left hepatectomy is envisaged, the right hepatic artery may be involved by tumor [105]. It is necessary that the distal stump of the hepatic artery is suitable for reconstruction. Failure to obtain adequate arterial vascularization due to intrahepatic stenosis or thrombosis leads to critical complications, especially infectious, with the formation of postoperative liver abscesses and liver necrosis [106]. The preferred mode of arterial reconstruction is through end-to-end anastomosis (Fig. 3.8) between the proper hepatic artery and the right hepatic artery, with alternatives being the use of the splenic, gastroduodenal, left gastric artery, or graft.

3.3 Colorectal Neoplasia

Overall, colorectal cancer (CRC) ranks third in terms of incidence, but second in mortality with 881,000 deaths estimated in 2018 [107, 108]. In Brazil, between 2020 and 2022, about 40,000 people will die from CRC [109]. Incidence, hospitalizations, and mortality are unfortunately increasing [110].

At the Institute of Cancer of the Hospital das Clínicas/University of São Paulo Medical School-ICESP/HCFMUSP, between 2008 and 2018, among the 103,000 patients treated, 25% had neoplasms of the digestive tract, of which 45% were CRC. These patients generated 260,000 consultations and about 8500 colorectal surgeries in 10 years.

3.3.1 Pathogenesis

The colon and rectum have endodermal origin with simple columnar epithelium lining; consequently adenocarcinoma contributes to more than 96% of colorectal neoplasia, the histopathological type in which treatment this chapter focuses on [111].

The oncogenesis of colorectal adenocarcinoma is related to three main pathways, where the sporadic adenoma-adenocarcinoma sequence is the most frequent [112–116]. Age above 45 years old, personal or family history of CRC, alcohol abuse, smoking, inflammatory bowel disease, and radiotherapy history are the main factors related to CRC [116, 117].

3.3.2 Staging and Therapeutic Planning

The established Tumor Node Metastases (TNM) staging system is also used for CRC [118]. In addition to providing prognosis, staging guides treatment.

CRC staging is performed with the following steps: physical and proctological examination are individually complemented with colonoscopy and computed tomography (CT) scan of the chest, abdomen, and pelvis. For rectal cancer, magnetic resonance imaging (MRI) of the pelvis is highly recommended for adequate locoregional staging [119]. The serum human carcinoembryonic antigen (CEA) is acquired for long-term follow-up purposes [120].

A proper and detailed staging predicts the risks of lymph node metastasis, distant metastasis, local recurrence, and survival. Specifically, rectal adenocarcinoma is classified between low and high risk of lymph node metastasis; and between good and poor prognosis for survival, local recurrence, and metastases [121–123]. Treatment is indicated according to severity. For lower stages, less aggressive

treatments can be offered; while for more advanced stages, more complex treatments are usually necessary preceded or not by chemoradiotherapy (CRT) [124–128].

CRT before surgery is recommended in two situations: for distal rectal lesions at high risk of abdomino-perineal resection or in cases of poor prognosis with the main objective of decreasing local recurrence [129]. More recent CRT protocols intensifying the chemotherapy regimen show a tendency to offer a higher chance of cure [130]. CRT can also be indicated for palliative purposes in more advanced cases (e.g., unresectable distant metastasis). In dedicated cancer centers, these cases are discussed in multidisciplinary meetings with Radiology, Radiotherapy, Oncology, and Surgery with the aim of offering widely the best treatment to these fragile patients [131].

The degree of disease invasion in the colorectal wall (T stage) and – in more advanced cases – of adjacent organs or structures (T4b) can be predicted with high accuracy in preoperative staging [127]. This prediction is correct in more than half of the cases [132, 133]. Cure is related to surgical resection with free margins (R0) and monobloc resected organs or part of them (28). Although surgery is the only method that allows cure, it is associated with significant morbidity and mortality and postoperative dysfunctions [134–136].

To minimize risk, it is recommended: (1) knowledge of the particularities of colorectal neoplasms according to their topography; (2) thorough preoperative surgical planning, multidisciplinary with radiology, and surgical specialties such as: urology, gynecology, plastic surgery, orthopedics, and vascular surgery; and (3) evaluation of comorbidities, surgical risk, and possible need for pre-rehabilitation for more complex cases.

3.3.3 Right, Left, and Right Colon Adenocarcinoma: Surgical Treatment and Vascular Complications

Colorectal anatomy is determined by its embryological origin. Similarly, the territory of lymph node drainage obeys the principle of embryology.

The right colon – from the midgut – has its irrigation and lymphatic drainages related to superior mesenteric artery (SMA). The left colon – from the hindgut – has irrigation and drainage related to inferior mesenteric artery (IMA).

The rectum is divided into proximal and distal. The first also originates from the hindgut, thus follows the left colon in irrigation and drainage. Its most distal portion originates in the tailgut with irrigation and drainage related to pudendal vessels [137].

Adenocarcinoma of the right colon – intraperitoneal, is related to vital vascular structures: the SMA and mesenteric vein (SMV). Its inadvertent or scheduled lesion is associated with high morbidity and mortality and should always be treated immediately by a specialized surgical team used to vascular reconstructions [137, 138].

The recently described total excision of the mesocolon (TMcE) involves greater dissection of SMA and SMV with the objective of extended lymphadenectomy – D3 [139]. Its precise definition and oncological value are still discussed [140–142]. It is recommended that the dissection of vital vessels such as those that irrigate and drain the entire small intestine involve teams trained in vascular surgery. The vascular surgeon, in turn, should be prepared for urgent call to repair any lesions of these important vessels since TMcE is increasingly performed.

The neoplasm of the left colon is related to inferior mesenteric artery (IMA) and vein (IMV). Because of oncological and/or tactical necessity, these vessels are ligated in their origin [137]. When treated with gentle dissection, they are rarely related to major complications. The advent of laparoscopic/robotic surgery with the concurrent use of other forms of hemostasis (harmonic scalpel, vascular sealers with or without association of metal or resin clips) requires the colorectal surgeon to master its correct use. Anecdotal severe vascular lesions in this laparoscopic surgical step were related to the inadequate use of energy devices. Neoplasm of the proximal/high rectum and rectosigmoid junction is dealt similarly to the neoplasm of the left colon.

Extraperitoneal rectal adenocarcinoma is surgically treated by total mesorectal excision (TME). This treatment is often preceded by neoadjuvant chemoradiotherapy. The relationship with other organs, nerves, and vessels, in addition to the confinement in a non-distensible bone cavity, makes surgical treatment of rectal neoplasia – especially after CRT – more difficult [143].

TME requires traction/counter-traction technique which, under direct or laparoscopic vision, uses dissection, cutting, and energy, to remove the rectum of the pelvis in a virtually bloodless manner [144]. Anatomical landmarks that show the plan between the mesorectal fascia/parietal endopelvic fascia are the pelvic autonomic nerves: superior hypogastric plexus, right and left hypogastric nerves, and the right and left lower hypogastric plexus/neurovascular bundle. TME offers free circumferential oncological margins. Accomplishing appropriate distal margin free of disease and high ligation of the AMI in its origin, TME resects the entire territory of lymph node drainage together with the rectal adenocarcinoma. TME is the surgical treatment of choice for adenocarcinoma of the rectum by the association of the best oncological resection with two other important factors: nerve preservation and the reduction of presacral vessels injury [145]. This way it meets the modern concept of the oncological surgery: resection of the tumor together with its lymphatic drainage, with minimal dysfunction [146].

Operating in the surgical plan described by the TME, severe vascular lesions are rare. The lesions of the presacral venous plexus – which carry high morbidity and mortality – are mostly related to manual blunt dissection of the retrorectal space [147]. These lesions are increasingly rare with TME. In case of lesions of the presacral vessels, several are the repair techniques ranging from tacks specially designated for this as the packaging of the pelvis with compresses and programmed re-intervention [148, 149].

Vascular problems are usually related to locally advanced T4b lesions, which require surgery beyond the regular TME planes to acquire neoplasia-free surgical

margin. In these cases, vascular lesions are more frequent, and its control requires surgical skill, a good field illumination, and surgical material suitable by the location on the side wall of a narrow bone cavity. The previous radiological knowledge of the possible involvement of larger vascular structures such as internal veins and iliac arteries or their tributaries makes necessary the presence of vascular surgeons in the surgical team.

Lateral internal iliac lymphadenectomy is also increasingly performed. Although still controversial whether it should be performed routinely or according to the result of restaging after CRT with MRI, usually this treatment occurs in an area already treated with radiotherapy [150, 151]. This irradiated tissue increases the difficulty of lymphadenectomy, where the planes are more adhered. Dissection of the internal iliac vessels and repair of any lesions should consider this characteristic. In addition, adjuvant radiotherapy treatment may be indicated after surgery in cases where surgery may have presented compromised margins. In these cases, the type of repair of any lesions should also be individualized.

Intraoperative radiotherapy is not performed in our institution; however, if scheduled, any vascular repairs should consider this possibility in the treatment of locally advanced tumors.

3.3.4 Types of Tumor Most Frequently Associated with Vascular Complications

Vascular intraoperative complications are mostly related to advanced stages tumors – and not its histopathology. Whether by local invasion of vascular structures, lymph node spreading, need for chemotherapy, radiotherapy, or both, in a neoadjuvant or palliative manner, this advanced stage of disease is the most challenging condition. The advanced progression of the disease may present with hemorrhagic or ischemic symptomatology.

3.3.5 Vascular Complication Related from Direct Invasion of the Tumor

Colorectal neoplasms rarely cause direct invasion of vascular structures with acute cases of severe life-threatening bleeding or ischemia. However, in the face of these advanced cases, staging should always be considered before therapeutic decision. The possibility of metastatic disease with a poor prognosis requires palliative oncological treatment, thus minimally invasive treatments (e.g., endovascular or radio intervention) – although not curative – are indicated because they offer control of hemorrhagic or ischemic symptomatology, without intraoperative risks or postoperative morbidity and mortality. Surgery is reserved for few cases, considering

principles of bioethics, with a multidisciplinary discussion about prognosis, once clinical conservative control is no longer possible.

3.3.6 Vascular Complication Secondary from the Treatment of Colorectal Adenocarcinoma

3.3.6.1 Exclusive Nonoperative Treatment

Chemotherapy, radiotherapy, or chemoradiotherapy exclusively are indicated in cases where the patient refuses radical surgical treatment or in cases where surgical treatment cannot be performed – either due to lack of clinical conditions of the patient or advanced disease with a reserved prognosis [152]. Thus, vascular complications related to this nonsurgical treatment will not be contemplated in this chapter.

3.3.6.2 Chemoradiotherapy Treatment Followed By Surgery

Neoadjuvant treatment is recommended for patients with colorectal neoplasia with a worse prognosis to preoperative staging or due to proximity to the anal sphincter [122]. Neoadjuvant treatment offers oncological advantages – such as decreased tumor volume, local staging of advanced neoplasia, and increased disease-free pathological margin [130, 153–159]. For extraperitoneal rectum neoplasms, curative treatment today involves neoadjuvant chemoradiotherapy followed by surgery [159]. The same is not the case for intraperitoneal rectum neoplasms or colonic neoplasms.

There are locally even more advanced T4b tumors, described above – with invasion of adjacent organs, sometimes perforation and even pelvic sepsis. Whenever possible, neoadjuvant treatment is indicated as mentioned above. In this situation, the usual TME surgical planes are compromised [134]. Therefore, if the intention is to cure, surgery beyond TME planes is necessary [160]. In this context, the proximity of internal iliac vessels and consequently the risk of vascular lesions is increased. Preoperative planning with multidisciplinary teams with precise radiological determination of possible sites of deep invasion of adjacent organs and structures is recommended. Eventually, even increased targeted radiotherapy treatment to places where a small margin is predicted can be planned, even with radical surgery.

After detailed local staging and individualized QTRT, a multidisciplinary surgical team composed of colorectal surgery, urology, gynecology, vascular, plastic, and orthopedic surgery is established. This avoids last-minute calls and allows planning of surgical intervention as a whole – including access options, competing moments, and specific materials – reducing the possibility of intraoperative complications.

This planning involves the preparation and adequacy of the clinical conditions of patients with nutritional corrections, blood crisis, and anemia. Pre-rehabilitation is increasingly recommended for these patients.

Frank conversation with the patient and his/her family members, explaining about the possible risks and associated dysfunctions, including other therapeutic options, is mandatory.

3.4 Future Perspectives

The development and efficiency of new technologies in the areas of preoperative imaging, with the possibility of virtual reconstruction and printing of 3D physical models of the tumor with its anatomy/irrigation, the knowledge and visualization of its anatomical relationships with noble vascular structures, and other organs for an even clearer, real, and individualized preoperative planning, are studied and awaited.

Similarly, image-guided surgery with the possibility of fusion on the same screen, in real time, of images acquired by radiology in the preoperative period and those of the surgical field is also intensely studied and equally expected. Other forms of intraoperative radiotherapy, robotic technology with hemostasis and more precise dissection, and the use of contrasts that show the complete vascularization of the segments treated in real time are already realities that help us in the treatment of colorectal neoplasia that should reduce intraoperative and postoperative vascular complications in the near future.

Editor's Comments

Visceral vascular reconstruction may be necessary for patients undergoing resections of intra-abdominal neoplasms with the intention of cure. In the venous segment, the restoration and patency of the superior-portal mesenteric axis are indisputable.

In this territory, after en bloc resection, restoration can be done through primary end-to-end anastomosis, primary raffia, venoplasty with patch placement, and graft interposition. Biological substitutes have the advantage of greater biocompatibility, therefore, in theory, with lower risks of infection and thrombosis. These substitutes include bovine pericardium, allografts, left renal vein, internal jugular vein, external iliac vein, femoral vein, saphenous vein, and parietal peritoneum. Among the synthetic substitutes, the most used is the PTFE prosthesis, which has the advantages of varying diameters and lengths and immediate availability.

The meta-analysis by Song W et al. included 257 patients with graft reconstructions and 570 patients without grafts (i.e., end-to-end anastomosis or lateral wedge), all undergoing resection of pancreatic neoplasms. In the long term ($\geq$6 months), the graft group was associated with a higher rate of thrombosis, and the sub-analysis according to the type of graft used (autologous vein or prosthesis) showed a higher incidence of thrombosis for the autologous substitute when compared to the group without a graft [161].

The parietal peritoneum can be used as a substitute in this territory, both in the form of a patch and a tubular graft. The main advantages are biocompatibility, easy to obtain, versatility in the defect's size to be repaired, and dispensing with other incisions to obtain autologous grafts.

In the systematic review by Lapergola et al. [162], this substitute was used in 94 patients, with 66 due to malignant neoplasms (70.2%). The patch was used in 70 patients and the tubular graft in 24 patients. The sites for obtaining the peritoneum were the posterior sheath of the rectus abdominis muscle, diaphragm, sickle-cell, prerenal, and subcostal ligament. The affected veins were: superior-port mesenteric (45 patients, 47.9%), inferior vena cava (40 patients, 42.5%), hepatic (8 patients, 8.5%), and left portal branch (1 patient, 1%).

The postoperative mortality rate was 5.3% (5 patients). The follow-up time reported in 85 patients (90.4%) varied between 7 days and 47 months. Reconstruction was patent and unchanged in 80 patients (94.1%) and with stenosis in 5 (5.9%), with no difference in patency between the patch group and the tubular group.

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Chapter 4
Urology

Arie Carneiro and Alan Roger Gomes Barbosa

4.1 Frequency of Urological Tumors

Urological tumors are a diverse group of oncological diseases which are relatively frequent among all general tumors. Prostate cancer is the second most frequent diagnosed cancer in men, leading to 15% of all cancers diagnosed [1], being by far the type that most collaborate for the frequency of urological tumors in population.

Other important tumors in frequency are bladder cancer, the seventh most commonly diagnosed in men and the eleventh considering both genders [2], and adrenal tumors, which affect 3–10% of general population, the majority of them being benign nonfunctional adrenocortical adenomas and the minority adrenocortical carcinomas [3].

Other less prevalent, but not less important, due to their morbidity and lethality are renal cell cancer, representing 2–3% of all cancers [4], testicular cancer, which includes 1% of all male tumors and 5% of urological tumors [5], and penile cancer, which is uncommon in developed countries, but in some parts of the world, such as, South America, South East Asia, and Africa, it represents 1–2% of malignant tumors in men [6].

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4.2 Urological Tumors Related to Vascular Complications

4.2.1 Kidney Cancer

4.2.1.1 Diagnosis

Patients with kidney tumors frequently present asymptomatic or with unspecified symptoms. Hematuria and flank pain can be present and just in fewer cases the classical triad with hematuria, flank pain, and flank mass can be found. In case of a metastatic disease, bone pain, adenopathy, and pulmonary symptoms are added as manifestations.

Physical examination is of fundamental importance as well as a complete medical history. Laboratory evaluations necessary are blood cell account, serum corrected calcium, kidney function, liver function, and urinalysis.

The frequency of incidentally diagnosed renal cell cancer has increased while imaging methods have been accessible worldwide. CT of abdomen and chest X-ray are the primary exams necessary for first evaluation. Chest CT is more accurate than X-ray to identify metastatic lung disease. In cases of allergy or moderate renal insufficiency, MRI of abdomen could be used in place of CT. Specially to evaluate vena cava condition, MRI has particular importance. Bone scan is necessary when alkaline phosphatase is elevated or when the patient presents bone pain, as well as CT or MRI of the brain in case of neurological signs and symptoms.

Needle biopsy is not generally necessary. The indications for biopsy remain in active surveillance, before ablation therapies or in cases of metastatic disease for guiding systemic treatment or suspicion of lymphoma.

PET CT or MRI is not standard method of diagnosis for renal cell carcinoma [4, 7, 8].

4.2.1.2 Staging

The classification is based on Tumor Node Metastasis (TNM) system (Table 4.1).

Specially for renal cancer, specific anatomic classification is important for decision of most appropriate treatment. Several classification systems are available such as Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, the R.E.N.A.L. nephrometry score, the C-index, and others.

4.2.1.3 Prognosis

The prognostic evaluation is based on anatomical factors – tumor size, venous invasion, extrarenal invasion, adrenal involvement, lymph node disease, and metastasis; histological factors – tumor grade, RCC subtype, and some findings such as sarcomatoid features, microvascular invasion, necrosis, and invasion of the collecting

Table 4.1 TNM system for kidney cancer

T – Primary tumor		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1	Tumor ≤7 cm or less in greatest dimension, limited to the kidney	
	T1a	Tumor ≤4 cm or less
	T1b	Tumor >4 cm but ≤7 cm
T2	Tumor >7 cm in greatest dimension, limited to the kidney	
	T2a	Tumor >7 cm but ≤10 cm
	T2b	Tumors >10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia	
	T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia
	T3b	Tumor grossly extends into the vena cava below diaphragm
	T3c	Tumor grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)	
N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in regional lymph node(s)	
M – Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	

Extracted from European Association of Urology Guidelines 2022 edition (https://uroweb.org/guidelines/prostatecancer)

system; clinical factors – performance status, symptoms related to disease, and metastasis; and molecular factors – expression of the BAP1 and PBRM1 genes and others needing external validation.

In general, prognosis is worse in higher stages of TNM and with higher grades. The overall survival in 5 years for all types of Renal Cell Carcinoma is 49%. The cancer-specific survival in 5 years of surgically treated RCC for each type is 71% for clear cell, 91% for papillary, and 88% for chromophobe [8].

4.2.1.4 Surgical Treatment

Surgical treatment is the first-line therapy to achieve cure in localized renal cell cancer. For T1 tumors, partial nephrectomy is the preferred technique, with oncological outcome equal to radical nephrectomy and with the advantage of saving nephrons. For other tumors where partial nephrectomy is not an option, radical nephrectomy is indicated. Both surgeries can be performed by open access,

laparoscopic surgery, and robotic surgery. Laparoscopic radical nephrectomy has lower morbidity than open nephrectomy. Adrenalectomy associated with the nephrectomy is not indicated if there is no involvement of the gland. Lymphadenectomy is not indicated for localized disease without lymph node involvement, being reserved for cases with adverse clinical features (large diameter of the tumor for example). If enlarged lymph nodes are present, it does not prove the survival benefit of lymphadenectomy, but it helps in staging the disease.

It is important to consider that active surveillance is an option for T1 tumors due to its low growth and rare progression to metastatic disease. For patients with comorbidities and elderly who are not fit for surgery and local therapy is indicated, cryoablation and radiofrequency ablation are other options for treatment.

In case of metastatic disease, cytoreductive nephrectomy is an option in selected patients with good performance status and when oligometastases can be treated.

4.2.1.5 Systemic Treatment

Adjuvant therapy in localized kidney cancer does not add benefit in survival after nephrectomy, and for this reason, is not indicated in this case. The main importance of systemic treatment in Renal Cell Cancer consists in cases of metastatic disease. Cytoreductive nephrectomy followed by sunitinib is non-inferior to sunitinib alone in metastatic cases. Systemic treatment can be performed associated with nephrectomy or alone, depending on the performance status of the patient and tumor conditions. In resume, for favorable-risk disease patients (by IMDC criteria), the first-line systemic therapy for metastatic renal cancer is sunitinib or pazopanib, and for intermediate and poor-risk patients, ipilimumab or nivolumab (with cabozantinib, sunitinib as other options, with no strong recommendations, and pazopanib an option only for intermediate risk) [8].

4.2.1.6 Vascular Lesions Related to Surgical Treatment

Radical or partial nephrectomy can be performed using conventional, laparoscopic, or robotic techniques.

The vascularization of the kidney is very important, irrigation being performed by the renal artery and venous drainage performed by the renal vein that flows directly into the vena cava and through the lumbar veins as well.

The renal hilum has a large number of anatomical variations and may have multiple arteries and/or multiple veins (Fig. 4.1).

As much as in partial nephrectomy and radical nephrectomy, a careful and rigorous dissection of the renal hilum must be performed, with the isolation of the arteries and veins, being watchful with lumbar veins to avoid lesions (Fig. 4.2).

In general, lumbar veins are located posterior to the renal vein and can be damaged during its dissection. The control of this type of bleeding is extremely complex because of the following:

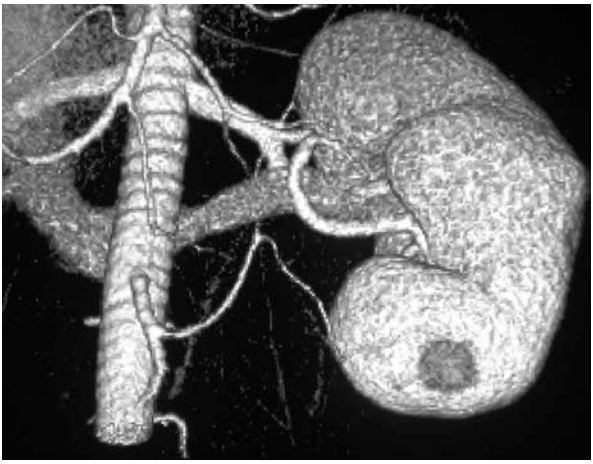

Fig. 4.1 Angiotomography demonstrating vascularization complexity of renal hilum

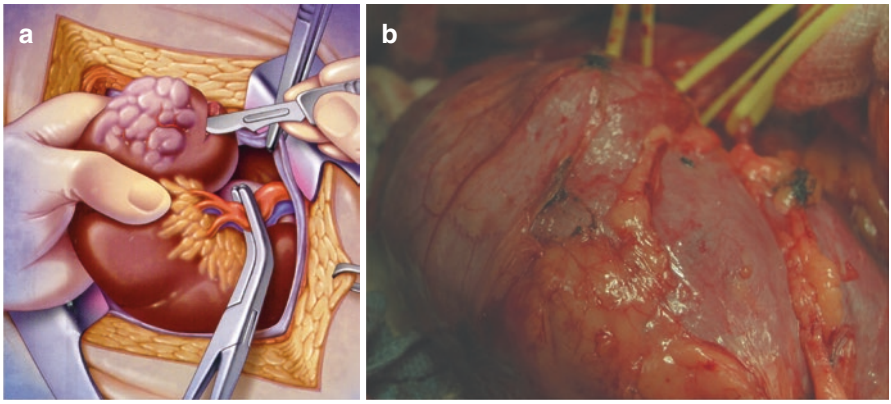

Fig. 4.2 Clamping of vascular hilum. (**a**) Clamping en bloc during open procedure. (**b**) Hilum vessels isolated and prepared for clamping

1. Difficulty to identify bleeding site due to its localization
2. Retraction of the vessel, making identification difficult

For those reasons, in some cases when it is not possible to adequately control lumbar vein bleeding, it can be necessary to quickly ligate renal vein and artery and remove the organ allowing adequate visualization for bleeding control.

These maneuvers are of high complexity and the surgeon must be prepared to perform quickly independently of the surgery access. In cases of minimally invasive surgery, the need for conversion to conventional technique (open) should be considered.

Another very relevant point is inadvertent lesions of the renal vein and vena cava. Sometimes during a partial nephrectomy and isolation of the vessels for clamping, an injury may occur. In these cases, we recommend compression maneuvers for the

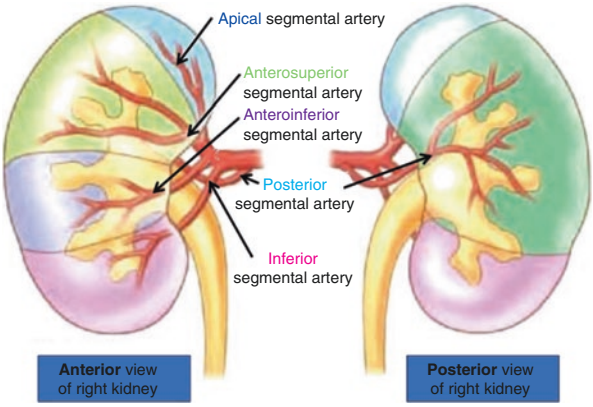

Fig. 4.3 Segmental renal arteries and irrigation areas. (From: https://www.memorangapp.com/flashcards/49859/Kidney+and+Suprarenal+Gland/)

team to prepare. After everything is prepared, a continuous suture or "x" suture must be performed with a prolene thread. It is important to remember that, in special situations, it is possible to ligate the renal vein, as the lumbar and collateral vessels are enough to maintain organ function.

Lesions of the renal artery are rare; however, it can happen in cases of anatomical variations. We must keep in mind that the renal artery ligation is directly related to function loss of the renal parenchyma irrigated by that vessel. It is common to find polar vessels that irrigate only particular segments of the kidney (Fig. 4.3).

During a kidney surgery, it is important to be attentive all the time to rigid and pulsating structures. Ligation and placement of a hem-o-lock must only be performed when the structure is well identified.

In cases of ligation of arteries, we should try to remove the ligature or clip as soon as possible and thereby allowing the flow to be reestablished. In cases where the artery has been sectioned, we must consider the possibility of reconstruction through a termino-terminal anastomosis, mainly in large vessels and trunk arteries. If this is not possible, nephrectomy should be considered or even an autotransplant with vascular graft.

The best way to avoid these types of problems is an adequate study of vascular anatomy through imaging exams before starting kidney surgery. With this, it is possible to foresee eventual difficulties and to determine factors of major attention that must be remembered during the surgery. Robotic and laparoscopic surgeons must be trained to have clearly the concepts of conversion in case of accidents. We recommend that before converting to open surgery, maneuvers to contain bleeding must be performed and we suggest the following steps:

1. Increase in pneumoperitoneum and placement of swabs for compression. This saves time for the anesthesiologist and the surgical team to be prepared.
2. "Gibson" incision in the flank region as a "hand-assistance" portal. With that, one of the surgeons places his hand and swabs to assist bleeding control, while the team makes the main incision to perform the nephrectomy.

3. Rapid dissection of the hilum or even in bloc ligation of the renal hilum. With this, it is possible to remove the kidney with reduced bleeding and open the field to work on identifying the focus of the bleeding.
4. Identification of the bleeding focus and control with suture with 4 or 5-0 prolene thread.

Direct conversion, without proper precautions and preparations, can compromise the result due to intense bleeding during opening in the absence of pneumoperitoneum and compressive maneuvers.

In summary, the renal hilum vessels are large and are high flow structures, so any type of injury can represent massive bleeding with risk of death to the patient. The surgeon must have adequate training and be prepared for these situations when indicating an access route. A careful preoperative analysis of imaging exams and vascular anatomical variations is of fundamental importance. In cases with lesions that invade or present a high risk of vessel involvement, having a vascular surgeon in the operating room is of fundamental importance.

4.2.2 Adrenal Cancer

4.2.2.1 Diagnosis

In 10–15% of the cases, adrenal cancer is found as an incidentaloma in imaging for other purposes. This number is increasing over the years due to the increasing access to CT and MRI in public and private health system. The majority of the cases is presented with hormone excess production (50–60%), such as hypercortisolism and virilizing syndromes. Other 30–40% of the cases may present with abdominal mass symptoms, which are nonspecific.

All patients with suspicion for adrenal cancer must be evaluated with complete medical history, clinical examination for symptoms, and signs of adrenal hormone excess. Hormone screening is necessary to identify if there is excess of glucocorticoids, sex hormones, and mineralo and adrenocortical steroids hormone precursors. Pheochromocytoma must be excluded.

Chest CT and abdominal-pelvic cross-sectional imaging with CT or MRI are recommended. Bone and brain imaging are reserved for symptomatic cases. Adrenal biopsy is not recommended, saved in cases of metastatic disease where histopathological findings are necessary to guide systemic treatment.

4.2.2.2 Staging

Staging at diagnosis is performed by the European Network for the Study of Adrenal Tumours (ENSAT) staging classification. Tumor stage, resection status, Ki67 index, and cortisol secretion are important keys to assess prognosis and define treatment. The Table 4.2 below shows ENSAT staging classification [9].

Table 4.2 ENSAT staging classification

ENSAT stage	Definition
I	T1, N0, M0
II	T2, N0, M0
III	T1–T2, N1, M0T3–T4, N0–N1, M0
IV	T1–T4, N0–N1, M1

T1 tumor ≤5 cm, *T2* tumor >5 cm, *T3* infiltration into surrounding tissue, *T4* tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein, *N0* no positive lymph node, *N1* positive lymph node, *M0* no distant metastases, *M1* presence of distant metastases

4.2.2.3 Prognosis

The prognosis is in general poor. The median survival is about 3–4 years. Five-year survival depends on the tumor staging: for locally disease, the range is about 60–80%, for locally advanced disease, 35–50%, and for metastatic disease, as low as 0–28%. The complete surgical resection is the only way for achieving the cure.

4.2.2.4 Surgical Treatment

Adrenalectomy is the only therapy option that can achieve the cure for Adrenal Cancer. If there is a suspicious or confirmed adrenal cancer, a complete *en bloc* resection is recommended. The resection should involve the adrenal, peritumoral, and periadrenal fat. It is not recommended as gold standard option enucleation of the tumor or partial adrenalectomy. If locally advanced, involved sites must be *resected en bloc* with the primary tumor. Nephrectomy is not indicated unless if involved by the tumor. Open surgery is the standard technique for adrenalectomy, but, for experient surgeons, when the tumor size is less than 6 cm and without local invasion, laparoscopic surgery is an option. Associated lymphadenectomy is recommended, including periadrenal, renal hilum, and enlarged nodes.

4.2.2.5 Systemic Treatment

Adjuvant therapy is not recommended for all cases. The use of adjuvant therapy with mitotane is recommended to be considered in patients without macroscopic residual tumors (R0) with high risk of recurrence. For cases with low and moderate risk of recurrence, the indication should be individualized. When indicated, the prescription of mitotane should ideally start within 6 weeks from surgery. There is no consensus about radiation therapy being reserved associated to mitotane in R1 or Rx resection or Stage III. In cases of advanced adrenal cancer, mitotane is the drug of choice [9].

4.2.2.6 Vascular Lesions Related to Surgical Treatment

Adrenalectomy may be performed by conventional, laparoscopic, or robotic open route. The choice of the access route takes into consideration tumor features and also surgeon experience, who must choose the access route according to his expertise and training to control any type of inadvertent injury or even tactical resection of vascular segments.

The vascularization of the adrenal gland is well-known and has few variations. Irrigation is performed by superior suprarenal artery (branch from inferior phrenic artery), middle suprarenal artery (branch from abdominal aorta), and inferior suprarenal (branch from renal artery). Venous drainage is performed through the adrenal vein that flows into the left renal vein and directly into the right vena cava. Collateral and lumbar veins are also present (Fig. 4.4).

In adrenalectomy, the first step is the identification of the adrenal vein and its ligation. Some tumors are producers of substances that can cause patient hemodynamic instability during adrenal manipulation. As the adrenal is situated immediately above the kidney, it may be necessary to dissect the renal hilum and the vena cava to identify the adrenal vein. This can lead to renal hilum damage and should be managed as described above in kidney cancer section.

Right adrenalectomy is always more complex and challenging because we must keep away the liver properly for a good exposure and the renal vein is usually very cranial and very close to the hepatic veins. Therefore, any injury in this location is extremely difficult to control because, in general, liver rotation maneuvers are necessary for its exposure.

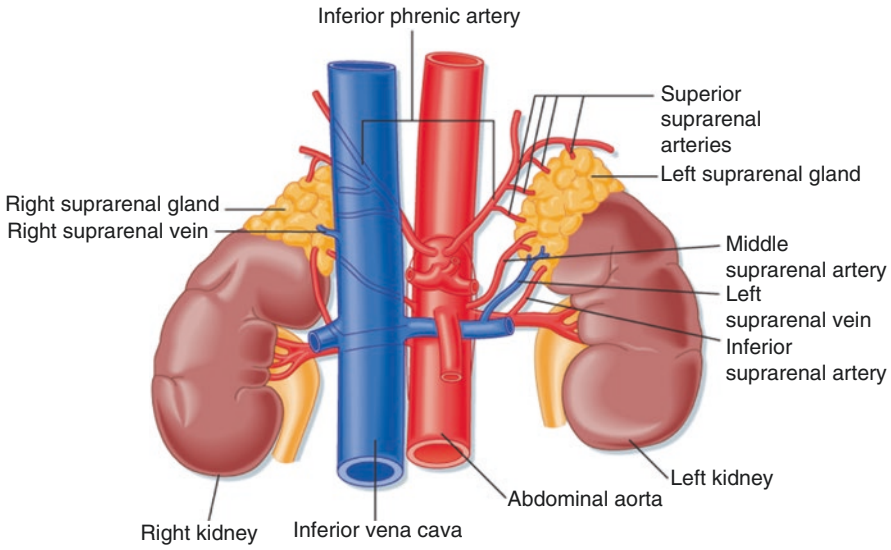

Fig. 4.4 Irrigation and venous drainage of adrenal glands

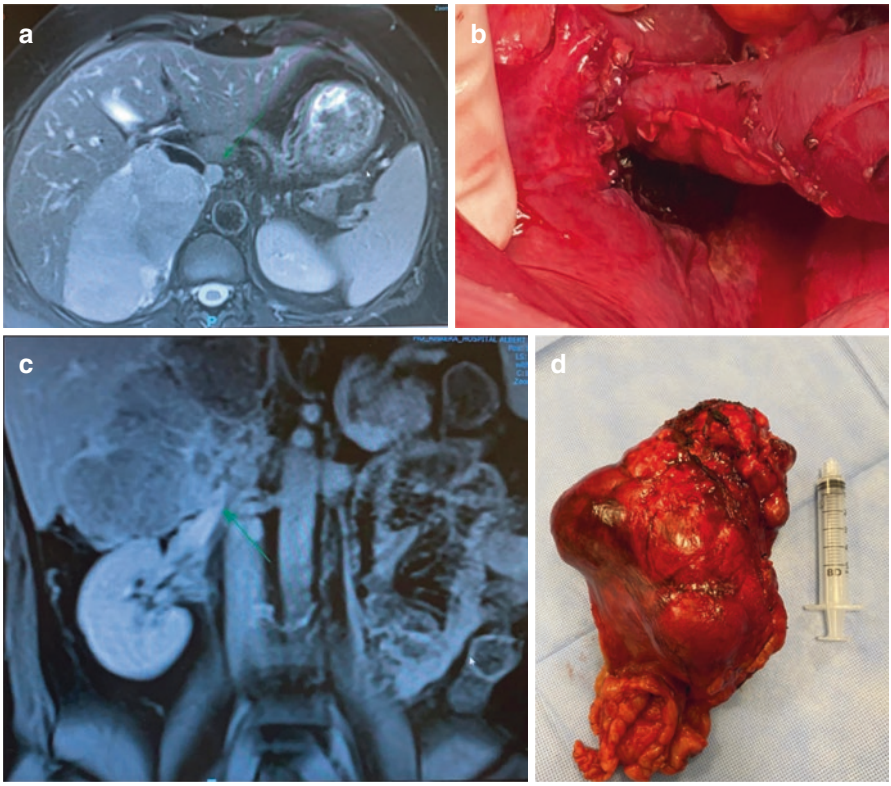

Fig. 4.5 Large adrenal tumor with direct contact with the liver and vena cava. (**a**) Axial image of MRI. (**b**) Area after resection and reconstruction of vena cava with bovine pericardium patch. (**c**) Coronal image of MRI. (**d**) Removed tumor

Adrenal carcinoma has the characteristic of being aggressive and infiltrative. In advanced cases, it usually involves invasion of the liver and also the vena cava (Fig. 4.5). In these cases, it is of fundamental importance to perform a procedure with a multidisciplinary team in which the urology team accesses and dissects the kidney and hilum, the liver team dissects the liver allowing its rotation and perform a cranial and caudal vascular control of the cava, and the vascular surgery team performs the clamping and resection of the vena cava wall with reconstruction using a bovine pericardium patch or prosthesis.

In cases of need for conversion of minimally invasive surgery to conventional surgery, the surgeon must use the same technique suggested in the nephrectomy section and must also be able to dissect and perform a liver rotation maneuver and in some cases chest opening and supra-diaphragmatic control.

4.2.3 Testicular Cancer

4.2.3.1 Diagnosis

The clinical presentation of testicular cancer is a scrotal mass, generally painless, but in up to 27% of cases, pain may be present as well. In 10% of cases, the diagnosis is delayed due to testicular cancer be confound to orchioepididymitis. In cases of suspicion, an ultrasound of the testis must be done. Other clinical features may be gynecomastia – in up to 7% of cases – and symptoms of metastasis such as abdominal mass, abdominal, and flank pain.

Ultrasound must be done in young patients with retroperitoneal mass, visceral mass, elevated human chorionic gonadotropin (hCG) or alpha-fetoprotein (AFP), or with fertility problems, even with no testicular masses.

As an option for the ultrasound, MRI of the testis can be performed, with higher sensitivity and specificity than US but with elevated costs, what is not worthy to be considered the method of choice.

Serum tumor markers must be performed at diagnosis to contribute for diagnosis and for staging as well. The time for assessment must be before orchiectomy and 5–7 days after. The three tumor markers are AFP, hCG, and lactate dehydrogenase (LDH).

4.2.3.2 Staging

Staging for testicular cancer is based on serum tumor markers as listed above (AFP, hCG, and LDH) after orchiectomy, abdominopelvic CT, testis ultrasound, bone scan or MRI column (in case of symptoms), and brain scan (in case of symptoms or metastatic disease in both lungs or high hCG values).

The recommended system is TNM. An extra classification is based on Serum tumor markers, as S0, S1, S2, and S3 (Table 4.3).

4.2.3.3 Prognosis

Prognostic staging is divided into three groups:

(a) Good prognosis: It consists of 56% of non-seminoma and 90% of seminoma tumors. The patient must have no non-pulmonary visceral metastasis and for non-seminoma cancer, AFP <1000 ng/ml, hCG <5000 iU/l, and LDH <1.5 × normal limit value. For this group, 5-year progression-free survival (PFS) is 89% and 5-year survival 92% for non-seminoma cancers and 82% and 86%, respectively, for seminoma cancers.
(b) Intermediate prognosis: It consists of 28% of non-seminoma and 10% of seminoma tumors. For non-seminoma cancer, the patient must have no non-

Table 4.3 TNM system for testicular cancer

pT – Primary tumor			
pTX	Primary tumor cannot be assessed (see note 1)		
pT0	No evidence of primary tumor (e.g., histological scar in testis)		
pTis	Intratubular germ cell neoplasia (carcinoma in situ)		
pT1	Tumor limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade tunica albuginea but not tunica vaginalis[a]		
pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis		
pT3	Tumor invades spermatic cord with or without vascular/lymphatic invasion		
pT4	Tumor invades scrotum with or without vascular/lymphatic invasion		
N – Regional lymph nodes – clinical			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension		
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor		
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
Pn – Regionat lymph nodes – pathological			
pNX	Regional lymph nodes cannot be assessed		
pN0	No regional lymph node metastasis		
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumor		
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M – Distant metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
	M1a Non-regional lymph node(s) or lung metastasis		
	M1b Distant metastasis other than non-regional lymph nodes and lung		
S – Serum tumor markers (prechemotherapy)			
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
S1	*LDH (U/I)*	*hCG (mIU/mL)*	*AFP (ng/mL)*
S2	<1.5 × N and	<5000 and	<1000
S3	1.5–10 × N or	5000–50,000 or	1000–10,000
	>10 × N or	>50,000 or	>10,000

[a]Extracted from European Association of Urology Guidelines 2022 edition (https://uroweb.org/guidelines/testicular-cancer)

pulmonary visceral metastasis and AFP between 1000 and 10,000 ng/ml, hCG between 5000 and 50,000 IU/l, or LDH between 1.5× and 10× normal limit value. For the seminoma group, any condition that does not fit for good prognosis classifies the patient in the intermediate-prognosis group. Five-year PFS is 75% and 5-year survival 80% for non-seminoma and 67% and 72% for seminoma, respectively.

(c) Poor prognosis: No seminoma cancer is classified as poor-prognosis. For non-seminoma, if mediastinal primary tumor, non-pulmonary visceral metastasis, AFP >10,000 ng/ml, hCG >50,000 IU /l, or LDH >10 × normal limit value are present (only one is enough for this classification). The patient is classified as a poor-prognosis case (16% of cases). 5-year PFS is 41% and 5-year survival 48%.

Another prognostic evaluation is based on the risk for metastatic relapse in clinical stage I. The risk factors for occult metastatic disease in this stage are, for seminoma, tumor size >4 cm and invasion of rete testis; and for non-seminoma, vascular or lymphatic or peritumoral invasion, proliferation rate >70% and percentage of embryonal carcinoma >50%.

4.2.3.4 Surgical Treatment

Orchiectomy is the first step in case of testicular tumors. The procedure is performed when a testicular cancer is suspicious or confirmed, and in case of doubt, a frozen biopsy is taken during the procedure. The procedure starts with an inguinal exploration with exteriorization of the testis and, then, spermatic cord is divided, at the internal inguinal ring level.

Retroperitoneal lymphadenectomy is useful in particular cases. For residual tumors, in seminomas, after systemic treatment, when PET-CT shows residual mass larger than 3 cm, lymphadenectomy is an option instead of new chemotherapy. For non-seminomas, retroperitoneal lymphadenectomy is indicated as an option for Stage I, IIA, and B (if lymph nodes <2 cm and pure teratoma) and in cases of residual tumors, if the residual mass is larger than 1 cm.

4.2.3.5 Systemic Treatment

Systemic treatment in testicular cancer consists of chemotherapy and radiotherapy and its indications are guided by staging. Stage I is defined as tumor restricted to the testis. Stage II consists of cases with retroperitoneal lymph node metastasis. This stage is subdivided as IIA, up to 2 cm, IIB with 2–5 cm, and IIC for masses >5 cm. Stage III is defined as tumor with other metastasis.

The decision of treatment differs between seminoma and non-seminoma. For seminomas, in Stage I, if invasion of rete testis or mass >4 cm, adjuvant chemotherapy is indicated (1 or 2 cycles of carboplatin). In Stage II A or B, options for systemic treatment are radiotherapy (2 Gy × 15, total 30Gy, in paraaortic and iliac

ipsilateral field, if IIB, add 6 Gy in major lymph nodes) or chemotherapy with 3 cycles of BEP – bleomycin, etoposide, and cisplatinum (4 cycles of EP if bleomycin contraindicated). Finally, in Stage IIC or III, the indication of systemic therapy consists of 3 or 4 cycles of BEP (3 cycles if good prognosis). For residual masses, larger than 3 cm, chemotherapy is again an option (lymphadenectomy is the other option as cited above).

For non-seminomas, in Stage I, if lymphovascular invasion, the option is cycle of BEP (retroperitoneal lymphadenectomy is an option as cited above, surveillance is another option). For Stage IIA or B, 3 or 4 cycles of BEP (3 if good prognosis). In cases with lymph nodes <2 cm and pure teratoma, surveillance or lymphadenectomy is the option. Finally, for Stage IIC and III, 4 cycles of BEP are indicated. Residual masses larger than 1 cm are treated with retroperitoneal lymphadenectomy and if, after resection, viable tumor is found, chemotherapy has an important role [10, 11].

4.2.3.6 Vascular Lesions Related to Surgical Treatment

Retroperitoneal lymphadenectomy (RL) is performed as a form of recurrence prophylaxis or in cases of recurrence after chemotherapy. RL can be performed by conventional, laparoscopic, or robotic open route; however, it is known that minimally invasive techniques are more complex and should only be performed by surgeons with experience.

RL can be performed by distinct techniques and steps, but a recommended technique is the "split and roll" technique which can start with dissection at 12 o'clock of the aorta, right inferior to the left renal vein, and continue caudally, taking care in identifying inferior mesentery artery. The left para-aortic packet is dissected laterally aorta, being necessary to ligate gonadal vein and to identify left ureter and protect it from lesions. Dissection continues caudally until position of ureter above left common iliac artery. The lymphatic tissue is rolled laterally from aorta and left common iliac artery and then, inferiorly from left renal vein. The lateral limit consists of dissection of the lower pole of the kidney and left ureter. In this procedure, lumbar arteries on the left side of aorta must be ligated. Left genitofemoral nerve and sympathetic trunk must be identified and preserved when possible. Vena cava split is performed with dissection from renal hilum to the right common iliac artery, until position of ureter above this artery. Right gonadal vein is ligated and divided. The lymph node tissues are rolled medially. Lymphatic dissection from interaortocaval packet is completed with rolling medially the packet from aorta. Control of lumbar arteries must be done, as well as lumbar veins. The right paracaval packet is smaller because of the position of the right kidney and ureter near to the inferior vena cava. The lymphatic tissue is rolled laterally and superiorly from the right common iliac artery until ureter position over the artery. The dissection continues superiorly until renal hilum and crus of the diaphragm.

During the procedure, there is constant contact with the aorta, vena cava, and lumbar vessels; therefore, a careful dissection is of fundamental importance and that the surgeon may be able to perform vascular sutures.

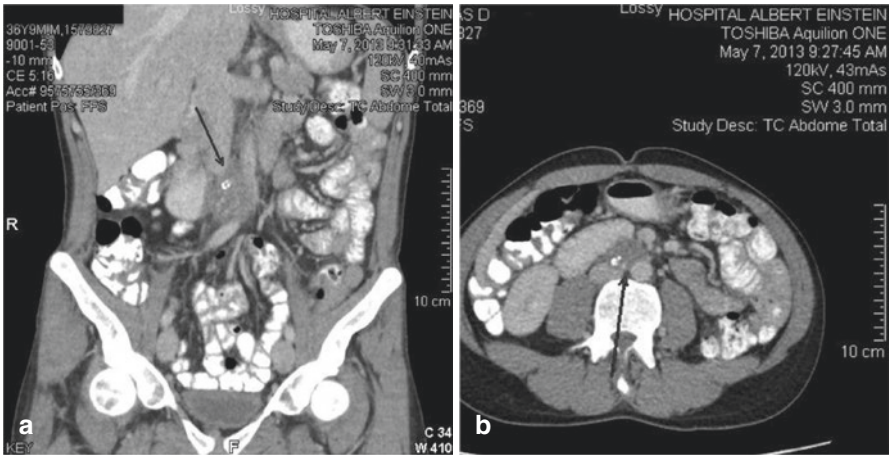

Fig. 4.6 Retroperitoneal refractory seminomatous tumor. Images of computed tomography showing retroperitoenal refractory seminomatous tumor, (**a**) coronal plane (**b**) axial plase (Personal gallery)

RL of larger tumors and refractory to chemotherapy are even more complex, being the mass, in general, in close contact with the vessels and with firm adhesions, increasing the risk of dissection (Fig. 4.6). In this type of surgery, it is of fundamental oncological importance to remove the tumor completely, and in some cases, it is necessary to resect the vessel wall and reconstruct it.

In cases of refractory seminomatous tumors, chemotherapy is even more complex, even in minor lesions. Chemotherapy has an effect on vascular structures with a reduction in the outer layer of the arteries, making the arteries more fragile and easier to damage. In these cases, we strongly recommend always having a vascular team available in the operating room in case of accidents, for reconstructing procedures [12] (Fig. 4.7).

In non-seminomatous tumors, we do not find this type of vascular changes and the surgery is usually easier; however, in cases with suspected vascular invasion, extra care must be taken.

4.2.4 Prostate Cancer

4.2.4.1 Diagnosis

Diagnosis of prostate cancer is achieved by prostate biopsy (transperineal or transrectal). A multiparametric MRI may be performed before prostate biopsy if possible to guide the procedure and increase sensitivity by adding fragments of suspicious areas. Indication of prostate biopsy consists of altered screening exams or clinical suspicious of prostate cancer. An increase of PSA is one of indications, as other

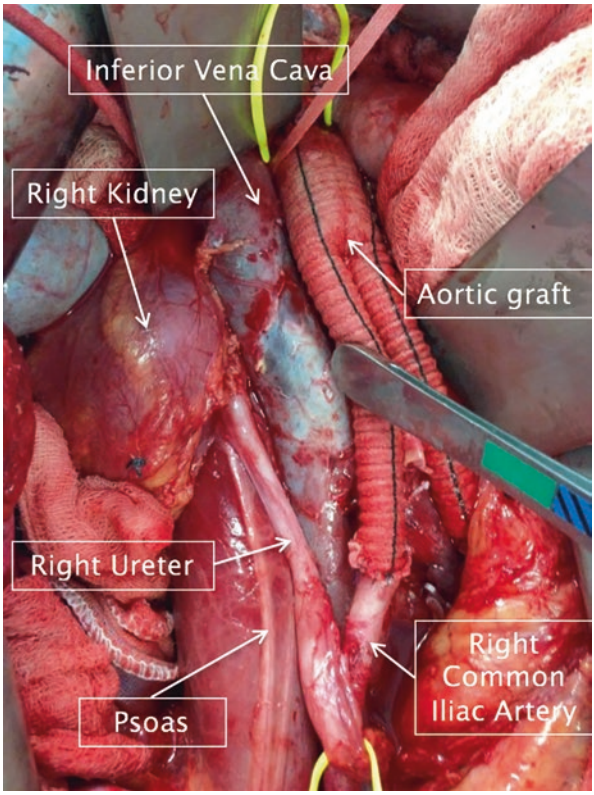

Fig. 4.7 Bilateral aortoiliac bypass. (Personal gallery)

situations may elevate PSA; alternatives for evaluation of PSA levels are options to increase specificity of the exam, such as, PSA density and free/total PSA ratio. Another absolute indication of biopsy is altered rectal digital exam (palpable nodule, induration mass).

Diagnosis is given by pathologist, by type of tumor (most Adenocarcinomas) and Gleason/ISUP grade, which helps in staging and prognostic evaluation.

4.2.4.2 Staging

Tumor staging is defined with TNM classification (Table 4.4). For this evaluation, when low risk with localized disease and when favorable intermediate risk, no complementary image is necessary. For unfavorable intermediate-risk and for high-risk cases, abdominopelvic imaging (CT or MRI) and bone scan are necessary. For local imaging assessment, MRI of the prostate is the best imaging exam and first option for this reason.

Table 4.4 TNM system for prostate cancer

T – Primary tumor (stage based on digital rectal examination [DRE] only)		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1	Clinically inapparent tumor that is not palpable	
	T1a	Tumor incidental histological finding in 5% or less of tissue resected
	T1b	Tumor incidental histological finding in more than 5% of tissue resected
	T1c	Tumor identified by needle biopsy (e.g., because of elevated prostate-specific antigen [PSA])
T2	Tumor that is palpable and confined within the prostate	
	T2a	Tumor involves one half of one lobe or less
	T2b	Tumor involves more than half of one lobe, but not both lobes
	T2c	Tumor involves both lobes
T3	Tumor extends through the prostatic capsule	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall	
N – Regional (pelvic) lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M – Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	
	M1a Non-regional lymph node(s)	
	M1b Bone(s)	
	M1c Other site(s)	

Extracted from European Association of Urology Guidelines 2022 edition (https://uroweb.org/guidelines/prostate-cancer)

4.2.4.3 Prognosis

Prognostic assessment of prostate cancer is defined by biopsy results primarily. Considering only ISUP grade, there is a correlation with biochemical progression-free survival. For ISUP 1, this rate is about 97% in 5 years, while for ISUP 4, this rate lowers to 64% and 49% in ISUP 5.

D'Amico stratification risk is globally used to classify prostate cancer in three groups:

(a) Low-risk group: PSA <10 ng/ml, ISUP 1, T2a clinical stage.
(b) Intermediate-risk group: PSA between 10 and 20 ng/ml, ISUP 2 or 3, T2b clinical stage.
(c) High-risk group: PSA >10 ng/ml, ISUP 4 or 5, T2c clinical stage.

This stratification is important to evaluate recurrence risk in 5 years. For low-risk group, recurrence risk in 5 years is less than 25%, for intermediate risk, between 25% and 50%, and for high-risk group, this rate is above 50%.

4.2.4.4 Surgical Treatment

Before detailing surgical treatment, it is important to consider that non all of prostate cancers must be actively treated at diagnosis. Active surveillance is a good option in low-risk cancers, reducing the risk and comorbidities added by surgical treatment or radiotherapy and hormonal blockage without compromising oncological outcomes when well-delineated and conducted.

Another consideration is that surgical treatment and radiotherapy (with or without antiandrogen deprivation therapy – ADT) are both options for active treatment, with similar oncological outcomes in general. The decision between both options must be done individually, respecting patient desire, expectations, and considering individual medical features.

Radical prostatectomy can be performed by open, laparoscopic, or robotic surgery. All of the 3 options can be performed, with similar oncological outcomes, but robotic surgery has shown lower admissions, lower blood loss, and faster functional recovery.

Extended pelvic lymphadenectomy is not indicated for low-risk patients. Its indication is reserved for intermediate-risk group when the risk of lymph node involvement is considerable (e.g., higher than 5% for MSKCC nomogram) and for high-risk group and for locally advanced cases when prostatectomy is performed. Extended templated of pelvic lymphadenectomy consists of lymph nodes above external iliac vessels, in the obturatory fossa, and lateral and medial to internal iliac vessels.

4.2.4.5 Systemic Treatment

For localized disease, systemic treatment consists of androgen deprivation therapy (ADT) associated to radiotherapy in intermediate-risk patients, for 6 months, and in high-risk patients for 2–3 years. In cases of locally advanced disease (T3, T4, and N1), ADT as monotherapy may be indicated when surgery or radiotherapy is not an option and PSA doubling time is <12 months, PSA >50 ng/ml or tumor is low differentiated.

After surgery, ADT may be indicated if lymph node involvement, associated or not with radiotherapy.

For metastatic disease, first-line therapy consists of ADT. ADT can be achieved by bilateral orchiectomy or LHRH agonists or antagonists. Antiandrogens as monotherapy are not indicated. Both protocols can be used in M1 cases, depending on patient conditions: ADT plus Abiraterone plus Prednisone OR ADT plus Docetaxel. In cases of resistant castration prostate cancer, for M0 patients, Apalutamide and

Enzalutamide are options of treatment, and for M1 patients, Abiraterone, Docetaxel, Enzalutamide, Radium 223, and Sipuleucel T are available options [13–16].

4.2.4.6 Vascular Lesions Related to Surgical Treatment

Radical prostatectomy (RP) may be or may not be accompanied by pelvic lymphadenectomy. It can be performed by open, laparoscopic, or robotic surgical access. Prostatectomy itself does not usually take major vascular risks. Only in minimally invasive techniques, special attention must be given to the epigastric arteries during puncture of the trocars. Always a surgery is finished, the trocars must be removed under vision in order to assess any bleeding from the site. The control of epigastric artery lesions can be performed by clipping a hem-o-lock clip under vision or through a transcutaneous suture with a "Carter-Thomason" needle.

Primary or salvage pelvic lymphadenectomy (Fig. 4.8) consists of removing the lymph nodes from the template composed of these limits:

- Cranial = crossing of the ureter over iliac vessels
- Caudal = inguinal canal
- Lateral = genitofemoral nerve
- Medial = bladder wall

With that, the entire external iliac lymph node chain, as well as obturator, internal iliac, and part of the common iliac chains are removed (and eventually also from the sacral region). During this procedure, lesions of arteries with large blood flow can occur and the surgeon must be prepared for a vascular suture.

We recommend special care with the internal and external iliac veins as it can be difficult to identify its limits and its conformation may be altered with the surgical presentation.

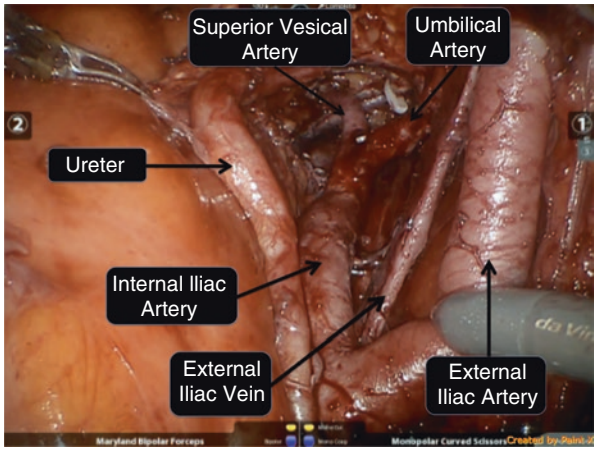

Fig. 4.8 Extended pelvic lymphadenectomy

The first anterior branch of the internal iliac artery is the obliterated umbilical artery. In general, we use this artery for presentation and do not ligate it. However, it can be connected without any impact to the patient. The first posterior branch of the internal iliac is the gluteal artery and its ligation can cause lameness to the patient.

The external iliac artery becomes the femoral artery and is responsible for irrigating the lower limbs. Its ligation can impact the loss of the limb and flow should be reestablished as soon as possible. The internal iliac artery is responsible for the irrigation of the pelvic floor and due to vast vascularity in this region; if necessary, it can be ligated, both the artery and the vein.

4.2.5 Bladder Cancer

4.2.5.1 Diagnosis

The most common clinical feature is hematuria, and when macroscopic, is associated with higher stage of disease. Carcinoma in situ may present with lower urinary tract symptoms and irritative voiding.

Cystoscopy is vital for diagnosis of bladder cancer and cannot be replaced by ultrasound, CT, or cytology. During cystoscopy, resection of the suspicious tumor can be performed and taken to analysis. If not possible to complete resection, partial resection or biopsy can be performed. During initial work-up, renal and bladder ultrasound and/or computed tomography-intravenous urography (CT-IVU) may be performed. Absolute indications for CT urography are tumors located in the trigone and multiple or high-risk tumors, for the risk of concomitant upper tract urothelial carcinoma. In cases of high-grade tumors, urine cytology is a complementary exam to cystoscopy for detection.

4.2.5.2 Staging

Bladder cancer staging is defined by TNM classification, as shown in Table 4.5.

A risk stratification needs to be performed to guide treatment decision. Tumors can be classified in one of three groups:

(a) Low-risk group: All TaG1 less than 3 cm, primary and solitary (all of them present).
(b) High-risk group: All tumors which present with one of these features: T1, G3 (high grade), Cis. Or, if the tumor is TaG1G2 and multiple, recurrent, and larger than 3 cm (all of them present). A subgroup is the highest-risk group, that is defined as T1G3 tumors with Cis, or, multiple or larger than 3 cm, or high-grade recurrent, or with lymphovascular invasion or urothelial carcinoma variants.
(c) Intermediate-risk group: those tumors which do not fit in low or high-risk groups.

Table 4.5 TNM system for bladder cancer

T – Primary tumor		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma in situ "flat tumor"	
T1	Tumor invades subepithelial connective tissue	
T2	Tumor invades muscle	
	T2a	Tumor invades superficial muscle (inner half)
	T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumor invades prostate stroma, seminal vesicles, uterus, or vagina
	T4b	Tumor invades pelvic wall or abdominal wall
N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed tissue	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M – Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

Extracted from European Association of Urology Guidelines 2022 edition (https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer)

4.2.5.3 Prognosis

Prognostic evaluation is based on EORTC Genito-Urinary Cancer Group scoring system and risk tables. This score reflects probability of recurrence and progression at 1 and 5 years.

4.2.5.4 Surgical Treatment

Surgical treatment is initially based on Transurethral Resection of the Bladder tumor (TURBT). This procedure is diagnostic and potentially therapeutic at the same time. If TURBT is incomplete or with no muscle sample, or consists of T1 or

high-grade, second TURBT is indicated within 2–6 weeks. Conditions that do not indicate second TURBT are complete TURBT in Ta low-grade tumors, or in cases of primary Cis.

Cystectomy is indicated for muscle-invasive tumors. Cystectomy can be performed by open, laparoscopic, or robotic surgery. Robotic surgery has longer operative time, higher costs, but, otherwise, lower hospital stay and lower blood loss. These procedures include removal of regional pelvic lymph nodes and extended pelvic lymphadenectomy has better outcomes in survival rates than limited lymphadenectomy. Cystectomy must be performed within 3 months from diagnosis, under risk of progression and cancer-specific mortality if performed more than 3 months after diagnosis.

Another role of cystectomy includes in metastatic tumors, for symptoms control. TURBT can be performed as part of a multimodal therapy associated with radiotherapy and chemotherapy in this group of tumors.

An important step in cystectomy is urinary diversion. It is important to consider that no oncological or quality of life outcomes is proved to be superior comparing different urinary diversions each other. Options of diversion are cutaneous ureterostomy, ileal conduct (Bricker), orthotopic bladder, and others.

4.2.5.5 Systemic Treatment

Neoadjuvant therapy has a consolidated role in cases of muscle-invasive bladder cancer. Neoadjuvant chemotherapy with cisplatin combination improves overall survival in 5–8% in 5 years. Recommendation from guidelines consists of indicate neoadjuvant chemotherapy with gemcitabine plus cisplatin (GC) OR methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) for T2 to T4a tumors, N0M0.

Adjuvant therapy is indicated for T3 or T4 tumors or N+ if neoadjuvant chemotherapy was not performed.

Considering metastatic disease, options for treatment are GC OR MVAC or HD-MVAC, paclitaxel, cisplatin, and gemcitabine (PCG). If not eligible for cisplatin (such as performance status 2 or glomerular filtration rate <60), options are pembrolizumab (if PD-L1 positive), atezolizumab (if PD-L1 positive), or carboplatin plus gemcitabine (if PD-L1 negative) [17–19].

4.2.5.6 Vascular Lesions Related to Surgical Treatment

Radical cystectomy consists of similar vascular risks as prostatectomy, being extended pelvic lymphadenectomy the major risk for greater vascular lesions. Care must be taken as exposed in vascular lesions session of the prostate cancer. Internal iliac and external iliac vessels must be carefully manipulated and lymph nodes templates carefully dissected.

Editors Comments

The relationship between urological tumors and the circulatory system occurs in several ways. In general, cancer patients are at higher risk for venous thromboembolic events (VTE), although malignant neoplasms such as prostate cancer are less related to thrombotic events than those of the pancreas and stomach, for example. However, oncological surgeries of the abdomen and pelvis, such as those of the genitourinary tract, are among those that are most associated with the occurrence of deep venous thrombosis and pulmonary embolism.

In addition to being exposed to an increased risk of thrombosis and recurrence of thrombosis, individuals with cancer also have a higher bleeding rate due to anticoagulant treatment. These hemorrhagic events occur more frequently in the digestive and genitourinary tracts, mainly from neoplastic lesions [20, 21].

Renal dysfunction also increases the risk of thrombosis by causing an increase in serum levels of coagulation factors, such as plasminogen activator inhibitor (PAI1) and von Willebrand factor, among others. Renal failure also provides a higher risk of bleeding once it is also characterized by disorders of the coagulation cascade and activation of the fibrinolytic system, decreased platelet activity, and impaired vessel–wall–platelet interactions [22]. The increased risk of bleeding in individuals with renal failure may also be due to the increased plasma concentration of anticoagulants used in VTE treatment. Low molecular weight heparins have almost exclusively renal elimination, whereas direct oral anticoagulants have different degrees of renal excretion – dabigatran 80%, edoxaban 50%, rivaroxaban 33%, and apixaban 27%. Warfarin is a medication with almost total elimination via the liver. However, warfarin increases the risk of bleeding as renal dysfunction worsens. Patients with creatinine clearance <30 mL/min have an almost five times greater risk of bleeding than an individual with preserved renal function. This can be attributed in part to the platelet dysfunction caused by uremia. There are animal studies that also show a negative regulation in the metabolism of some liver enzymes, such as cytochrome P-450, in the presence of renal failure [23, 24].

The intimate relationship between the genitourinary tract organs and large vessels makes the resection of urological tumors challenging, especially tumors of the kidney and adrenal gland. The dissection of the renal hilum can be quite laborious and, due to frequent anatomical variation, requires careful evaluation with imaging tests such as computed tomography in the preoperative planning. Inadvertent lesions of arterial and venous lumbar branches, in addition to the aorta and inferior vena cava, are a concern due to the difficulty in controlling the resulting bleeding, especially when the tumor has not yet been removed, making it challenging to identify and treat the injured vessel.

When there is an invasion of large vessels or visceral branches, such as the renal ones, en bloc resection of the tumor with the vascular structures brings the need for revascularization. The aorta and vena cava are, as a rule, reconstructed with synthetic vascular prostheses, whereas, in the renal vessels, autologous substitutes, such as the internal saphenous vein, may be an option. The renal vein may

eventually be disconnected with less repercussion, preferably as distally to the hilum as possible, despite our preference for reconstructing it.

Pelvic tumors, such as prostate and bladder tumors, rarely require vascular intervention. Testicular cancer, in turn, can spread through the retroperitoneal lymphatic chain, which has an intimate relationship with the great vessels of the abdomen and pelvis, and lumbar branches. Retroperitoneal lymphadenectomy can be too laborious and, in cases of more extensive involvement and greater adherence, require en bloc resection with vascular reconstruction.

A rare complication already described by our group was the occurrence of an aortic pseudoaneurysm in a patient with a retroperitoneal mass originating from an embryonic testicular carcinoma (Fig. 4.9). After eight cycles of chemotherapy, control tomography showed a 50% reduction in mass and a pseudoaneurysm of the aorta in the segment surrounded by the tumor. This patient was operated on with en bloc resection involving the tumor and the aorta with the pseudoaneurysm, with aorto-biiliac reconstruction with a bifurcated Dacron prosthesis [25].

Vascular tumors, such as inferior vena cava sarcomas, are a differential diagnosis with primary kidney neoplasms. Frequently, the diagnosis ends up being made during the surgical procedure.

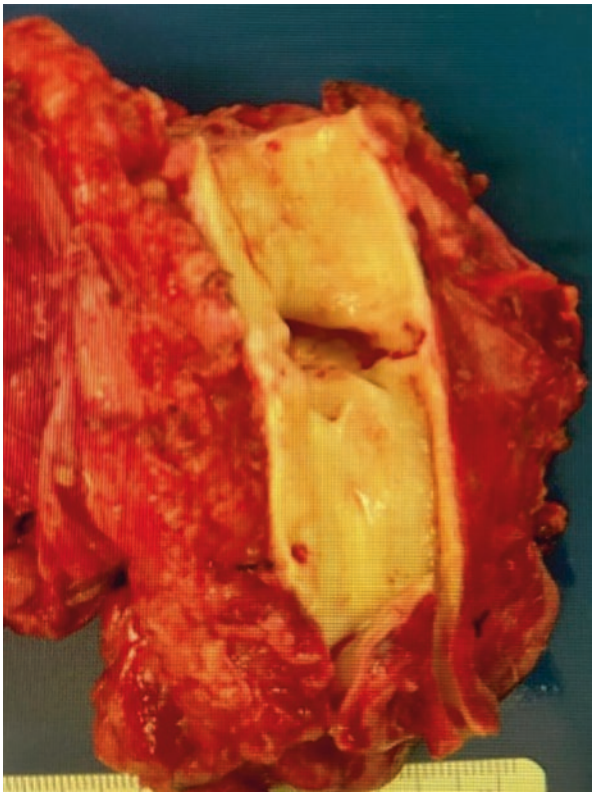

Fig. 4.9 Longitudinal section of the aorta resected en bloc with the tumor. In the center of the image, notice the rupture of the artery wall

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Chapter 5
Gynecological Cancer and Breast Cancer

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5.1 Gynecological Cancers

5.1.1 Principles of Surgery in Gynecological Cancers

5.1.1.1 Introduction

The gynecologic oncologist should be able to evaluate women with gynecologic cancer, adequately manage the treatment, perform the surgical procedures, supervise the postoperative care, and share multidisciplinary decisions with other specialties. Although not having a formal regulation of the specialty in most countries, women when not treated by a specialist usually undergo an inappropriate treatment. McGowan et al. [1] reviewed 291 cases of ovarian cancer and 97% of cases treated by a gynecologic oncologist had an adequate staging procedure. Conversely, only 52% and 35% had adequate surgical staging when treated by a general gynecologist or general surgeon, respectively. Moreover, two large British studies retrospectively analyzed 1800 cases of ovarian cancer [2, 3] and revealed better survival when the specialist performed the surgery. Other two systematic reviews in ovarian cancer suggested benefit in outcomes when a specialist treats patients, with 2.3 higher likelihood of having a complete cytoreduction [4] and also it was the main prognostic factor, regardless of disease stage.

Nevertheless, another main factor for adequate treatment in gynecologic oncology is the availability of novel drugs and complex treatments. Treatment and resources might be centralized depending on the type and stage, leading to higher

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volume and quality of treatment in those specialized centers. Bristow et al. [5] underwent a meta-analysis of 6885 ovarian cancer cases and noted an increase of 50% in median survival when the treatment is performed in specialized high volume centers.

5.1.1.2 Diagnosis and Staging

While being solid tumors, almost all gynecologic cancers need a diagnostic biopsy. Moreover, an incisional biopsy may be sufficient for the diagnosis of vulvar, vaginal, or cervical cancer. However, an excisional biopsy may be mandatory for the differential diagnosis between a premalignant or invasive cervical and vulvar cancer. A fragment image guided biopsy ("Tru-Cut") may also diagnose disease dissemination (lymph node or visceral). Of note, for ovarian cancer cases, most require a surgical exploration for diagnosis.

The International Federation of Gynecology and Obstetrics (FIGO), which is mainly surgically staged, supports the current staging system for gynecologic cancers. In 2018, the FIGO staging system had a significant change for cervical cancer, when surgical and imaging data were incorporated as well as the lymph node involvement [6]. A gynecologic oncologist is the professional who should perform the surgical staging, as an accurate diagnosis and staging determine the subsequent treatment.

5.1.1.3 Types of Surgical Procedure

Primary Surgery

Surgery is usually the treatment method for premalignant vulvar and cervical lesions, where the resection has a diagnostic and curative intent. In case of localized disease (stages Ib-II vulvar cancer and stages Ia2-Ib2 cervical cancer), radical surgery is performed to treat the primary tumor as well as regional lymph node dissection for staging purposes. Recently, regional full lymph node dissection is being replaced by sentinel node mapping and biopsy that is not only accurate in predicting node positivity but also mitigates surgical morbidity related to full lymph node dissection, such as neurovascular injuries, lymphocyst formation, and lymphedema [7, 8].

In a primary radical surgery, the procedure is characterized by a curative intent without adjuvant treatment, unless when pathological adverse prognostic factors are found after surgery. Surgery as the sole treatment is also indicated for early-stage endometrial and some ovarian cancers. The indication of adjuvant treatment is usually based on the risk of occult distant metastasis (lung, peritoneum, liver) or locoregional recurrence.

Surgery After Recurrence

In case of recurrence after a nonsurgical treatment (e.g., Locally advanced cervical cancer treated with radiotherapy), surgery may be the only offered method with curative or palliative intent (when systemic disease). The main example is the indication of pelvic exenteration in cases with resectable exclusive pelvic recurrences of gynecologic tumors (cervix, uterine corpus, or vulva) that previously had radiotherapy in the pelvis. A 5-year survival rates may vary from 23% to 61% in these cases [9]. However, a high morbidity rate is expected (30–50%), due to the radical complex surgery that may involve resection of the bladder, rectum, vagina, and subsequent definite urinary and fecal derivations [9] (Fig. 5.1).

Yet, surgery in recurrent disease also has a place in ovarian cancer. The secondary cytoreduction is indicated for selected cases before systemic therapy, when complete resectable recurrent disease is diagnosed.

Surgery for Distant Metastasis

In selected cases, surgical resection of metastatic disease positively impacts survival. Fuller et al. [10] reported 15 cases submitted to lung segmentectomy due to gynecologic metastasis and found progression-free survival of 36% and 26% in 5 and 10 years, respectively. Levenback et al. [11] published data on 45 cases that underwent lung segmentectomy after uterine sarcoma recurrence and found a 41% 5-year survival rate, much higher than expected. For ovarian cancer, it is less likely to recur only with visceral metastasis; however, hepatic and spleen resections after recurrence seem to be beneficial [12] (Fig. 5.2).

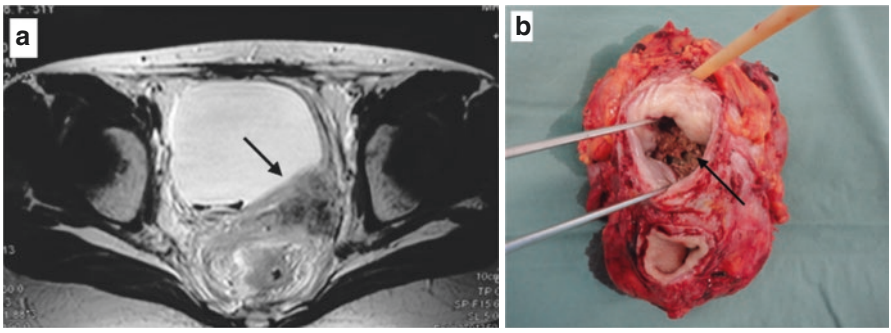

Fig. 5.1 (**a**) Magnetic resonance showing a pelvic recurrence of cervical cancer after chemoradiation (arrow); (**b**) Example of surgical specimen after total pelvic exenteration that includes resection of bladder, urethra, vagina, and rectum. The arrow depicts the recurrent cervical cancer

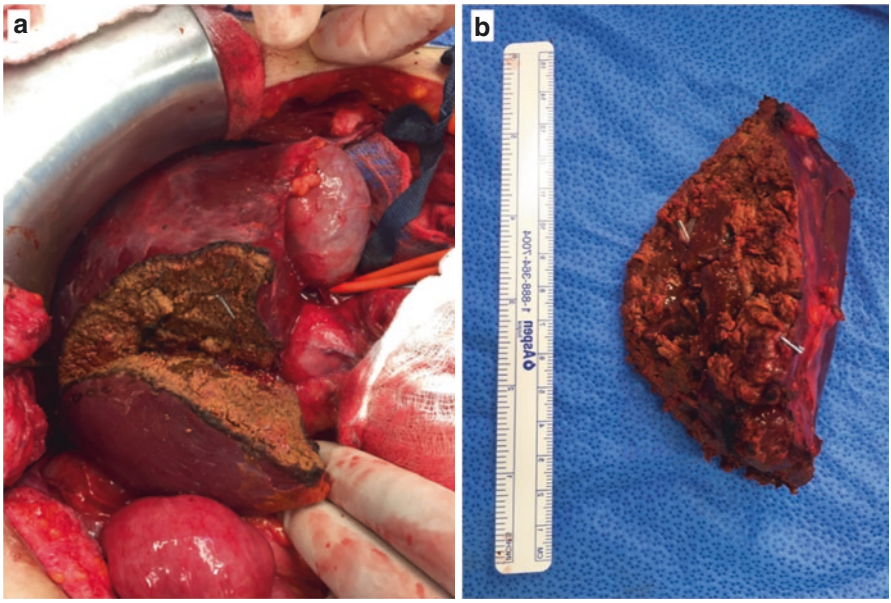

Fig. 5.2 (**a**) Intraoperative aspect of partial hepatectomy of segment IV for a recurrent ovarian carcinoma. (**b**) The surgical specimen of the liver

Reconstructive Surgery

Reconstructive surgeries may be done at the same time of radical surgical resection or for complication's treatment such as dehiscence. Vulvar reconstruction is currently performed through myocutaneous or fasciocutaneous local and regional flaps, more commonly advancement and rotation flaps. The best choice depends on the defect extension and surgeon's experience and the most used are "V-Y," gracilis, rhomboid, gluteus, rectus abdominis muscle, lateral vastus muscle, and fascia lata [13].

Vaginal reconstructions are generally performed as a second step surgery. Both loco-regional myocutaneous flaps and microsurgical free flaps (e.g., small bowel) are used and depend on the reconstruction's extension and previous pelvic radiation.

Palliative Surgery

Palliative surgeries have the aim of decreasing or mitigating symptoms and improving quality of life, without curative intent. However, futile procedures should be avoided. The palliative procedure should give, with limited risk and rapid recovery, symptoms' relief at least equivalent to other nonsurgical treatments such as radiotherapy, chemotherapy, or supportive care during a period of time of 6–12 months.

Palliative surgery is mostly used for treatment of bowel and urinary obstruction. Urinary and fecal derivations may be used for fistula palliative treatment when the systemic treatment is impaired. However, treatment decision should be shared with the patient and a nephrostomy rather than urinary derivation is usually carried out in case of limited expectative of life [14].

For ovarian carcinoma with peritoneal recurrence, bowel obstruction negatively impacts quality of life. In most cases, an internal bowel deviation ("by pass") or an ostomy is done, but surgical resolution sometimes is not feasible due to intense peritoneal dissemination. In a study that included 68 cases with palliative surgery for ovarian cancer, Pothuri et al. [15] reported in 64 cases with bowel obstruction a successful rate of 71%, meaning the tolerance of diet without residues up to 60 days after surgery.

5.1.2 Oncologic Treatment of the Most Common Gynecologic Cancers

5.1.2.1 Cervical Cancer

Diagnosis

Cervical cancer is the third malignant neoplasia in women in the world and the fourth cause of death due to cancer. Annually, about 500,000 cases are diagnosed around the world and result in nearly 270,000 deaths. However, the incidence varies between demographic regions and 85% of new cases occur in low-middle income countries due to lack of effective screening programs [16]. Infection by high-risk HPV is considered as a necessary cause as they are found in nearly 99.7% of cases. There are 14 high-risk HPV types and the most commonly related to cancer are types 16 and 18 (70–75% of cases). Other established risk cofactors are smoking and concomitance of other sexually transmitted diseases (STD) such as Chlamydia and Trichomoniasis [17]. Notably, the current vaccines against HPV include types 16 and 18. Moreover, most of HPV infections are transitory, with spontaneous regression between 6 and 24 months, leading to persistent infection in only 10% of cases [18].

Nevertheless, premalignant lesions are called cervical intraepithelial neoplasia (CIN) and precede cervical cancer. CINs are divided into low grade (CIN I) and high grade (CIN II and CIN III). Most CIN I regress spontaneously (60%) and only 10% progress to CIN III. Moreover, it is estimated that only 1% of CIN I become invasive lesions and it is expected after a span time of 10 years [18]. Cervical cancer screening may be considered as a model in cancer screening, where: (a) the basic cause is well known (infection by high-risk HPV); (b) there are premalignant lesions that may take a long time to progress (CIN I into cancer); (c) the organ can be easily

accessed for clinical exam and there are preventive exams such as HPV-DNA and oncotic cytology (pap smear); (d) after a diagnosis of a premalignant lesion (high-grade CIN), it is possible to intervene and treat (conization), finally preventing cancer development.

Most cervical cancer cases are squamous cell carcinomas (80–85%) followed by adenocarcinomas (15–20%) and dissemination occurs by: (a) direct invasion into vagina, parametrium, and to adjacent organs such as bladder and rectum; (b) indirect extension mainly by lymphatic dissemination to pelvic lymph nodes and further para-aortic lymph nodes. Distant visceral metastases are less common during presentation, but may disseminate to the lungs, liver, and bones.

Staging and Prognosis

The premalignant lesions and also early-stage diseases are asymptomatic. However, in case of more advanced disease, symptoms such as vaginal bleeding, abnormal vaginal discharge, dyspareunia, and also pelvic pain may be found. Moreover, involvement of adjacent organs may lead to urinary incontinence, rectum pain, lumbar pain, and lower limb edema.

The most recent staging system for cervical shifted from clinical to the consideration of surgical and imaging findings [6]. One of the main changes was the incorporation of the lymph node status, one of the most important prognostic factors. Briefly, early-stage tumors are localized in the cervix and include stages Ia-Ib2, and advanced tumor are those with stages ≥Ib3. The stage Ia is usually diagnosed after a conization and has <5 mm of depth of invasion. In stage Ib, the tumor has depth of invasion of ≥5 mm and categorized as Ib1, Ib2, and Ib3 when tumor size is <2 cm, ≥2–4 cm, and ≥4 cm, respectively. Moreover, in stage II the tumor extends outside de cervix (IIa into vagina and IIB into parametrium) and stage III the tumor extends to lower third of vagina (IIIa), pelvic sidewall (IIIB) or pelvic, and paraaortic lymph nodes (IIIC1 and IIIC2). Finally, invasion of adjacent organs such as bladder is considered as stage IVa, and distant metastasis as stage IVb.

Notably, staging may be done by physical exam, surgery, or imaging, and ideally pelvic magnetic resonance is the best tool to evaluate pelvic local extension and PET-CT for metastatic staging, mainly for those with stages ≥Ib3 (Fig. 5.3).

Oncological Treatment

Staging determines the type of treatment in cervical cancer. For stage Ia1, the risk of lymph node metastasis is <1% and lymph node dissection is only indicated when lymphovascular space invasion is present. A simple hysterectomy is sufficient for treatment and for women who desires to preserve fertility; a conization with free margins is indicated [19].

For stage Ia2, the risk of lymph node metastasis increases up to 6–8% and node staging is warranted. Moreover, a modified radical hysterectomy (type B) is the

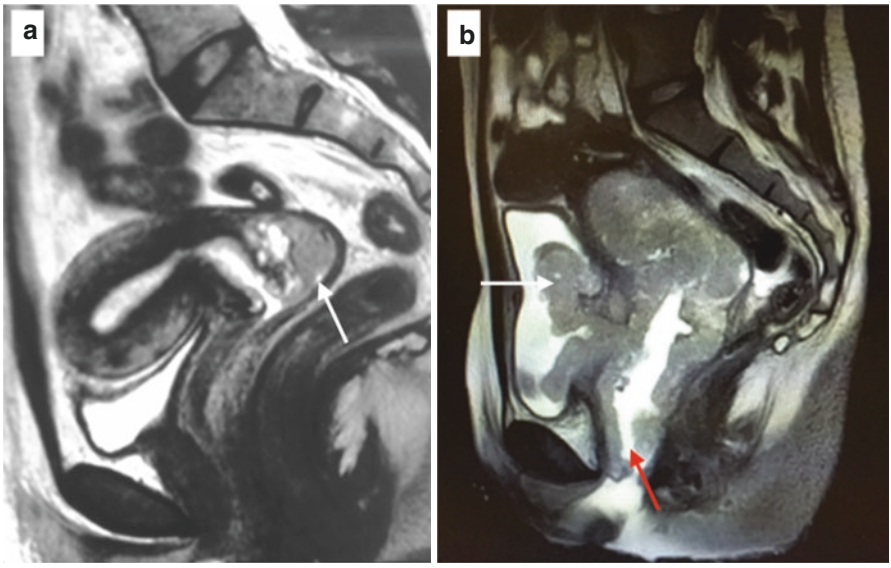

Fig. 5.3 (**a**) Sagittal section of magnetic resonance imaging showing a stage Ib3 cervical cancer. (**b**) Magnetic resonance showing a locally advanced stage IVa cervical with extension to the bladder (white arrow) and external 1/3 of vagina (red arrow)

chosen treatment. For other early-stage diseases (Ib1 and Ib2), radical hysterectomy (type C1 or C2) and pelvic lymph node dissection are the standard treatment. It is well-established that radiotherapy has the same survival rates even for early-stage diseases. Therefore, patients who mostly benefit with surgery are those young without comorbidities in which adjuvant radiotherapy is not needed, as addition of treatment types also increases the morbidity rates [20]. Radical hysterectomy implies in parametrial resection morbidity due to autonomic nerves lesions. In order to decrease the risk of autonomic nerve injuries, nerve-sparing surgeries are now performed (type C1) or even less resection of the parametrium (type B) [21]. Notably, in women who desire to preserve fertility, radical trachelectomy is indicated, where the uterine corpus and the ovaries are preserved. It is indicated for tumors of up to 2 cm and with no extrauterine disease. Fertility sparing surgery does not negatively impact survival [22] (Fig. 5.4).

Sentinel lymph node mapping has been developed to increase the accuracy of the status of the lymphatic basin, decrease the morbidity of full lymph node dissection and low volume metastasis detection, and define the site of node metastasis in anatomic templates. It has been studied in cervical cancer by leading gynecological oncology groups worldwide, but despite the encouraging data, it has not been adopted as a standard of care yet [23]. Moreover, a recent phase III trial [24] and others' retrospective demonstrated a negative impact in survival for radical hysterectomy when performed by minimally invasive surgery and also without negative impact in morbidity. So, the current standard of care is the open approach [25] (Fig. 5.5).

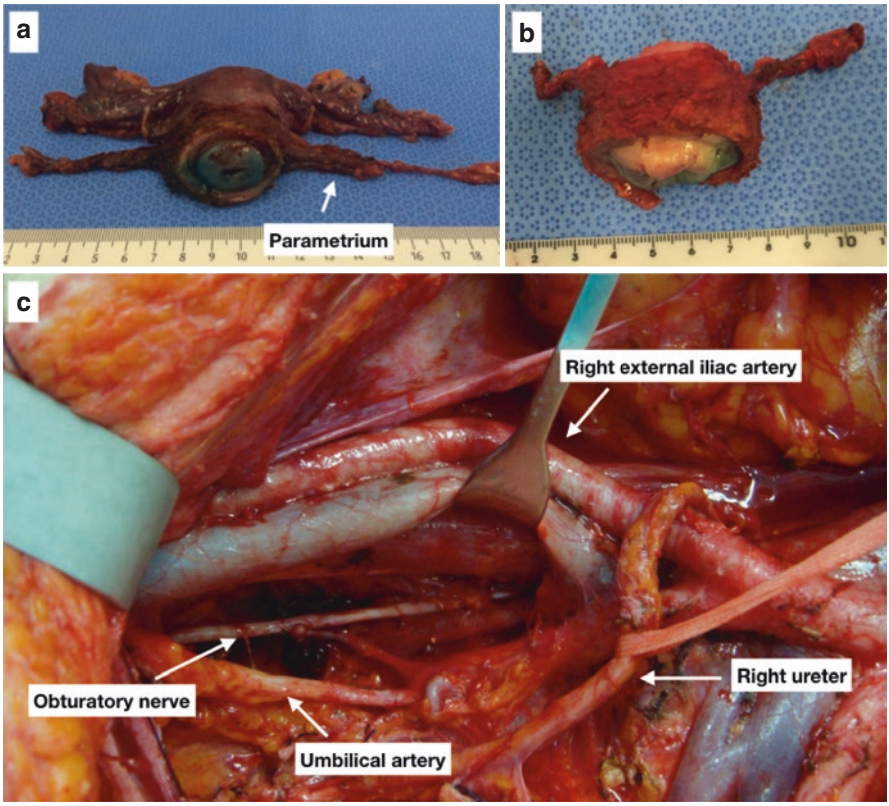

Fig. 5.4 (**a**) Example of surgical specimen after radical hysterectomy. (**b**) Surgical specimen after a radical trachelectomy. (**c**) Intraoperative aspect after systematic pelvic lymph node dissection

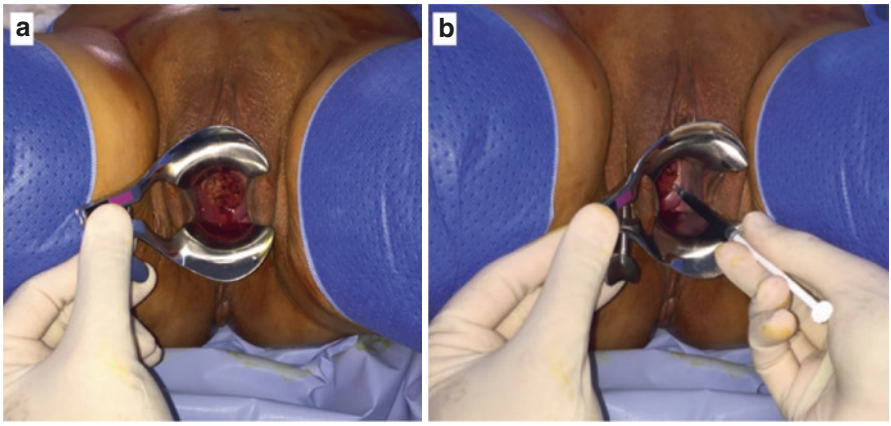

Fig. 5.5 (**a**) Clinical aspect of a stage Ib2 cervical cancer. (**b**) Injection of patent blue dye near the cervical tumor at 3 o'clock

After surgical treatment and staging of early-stage disease, unfortunately adverse prognostic factors may be found in the definitive pathological specimen. The high-risk prognostic factors are positive lymph nodes, positive surgical margins, and parametrium invasion. For high-risk factors, adjuvant pelvic radiotherapy with concomitant platinum-based chemotherapy is indicated [26]. Moreover, intermediate-risk factors are the association of 2 out of the 3 factors: size, presence of lymphovascular space invasion, and depth of invasion. Also known as the "Sedlis" criteria, it indicates adjuvant radiotherapy [27].

For locally advanced tumors, the standard treatment is radiotherapy (including external beam radiotherapy and brachytherapy) with concomitant chemotherapy, usually platinum-based [28]. In case of pelvic recurrence or persistence of disease without concomitant distant metastasis, radical surgical procedures such as pelvic exenteration may be the only treatment with curative intent. However, definite urinary and/or fecal derivation might be needed due to pelvic viscera involvement [9]. Finally, for stage IVb or distant recurrence, palliative treatment with carboplatin and paclitaxel is the standard of care with addition of Bevacizumab, if available [29].

5.1.2.2 Endometrial Cancer

Diagnosis

Nearly 95% of uterine cancers are originated in the endometrium. Endometrial cancer (EC) is the 7th cause of women cancer around the world with nearly 200,000 cases diagnosed each year. It is the most frequent gynecological cancer in developed countries [16].

The diagnosis is mainly done after 50 years (75%), 20% of cases occur between 40 and 50 years old and less than 5% before 40 years. In most cases, EC is diagnosed in early stages, where the disease restricted to the uterus generally has favorable prognosis. The major risk factor is continuous exposure to estrogen without contraposition of progesterone, and it is the type of cancer with most increased risk related to obesity [30]. Most EC cases are sporadic; however, 8–10% may be related to an autosomal dominant hereditary cancer syndrome called Lynch Syndrome. It is caused by germline mutation of the DNA repair genes, being the most prevalent include MLH1, MSH2, MSH6, and PMS2. The principal primary sites of cancer in Lynch Syndrome are colorectal (penetrance of 70%) and endometrium (penetrance of 40–50%) [31]. Yet, small bowel, renal pelvis, ovaries, and stomach are also at a higher risk. The current protocol indicates universal immunohistochemical protein expression analysis of DNA repair genes in the resected tumor. Any loss of expression found means that the gene may have impaired function and the patient should have further germline evaluation in blood or saliva.

Pelvic ultrasonography is the most important tool for initial endometrial evaluation. In postmenopausal women, the endometrial thickness should be no greater than 5 mm. Additionally, as most of cases (95%) of EC are symptomatic even in early stages, population-based pelvic ultrasonography might have no impact in

decreasing risk of death for EC. The most common symptom is vaginal bleeding (90%), followed by abnormal vaginal discharge and pelvic pain. Notably, 5–20% of women with postmenopausal vaginal bleeding have EC [32]. The method for EC diagnosis is the endometrial biopsy, and it can be done by an office biopsy or under anesthesia in case of curettage or hysteroscopy.

Regarding histologic types, about 80% of cases are endometrioid and categorized in grades 1, 2, and 3. Moreover, non-endometrioid high-grade histologies comprise: serous, clear cell, and carcinosarcoma. Recently, a molecular profile was described and it impacts survival independently of the histological type and grade. Molecular types are divided into 4 categories: MSI high (hypermutated), *POLE* (ultramutated), Copy-number low (endometrioid), and Copy-number high (serous-like) where *POLE* cases have a very good prognosis and the Copy-number high the worst outcomes [33].

Staging and Prognosis

EC frequency is distributed per stage as: stage I (uterus restricted) 72%; stage II (cervical invasion) 12%; stage III (adnexal, parametrial or pelvic/paraaortic lymph node metastasis) 13%; and stage IV (pelvic viscera invasion or distant metastasis). The 5-year overall survival for local disease, loco-regional disseminated, and distant metastases are 95%, 67%, and 23%, respectively.

Since 1988, the clinical staging of EC shifted from clinical to surgical approach after a landmark study (GOG33) [34] that surgically evaluated the patients with total hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection. In GOG 33, 621 cases with clinically uterine-confined disease actually had 6% of peritoneal metastasis, 5% of adnexal metastasis, 16% cervical invasion, and 11% of lymph node metastasis (Fig. 5.6).

The main uterine risk factors for lymph node metastasis are high-grade histologies, deep myometrial invasion (≥50%), presence of lymphovascular space invasion, and cervical invasion. Lymph node metastasis is recognized as an important prognostic factor in EC; however, the impact of systematic lymph node dissection is still debated. Further, two randomized clinical trials that examined the therapeutic value of pelvic lymph node dissection in presumed uterine-confined disease found no survival benefit [35, 36]. Recently, SLN mapping has emerged as an acceptable surgical strategy when deciding between complete lymphadenectomy and no node dissection. This approach can help avoid the morbidity that is associated with a complete lymphadenectomy, such as neurovascular injury, lymphocyst formation, and lymphedema [37]. A recent meta-analysis that included 55 studies and 4915 patients reported an overall SLN detection rate of 81% (95% CI; 77–84%) versus 50% for bilateral SLNs (95% CI; 44–56%). Moreover, the use of indocyanine green increased the bilateral SLN detection rate compared with blue dye (74.6% vs. 50.5%) [5]. Yet, the studies noted an overall sensitivity of 96% (95% CI; 91–98%) and false-negative rates of less than 5% when analyzed per hemipelvis [38]. Since 2014, the National Comprehensive Cancer Network (NCCN) guidelines have

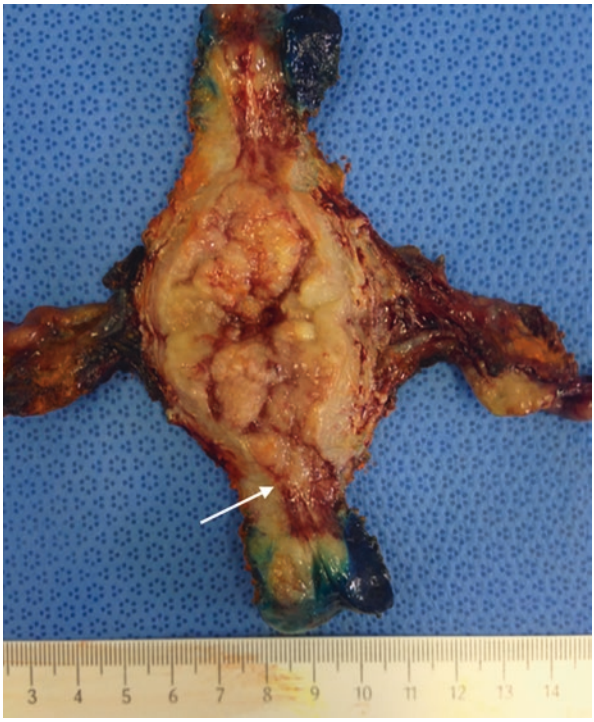

Fig. 5.6 Pathological specimen of total hysterectomy and bilateral salpingo-oophorectomy in endometrial cancer with cervical invasion (arrow)

recommended SLN mapping as an alternative option for node staging in endometrial cancer [39] (Fig. 5.7). Of note, there has been no prospective randomized trial performed yet. Moreover, the standard surgical access for EC staging should be by minimally invasive approach, either by laparoscopy or robotic-assisted, as three large randomized trials supported less complication rates without negative impact in survival [40–42].

Oncological Treatment

Adjuvant treatment in EC is based on recurrence risk. Women are usually cured with only surgery in the absence of risk factors such as high-grade histologies, deep myometrial invasion (≥50%), and presence of lymphovascular space invasion, cervical invasion, or advanced stage. The main adjuvant treatment in EC is radiotherapy. Some randomized trials have addressed the role of adjuvant radiotherapy in stage I EC and the results may be summarized in 3 topics: (a) Adjuvant external beam radiotherapy (EBRT) in the pelvis decreases the risk of loco-regional recurrence in intermediate-risk tumors (e.g., endometrioid stage Ia grade 3 or stage Ib grades 1 and 2), but do not impact overall survival; (b) EBRT significantly increases morbidity and negatively impacts quality of life; (c) Vaginal brachytherapy is adequate in decreasing the risk of local recurrence and also has a better toxicity profile [43].

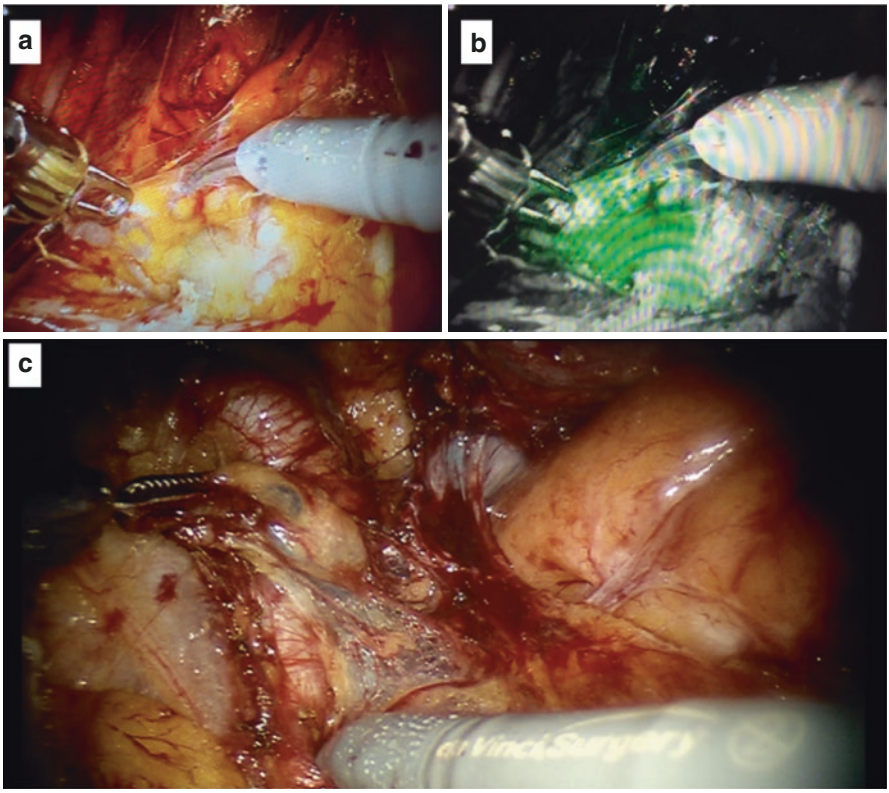

Fig. 5.7 Intraoperative aspect of sentinel lymph nodes mapped in robotic-assisted surgery. (**a**, **b**) Lymph node mapped with indocyanine green before and after near infrared imaging. (**c**) Aspect of lymph node mapped with blue dye

However, about 1/3 of cases apparently with disease confined to the uterus will develop distant recurrence [44] and recent phase III trials [44] addressed the value of adding chemotherapy to radiation in intermediate-risk tumors. Although with different scheduling of treatment, the studies did not find differences in survival. Nevertheless, our current practice suggests adjuvant chemotherapy with carboplatin and paclitaxel for early-stage non-endometrioid histologies and for cases with extrauterine diseases (e.g., positive lymph node or adnexal metastasis).

5.1.2.3 Ovarian Cancer

Diagnosis

Ovarian cancers are highly heterogeneous tumors and are divided into epithelial malignant neoplasms (80–85%), sexual cord-stromal malignant tumors (10–15%), and germ cell malignant tumors (<5%). As most cases are originated in the

epithelium, we will report only the ovarian carcinoma (OC) in this section. The risk of developing an ovarian carcinoma during life is about 1/70 women; however, 70–75% of cases are diagnosed in advanced stages (III and IV). It represents about ¼ of gynecologic cancers, but nearly ½ of deaths due to gynecologic cancer and the risk increases with age, mostly in the 6th and 7th decades of life. The most common histological type is high-grade serous (80%), followed by endometrioid, clear cell, mucinous, and low-grade serous [16].

One established protective factor of OC is use of oral contraceptives for at least 5 years [45], and unfortunately, trials that addressed population-based screening with pelvic ultrasonography and serum marker Ca125 did not show impact in earlier diagnosis and survival. Yet, screening is not advised for OC due to a high number of surgeries for false-positive findings and would be detrimental rather than beneficial [46]. Family history and germline mutation of BRCA1 and BRCA2 are well-known risk factors for OC development, with a life risk of 30–60% for BRCA1 and 15–30% for BRCA2. About 10–18% of OCs have germline mutation on BRCA1 or 2 and other 8% in other genes such as BARD1, BRIP1, CHEK2, MRE11A, MSH6, NBN, PALB2, RAD50, RAD51C, or TP53 [47]. The current indication for genetic test is for all cases of OCs regardless of age or family history, with exception for mucinous type [48]. In case of negative germline test, other 5% have somatic test positive (within the tumor). Moreover, women with known germline mutation have indication of risk reducing salpingo-oophorectomy at age 35–40 years [48].

The mutational status confers different clinical characteristics with prognostic and predictive value, as they have better response to platinum-based therapy, better prognosis, and better response to novel treatments called “poly-ADP-ribose polymerase” (PARP) inhibitors [49].

The clinical symptoms are vague and unspecific and usually related to disease dissemination such as abdominal distention and pain. The most common site of dissemination is the peritoneum followed by lymph node and distant mainly to the lungs and liver. In imaging, OC is suspected in case of a solid cystic mass, usually bilateral, and the peritoneal dissemination may be also found directly as nodules or peritoneal thickening or indirectly as ascites. Magnetic resonance is the best imaging tool for ovarian evaluation and peritoneal, lymphatic, and distant metastases can be evaluated by either magnetic resonance or computed tomography [49] (Fig. 5.8).

The most important serum marker is Ca125. Despite having increased values in more than 90% of OCs, abnormal values are only seen in 50% of early-stage cases. Moreover, it is not specific for OC, as it also increases in benign disease mainly found in premenopausal women such as endometriosis and leiomyomatosis [49]. Interestingly, other markers such as Ca19.9 and CEA may be increased in mucinous ovarian cancer. Yet, mucinous ovarian tumors are mostly metastatic from gastrointestinal sites and other primary tumors should be excluded.

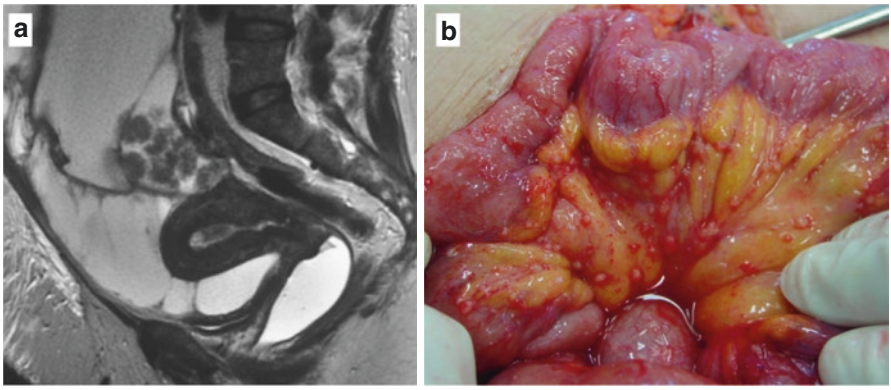

Fig. 5.8 (**a**) Pelvic magnetic resonance imaging showing an ovarian tumor with solid component (arrow). (**b**) Intraoperative aspect of carcinomatosis with implants in the small bowel and mesentery

Staging and Prognosis

Surgery has a major role in OC, not only for the diagnosis, but also for staging and treatment. About 70–75% of cases are diagnosed as stages III (peritoneal disease outside de pelvis) or stage IV (distant metastasis – visceral or outside the abdomen). Prognosis depends on stage, where early stages have >80% of overall survival in 5 years and stages III–IV of only 30–50% depending on the primary treatment [49]. Moreover, histologic type is also an important prognostic factor, as worse survival rates are found in clear cell and mucinous histologies due to less response to platinum-based chemotherapy.

In case of presumed early-stage I (disease restricted to the ovaries) or II (tubal involvement or pelvic extension), a comprehensive staging should be done that includes: hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, omentectomy, peritoneal evaluation with biopsies, and pelvic and paraaortic lymphadenectomy. In young women, it is possible to stage the tumor and preserve fertility in very selected cases, sparing the uterus and contralateral adnexa [49].

Moreover, for advanced stages (III and IV), surgery is called cytoreduction and has an important value. The objective is to resect all visible disease and therefore visceral (e.g., recto sigmoid and spleen) and peritoneal resections are usually included in the surgical procedure (Fig. 5.9).

Oncological Treatment

It is well established that the residual tumor volume after surgery is one of the major prognostic factors and the current objective is no residual macroscopic disease [49–51]. Despite the controversy generated after 3 phase III trials that did not demonstrate differences in survival after neoadjuvant chemotherapy when compared to frontline surgery [52–55], upfront or primary cytoreduction is still considered the

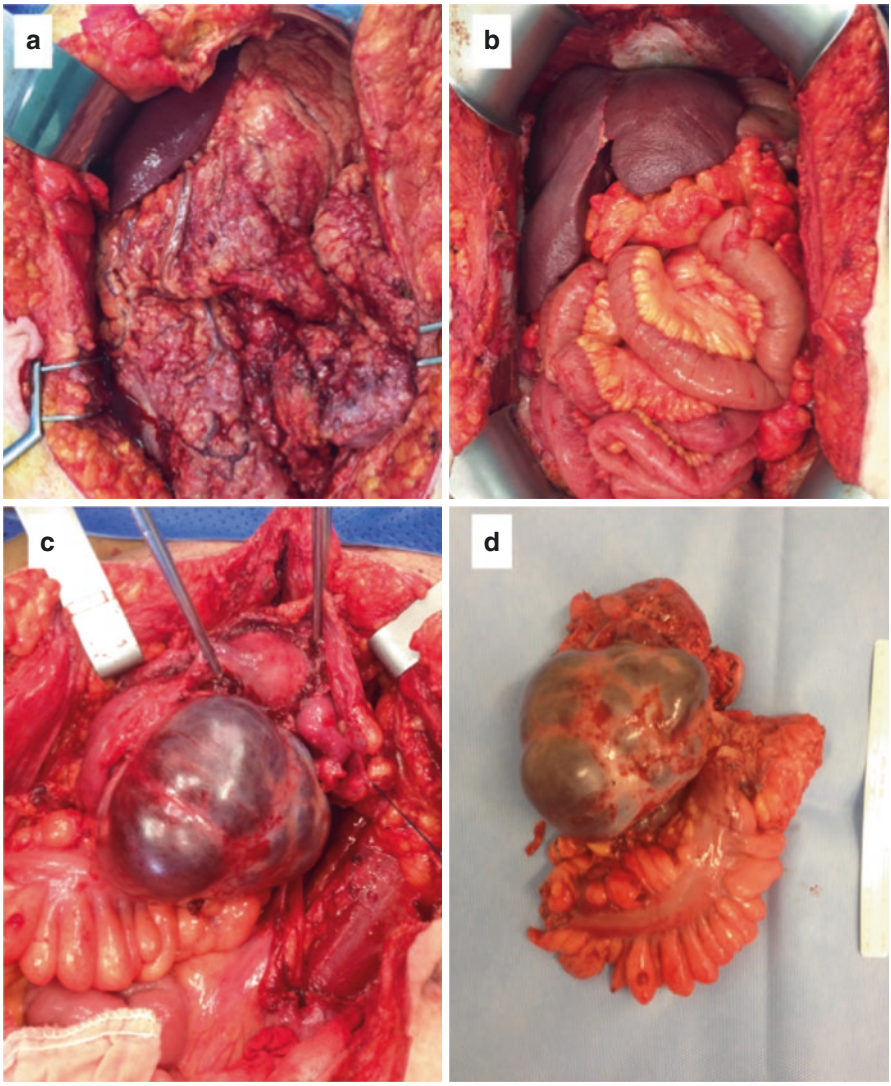

Fig. 5.9 (**a**) Intraoperative aspect of a stage IIIC ovarian carcinoma showing upper abdomen dissemination and "omental cake". (**b**) Intraoperative aspect after primary optimal cytoreduction. (**c**) Example of ovarian carcinoma with pelvic peritoneal dissemination. (**d**) Surgical specimen after posterior-modified pelvic exenteration (including rectal resection) and pelvic peritonectomy for optimal cytoreduction

standard of care for advanced ovarian cancer with peritoneal dissemination (stage III), and neoadjuvant chemotherapy of 3–4 cycles followed by interval cytoreduction should be reserved for patients not suitable for a high complexity surgery (frailty, age, and comorbidities) or if the complete resection not feasible even by trained surgeons. Despite great evolution in imaging for prediction of complete

(optimal) cytoreduction, the current best way to evaluate peritoneal extension of disease is assessment by laparoscopy [56]. Notably, the OCs, especially the high-grade serous, are very sensitive to platinum-based chemotherapy, and an overall response rate of 90% after neoadjuvant chemotherapy is expected [49, 52].

Most cases even in early-stage disease receive adjuvant chemotherapy, except for low-grade tumors restricted to the ovaries (stages Ia and Ib). The standard chemotherapy regimen is intravenous carboplatin and paclitaxel for 6 cycles every 21 days. In case of BRCA-mutated cases, PARP inhibitors are added to frontline treatment as maintenance. Unfortunately, almost 70% of primary advanced cases recur within 5 years, with median time of 12–24 months depending on primary treatment. Recurrent disease is considered as platinum-resistant when occurs in less than 6 months after the last platinum-based chemotherapy. It reflects a worse prognosis and non-platinum single agent chemotherapy with gemcitabine, liposomal doxorubicin, and topotecan is usually used. In case of platinum-sensitive recurrence, a doublet based on platinum chemotherapy is administrated. Yet, PARP inhibitors and anti-VEFR drugs (Bevacizumab) are also active in recurrent disease [49].

5.1.2.4 Vulvar Cancer

Diagnosis

Vulvar cancer is the less frequent gynecological tumor, with incidence of 2–3 cases/100,000 women, corresponding to 3–5% of the gynecological cancers, with median age of 70 years old. The most common histological type is the vulvar squamous cell carcinoma (VSCC) in 95% of cases, followed by melanomas [57].

We may categorize it into two types. First is related to high-risk HPV infection (40% of cases), being multifocal, and related to presence of usual type or high-grade vulvar intraepithelial neoplasia (VIN) in younger women. The second is related to vulvar atrophy and sclerosus lichen, unifocal, and to the presence of differentiated VIN.

Staging and Prognosis

Surgery is the cornerstone of treatment and inguinal lymph node metastasis is the most important prognostic factor [58]. The current management of vulvar squamous cell carcinoma depends on the extension of disease and includes primary tumor resection with safety margins as well as inguinofemoral lymph node staging [7].

Oncological Treatment

For tumors with up to 4 cm without clinical inguinal lymph node metastasis, sentinel lymph node biopsy with blue dye and technetium can be considered as the standard of care. In case of positive sentinel lymph node, a systematic inguinofemoral

lymphadenectomy should be carried out followed by inguinal and pelvic radiation [7].

In case of multicentric tumors, those of >4 cm or clinical-positive lymph nodes, a primary systematic inguinofemoral lymphadenectomy should be done.

Moreover, surgical margins of 2 cm are desired, and in case of locally advanced disease that invades urethra or anus or fixed inguinal lymph nodes, treatment should start with neoadjuvant radiotherapy with concomitant chemotherapy in order to preserve the bladder and anus [7] (Fig. 5.10).

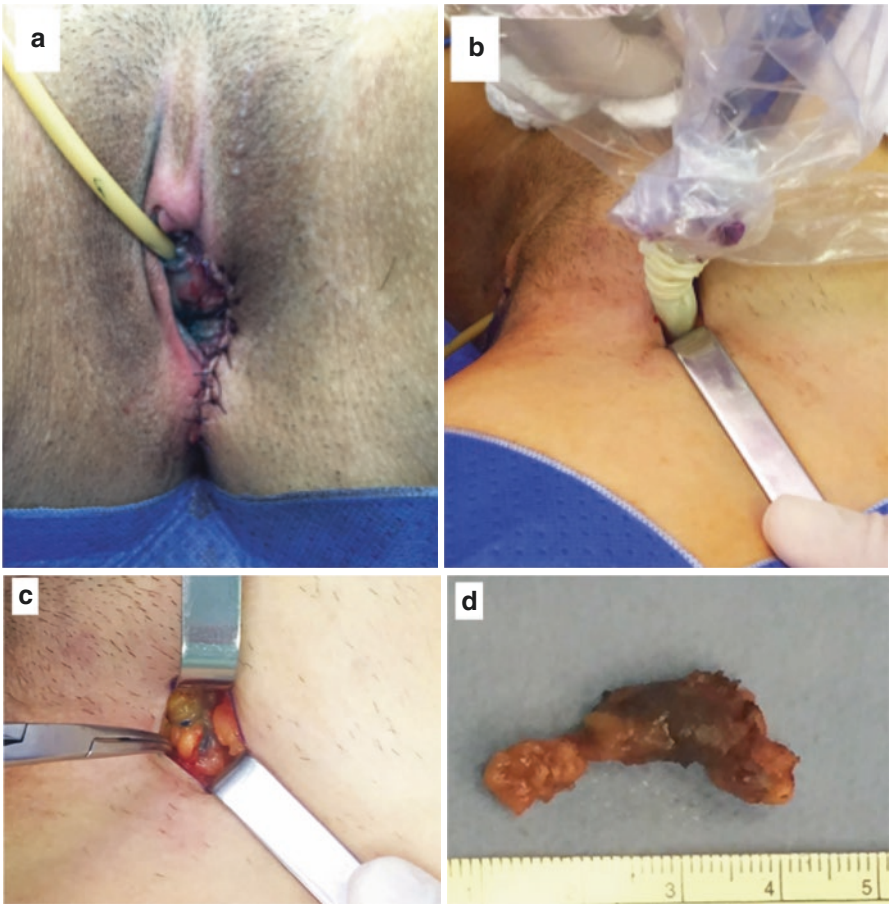

Fig. 5.10 (**a**) Immediate postoperative aspect of a wide local resection for vulvar cancer. (**b**) Intraoperative aspect of inguinal sentinel lymph node biopsy colored by both blue dye and (**c**) technetium. (**d**) Resected sentinel lymph node

5.1.3 Anatomy Considerations Related to Systematic Lymphadenectomy and Vascular Complications

Anatomy is the basis for skilled surgeons, and despite gynecologic tumors have its origin in the pelvis, it is crucial for a gynecologic oncologist to dominate anatomy of pelvis, upper abdomen, retroperitoneum, and all pelvic lymphatic drainage as female tract cancers may disseminate into all these regions.

Lymphatic channels drain from the vulva into inguinofemoral lymph nodes, usually first to superficial (above the cribriform fascia) inguinal lymph nodes and then to the deep or femoral lymph nodes. The vagina may be divided into three parts, and the upper 1/3 drains into pelvic lymph nodes, the middle 1/3 to both pelvic and inguinal lymph nodes, and the lower 1/3 to the inguinal lymph nodes. Yet, lymphatic channels drain from the cervix by the parametrium following the uterine arteries to the pelvic lymph nodes (external iliac, internal iliac, and obturator lymph nodes). From these lymph nodes, the lymphatic drainages run up to the paraaortic lymph nodes. In up to 10% of cases, the uterine cervix can drain directly to presacral, common iliac, or even to paraaortic areas through alternative lymphatic channels that run below the ureters.

Despite the argument that the uterine corpus may also drain directly to the retroperitoneum through the infundibulopelvic ligaments, its most important drainage is also by the cervix and parametrium. The ovarian drainage is the most erratic and follows three routes: (a) the major drainage is along the lymphatic channels of the infundibulopelvic ligaments directly to the paraaortic lymph nodes; (b) along with the broad ligaments to pelvic lymph nodes; and less frequently, (c) channels following the round ligaments into the inguinal lymph nodes.

The para-aortic or retroperitoneal lymph nodes are part of the lumbar lymph nodes and six groups are usually described: paraaortic (left-sided), preaortic, retroaortic, paracaval, retrocaval, and interaorto-caval. The preaortic has drainage from the colon and rectum, whereas the paraaortic, paracaval, and interaorto-caval receive drainage from the pelvic viscera. Systematic lymphadenectomy for gynecologic tumors should have lymph nodes resected from all these areas, and retroperitoneal lymphadenectomy may go up to the inferior mesenteric artery or up to the renal vessels depending on the indication. There are usually 15–20 lymph nodes in each paraaortic and paracaval areas and 10–15 pelvic lymph nodes in each hemipelvis. The surgeons should be warranted by anatomic variations, commonly found such as left renal vein crossing behind the aorta or renal polar arteries (Fig. 5.11). Most of them can be found preoperatively by careful evaluation of imaging (computed tomography). Distally, the lymph nodes located along with the circumflex vessels should be spared as their resection correlates to a higher risk of lower limb lymphedema and are not expected of being the first site of lymph node metastasis [59].

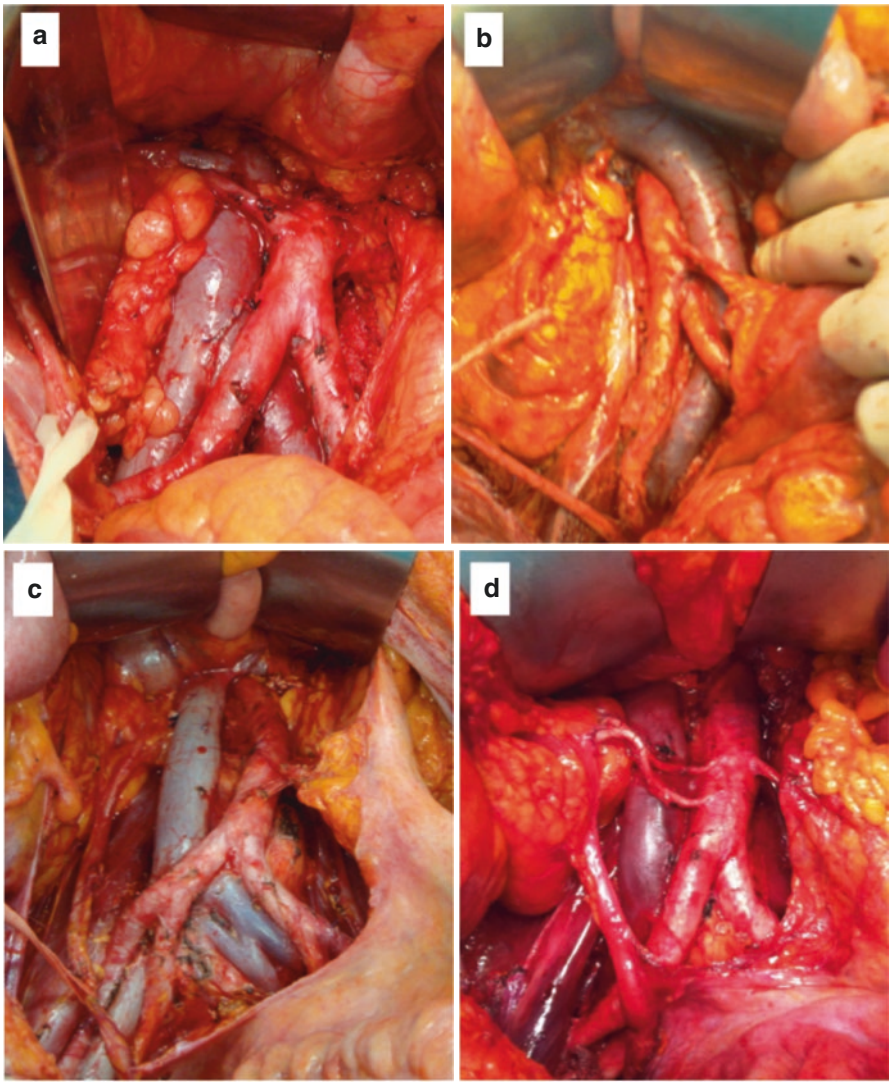

Fig. 5.11 Examples of intraoperative findings of anatomic variations. (**a**) Right renal arteries crossing anteriorly to vena cava. (**b**) "Trans-positioned" left-sided vena cava. (**c**) Anatomic variation of left common iliac vein. (**d**) Right renal polar arteries

5.1.4 "Out of the Box" Surgical Procedures in Gynecologic Cancer Related to Vascular Surgery

In exclusive pelvic recurrence of gynecologic cancers after radiation therapy, surgery may be the only treatment with curative intent. Pelvic exenteration is a widespread major pelvic surgery in gynecologic oncology [9]; however, other ultra-radical

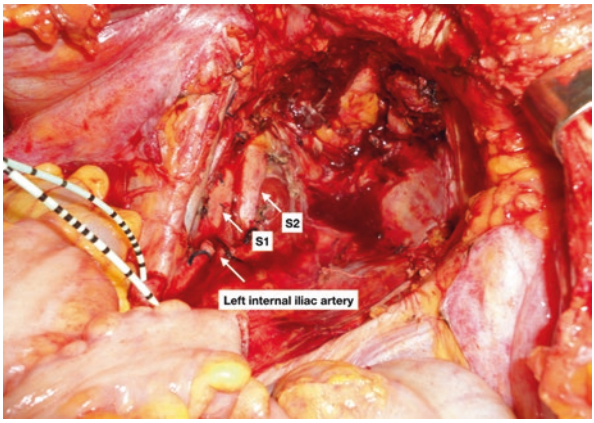

Fig. 5.12 Intraoperative aspect after lateral extended endopelvic resection associated to total pelvic exenteration in cervical cancer

surgical procedures have been reported and some of them include vascular resections (Fig. 5.12).

In 2008, Caceres et al. [60] reviewed the records of 14 cases treated at MSKCC with extended pelvic resections due to pelvic uterine and cervical cancer recurrences that included side wall muscle resections ($n = 5$), pelvic bone ($n = 5$), lumbosacral nerve root ($n = 1$), and also common and/or external iliac vessel with bypass ($n = 5$). They reported overall negative margins of 78% and 71% survival rate at median follow-up of 26 months. Seven cases (50%) also had intraoperative radiotherapy. Moreover, data from Mayo Clinic [61] included 25 patients with recurrent endometrial cancer who underwent ultra-radical procedures that included the iliac vein as well as psoas, obturator internus muscle, or bone, followed by intraoperative radiotherapy in 84% of cases. They reported a 5-year overall survival of 53%.

Recently, Tinelli et al. [62] published the largest series to date that included 50 cases with gynecologic malignancies admitted for major surgery that showed retroperitoneal or pelvic vascular involvement at preoperative imaging. Fifteen (30%) cases had preoperative involvement of both artery and vein (Tinelli's score ≥ 4). Twenty-three cases had major vascular surgeries, with psoas muscle excision (8.7%), pelvic sidewall (56.5%), and urologic structure (17.4%) or bowel resection (45.5%). Regarding the vascular procedures, 18 (36%) cases had arterial involvement among whom seven (39%) had arterial resection, six had graft reconstruction, and one had reimplantation of renal artery. Moreover, 10 (43.4%) cases had venous involvement and seven concomitant artery involvement. R0 resections were achieved in 88% of cases. Perioperative median blood loss was 600 ml (higher in major vascular procedures) and median operative time was 420 min for major vascular surgeries. No trans-operative death was reported and major complications were found in 12% of cases and there was only one case of vascular complications. Yet, 72% of cases were alive with no evidence of disease after median follow-up of 13 months.

Furthermore, Martínez-Gómez et al. [63] proposed a 2-step procedure aiming to decrease the risk of graft infection. A femoro-femoral crossover bypass is carried

out by bilateral groin incisions 15 days before the surgery for tumor resection. The common iliac artery is then embolized and the common iliac femoral artery ligated up to the bypass. They reported 11 cases, with R0 resections in nine (81.8%). No vascular postoperative complications were observed.

In summary, "out of the box surgery" is feasible for high selected cases and remains as the only treatment with curative intent.

5.2 Breast Cancer

5.2.1 Most Common Tumor Types

Globally, breast cancer is the second most frequently diagnosed malignancy just behind lung cancer, accounting for over two million cases each year. It is also the leading cause of death due to cancer among women worldwide [64]. In Brazil, breast cancer is the most common cancer among women, with roughly 66.280 cases diagnosed per year [65]. Unfortunately, breast cancer is also the most common cause of death due to cancer among women in Brazil, with 16.724 deaths per year [65]. However, due to decades of intensive medical research and improvements in both screening and treatment, the mortality rates for breast cancer have been steadily declining worldwide. Currently, most breast cancer patients are cured, and in developed countries, the 10-year overall survival (OS) rate is 84% [66].

Adenocarcinomas are the most common tumor type, representing 95% of breast malignancies. Ductal invasive carcinoma (IDC) is the most common histological type of breast adenocarcinoma, accounting for 55% of diagnosed breast cancers [67]. Following IDC, invasive lobular carcinoma (ILC, ~15% of cases), in situ carcinomas, and special subtypes (such as tubular carcinomas and medullary carcinomas) are also diagnosed [67]. Immunohistochemical analysis (IHC) of breast cancer is mandatory, and it is able to detect expression of estrogen receptors and progesterone receptors, as well as HER2 status and Ki67 proliferation rate. The latter is performed in most countries, except in the United States. Non-epithelial malignancies such as sarcomas and phyllodes tumors are uncommon, representing ~1% of breast tumors [68].

5.2.2 Types of Tumor Most Frequently Associated with Vascular Complications

Adenocarcinomas are the tumors most frequently associated with vascular complications, due to their high incidence. Venous thromboembolism (VTE) is the most common vascular complication in breast cancer patients.

5.2.3 Diagnosis

Greater availability of screening programs has facilitated the diagnosis of breast cancer in asymptomatic patients and at earlier stages of disease. In the United States, curable cases of breast cancer (i.e., those that are localized or metastatic to regional lymph nodes only) account for 90% of diagnosed cases [69]. Approximately 25% of breast cancer cases develop in patients between 55 and 64 years of age (median age, 62 y) [69]. Among a large cohort of breast cancer patients treated at a cancer center in Brazil (5095 patients treated between 2000 and 2012), curable cancer cases accounted for 89.9% of the diagnosed cases [70]. Within this same cohort, 45.6% of the patients were 50–69 years old, while a surprisingly high incidence (40%) of patients were younger than 50 years of age. It should be noted that these percentages may be specific for this cancer center rather than representing a general profile for breast cancer cases [70].

A key imaging exam for detecting breast cancer is a mammogram. The findings of this exam are further supported by those from breast ultrasound and breast magnetic resonance exams. In average-risk women, annual mammographic screening is suggested to begin usually around 40 years of age, although most countries have specific recommendations, due to conflicting data on this subject (concerning harms and benefits from screening). As an example, the *Brazilian Ministry of Health* recommends biennial mammographic screening for women in the age group of 50 years to 69 years only [71]. The *Brazilian Mastology Society* (Sociedade Brasileira de Mastologia), on the other hand, suggests annual mammographic screening starting at 40 years of age [72]. There is no current recommendation to use other imaging exams for screening, except breast magnetic resonance in high-risk women (e.g., hereditary breast cancer syndromes). Suspicious findings in these exams are classified according to the Breast Imaging Reporting and Database System (BI-RADS™), a standardized risk assessment tool which helps physicians decide whether a biopsy is needed or not [73]. A final diagnosis is obtained only after a percutaneous or surgical biopsy is performed, with the former being the preferred method. Thus, a biopsy is a crucial step in breast cancer treatment as it directly affects the treatment strategy recommended.

5.2.4 Staging/Prognosis

The staging system most often used for breast cancer is the American Joint Committee on Cancer (AJCC) TNM 8th edition® [74]. In addition to anatomic staging (e.g., tumor size, nodal metastasis, and distant metastasis), the latest edition also includes breast cancer prognostic staging which uses tumor grade, HER2/estrogen receptor/progesterone receptor status, and genomic profiling (if available, such as OncotypeDx®). This expansion of staging criteria represents the importance of IHC data on prognosis and therapeutic guidance. For example, IHC data allow breast

cancer to be categorized according to genomic profiling, whereby luminal (luminal A = hormone receptor-positive + HER2-negative; luminal B = hormone receptor-positive + HER2-positive), HER2-enriched (hormone receptor-negative, HER2-positive), and triple-negative (hormone receptor-negative and HER2-negative) tumors can be identified. Different genomic profiles have different prognoses, despite potentially similar anatomical staging. For example, a luminal G1 T2 N0 M0 is classified as stage IB, yet a triple-negative G1 T2 N0 M0 is classified as stage IIA. Prognosis and cure rates in the United States are excellent, with a 98% 5-year overall survival rate among localized breast cancer patients and an 85% 5-year overall survival rate among locally advanced breast cancer patients [69]. Breast cancer overall survival rates of the aforementioned Brazilian cancer center cohort are very similar to the US rates, especially among localized breast cancer patients [70]. Among the latter, OS exhibits a substantial increase over the last decade, potentially due to improvements in adjuvant treatment.

5.2.5 Oncological Treatment

Breast cancer treatment is usually multidisciplinary, involving surgery, systemic treatment, and radiotherapy [74]. Surgery is the only mandatory treatment for curable breast cancer, although most patients will undergo systemic treatment and radiotherapy as well. Surgery may be conservative or radical (mastectomy) and may or may not include immediate reconstruction. The goal of surgery is to remove a tumor with minimal free margins. Radical surgery was the gold standard until the 1980s, when Umberto Veronesi and Bernard Fisher published their randomized clinical trials on breast conserving surgery, showing that this new treatment was as effective as the latter (same overall survival). While the type of surgery performed does not affect overall survival, it does affect local recurrence rates (radical surgery has a lower recurrence rate, ~2%, while breast conserving surgery has a ~ 8% recurrence rate) [68]. This recurrence rate difference is minimal; hence, we suggest conservative treatment whenever it is technically feasible (depending on tumor and breast size) due to its superior cosmetic result. Radical surgery nowadays is usually reserved for locally advanced disease or with prophylactic intent (in patients with hereditary breast cancer syndromes). Axillary surgical staging is always necessary; with a sentinel node biopsy performed for localized disease (cN0) and an axillary lymphadenectomy performed for regional disease (cN1, 2, or 3). Axillary status is very important for adjuvant/neoadjuvant treatment decisions since it is considered to be one of the most important prognostic factors in breast cancer. A-positive axillary lymphnode will frequently indicate the need of systemic treatment and radiotherapy. Regarding systemic treatment, this may involve cytotoxic chemotherapy (such as anthracyclines and taxanes), endocrine therapy (drugs that affect the metabolism of estrogen and progesterone, such as tamoxifen and aromatase inhibitors), and/or targeted therapy (drugs which act on specific targets and generally have fewer side effects, such as trastuzumab) in either neoadjuvant or adjuvant settings.

Most patients will undergo some form of systemic adjuvant treatment. In luminal cancers, patients with tumors >10 mm or positive axillary lymph nodes will often need adjuvant chemotherapy and will always need adjuvant endocrine therapy (the choice between tamoxifen and aromatase inhibitors depends on menopausal status). In HER2-enriched and triple-negative tumors, the systemic treatment indication is even more aggressive, with cytotoxic chemotherapy indicated to patients with tumors >5 mm, disregarding axillary status. The most common chemotherapy regimen includes doxorubicin, cyclophosphamide, and paclitaxel, although other regimens and other drugs such as carboplatin or epirubicin may be used. In HER2-enriched tumors, targeted therapies (such as trastuzumab) are added to cytotoxic chemotherapy regimens, with excellent results. Endocrine therapy is not indicated in tumors with negative hormone receptors on IHC. Neoadjuvant treatment is usually indicated for disease downstaging before surgery. IHC can help decide whether neoadjuvant or adjuvant treatment is more beneficial and appropriate drug options. Generally, luminal tumors do not respond well to cytotoxic drugs (luminal A tumors are usually only treated with endocrine therapy and may use these medications on a neoadjuvant setting), triple-negative tumors respond very well to cytotoxic drugs yet do not respond to endocrine therapy, and HER2-enriched tumors respond very well to cytotoxic drugs in combination with anti-HER2 targeted therapy. Nowadays, it is very common to select neoadjuvant chemotherapy for treatment of triple-negative and HER2- enriched tumors, despite their size due to the great responses exhibited by these two tumor types to systemic treatment. As a result, pathological complete response rates up to 60% have been observed in these cases [75]. Conversely, if a patient does not present a complete pathological response, systemic treatment can be applied after neoadjuvant chemotherapy to improve OS [76, 77]. However, the latter option is not available for luminal tumors.

Radiotherapy is generally performed in an adjuvant setting. However, in selected cases, it is administered intraoperatively. After breast conserving surgery, radiotherapy is mandatory, and it is only applied to locally advanced cases after radical surgery. Patients with systemic metastasis are considered incurable and they can receive systemic treatment with palliative intent. Nonetheless, due to the multidisciplinary aspects of breast cancer treatment, it usually extends over several months, and unfortunately, can be accompanied by many side effects, including vascular events.

5.2.6 Vascular Complications in Breast Cancer

Vascular complications in breast cancer may arise due to the disease itself, yet also as a result of treatment. Disease-related and treatment-related complications include the following:

- Disease-related: venous thromboembolism (VTE)
- Treatment-related:

- Surgery-related: VTE, superior member chronic lymphedema, port-a-cath complications
- Systemic treatment-related (both cytotoxic and endocrine therapies): VTE, cardiovascular toxicity

5.2.7 General Information Regarding VTE

VTE includes both deep vein thrombosis (DVT) and pulmonary embolism (PE) events. It is an important cancer-related comorbidity which may develop at any stage of disease. In the general population, VTE has a low incidence. For example, the estimated incidence of VTE in the United States is 117 cases per 100.000 people [78], while the estimated incidence of DVT in Brazil is 60 cases per 100.000 people [79]. Cancer patients have a 4-fold higher risk of VTE, although this number may vary substantially according to cancer type, disease stage, and ongoing treatment [80]. The pathogenesis of cancer-associated VTE is complicated and multifactorial. The disease itself creates a hypercoagulability state by four mechanisms: production of procoagulant factors, fibrinolytic activity, production of inflammatory cytokines, and blood cell interactions. In addition to cancer thrombophilia, other conditions can also increase the risk for VTE in cancer patients, including patient-related factors and treatment-related factors. Table 5.1 summarizes the most important VTE risk factors known to date [81].

Regarding the incidence of VTE in breast cancer, Walker et al. [82] analyzed a British cohort of 13.202 women with breast cancer and observed VTE risk during all phases of treatment. Patients were treated between 1997 and 2006 and were followed through 2010. VTE events were reported in 611 patients, which corresponds to a VTE rate of 8.4 cases per 1000 person-years. Among those affected, 273 developed pulmonary embolisms. Moreover, the greatest risk for VTE was observed during chemotherapy (relative risk 10.8 during treatment), followed by tamoxifen (relative risk 5.5 in the first 3 months) [82, 83]. Aromatase inhibitors were actually associated with decreased VTE risk (relative risk 0.8) in this cohort, despite previous data that considered this medication to be a VTE risk factor [81–83]. In this cohort, patients probably used doxorubicin, cyclophosphamide, and paclitaxel in most cytotoxic treatments. It is also possible that platinum-based chemotherapy and central venous catheters were used in some patients, both of which are known VTE risk factors. Many patients in this cohort also used either tamoxifen or aromatase inhibitors after chemotherapy regimens. The relative risk of VTE for surgical patients was 1.5 during hospitalization, increasing to 2.2 in the first month after discharge [82, 83].

Regarding VTE and breast cancer mortality, Chew et al. [84] observed a higher mortality rate in breast cancer patients diagnosed with VTE. The authors analyzed a cohort of 108.255 breast cancer patients treated in the United States between 1993 and 1999. They found the 2-year cumulative incidence of VTE was 1.2%, while the overall 2-year survival rate decreased among the patients diagnosed with VTE

Table 5.1 Identified VTE risk factors

Patient-related factors	Cancer-related factors	Treatment-related factors
Age >65 years	Primary site of cancer Pancreas Stomach Brain Lung Colon Hematologic Others such as kidney, ovary, uterus	Pharmacologic management Platinum chemotherapy Antiangiogenic agents Tamoxifen and aromatase inhibitors Erythropoietin-stimulating factors
African-American race	Metastatic disease	Surgery (breast and colon highest risk)
Females with colon cancer	Initial year after diagnosis (first 3–6 months highest risk)	Presence of central venous catheter
Comorbidities Renal, infection, pulmonary, hepatic diseases Anemia Obesity History of thrombosis or prothrombotic mutations		Hospitalization
Pre-chemotherapy lab values Platelet count > or = 350 × 10^9/L Leukocyte count > or = 11 × 10^9/L		

(hazard ratio: 2.3). The greatest decrease in survival was observed among early-stage breast cancer patients diagnosed with VTE (hazard ratio: 5.1).

5.2.8 VTE Prophylaxis in Breast Cancer

Despite its low incidence in breast cancer patients (in absolute numbers), VTE is a public health problem. In the United Kingdom, approximately 17% of patients in anticoagulation clinics are breast cancer patients [82]. VTE is a potentially lethal disease and can require a long and expensive treatment regimen. Hence, prophylaxis may represent an interesting strategy. Both the European Society of Medical Oncology (ESMO) [85] and the American Society of Clinical Oncology (ASCO) [86] have established guidelines for VTE management. For breast cancer patients, VTE prophylaxis may be relevant perioperatively, or during systemic treatment (either chemotherapy or endocrine therapy).

During systemic treatment, it is recommended that prophylaxis be applied only when breast cancer patients are hospitalized with an acute medical complication and/or with restricted movement. Under these conditions, both ESMO and ASCO

guidelines recommend pharmacologic prophylaxis, with ESMO suggesting low-molecular-weight heparin (LWMH), unfractionated heparin (UFH), or fondaparinux. Hospitalized patients without acute illness or restricted mobility may also receive pharmacological prophylaxis, although it is not mandatory. In contrast, both sets of guidelines do not recommend VTE prophylaxis for patients who require hospitalization for chemotherapy administration, although this situation is not common in most breast cancer chemotherapy regimens. Prophylaxis is also not recommended for most ambulatory patients undergoing systemic treatment (either chemo or endocrine therapies), except for those with high-risk features (measured according to Khorana scoring), a rare situation for breast cancer patients.

While VTE pharmacological prophylaxis is well-established for major cancer surgical procedures, it is not as established for smaller and less invasive cancer surgical procedures. For breast cancer, surgical VTE prophylaxis is more controversial. Breast cancer surgery recovery is usually quick, with early ambulation and early hospital discharge. Similarly, following breast conserving surgery, hospital discharge usually occurs the same day as surgery. With more extensive surgeries such as mastectomy with immediate reconstruction, patients also usually present with early ambulation and hospital discharge occurs on average up to 48 h after surgery. Many researchers have investigated the need for pharmacological prophylaxis in patients with breast cancer after observing differences in recovery. For example, Andtbacka et al. [80] analyzed VTE incidence in a large retrospective cohort of breast cancer patients surgically treated at MD Anderson Cancer Center (Houston, TX, USA). Data from 3898 patients who underwent 4416 surgical treatments for breast cancer between 2000 and 2003 were examined. At that time, the MD Anderson Cancer Center only used mechanical prophylaxis (both compressive stockings and intermittent compression) combined with patient preoperative orientation about VTE and early ambulation with physiotherapy for VTE prophylaxis in breast cancer patients undergoing surgery. Among this cohort, all types of breast cancer surgery were performed, with approximately 18% of the procedures being more extensive with immediate reconstruction. Only seven patients developed VTE within 60 days of surgery (representing a rate of 0.16% per procedure). Six of the seven patients underwent mastectomy, while the additional patient underwent conservative breast surgery with axillary lymphadenectomy. The authors concluded that pharmacological prophylaxis is not needed in breast cancer surgery if mechanical prophylaxis, early ambulation, and preoperative orientation are achieved. Based on this study and others, the American Society of Breast Surgeons (ASBS) has issued the following consensus guidelines regarding VTE prophylaxis for patients undergoing breast operations [87]:

1. There is insufficient evidence to determine whether the published VTE prophylaxis guidelines for patients undergoing major orthopedic or general surgical operations for cancer should be uniformly applied to breast surgery patients.
2. Overall VTE incidence after breast cancer surgery is low.

3. Most breast cancer surgeries with general anesthesia and without immediate reconstruction will have a low incidence of VTE with mechanical prophylaxis and early ambulation.
4. Pharmacological prophylaxis (no suggested medication) may be performed when:
   (a) The duration of general anesthesia is >3 h
   (b) Patients have a Caprini score >5
   (c) Mastectomy with immediate reconstruction is performed
5. Pharmacological prophylaxis (no suggested medication) should be administered to all patients undergoing mastectomy with autologous flap reconstruction unless specific contraindications are identified.

5.2.9 VTE Treatment in Breast Cancer Cases

See Chap. 14

5.2.10 Special Situations in VTE Treatment

5.2.10.1 Vena Cava Filters (VCF)

Regarding VCF, ASCO guidelines have more contraindications than ESMO guidelines due to increasing reports of harmful long-term side effects from VCF. ASCO guidelines suggest VCF only for patients with acute VTE (less than 4 weeks), life-threatening thrombus burden, contraindications for anticoagulants in an acute setting, or patients with progressing VTE despite optimal anticoagulation. Meanwhile, ESMO guidelines suggest VCF for all patients with progressive VTE, despite adequate anticoagulation, and for any patients with anticoagulation contraindications (even temporary ones).

5.2.10.2 Central Nervous System Metastasis

Brain metastasis may occur in breast cancer patients. If concomitant to VTE and anticoagulant treatment, fear of brain hemorrhage may arise. Since data on this subject are scarce, ASCO guidelines suggest maintaining (or initiating if necessary) anticoagulant treatment.

5.2.10.3 VTE and Patients Receiving Tamoxifen

Breast cancer patients with VTE should discontinue endocrine therapy. ESMO guidelines suggest replacing tamoxifen with an aromatase inhibitor and administering long-term anticoagulant treatment for 6 months (LMWH is preferred).

5.2.10.4 VTE and Patients Receiving Chemotherapy

ESMO guidelines suggest that anticoagulation treatment should be administered for 6 months to patients with VTE under adjuvant chemotherapy (LMWH preferred). Both ASCO and ESMO guidelines suggest (with low evidence) that it should be discussed with patients for anticoagulation for more than 6 months in selected cases of metastatic cancer under ongoing palliative chemotherapy.

5.2.10.5 Incidental Finding of VTE

ASCO guidelines suggest that asymptomatic VTE patients should be treated in the same manner as symptomatic patients. For cases of asymptomatic subsegmental PE, splanchnic or visceral vein thrombi anticoagulation should be offered on a case-by-case basis.

5.2.11 Superior Member Chronic Lymphedema

Arm lymphedema is a well-characterized side effect of breast cancer surgery that is due to lymphatic vessel damage. The latter occurs during axillary surgery which is crucial for correct staging and treatment. Axillary surgery itself does not affect OS (only regional recurrence, which is rare), and it is necessary for pathological staging, one of the most important prognostic indicators of breast cancer. Detection of axillary lymph node metastasis usually indicates a need for adjuvant chemotherapy and radiotherapy, and these treatments will impact OS. Considering that complete axillary surgery does not affect OS and axillary local recurrence is rare [88], breast surgeons have pursued axillary surgery downstaging over the past few decades. Initially, sentinel lymph node biopsy was introduced by Giuliano and coworkers (1994) [89] and by Veronesi et al. (2003) [90] for cN0 patients. Use of this type of biopsy led to a decrease in chronic lymphedema rates from 20–30% to around 3% [91]. Then, the ACOSOG Z11 trial [88] demonstrated that certain pN1 patients may omit axillary lymphadenectomy without OS penalty and with local recurrence rates around 1%. In addition, the AMAROS trial (2013) [92] demonstrated that selected pN1 patients may replace axillary lymphadenectomy with axillary radiotherapy without OS penalty. The latter replacement diminished lymphedema rates from 23% to 11% compared to surgery. The need for complete lymphadenectomy in cN1 patients who undergo neoadjuvant chemotherapy and become ypN0 was also found to be diminished based on results from the SENTINA (2013) [93] and ACOSOG Z1071 [94] trials. Prior to these publications, all cN+ patients who received neoadjuvant chemotherapy had to undergo complete axillary lymphadenectomy despite achieving a clinical and pathological response. However, in the SENTINA and ACOSOG Z1071 trials, cN1 patients who became ypN0 exhibited good OS despite radical surgery. Thus, under special circumstances, the sentinel lymph node appears

to be sufficient for correct axillary pathological staging. Below we provide a summary of axillary surgery indications in breast cancer patients:

1. cT1–3 cN0 patients → perform sentinel node biopsy.
2. cT4 patients → perform axillary lymphadenectomy.
3. pT1–2 pN1 patients who fulfill ACOSOG Z11 criteria may omit lymphadenectomy → must undergo conservative surgery, maximum of 2 positive lymph nodes with macrometastasis, without neoadjuvant treatment, without radiotherapy contraindication.
4. pT1–2 pN1 patients who fulfill AMAROS criteria may undergo axillary radiotherapy instead of lymphadenectomy → including mastectomy patients, up to 4 positive lymph nodes with macrometastasis (we usually consider a maximum of 2 according to ACOSOG Z11), without neoadjuvant treatment, without radiotherapy contraindication.
5. cN1 patients who undergo neoadjuvant chemotherapy and become ycN0 may undergo sentinel node biopsy → if ypN0 (preferably with at least three sentinel nodes removed and using both radioactive tracer and blue dye or clipping compromised lymph node prior to chemotherapy) axillary lymphadenectomy may be omitted.
6. cT4 or cN2–3 patients who undergo neoadjuvant treatment must also undergo complete axillary lymphadenectomy despite treatment response.

For decades, we have been advising breast cancer patients to avoid chronic lymphedema by avoiding heavy lifting, venipuncture, blood pressure measurements, and other activities. However, recent studies have shown that data supporting these conditions are often false or do not provide sufficient evidence. To date, the only evidence-based risk factors which have been substantiated for chronic lymphedema are weight gain after treatment and arm infection/inflammation. Thus, the most recent recommendations for patients emphasize weight control and skin trauma care (e.g., avoid infections). There are no contraindications for physical activity [91] and exercise is encouraged.

Treatment of chronic lymphedema is difficult, and once it is established, there is no cure. Treatment primarily focuses on preventing lymphedema progression. The most common treatment is mechanical, with physical therapy and use of compressive stockings. To date, pharmacological treatment for lymphedema has not been robustly supported, hence it is seldom used. Meanwhile, surgical treatments such as lymphovascular anastomosis, debulking, and lyposuction are possible options, although they are usually reserved for patients who are refractory to mechanical treatment.

Key Messages

- Breast cancer is the most common type of cancer among women and is associated with vascular comorbidities.
- VTE is the most common vascular morbidity in patients with breast cancer and is associated with decreased OS.

- VTE risk increases during all stages of breast cancer treatment, including surgery, chemotherapy, and endocrine therapy.
- VTE prophylaxis is a possible strategy for certain surgical patients and for cancer patients hospitalized with acute illness or movement restriction.
- VTE treatment during breast cancer treatment is divided into acute and long-term arms, the latter of which may last up to 6 months or more.
- Chronic arm lymphedema is a common side effect of axillary surgery. Surgery downstaging is an important feature and a reality for many breast cancer patients nowadays.
- Weight gain and arm infection/inflammation are the most important lymphedema risk factors.
- Lymphedema treatment is difficult and aims to stop disease progression. It focuses on mechanical treatment and physical therapy.

Editor's Comments

Gynecological tumors are among the most associated with venous thromboembolic phenomena (VTE), in addition to the malignancy of the disease, advanced age, association with other comorbidities, and pelvic surgery [95]. Among gynecological tumors, the ovarian is the one with the highest relationship with VTE [95, 96].

As in other types of cancer, VTE can occur as an initial manifestation of cancer disease, as a complication of antineoplastic treatment, or associated with disease progression [97]. A recent study showed a high prevalence of VTE diagnosed before cancer treatment started in these patients – 7.3% in women with cervical cancer, 11.5% in those with an endometrial tumor, and 27% in patients with ovarian cancer [96]. Considering the cases of cancer-associated thrombosis, women with ovarian cancer are also among the patients with a higher risk of recurrence of VTE, which is three times higher than that of individuals without cancer.

Surgical treatment of gynecological cancer also has a high risk of VTE, which goes beyond the hospital stay since about 75% of VTE diagnoses are performed more than 7 days after surgery [98, 99]. Ovarian cancer, hospital stay longer than 5 days, and a previous history of deep venous thrombosis are factors associated with a higher risk of VTE [99]. The extension of the prophylaxis period in these patients should therefore be considered (see Chap. 14).

The pelvic tumor's situations of vascular involvement were addressed in this chapter, and further information is available in Chap. 13. A different form of vascular involvement is the tumor's intravenous spread, as in (rare) cases of leiomyosarcoma of the uterus when the tumor mass invades pelvic veins and progresses through the inferior vena cava reaching the right atrium [100, 101]. The resection of these masses is complex and may require extracorporeal circulation to open the atrium.

This chapter also discussed the lymphatic spread of gynecological tumors and the consequent need for lymphadenectomy as part of these tumors' treatment. The potentially resulting lymphedema is discussed in detail in Chap. 16. Genital tumors

(vulva) and those located in the lower 2/3 of the vagina have lymphatic drainage for superficial and deep inguinofemoral lymph nodes. The expansion of this mass next to the femoral vessels can cause skin ulceration and the risk of the femoral artery's rupture (femoral blowout) caused by invasion or scarification of the artery wall, eventually exposed through the ulcerated lesion [102, 103].

One of the types of cancer most often associated with lymphedema after surgical or radiotherapy treatment is breast cancer. In Chap. 16, issues such as diagnosis, conservative treatment, and surgical treatment are discussed. Treatment based on sentinel lymph node biopsy (BLS), if not abolished, at least significantly reduced the occurrence of lymphedema in patients with breast cancer – the literature points to lymphedema by about 3% in patients undergoing BLS and 20% in those who had axillary dissections 12 months after the procedure [104, 105].

The measures classically recommended for prevention, such as avoiding venipuncture, compressions, or carrying weight on the limb ipsilateral to that of the treated breast, do not have a definitive scientific basis [105, 106].

Breast cancer is not among the most associated with venous thromboembolic phenomena. As seen in this chapter, cases of VTE usually occur during chemotherapy. Anti-estrogenic chemoprophylaxis with tamoxifen, used in patients with hormone receptor-positive breast cancer, is associated with a higher risk of VTE, mainly if used in conjunction with chemotherapy [107–109]. This risk increases 2 to 3 times in older women, and the risk seems to persist throughout the treatment with tamoxifen [110]. We advise a patient using tamoxifen to stop taking the drug several days before an eventual elective surgery to reduce the risks of postoperative VTE [111]. Another option of treatment in these patients, aromatase inhibitors, such as anastrozole, are associated with a much lower risk of VTE than tamoxifen [112].

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Chapter 6
Orthopedics: Musculoskeletal Tumors

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6.1 Introduction

Historically, most bone and soft tissue sarcomas have been treated with amputation. Nowadays, most tumors of the musculoskeletal system can be treated with limb preservation surgery since the surgical margins are adequate without compromising oncological outcome [1, 2].

The advances that allowed for an oncological treatment and limb preservation were in diverse fields: evolution in diagnosis and surgical planning with high definition magnetic resonance imaging; adjuvant therapies such as chemotherapy, immunotherapy, and radiation therapy; use of reconstructive surgical techniques with the use of modular endoprosthesis for bone reconstruction [1]; use of local or microsurgical flaps to cover large soft tissue defects and the possibility of vascular reconstructions in cases where there is compromise of major vascular structures [3].

Furthermore, we have experienced a greater amount of teamwork in most musculoskeletal oncology treatment reference centers in the twenty-first century, with constant meetings, case discussions, and combined treatment strategies. That allows for more refined and complex surgeries, sometimes with two or more surgical teams in the same procedure.

More than 200 tumors may affect the musculoskeletal system, with specific clinical behavior and treatment. In general, we can divide these tumors into benign or malignant, and those that affect bone or soft tissue [4].

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6.2 Benign Tumors

Benign bone tumors, despite being more common than malignant ones, rarely require some vascular reconstruction. However, some of these tumors can grow substantially and extrinsically compress the neurovascular structures. The benign bone tumors most associated with vascular complications are osteochondroma, giant cell tumor, and aneurysmal bone cyst [5, 6].

Less frequently, some benign soft tissue tumors may also evolve with symptomatic vascular compressions or may require treatment by vascular techniques to be resected in cases where there is high surgical morbidity, or in those that would be unresectable without a vascular approach. Benign soft tissue tumors are more common than malignant ones, but will rarely need a vascular approach, unless they are vascular histological subtypes or malformations such as hemangiomas [7, 8].

6.3 Bone Sarcomas

Sarcomas are the most common primary malignant bone tumors. Among them, the most frequent are the osteosarcoma, chondrosarcoma, and Ewing's tumor [9]. Bone metastases are usually caused by primary carcinomas such as the prostate and breast, but the most aggressive, hyper-vascularized lesions that will require preoperative embolization from kidney, thyroid, and lung primary cancers [10]. Bone sarcomas that grow aggressively can also involve vascular structures.

Bone sarcomas can present good response to chemotherapy, but surgery is still essential for the treatment of the primary tumor. Some of them grow aggressively and can also involve vascular adjacent structures. For this reason, the evolution in surgical treatment with reconstructive techniques has gained space, providing an adequate control of the tumor and being important for limb preservation with good function [11].

6.4 Soft Tissue Sarcomas

Soft tissue sarcomas, on the other hand, comprise a set of malignant tumors that can be aggressive and, more frequently, can infiltrate arterial and venous vascular structures, requiring reconstruction to allow an adequate oncological resection with preservation of the limb.

In children, the most common sarcoma is rhabdomyosarcoma, but it rarely requires surgical treatment and vascular reconstruction since its main treatment is chemotherapy [9].

In adults, the most common soft tissue sarcomas are pleomorphic sarcoma, leiomyosarcoma, liposarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor, fibrosarcoma, angiosarcoma, epithelioid sarcoma, clear cell sarcoma, and alveolar sarcoma [12].

6.5 Diagnosis

The diagnosis of bone tumors may be suspected by the findings of history, physical examination, and plain radiography, which is the main exam for analysis of the differential diagnosis. Other imaging techniques such as magnetic resonance, tomography, and bone scintigraphy are important for tumor delimitation, staging, treatment, and surgery planning, but these are not so important for diagnosis. Biopsy is not usually necessary for the diagnosis of benign bone tumors, but it must be performed in those cases of aggressive benign tumors and in suspected cases of malignancy [13].

Soft tissue tumors are usually better evaluated with the MRI exam with contrast, with which we will be able to assess the size, limits of the lesion, and if there is suspicion of malignancies. Biopsy is usually performed in suspected cases of malignancy, but it can be prescinded in benign cases or in cases of low-grade lipomatous tumors [14].

Sarcomas include several mesenchymal neoplasms with widely varying prognosis, clinical behavior, and treatment. Due to its rarity and histological similarity, the accurate diagnosis of sarcomas can be a challenge. Anatomopathological and immunohistochemical examination usually confirm the diagnosis, but there is the possibility of molecular genetic analysis. The correlation with clinical, radiological, morphological and immunohistochemical findings is particularly important in these types of tumors [15].

6.6 Staging

Staging should be performed to define the therapeutic approach and prognosis of patients with malignant bone and soft tissue tumors.

In the case of bone sarcomas, the spread of the disease occurs mainly by hematogenous route, with the lung being the main site of metastasis in more than 90% of cases. Lymph node and bone metastases can also occur, but less frequently. Thus, the staging of bone sarcomas includes magnetic resonance imaging of the lesion site and of the entire affected bone, computed tomography of the chest in addition to radiography of the tumor site [16].

In the case of soft tissue sarcomas, the pattern of dissemination is also via hematogenous, similar to bone sarcomas, but there are some histological types more related to lymph node dissemination, such as rhabdomyosarcoma, epithelioid, and synovial sarcoma. Other sarcomas such as myxoid liposarcoma can present bone metastases, soft tissues, and retroperitoneum. In general, staging is done with local resonance and chest tomography as well as abdomen and pelvis tomography. PET-CT can be required in selected cases in which dissemination is more likely to be diffused [15].

The most used classification for bone and soft tissue bone sarcomas is from the AJCC (American Joint Committee on Cancer), which was revised in 2018 and is in its eighth edition [17] (Table 6.1).

Table 6.1 (a) AJCC staging for bone sarcomas. (b) AJCC staging for soft tissue sarcomas

(a) Appendicular skeleton, trunk, skull, and facial bones	
Definition of primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤8 cm in greatest dimension
T2	Tumor >8 cm in greatest dimension
T3	Discontinuous tumors in the primary bone site
Definition of regional lymph node (N)	
N category	N criteria
NX	Regional lymph node cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph nodes metastasis
Definition of distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Lung
M1b	Bone or other distant sites
Histologic grade (G)	
G	Definition
GX	Grade cannot be assessed
G1	Well differentiated, low grade
G2	Moderately differentiated, high grade
G3	Poorly differentiated, high grade
(b) Trunk and extremity	
Definition of primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor

Table 6.1 (continued)

T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and ≤10 cm in greatest dimension
T3	Tumor more than 10 cm and ≤15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension
Definition of regional lymph node (N)	
N category	N criteria
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
Definition of distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
Definition of grade (G): FNCLCC histologic grade	
G	G definition
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count, and necrosis score of 2 or 3
G2	Total differentiation, mitotic count, and necrosis score of 4 or 5
G3	Total differentiation, mitotic count, and necrosis score of 6, 7 or 8

6.7 Prognosis

The prognosis of patients with malignant tumors of the musculoskeletal system depends on some factors. The main prognostic factors are the patient's age, tumor size, histological grade, tumor location, and surgical margins. But the most important is the presence of metastases at diagnosis, with distant metastases having a worse prognosis than loco-regional ones in the case of soft tissue sarcomas [18]. Other factors that lead to a worse prognosis are as follows:

- Age over 60
- High-grade histology
- Tumor size larger than 5 cm
- Deep and proximal tumor location
- Surgical resection without oncological margins

Specifically in the case of bone sarcomas, exclusive lung metastasis has a slightly better prognosis than non-lung distant metastasis.

The AJCC prognostic stage groups for bone sarcoma are shown in Table 6.2 and for soft tissue sarcoma are shown in Table 6.3.

Table 6.2 AJCC prognostic stage groups for bone sarcoma in the appendicular skeleton, trunk, skull, and facial bones

Stage	Primary tumor (T)	Regional lymph node (N)	Distant metastasis (M)	Histologic grade (G)
IA	T1	N0	M0	G1 or GX
IB	T2 or T3	N0	M0	G1 or GX
IIA	T1	N0	M0	G2 or G3
IIB	T2	N0	M0	G2 or G3
III	T3	N0	M0	G2 or G3
IVA	Any T	N0	M1a	Any G
IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

Table 6.3 AJCC prognostic stage groups for soft tissue sarcoma in the trunk and extremity

Stage	Primary tumor (T)	Regional lymph node (N)	Distant metastasis (M)	Histologic grade (G)
IA	T1	N0	M0	G1, GX
IB	T2, T3, T4	N0	M0	G1, GX
II	T1	N0	M0	G2, G3
IIIA	T2	N0	M0	G2, G3
IIIB	T3, T4	N0	M0	G2, G3
IV	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

6.8 Treatment

The oncological treatment of patients with malignant musculoskeletal tumors may be rather complex and depends on several variables: the type of tumor (bone or soft tissue), the histological type and grade, its location, the stage of the disease, its size and prognosis, among others.

In general, low-grade bone and soft tissue sarcomas are treated surgically. Low-grade bone sarcomas can be treated with an intralesional, or marginal approach. Low-grade soft tissue sarcomas should be treated with marginal resection [14].

High-grade bone and soft tissue sarcomas will require other treatment modalities such as chemotherapy and radiotherapy, as well as larger resection surgeries, with wide margins and resection of larger areas of soft tissues. It is precisely in these cases that there is a greater risk of invasion of neurovascular structures [18].

Despite a small increase in local recurrence, limb-sparing surgery can be performed without detriment to the prognosis of patients with sarcomas, when compared to patients who undergo amputation. However, in these patients there is a greater risk of amputation due to damage to the arterial supply. Thus, vascular reconstruction gains great importance, since it allows surgery with limb preservation [19].

In bone sarcomas, invasion of neurovascular structures is still considered a relative contraindication for limb-preserving surgery. Despite the increase in reports of successful cases, there is still a poverty in the literature in relation to the series of cases of bone sarcomas with vascular reconstruction. This is mainly due to the fact that, when there is an invasion of neurovascular structures of bone sarcomas, there is an association of a large volume tumor with great bone destruction and invasion of other soft tissues, being very difficult to associate a successful vascular and bone reconstruction with soft tissue coverage. In general, these cases end up requiring amputation [20, 21].

Most soft tissue sarcomas are relatively resistant to chemotherapy and exclusive radiation therapy. It is precisely in this group of tumors that we have the largest number of cases that will require vascular reconstruction. In these cases, the tumor can invade these structures and reconstruction is essential to allow for oncological surgery with wide margins, while preserving the limb. The biggest challenges are those tumors of large volume which infiltrate vascular structures in long segments and which require major reconstructions. One factor to consider is the association with radiotherapy. There is a consensus that large deep high-grade sarcomas can benefit from radiation therapy. Nevertheless, there is no consensus on which modality is better: preoperative or postoperative radiation. Preoperative radiation can increase the wound complications such as dehiscence and infection. And if a vascular anastomosis is in the surgical plan, it should be done out of the radiation field which can make the reconstruction very extensive and complex. On the other hand, postoperative radiation, performed after soft tissue healing, does not harm vascular anastomosis, which can be shorter, but has other disadvantages, such as more long-term side effects and a larger field or radiation. Each case should be assessed individually in order to decide which modality is better [18].

In general, the growth of sarcomas usually causes a compression of vascular structures, but without infiltrating these structures at first. At this stage, the oncology surgeon can still try to resect the tumor and dissect the vascular structures without the need for reconstruction. In some cases, there may be minor damage to the vessel wall that can be directly repaired.

With the growth of the tumor, the first structures that are usually collapsed are the veins, which can cause their occlusion by extrinsic compression and thrombosis. In the case of more advanced tumors, vascular involvement may be circumferential and tumor resection with oncological margins is not possible without segmental vessel resection followed by vascular reconstruction. In these cases, vascular reconstruction is essential to allow tumor resection and limb preservation surgery.

Concerning function, there seems to be no significant difference between patients who underwent sarcoma resection surgery with and without vascular reconstruction [19].

Among the complications of vascular reconstructions, we have thrombosis of the reconstructed vessel anastomosis, infection, tumor local recurrence, and the need for future amputation due to local complications [3, 19].

In the past, the involvement of vascular structures was an impediment to tumor resection with limb preservation. Currently, vascular reconstruction is a procedure that can be performed with a low rate of complications and that allows the adequate oncological treatment of musculoskeletal tumors with the possibility of preserving a limb with good function [3, 19, 22] (Figs. 6.1 and 6.2).

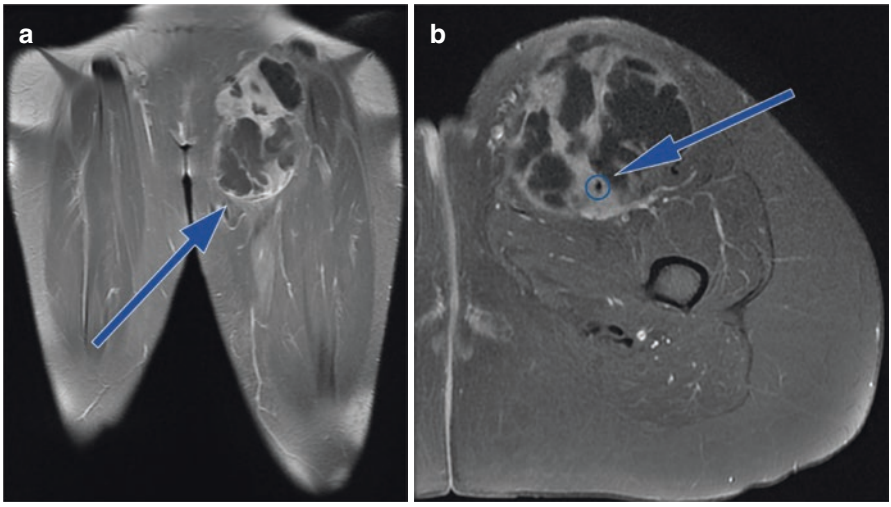

Fig. 6.1 (**a**) T2-weighted magnetic resonance coronal section showing anterior thigh sarcoma. (**b**) T2-weighted magnetic resonance axial section showing femoral artery involvement by the sarcoma

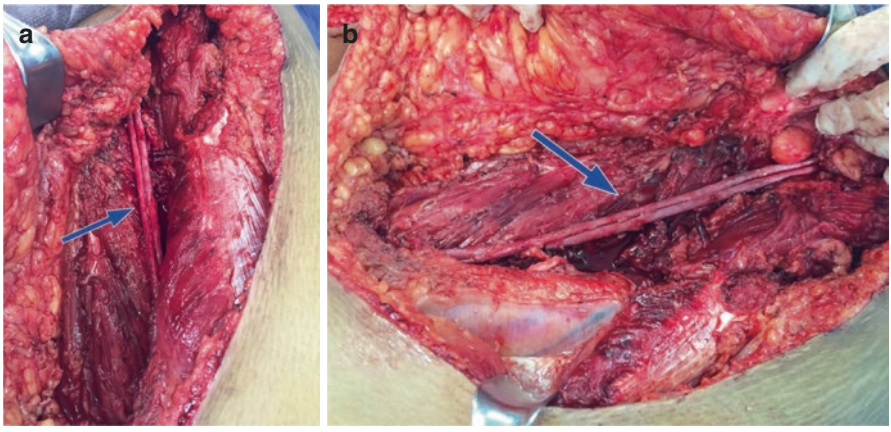

Fig 6.2 (**a**, **b**) Femoral artery and vein reconstructed with saphenous graft after tumor resection

6.9 Embolization

Primary and metastatic bone tumors can grow very aggressively, causing great bone destruction and invasion of soft tissues. They can cause severe pain and pathological fractures, and in many cases, there will be an indication for surgical resection of the tumor in association with other treatment modalities. However, the size of the tumor, its vascularization, and proximity to noble structures can make it difficult or impossible to resect the tumor [23].

Transarterial embolization can be an adjunctive treatment modality for major resection surgeries, or therapeutic in some types of bone tumors [24].

In the case of surgery adjuvance, it decreases intraoperative bleeding, facilitating tumor resection and decreasing hemorrhagic complications. In general, transarterial embolization is used mainly in the preoperative of hypervascular bone metastases such as kidney and thyroid cancers [7].

In the treatment of primary bone tumors, the most commonly treated tumors with embolization are giant cell tumor and aneurysmal bone cyst when these tumors are located in the pelvis, sacrum, and spine and in which complete resection surgery is not possible or brings great morbidity to the patient [23].

Other lesions such as telangiectatic osteosarcoma and vertebral hemangiomas can also be embolized as a form of neoadjuvant or definitive treatment [8].

6.10 Discussion

The need for vascular reconstruction on sarcoma resection surgery increases the morbidity of these operations compared to resections without reconstruction. However, vascular reconstruction does not appear to alter the oncological outcome (local recurrence and local overall survival) when compared to patients who did not undergo reconstruction. This is important when making a decision to perform a limb-preserving surgery or an amputation [20].

The most frequent complications in patients undergoing resection of sarcomas and vascular reconstruction are usually residual edema, bleeding, thrombosis, lymphorea, and healing problems of skin ulcers. Anyway, the functional outcomes of patients who have undergone limb-salvage surgery with vascular reconstruction usually are satisfactory [3].

Historically, invasion of major vascular structures has been considered a barrier to the removal of large neoplasms, but today there is an understanding that the resection and reconstruction of a main artery should not prohibit the resection of any given tumor. Most arterial reconstructions performed in this setting have a high degree of success and do not appreciably increase overall morbidity and mortality [19].

Nowadays, limb-salvage surgery with arteriovenous reconstruction and other reconstructive techniques is an effective alternative to amputation for the treatment of lower extremity sarcomas of bone and soft tissue and facilitates functional recovery [1]. Therefore, patients can avoid amputation, despite malignant involvement of major vessels to their extremities without compromising oncologic outcome [3, 19].

6.11 Spinal Tumors and Vascular Surgery

6.11.1 Introduction

The spine is one of the segments most affected by tumors [25]. However, vast majority of tumors that affect the vertebrae are metastatic lesions. The vascular anatomy of thoracolumbar spine with its peculiarities (great vascular intercommunication and absence of valves) justifies great occurrence of metastases to spine [26].

Hypervascularized spinal tumors, whether primary (aneurismal bone cyst, giant cell tumor, aggressive hemangiomas) or metastatic (renal, thyroid), have great potential for intraoperative blood loss, which can add enormous morbidity [27].

Complex procedures such as sacrectomy or vertebrectomy have major potential for bleeding. Preoperative embolization and surgical performance in conjunction with a vascular surgeon can contribute significantly to minimize blood losses [28].

6.11.2 Diagnosis

The diagnosis of bone tumors may be suspected by the findings of history, physical examination and radiography, which is the main exam for analysis of the differential diagnosis. Tests such as magnetic resonance (MRI), tomography, and bone scintigraphy are important for tumor delimitation, staging, treatment planning, and surgery.

6.11.3 Staging

Staging should be performed to define the therapeutic approach and prognosis of patients with malignant bone and soft tissue tumors.

6.11.4 Osteoblastic Tumors

The two major spine osteoblastic tumors are osteoid osteoma and osteoblastoma. They correspond to tumors that form osteoblastic tissue, with presence of mature osteoid, reactional sclerosis and, in the case of osteoid osteoma, a characteristic niche where there is presence of immature osteoid, newly formed vessels.

The diagnosis of both lesions can be difficult and radiography is not sufficient for the diagnosis, requiring tomography or MRI. Definite diagnosis is made via histopathological analysis. These tumors are usually seen in the posterior elements of the spine. Definitive treatment consists of resection or ablation of the lesion with part of sclerosis halo that appears around it. Prognosis is good, as long as entire lesion can be resected.

Malignant osteoblastic tumor that affects the spine is osteosarcoma. However, its primary occurrence in spine is very rare, and in most cases, it corresponds to a metastasis of a previous osteosarcoma of one extremity. The cancer treatment consists of neoadjuvant chemotherapy, en bloc resection, and postoperative chemotherapy. Prognosis of spinal osteosarcoma is reserved, since the complete resection of lesion is impaired by the local anatomical complexity [29, 30].

6.11.5 Chondroblastic Tumors

Cartilaginous tumors that affect spine are chondroma and osteochondroma, which are benign, and chondrosarcoma, which is malignant. Chondromas can affect the vertebral body and the posterior elements. Osteochondroma is usually located in the spinous or transverse process.

Chondrosarcoma can affect any location in vertebra and spine. Tumors grow slowly without giving many symptoms until they compromise neural elements, when they normally already have large volumes. They can be of low, moderate, or high degree of malignancy. Low-grade tumors can be treated with curettage and filling the defect created with cement. Tumors of moderate or high degree should be resected completely, with wide margins. Chondrosarcoma is not sensitive to either chemotherapy or radiation therapy [31–33] (Fig. 6.3).

6.11.6 Ewing Sarcoma

This is a tumor of high degree of malignancy, which presents its highest incidence in childhood and adolescence. They are tumors formed by large masses of small round cells, highly malignant, and that, from the bone marrow, destroy the bone and grow towards surrounding soft tissues.

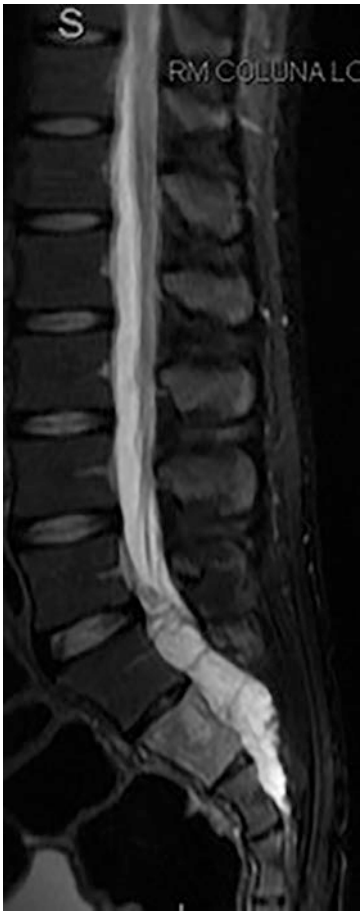

Fig. 6.3 Example of chondrosarcoma on MRI T2-weighted exam

The spine is one of the most frequent sites in Ewing's sarcoma, followed by diaphysis of long bones of pelvis and scapular.

Clinical cancer treatment is chemotherapy with multiple drugs. It is usually done in neoadjuvant way. But it can be modified depending on whether there is a neurological deficit, when neurological decompression with subsequent chemotherapy is performed. Radiotherapy is used in cases where it was not possible to obtain free margins or when chemotherapy was unsatisfactory.

The surgical technique will depend on the area and extend of impairment. The combined approach is often necessary with posterior instrumentation and anterior vertebrectomy [34, 35].

6.11.7 Tumors of Hematopoietic Origin

Representatives of this category include lymphoma and multiple myeloma. MRI imaging is useful in demonstrating involvement of bone marrow. Treatment protocol for lymphoma is systemic chemotherapy and local radiation therapy. Surgery has a limited role, being indicated only for diagnosis through biopsy.

Multiple myeloma are tumors of plasma cells and are often accompanied by presence of abnormal proteins in the blood and urine. It usually affects individuals older than 50 years and the most common locations are spine, pelvis, ribs, sternum, and skull. Low back pain and sciatica are common symptoms. Sternal or iliac puncture is often indicated for diagnosis. In the spine, lesions appear as lytic lesions. Imaging images such as radiography, tomography, and MRI are important for diagnosis and monitoring of lesions. The main surgical indications are surgery for neurological decompression and pathological fractures, sometimes requiring a double approach (anterior and posterior) [36–38].

6.11.8 Giant Cell Tumor

Spinal impairment is rare. When present, it destroys vertebral body, pedicle, and lamina. It affects individuals over 40 years and can show symptoms only when it causes neurological changes or pathological fractures. Diagnostic imaging is performed with radiographs or tomographies that show area of bone lysis, or earlier, by MRI. The tumor consists of giant cells that destroy the bone without any sign of reaction. The tumor can be quite vascularized, sometimes being confused with an aneurysmal bone cyst. Treatment consists of complete curettage or resection of the tumor, followed by use of an adjuvant method (phenol, cryotherapy, or thermotherapy) and filling the resected area with bone cement [39].

6.11.9 Chordoma

Tumor derived from tissue remaining of notochord. It can be located anywhere in the spine, but it is frequent in the sacrococcygeal region and skull basis. The main symptoms are low back pain, sphincter dysfunction, and headache. Sacral radiography often does not show lesions due to presence of gases and feces. Thus, tomography or MRI imaging is often used. Biopsy is essential for diagnosis. Tumor resection "en bloc," with a normal tissue margin, is the objective of surgical treatment. The main approaches used are exclusive posterior; combined anterior and posterior (anterior access can be open or laparoscopy). Surgical complications

should be widely discussed with the patient and family due to the high degree of surgical morbidity (permanent neurological deficits such as sphincter dysfunction, motor deficit, and possible need for colostomy due to intestinal injury) [40, 41] (Figs. 6.4 and 6.5).

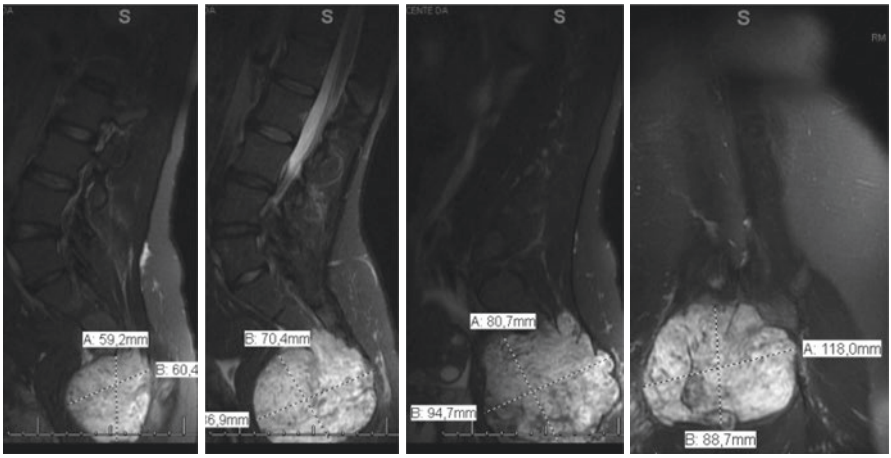

Fig. 6.4 Example of chordoma in the sacrococcygeal topography

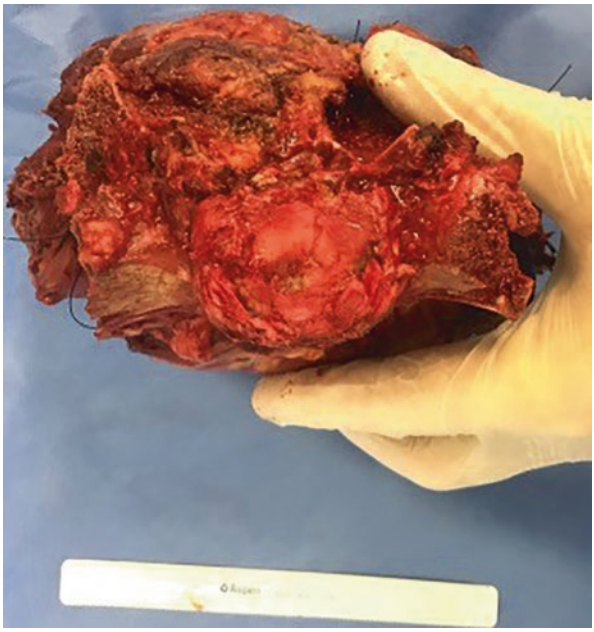

Fig. 6.5 Chordoma resection specimen

6.11.10 Aneurysmal Bone Cyst

Pseudotumoral lesion, benign aggressive, with expansive osteolytic characteristics constituted by spaces of varying size, full of blood, separated to each other by trabeculae of connective tissue. They occur in children, adolescents, and young adults. It affects the posterior elements of the spine. It can evolve towards vertebral body and compromise the disc. Usually, patients complain of local pain for several weeks. There may be sensory or motor dysfunction due to neural compression. Exams such as tomography and MRI are essential for diagnosis and therapeutic planning. Treatment of choice is curettage of lesion, followed by bone graft. Eventually, wide resection may be an indication. In the spine, preoperative tumor embolization is often used, thus achieving surgery with less bleeding and obtaining better margins. Chemotherapy and radiotherapy are not indicated [42, 43].

6.11.11 Eosinophilic Granuloma

It affects children and adolescents and lesions are almost always located in the skull, femur, femur, jaw, ribs, vertebrae (flat vertebrae), and flat bones. Clinical manifestations include pain and inflammatory symptoms. The involvement of vertebrae may be accompanied by kyphosis or scoliosis, and the involvement of vertebral body with collapse of vertebra is common. Spine lesions are treated expectantly, as they usually evolve to cure and without functional sequelae most of the time. The treatment of multiple lesions and systemic disease is performed with corticoids and chemotherapy [44].

6.11.12 Spinal Metastases

The skeleton is the third most common site of metastasis involvement, after lung and liver. The major primary metastasis sites for spine are prostate, breast, melanoma, lung, and kidney.

The main clinical complaint is pain which can be explained by three mechanisms: tumor infiltration, neural compression, and pathological fracture. The treatment of these lesions depends on several factors, including clinical aspect of the patient, lesion stability, and sensitivity to radiotherapy. Stable and radiation-sensitive lesions are treated with orthoses and radiotherapy. Unstable lesions are addressed surgically. Regarding the approach, posterior access exclusively or combined approaches can be used (anterior and posterior). Highly vascularized lesions can be embolized prior to the surgical procedure [25, 28, 45–47].

6.11.13 Surgical Planning

Regarding surgical access to the thoracolumbar spine, the anterior, posterior, or combined approach can be used. Each access has its indications and a single route is often not possible [48].

Regarding the level of the lesion at which approach is aimed, lesions located at T1 or T2, combined sternotomy and anterior neck dissection afford good exposure with favored entry site on the left side. For T3 to T4 region, a combination of the anterolateral cervical approach, a partial median sternotomy, and an anterolateral thoracotomy provide relatively wide access. T5 to L4 levels may be effectively approached by thoracotomy (T5–T10), thoracoabdominal approach (T11–L1), and retroperitoneal approach (L2–L4) [48].

Among the classifications popularly used to describe spinal injuries and propose treatment, the Weinstein-Boriani-Biagini surgical staging system stands out [49, 50]. In this system, an axial section of the spine is used as reference, subdividing the zones in a clockwise direction and in zones from A to E (Fig. 6.6).

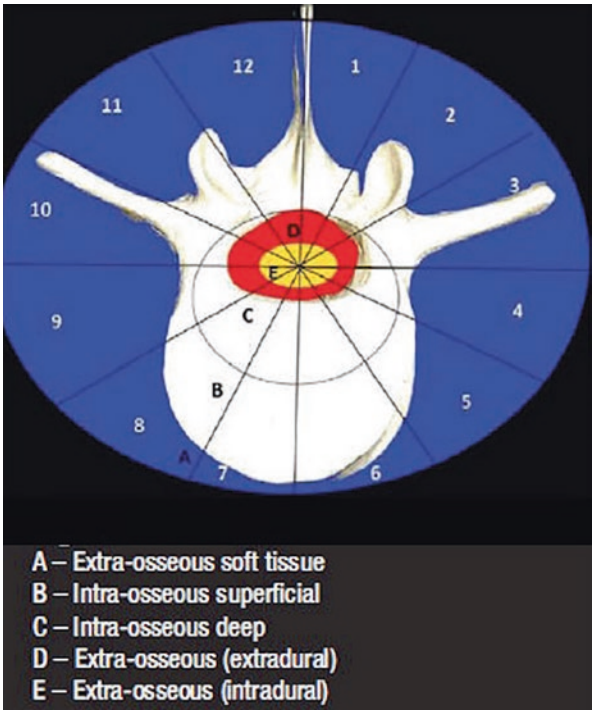

Fig. 6.6 Weinstein-Boriani-Biagini surgical staging system

6.11.14 Procedures

Vertebrectomy This is indicated for lesions in zones 4–8, or 5–9 with at least one pedicle free of tumor. The posterior approach involves excision of the posterior elements. The anterior approach allows the ligature of segmental vessels, proximal and distal discectomies, the "en bloc" removal of the vertebral body, and the anterior reconstruction.

Sagittal resection: indicated for unilateral lesions from zones 2–5 or 8–11, with the lesion possibly involving the pedicle or transverse process.

Posterior arch resection: indicated for lesions restricted to zones 10–3. The posterior elements are resected through a single posterior approach [49, 50].

Sacrectomy This is indicated for sacral lesions in which "en bloc" resection of the lesion is aimed. They can be partial, total, or extended (when resection of lumbar vertebrae is performed). There are several techniques for performing total sacrectomy. A widely used technique occurs in two stages. The first consisting of a midline anterior incision, dissection of visceral/neural structures, and ligation of internal iliac vessels, followed by an anterior L5-S1 discectomy. The second stage consisted of mobilization of an inferiorly based myocutaneous rectus abdominal pedicle flap for wound closure, followed by an L5 laminectomy, bilateral L5 foraminotomy, ligation of the thecal sac, division of sacral nerve roots, and transection of the ilia lateral to the tumor and sacroiliac joints [51, 52] (Fig. 6.7).

6.11.15 Spinal Tumors, Embolization, and Vascular Surgery

Among the highly vascularized spinal tumors, renal cell carcinoma and thyroid cancer stand out in the metastatic category. In primary lesions, aneurysmal bone cyst, aggressive hemangioma, and giant cell tumor stand out [45–47]. In these tumors, use of preoperative embolization can contribute to minimize blood loss and facilitate surgical dissection. Reported rates of complete devascularization for all tumor types in general are around 68% [27, 28]. The major complications are usually transient and occur in less than 3% of cases [27, 28].

The surgery performance in conjunction with vascular surgeon often occurs in complex spine procedures such as corpectomy, single or multiple vertebrectomy, and sacrectomy.

Indications for such procedures are given in malignant or benign aggressive tumors in which complete resection of the lesion is aimed.

In these procedures, it is often necessary to approach multiple blood vessels, which may be direct branches or not of the aorta. In sacrectomy, the combined anterior and posterior approach can facilitate the resection. In the anterior approach, whether laparoscopic or open, with aid of vascular surgeon, vascular and intestinal

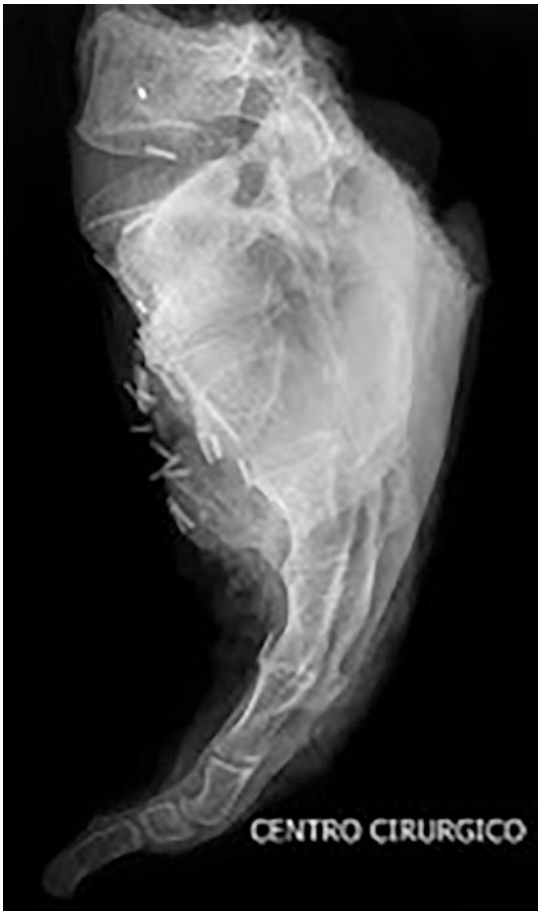

Fig. 6.7 Radiological imaging of extended sacrectomy resection specimen

structures anterior to sacrum can be isolated. Then, in the posterior approach, sacrectomy is performed with greater safety [51, 52].

Thus, a multidisciplinary approach and use of different therapeutic strategies are of great importance for patient safety.

Editor's Comments

According to Schawarzbach et al. [53] vascular involvement by extremity sarcomas can be classified into four types:

- Type I: when there is arterial and venous involvement. After en bloc resection, the artery is reconstructed, and venous reconstruction is not necessary if reflux through the stumps is adequate.
- Type II: if there is only arterial involvement with immediate reconstruction.

- Type III: when there is only venous involvement, reconstruction is necessary only if there is no adequate venous reflux.
- Type IV: if there is no involvement of trunk vessels.

Arterial injuries must be corrected for the risk of loss of the limb. Correction of venous lesions is optional; however, we believe it should also be operated on whenever there is a trunk venous injury since there is no technical or clinical justification for not performing venous reconstruction.

From a technical point of view, surgeries for tumor resections are elective, therefore scheduled in most situations. In this way, vascular substitutes are already chosen previously and the operative time added to the central procedure does not justify a simple venous ligation.

From a clinical perspective, patients submitted to venous ligation may evolve with significant symptoms and sequelae. Matsushita M et al. [54] performed venous ligations in 10 patients (inferior vena cava = 2, the external iliac and common femoral veins = 3, the femoral vein = 3, and the popliteal vein = 2). Two patients evolved with difficult to control edema and venous claudication, and one patient evolved with dermatofibrosis, eczema, and claudication. These three patients had involvement of the femoral vein.

In the extremities, extensive resections associated with ganglionic emptying and radiotherapy favor the appearance of lymphatic edema [55], leading to discomfort and heaviness and predisposing the member to episodes of bacterial infection. The treatment aims to decrease the affected limb's volume, leading to relief of symptoms, and is initially conservative through lymphatic drainage associated with elastocompression. Patients with more advanced clinical conditions can be submitted to surgical treatment. The methods can be ablative when there are many structural (dermolipectomy or liposuction) or physiological changes (lymphatic-lymphatic bypass, lymphatic-venous bypass, vascularized omental flap transfer, and vascularized lymph node transfer).

Joint resection of nerves (sciatic, common fibular) may be necessary to obtain oncological safety margins. For this reason, patients should be alerted in the preoperative period of possible significant sensory-motor sequelae, which are often irreversible [56].

Physiotherapy associated with orthoses' use contributes to most of these patients evolving with entirely satisfactory mobility and quality of life, a choice that prevails over primary amputation.

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Chapter 7
Retroperitoneal Tumors

Fábio de Oliveira Ferreira

7.1 Introduction

The retroperitoneal space is composed of retroperitoneal organs, connective tissue, nerves, lymphatic vessels, and blood vessels, including the abdominal aorta and its branches, and the inferior vena cava and its tributaries. Different types of lesions can occupy the retroperitoneal space and represent a true diagnostic challenge, not rarely associated with vascular problems. The retroperitoneum limits are the diaphragm, the pelvic floor, the posterior leaflet of the parietal peritoneum, the paravertebral musculature, and the posterior musculature of the abdominal wall (major psoas, minor psoas, lumbar square, internal obturator, and piriform muscles) [1–3].

The diagnosis of a retroperitoneal mass generally occurs as a consequence of incidental findings or during the investigation of increasing abdominal volume, mass perception, or abdominal pain. Depending on the etiology and location of the mass, neurological symptoms, ascites, and gastrointestinal symptoms may be present, as well as fever secondary to tumor necrosis, digestive hemorrhage due to hollow viscera invasion, and systemic manifestations, such as fatigue and weight loss. The presence of venous thrombosis, vascular stenosis, collateral veins in the abdominal wall, and edema of lower limbs and scrotum also can occur as a consequence of associated vascular phenomena.

In general, 80% of retroperitoneal neoplasia are malignant. With the exception of visceral tumors, 55% are sarcomas and stromal tumors, 40% are lymphomas and 5% correspond to other primary tumors and lymph node metastases. A prolonged clinical history, the scarcity of symptoms, and the radiologic appearance of a

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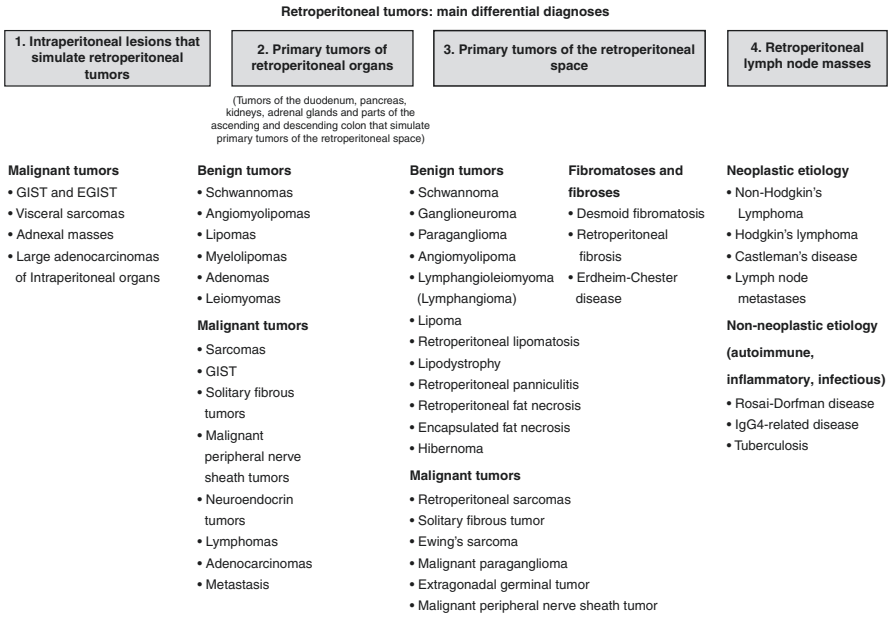

Fig. 7.1 Main differential diagnoses of retroperitoneal masses

nonaggressive lesion are characteristics that favor the diagnosis of a benign lesion (20%), most often surprised during routine exams [4–6].

The main diagnostic hypotheses regarding a retroperitoneal mass can be divided into four groups, including lesions that are not primarily tumors of the retroperitoneal space, but, due to similarities in clinical presentation, should be included in the list of differential diagnoses: (1) intraperitoneal lesions that simulate retroperitoneal tumors; (2) primary tumors of retroperitoneal organs; (3) primary tumors of the retroperitoneal space; and (4) retroperitoneal lymph node masses. In each of these groups, we will find a list of possible diagnoses (Fig. 7.1).

7.2 General Considerations

Most of the time, clinical history, physical examination, and appropriate image tests allow us to think about the diagnostic hypothesis, even before obtaining material for pathological analysis. An initial total abdominal computed tomography (CT) with intravenous contrast guides the next steps. Most of the time, chest and mediastinal CT should be included since the beginning. In some cases, magnetic resonance image (MRI) allows a more detailed assessment of the nature of the lesion and its relationship to vessels, nerves, and muscles, offering complementary information to

CT. Specific angiographic studies can be useful in the evaluation of invasion, displacement, and/or involvement of vascular structures, although they are not necessary in most cases. The PET/CT 18F-FDG can add value in the investigation of retroperitoneal lymphadenopathy, helping to distinguish between lymphomas, germ cell tumors, and metastatic carcinomas. Other specific tests, such as scintigraphy with metaiodobenzylguanidine (131I-MIBG), scintigraphy with somatostatin receptors (Octreoscan), and PET/CT – 68GA-Dotatate, may be necessary to elucidate the diagnosis in the suspicion of secreting tumors (pheochromocytomas, paragangliomas, and neuroendocrine tumors).

The radiological differentiation between large intraperitoneal tumors, large primary tumors of retroperitoneal organs, primary tumors of the retroperitoneal space, and large lymph node masses can be challenging. Among intraperitoneal tumors, stromal tumors (GIST and EGIST), visceral sarcomas, and adnexal masses deserve special mention. Primary epithelial tumors of intraperitoneal organs can also manifest as large tumors and simulate primary tumors of the retroperitoneal space; however, it is not our aim to discuss them. Large primary tumors of retroperitoneal organs can be difficult to differentiate radiologically from primary tumors of the retroperitoneal space and should also be remembered. Another group of lesions that can simulate primary tumors of the retroperitoneal space are lymph node masses. In addition to the specific complaints reported by the patient, one should actively question the presence of B symptoms (fever, night sweats, weight loss), recent travel story, exposure to infectious diseases, use of illicit drugs, contact with animals, family history of autoimmune diseases, personal history of fertility and cryptorchidism (men), and gynecological and obstetric history (women), in addition to personal and family cancer history. In physical examination, palpation of all lymph node bases is essential. The detection of peripheral lymphadenopathy directs the diagnostic investigation to the group of diseases that lead to diffuse lymph node involvement, including retroperitoneal lymph nodes. In men, careful testicular examination should be performed. Even in the absence of findings, the diagnosis of a primary testicular cancer metastatic to retroperitoneal lymph nodes should be considered and testicular ultrasound performed, especially in young patients.

In addition to chest, abdomen, and pelvis CT scans, initial studies should include measures of lactate dehydrogenase (LDH), alpha-fetoprotein (AFP), and beta-human chorionic gonadotropin (ß-HCG). Other tumor markers and specific serum measurements should also be done depending on the clinical suspicion. High levels of LDH are suggestive of lymphoma and high levels of AFP and ß-HCG are suggestive of germ cell tumors.

Some examples of tumors that present as retroperitoneal masses and illustrate the diversity of situations are presented below. Most of the cases that illustrate this chapter are the result of personal experiences; otherwise, the source will be mentioned in the text (Fig. 7.2).

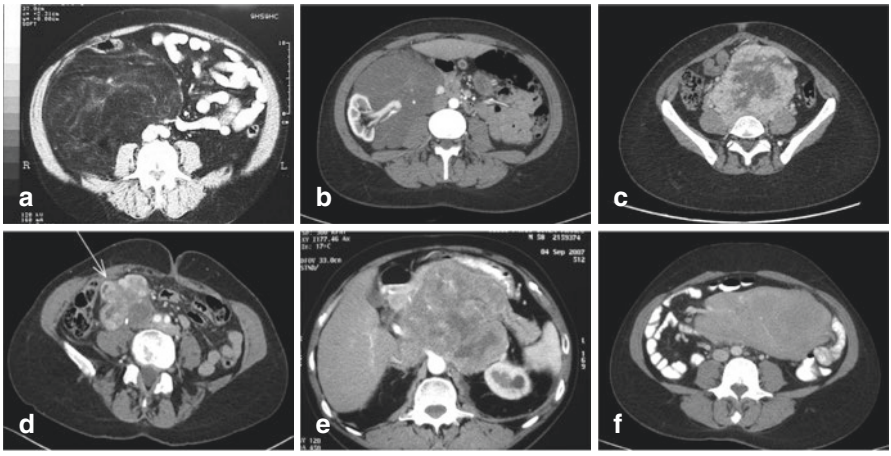

Fig. 7.2 Examples of tumors that manifest as retroperitoneal masses. See how difficult it is to predict the diagnosis without clinical history data. (**a**) Retroperitoneal liposarcoma. (**b**) Retroperitoneal ganglioneuroma. (**c**) Paraganglioma. (**d**) Leiomyosarcoma of the vena cava. (**e**) Gastric GIST. (**f**) Retroperitoneal non-Hodgkin lymphoma

7.3 Differential Diagnoses

7.3.1 Group 1. Intraperitoneal Tumors That Simulate Retroperitoneal Lesions

Gastrointestinal Stromal Tumor (GIST) and Extra-Gastrointestinal Stromal Tumor (EGIST)

Gastrointestinal stromal tumors (GISTs) represent 1% of the digestive tract tumors. GISTs are rare tumors in individuals below 40 years of age, with a mean age of 64 years at diagnosis [7]. They are most common in the stomach (60%) and small intestine (30%) and rare in the colon and rectum (6%) and in the esophagus (0.7%) [8–10]. These tumors arise from Cajal's interstitial cells at the interface between the autonomic innervation of the intestinal wall and the smooth muscle, acting in the control of peristalsis ("pacemaker cells") [11]. Occasionally, they are considered primary of the omentum, mesentery, or peritoneum, possibly originating from Cajal cells that dispersed during embryogenesis, a condition in which they are called extra-gastrointestinal stromal tumors (EGISTs) [12]. It is assumed that GISTs and EGISTs originate from CD34-positive Cajal stem cells that are differentiated from the pacemaker cell phenotype [13]. They generally appear as subepithelial lesions that can cause ulceration in the epithelial lining, but can reach large dimensions through exophytic growth and occupy the abdominal cavity, simulating retroperitoneal tumors. Although the majority is sporadic, about 5% of patients have some autosomal dominant familial syndrome, including familial GIST syndrome, type 1 neurofibromatosis (NF1), and Carney-Stratakis syndrome. Phenotypic, histological, and molecular characteristics are similar in familial and sporadic forms [14].

The CD117 antigen (KIT, kinase tyrosine) is a transmembrane receptor product of the KIT protooncogene (human homologue of the viral oncogene v-KIT). Over 80% of GISTs have a mutation in the KIT gene. Thus, the diagnosis of GIST is often made from the immunohistochemical expression of the KIT protein [15]. Other changes can also occur, such as activating mutations in the platelet-derived growth factor receptor alpha (PDGFRA) and function gains that lead to an abnormally activated structural variant of the KIT protein [16, 17]. Although some GISTs are negative for the mutation, more than 90% are positive for KIT expression. The remaining 10% negative for KIT expression may also be negative for mutations in the KIT gene, but harbor activating mutations in the PDGFRA gene [18]. Thus, only 10–15% of GISTs do not have a KIT or PDGFRA mutation. However, regardless of the mutational status of KIT and PDGFRA, DOG-1 (Discovery on GIST-1) and PKC-theta (protein kinase C theta) immunohistochemistry expression is also used for diagnosis [19]. In most suspected cases, a combination of CD117 and DOG1 in the immunohistochemistry assessment is sufficient to confirm the histological diagnosis [20].

About 10–30% of GISTs progress to malignancy, with exophytic growth observed in 79%, while intraluminal or mixed growth is less common [10]. Through exophytic growth, they are diagnosed as large masses that can manifest through gastrointestinal bleeding, increased abdominal volume, or abdominal pain (Fig. 7.3). Larger tumors can cause obstruction of the gastrointestinal lumen by endoluminal growth or by compression of the gastrointestinal tract. Perforated neoplasms show signs of peritonitis or intraperitoneal bleeding secondary to pressure necrosis and ulceration. Despite the size of the lesion, it is not uncommon for the patient to be in

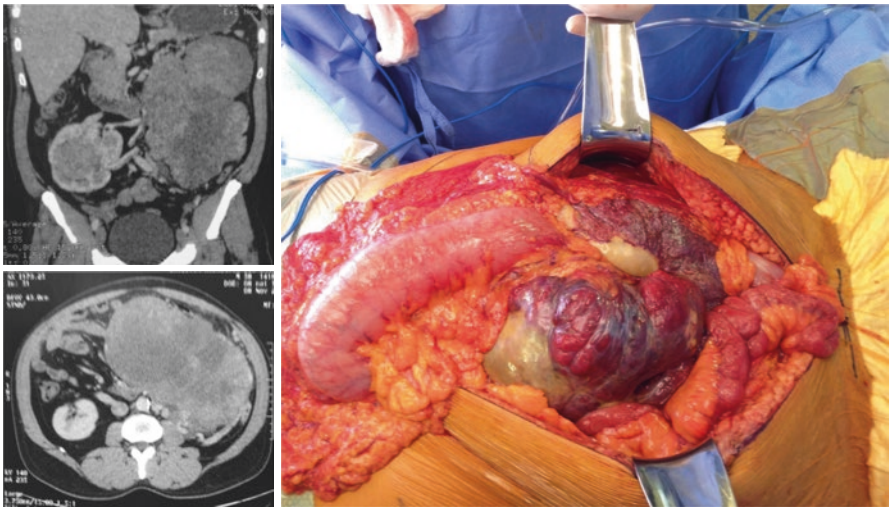

Fig. 7.3 A 60-year-old male patient, complaining of pain associated with increased abdominal volume. On physical examination, a large abdominal mobile mass was noted. A heterogeneous lesion is observed on CT scan, with areas of necrosis and a "geographical" contour. Renal anatomical variation. Operative finding of a massive primary lesion of the proximal jejunum. Segmental enterectomy was performed with complete resection. Definitive diagnosis of GIST

good general condition. On physical examination, the relative mobility of the lesion can clinically suggest the diagnosis of GIST, once the origin can be in mobile segments of the gastrointestinal tract. Bulky pelvic lesions characteristically compress the rectum and displace or involve the bladder and prostate. Large tumors can generate peritoneal and liver metastases [21].

There are no serum tumor markers specific for GISTs and the presumptive diagnosis requires familiarity with its radiological appearance. In potentially resectable tumors, preoperative biopsy is not mandatory; however, it will be mandatory if metastatic disease is suspected or if the use of preoperative imatinib is considered.

Location, size, and rate of mitosis are independent prognostic factors, as well as information about tumor capsule integrity [22, 23]. Extra-gastric tumors are considered to be more aggressive than gastric ones, a fact that has been questioned [24]. Different classifications have been proposed to categorize the risk of recurrence, including the modified NIH classification, where lesions are classified into four groups according to the risk of recurrence: (1) Very low risk (any location *and* <2 cm *and* <5 mitoses/50HPF). (2) Low risk (any location *and* 2.1–5 cm *and* <5 mitoses/50CGA). (3) Intermediate risk (gastric location *and* <5 cm *and* 6–10 mitoses/50HPF or gastric location *and* 5.1–10 cm *and* <5 mitoses/50HPF). (4) High risk (any location with perforated tumor *or* >5 cm *and* >5 mitoses/50HPF *or* >10 cm *and* >10 mitoses/50HPF *or* nongastric *and* 2.1–5 cm *and* >5 mitoses/50HPF *or* 5.1–10 cm *and* <5 mitoses/50HPF) [25].

Some guidelines recommend neoadjuvant therapy with imatinib to reduce tumor size and minimize morbidity in patients with primary GISTs considered resectable with high morbidity [26, 27]. The appropriate time for surgical intervention is not standardized. In general, patients are treated for 6–9 months with the tyrosine kinase inhibitor and then considered for surgery if the tumor is amenable to complete resection [28]. Although it has been shown that the tumor burden continues to decrease even after 1 year of imatinib, the average time to obtain the best response is 3.5 months, with little decrease in size after 9 months [29]. All patients treated with preoperative imatinib should resume therapy with tyrosine kinase inhibitor postoperatively to maximize the benefit of the drug.

During laparotomy, the abdomen must be fully explored to exclude metastatic spread, with special attention to the liver and peritoneal surfaces. The goal of surgical treatment is complete resection with free margins. Surgical maneuvers must carefully avoid tumor rupture, which increases the risk of peritoneal recurrence. Very wide margins are generally not necessary; however, just-tumor resection should be avoided as opposed to segmental resection of the tumor's origin viscera. In cases of macroscopic invasion of adjacent organs, *en bloc* resection is recommended. Due to the low rate of lymph node disease, routine lymphadenectomy is not necessary, being indicated only in situations of clinically compromised or suspected lymph nodes.

In the adjuvant scenario, considering high-risk patients undergoing complete resection, the rates of recurrence-free survival and overall survival are 65.6% versus 47.9% and 92% versus 81.7%, respectively, comparing 3 years and 1 year of adjuvant treatment [30].

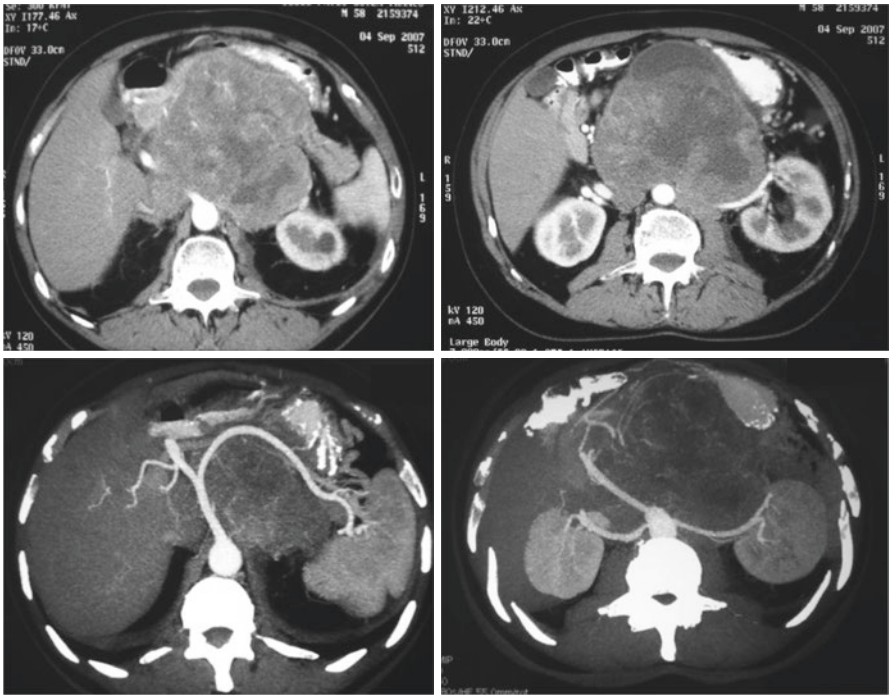

Fig. 7.4 CT shows a large heterogeneous lesion containing areas of necrosis. Note the relationship with vascular trunks. An echo-endoscopy with trans-gastric biopsy was performed, confirming the diagnosis of GIST

The involvement of large vessels is not common; however, the involvement of visceral vascular trunks can occur (Fig. 7.4).

Visceral Sarcomas

Visceral sarcomas are rare tumors in general. Visceral leiomyosarcomas typically appear on CT as large masses with varying degrees of necrosis and heterogeneous contrast enhancement, sometimes with dystrophic calcification [31]. In addition to the characteristics of direct invasion and distant metastasis, other aspects may suggest malignancy in the differentiation between gastrointestinal leiomyomas and leiomyosarcomas: size >5 cm, lobed contours, heterogeneous enhancement, infiltration of mesenteric fat, ulceration, regional lymphadenopathy, and exophytic growth pattern [32]. Due to endoluminal involvement, they can lead to intestinal obstruction. In the absence of invasion of adjacent structures, segmental resection with a wide margin is the treatment of choice. *En bloc* resection is necessary if adjacent organs are macroscopically compromised. Lymph node metastases are rare; however, in the case of intestinal resections, in our view, the inclusion of the lymph node base relative to the affected segment should be considered (Fig. 7.5).

Uterine sarcomas are relatively rare tumors of aggressive behavior that represent less than 10% of cancers of the uterine body. They arise from the myometrium or

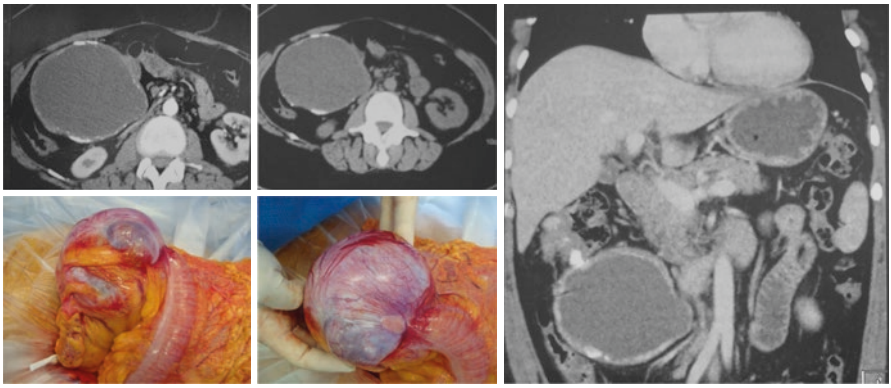

Fig. 7.5 A 45-year-old female patient complaining of mass in the right hypochondrium, with noticeable mobility on physical examination. A cystic lesion with peripheral calcifications is observed on CT. Colonoscopy demonstrated signs of extrinsic compression and irregularity in the mucosa of the proximal transverse colon. Note the intraoperative finding of primary solid-cystic mass of the transverse colon wall. Segmental colectomy with regional lymphadenectomy was performed. Definitive diagnosis of high-grade sarcoma with epithelioid component and ossification, primary of the transverse colon

from the connective tissue elements of the endometrium [33]. Uterine leiomyosarcomas represent 60–70% of cases. They must be carefully investigated in order to avoid diagnostic confusion with uterine leiomyomas. Uterine leiomyosarcomas usually occur in perimenopause, at an average age of 50 years and appear as large pelvic masses, which can cause bleeding or a sensation of vaginal or abdominal pressure. Unfortunately, the diagnosis is rarely suspected before an operation, often being detected accidentally after hysterectomies and nononcological myomectomies, which are extremely harmful for the effective control of the disease [34].

Despite its rarity, visceral sarcomas must be remembered among the differential diagnoses of retroperitoneal tumors, although in most cases they are primary tumors of intraperitoneal organs. Vascular involvement is uncommon.

Adnexal Masses

Pelvic adnexal masses that acquire large volumes are capable to occupy the extension of the abdominal cavity and generate diagnostic doubts. In the suspicion of tumors of gynecological origin, ultrasound assessment, status in relation to menopause, and the value of CA-125 are important factors to be considered in the interpretation of malignancy [35, 36]. Smooth contoured lesions (unilocular or multilocular) and the absence of intra-tumor blood flow at the doppler ultrasound suggest benign lesions, while irregular solid tumors, ascites, papillary projections, and intra-tumor blood flow are signs of malignancy [37]. Multilocular cystic lesions with solid areas, bilateral lesions, and intra-abdominal metastases also favor the possibility of an adnexal malignancy. Despite the importance of the information provided by ultrasonography, larger tumors must be evaluated by CT and/or MRI in order to accurately determine the origin of the tumor and its relationship to adjacent organs. Primary mucinous tumors of the ovary, as well as benign tumors and

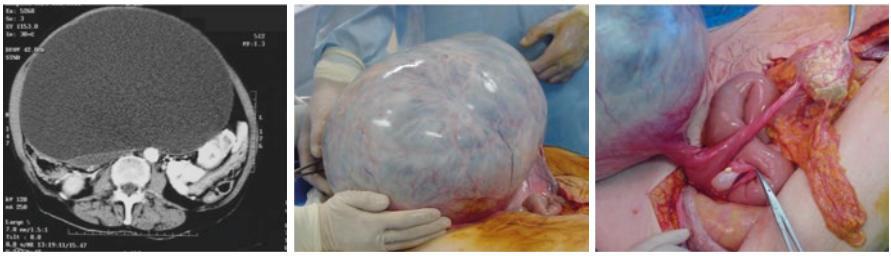

Fig. 7.6 An 81-year-old female patient with increased abdominal volume and normal Ca125 value. A large cystic, homogeneous, and uninoculated lesion is showed on CT, occupying the entire length of the abdominal and pelvic cavity. Intraoperative appearance shows a smooth capsule and the adnexal origin. Definitive pathological diagnosis of ovarian mucinous cystadenoma

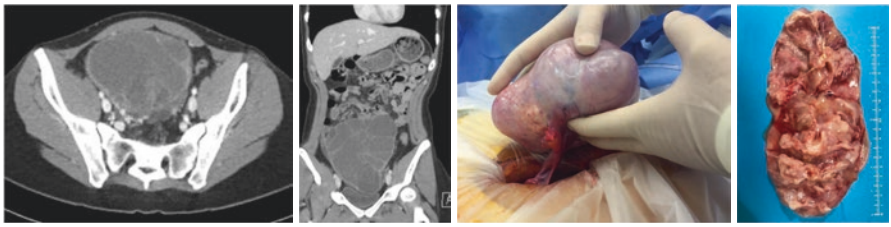

Fig. 7.7 A 29-year-old female patient complaining lumbar pain and increased abdominal volume. The Ca125 tumor marker was normal. The CT shows a complex multiseptated pelvic lesion occupying the lower abdomen and the pelvis. Intraoperative view of the mass originating from the right ovary. The surgical specimen shows the multiloculated aspect of the lesion and its mucinous content. Pathological diagnosis of ovary "borderline" mucinous tumor

"borderline" tumors, can acquire large volumes, configuring among the diagnoses of intraperitoneal lesions that simulate retroperitoneal tumors. Some scoring systems using clinical, laboratory, and image data help to differentiate between benign and malignant lesions and can be useful [38]. Figures 7.5 and 7.6 show examples of large adnexal masses that may raise doubts about the possibility of a retroperitoneal tumor (Figs. 7.6 and 7.7).

Krukenberg tumors, described by Friedrich Ernst Krukenberg, represents 1–2% of ovarian tumors and are considered metastatic ovarian tumors [39]. They are characterized by the presence of adenocarcinoma with signet ring cells rich in mucin, originating mainly from primary gastrointestinal tumors, the stomach being the most common primary site (70%). Gastric and colorectal origin account for 90% of Krukenberg tumors, which are bilateral 80% of the time [40, 41]. Some hypotheses are postulated to explain the dissemination mechanism that gives rise to ovarian metastases. In Krukenberg tumors, the chances of lymphatic and hematogenous dissemination are the most likely, since they also occur in cases of early tumors, confined to the mucosa and submucosa, where there is a rich blood and lymphatic network. The lack of peritoneal involvement in part of the cases also favors this hypothesis as opposed to the transcelomic theory [42].

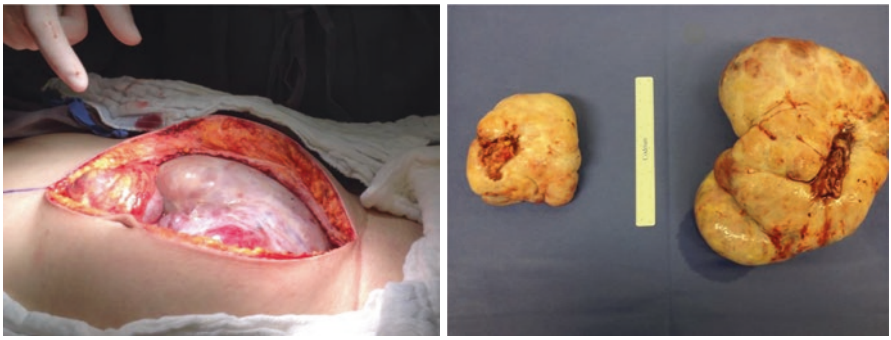

Fig. 7.8 A 39-year-old female patient with a history of gastric cancer. Bilateral adnexal masses. Pathological diagnosis compatible with metastasis of gastric adenocarcinoma with signet ring cells (Krukenberg tumor)

Ovarian metastases can be asymptomatic or manifest through nonspecific gastrointestinal symptoms, such as abdominal or pelvic pain, increased abdominal volume, ascites, or dyspareunia. Occasionally, they can become hormone-secreting tumors, leading to vaginal bleeding, irregular menstrual cycle, hirsutism, and virilization [39]. If ovarian masses are suspected, Krukenberg tumors should be distinguished from primary ovarian neoplasms with signet ring cells with or without mucinous material. In large masses, the differential diagnosis involves radiological and endoscopic evaluation and the measurement of tumor markers (CEA, Ca-72.4, Ca-125, Ca-19.9) to investigate primary gastrointestinal tumors (Fig. 7.8). Vascular involvement is not a common problem.

7.3.2 Group 2. Primary Tumors of Retroperitoneal Organs

The involvement of retroperitoneal organs (duodenum, pancreas, kidneys, adrenal glands, and parts of the ascending and descending colon) by nonepithelial tumors is rare. In all organs, however, we can find neoplasms represented by a spectrum of tumors similar to those that can arise in other locations: lipoma, myelolipoma, adenoma, leiomyoma, liposarcoma, leiomyosarcoma, desmoid tumor, schwannoma, peripheral nerve sheath tumor, tumor solitary fibrous tissue, neuroendocrine tumor, and lymphoma, among others. Theoretically, any of these lesions that originate in a retroperitoneal organ and reach a significant size may present radiologically as a tumor of the retroperitoneal space.

Primary malignant duodenal tumors represent only 0.3% of all gastrointestinal tumors. Despite the rarity, there is a relatively high proportion of duodenal tumors compared to other segments of the small intestine. The most common neoplasms are epithelial (adenocarcinoma, adenoma, Brunner's glandular hyperplasia), but in the presentation simulating tumors of the retroperitoneal space, tumors of mesenchymal origin (GIST, leiomyomas, leiomyosarcomas, neurofibromas), lymphomas,

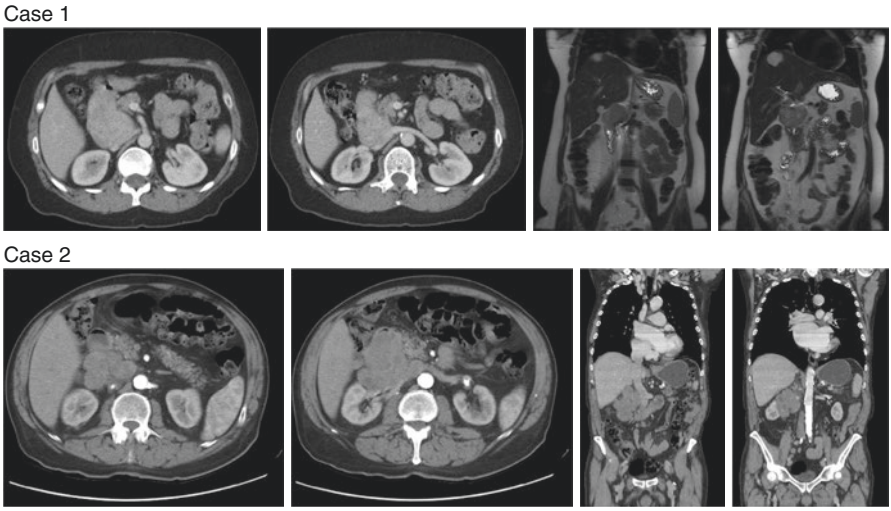

Fig. 7.9 Case 1 – A 48-year-old female patient complaining of postprandial packing. CT shows a retroperitoneal mass displacing the structures of the hepatic hilum, with possible involvement of the duodenal-pancreatic sulcus, compressing and displacing the right renal vein. It is difficult to distinguish between a primary tumor of a retroperitoneal organ and a primary tumor of the retroperitoneal space. Upper gastrointestinal endoscopy demonstrated the duodenal involvement. Definitive diagnosis was done during the surgery. It was a leiomyosarcoma primary of the vena cava. Case 2 – A 78-year-old male patient complaining of abdominal pain in the right hypochondrium and melena. CT shows an expansive and heterogeneous solid lesion, with lobulated contours, located on the posterior wall of the second portion of the duodenum, with extensive posterior expansive component. Note the compression and displacement of the inferior vena cava and the renal vessels on the right. Echo-endoscopy biopsy revealed the diagnosis of duodenal GIST

and neuroendocrine tumors (carcinoid, gastrinoma, and neuroendocrine carcinoma) should be considered (Fig. 7.9) [43]. Nonampullary and periampullary duodenal adenocarcinomas constitute the largest group of lesions and must be considered in the differential diagnosis of retroperitoneal tumors; however, in our experience, the primary duodenal GIST can most commonly acquire large dimensions and, due to exophytic growth, simulate a primary tumor of the retroperitoneal space.

When the organ of origin of the tumor is the pancreas, although ductal adenocarcinoma is the most common type, a variety of other benign and malignant tumors can manifest as a retroperitoneal mass, including epithelial (exocrine and endocrine) and nonepithelial tumors (mesenchymal origin from vessels, stroma, adipose cells, and neural cells), in addition to lymphomas and metastases. Most of the rare pancreatic tumors are frequently diagnosed at an advanced stage due to symptoms related to the mass effect. In general, the presence of hemorrhage in a solid-cystic tumor suggests a solid and pseudopapillary tumor; an enlarged pancreas without dilation of the main pancreatic duct may suggest primary lymphoma of the pancreas; the presence of an intralesional fat component is suggestive of a benign lesion [44]. The size of pancreatic neoplasms varies widely, from microscopic foci to large

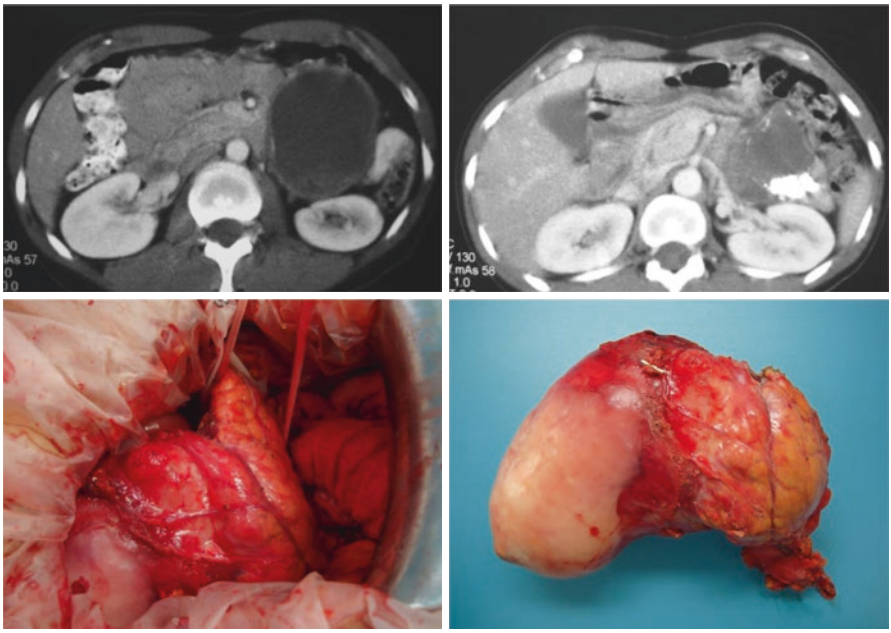

Fig. 7.10 A 45-year-old female patient, complaining of discomfort on the left flank. CT scan shows a solid-cystic lesion with peripheral calcifications located near to the inferior border of the pancreas. During the surgery, a primary lesion of the pancreas projecting into the retroperitoneum was confirmed. Definitive pathological diagnosis of a pancreatic mucinous cystadenoma

cystic neoplasms that may project in the retroperitoneum and also simulate a primary tumor of the retroperitoneal space (Fig. 7.10).

The adrenal gland can be the site of several different tumors that may appear occupying the retroperitoneal space: adenomas, pheochromocytomas, carcinomas, lymphomas, myelolipomas, ganglioneuromas, neurilemomas, ganglioneuroblastomas, and also metastasis from different primary tumors (Fig. 7.11). Increases in the adrenal gland may also be secondary to tuberculosis, a disease that should be included in the list of differential diagnoses [45].

Renal masses are divided into pseudotumor, benign solid masses (adenomas, oncocytomas, angiomyolipomas, others), and malignant solid masses (renal cell carcinoma, collecting duct carcinoma, medullary carcinoma, transitional cell carcinoma, lymphomas, leukemias, sarcomas, and metastases) [46]. Larger lesions can also hamper the interpretation of the renal origin and simulate an origin in the retroperitoneal space and should be considered among the differential diagnoses.

The retroperitoneal segments of the ascending and descending colons are seats of epithelial tumors, but nonepithelial lesions are rare. As in the duodenum, lesions of mesenchymal origin, lymphomas, and neuroendocrine tumors can occur and manifest themselves simulating a tumor of the retroperitoneal space.

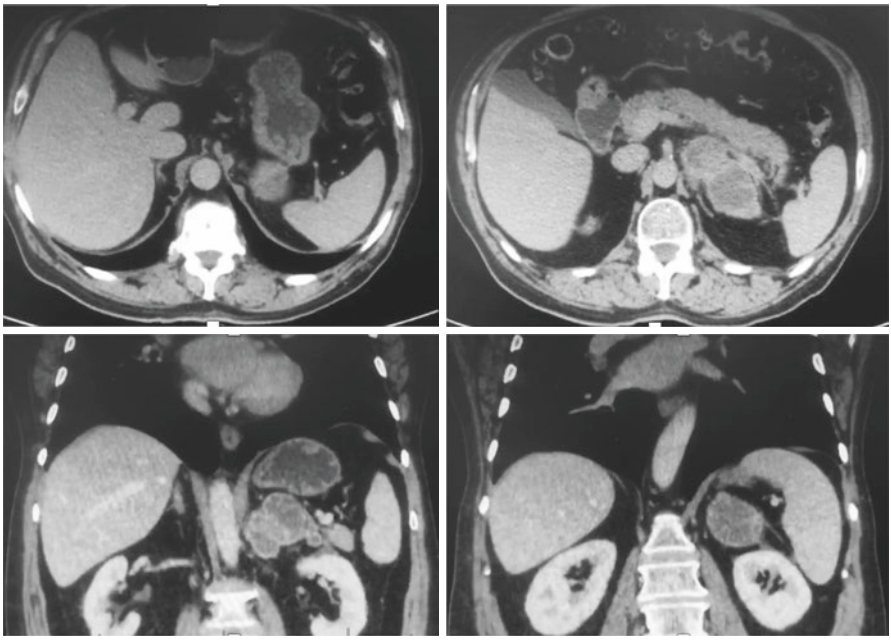

Fig. 7.11 A 60-year-old male patient with a history of lower limb Merckel cell carcinoma. He first developed a brain metastasis that was treated with radiation therapy. Subsequently, a solid-cystic mass appeared, occupying the left adrenal gland, suggestive of metastasis

As we have seen, tumors of primary retroperitoneal organs, when acquiring greater volume, can simulate primary tumors of the retroperitoneal space and should be considered in the list of deferential diagnoses. In these groups of tumors, the risk of vascular involvement is varied, being associated with the organ of origin. Large primary tumors of the pancreas, adrenal, and kidney can involve the local vascular pedicles adding technical difficulty and morbidity to surgical procedures.

7.3.3 Group 3. Primary Tumors of the Retroperitoneal Space

7.3.3.1 Benign Tumors

Approximately 20% of primary neoplastic lesions in the retroperitoneal space are benign. Schwannomas, ganglioneuromas, paragangliomas, angiomyolipomas, lipomas, retroperitoneal desmoid fibromatosis, and retroperitoneal fibrosis are the most common retroperitoneal benign tumors.

Schwannomas
Schwannomas (also called neurilemomas) represent the most common type of peripheral nerve tumor. They are encapsulated tumors that originate from Schwann

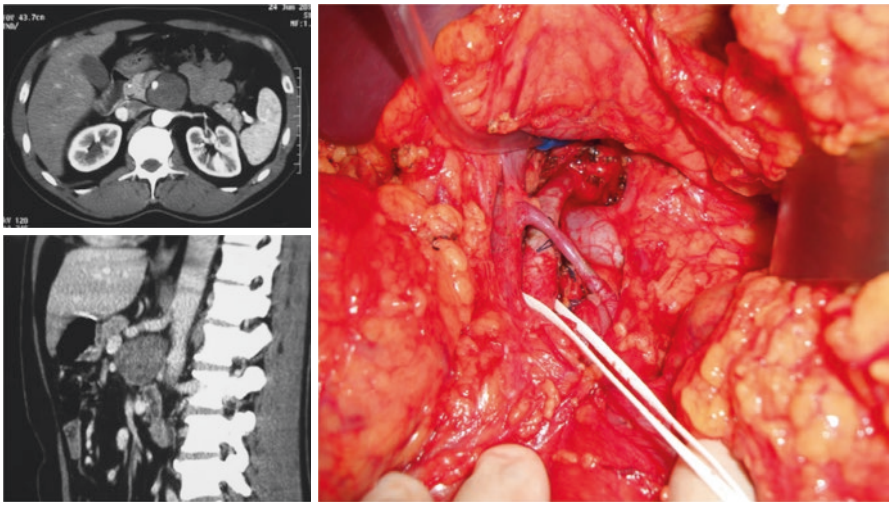

Fig. 7.12 A 47-year-old male patient. Incidental finding of retroperitoneal tumor on routine ultrasound. Complementary investigation with CT showing a solid lesion in close contact with the superior mesenteric artery. A biopsy was performed by echo-endoscopy showing a tumor of neurogenic origin. Surgery was performed with complete resection bordering the superior mesenteric artery. Definitive pathological analyses confirmed the diagnosis of schwannoma

cells and grow from peripheral nerves or nerve roots in an eccentric manner, incorporating the nerve into the lesion capsule. Sporadic schwannomas affect patients of all ages, with a higher incidence between 20 and 50 years. Many schwannomas are discovered incidentally. Lesions with a long course of evolution can suffer degenerative changes (nuclear pleomorphism, hyalinization of blood vessels, hemorrhage, focal necrosis, and calcification), a condition in which the image is distinct and can cause diagnostic misunderstanding [47]. Schwannomas and neurofibromas can occur sporadically or in association with neurofibromatosis (NF). Neurofibromas are seen in NF1 and can undergo malignant transformation. Schwannomas are associated with NF2 and do not develop into malignant lesions, with the exception of atypical variants.

Schwannomas are treated surgically; however, not all patients need to be operated. Asymptomatic patients or patients with few symptoms and high surgical risk can be observed. Sometimes, however, the lack of a definitive diagnosis can corroborate to surgical indication (Fig. 7.12). In retroperitoneal lesions, pain and symptoms resulting from compression of adjacent organs and structures are the main reasons for surgical resection. Complete resection should be sought; however, when the resection implies in partial or total nerve sacrifice and consequent functional deficit, intracapsular resection is allowed to preserve function, minimizing the residual neurological deficit [48]. Large schwannomas of the retroperitoneal space can determine vascular involvement. In this condition, when surgery is indicated, *en bloc* resections followed by revascularization are required (Fig. 7.13) [49].

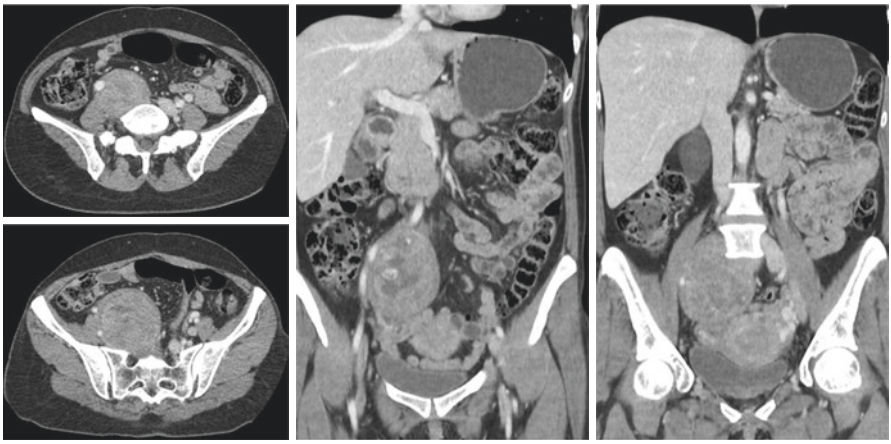

Fig. 7.13 A 53-year-old female patient complaining of abdominal pain with radiation to the posterior region of the right lower limb. The CT shows a solid retroperitoneal mass with wide contact to L5 and S1 vertebral bodies. The lesion compresses and displaces the right iliac vessels. An image-guided biopsy was performed and the diagnosis of schwannoma was confirmed

Ganglioneuromas

Ganglioneuromas, neuroblastomas, and ganglioneuroblastomas are tumors that belong to the group of peripheral neuroblastic tumors formed by mature ganglion cells. Ganglioneuromas are rare slow-growing tumors that arise from sympathetic ganglion cells derived from embryonic neural crest cells and possibly represent the final stage of neuroblastoma maturation. They are benign, large, and encapsulated tumors, more common in young women. Ganglioneuromas can occur anywhere in the sympathetic chain, being more common in the mediastinum, retroperitoneum, and adrenal glands. They are commonly asymptomatic, except when having a mass effect and compression of local organs and structures. In the presacral location, they can cause root compression and pain [50]. Immunohistochemistry shows strong S100 positivity in ganglion cells and Schwann cells [51].

The treatment of choice is complete surgical resection. In the retroperitoneum, ganglioneuromas may involve vascular trunks and nerves, making resection laborious or even contraindicated due to the risk of extensive visceral devascularization. It is not uncommon to find the tumor capsule attached to vascular structures, which makes total excision a high-risk procedure. Thus, the indication for surgery should be evaluated sparingly, since slow growth and the absence of symptoms may not interfere with quality of life, favoring active surveillance with imaging tests as an alternative to a high-risk operation. In this case, through tumor growth and onset of symptoms, the operation should be reconsidered (Figs. 7.14 and 7.15).

Paragangliomas

Paragangliomas are rare neuroendocrine tumors that arise from extra-adrenal autonomic paraganglia, small organs made up mainly of neuroendocrine cells derived from the embryonic neural crest, similar to those that migrate to the adrenal gland.

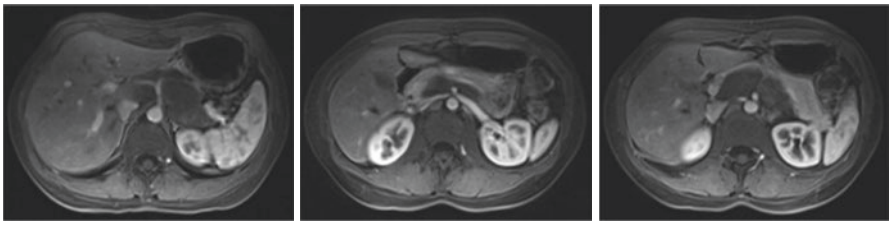

Fig. 7.14 A 32-year-old female patient had a preaortic retroperitoneal mass found during a routine abdominal ultrasound. MRI shows a solid expansive lesion, poorly vascularized, with lobulated contours and well-defined limits measuring 8.2 × 5.0 × 4.1 cm, located in the retroperitoneum, displacing the pancreas anteriorly and maintaining contact with the left adrenal gland. The lesion involves the celiac trunk and its branches, which are patent, with normal caliber and regular contours. It also maintains contact with the superior mesenteric artery and the inferior vena cava and has a compressive effect on the splenic vein. An image-guided biopsy was performed and revealed the diagnosis of ganglioneuroma. The patient has been in follow-up for 5 years, asymptomatic, with imaging tests demonstrating the stability of the lesion

Histologically, paragangliomas are indistinguishable from pheochromocytomas, which is why they are also called "extra-adrenal pheochromocytomas," just as pheochromocytomas are called "intra-adrenal paragangliomas."

Most parasympathetic paragangliomas are not functional and are distributed along the glossopharyngeal and vagus nerves, in the neck and at the base of the skull. In contrast, sympathetic paragangliomas usually secrete catecholamines and are located in the sympathetic paravertebral ganglia of the chest, abdomen, and pelvis. About 75% of the sympathetic paragangliomas arise in the retroperitoneum, most often at the junction of the vena cava with the left renal vein, in the Zuckerkandl organ or next to the aortic bifurcation, close to the emergence of the inferior mesenteric artery. Thus, more often, retroperitoneal paragangliomas originate from sympathetic ganglia and are secretory, presenting clinically as pheochromocytomas, with hypertension, episodic headache, sweating, and tachycardia [52]. Most paragangliomas are benign, diagnosed between the third and fifth decades of life [53]. Malignant paragangliomas are rare (20% of abdominal paragangliomas). Malignancy is defined by the appearance of metastases during the course of the disease [54].

Sporadic paragangliomas are more common in patients over 40 years of age and hereditary forms are more common in younger patients. The proportion between men and women is the same in hereditary forms; however, sporadic cases are more common in women (71% vs. 29%) [55]. Unlike the data suggested by the "Rule of 10" (10% bilateral or multiple, 10% familial, 10% extra-adrenal, 10% malignant), today it is considered that about 25% of paragangliomas are multiple and 30–50% are associated with some hereditary syndrome, the multiplicity being rare in sporadic cases (1.2%) [56]. Previously, hereditary paragangliomas were associated with von Hippel Lindau disease (BVS), multiple endocrine neoplasia type 2

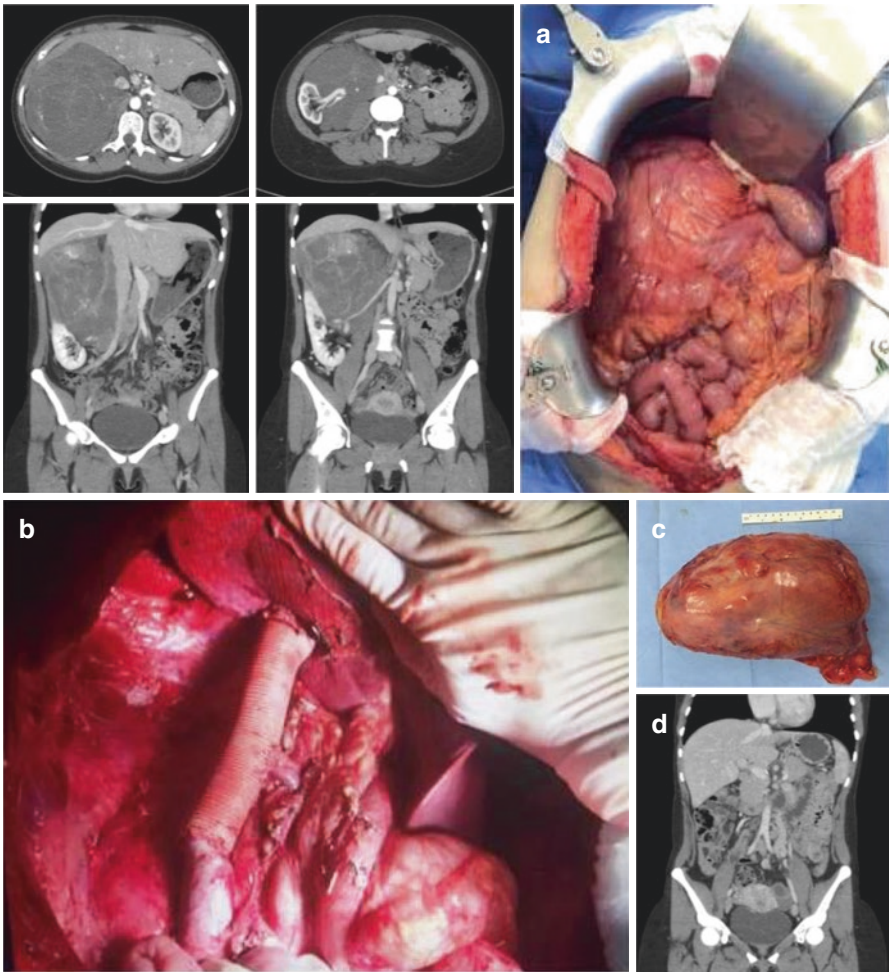

Fig. 7.15 A 26-year-old female patient complaining of abdominal pain. CT shows a large heterogeneous solid retroperitoneal mass, lobulated, with calcifications in between, in the topography of the right adrenal gland. The mass almost completely surrounds the circumference of the inferior vena cava, displaces the right hepatic lobe anteriorly, the pancreas contralaterally and the right kidney inferiorly. There is no clear cleavage plane with the inferior vena cava, that is laterally displaced. (**a**) Wide laparotomy with visualization of the lesion occupying the upper right hemiabdomen. (**b**) *En bloc* resection was necessary, including the right kidney and a large segment of the vena cava; note the reconstruction of the vena cava segment with a prosthesis and the reimplantation of the left renal vein in the prosthesis. (**c**) Operative specimen. (**d**) CT scan control 6 months after the operation. The patient is asymptomatic for 4 years, with no evidence of disease. (*Courtesy of Frederico José Teixeira Jr – oncologic surgery and Luciana Ragazzo Araujo Teixeira – vascular surgery*)

(MEN2), and neurofibromatosis type 1 (NF1) [57]. More recently, it has been shown that 30% of them are secondary to mutations in germ lines of other genes: SDH (succinate dehydrogenase), SDHAF2, TMEM127, and MAX. SDHB mutations are associated with a higher risk of malignancy (31%) and a worse prognosis [58].

Paragangliomas are highly vascularized tumors, usually associated with blood vessels and neural structures. They are usually diagnosed by investigating symptoms related to elevated levels of metanephrines and catecholamines or as an incidental finding on imaging. Histological diagnosis is almost always required, especially when biochemical tests show increased dosage of catecholamine metabolites [59, 60]. Immunohistochemical staining confirms the neuroendocrine nature of cells, with strong diffuse positivity for specific neuron enolase (NSE), synaptophysin, and/or chromogranin, usually with negative staining for keratins [61].

Among catecholamine-secreting tumors, 15–20% are extra-adrenal, most of which are abdominal or pelvic [57]. The most common extra-adrenal sites are abdominal para-aortic regions (75%), urinary bladder (10%), chest (10%), and base of the skull, neck, and pelvis (5%) [62].

In retroperitoneal paragangliomas, due to the greater possibility of being catecholamine secretors, adequate initial investigation is essential in order to avoid potentially serious complications resulting from invasive procedures capable of causing the release of catecholamines and vasoactive peptides. A presumptive diagnosis can be made by the association of biochemical and imaging tests. The screening test recommended for initial evaluation is the measurement of free plasma metanephrines or urinary unconjugated differential metanephrines [63]. Compared to plasma or urinary catecholamines and vanillylmandelic acid, metanephrine levels are more sensitive (98%). It is important to keep in mind that some substances (caffeine) and drugs (beta-blockers, sympathomimetics, tricyclic antidepressants, monoaminoxidase inhibitors, alpha methyl dopa, levodopa, and paracetamol) and acute events (acute myocardial infarction, acute lung edema, and stroke) can increase catecholamine concentrations and generate false positive results. Plasma chromogranin A, a co-secreted protein, is often increased in functional and non-functional paragangliomas and also assists in the diagnosis (sensitivity 83–89%). Likewise, there is a risk of false positive results in the measurement of chromogranin A as a consequence of organic disorders (liver or kidney failure) and use of proton pump inhibitors [64].

Once a paraganglioma has been identified, functional tests will be necessary to complement the investigation and evaluate the existence of metastases and/or multiple tumors [52]. It is important to note that biopsy is contraindicated in patients with suspected paraganglioma, unless the results of the biochemical analysis for catecholamine secretion are negative or the patient is prepared with alpha-adrenergic block, otherwise the biopsy may trigger a hypertensive crisis secondary to the release of catecholamines. For the same reason, surgical interventions must be performed in reference centers, with interaction between the teams of endocrinology, anesthesia, and surgery, so that the preoperative and intraoperative periods are conducted by a team of experienced professionals. During the surgical procedure, constant communication of the operative steps is essential in order to allow the anesthesiologist to be

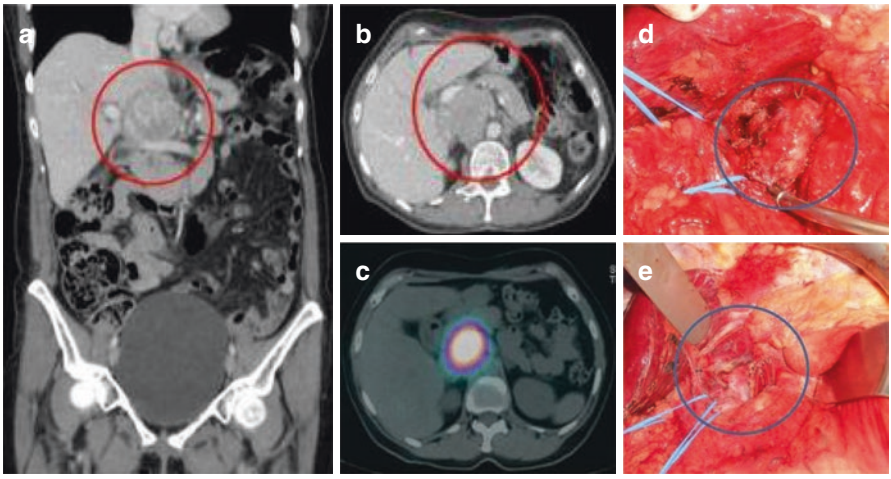

Fig. 7.16 A 74-year-old female patient with difficult to control systemic arterial hypertension. The investigation led to the finding of retroperitoneal mass and elevation of serum catecholamines. The patient was treated with alpha-adrenergic block and prepared for surgery. (**a**, **b**) CT shows a solid vascularized lesion with signs of compression of the portal vein and inferior vena cava, insinuating itself posteriorly to the hepatic hilum. (**c**) MIBG scintigraphy showing the tumor in the highlight area. (**d**) Intraoperative appearance of the tumor and vascular control of the portal vein and inferior vena cava. (**e**) View of the operative field with exposure of the inferior vena cava and segment I of the liver after complete resection. Definitive diagnosis of paraganglioma. (*Courtesy of Frederico José Teixeira Junior, oncologic surgery*)

prepared and to anticipate great variations in blood pressure. The patient must be properly monitored and have adequate vascular access (Fig. 7.16).

Angiomyolipoma and Lymphangioleiomyoma (Lymphangioma)

Angiomyolipomas are benign tumors that contain atypical blood vessels and smooth muscle in varying proportions [65]. The most common site for angiomyolipoma is the kidney, where it presents as an intrarenal mass. Occasionally, however, it can grow exophytically in the retroperitoneum, reach large dimensions and, due to its high fat content, simulate the diagnosis of liposarcoma [66, 67]. Based on the fat content, they are divided into "fat-rich" (classic type) and "fat-poor," both benign, without metastatic potential. A third rare type is the epithelioid form, which has malignant potential and is part of the family of perivascular epithelial cell neoplasms (PEComas) [68–70].

Isolated sporadic angiomyolipomas represent 80% of the cases, the others being associated with the tuberous sclerosis complex (Bourneville-Pringle disease), a rare autosomal dominant genetic condition. The changes affect cell proliferation and differentiation, resulting in hamartomatous lesions in many organs, including the kidneys, with renal angiomyolipoma being the most common association (50–80%). Although rare and benign, large lesions and the association with tuberous sclerosis increase the risk of complications, including intralesional bleeding, which can be one of the initial manifestations. Sporadic angiomyolipoma occurs mainly in women

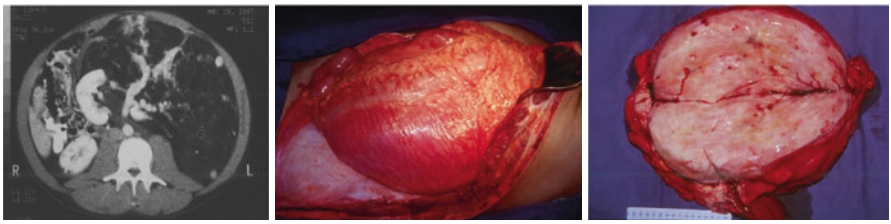

Fig. 7.17 Large angiomyolipoma simulating a liposarcoma in a young patient with tuberous sclerosis complex. (*Courtesy of Ademar Lopes, oncologic surgery*)

in the fourth and fifth decades of life. Angiomyolipoma associated with tuberous sclerosis is typically a larger, multifocal, or bilateral tumor, more frequent in younger patients (Fig. 7.17) [71, 72].

Lymphangioleiomyomatosis (lymphangiomyomatosis; LAM) is a rare disease of unknown etiology, observed only in women, usually in the reproductive period, often associated with pulmonary involvement. Two forms of lymphangioleiomyomatosis are described: sporadic (S-LAM) and associated with the tuberous sclerosis complex (TSC-LAM). Both forms are related to mutations in the TSC1 or TSC2 genes, which results in overactivation of the mTOR pathway. Postmenopausal occurrence is very rare [73].

Extrapulmonary involvement in the form of angiomyolipomas and retroperitoneal adenopathy can occur in up to 75% of cases. The evolution tends to be slow, progressive, and hormone-dependent, characterized by the formation of diffuse thin-walled cysts in the lungs and angiomyolipomas in the kidneys [74, 75].

The lymphangioleiomyomas (lymphangiomyoma) of the retroperitoneum and pelvis are benign lymph-filled tumors that occur in 16–38% of patients with LAM They can be asymptomatic or generate nausea, bloating, abdominal pain, edema of the lower extremities, or urinary symptoms due to displacement of the bladder, in addition to chyluria due to lymphangioleiomyomatous connections with the renal collecting system. The worsening of symptoms throughout the day is explained by the variation in size due to gravity, food intake, and exercise [76]. Retroperitoneal and pelvic lymphadenopathy are more common than mediastinal lymphadenopathy, consistent with its origin in the lower abdomen or pelvis. Several reports of lymphangioleiomyomatosis describe lesions in the uterus and ovaries, in addition to uterine leiomyomas (fibroids). Sometimes, intravenous progression through the gonadal veins can reach the inferior vena cava with upward migration to the cardiac atrium (Fig. 7.18) [77, 78].

The retroperitoneal location and the possibility of associated lymphadenomegaly add angiomyolipomas and lymphangioleiomyoma in the list of differential diagnoses of retroperitoneal tumors with the possibility of vascular involvement.

Lipomas

Lipomas are benign proliferations of mature adipose cells. They are classified according to morphology into: fibrolipoma, conventional lipoma, angiolipoma, spindle cell lipoma, and myelolipoma. The occurrence in the retroperitoneal space

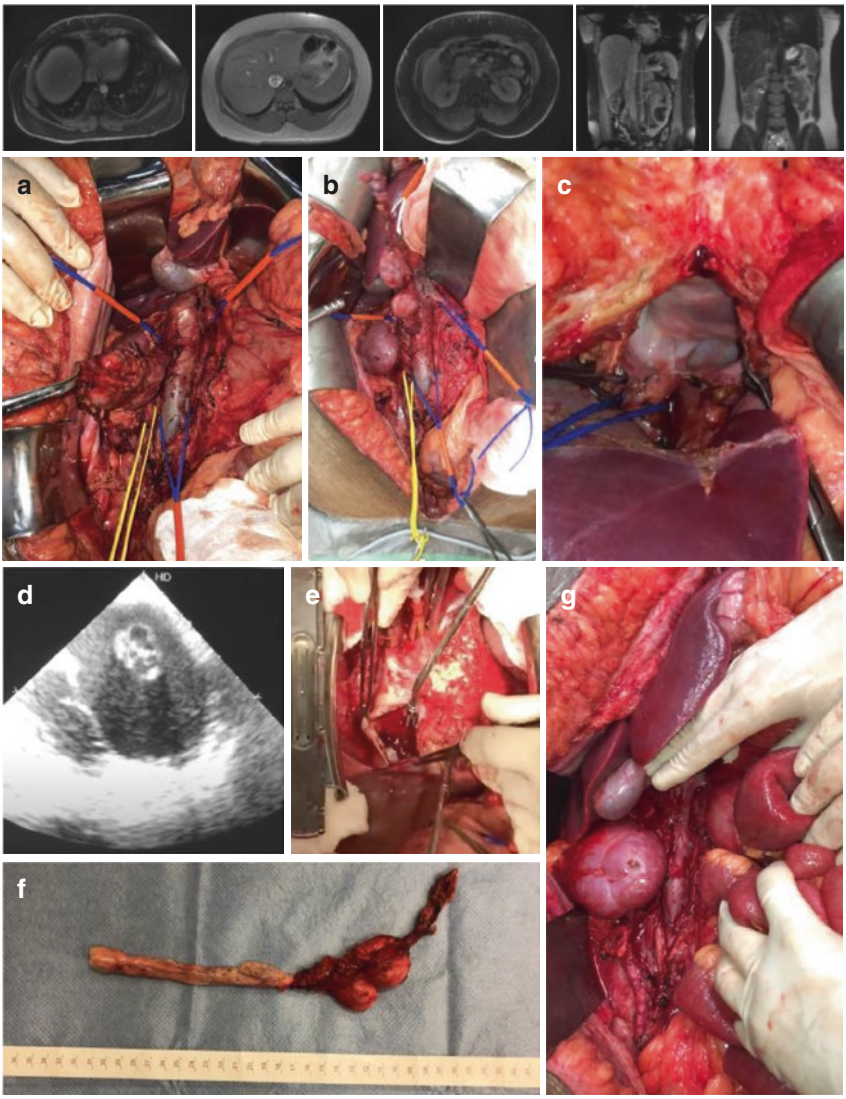

Fig. 7.18 A 31-year-old female patient with a history of previous hysterectomy for large uterine leiomyoma. After hysterectomy, an atrial cardiac mass was found. The echocardiogram revealed a 4 cm mobile and heterogeneous mass partially filling the lumen of the inferior vena cava, projecting into the right atrium. MRI images demonstrate the extent of the lesion through the right gonadal vein and progression within the inferior vena cava to the right atrium. (**a**, **b**) Operative field showing dissection and repair of the inferior vena cava, the right and left renal veins and the right gonadal vein filled with tumor (upper portion of photo **b**). (**c**) View of the inferior vena cava (suprahepatic portion) and pericardium, exposed before completing the sternotomy. (**d**) Ultrasonographic record of the atrial thrombus. (**e**) Sternotomy and opening of the right atrium with the patient in extracorporeal circulation. (**f**) Operative specimen showing the gonadal vein with tumor thrombus and the thrombus in the shape of the inferior vena cava with the intra-atrial portion. (**g**) Suture of the inferior vena cava and final aspect of the operation. The patient is asymptomatic with 2 years of follow-up, with no evidence of disease. (*Courtesy of Frederico José Teixeira Junior, oncologic surgery; Nelson de Luccia, vascular surgery; and Fábio Gaiotto, cardiac surgery*)

is rare. Among primary retroperitoneal lesions, they represent only 0.2% of neoplasms. Retroperitoneal lipoma can appear in different tissues: adipose, conjunctive, muscular, lymphatic, or nervous. It can also originate from the mesentery, Gerota's fascia, or the urogenital tract [79].

The clinical presentation is variable. They can be asymptomatic, found during routine imaging exams, or course with an increase in volume and generate symptoms resulting from the compression of adjacent organs and structures. Generally, additional tests are not necessary beyond computed tomography; however, due to its rarity occupying the retroperitoneal space, uncertainty leads to further investigation to exclude other diagnostics and MRI can help. The definitive diagnosis between a lipoma and a well-differentiated liposarcoma depends on pathological examination [80]. Fluorescent in situ hybridization (FISH) for amplification of MDM2 has been considered a useful test for definitive distinction between a lipoma and a well-differentiated liposarcoma, with the gene being amplified in the liposarcoma. Surgery is the therapeutic modality of choice. It is important to mention, however, that even in the conviction of a benign lesion, an effort must be made to achieve a complete resection, without fragmentation of the lesion. Due to its benign characteristics, vascular involvement is not expected (Fig. 7.19).

7.3.3.2 Malignant Tumors

Retroperitoneal Soft Tissue Sarcomas

Retroperitoneal sarcomas represent 10–15% of total soft tissue sarcomas and constitute an important diagnosis among primary malignant neoplasms of the retroperitoneal space [81]. Due to the absence of specific symptoms in the early stages, the diagnosis is usually postponed until growth leads to compression, displacement, and/or invasion of adjacent organs and structures, including large vessels. One third of patients will experience some neurological symptom secondary to the effect of compression or stretching of lumbar or pelvic nerve plexuses. Gastrointestinal symptoms and nonneoplastic ascites secondary to extrinsic compression and/or invasion of vascular structures can occur, respectively, in 10% and 15% of cases [5, 82].

In adults, the most common histological types of retroperitoneal sarcomas are liposarcomas and leiomyosarcomas, followed by nonclassifiable undifferentiated sarcomas, including pleomorphic sarcomas. Other less common histologies are malignant tumor of the peripheral nerve sheath, synovial sarcoma, solitary fibrous tumor, and small round cell desmoplastic tumor [83]. In children, the most common histological types are extra-skeletal Ewing tumor/primitive neuroectodermal tumor (PNET), alveolar rhabdomyosarcoma, and fibrosarcoma [84].

Among liposarcomas, the most common subtypes are well-differentiated and dedifferentiated sarcomas. Well-differentiated liposarcomas have no metastatic potential, but local recurrences are relatively common. Dedifferentiated liposarcomas are defined by the presence of regions of nonlipogenic sarcomatous tissue within a well-differentiated tumor, sometimes difficult to distinguish from undifferentiated pleomorphic sarcomas [85]. They are high-grade tumors, with high

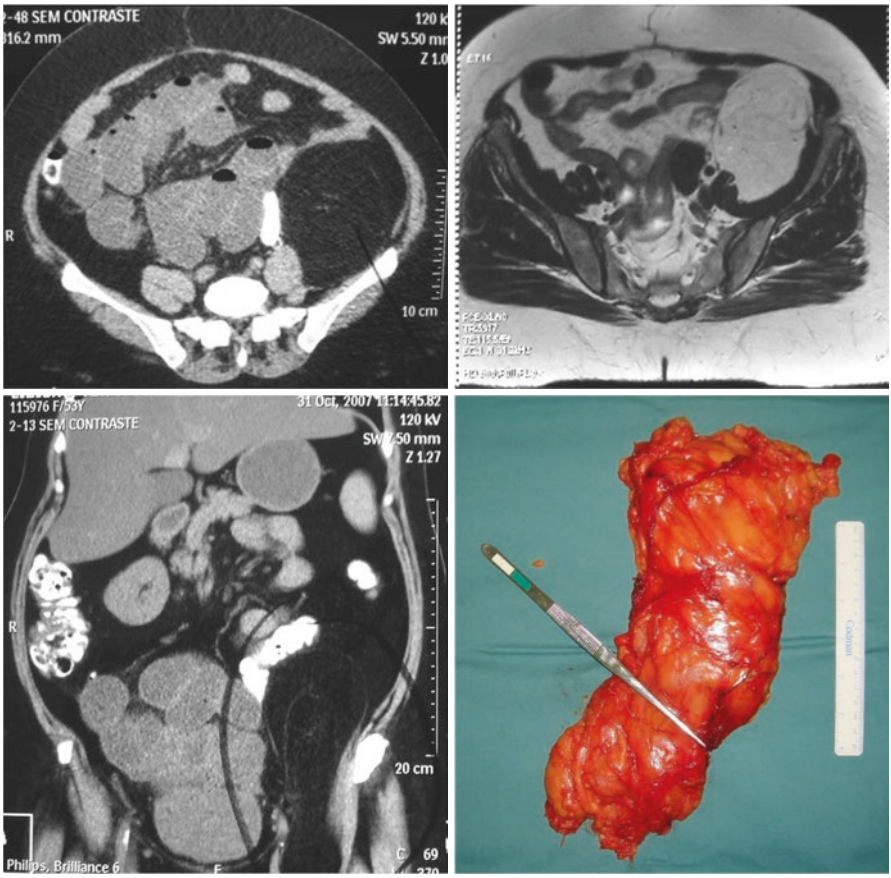

Fig. 7.19 A 53-year-old female patient complaining of bulging in the right iliac fossa. MRI shows a homogeneous lipomatous lesion in the left pelvic topography projecting to the left thigh. Definitive pathological diagnosis of lipoma

metastatic potential and risk of death. The other subtypes (myxoid and round cells) are less common in the retroperitoneum [86, 87]. Liposarcomas can reach large volumes and constitute a real surgical challenge (Fig. 7.20).

When the hypothesis is a leiomyosarcoma, special attention should be paid to the possibility of primary origin in retroperitoneum vessels, including the origin in the inferior vena cava and its tributaries (Figs. 7.21 and 7.22). In this case, the risk of lung metastases is high and 10% of patients present with distant metastases at diagnosis [88]. Leiomyosarcomas can also originate from the wall of the gastrointestinal tract and uterus, a situation in which they are considered visceral sarcomas rather than retroperitoneal tumors and are at increased risk of peritoneal and hepatic spread.

Once the diagnosis of retroperitoneal sarcoma is confirmed, surgical resection is the only potentially curative approach. The most important prognostic factor is a complete resection at the initial presentation. Upon complete resection, the degree

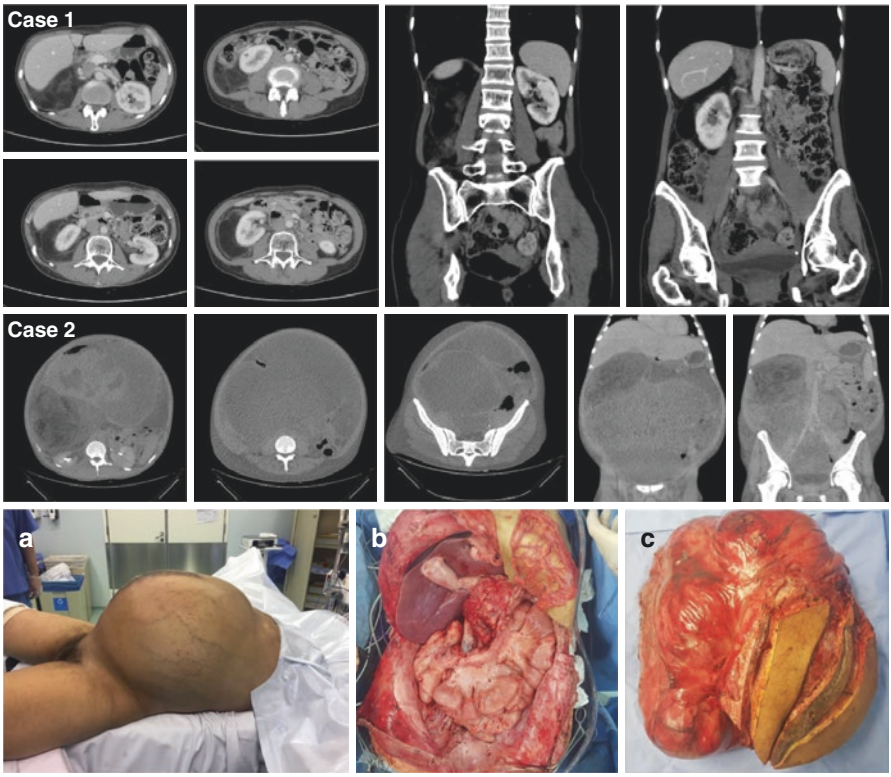

Fig. 7.20 Case 1 – A 75-year-old female patient. CT shows an extensive well-defined lesion predominantly containing fat, suggestive of well-differentiated liposarcoma, molding itself in the retroperitoneal space through the displacement of adjacent organs and involving the right kidney. The patient was operated on and the diagnosis was confirmed. Case 2 – A 37-year-old male patient, complaining of an increase in abdominal volume for a year and a half, associated with weight loss and asthenia. The biopsy was performed in an external service, resulting in a high-grade liposarcoma. Due to the low performance status, the patient was admitted for clinical compensation and nutritional support and prepared for the operation. Note a large volume heterogeneous lesion on CT scans, occupying the entire length of the abdominal and pelvic cavity. (**a**) Patient in the operating room (note the large abdominal volume, the dilation of the superficial veins at the abdominal wall, and the edema of the lower limbs, compatible with compression of the vena cava). (**b**) Operative bed showing *en bloc* resection, including the right kidney and the right and transverse proximal colon. (**c**) Operative specimen weighing 27 kg (note the need for associated resection of the abdominal wall in the area of tumor invasion). The patient had excellent postoperative recovery and is at 1 year of follow-up, with no evidence of disease

of histological malignancy is the second factor to be considered, with a worse prognosis for high-grade tumors. Depending on the size and location, a resection with microscopically negative margins (R0) is not always feasible. For this reason, complete macroscopic resections with compromised microscopic margins (R1) are common, although not desirable. This characteristic justifies the high rates of locoregional recurrence observed in different series [89, 90].

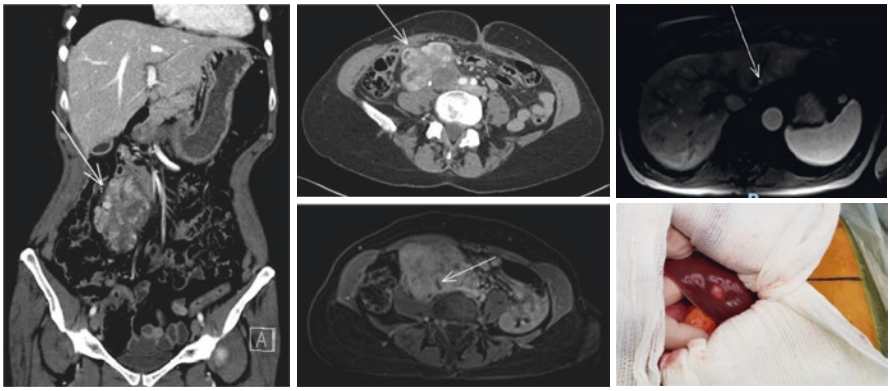

Fig. 7.21 A 59-year-old female patient noticed an abdominal mass on self-examination. MRI showed a retroperitoneal mass with lobulated contours, with heterogeneous sign, exuberant vascularization, and areas of necrosis, in contact or originating in the inferior vena cava, with involvement of the right ureter and hydronephrosis. Note that the vena cava is not seen from the confluence of the common iliac veins up to the level of L3–L4. The patient underwent an image-guided biopsy and the pathological examination revealed a high-grade leiomyosarcoma. Neoadjuvant radiotherapy was performed, followed by surgery. During the operation, the presence of liver metastases was detected, which led to the interruption of the procedure (shown in the last photo). Two years after the date of the surgery, the patient is undergoing systemic treatment with stable disease

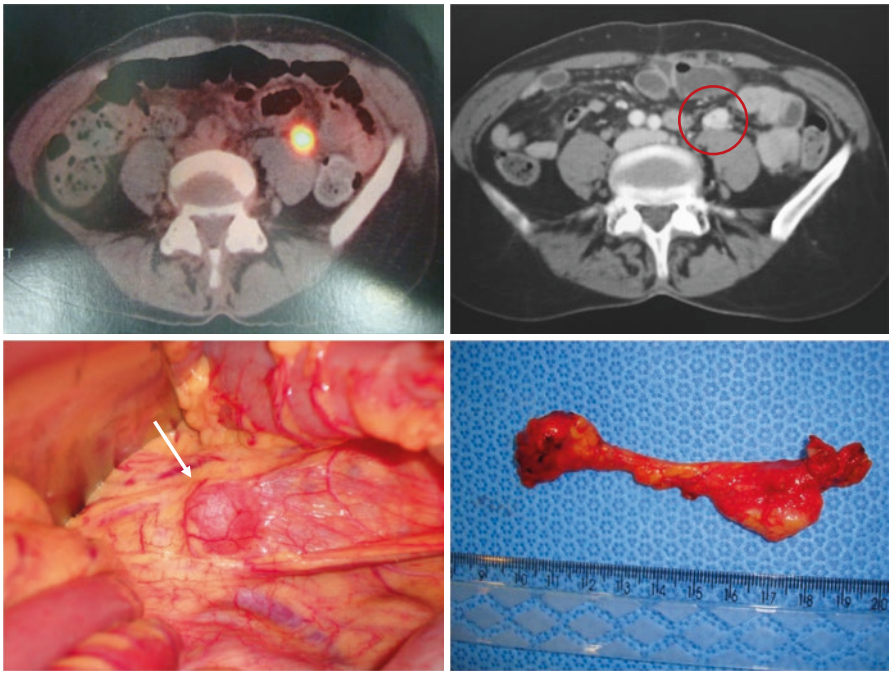

Fig. 7.22 A 63-year-old female patient previously treated for lung cancer. In follow-up exams, a solid nodule was noted in the anterior portion of the left psoas muscle with increased metabolism on PET-CT. The patient underwent an image-guided biopsy that revealed the diagnosis of high-grade leiomyosarcoma. During the operation, it was possible to conclude that it was a primary leiomyosarcoma of the left gonadal vein

Ideally, patients with retroperitoneal sarcomas should be treated in centers with experience [91]. The lack of prospective randomized clinical trials regarding the use of neoadjuvant and adjuvant treatments leads to a wide variation in treatment protocols. Despite the lack of evidence, considering that large size, depth, and high-grade tumors have higher metastatic potential, some reference centers advocate a possible benefit of systemic chemotherapy, particularly in chemosensitive histologies. Likewise, since obtaining wide three-dimensional margins is not routine, the use of perioperative radiotherapy is also discussed in order to reduce the rates of local recurrence. In this sense, it is possible to point out some advantages of preoperative radiotherapy in relation to the postoperative one: smaller radiation field, lower dose rate, and greater safety by avoiding the irradiation of uncommitted structures, which will occupy the tumor bed after resection, making postoperative planning difficult and increasing the risk of actinic complications. In practice, despite these premises, there is great disagreement as to the best approach for the treatment of patients with retroperitoneal sarcomas. The therapeutic decision is influenced by factors such as histological type, degree of malignancy, tumor size, and tumor location in the retroperitoneal space.

Among low-grade sarcomas, the most common are the well-differentiated liposarcomas. In most cases, well-differentiated retroperitoneal liposarcomas are amenable to complete resection and the treatment begins with the operation. In larger tumors, however, where complete resection is expected to be difficult, the use of preoperative radiotherapy should be discussed on a case-by-case basis, although there is little enthusiasm for the use of radiation in low-grade retroperitoneal tumors. In general, adjuvant chemotherapy and radiotherapy are not indicated for low-grade sarcomas that are totally resected. When the histology is considered chemosensitive (synovial, myxoid liposarcomas, intermediate, and high-grade round cell liposarcoma), the use of neoadjuvant chemotherapy with or without radiotherapy should be discussed. Among sarcomas of intermediate or high grade with histology not sensitive to chemotherapy, the use of preoperative radiotherapy followed by surgery or exclusive surgery is the most common strategy. The use of intraoperative radiotherapy is an interesting option to be offered in some cases, either as an exclusive modality or as part of the strategy to minimize the necessary pre- or postoperative doses, reducing the risk of side effects (Fig. 7.23). For primary leiomyosarcomas of the inferior vena cava and dedifferentiated liposarcomas, due to the high metastatic potential, neoadjuvant chemotherapy with or without preoperative RT should be discussed.

The role of neoadjuvant radiotherapy in retroperitoneal sarcomas is being evaluated in a prospective randomized trial [92]. In this study, patients were randomized to receive preoperative radiation therapy (50.4 Gy), followed by surgery or exclusive surgery. In an exploratory analysis, preoperative radiotherapy benefited exclusively the subgroup of liposarcomas (71.6% vs. 60.4%; HR = 0.64, 95% CI 0.40–1.01, $p = 0.049$).

Some factors are pointed out to justify the nonresectability and/or contraindication for surgical approach: extensive vascular involvement, peritoneal implants, nonresectable distant metastases, and involvement of the mesentery root or spinal

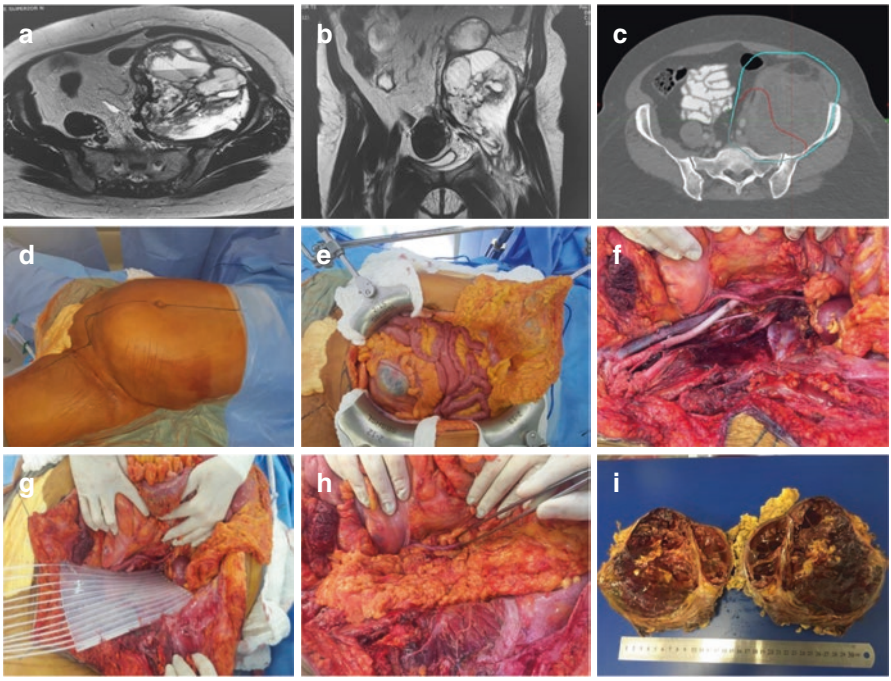

Fig. 7.23 A 60-year-old female patient complaining of pain and edema of the left lower limb for 6 months. (**a**, **b**) MRI shows an expansive (20 cm × 16 cm) heterogeneous lesion in the lower left retroperitoneal region, insinuating itself through the femoral canal, medially displacing the iliac vessels, the gonadal vein, and the ureter, with a necrotic and hematic component and peripheral nodular foci. Observe the contact of the lesion with the iliac and femoral vessels, without signs of invasion or irregularities, in addition to wide contact with the left iliac muscle and extension below the inguinal ligament, following the ileo-psoas tendon in the plane of the myotendinous transition. An image-guided biopsy was performed which revealed the diagnosis of pleomorphic sarcoma (high grade). (**c**) Neoadjuvant radiotherapy planning. (**d**) Patient in the operating room with planning to perform Karakousis incision. (**e**) View of the operative field with the lesion occupying the retroperitoneal space in the lower left quadrant. (**f**) Operative bed after complete marginal resection with wide dissection of the iliac vessels and left ureter. (**g**) Positioning the applicator to perform a complementary dose of intraoperative radiotherapy. (**h**) Rotation of an omentum flap interposed between the iliac vessels and the ureter to protect the retroperitoneal space. (**i**) Surgical specimen with a high rate of necrosis. After postoperative recovery, the patient received adjuvant chemotherapy and is at 3 years of follow-up, with no signs of disease

cord. In our view, vascular involvement, in most cases, does not represent a contraindication to surgery or even to achieve a radical operation and will be discussed later. When complete resection is not possible, partial resections are contraindicated and will be performed exceptionally for palliation and relief of symptoms.

Solitary Fibrous Tumor

Solitary fibrous tumor comprises a histological spectrum of fibroblastic mesenchymal neoplasms that are rarely metastatic. They can occur at any location and age, with no preference for gender, and are most common between the fifth and seventh

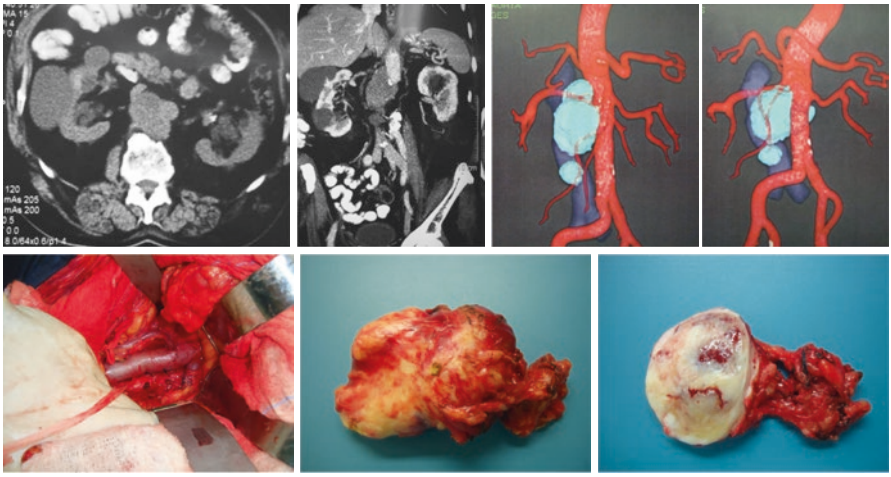

Fig. 7.24 Example of solitary fibrous retroperitoneal tumor diagnosed in a 75-year-old male patient. The definitive diagnosis only occurred after histological analysis of the specimen. Note the relationship of the lesion to the aorta and vessels of the right renal pedicle

decades, in the pleura, peritoneum, and meninges. About 30% of solitary fibrous tumors appear in the peritoneal cavity, retroperitoneal soft tissues, and pelvis, the retroperitoneum being the most common intra-abdominal site (Fig. 7.24). Large tumors can involve multiple organs that can make differential diagnosis difficult [93].

The characterization of malignancy based on histological aspects (mitotic activity, necrosis, hemorrhage, size, cellularity, nuclear pleomorphism, and stromal or vascular invasion) is controversial, as these criteria have a low correlation with clinical outcome [94, 95]. The anaplastic variant represents a clearly malignant tumor, with aggressive behavior and rapid progression, but occurs in less than 1% of cases [96]. The lipomatous variant is even more rare. Most are benign, although they are included among malignant variants due to the possibility of an immature lipoblastic component. A focal myxoid change is common, probably resulting from increased mucin production by connective neoplastic cells tissue [97]. The solitary fibrous tumor has a broad spectrum of biological behavior. Most are indolent and have a low risk of local recurrence or metastasis. Late recurrences can occur, even for tumors initially classified as "benign." Among tumors classified as malignant, 10–40% will have liver metastases after 5 years, which highlights the need for continued long-term follow-up, especially for individuals of high risk (≥4 mitoses for 10 high magnification fields, presence of necrosis or hemorrhage, large size, high cellularity, nuclear pleomorphism, and stromal or vascular invasion) [98, 99].

The most common symptom is a palpable abdominal mass, followed by pain and weight loss. Small tumors are typically asymptomatic, and symptoms begin when the lesion reaches larger sizes (>20 cm). The presentation can rarely be secondary to hypoglycemia as a manifestation of para-neoplastic syndrome. Refractory hypoglycemia (Doege-Potter syndrome) occurs in less than 5% of cases and is seen

mainly in large peritoneal and pleural tumors, caused by the secretion of insulin-like growth factor 2 (IGF-2). The IGF-2 gene is among the target genes of EGR, possibly deregulated by the chimeric transcription factor NAB2-STAT6, a molecular characteristic of solitary fibrous tumor [100].

Solitary fibrous tumors are characterized by a recurrent inversion of the long arm of chromosome 12 (12q13). This inversion results in the fusion of two genes, NAB2 (NGFI-A binding protein 2) and STAT6 (signal transducer and transcription activator factor 6). The fusion creates a chimeric transcription factor NAB2-STAT6 that is constitutively located in the nucleus, being a distinct molecular characteristic of solitary fibrous tumor, present in up to 100% of cases, not detected in other tumors [101, 102].

For localized disease, complete surgical resection with negative margins (R0) is the standard treatment. There is not enough evidence to justify the use of neoadjuvant or adjuvant therapy in a systematic way, although the use of adjuvant radiotherapy for tumors considered to be at high risk is discussed [103]. After incomplete resections or resections with compromised microscopic margins, the use of radiotherapy should be discussed individually. Given the rarity of these tumors, the role of adjuvant chemotherapy is unknown.

For unresectable or metastatic disease, there is no established standard of treatment. The use of oral antiangiogenic tyrosine kinase inhibitors associated with temozolomide provides therapeutic benefits similar to traditional chemotherapy with less toxicity and has been considered a therapeutic option [104]. The use of target drugs with agents directed to vascular endothelial growth factor (VEGF) and other tyrosine kinase signaling pathways are being evaluated for the treatment of advanced disease (sunitinib, sorafenib, axitinib) [105–107].

Although rare, the solitary fibrous tumor must be part of the list of differential diagnoses of retroperitoneal tumors. In the image, the finding of a solid, circumscribed, richly vascularized tumor nourished by prominent vessels should resemble the hypothesis of a solitary fibrous tumor. When there is a risk of intraoperative bleeding, preoperative arterial embolization should be considered (Fig. 7.25).

Ewing's Sarcoma

Ewing's sarcoma is a rare malignancy in adults. In children, it usually presents as a primary bone tumor. Occasionally, they appear in the soft tissues (extra-osseous Ewing's sarcoma). Tumors of the Ewing family include the primitive peripheral neuroectodermal tumor (PNET). As these tumors share histological, immunohistochemical, and unique chromosomal translocations, they are considered to be of common origin [108]. The involvement of the extra-osseous site is reported in up to 11%, including the retroperitoneum, the adrenal glands, and the soft parts of the extremities [109]. Despite the rarity, they should be remembered in the differential diagnosis of retroperitoneum tumors, particularly in young people (Fig. 7.26).

Both extra-osseous Ewing tumors and PNET respond to the same chemotherapy regimens as osseous Ewing's sarcoma and are treated in the same way [110]. Ewing's sarcomas of the retroperitoneal space should be discussed in a multidisciplinary setting once treatment may involve chemotherapy, radiation, and surgery.

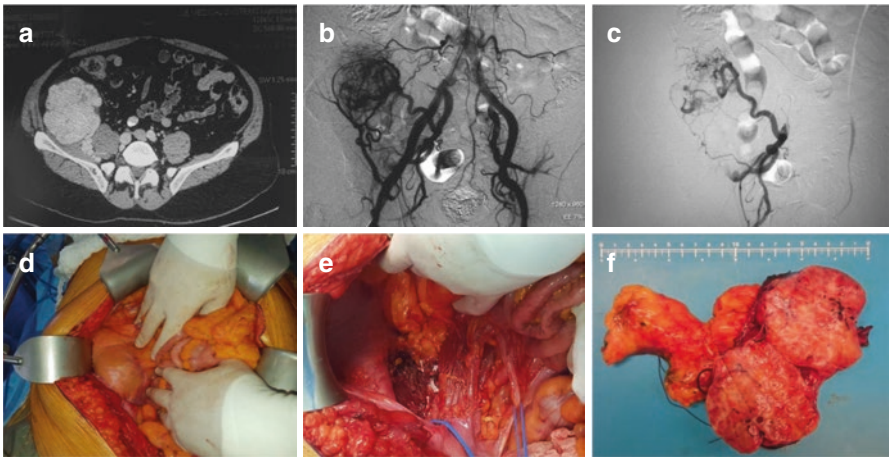

Fig. 7.25 A 71-year-old male patient with retroperitoneal mass found during routine ultrasound. On physical examination, the patient had a palpable mass in the right iliac fossa, with a noticeable thrill and audible murmur. (**a**) CT shows an expansive process with intense post-contrast enhancement in the arterial, portal, and venous phases, with lobulated contour and foci of hypodense images suggestive of a fibrous component. (**b**) Arteriography showing that the lesion is nourished by two dominant arteries, branches of the right internal and external iliac arteries. Due to the rich vascularization, biopsy was contraindicated, and preoperative embolization was programmed. (**c**) Selective microcatheterization of the arterial branches responsible for the vascularization of the lesion, followed by embolization with PVA microparticles until vascular stasis. The control arteriography showed adequate devascularization of the lesion. (**d**) View of the lesion occupying the retroperitoneal space in the right iliac fossa. (**e**) View of the operative field with exposure of the right ureter and iliac vessels. There was no bleeding because the arterial branches were properly occluded by preoperative embolization, performed hours before the operation; (**f**) Surgical specimen: definitive diagnosis of solitary fibrous tumor. (*Preoperative embolization: Francisco Carnevale, interventional radiologist*)

Malignant Paraganglioma

Since it is not possible to define the malignancy based on histological findings, the determination of malignancy in paragangliomas is not straightforward. Nuclear pleomorphism, necrosis, rate of mitosis, and local invasion, characteristics commonly seen in malignant tumors, can also be seen in benign paragangliomas. About 25% of paragangliomas are malignant, defined by the development of metastases. The highest rates of malignancy are observed in paragangliomas associated with mutations inherited in the ß-subunit of the succinate dehydrogenase gene (SDHB), which are usually abdominally located and secretory. In multiple endocrine neoplasia syndrome type 2 (MEN2), 3–5% of paragangliomas are malignant [57].

Several scoring systems have been proposed to calculate the risk of malignancy for pheochromocytomas considering invasion, histological growth patterns, cytological characteristics, and mitotic activity. One of the most used is the "Pheochromocytoma of the adrenal gland scoring scale (PASS)" and can also be applied to paragangliomas. A PASS score <4 or >6 suggests benign and malignant lesions, respectively, while a value between 4 and 6 suggests an intermediate risk

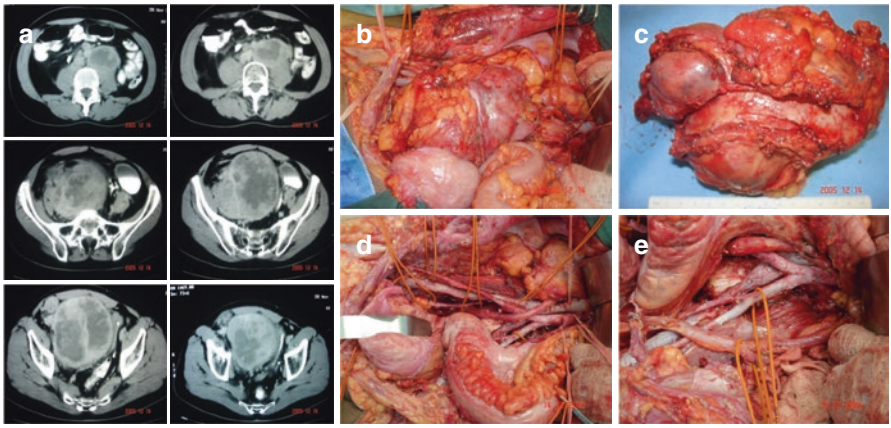

Fig. 7.26 A young male patient with a large retroperitoneal mass, previously submitted to image-guided biopsy resulting in a tumor of the Ewing/PNET family. The patient received systemic chemotherapy according to the specific protocol, with partial response. (**a**) CT shows the appearance of the mass after chemotherapy, displacing the bladder, the small intestine, and the colon and compressing the rectum. Note the extensive area of necrosis and the involvement of retroperitoneal lymph nodes. (**b**) Operative field after bilateral Karakousis incision: repair of the spermatic cord, the inferior vena cava, and the right ureter – observe the displacement of the adjacent organs. (**c**) Operative specimen: observe the groove determined by the impression of the vessels in the lesion. (**d**, **e**) Operative field after tumor complete resection with vascular preservation – observe the wide retroperitoneal and pelvic dissection and the return of the organs to the usual position

[111, 112] (Fig. 7.27). The biochemical phenotype also does not allow the differentiation between benign and malignant paragangliomas; however, the presence of large noradrenaline-producing paragangliomas and increased levels of plasma dopamine or its metabolite suggest malignancy. Malignancy is also more often associated with very high plasma levels of chromogranin A [52].

The diagnostic approach of paraganglioma requires evidence of excessive catecholamine release and anatomical documentation of a tumor. The increase in plasma metanephrine fractions has high sensitivity (97%) and specificity (93%) for diagnosis. On the other hand, the measurement of catecholamine fractions (epinephrine and dopamine) is less sensitive, although clearly high values (>2 times the upper limit of the normal range) are also diagnostic. Mild elevations in the levels of metanephrine and catecholamine fractions in plasma and urine may be secondary to the use of drugs leading to false positive results (tricyclic antidepressants, antipsychotic agents, levodopa, and serotonin and norepinephrine reuptake inhibitors). Thus, when investigating catecholamine-secreting tumors, tricyclic antidepressants and other psychoactive agents should be reduced and discontinued at least 2 weeks before any hormonal assessment [52].

Combined α- and β-adrenergic block should be proposed for patients with secretory paragangliomas that are candidates for surgery. Treatment must begin at least 7 days before the operation, in order to control blood pressure and prevent intraoperative hypertensive crises. Adrenergic blockade can be performed with a

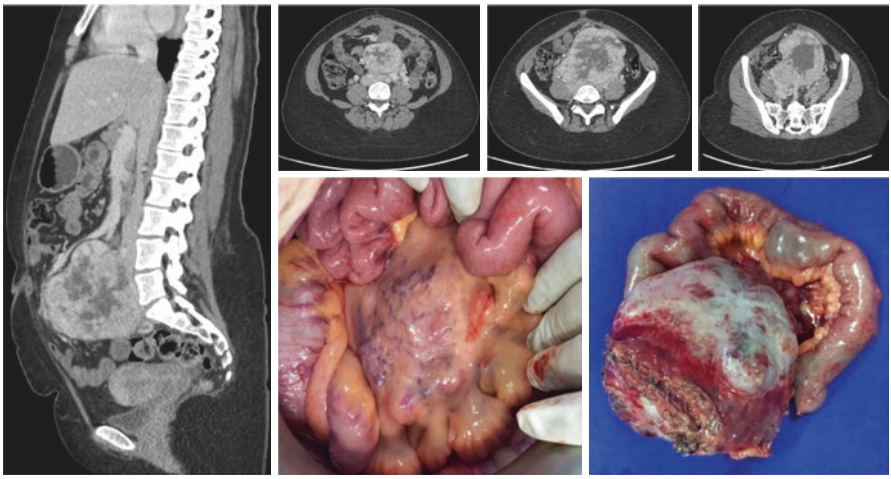

Fig. 7.27 A 21-year-old female patient with abdominal mass found during obstetric ultrasound. Increased plasma catecholamines were found. After pregnancy, she was prepared for surgery with adrenergic block. The definitive diagnosis was paraganglioma. PASS calculation: Wide nests or diffuse architecture (in more than 10% of the tumor): 0 out of (2); central or confluent tumor necrosis: 2 out of (2); high cellularity: 0 out of (2); cell monotony: 0 of (2); spindle cell component: 0 of (2); mitosis figures >3/10 CGA: 0 of (2) (identified 01 mitosis in 10 HPF); atypical mitosis figures: 0 of (2); extension in adipose tissue: 0 of (2); vascular invasion: 1 of (1); capsular invasion: 1 of (1); accentuated nuclear pleomorphism: 0 of (1); nuclear hyperchromasia: 0 of (1) – *total score*: 04 = intermediate risk for malignancy. (*Courtesy of Tibério Moura de Andrade Lima, surgical oncology*)

nonselective or selective α-adrenergic receptor antagonist, accompanied by a sodium-rich diet and generous fluid intake. The β-adrenergic antagonist should be administered to control tachycardia after α-adrenergic block has been effective in normalizing blood pressure. Only with β-adrenergic block, severe hypertension or cardiopulmonary decompensation can occur as a result of unopposed adrenergic stimulation. However, care should be taken with the risk of sustained postoperative hypotension as a consequence of preoperative α-adrenergic block [52].

Although a laparoscopic approach may be recommended for benign paragangliomas, malignant tumors are usually large and/or located in areas that are difficult to manage laparoscopically. In cases of proven or suspected malignancy, open surgery is recommended, preserving the principles of oncological surgery to avoid capsule rupture and minimize the risk of local recurrence [113, 114].

Radionuclide treatment should be considered in patients with nonresectable metastatic disease. Likewise, external radiotherapy can also be considered in the treatment of inoperable paragangliomas and for pain control of bone metastases. In recurrent or metastatic disease, “debulking” palliative surgery, ablation, and radiotherapy procedures represent alternatives to decrease tumor burden and catecholamine secretion [52]. Patients with secretory retroperitoneal paragangliomas require special attention and should be treated at referral centers.

Extragonadal Germinal Tumor

Germ cell tumors are classified as extragonadal if there is no evidence of a primary tumor in the testicles or ovaries. They are classified as seminomatous (dysgerminomas, in women), nonseminomatous (non-dysgerminomas, in women), mature teratomas, and immature teratomas. Nonseminomatous tumors include yolk sac tumors, choriocarcinomas, embryonic carcinomas, teratomas, and mixed tumors. They usually appear in midline locations, most commonly in the anterior mediastinum and retroperitoneum.

The differential diagnosis is made mainly with retroperitoneal metastasis of a primary testicular germ cell tumor and other poorly differentiated histologies. As testicular palpation is not sufficient to exclude a primary testicular tumor, testicular ultrasound should be performed in all patients [115]. The distinction between true extragonadal germ cell tumors and retroperitoneal metastasis from primary regressed testicular tumors is difficult [116, 117]. Extragonadal nonseminomatous tumors are associated with elevations in serum AFP and/or HCG-ß in 85% of cases. The frequency of abnormalities in tumor markers is different between mediastinal and retroperitoneal tumors. Mediastinal nonseminomatous tumors are more likely to result in pronounced elevations of serum AFP and less likely to result in elevations of HCG-ß compared to gonadal and retroperitoneal tumors [118].

Extragonadal germ cells tumors usually present as bulky masses in the retroperitoneal space. Clinical behavior, prognosis, and treatment are similar to those of metastatic testicular germ cell tumors. Generally, systemic chemotherapy with cisplatin-based regimens is the initial approach. Thus, surgery is not the first step, being reserved for the rescue of residual masses [119].

Mature cystic teratomas are extremely rare and usually appear as a well-circumscribed complex cystic mass that contains a variable amount of fluid, fat or sebum, and calcification. Although most teratomas are benign, a variety of malignant components may be present or develop from clonal transformation, but in the retroperitoneum, they rarely undergo malignant transformation.

Most malignant retroperitoneal germ cell tumors are metastases from primary gonadal tumors, seen in 30% of patients of gonadal GCTs [120]. As mentioned earlier, careful examination of the testicles is essential in all patients with retroperitoneal masses. Occasionally, the primary testicular tumor is not visible or small intratesticular scars are found in patients with retroperitoneal GCT. These scars represent regressed GCTs, a phenomenon known as "burnout" [121]. Retroperitoneal GCTs are usually large in presentation. Symptoms and signs include a palpable mass with or without pain, weight loss, constipation, back and hip pain, dyspnea, leg swelling, fever, varicocele, and urinary retention. Involvement, displacement, and compression of the abdominal vessels are common (Fig. 7.28).

Retroperitoneal teratomas represent 1–11% of primary retroperitoneal tumors. The incidence is bimodal, with peaks in the first 6 months of life and early adulthood, usually identified after reaching large sizes. The chance of malignancy is around 25%. Surgical resection remains the basis of therapy and is necessary for a definitive diagnosis. As the preoperative diagnosis is based on needle biopsy, it is possible that complete resection reveals the presence of germ cell tumor elements and the patient will be a candidate for adjuvant chemotherapy [122].

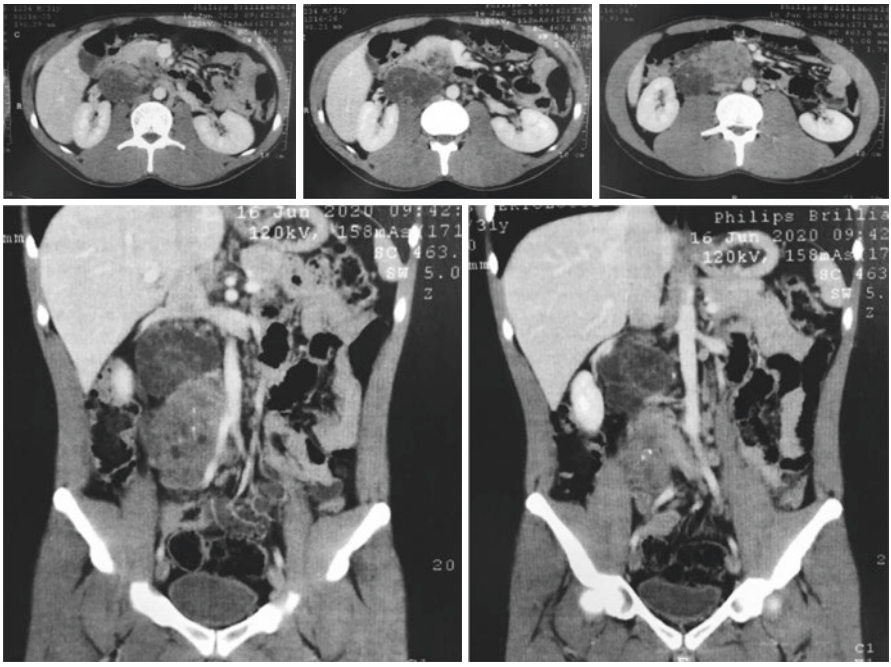

Fig. 7.28 A 31-year-old male patient who sought medical attention complaining of low back pain on the right. The images showed a large retroperitoneal mass, predominantly solid with areas of necrosis and involvement of the right common, the common iliac artery and the right renal pedicle. The inferior vena cava also seems to be involved. The patient did not report testicular changes, however, as part of the investigation; AFP and HCG-ß were collected and proved to be increased. The testicular ultrasound performed in the sequence revealed a 6 mm lesion in the right testicle. The patient underwent radical orchiectomy, and the pathological examination confirmed the presence of a small area of embryonic carcinoma. The patient was treated according to a systemic chemotherapy protocol, with normalization of the markers, but with persistence of a large residual retroperitoneal mass. He is currently scheduled for surgery with the possibility of associated vascular resection

Large retroperitoneal masses and recurrences are associated with a greater chance of involvement of large vessels. Upon surgical indication, the possibility of vascular resections should be provided. Depending on previous chemotherapy regimens, there is a possibility of impaired renal function. During surgery, there may be a need for transient clamping of the renal vessels or nephrectomy, contributing to the risk of postoperative renal failure. In this condition, the possibility of renal revascularization or renal auto-transplantation should be considered.

7.3.3.3 Fibromatoses and Fibroses

Desmoid Fibromatosis

Desmoid fibromatosis (DF), also known as “desmoid tumor,” “aggressive fibromatosis,” or “deep musculoaponeurotic fibromatosis,” is a disease characterized by locally aggressive behavior. It can develop anywhere, being more common on the

trunk, extremities, abdominal wall, and intra-abdominal region (small bowel and mesentery). In patients with Familial Adenomatous Polyposis (FAP), they are more common in the intra-abdominal region. Most of the time, DF appears as a painless mass with slow growth. In progression, intra-abdominal masses can cause intestinal obstruction, ischemia, and perforation [123].

The conclusive diagnosis is established by pathological examination. Nuclear positivity for beta-catenin in immunohistochemistry suggests the diagnosis of DF, although the lack of expression does not exclude the diagnosis. Other entities (superficial fibromatosis, low-grade myofibroblastic sarcomas, solitary fibrous tumors) may also show nuclear positivity for beta-catenin [124]. The diagnosis can be improved through Next-Generation Sequence with detection of mutations in the CTNNB1 gene. Changes that result in the activation of the Wnt pathway may be present and also help in the diagnosis [125].

Most of the time, DFs have slowed an indolent growth. Periods of growth arrest and even spontaneous regression can occur [126–128]. Intra-abdominal desmoids acquire singular importance in FAP patients and can be the cause of death in up to 11%, once the possibility of complete resection is low due to diffuse infiltration of the mesentery or due to multiplicity [129]. Resection can lead to severe morbidity, resulting in extensive enterectomy, intestinal ischemia, risk of obstruction, and intestinal fistulas [130]. In addition, recurrence rates are high and the recurrent disease tends to be more aggressive compared to the initial one [131]. For these reasons, conservative treatment strategies have been advocated rather than a surgical approach, at least in the early stages of treatment [132].

The most current strategy for treating DF is multimodal. Some options are watchful-waiting, systemic therapy with noncytotoxic drugs (nonhormonal anti-inflammatory ± tamoxifen), radiotherapy, target drugs (imatinib), and cytotoxic chemotherapy. For patients with large resectable intra-abdominal DF, surgery should be considered, although the chance of insufficient margins and incomplete resection is high, particularly if there is involvement of the mesentery, vessels, or vital organs (Fig. 7.29) [133].

Mesentery desmoid fibromatosis is part of the list of differential diagnoses of retroperitoneal masses and should be remembered. The diagnosis must be confirmed ideally by image-guided biopsy.

Retroperitoneal Fibrosis

Retroperitoneal fibrosis, also known as "Ormond's disease," "fibrous periureteritis," "plasma periureteritis," "chronic periureteritis," "sclerosing retroperitoneal granuloma," and "fibrous retroperitonitis," encompasses a series of diseases characterized by the presence of fibrous-inflammatory tissue that usually surrounds the abdominal aorta and the iliac arteries, extending into the retroperitoneum, involving neighboring structures and enveloping the ureters. In general, it is an idiopathic manifestation; however, it can be related to the use of drugs, malignant neoplasms, infections, and previous surgeries [134].

The pathological findings of idiopathic and secondary retroperitoneal fibrosis forms are indistinguishable. Idiopathic disease seems to be related to a local inflammatory reaction to antigens in abdominal aortic arteriosclerosis plaques; however,

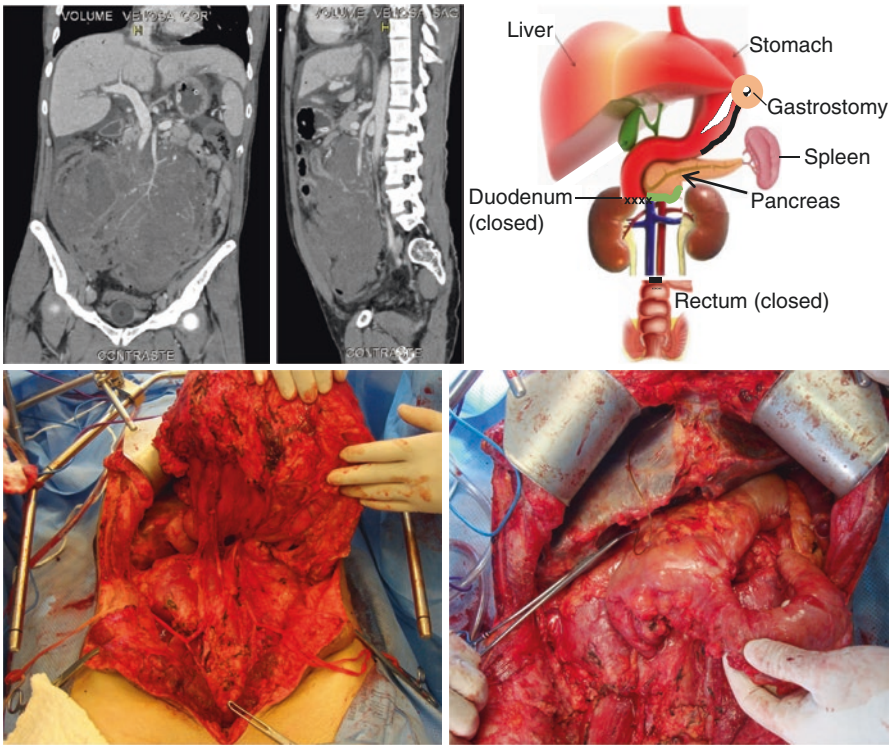

Fig. 7.29 A 27-year-old male patient with familial adenomatous polyposis associated with a mesentery desmoid tumor (Gardner's syndrome). History of previous surgeries for resection of the desmoid tumor without success and failure of drug treatments. He presented with disease progression and intestinal perforation generating an abdominal sepsis. CT images show the presence of a large mass involving the root of the superior mesenteric artery and encompassing practically the entire small bowel. Presence of air in the bile ducts can be observed. In these moments, the patient was in the ICU, intubated, with vasoactive drugs. After discussion with family members and the ethics committee, a laparotomy was proposed, knowing the possibility of total enterectomy and the need for permanent parenteral nutrition. The diagram in the figure represents the surgery performed, with total enterectomy associated with total colectomy and closure of the duodenum distally to the duodenal papilla. The intraperitoneal rectum was closed. In order to create a drainage pathway for bile, saliva, and gastric juice and to allow the intake of fluids orally for patient comfort, we chose to split the stomach by creating a tube of the great gastric curvature and perform a gastrostomy. The patient evolved well, with discharge on the 30th postoperative day. He received home parenteral nutrition for 1 year until he underwent a multivisceral transplant at a specialized service in Indiana, United States. The patient has 10 years of follow-up after transplantation, is fed by mouth, has no stoma, and has a good quality of life. The case illustrates the difficulty in managing desmoid fibromatosis of the mesentery and, at the same time, the evolution of surgery in the area of transplants, which makes it possible to offer survival and quality of life in extreme situations

constitutional symptoms, high levels of acute phase proteins, the association with other autoimmune conditions, and manifestation in other organs suggest that retroperitoneal fibrosis is a manifestation of systemic autoimmune and/or inflammatory disease. For this reason, clinical treatments are generally recommended as the use of steroids, immunosuppressive agents, and tamoxifen. The patient generally

appears in good clinical condition; however, there is a risk of renal failure secondary to ureteral involvement [134].

The idiopathic form is an immune-mediated disease that can be isolated, associated with autoimmune diseases or related to immunoglobulin G4 disease. Although there are no standardized classification criteria, idiopathic retroperitoneal fibrosis is part of the spectrum of chronic peri aortitis, which includes inflammatory aneurysms of the abdominal aorta and retroperitoneal fibrosis. In one third of the cases, the perivascular tissue is not limited to the abdominal aorta and the iliac arteries, but also involves the thoracic aorta and the origin of the epi-aortic arteries (diffuse peri aortitis) [135, 136].

Although retroperitoneal fibrosis may belong to the spectrum of IgG4-related disease, there appears to be no major difference between IgG4-related and unrelated retroperitoneal fibrosis, except for a higher frequency of extra-retroperitoneal lesions in the IgG4-related disease subset [137]. The inflammatory infiltrate is represented by B and T lymphocytes, macrophages, and plasma cells and can be diffused or arranged in pseudo-nodular perivascular aggregates.

The clinical features of idiopathic or secondary retroperitoneal fibrosis are nonspecific and the diagnosis is generally not considered until there is significant involvement of retroperitoneal organs, most often the kidneys. The most common symptom is lower back and abdominal pain. Malaise, anorexia, weight loss, fever, nausea, and vomiting can be reported, as well as testicular pain, varicocele, and hydrocele secondary to compression of retroperitoneal vessels [138, 139]. There may be complaints of lameness related to arterial involvement of the lower extremities or symptoms of mesenteric ischemia due to compression of the mesenteric arteries. When the thoracic aorta and/or epi-aortic arteries are involved, patients may experience dry cough, hoarseness secondary to recurrent laryngeal nerve palsy, and claudication of the upper limbs. Stenosis of the arteries is rare, but venous compression (mainly of the inferior vena cava) is common and can cause edema in the lower limbs through a combination of venous and lymphatic compression, leading to the appearance of collateral circulation. Despite vascular compression, inferior vena cava syndrome, deep vein thrombosis, and pulmonary embolism are rare events [134, 140].

Although rare, retroperitoneal fibrosis should be included in the list of diagnoses of retroperitoneal masses. Due to the inflammatory nature of the lesion, treatment is done with nonsteroidal anti-inflammatory agents. As mentioned, there is a risk of different associated vascular problems.

Erdheim-Chester Disease

Erdheim-Chester disease is a rare systemic histiocytic disorder of non-Langerhans cells, most common in men (3:1), in the age group between 50 and 60 years old [141, 142]. It manifests most commonly through multifocal sclerotic lesions of long bones, with or without histiocytic infiltration of extra-osseous tissues. It is caused by the clonal proliferation of myeloid progenitor cells, as demonstrated by the detection of the characteristic BRAF V600E mutation in subsets of dendritic cells, mature monocytes, compromised myeloid progenitors, and CD34 + cells [142].

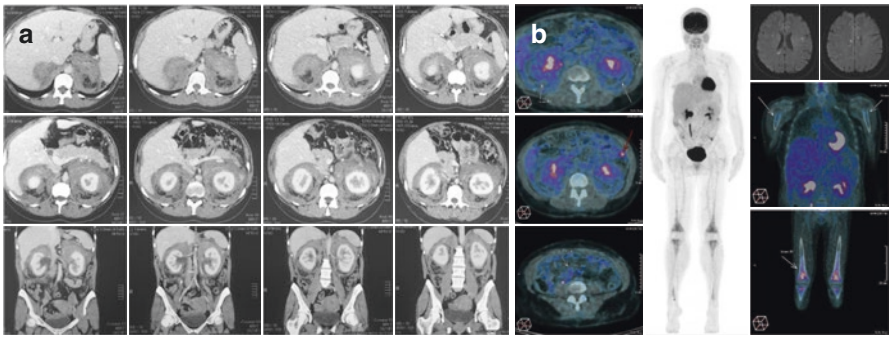

Fig. 7.30 A 50-year-old asymptomatic female patient with history of ischemic stroke at a young age. A retroperitoneal mass was found during check-up exams. (**a**) Note in CT scan the Infiltration of perirenal tissues as a "shell" and bilateral mild hydronephrosis due to ureteral involvement. (**b**) Additional images show the involvement of other organs associated with the disease. Brain MRI shows multiple intra-axial, oval, and linear lesions with distribution along the perivascular encephalic spaces; PET-CT shows an increase in metabolic expression in retroperitoneal tissues, especially in peri and pararenal spaces, and peritoneal densification in parietocolic gutters, greater omentum, and pelvic excavation; in bones, gross, irregular, heterogeneous, diffuse spinal cord sclerosis is observed in the femurs and tibiae. The immunohistochemical profile observed in the biopsy in correlation with the histological aspects was consistent with fibrosis associated with lymphoplasmocytic infiltrate and histiocytes. In the molecular analysis, a mutation was observed in codon 600 c.1799T> A (V600E) of the BRAF gene

Infiltration of perirenal tissues as a "shell" is common and can cause hydronephrosis due to ureteral involvement. This aspect should alert to the possibility of the syndrome among the differential diagnoses of retroperitoneal masses. Different sites may be involved, including the retroperitoneum (60%), with long bones being the most common sites (95%). Other sites of involvement are maxillary sinus, large vessels, heart, lungs, central nervous system, skin, pituitary gland, and orbit (Fig. 7.30) [143]. The circumferential lining of the soft tissues of the thoracic and abdominal aorta ("coated aorta") is visualized by CT in two thirds of the patients and is often confused with primary or secondary retroperitoneal fibrosis, sclerosing mesenteritis, and other retroperitoneal neoplasms, including lymphomas and germ cell tumors [144].

7.3.4 Group 4. Retroperitoneal Lymph Node Masses

The location of lymphadenopathy can be useful in identifying the etiology of different diseases that are associated with lymph node involvement [145]. When the location includes the retroperitoneal lymph node base, lymphomas and Castleman's disease must be remembered. Another cause is the secondary involvement by metastases of primary tumors of the digestive and genitourinary tracts, with emphasis on testicular tumors. Among the infectious causes, bacterial and fungal

infections are the main ones. Among inflammatory and autoimmune diseases, one possibility is the Rosai-Dorfman disease.

7.3.4.1 Neoplastic Etiology

The finding of a retroperitoneal lymph node mass in association with the presence of lymphadenopathy in superficial chains (supraclavicular, axillae, and inguinal regions) favors the diagnosis of lymphoproliferative or infectious diseases. However, the absence of peripheral lymphadenopathy does not exclude these diagnoses, because, although more rarely, in both situations the manifestation can be exclusively in the retroperitoneum. When there is primary involvement of retroperitoneal lymph nodes, the diagnosis of lymphoma must be remembered. For this reason, as previously exposed, it is important to actively inquire about the presence of "B symptoms" (fever, night sweats, weight loss). The presence of hepato-splenomegaly should also be investigated, as it contributes to the hypothesis of lymphoproliferative, infectious, and autoimmune diseases, although it does not allow the differentiation between them.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma (NHL) consists of a diverse group of malignant neoplasms derived from B cell progenitors (bone marrow-derived), T cell progenitors (thymus-derived), mature B cells (B cells or plasma cells), mature T cells (cytotoxic T cells, helper T cells, or T regulatory cells) or, more rarely, natural killer cells. The clinical presentation of NHL is variable, depending on the subtype and areas affected.

Aggressive forms of NHL account for 50%. They present in an acute or subacute form with a rapidly growing mass, B symptoms, and high levels of lactic dehydrogenase (LDH) and uric acid. Five percent are classified as very aggressive. The rest are indolent lymphomas, with slow-growing lymphadenopathy, hepatomegaly, splenomegaly, or cytopenia at blood count [146, 147]. Some aspects should be valued in the suspicion of NHL: personal or family history of lymphoma or other previous hematopoietic malignancy, history of radiation or chemotherapy, use of immunosuppressive agents, organ transplantation, and other associated diseases. Some infectious agents may also be related: human immunodeficiency virus (HIV), human T lymphotropic virus type I (HTLV-I), Epstein-Barr virus (EBV), hepatitis B virus, hepatitis C virus, Borrelia burgdorferi, and Chlamydia psittaci [148–152]. Other associated disorders include autoimmune diseases: lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, and Hashimoto's thyroiditis [153]. Some rarer conditions are also associated: immunodeficiency disorders, mixed cryoglobulinemia, multicentric Castleman's disease, inflammatory gastrointestinal diseases (gastrointestinal nodular lymphoid hyperplasia, chronic gastritis associated with Helicobacter pylori, and celiac disease), and also obesity [154].

Up to 40% of patients with NHL have B symptoms, more common in patients with aggressive and highly aggressive histology (47%), especially when there is

hepatic and extra nodal involvement. In indolent lymphomas, less than 25% of patients have B symptoms, which, when present, are usually associated with advanced stage and large lymph node masses [155]. In general, retroperitoneal lymphadenomegaly does not lead to vascular obstruction or compression to the point of impairing blood flow, an aspect that may contribute to the formulation of the diagnostic hypothesis.

More than two thirds of patients with NHL have peripheral lymphadenopathy, usually painless. Both in NHL and in infectious conditions, the presence of lymphocytosis and lymphadenopathy is observed. For this reason, the initial assessment should focus on excluding bacterial (pertussis, tuberculosis), viral (infectious mononucleosis, cytomegalovirus, and human immunodeficiency virus), and parasitic (toxoplasmosis) etiologies.

The involvement of retroperitoneal and mesenteric lymph nodes is common in most histological subtypes of NHL; however, in general it does not produce symptoms. Biopsy is necessary and should be done before starting steroid treatment. The choice of the biopsy site depends on clinical features and location of the involved lymph nodes. Increased lymph nodes (>2 cm) undergoing progressive increase should preferably be chosen. The enlarged peripheral lymph nodes are generally preferred because of their easy access. When choosing peripheral lymph nodes, the diagnostic rates vary according to the lymph node base: supraclavicular (75–90%), cervical and axillary (60–70%), and inguinal (30–40%) [156]. In general, a tissue biopsy is necessary for the complete histopathological evaluation, preferably of an intact lymph node. Fine needle aspiration biopsies that suggest the presence of lymphoma, in most cases, should be followed by a definitive tissue biopsy [157]. In patients with exclusively retroperitoneal disease, image-guided thick needle or laparoscopic biopsies can provide sufficient tissue for diagnosis [158, 159]. The PET/CT can help in selecting a biopsy site (Fig. 7.31) [160].

Hodgkin's Lymphoma

Hodgkin's lymphomas (HLs) are lymphoid neoplasms in which the malignant Hodgkin/Reed-Sternberg cells are mixed with a heterogeneous population of non-neoplastic inflammatory cells. They are divided into two main categories, classic and predominant in nodular lymphocytes, based on morphology and immunophenotype. The classic form comprises 90% of Hodgkin's lymphomas, generally progressing slowly, and is subdivided into nodular sclerosis, mixed cellularity, rich in lymphocytes, and with lymphocyte depletion forms [161].

"B" symptoms are present in 40% of HL cases. Most patients present with asymptomatic lymphadenopathy; however, constitutional symptoms, fatigue, and itching can be referred. Retroperitoneal lymphadenopathy can cause abdominal discomfort or pain. Some patients have increased abdominal volume secondary to splenomegaly, hepatomegaly and, more rarely, ascites. Extensive intra-abdominal disease can cause ureteral obstruction and compression of the renal veins, but gastrointestinal tract involvement is rare. Common affected lymph node bases are cervical and supraclavicular (60–80%), axillary (30%), and inguinal (10%). Although not detectable on physical examination, mediastinal and retroperitoneal lymph

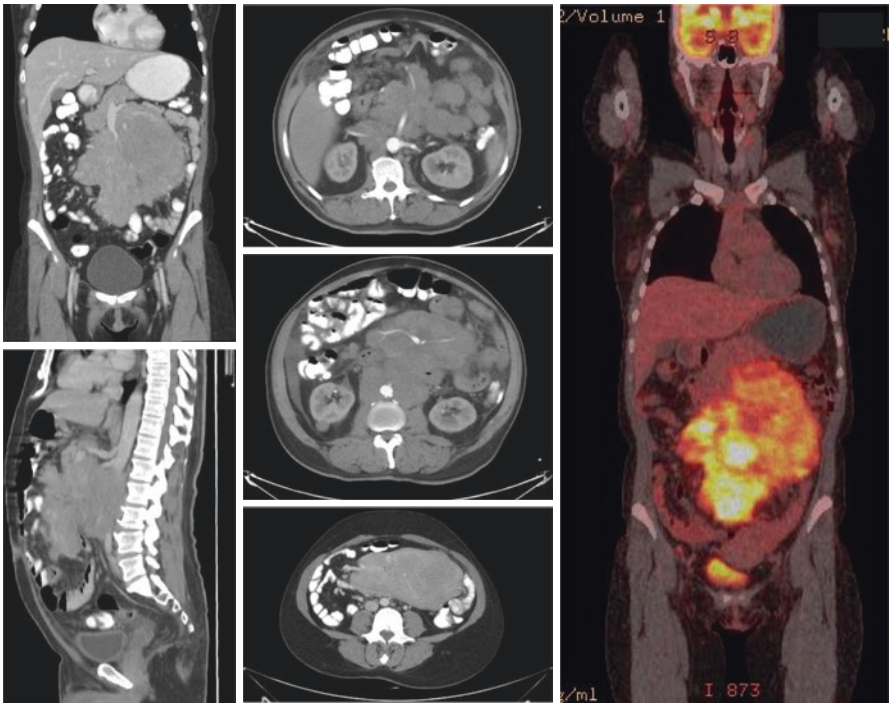

Fig. 7.31 A 46-year-old female patient, complaining of abdominal pain for 3 months. CT shows a large volume abdominal mass, characterized by multiple confluent mesenteric lesions that may represent lymph node clusters, involving the superior mesenteric vein and its branches and the duodenal arch, with wide contact with the head of the pancreas. Image-guided biopsy revealed the diagnosis of diffuse large B-cell NHL. Staging PET-CT confirms tomography findings (SUV max: 14.8), with additional finding of multiple focal areas in the axial and appendicular skeleton, compatible with lymphoproliferative disease in activity

nodes are involved in 50% and 30% of patients, respectively; however, isolated infra-diaphragmatic lymphadenopathy is uncommon (<10%). Thus, finding isolated retroperitoneal lymph node mass, the diagnosis of Hodgkin's Lymphoma is less likely. When peripheral lymphadenopathy is not identified, CT and PET-CT can identify a suspicious site to guide the biopsy [162].

Castleman's Disease

Castleman's disease (angiofollicular lymph node hyperplasia) includes a heterogeneous group of lymphoproliferative disorders. The histopathological characteristics of lymph nodes in patients with Castleman's disease are believed to be exacerbated reactive changes in response to normal antigenic stimuli or represent a low-grade neoplastic process.

Castleman's disease (CD) is classified based on the number of regions of enlarged lymph nodes and the presence or absence of infection with human herpes virus 8 (HHV-8). The cases must be classified because clinical characteristics and

treatments are different. The unicentric form (UCD – 75%) involves one or more enlarged lymph nodes in a single region of the body. The multicentric form (MCD – 25%) involves several lymph nodes chains. Castleman's disease can also be associated with other cancers, including non-Hodgkin's lymphoma, Hodgkin's lymphoma, and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes) [163].

Although UCD can occur at any age, it is usually a disease of young adults (30–35 years old) with a slightly increased incidence in women. It can affect any lymph node chain. The sites referenced are abdomen/retroperitoneum (30–40%; isolated retroperitoneum 14%), neck (20–23%), chest/mediastinum (16–24%; 70% in some series), inguinal (9%), pulmonary hilum (7%), and armpit (7%). The presentation in the form of retroperitoneal lymph node mass may occur in young adults, being diagnosed incidentally or in the investigation of general symptoms such as fever, growth failure, and weight loss. The duration of symptoms and lymph adenomegaly can vary from weeks to months [163, 164].

Although it is a rare condition, the diagnosis of hyaline vascular UCD is part of the differential diagnosis of solid and heterogeneous mass in the retroperitoneum. Lesions are typically confined to the lymph node tissue. Laboratory studies are generally normal, but there may be an increase in C-reactive protein and erythrocyte sedimentation rate, as well anemia, thrombocytopenia, hypoalbuminemia, renal dysfunction, and polyclonal hypergammaglobulinemia. Complete surgical resection of the lymph nodes involved is considered the standard approach for the UCD, almost always curative. In unresectable disease, embolization strategies and the use of rituximab can convert to a resectable condition.

In MCD, the etiology is not well known. It seems to be related to autoimmune, autoinflammatory, neoplastic, and infectious mechanisms. IL-6 is a multifunctional cytokine involved in a wide range of activities, including plasmacytosis, hypergammaglobulinemia, thrombocytosis, production of proteins in the acute phase by the liver, and activation of macrophages and T cells. Apparently, IL-6 is related to symptomatology, histopathology, and pathogenesis in part of the patients [165]. MCD patients have lymphadenopathy in several lymph node chains, including the retroperitoneum [166]. The disease development course is variable. Most patients have fever and nonspecific symptoms suggestive of inflammatory disease, including night sweats, weight loss, weakness, and fatigue. Other signs and symptoms include hepatosplenomegaly, cytopenia, organ dysfunction, and skin manifestations (rashes, pemphigus, hemangioma), in addition to loss of appetite, nausea, vomiting, severe abdominal pain, fatigue, and peripheral neuropathy. Neuropathy can range from mild sensory neuropathy to severe sensory and motor neuropathy, associated with POEMS syndrome [167–169].

A diagnosis of idiopathic CMD/HHV-8 (iMCD) should be suspected in patients with peripheral lymphadenopathy, constitutional symptoms, and elevated C-reactive protein. PET-CT demonstrate several regions of enlarged lymph nodes, usually with a relatively low SUV. The established diagnostic criteria require characteristic pathological lymph node biopsy, enlargement of multiple lymph node chains, and

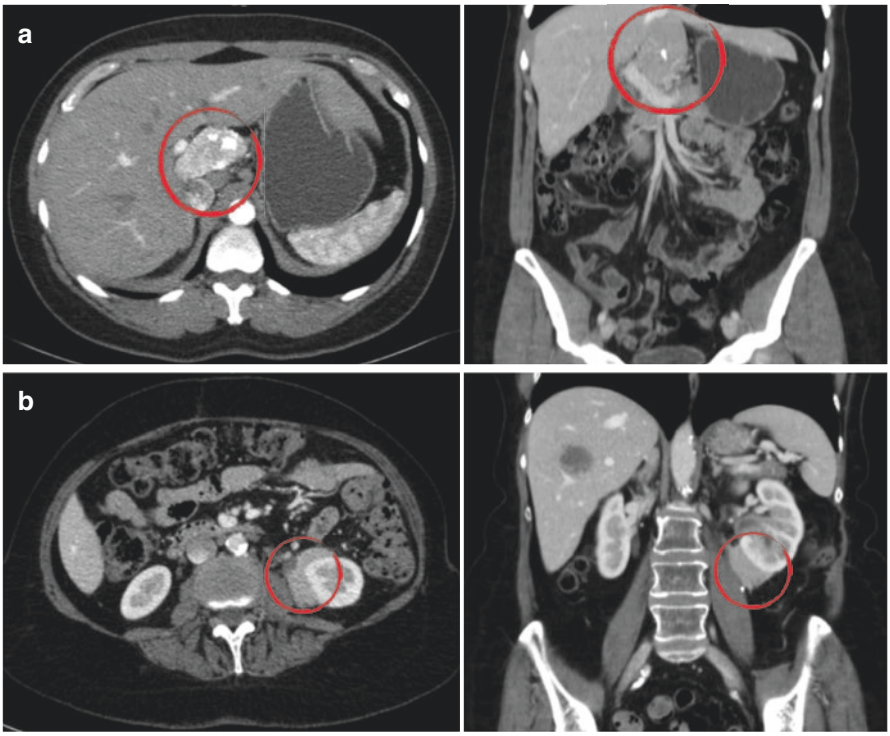

Fig. 7.32 (**a**) Example of the hyaline-vascular type: vascularized nodular lesion superior to the head of the pancreas and close to the hepatic hilum, with enhancement in the arterial phase, with calcifications inside. In the present case, the lesion has contact with the portal vein and is associated with some adjacent arterial collaterals, probably related to its irrigation. (**b**) Example of the plasmocytic type: An infiltrative and vascularized lesion next to the medial aspect of the left kidney, involving the collecting structures, with homogeneous contrast enhancement observed on CT. The liver lesion is a hemangioma. (*Courtesy of Hilton Leão Filho, radiologist*)

multiple clinical and laboratory abnormalities, besides exclusion of infectious disorders, malignancies, and autoimmune diseases [168]. If available, treatment with anti-IL-6 monoclonal antibody has been recommended, with or without association with corticosteroids. Surgery has no role in the treatment of CDM [163].

From a microscopic point of view, Castleman's disease can be classified according to the type of lymphoid tissue. The microscopic subtypes are divided into (1) hyaline-vascular type (most common), tends to be localized and is rarely multicentric; (2) plasmocytic type, more likely to be multicentric and more rarely located; and (3) mixed type, the combination of both (rare) (Fig. 7.32).

Lymph Node Metastases

When the image is suggestive of retroperitoneal lymph node involvement, the hypotheses must include the possibility of secondary involvement due to metastasis of different primary tumors. Male patients, especially at a young age, should be

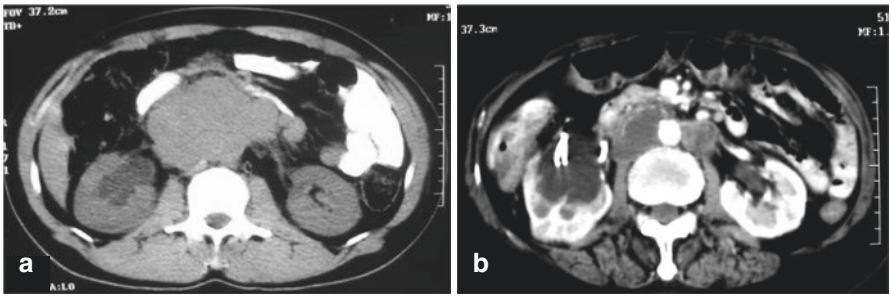

Fig. 7.33 (**a**) A 32-year-old male patient, complaining of increased abdominal volume and weight loss. Absence of peripheral lymphadenomegaly. Absence of clinical detectable changes in testicular palpation. Ultrasound of testicles and tumor markers was requested as part of the initial investigation, with the finding of a 10 mm nodule in the left testis and a slight increase in HCG-ß. Radical orchiectomy was performed, and the pathological analysis showed a pure seminoma. The patient was treated with chemotherapy with complete response, without intervention on the retroperitoneal mass. (**b**) A 70-year-old female patient complaining of vaginal bleeding and pelvic pain. Vaginal touch showed a tumor on the uterine cervix. Note on CT the presence of secondary retroperitoneal lymphadenomegaly from a primary squamous cell carcinoma of the uterine cervix. Double J catheter was placed on the right kidney due to uretero-hydronephrosis

questioned about testicular changes, history of cryptorchidism, fertility, and sperm test results. Even with a normal testicular examination, testicular ultrasound should be performed. Testicular germ neoplasms occur between 15 and 35 years and after 60 years. It is not uncommon to find a large retroperitoneal mass without evidence of a primary testicular tumor (Fig. 7.33a). For this reason, in addition to scrotum ultrasound, it is imperative to request the tumor markers AFP and HCG-ß, in addition to LDH measurement. Once the presence of a testicular lesion is verified, radical orchiectomy will allow the definitive diagnosis, without intervention on the retroperitoneal mass. When there is no testicular alteration in the presence of increased markers, a thick needle image-guided biopsy of the retroperitoneal mass may be necessary.

In women with retroperitoneal lymphadenomegaly, genital tract neoplasms should be investigated, starting with the interrogation of gynecological complaints (bleeding, discharge, and dyspareunia), use of medications (contraceptives and hormone replacement), and family history of neoplasms. The gynecological examination must be complete and include a Pap smear. If some abnormality is detected, the investigation follows with complementary exams (Fig. 7.33b).

In general, data from clinical history, physical examination, and imaging aspects direct us to the suspicion of retroperitoneal lymph node metastases secondary to tumors of the digestive and genitourinary tract, which should be investigated. Metastases from solid tumors from other sites may also occur, although are uncommon to present as a retroperitoneal mass simulating a primary tumor of the retroperitoneal space.

7.3.4.2 Nonneoplastic Etiology (Autoimmune, Inflammatory, Infectious)

Autoimmune, inflammatory, and infectious diseases that lead to retroperitoneal lymphadenomegaly are included in the list of differential diagnoses and should be considered in the investigation. Active questioning about past infections, reports of infectious conditions in the social environment, place of last trips, use of drugs and medications, in addition to the possibility of immunosuppression, are aspects to be questioned.

Rosai-Dorfman Disease

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) is a rare non-Langerhans cell histiocytosis [170]. It often presents with marked cervical adenopathy, but other lymph node sites, including the retroperitoneum, may be involved. Patients usually have fever when there is massive lymphadenopathy. Laboratory evaluations show leukocytosis, polyclonal hypergammaglobulinemia, hypochromic or normocytic anemia, and elevated ESR.

Treatment is variable, depending on the involvement of the lymph node chain. Slow spontaneous resolution (months to years) may occur [171]. The most common sites of extra-nodal involvement are skin, upper respiratory tract, and bone; however, other sites may also be affected: genitourinary tract, lower respiratory tract, oral cavity, and soft tissues. The prognosis is correlated with the number of lymph node bases involved and the number of extra-nodal sites affected [170].

Although retroperitoneal involvement is uncommon, the diagnosis of Rosai-Dorfman disease is among the entities capable of generating retroperitoneal masses and should be remembered [172, 173].

IgG4-Related Disease

The disease related to immunoglobulin G4 (IgG4-RD) is an immune-mediated fibroinflammatory condition that affects multiple organs, with different forms of presentation: autoimmune pancreatitis, sclerosing cholangitis, enlarged salivary glands or sclerosing sialadenitis, orbital disease, and retroperitoneal fibrosis. It is often accompanied by chronic peri-aortitis and ureteral involvement, with consequent hydronephrosis and kidney damage [174, 175].

IgG4-RD is characterized by dense lymphoplasmacytic infiltration, with a predominance of IgG4-positive plasma cells, fibrosis, obliterative phlebitis, and an increased number of eosinophils [176]. In histology, fibrosis associated with IgG4-RD has a “storiform” pattern, characterized by the arrangement of fibroblasts and inflammatory cells in a “wagon wheel” shape [177]. Serum IgG4 levels are elevated in two thirds of patients, but all cases have typical histopathological changes in the tissue [178].

Lymphadenopathy is usually seen with other clinical or laboratory manifestations, although it can be an isolated manifestation [179]. Lymph nodes rarely undergo storiform differentiation, which makes diagnosis from biopsies difficult. In addition, a large number of plasma IgG4-positive cells can be found in several diseases, the specificity of this finding being low. Different histological patterns with

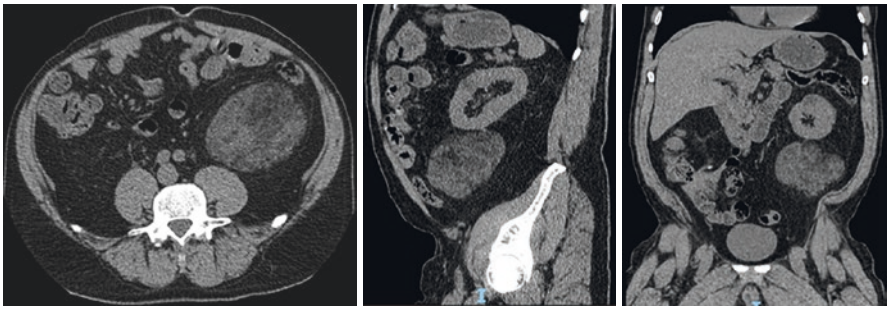

Fig. 7.34 A 62-year-old diabetic male with renal function deficit. In a routine consultation, an abdominal mass was palpated on the left flank. The CT shows a homogeneous infrarenal solid mass. Thick needle image-guided biopsy was inconclusive. The patient was taken to surgery with a finding of a retroperitoneal mass in contact with Gerotta's fascia, adhered to retroperitoneal muscle planes, with no signs of macroscopic invasion of the kidney. The freezing test was inconclusive for malignancy. Due to the deficit in renal function and the absence of conclusive malignancy, complete marginal resection with renal preservation was performed. The definitive diagnosis was compatible to an IgG4-related inflammatory pseudotumor, with positive immunohistochemistry and increased serum dosage

an abundance of IgG4-positive cells are possible, most with eosinophil infiltration, which also contributes to confusing the diagnoses with other entities as Castleman's multicentric disease, follicular hyperplasia, interfollicular expansion, progressive transformation of the germinal center, and nodal inflammatory aspect, similar to a pseudotumor [177]. In this sense, retroperitoneal fibrosis is one of the most common subsets of IgG4-positive and some series suggest that IgG4-RD is responsible for most cases of retroperitoneal fibrosis previously considered "idiopathic" [180, 181]. When presenting as a retroperitoneal tumor, the difficulty of defining the diagnosis sometimes leads to surgical intervention and the definitive diagnostic conclusion is postoperative, which justifies the existence of patients operated on without having received previous medical treatment (Fig. 7.34).

The presence of IgG4-RD appears to be associated with an increased risk of malignancy; however, these data need to be confirmed. On the other hand, a history of malignancy appears to be associated with the subsequent development of IgG4-RD [182, 183].

Initial therapy with glucocorticoids or with an immunosuppressive agent and/or biological agent (rituximab) is necessary in most patients to achieve disease remission [184]. Many patients follow an indolent course and respond well to treatment, but a significant proportion can have high morbidity or fatal complications, such as peri-aortitis, severe retroperitoneal fibrosis, or pachymeningitis. Vascular surgical interventions, including stenting to relieve mechanical obstruction as well as other vascular procedures, may be indicated in selected patients.

Tuberculosis

Extrapulmonary tuberculosis can simulate different diseases, including retroperitoneal lymph node mass of different etiologies. The manifestations are usually

subacute or chronic, with complaints of fever, night sweats, and organic dysfunction associated with anorexia and weight loss. Hepatomegaly and splenomegaly may also be present.

Up to 20% of tuberculosis cases are extrapulmonary. The most common extrapulmonary sites are lymph nodes, bones, joints, liver, central nervous system, and adrenal glands [185]. The prevalence of tuberculosis increases in areas of less favored socioeconomic conditions and malnutrition. Any lymph node base can be involved; however, the hilar and paratracheal lymph nodes are the most commonly affected. In the retroperitoneal space, it may present as lymphadenopathy, involvement of retroperitoneal organs or, more rarely, as retroperitoneal fibrosis. As in other entities, in the suspicion of retroperitoneal tuberculosis, the search for peripheral lymph nodes must precede the indication for biopsy of the retroperitoneal mass.

Isolated peripheral tuberculous lymphadenopathy is usually caused by reactivation of the disease from hematogenous dissemination that occurred during primary infection a few years earlier. Abdominal tuberculous lymphadenopathy can occur due to ingestion of sputum or milk infected with Mycobacterium tuberculosis. Although most cases of tuberculous lymphadenitis occur in the setting of reactivation of latent infection, miliary spread with prominent involvement of the lymph nodes in the setting of primary infection can also occur [186]. In countries where tuberculosis is endemic, extrapulmonary tuberculosis occurs in up to 60% of HIV-infected patients, often accompanied by pulmonary involvement [187]. Most extrapulmonary cases, including tuberculous lymphadenitis, occur among HIV patients with CD4 counts <300 cells/μL (usually below 100 cells/μL) [188].

Clinical manifestations depend on the location of the lymphadenopathy and the patient's immune status [189]. The most common presentation in young adults is chronic nonisolated lymphadenopathy. Fever can be present in 20–50% in patients not infected with HIV and 60–80% in infected patients [190]. When there is peripheral involvement, the physical examination reveals firm lymph nodes or lymph node clusters attached to adjacent structures, with hardened overlying skin. Other possibilities of findings include fluctuation, drainage, or nodular erythema. Peritoneal tuberculous lymphadenopathy usually involves lymph nodes in the periportal, peripancreatic, and mesenteric chains [191].

In the peritoneum and retroperitoneum, the involvement is predominantly from mesenteric, anterior pararenal, superior para-aortic, and omentum lymph nodes. The anatomical distribution and specific patterns of lymphadenopathy seen on CT can be useful in differentiating between tuberculosis and lymphomas [192].

7.4 Image Diagnostics

The correct interpretation of images of retroperitoneal tumors, in addition to the experience of the radiologist, depends on complete clinical information, which is fundamental for the formulation of the diagnostic hypothesis and to guide the choice

of the appropriate imaging method. CT of the abdomen and pelvis, in line with the story and physical examination, guides the first steps of radiological investigation. Chest and mediastinal CT, whose presence or absence of additional findings helps in making the diagnostic hypothesis, should also be performed in the beginning of the investigation. Depending on the clinical suspicion, other imaging tests and specific laboratory tests may be necessary.

According to the division proposed in our chapter, our suggestion is to start trying to classify the type of retroperitoneal finding in one of the four groups presented: (1) intraperitoneal lesions that simulate retroperitoneal tumors; (2) primary tumors of retroperitoneal organs; (3) primary tumors of the retroperitoneal space; and (4) retroperitoneal lymph node masses.

7.4.1 First Step: Differentiation Between Retroperitoneal and Intraperitoneal Lesions

Distortion of the anatomy by large masses can make it difficult to distinguish between true retroperitoneal tumors and intraperitoneal lesions [1]. The displacement of retroperitoneal organs suggests primarily retroperitoneal tumor. On the other hand, the wide mobility on physical examination, as well as the change of location in the image with the change of position, is the aspect that favors the diagnosis of intraperitoneal lesion (Fig. 7.35). A simple test that can help in the investigation is to ask the radiologist to acquire complementary images in different positions.

When the lesion is found to be intraperitoneal, the diagnoses will generally be considered among the following possibilities: GIST, EGIST, visceral sarcomas, and adnexal masses. It is important to remember that large primary tumors of intraperitoneal organs and visceral metastases from different primary tumors can generate intraperitoneal masses; however, in general, the primary site is identified. On CT, GISTs and EGISTs appear as heterogeneous lobulated tumors, with the possibility of infiltration of mesenteric fat and low probability of lymph node involvement. Tumors with low metastatic potential tend to be more homogeneous and have an endoluminal growth pattern [21, 193]. Visceral sarcomas usually present as masses with varying degrees of necrosis and heterogeneous contrast enhancement. The presence of secondary pulmonary lesions favors the diagnosis of visceral sarcoma [31]. In women, the hypothesis of large-volume adnexal masses simulating retroperitoneal tumors should be considered. The presence of multilocular cystic lesions, solid areas, bilateral lesions, ascites, and peritoneal metastases should alert to the possibility of large gynecological tumors. The adnexal masses can be either primary of the ovary or metastatic, such as Krukenberg tumors. Thus, previous history of tumors of the digestive system must be considered [37].

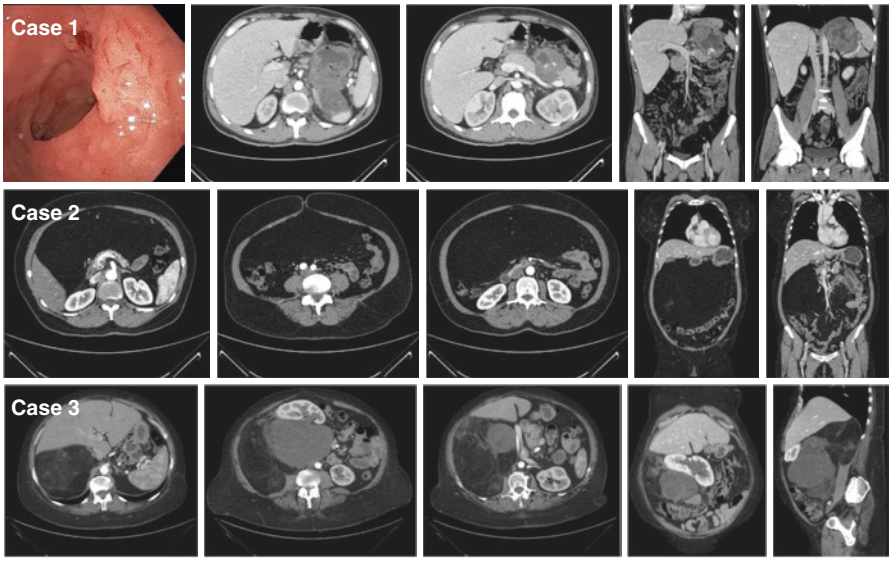

Fig. 7.35 Case 1 – Gastric GIST: in large tumors primary of intraperitoneal organs, there may be some difficulty in the differential diagnosis to retroperitoneal primary tumors. In the case presented, upper gastrointestinal endoscopy with biopsy revealed the diagnosis of GIST primary of the stomach. Note the aspect of a heterogeneous lesion with lobulated contours. Case 2 – Well-differentiated liposarcoma primary of the large omentum. This tumor was mobile on physical examination. Note that the retroperitoneal organs were not involved by the lesion. Case 3 – Primary dedifferentiated liposarcoma of the retroperitoneal space. Note the well-differentiated component of the lesion, with a lipomatous aspect, and the undifferentiated component, represented by a more solid area. Observe the displacement and involvement of the left kidney by the lesion, favoring the diagnosis of primary lesion of the retroperitoneal space

7.4.2 Second Step: Differentiation Between Retroperitoneal Tumors and Lymph Node Masses

Excluding the diagnosis of intraperitoneal lesions, the next step may be to differentiate between retroperitoneal tumors and lymph node masses. The presence of peripheral lymphadenopathy favors the hypothesis that the retroperitoneal lesion corresponds to a lymph node mass. In the absence of peripheral lymphadenomegaly, the location of the lesion in the retroperitoneum must be considered. Thus, when the location is not central, the tendency will be to direct the reasoning to the hypothesis of primary tumors of retroperitoneal organs or primary tumors of the retroperitoneal space. The greatest difficulty in distinguishing occurs in situations of large masses involving large vessels, when both primary retroperitoneal lesions and lymph node masses can occur (Fig. 7.36). In this condition, clinical aspects, specific imaging characteristics, and other complementary exams must be done. If the hypothesis is

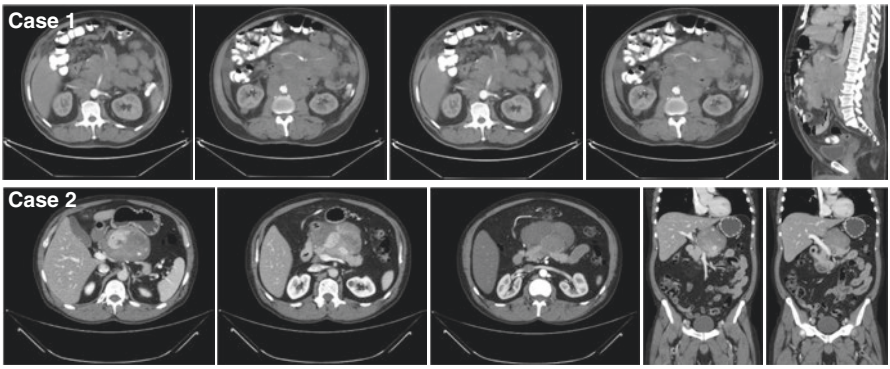

Fig. 7.36 Case 1 – Diffuse non-Hodgkin's lymphoma of large B cells. The mass represents a lymph node conglomerate. When all CT sections are observed in detail, the presence of lymphadenomegaly is also noted in the latero-cava, intercavo-aortic, and later aortic chains. Case 2 – Dedifferentiated liposarcoma. Note on the CT the aspect of an expansive solid lesion, with a hypervascularized component and areas of liquefaction/necrosis, with an infiltrative aspect, occupying the epiploic retro cavity, with densification of adjacent fatty planes. Despite the dimensions and aspect of a high-grade lesion, there is no associated lymphadenomegaly

compatible with a lymph node mass, the next step will be the differentiation between the diseases that develop with retroperitoneal lymph node masses, which is our fifth step, discussed later. Excluding the diagnosis of lymph node mass, our suggestion is to progress in the distinction between primary tumors of retroperitoneal organs and primary tumors of the retroperitoneal space.

7.4.3 Third Step: Differentiation Between Primary Tumors of Retroperitoneal Organs and Primary Tumors of the Retroperitoneal Space

Excluding the hypotheses of intraperitoneal tumor and lymph node mass, the next step is to try to differentiate whether the origin occurs from a retroperitoneal organ (duodenum, pancreas, adrenal gland, kidney, and colon segments) or corresponds to a primary tumor of the retroperitoneal space. The determination of whether a lesion arises from a retroperitoneal organ or from tissues in the retroperitoneal space can be suggested by the relationship between the lesion and adjacent structures. Some signs help with image evaluation: "beak sign," "embedded organ sign," "crescent shape sign," "phantom organ sign," and the "prominent feeding artery sign." As explained by Shaaban et al., the "beak sign" relates to the shape of a solid organ at the edge of its interface with an adjacent mass. A sharp beak shape implies that the mass arises from the adjacent organ. If the mass is incorporated and completely surrounded by the parenchyma of an organ, it is assumed that it is primary of that organ

(the "embedded organ sign"), while organs with rounded edges suggest displacement by the mass. If the mass displaces the organ, but does not originate from it, the organ can take the form of a "crescent moon" ("crescent shape"). The "phantom organ sign" occurs when a large mass arises from a small organ, so that the original organ is obliterated and not seen. Hypervascular retroperitoneal masses can have large nourishing arteries that help in the identification of the organ of origin (the "prominent feeding artery sign") (Fig. 7.37) [194].

The assessment of the presence of fat in a retroperitoneal lesion is one of the useful "tools" for the differential diagnosis. Fat is easily recognized in imaging studies, with the consideration that while CT is limited in demonstrating small amounts of fat, MRI is more sensitive in detecting microscopic fat. Among primary lesions of retroperitoneal organs, adenomas are the most common adrenal tumors that contain microscopic fat, while myelolipomas are the most common adrenal masses that contain macroscopic fat. Other adrenal masses, such as pheochromocytoma and adrenocortical carcinoma, rarely contain fat. Among renal masses, angiomyolipomas are the ones that most commonly contain fat. Changes in renal cortex, prominent vessels, and well-defined contours favor the diagnosis of angiomyolipoma [195].

Among the diagnoses of pancreatic lesions, the solitary fibrous tumor of the pancreas is predominantly solid, without fat content, may contain calcifications, and is enhanced in the arterial phase. Pancreatoblastoma is predominantly cystic, may contain calcifications, and has contrast washout. Acinar cell carcinoma is generally solid, with calcifications, circumscribed and hypovascular. Hemangiomas are cystic, may contain calcifications, develop areas of hemorrhage, and are enhanced in the arterial phase. Lymphangiomas are generally polycystic, with septa that are highlighted. Lymphomas are predominantly solid and cause diffuse involvement, without ductal dilation, and generally present associated lymph node enlargement. Pancreatic dermoid cysts can contain solid areas, calcifications, fatty content, and have areas of hemorrhage. Other tumors such as leiomyosarcomas, lipomas, schwannomas, and pancreatic hamartomas can have variable image characteristics [44].

If a lesion of duodenal origin is suspected, upper gastrointestinal endoscopy and endoscopic ultrasound may help. In the face of larger masses, the diagnosis of primary GIST of the duodenum must be remembered. If primary lesions of the retroperitoneal segments of the ascending and descending colon are suspected, further colonoscopy investigation should be performed.

7.4.4 Fourth Step: Differentiation Between Primary Tumors of the Retroperitoneal Space

Excluding origin from retroperitoneal organs, we will move on to the most difficult moment of image interpretation, differentiating between primary solid tumors of the retroperitoneal space. Based on the frequency of appearance, an idea is to start from

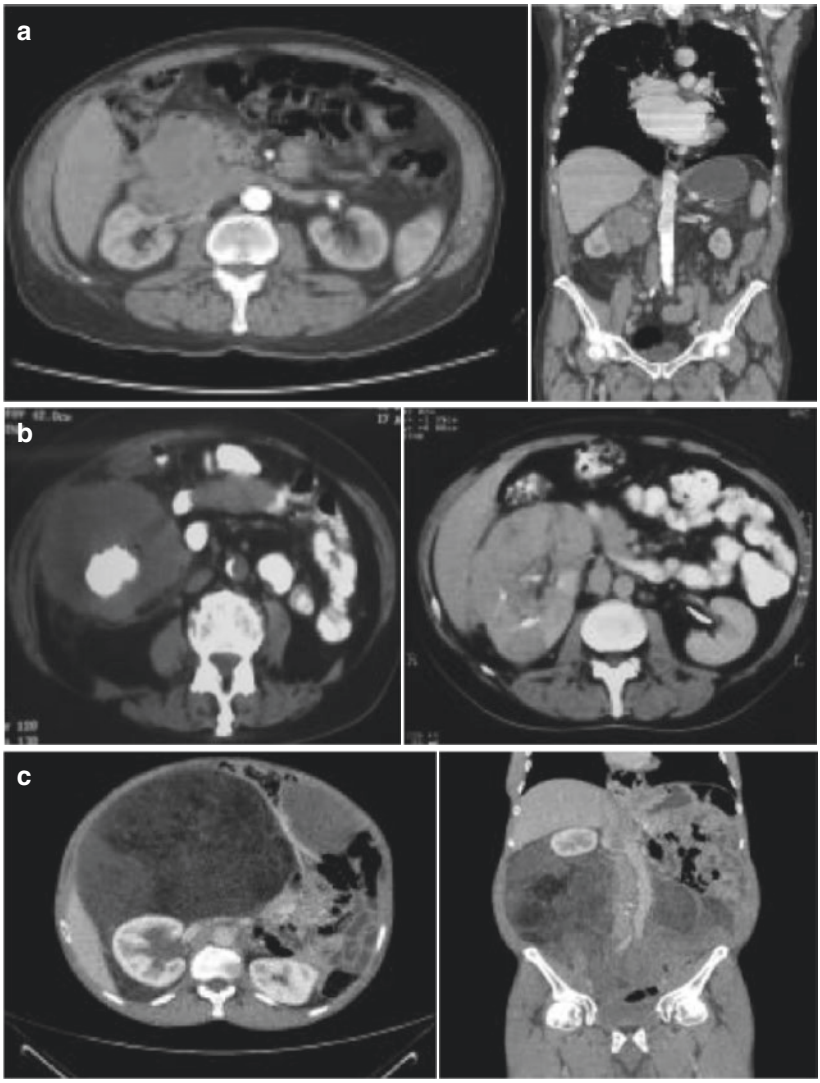

Fig. 7.37 (**a**) The "beak sign" reports to the shape of a solid organ at the edge of its interface with an adjacent mass. Note the sign of the acute beak in the lower portion of the lesion, close to the right kidney, suggesting that the origin of the lesion is in the adjacent organ, I this case, a primary GIST of the duodenum. (**b**) Two examples of "embedded organ sign," a neuroendocrine tumor of the right colon and a renal clear cells carcinoma, where the mass is incorporated and surrounded by the parenchyma of an organ, what suggests that it is primary of the organ. (**c**, **d**) If the mass displaces the organ, but does not originate from it, the organ can take the form of a "crescent moon" ("crescent shape"). Note this aspect in the relation of the mass with the lower border of the liver in (**c**) (retroperitoneal liposarcoma) and in the relationship of the mass with the right kidney and the aorta in (**d**) (metastasis of ovarian teratoma). (**e**) The "phantom organ sign" occurs when a large mass arises from a small organ, so that the original organ is obliterated and not seen, as in this example of a borderline tumor of the right ovary (the ovary is not seen). (**f**) Note the large nourishing arteries that help in the identification of the origin (the "prominent feeding artery sign"). In the figure, the prominent nourishing arteries are branches of right iliac arteries, suggesting a retroperitoneal origin (retroperitoneal solitary fibrous tumor)

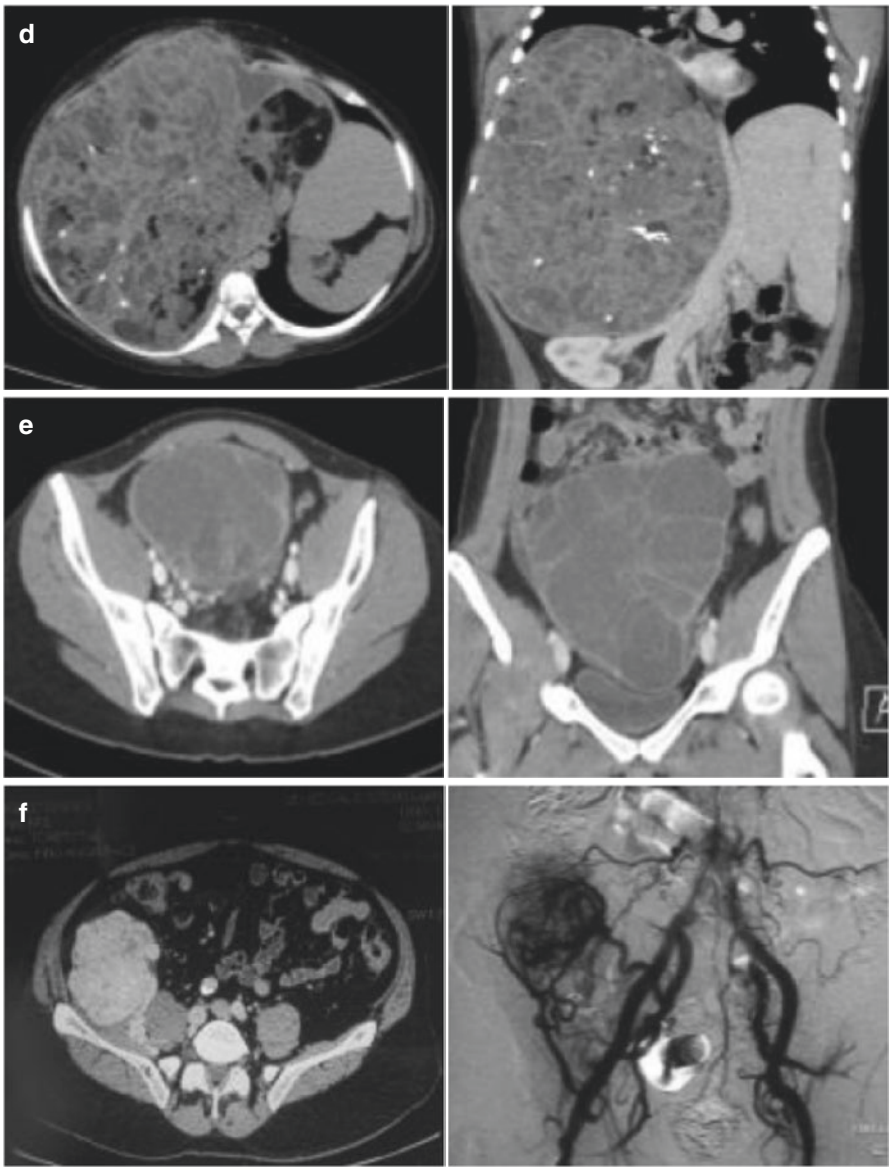

Fig. 7.37 (continued)

the hypothesis of retroperitoneal sarcoma and analyze specific characteristics that may allow confirmation or direct the reasoning towards other hypotheses.

Sarcomas usually appear on CT as masses that laterally displace hollow viscera and parenchymal organs. Most retroperitoneal sarcomas are liposarcomas (about 70%), so assessing the presence or absence of fat in the lesion is an additional step. If the fat component is not clearly the result of a retroperitoneal organ, the diagnosis of liposarcoma must be considered, remembering that the presence of septations,

dense areas, and calcifications may suggest dedifferentiation or the sclerosing and inflammatory variants of liposarcomas [196].

Well-differentiated liposarcomas appear as well-defined lesions, predominantly containing fat. The appearance may be indistinguishable from the lipoma and, for this reason, any purely fatty retroperitoneal lesion should be considered a well-differentiated liposarcoma until the definitive pathological diagnosis. Areas of dedifferentiation occur within a well-differentiated liposarcoma and dedifferentiation is suggested by nonlipomatous focal nodular regions. The myxoid variant generally presents less attenuation than the adjacent muscle, with low signal intensity in T1-weighted images and high signal intensity in T2-weighted images. Most myxoid liposarcomas have enough fat to suggest a diagnosis of liposarcoma. It is common to see thick septa and irregular or nodular soft tissue components. Round cell and pleomorphic liposarcomas, on the other hand, exhibit attenuation of the soft tissue tumor and signal intensity with a minimum amount of fat [194].

The presence of fat from the well-differentiated component of liposarcomas is not always recognized and is sometimes interpreted as a normal part of retroperitoneal fat. Failure to recognize the presence of abnormal fat (the well-differentiated component of liposarcoma) can result in incomplete resections, leading the less experienced surgeon to remove the undifferentiated portion of the lesion and not remove the well-differentiated component. Several foci of dedifferentiation contained in a single lesion can also be misinterpreted as a multifocal disease and lead to a contraindication to surgery due to suspected sarcomatosis [196]. The following examples illustrate these points (Figs. 7.38, 7.39, and 7.40).

Although rare in the retroperitoneum, lipomas can also simulate liposarcomas. Lipoma is a benign mesenchymal tumor composed of mature adipose tissue. On CT, lipomas appear as well-defined homogeneous masses with attenuation of fat. Areas of soft tissue attenuation can be seen in the tumor and represent fatty necrosis, septa, or adjacent normal structures. Other benign conditions with a fat content should be remembered: retroperitoneal lipomatosis, lipodystrophy, retroperitoneal panniculitis (mesenteric panniculitis), retroperitoneal fat necrosis, encapsulated fat necrosis, and hibernoma [194].

Leiomyosarcomas correspond to the second most common histological type of sarcoma in the retroperitoneum. The presence of a large, heterogeneous, necrotic retroperitoneal mass, contiguous to a vessel, should resemble the diagnosis of primary leiomyosarcoma of retroperitoneal vessels, which most commonly originate in the inferior vena cava, below the level of the hepatic veins, but can also be primary from other veins, such as the renal and gonadal veins, among others. There is usually an exophytic component, which can make it difficult to differentiate from other retroperitoneal lesions that cause extrinsic vascular compression (Fig. 7.41). Specifically, for inferior vena cava leiomyosarcomas, the extent of involvement and the relationship with renal and retrohepatic veins should be described in image evaluation. Lumbar vessels and collateral veins in the retroperitoneum can be a significant source of intraoperative blood loss and must also be identified in preoperative CT. The compressive venous effects increase the risk of venous and pulmonary thromboembolism and preventive care should be taken [197].

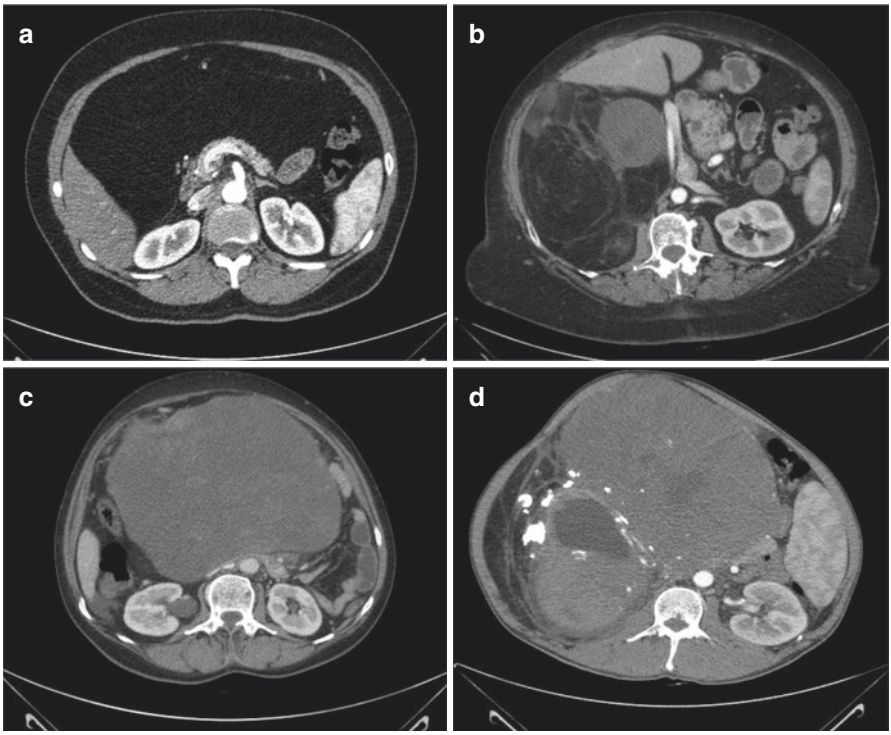

Fig. 7.38 (**a**) Well-differentiated liposarcoma in its entirety, without areas of dedifferentiation. Radiologically, it can be difficult to differentiate by CT a well-differentiated liposarcoma from a lipoma. (**b**) Liposarcoma with lipomatous aspect (well-differentiated component) and dense solid area (differentiated component). The operation should be a "*en bloc*" resection, taking care not to consider the well-differentiated area as part of the retroperitoneal fatty tissue. (**c**) Dedifferentiated liposarcoma without lipogenic sarcomatous tissue, sometimes difficult to distinguish from undifferentiated pleomorphic sarcomas. (**d**) Dedifferentiated liposarcoma with an epithelioid/pleomorphic pattern and areas of calcification

Excluding the diagnoses of liposarcoma and leiomyosarcoma, in some situations specific characteristics of the image may suggest other diagnoses. Some subtypes of sarcoma usually have cystic elements and can be confused with an abscess or even a hematoma.

The finding of a solid, circumscribed, vascularized tumor with prominent vessels must resemble the hypothesis of a solitary fibrous tumor. They usually have a homogeneous appearance, although cystic areas, calcifications, myxoid degeneration, or hemorrhage may be present, particularly in large tumors. They can be lobulated, with a tendency to displace rather than invading adjacent organs and tissues. The edges are rarely infiltrative and are commonly well-defined. In MRI, usually solitary fibrous tumors exhibit low signal intensity in T1 and variable signal in T2, with a significant increase in signal intensity after intravenous gadolinium administration. Hypocellular tumors generally show low signal in T2-weighted images,

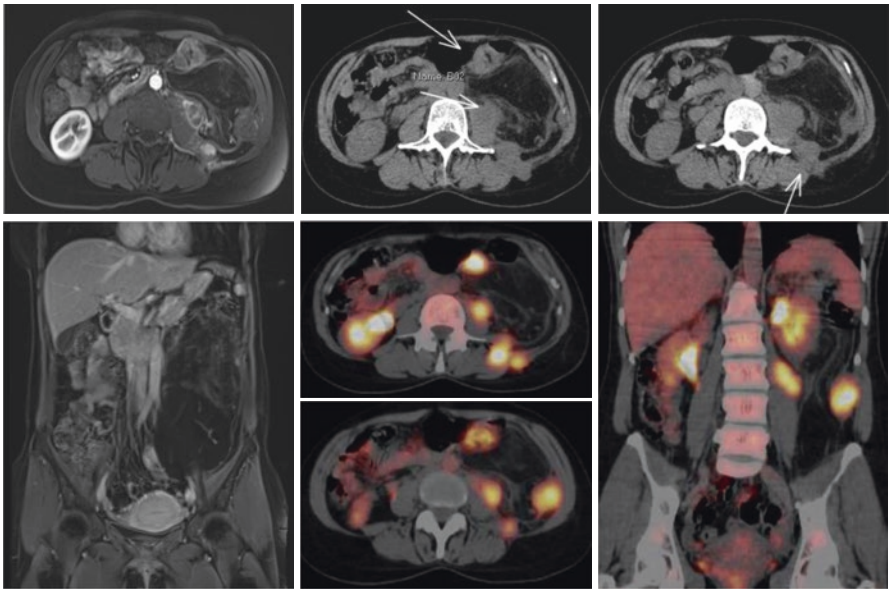

Fig. 7.39 Large retroperitoneal liposarcoma with well-differentiated areas and foci of dedifferentiation, evident in PET-CT. This type of finding can be misinterpreted as a multifocal disease and lead to a contraindication to surgery due to suspected sarcomatosis; however, it is a single lesion

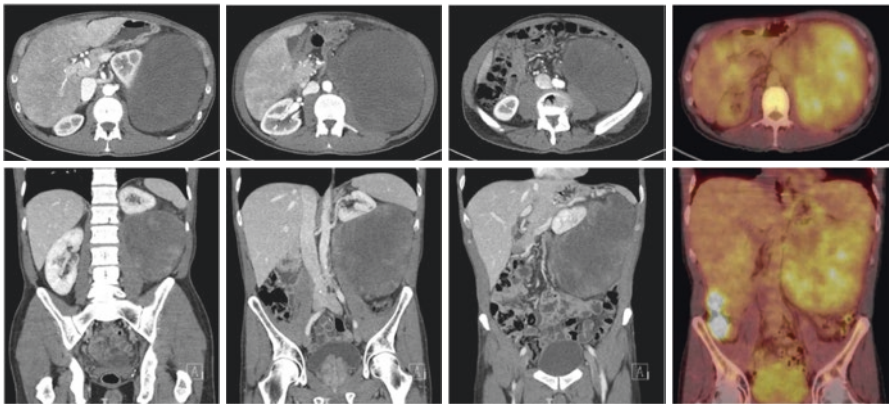

Fig. 7.40 CT scan shows a certain heterogeneity inside the lesion. In PET-CT, we observed intratumor variations in glycolytic metabolism, with variations in SUV values. This finding can guide the most appropriate place to perform image-guided biopsy. The definitive pathologic diagnosis was an inflammatory liposarcoma with de-differentiated areas

whereas hypercellular tumors, highly vascular edematous tumors, or those with necrosis or myxoid degenerative changes demonstrate high signal intensity [198]. In the image, the main differential diagnoses of solitary fibrous tumor are synovial sarcoma, de-differentiated liposarcoma, leiomyosarcoma, GIST and, when present

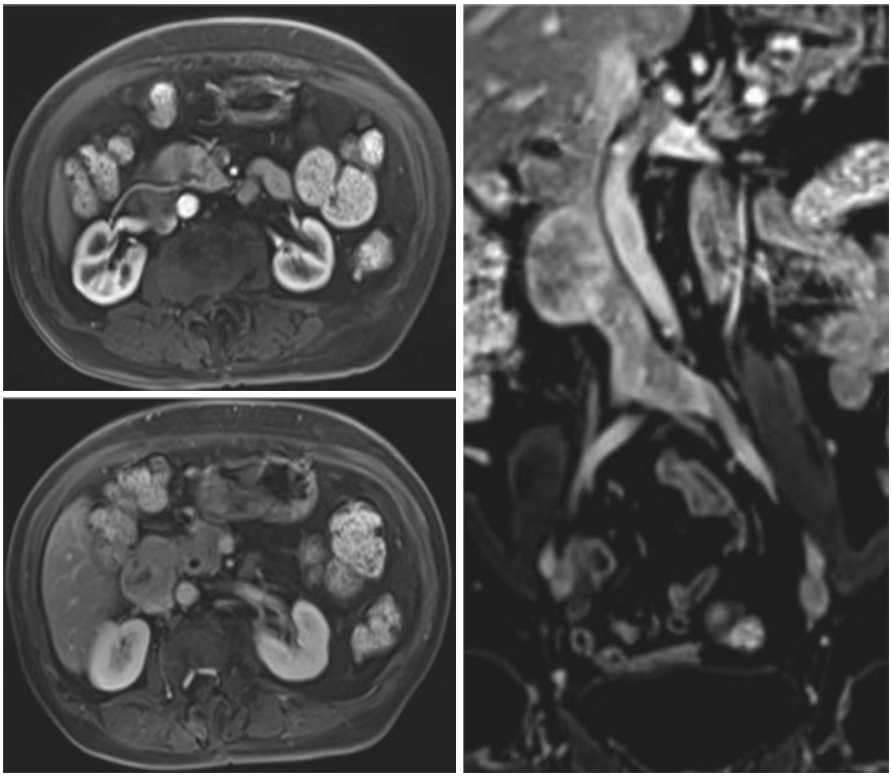

Fig. 7.41 The MRI shows two solid nodular lesions on the right flank, located anterior to the inferior vena cava, causing slight compression on it, in close relationship with the duodenum. The lesions exhibit a heterogeneous signal, enhanced by contrast and restriction to diffusion, the largest measuring 5.2 × 4.4 × 3.8 cm and the other measuring 3.2 × 2.6 cm. Note that it is difficult to determine whether the lesion is primary of the vena cava or causes compression on it; however, if the biopsy reveals the diagnosis of leiomyosarcoma, the chance of primary vascular lesion is high, as in the example

in the mesentery, desmoid fibromatosis. In the pelvis, other tumors with a fibrous component constitute differential diagnoses: mesothelioma, Brenner's ovarian tumor, fibroma or fibrotecoma, and uterine leiomyoma [199–201].

Among the other primary tumors of the retroperitoneal space, benign tumors of the peripheral nerve sheath are generally rounded and well defined, but malignant lesions may show invasion of local structures. The appearance of a tumor in dumbbells with expansion of the intervertebral foramen is suggestive of neurofibroma. Schwannomas and paragangliomas can be confused with sarcomas, particularly if located in the midline, adjacent to the aorta or vena cava. In CT, schwannomas and neurofibromas can be similar, appearing as hypodense lesions in relation to the muscle and enhance with contrast. In MRI with T1-weighted image, schwannomas appear with intermediate signal intensity, similar to muscle, and very clear signal in T2-weighted image, although cystic lesions have low signal intensity. Schwannomas

grow uniformly and often have a border with low signal strength, consistent with the capsule. Fusiform appearance and "target" image can be seen in both schwannomas and neurofibromas. Sometimes it is possible to identify the nerve from which the lesion originates, usually positioned eccentrically. A heterogeneous appearance with cystic degeneration can also occur, characterizing the so-called "ancient schwannoma" [47].

Ganglioneuromas, because they originate from sympathetic ganglia, appear more commonly in the retroperitoneum in a central or paravertebral position or next to the adrenal glands, in addition to the intraspinal canal. They can be regular or irregular in shape, round, oval, lobular, or in dumbbells. In pre-contrast CT, they appear as a hypodense mass. With the increase in cellularity and the decrease in the mucous matrix, the density of the lesions may be slightly increased, but less than the density of the local musculature. The components of myxoid matrix delay the absorption of contrast, which is observed in later stages of image acquisition. In MRI, ganglioneuromas appear as hypodense lesions in T1-weighted image, hyperintense in heterogeneous form in T2-weighted image, and hyperintense in SPAIR (Spectral Attenuated Inversion Recovery). A "twisted" pattern (a low signal part is found in T2WI when the mass is shown in a high signal) can be a characteristic finding that corresponds to the microscopic interweaving patterns of Schwann cells and collagen fibers. Calcifications can be observed, as well as the "pseudopod sign," formed by growth between adjacent tissues. Blood vessels are usually pushed and moved, with no signs of stenosis or invasion, although they can often be involved, which can make dissection laborious and risky [202].

Paragangliomas are part of the list of differential diagnoses. When paraganglioma is suspected, CT and MRI are the exams of choice for the first approach, with MRI being more sensitive and specific, especially in the detection of extra-adrenal disease. They are highly vascularized tumors, with high intracellular water content and frequent intra-tumor cystic areas, with high signal in the T2-weighted image and strong enhancement after the administration of intravenous contrast. In large tumors with hemorrhagic and/or necrotic areas (more common in malignant lesions), the signal intensity may be low in T2-weighted images [203]. With the diagnostic hypothesis of paraganglioma, a functional image is generally recommended. Whole-body studies allow for better assessment of extra-adrenal disease localization, as well as identification of multiple tumors and/or metastatic sites [204]. Scintigraphy with ^{123}I-metaiodobenzylguanidine (MIBG) has high rates of sensitivity (83–100%) and specificity (95–100%), although in malignant paragangliomas sensitivity is lower since dopamine-secreting tumors generally do not capture MIBG. MIBG has chemical similarities to norepinephrine and is concentrated in the tissues of chromaffin cells through the human norepinephrine transporter factor (hNET), responsible for the capture of catecholamines [60]. So, in patients with negative MIBG, somatostatin analogs can be used. The somatostatin analogs marked with gallium-68 are also part of the

research arsenal. PET 68Ga-DOTATOC (DOTA0-D-Phe1-Tyr3-octreotide) has high sensitivity, especially in the detection of small lesions or neoplasms with low density of somatostatin receptors. In addition, it allows a better identification of metastases located in the lungs and bones. Particularly in the detection of pheochromocytomas and malignant paragangliomas, PET 68Ga-DOTATOC is superior to PET-18F-FDG. Dopamine (DA) and dihydroxyphenylalanine (DOPA) are also transported by hNET to chromaffin cells and, therefore, can be used as radiolabels (PET 6- [18F] -fluoroDOPA). However, like MIBG, they have low sensitivity (70–88%) in detecting paragangliomas with mutations in the SDHB gene, where PET 18F-FDG is superior (sensitivity 97–100%), making it useful in identifying metastatic glucose-hungry lesions, especially if they are negative for MIBG [205].

Germ cell tumors in the retroperitoneal space are usually large in presentation. The involvement, displacement, and compression of the abdominal vessels are common. In the images, primary and metastatic malignant teratomas appear as enlarged soft tissue masses with foci of fat and calcifications. Clinical characteristics and tumor markers are fundamental for the diagnostic conclusion in the suspicion of germ cell tumors and must be considered in line with the aspects of the image.

Some specific image characteristics may suggest the diagnosis of retroperitoneal fibrosis. CT-evaluated retroperitoneal fibrosis exhibits attenuation numbers similar to those of the muscle. The mass is usually confluent, involving (but not dislocating) the aorta, often surrounding and compressing the inferior vena cava and causing medial deviation of the ureters. Lymphadenopathy located adjacent to the mass can be observed. The radiologist must assess the involvement of the renal vessels. In the evaluation of retroperitoneal fibrosis, MRI has a higher resolution compared to CT and can provide a better definition of the lesion limits in relation to adjacent tissues when using fat saturation techniques. On MRI, idiopathic retroperitoneal fibrosis appears as a hypointense lesion in T1-weighted images. In T2-weighted images, the signal intensity is proportional to the disease activity. Diffusion-weighted image characteristics and signal intensity values in T2-weighted MRI may contribute to clarify the differential diagnosis of retroperitoneal fibrosis and fibrosis-like malignancies. Differentiating between desmoid fibromatosis and malignant neoplasms of the retroperitoneum can be difficult. In MRI, the findings are variable and related to cellularity and fibrous content. They can be hypointense or isointense to muscle in T1-weighted images and predominantly hyperintense in T2-weighted images, with hypointense bands that represent dense collagen bundles. T2 hyperintensity may decrease over time, as the tumor's cellularity decreases and collagen deposition increases. With gadolinium administration, desmoids generally show moderate to marked enhancement. Hypointense bands may become more apparent because the collagen bundles are not enhanced by contrast [206, 207] (Fig. 7.42).

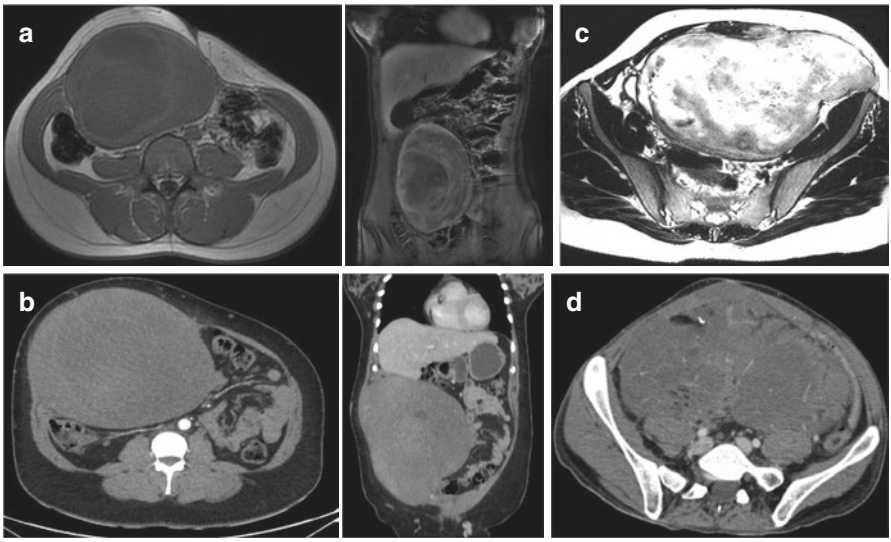

Fig. 7.42 Examples of desmoid fibromatosis. The lesions can reach a large volume and generate diagnostic doubt. The MRI brings additional information to the CT, as it allows to evaluate the cellularity and the fibrosis content, which helps in monitoring the response to drug treatments. (**a**, **b**) DF originated in the abdominal wall and protruded into the peritoneal cavity. (**c**) Example of pelvic DF with hypersignal on MRI, suggesting active disease and hypercellularity. (**d**) Extensive DF of mesentery in a patient with familial adenomatous polyposis

7.4.5 Fifth Step: Diagnostic Differentiation Between Retroperitoneal Lymph Node Masses

Considering the aspect of the image suggestive of retroperitoneal lymph node mass, once again the data of clinical history and physical examination are crucial for the formulation of the diagnostic hypothesis. All lymph node chains should be evaluated, including the findings of chest, mediastinal, and abdominal CT. In lymphomas, CT usually shows a homogeneous retroperitoneal mass, with imprecise limits, which surrounds but does not deform the great vessels. Sometimes there are signs of infiltration of the mesentery. Among FDG-avid NHL staging exams, the PET-CT contributes to the investigation [160].

In the unicentric form of Castleman's disease, the most common radiological presentation is a mediastinal or hypervascular pulmonary hilar mass [208]. When seen in the retroperitoneum, it appears as a circumscribed mass with soft tissue attenuation. Smaller masses have homogeneous enhancement after contrast, while larger masses have heterogeneous enhancement. Calcification is uncommon, but when present, it can have varying patterns. MRI generally demonstrates a solid mass with slightly increased signal at T1 in relation to the muscle and hyperintense at T2. There may be intralesional "voids" in the T1 and T2 images, reflecting the

vascularization of the lesion, in addition to central linear hypointense septa. In PET-CT, lesions generally have SUV values (average 3.91) lower than those seen in lymphomas. In Castleman's disease, additional extra-abdominal findings aid in suspected diagnosis. Reticular or ground-glass opacities, mediastinal enlargement, pleural effusion and, more rarely, pulmonary nodules or rounded areas of consolidation may be observed in the chest. Most patients have multiple enlarged mediastinal and hilar lymph nodes. Parenchymal findings can also be observed, including subpleural nodules, interlobular septal thickening, and peri-bronchial vascular thickening. On PET-CT, retroperitoneal fibrosis related to the idiopathic multicentric form of Castleman's disease has relatively low SUV values (2.5–8). Higher values should raise the suspicion of lymphoma [163].

Metastases from solid tumors to retroperitoneal lymph nodes appear as solid or solid-cystic masses, single or multiple, in different locations. A previous history of malignancy or positive serum markers may suggest a diagnosis of metastatic adenocarcinoma, melanoma, or germ cell tumor. Once again, in young male patients with undefined retroperitoneal masses, testicular ultrasound should be considered. With the exception of epithelioid sarcomas, rhabdomyosarcomas, and clear cell sarcomas, the majority of sarcomas generally do not metastasize to lymph nodes. Therefore, the presence of lymph nodes with a neoplastic aspect increases the possibility of metastatic disease or lymphoma.

In some countries, including Brazil, extrapulmonary tuberculosis can present as retroperitoneal lymphadenopathy and must be remembered among the differential diagnoses. Large retroperitoneal mass, however, is a rare condition. The encapsulation of the abdominal aorta is also described. Tuberculosis can also spread from "Pott's disease" and form an abscess in the psoas muscle, inflammatory retroperitoneal mass, or retroperitoneal fibrosis.

7.5 Indications and Types of Biopsy

A frequent question in the approach of the retroperitoneal masses is to decide on the need for biopsy and to define the best way to do it. When the clinical-radiological aspects suggest with a high degree of suspicion that the retroperitoneal tumor corresponds to a diagnosis whose treatment is surgical in the first instance, preoperative biopsy may be dispensed. However, in case of diagnostic doubt or when therapeutic planning implies performing preoperative treatments, biopsy will be necessary and, in most cases, should preferably be image guided with a thick needle, avoiding surgical biopsies. Thick needle image-guided biopsies can be performed on an outpatient basis and have lower morbidity and cost. Another relevant advantage is the possibility of choosing intralesional areas containing viable tissue or areas that may suggest dedifferentiation [209]. The benefits of diagnostic completion using a minimally invasive procedure outweigh any considerations against performing the biopsy. The risk of complications is low, as well as the potential for neoplastic dissemination [210]. In retroperitoneal biopsies, special care must be taken to assess

the quality and representativeness of the material, avoiding inconclusive results. If necessary, a new material acquisition can be made before the patient leaves the CT scan. For this reason, the interaction between the interventional radiologist and the specialized pathologist is essential.

In the presence of peripheral lymphadenopathy, if the investigation moves towards the need for biopsy, the peripheral lymph nodes should preferably be accessed, without intervention on the retroperitoneum. The surgical approach in the case of retroperitoneum lymphomas is restricted to situations where simpler and less invasive ways of reaching a histological diagnosis were not conclusive or not possible, indicating a surgical biopsy, which can be performed by laparoscopy or laparotomy. Once again, it is advisable to have the pathologist in the operating room to assess the quality of the material and the amount of material available for further diagnostic complementation studies, such as conducting immunohistochemical reactions or even molecular tests.

When GIST is suspected, special care must be taken. Biopsies should preferably be performed by endoluminal endoscopic accesses, through puncture guided by echo-endoscopy, avoiding rupture of the capsule and peritoneal dissemination. Violation of the integrity of the tumor capsule as a result of percutaneous or open biopsy is associated with a higher risk of peritoneal recurrence. In echo-endoscopy biopsies, the sample is limited and so it is important to inform the pathologist about the diagnostic suspicion, which will allow a directed histopathological analysis, with the inclusion of c-KIT and DOG-1 in the immunohistochemistry panel.

7.6 Considerations About Surgical Indications and Preoperative Care

Operations related to primary tumors of the retroperitoneal space are often highly complex surgical situations. It is not possible to list the diversity of situations in which the complexity is secondary to problems imposed by the neoplasia; however, aspects associated with vascular problems certainly constitute a point of greater relevance. Examples are the involvement of large vessels (aorta, vena cava, and iliac vessels), primary tumors of the vena cava, intra-caval tumor thrombus, high risk of visceral devascularization due to involvement of vascular trunks, and the need for multivisceral resection, among others.

The complexity imposed by the neoplasm can be worsened by clinical problems such as old age, precarious nutritional status, sarcopenia, and organ dysfunction (cardiac, respiratory, renal, liver, neurological, endocrine, etc.). In this sense, the choice of the therapeutic path and decisions must be taken in a multidisciplinary way, in the presence of surgeon oncologists, clinical oncologists, radiotherapists, radiologists, pathologists, and other specialties, with emphasis on vascular surgery.

In addition to the clinical decision, equally important is the transparent clarification to the patient and his family about the therapeutic proposal and its risks, when clinical issues, risks, the possibility of sequelae, and the impact on quality of life

must be addressed. In the scenario of high complexity, other aspects are of extreme importance, such as the structure of perioperative and transoperative care, including the anesthesia, intensive care, and blood bank teams. The support of nursing, physiotherapy, physiatry, speech therapy, nutrition, rehabilitation, and psychology is also a fundamental part of the treatment process in all its phases so that the objectives are reached safely.

In addition to a careful clinical evaluation, the expectation and understanding of the proposal must be worked on in a particular way. In operations where a high risk of major complications and even death is expected, the indication is always difficult. Deep knowledge about the biological behavior of the disease is essential to avoid unsuccessful decisions. Concerns about pre- and postoperative care, hospital structure, and team composition are fundamental aspects for safety and good result of the procedures, respecting ethical issues in order to protect the patient, the doctor, and the hospital. It is mandatory filling out of terms of responsibility for surgery, anesthesia, transfusion, and others. In situations of high complexity, the wrong judgment can seal the patient's only chance to be free of the disease, either by an inappropriate indication or by the wrong contraindication. The cases presented in Figs. 7.43 and 7.44 illustrate the aspects discussed.

7.7 Associated Vascular Problems

We will discuss some situations whose knowledge is essential to allow patients in extreme situations to be properly evaluated and have the possibility to benefit from complete oncological resections, not being considered as having unresectable tumors due to associated vascular problems.

7.7.1 Circumferential Involvement of Large Vessels

The need for complete or partial resection of large vessels is not uncommon in retroperitoneum tumors, situations in which one of the concerns is the risk of massive bleeding. When there is circumferential involvement of the aorta and vena cava, surgery usually proceeds safely until vascular repair. After total vascular clamping, the "*en bloc*" resection phase of the tumor containing the large vessels is also safe; however, depending on the extent of the lesion, there may be considerable bleeding from lumbar and retroperitoneal vessels and visual access for hemostasis is impaired by the tumor volume. After resection, upon reestablishing arterial flow through aortic reconstruction, there is a significant increase in venous return pressure, with the risk of massive retroperitoneal bleeding until the reestablishment of venous flow with reconstruction of the vena cava. Depending on the time of ischemia, arterial flow is usually reestablished with priority. To minimize the risk of bleeding, both in the resection phase and after the restoration of arterial flow, an alternative is to

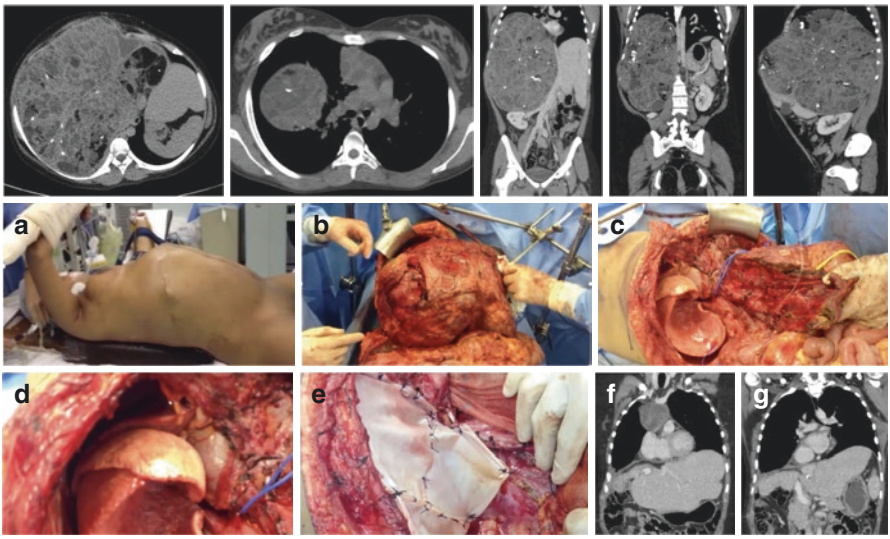

Fig. 7.43 A 12-year-old female patient underwent right adnexectomy with pathological result of immature teratoma. Two years later, she had a large volume peritoneal recurrence. A laparotomy was performed, and the lesion was considered unresectable. She was treated with systemic chemotherapy and evolved with disease stability followed by progression and loss of follow-up for a period of 8 years, when she returned to the institution due to clinical worsening. CT showed a massive lesion, cranially dislocating the diaphragm with pulmonary compression and dislocating the liver and other abdominal organs and structures, in addition to invading the abdominal wall. There was also a second mediastinal lesion. After a multidisciplinary discussion and agreement by the patient (at that time with 23 years old) and family members, a new resection attempt was proposed. (**a**) Positioning the patient in the operating room. (**b**) Intraoperative view: wide mobilization of the lesion achieved by total resection of the right diaphragm. (**c**) Aspect of the surgical bed after removal of the surgical specimen (tumor and diaphragm). Note the lower lobe of the right lung, the inferior vena cava repaired close to the heart and the aspect of liver deformity secondary to years of tumor compression. (**d**) Detail of the repair of the inferior vena cava close to the right atrium and the wide freno-laparotomy. (**e**) Replacement of the removed diaphragm with patches of bovine pericardium. (**f**) The patient had an excellent evolution with discharge on the 13th postoperative day. CT shows absence of abdominal disease and the presence of mediastinal lesion not removed in the abdominal intervention. (**g**) The mediastinal lesion was resected in a new operation. CT shows the final appearance after the end of the treatment. The patient has a follow-up period of 5 years, with no evidence of disease. She became pregnant and gave birth to a healthy child through cesarean delivery. The case illustrates the need for a surgical, anesthetic, and specialized intensive care team, in addition to adequate hospital structure and resources, so that there is a chance of therapeutic success in situations of high complexity, common points in the surgical treatment of different large retroperitoneal and intraperitoneal tumors

create an arterial and venous vascular bypass as an initial measure, preceding the resection phase. One way is to perform the "bypass" with the vascular prostheses themselves, leaving them redundant, keeping the arterial and venous flow diverted from the area to be resected with the tumor. After resection, prostheses are shortened easily, with wide exposure, minimizing the risk of excessive bleeding [211] (Figs. 7.45 and 7.46). In smaller tumors, where the resection phase is faster, the tactic of using a temporary bypass is not mandatory; however, it is essential that the

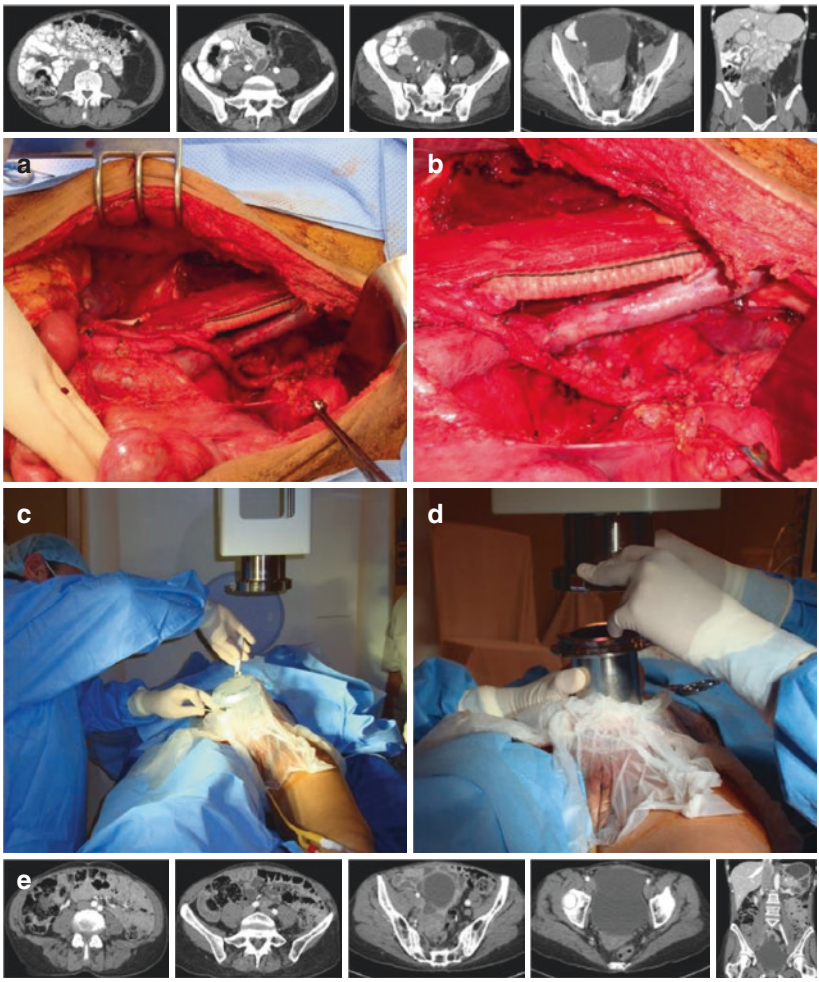

Fig. 7.44 A 47-year-old female patient with large local recurrence of a retroperitoneal liposarcoma. The CT images at the upper part of the figure shows a predominantly adipose expansive mass, with multiple septa and some solid nodular images, occupying the retroperitoneal space of the left flank and iliac fossa, insinuating itself posteriorly to the psoas and pelvis. The mass contacts the left side wall of the urinary bladder and compresses the left ureter at the intersection with the iliac vessels, without hydronephrosis. It dislocates the left colon and the small intestine loops and has contact with the external iliac, internal iliac, and obturator vessels on this side. The patient underwent neoadjuvant systemic chemotherapy and was then taken to surgery with an intraoperative radiotherapy schedule. (**a**, **b**) The surgery consisted of "*en bloc*" resection of the tumor with the left colon (descending, sigmoid, and high rectum) and left external iliac artery, which was replaced by a 6Fr Dacron prosthesis. (**c**, **d**) Intraoperative radiation with linear accelerator. She had a good postoperative recovery. The pathological result showed a low-grade "lipoma-like" liposarcoma with areas of necrosis at its largest extent and areas of dedifferentiation (high-grade) next to the iliac vessels. She was referred to receive a complementary dose of external radiotherapy. (**e**) Control tests 6 years after the end of treatment. The patient has been followed up for 10 years, with no evidence of disease. The case illustrates the importance of multidisciplinary interaction in therapeutic planning, in order to minimize the risk of recurrence in situations of marginal resections, common in retroperitoneal tumors. (*Fábio Ferreira, surgical oncology; Kenji Nishinari, vascular surgery; João Luís Fernandes, radiotherapy*)

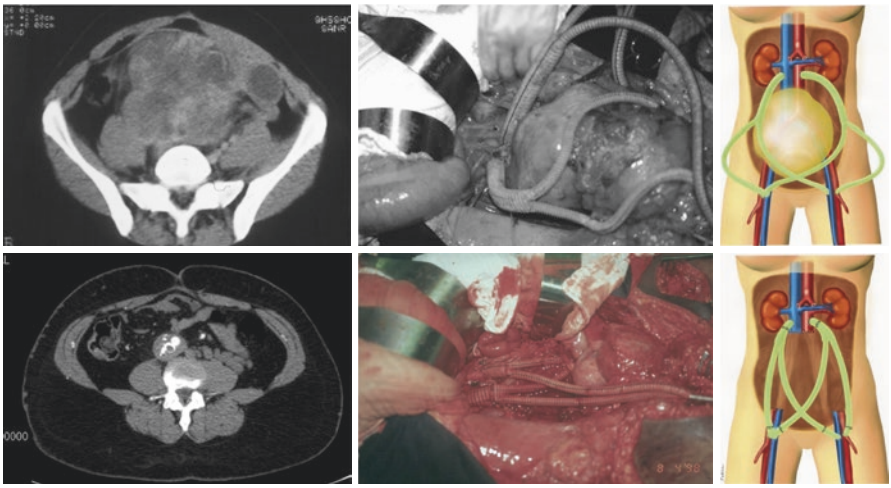

Fig. 7.45 A 29-year-old female patient, complaining of pain and abdominal swelling associated with lower limb edema. CT shows an extensive solid mass with circumferential involvement of the aorta and vena cava. A thick needle biopsy revealed the diagnosis of Schwannoma. Considering that she was a very young patient without clinical problems, surgery planning was carried out between the oncological and vascular surgery teams. To minimize the risk of bleeding, the alternative was to create an arterial and venous vascular bypass preceding the resection phase. The "bypass" was performed with the vascular prostheses themselves, maintaining the arterial and venous flow. After the "*en bloc*" resection, the prostheses were shortened with wide exposure and without excessive bleeding. She had a postoperative recovery without complications. Later, she had venous thrombosis, but without clinical repercussion. This patient was operated on in 1998 (first CT image) and the control CT image shown in the lower part of the figure was done in 2012. Currently, she has a follow-up period of 22 years and still doing well. (*Drawings authorized for reprinting by the authors: Nishinari et al.* [211])

proximal and distal vascular stumps are fully prepared, and the vascular surgery team is present to discuss reconstruction alternatives before the resection is completed. Lesions that involve the confluence of common iliac veins and aortic artery bifurcation, even if they are not large in volume, may require even more elaborate planning and reconstruction care (Figs. 7.47 and 7.48).

7.7.2 Primary Leiomyosarcoma of the Vena Cava

Retroperitoneal leiomyosarcomas are often primary tumors of the inferior vena cava [212]. When the need for segmental resection of the inferior vena cava is expected, depending on the location of the tumor, there is a chance of nephrectomy as a consequence of the involvement of the renal pedicle vessels. Static renal scintigraphy (99mTc-DMSA) to assess renal tubular function is useful for deciding whether nephrectomy is an alternative. If there is an absolute need for renal preservation, in cases of single kidney or dominant kidney at risk for resection, renal revascularization should be planned.

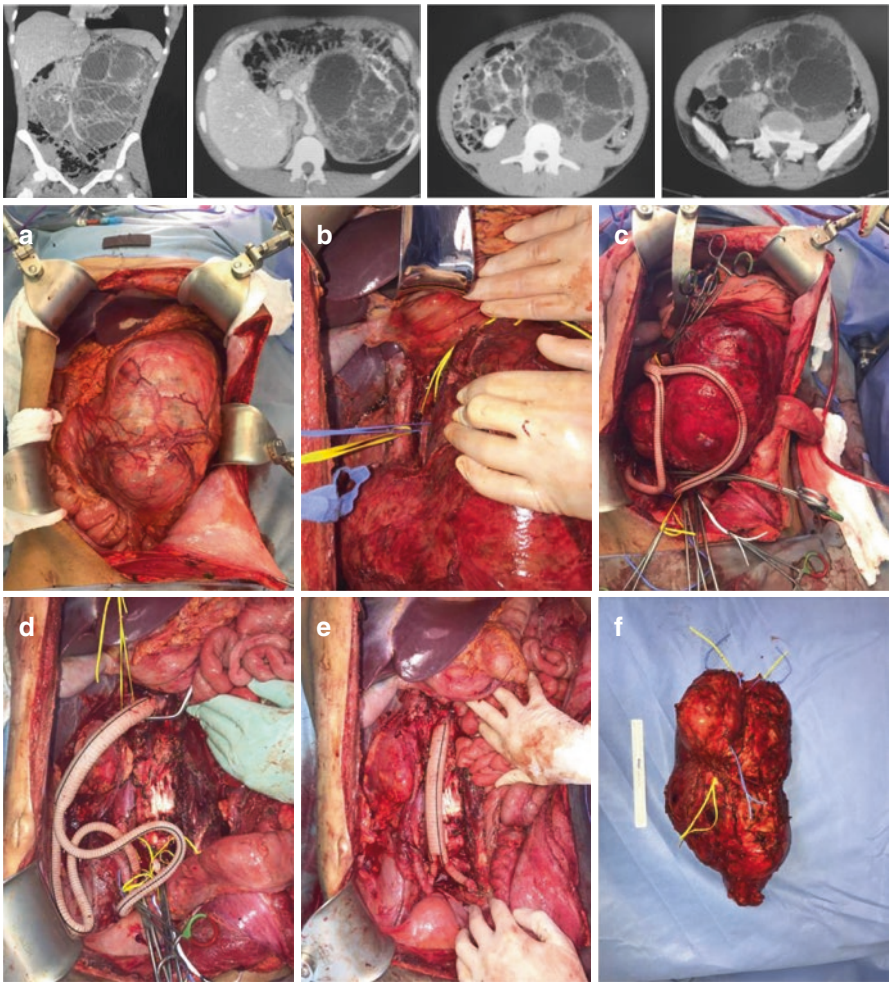

Fig. 7.46 A 29-year-old male patient diagnosed with a right testicle tumor was submitted to a radical orchiectomy. The pathological exam showed a nonseminomatous tumor with a teratoma component. During follow-up, he presented an extensive retroperitoneal recurrence that was treated with systemic chemotherapy with normalization of tumor markers, but with persistence of a large volume retroperitoneal residual mass. The patient was prepared for surgical intervention by the oncology and vascular surgery teams. Note the large volume of disease and extensive vascular involvement in CT sections. (**a**) Wide median laparotomy with left lateral extension. (**b**) Mobilization of the lesion with exposure and repair of the inferior vena cava and aorta. (**c**) Temporary "by-pass" made with the vascular prosthesis itself. (**d**) Operative bed after tumor resection showing the "redundancy" of the prosthesis. (**e**) Operative bed after shortening of the prosthesis. (**f**) Surgical specimen showing the "*en bloc*" resection of the tumor with the segments of the aorta and iliac arteries, and vena cava and iliac veins. No venous reconstruction was performed, and the vena cava was interrupted below the right renal vein. The patient had a good postoperative recovery, without major complications. The pathology showed a teratoma with a rhabdomyosarcoma component. The patient is at 3 years of follow-up, with no evidence of disease. (*Courtesy of André Luís de Freitas Perina, surgical oncology and Fávio Duarte, vascular surgery*)

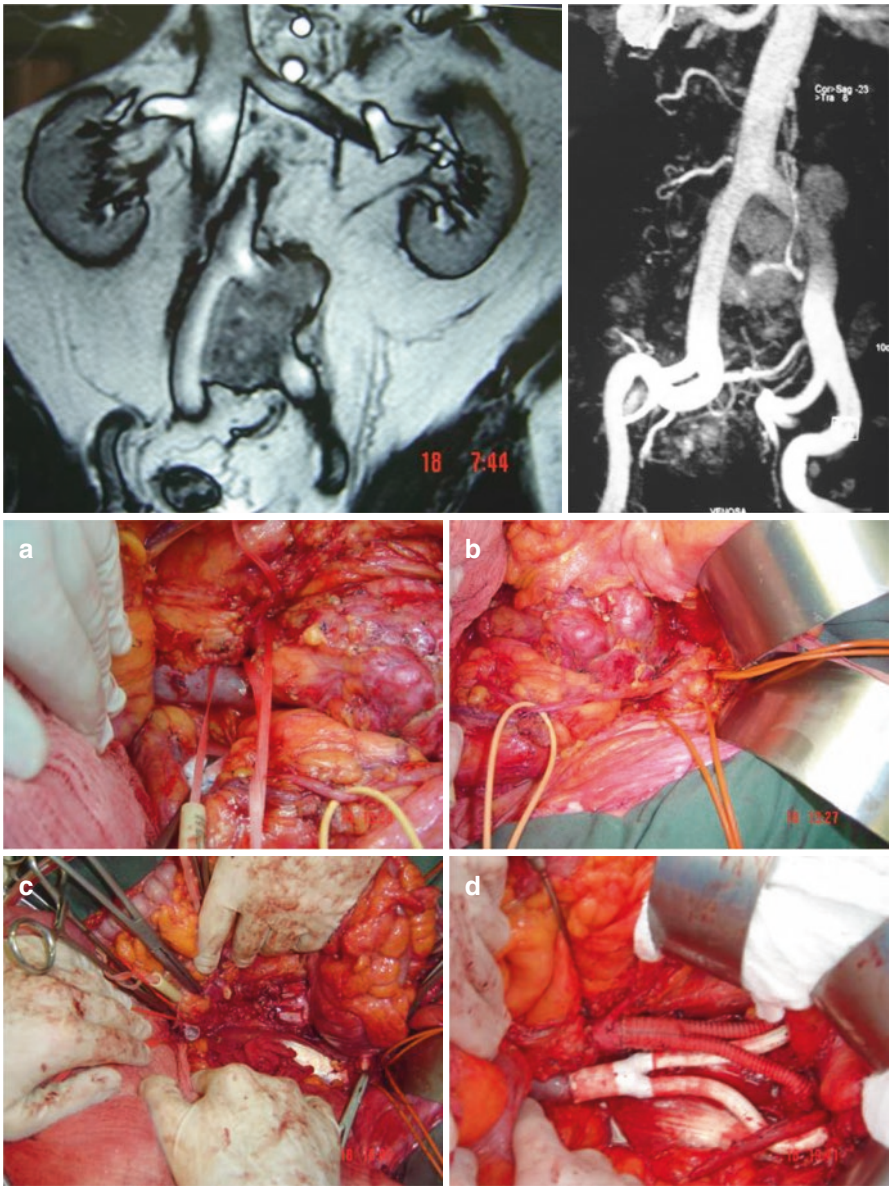

Fig. 7.47 A 68-year-old male patient with retroperitoneal pleomorphic sarcoma. MRI shows vascular involvement at the bifurcation of the aorta and at the confluence of common iliac veins. The surgery was jointly scheduled by the oncology and vascular surgery teams. In this case, the option was to precede the resection without doing a temporary "by-pass." During the resection phase, however, there was a significant bleeding, which was only adequately controlled after the reestablishment of the venous flow. (**a**) Isolation and proximal repair of the aorta, vena cava, and ureters. (**b**) Isolation and distal repair of the external iliac vessels bilaterally. (**c**) Operative bed after "*en bloc*" resection of the tumor with a segment of the aorta and common iliac arteries and a segment of the inferior vena cava and common iliac veins. (**d**) Arterial reconstruction with bifurcated Dacron prosthesis and venous reconstruction with bifurcated PTFE prosthesis. (*Fábio Ferreira, surgical oncology and Kenji Nishinari, vascular surgery*)

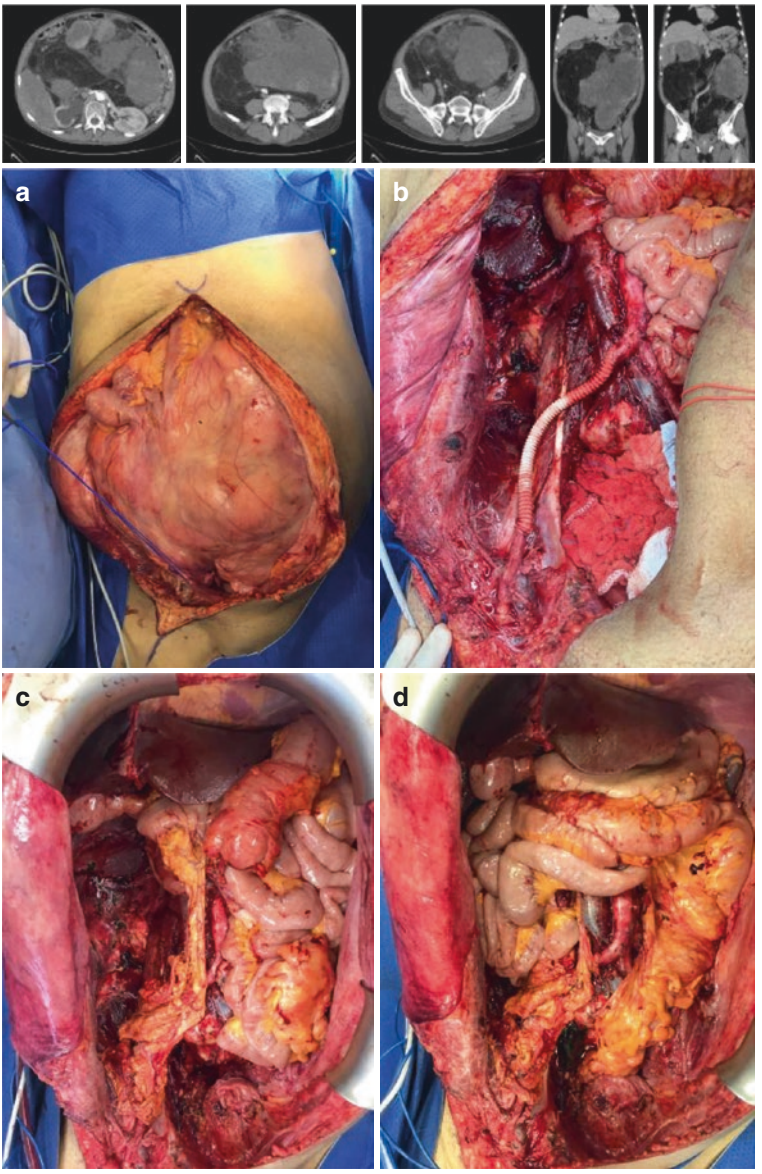

Fig. 7.48 A 47-year-old male patient with extensive dedifferentiated liposarcoma of retroperitoneum with clear involvement of the right iliac vessels (CT). He was treated according to institutional protocol with preoperative radiation followed by surgery. (**a**) View of the tumor after wide laparotomy – note the signs of visceral involvement. (**b**) Operative bed after "*en bloc*" resection (duodenum segment, ileum segment, right colon, transverse colon segment, right kidney, ureter, and right iliac vessels). Observe the iliac-femoral vascular reconstruction with prosthesis. Due to hemodynamic instability, option was made for nonvenous reconstruction. (**c**) Omentum flap to protect the prosthesis and isolate the areas of intestinal anastomosis. (**d**) Final view of the operative field after intestinal anastomoses. The patient had a prolonged recovery, being discharged 30 days after the operation. He has a follow-up period of 1 year, with no signs of recurrence, without functional restriction, with mild edema of the right lower limb. (*Courtesy of Tibério Moura de Andrade Lima, surgical oncology and Luciana Ragazzo Araujo Teixeira, vascular surgery*)

When the resection of large retroperitoneal vessels is foreseen, wide exposure is necessary. We prefer a wide median laparotomy. In large-volume tumors, if necessary, transverse incisions can be associated, both to the right and to the left, creating a wide exposure. Ample mobilization of the right colon, duodenum, and right kidney is generally necessary. Then, proximal and distal isolation of the vena cava is performed in the region of interest. Depending on the height of the lesion, it is essential to identify and isolate the vessels of the renal pedicle. In addition to the proximal and distal repairs to the area of interest, in situations where it is intended to open the vena cava for partial resections, some precautions must be respected: (1) Isolate and repair the right and left renal veins. (2) If possible, isolate and repair of the renal arteries for clamping if there is a need to interrupt the arterial flow in order to decrease the venous return to the vena cava through the renal veins. (3) After isolating the vena cava and the vessels of the renal pedicle, the venous flow of lumbar veins that drain into the vena cava must be stopped before opening (the lumbar veins must be connected or clipped individually along the entire length between proximal and distal cava repairs). (4) Immediately before clamping the vessels, the anesthetist is asked to infuse heparin intravenously; only then the clamping is proceeded. The infrarenal segment of the vena cava should be clamped first, the renal arteries second (if necessary), the renal veins in third and, finally, the proximal vena cava. This sequence allows "emptying" the vena cava in the territory of interest, minimizing the outflow of blood that can impair vision. If necessary, clamping of the renal arteries should be done for the shortest possible time, with intermittent unclamping if the ischemia time is prolonged. To avoid gas embolism, vascular clamping should not be released if the vena cava is opened. (5) During the reconstruction phase, small segments can be treated by primary suture as long as it does not cause stenosis. Partial loss of a larger segment may imply reconstruction with a pericardium patch or similar. Wider resections require replacement with prostheses. After the reconstruction of the vena cava, the vessels are sequentially unclamped, one at a time, observing if there are any bleeding points and the hemostasis is reviewed (Fig. 7.49).

This series of cases illustrates some of the most common situations of the association of vascular problems found in the surgical management of retroperitoneal tumors.

7.8 Conclusion

Retroperitoneal tumors represent a real challenge for different medical specialties. The variety of diagnoses, presentations, and treatments makes the search for the correct diagnosis a path to be followed step by step, in order to avoid errors potentially harmful to the patient. Upon diagnosis of retroperitoneal mass, singular importance must be given to the clinical-radiological characteristics in order to

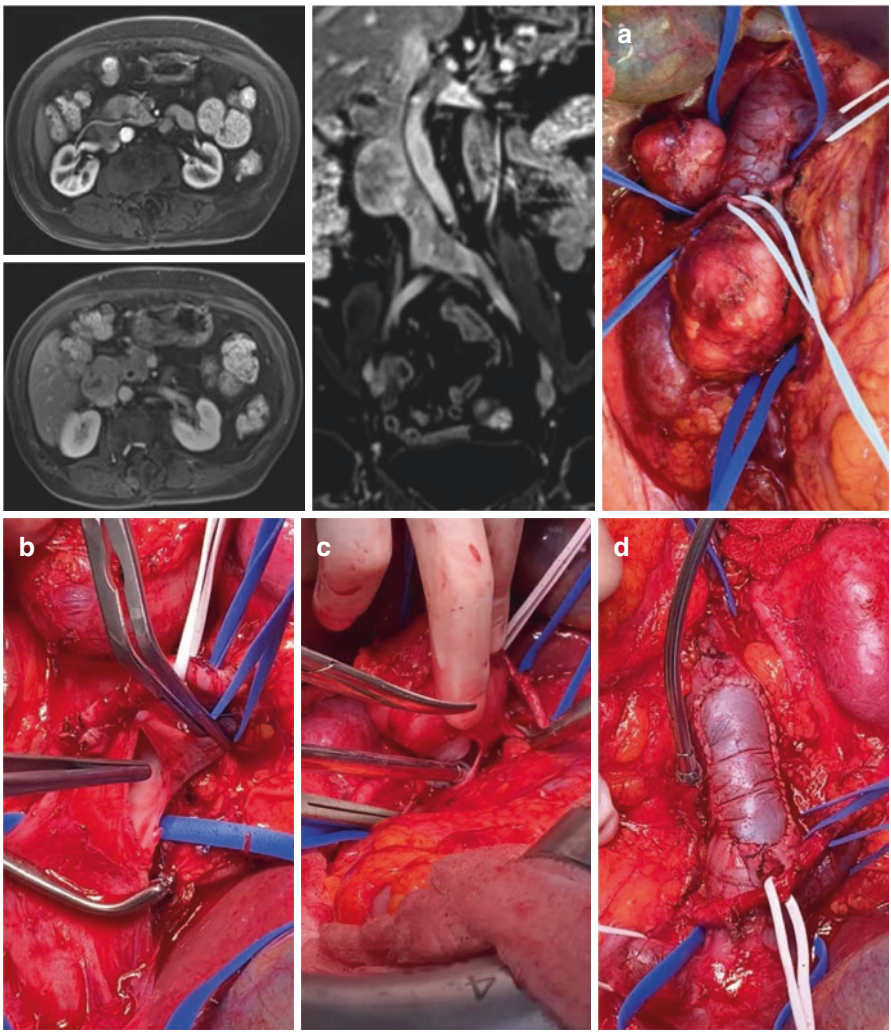

Fig. 7.49 A 74-year-old female patient had a retroperitoneal mass found during an image exam performed to investigate diverticulitis symptoms. MRI shows two solid nodular lesions located anterior to the inferior vena cava. The patient underwent an image-guided biopsy and was diagnosed with leiomyosarcoma. A diagnostic hypothesis of primary leiomyosarcoma of the inferior vena cava was made. (**a**) The patient was taken to surgery with the finding of two primary distinct lesions of the inferior vena cava, with the right renal artery passing between the lesions and the right renal vein free from invasion, which allowed renal preservation. (**b**) Primary suture of the vena cava after resection of the smaller and more cranial lesion. (**c**) Resection of the second lesion with a segment of the vena cava wall. (**d**) Repair of the vena cava segment with a bovine pericardium patch. (*Fábio Ferreira, surgical oncology and Kenji Nishinari, vascular surgery*)

classify retroperitoneal tumors according to their etiology, facilitating further investigation and referral among specialists. In our chapter, we chose to combine retroperitoneal tumors into four major groups: (1) intraperitoneal lesions that simulate retroperitoneal tumors; (2) primary tumors of retroperitoneal organs; (3) primary tumors of the retroperitoneal space; and (4) retroperitoneal lymph node masses. As we have seen, many retroperitoneal tumors are treated surgically, and the involvement of large retroperitoneal vessels is not uncommon. Even when the diagnosis does not require surgical treatment, associated vascular problems can occur. Thus, the knowledge of the theme brings an additional contribution to oncologists and vascular surgeons, who will certainly be consulted for joint action in oncological surgeries or to solve vascular problems secondary to different etiologies.

Editor's Comments

Retroperitoneum tumors often require the vascular surgeon's participation in surgical treatment, either in the rare primary vascular tumors or in tumors involving large vessels or trunk vessels.

Leiomyosarcoma of the Vein Cava

Leiomyosarcoma (LMS) is the histological type most associated with large vessels' primary tumors, with the inferior vena cava (IVC) being the most frequent location, representing 0.5% of soft tissue sarcomas in adults [213, 214]. Its prognosis is reserved, with 5-year survival after tumor resection between 25% and 50% [215–218]. Surgical resection is the only chance of cure for patients with this diagnosis.

LMS mainly affects middle-aged or elderly individuals, with female predominance (3:1) when the LMS is primary in the vena cava [219].

Localization

For classification concerning location, the IVC is divided into three segments: segment I (lower) – below the renal veins; segment II (medium) – from the renal veins to the retrohepatic vena cava; segment III (superior) – from the hepatic veins to the right atrium. About 80% of the tumors originate in segments I and II (with a slight predominance in the last) and only 20% in segment III [215, 216, 220]. The tumor may be present in more than one segment concomitantly.

Signals and Symptoms

Abdominal pain is a nonspecific symptom, but it is frequent [221]. Lower limb edema is a sign found in about 1/3 of the patients since the slow growth of the tumor favors the development of collateral circulation that reduces the clinical repercussion of IVC obstruction. Often, edema results from deep venous thrombosis in the lower limbs, being a more frequent sign in tumors located in segment I. Tumors of segment II can cause nephrotic syndrome due to obstruction of renal venous drainage. Tumors located in the upper segment, on the other hand, can impair drainage through the hepatic veins, causing hepatomegaly, jaundice, and ascites, in addition to a higher risk of pulmonary embolism [215, 216, 219, 220, 222–224].

IVC LMS may have extraluminal, endoluminal, or both growth, with the first being the most frequent (about 62% of cases) and the endoluminal being the rarest (5% of cases) [225]. Extraluminal growth can cause symptoms by compression or invasion of adjacent structures, such as stomach and duodenum.

The most frequent sites of metastases are the liver and lungs. Cachexia is a sign that can accompany patients with advanced disease.

Diagnosis

Computed tomography shows a tumor with an irregular, lobulated shape, which may partially obstruct the IVC lumen. Tumor necrosis and hemorrhage generate a heterogeneous aspect of the tumor mass. Since it provides greater tissue resolution, magnetic resonance imaging tends to be more useful in diagnosing the origin of the tumor and planning surgical treatment. Differential diagnosis with kidney tumors, lymphoma, and liposarcoma can be difficult. Webb et al. demonstrated that IVC light was imperceptible in 75% of patients with IVC LMS, which did not occur in tumors of another nature [226].

An echocardiogram is useful in segment III tumors to assess the extent of the tumor to the atrium.

PET-CT is an option to investigate images suspected of metastasis, a situation in which percutaneous biopsy may be necessary to assess a possible indication for neoadjuvant palliative therapy.

Staging

The staging of the LCI of the IVC obeys the TNM classification: TX – nonaccessible primary tumor; T1 – tumor ≤5 cm in the most extensive measure; T2 – tumor >5 cm in the most extensive measure; N0 – without evidence of positive lymph

nodes; N1 – with evidence of positive lymph nodes; M0 – without metastasis; M1 – with metastasis [221].

The classification according to the degree of differentiation adopted is proposed by the French Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC), based on differentiation (score 1–3, depending on the differentiation of mesenchymal tissue), on the number of mitoses (score 1–3, depending on the number of mitoses per 10 high magnification fields – 10 high power field), and in the presence of tumor necrosis (score 1–3, depending on the presence of tumor necrosis). This histological classification is determined as Grade 1 for total score 2–3; Grade 2, total score 4–5; and Grade 3, total score 6–8 [221].

Treatment

Treatment consists of resection of the IVC segment affected by the tumor en bloc with neighboring tissues or organs that may be affected. Information regarding chemotherapy and radiotherapy is scarce, both as adjuvant and neoadjuvant therapy, and chemoradiotherapy may be an option in particular situations such as complementary or palliative treatment [218, 221].

The IVC approach depends on the segment of origin of the tumor, the extension of the involved vascular wall (partial or circumferential), and the venous collateral circulation development.

A ligature is an option described in the treatment of tumors in segment I. However, resection of the tumor may compromise a previously efficient collateral circulation so that the editors prefer, whenever possible, to reconstruct the circulation through the inferior vena cava. Extensive venous thrombosis downstream or upstream can prevent the reconstruction of venous flow.

In cases of small tumors that involve less than 75% of the lumen and without infiltration of adjacent organs, partial resection of the IVC and reconstruction with a patch may be an option. The choice for a patch depends on the extent of the affected IVC and eventual contamination of the surgical bed that can occur when invasion and resection of organs of the gastrointestinal tract take place. In the latter case, autologous substitutes such as the saphenous vein or the external jugular vein are preferred. Heterologous substitutes (cadaver veins) have more restricted use due to less availability. Primary raffia, without a patch, can also be an option, as long as the suture is not done under tension. Bovine pericardium graft and synthetic vascular prostheses, both Dacron and PTFE (expanded polytetrafluoroethylene), are also options, especially in cases of more extensive circumferential involvement.

When there is a need to resect a segment of the VCI, the bypass with Dacron or PTFE is the option. The preference in venous reconstructions is for the use of reinforced PTFE. The making of arteriovenous fistula, to increase the patency of venous reconstruction, is less and less performed [220].

Reconstruction of the renal vein is always desirable, especially of the left renal vein when the right kidney is resected en bloc with the tumor.

Retroperitoneal Tumors with Vascular Involvement

Retroperitoneum tumors usually cause few symptoms in the early stages, so they are often diagnosed already quite bulky and often involving vascular structures [227]. Vascular reconstruction can transform unresectable tumors into resectable ones so that the involvement of arteries and veins no longer represents a contraindication for tumor resection [228, 229]. The involvement may be of trunk (visceral) vessels or the great vessels of the retroperitoneum (vena cava and aorta), either by invasion or by circumferential involvement (see Chap. 13).

Computed tomography and nuclear magnetic resonance show possible vessel entrapment by the tumor mass. However, when there is intimate contact, it may fail to differentiate this contact by proximity, which does not prevent the preservation of vessels from vascular invasion itself, which could require en bloc resection and vascular reconstruction. In some situations, intravascular ultrasound (IVUS) can increase the accuracy of vascular invasion diagnosis [230, 231]. The need for vascular reconstruction, however, is often defined only with intraoperative findings. Doppler ultrasound can help assess the caliber and patency of vessels potentially eligible as substitutes (e.g., internal saphenous vein).

Reconstruction techniques, as discussed above in the VCI LMS, include patch-making – when the vessel wall is partially resected in its circumference, bridges – when a segment of the vessel is removed en bloc with the tumor, in addition to the primary anastomosis end-to-end if there is no tension in the suture to approach the stumps. A ligature is an alternative in treating nonvital vessels for nutrition or venous drainage of a specific organ or tissue or if a venous segment presents with proximal and/or distal thrombosis to the segment removed en bloc with the tumor.

Arterial substitutes can be autologous (internal and external saphenous veins, femoral veins, internal and external jugular veins, upper limb veins, radial artery, hypogastric artery), normally used in the reconstruction of visceral branches and situations of contamination of the surgical bed. Among the synthetic substitutes, the main ones are the Dacron and PTFE vascular prostheses, essential in treating larger caliber vessels. Heterologous vessels (from cadaver donors) are a less available alternative in most centers. Reinforced PTFE is preferred for venous reconstructions and when the bridge exceeds joints. Patches can be made with autologous substitutes and bovine pericardium foil, in addition to the aforementioned synthetic material.

Reinforced PTFE prostheses with a suitable caliber for IVC reconstruction are rarely available in our country. The creation of a new IVC bifurcation is a relatively simple technique that allows the use of a smaller caliber prosthesis [227].

Concerning the surgical time, the ideal is that the vessels be connected, after systemic anticoagulation, as the last act before the en bloc removal of the tumor, followed by vascular reconstruction. If the artery and vein have to be reconstructed, the first is done before the second to minimize ischemia time. When vascular ligation is necessary before the tumor is fully mobilized, the artery and vein receive bridges with long vascular prostheses proximally and distally to the segment

affected by the neoplasia, allowing vascular ligation and the sequence the oncological time. After the dissection, the tumor is removed en bloc, and the bridges are shortened (Figs. 7.45 and 7.46 of Chap. 7).

Whenever possible, patients who have received venous bridges are kept on full anticoagulation for a minimum of 6 months. Regardless of the substitute used, exclusive arterial reconstruction does not require full anticoagulation in the postoperative period.

Results of the patency of reconstructions are found in Chap. 13.

Other Situations That Require Vascular Intervention

Rare cases of aortic pseudoaneurysm after chemotherapy in patients with germinal tumors and large retroperitoneal masses have been described (see comments in Chap. 4) [232]. These pseudoaneurysms occur when there is tumor invasion in the aortic wall and are attributed to tumor necrosis following treatment chemotherapy, including neoplastic cells that inhabit the arterial wall [232]. The treatment can be reconstruction with a synthetic vascular prosthesis in the same surgical procedure as the en bloc resection of the tumor or, in case of rupture, endovascular treatment with an endoprosthesis implant can be an alternative [232].

Venous aneurysms are very uncommon. A rare case of idiopathic infrarenal vena cava sac aneurysm has been described in association with a retroperitoneum ganglioneuroma, treated with sacculation resection and primary raffia of the lateral wall of the vena cava in the same act of tumor resection [233].

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Chapter 8
Neurosurgery

Guilherme Alves Lepski and Thales Bhering Nepomuceno

8.1 Introduction

The management of brain tumors includes careful preoperative planning guided by anatomical knowledge and advanced imaging to identify the relationship between the tumor, the surrounding functional brain, and the arterial and venous structures, as well as their patencies. The perioperative evaluation should aim to identify critical brain areas around the tumor, major vascular encasement or compression, and sufficient or critical brain perfusion. If a major vascular risk is identified preoperatively, a protective vascular surgery should be planned in advance to avoid inadvertent intraoperative damage. Proper vascular reconstruction can rarely be conducted safely without detailed planning and available material at hand. Therefore, an experienced neurosurgeon must be able to identify situations of risk and plan the operative strategies in advance to avoid irreversible neurologic deficits or patient death. The following sections in this chapter will address the diagnostic and therapeutic issues pertaining to these strategies.

8.2 Most Common Tumor Types

The most common intracranial tumors in adults are secondary metastases in extracranial tumor sites (with lung, breast, and melanoma being the most common) [1].

Meningioma is the most common primary intracranial tumor (37.3%), followed by pituitary adenoma (16.8%) and glioblastoma (14.6%). Glioblastoma (48.3%) is

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the most frequently diagnosed primary malignant intracranial tumor, whereas meningioma (53.3%) is the most frequent primary nonmalignant tumor [2, 3].

Other tumor entities like schwannomas (8.6% of all intracranial tumors) or paragangliomas may affect the skull base region and endanger nearby vascular structures. Because of their specific characteristics, we will not further address these types of tumors within the present chapter.

Nonmalignant tumors are more likely to be located near major brain arteries, venous sinuses, cranial nerves, and the skull base, and are more likely to adhere to them. Thus, resection of these tumors carries a greater risk of vascular lesions than surgery for malignant tumors, which are usually intraparenchymal and do not enclose major arteries.

8.3 Risk of Vascular Complications

The risk of vascular complications during brain tumor surgery is associated with multiple factors:

- Tumor type and location
- Degree of vascular adherence and invasiveness
- Type of surgical approach for tumor exposure

Depending on their implantation site, meningiomas can be located in close proximity to important brain vessels, such as the internal carotid artery (ICA) and its branches, the vertebral arteries, and the dural venous sinuses. The most critical meningioma locations for the scope of this evaluation are as follows:

- Sphenoid wing and clinoidal
- Parasagittal
- Petroclival
- Cavernous sinus
- Foramen magnum

Parasagittal meningiomas are known for their propensity to invade, compress, or occlude venous sinuses, due to their origin in the arachnoid granulations. Opening the venous sinus during surgery increases the risk of hemorrhage, venous ischemia, and air embolism. Depending on the patient's age and comorbidities, the surgeon may opt for subtotal resection in an attempt to avoid massive bleeding from the sinus or its secondary thrombosis. Alternatively, he/she may choose radical resection with sinus reconstruction techniques or bypass to lessen the risk of recurrence.

Tumors of the craniocervical transition, such as foramen magnum and jugular foramen meningiomas, adhere to the vertebral artery and its branches, like the posterior inferior cerebellar artery (PICA). Thus, surgery for these tumors carries a risk of hemorrhage and brainstem stroke. Another relevant structure is the sigmoid sinus, which can be damaged during craniotomy, leading to hemorrhage, air embolism, and venous sinus thrombosis. When dominant, a thrombosed sigmoid sinus can lead to hemorrhagic infarction in the cerebellum or brainstem, edema, or even arterial embolism in the case of foramen ovale patency [4].

Jugular paragangliomas are rare benign tumors derived from the neural crest; these are the most common tumors to originate in the jugular foramen, followed by schwannomas and meningiomas. They can encase and sometimes occlude and invade the jugular bulb and sigmoid sinus. They often encase the external and internal carotid arteries, requiring extensive skull base surgical approaches for tumor exposure and resection.

The endoscopic transsphenoidal (TS) approach to the skull base is a particularly important method to access and resect tumors of the sellar and parasellar regions, clivus, and anterior skull base, including pituitary adenomas, craniopharyngiomas, skull base meningiomas, and chordomas. During exposure, there is a risk of carotid artery and cavernous sinus lesions with a potential for significant hemorrhagic and ischemic complications [5, 6]. Some have estimated a 1.1% chance of vascular lesions in transsphenoidal surgeries [7], including iatrogenic pseudoaneurysms due to direct trauma to the artery wall [8, 9]. These lesions can be treated with endovascular stenting and/or coiling, but these procedures involve a risk of life-threatening hemorrhage and ischemic complications [10]. There are two types of iatrogenic pseudoaneurysms: saccular and fusiform [11]. Saccular pseudoaneurysms result from a more focal and complete laceration of the arterial wall. The apparent lumen of the opacified aneurysm is contained by an organized extraluminal hematoma. Factors that may increase the risk of vascular injury during the TS approach are anatomical variants of the sphenoid bone, carotid artery tortuosity and proximity to the contralateral side ("kissing carotids"), prior TS surgery, invasion of the cavernous sinus by the tumor, and small sella [12].

Fusiform pseudoaneurysms are probably caused by surgical peeling of the tumor capsule from the arterial adventitia of the adjacent vessel resulting in thinning of this layer and subsequent dilatation of the vessel. They generally do not progress to hemorrhage or stroke. For this reason, the treatment of iatrogenic fusiform pseudoaneurysms continues to be under debate. Patients should be closely followed-up with angio-magnetic resonance imaging (angio-MRI) and angiography, and endovascular treatment with stent is recommended if any progression is observed.

8.4 Tumor Encasement of Arteries

Most extra-axial tumors grow by displacing neurovascular structures around them. However, some tumors grow around arteries, veins, and cranial nerves, encasing them circumferentially, which results in difficult removal that may lead to vascular complications and even vessel compression and thrombosis that may result in a stroke.

Sphenoid wing meningiomas originate near critical vascular structures and encase arteries they grow, with reports of around 20% vascular injuries with ischemic complications during tumor resection [13]. McCraken et al. described a grading for sphenoid wing meningioma vascular encasing (E) based on the degree of circumferential involvement:

1. $0° \leq E < 90°$
2. $90° \leq E < 180°$

3. $180° \leq E < 270°$
4. $270° \leq E < 360°$
5. $E = 360°$

A correlation was found between increasing encasement of vascular structures and postoperative brain infarction, with a high risk of infarction when the tumor completely encases the internal carotid artery and its bifurcation, including the anterior cerebral artery (ACA) and middle cerebral artery (MCA) [13]. Encasements classified as grade 3 or more should alert the surgeon to perform a protective bypass if total resection is intended. This is further supported if a perfusion deficit is identified in the PWI/MRI, SPECT, or water-PET. For elderly patients or patients with significant comorbidities, partial resection followed by adjuvant radiotherapeutic treatment may be the best option.

Very often, pituitary adenomas invade the cavernous sinus and encase the cavernous carotid artery. In 1993, Knosp published his classification for pituitary tumor involvement of the cavernous sinus and carotid artery encasement, which is very useful to predict vascular risk and to plan surgical and adjuvant treatment strategies in advance (Fig. 8.1). Grades 2, 3, and 4 were associated with higher percentages of microscopic sinus invasiveness (88%, 86%, and 100%, respectively) [14].

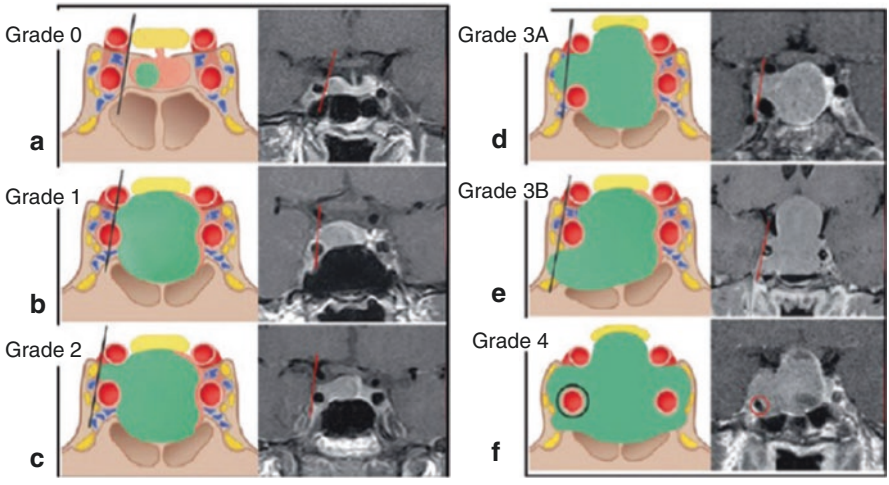

Fig. 8.1 Knosp's classification of pituitary tumor involvement of the cavernous sinus and carotid artery encasement. (**a**) Grade 0: the adenoma does not encroach on the compression stockings (CS) space. (**b**) Grade 1: the medial tangent is passed, but the extension does not go beyond a line drawn between the cross-sectional centers of the intracavernous and supracavernous ICAs (the intercarotid line). (**c**) Grade 2: the tumor extends beyond the intercarotid line but not past the tangent on the lateral aspects of the intracavernous and supracavernous ICAs. (**d**) Grade 3A: the tumor extends lateral to the lateral tangent of the intracavernous and supracavernous ICAs into the superior CS compartment. (**e**) Grade 3B: the tumor extends lateral to the lateral tangent of the intracavernous and supracavernous ICAs into the inferior CS compartment. (**f**) Grade 4: there is total encasement of the intracavernous carotid artery. (*Source*: Knosp et al. [51]. License: CC Attribution-Share Alike 4.0 International)

The dissection of tumors from vascular structures depends on the preservation of an arachnoid plane during extracapsular dissection, gently separating the tumor from the neurovascular structures [15]. We advocate bimanual tumor dissection with forceps, while the assistant constantly irrigates and aspirates the field to keep it clean. The invasion of the carotid artery wall by meningiomas of the cavernous sinus is well known and although limited to the adventitia, it prevents the surgeon from detaching the tumor from the artery through the arachnoid planes and makes complete resection impossible without sacrificing the artery [16]. In this situation, when a radical resection is planned, either a protective bypass should be performed in advance, prior to tumor removal, or the preoperative investigation should show that artery sacrifice is possible without major perfusion deficit (sufficient collateral flow). In many cases, an occlusion test must be performed preoperatively to address this risk and support decision-making (Fig. 8.2).

8.5 Oncological Treatment

Oncological treatment in neurosurgery depends on the histopathological and molecular diagnosis of the tumor and its location in relation to eloquent areas, venous sinuses, and major brain arteries. The aim of neuro-oncological treatment is gross total tumor resection whenever possible, followed by chemotherapy and radiotherapy in most malignant tumors. In symptomatic nonmalignant tumors, gross total resection is also the objective, with the possibility of radiotherapy for residual lesions [17, 18]. The specific treatment recommendations for each type of brain tumor are outside the scope of this chapter.

8.6 Preoperative Imaging

A complete preoperative imaging evaluation of vascular structures is imperative since vascular neuroanatomy is highly variable and the presence of a tumor can displace the structures to uncommon sites. If the surgeon is not prepared, he/she may risk damaging these structures during exposure.

The gold standard for evaluating vascular anatomy in the brain is the cerebral digital subtraction angiography (DSA). It can evaluate the position of the arteries, veins, and sinuses as well as the flow, defining which sinus or artery is dominant in relation to a vascular territory. The tumor can also be seen through the displacement of vascular structures and neovascular architecture with tumor blush. Angiography will also show the most important arteries supplying the tumor and help tailor the approach to reach it and achieve vascular control before tumor removal. By performing a balloon test occlusion (BTO) with temporary artery occlusion, the surgeon can assess neurologic deficits in case of insufficient perfusion, or sufficient collateral flow through the circle of Willis or other collateral anastomosis.

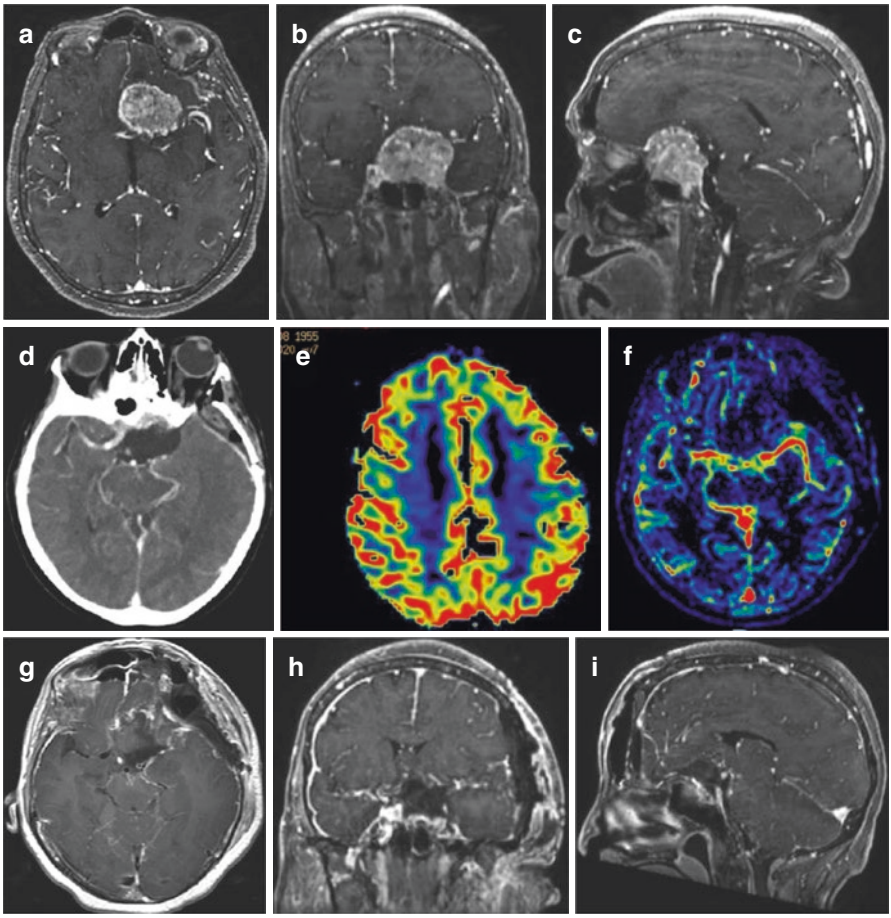

Fig. 8.2 A large medial sphenoid wing meningioma on a 45-year-old woman presenting with headache. (**a–c**) Axial, coronal, and sagittal T1-weighted MRI scans with Gadolinium, respectively, showing tumor extension and encasement of the left ICA. Preoperative ballon test occlusion revealed tolerance to ICA ligation. Accordingly, a subtotal Simpson II resection was performed using a fronto-orbito-zygomatic approach. (**d**) Postoperative computed tomography (CT) scan with contrast showing no ACI on the left side. (**e**, **f**) Postoperative PWI/MRI scans showing sufficient brain perfusion (the anterior territory is shown nicely perfused in **e**, and the left MCA is shown in **f**). (**g–i**) Postoperative T1 MRI scans with gadolinium showing gross total resection

Another essential tool is magnetic resonance imaging (MRI), which shows the location of the tumor in relation to other brain structures and makes it possible to plan the best strategy for tumor removal. MRI coupled with frameless stereotaxic technology, also called neuronavigation, provides localization of the tumor and important landmarks with high precision during surgery [19]. Multiple MRI sequences allow for the evaluation of fiber tracts with diffusion tensor imaging (DTI), vascular anatomy with magnetic resonance angiogram (MRA), and oxygen

consumption and functional activation with blood oxygen level dependent (BOLD) functional MRI, tissue diffusion and perfusion, and spectroscopy, showing metabolite concentrations. The novel PET/MRI (positron emission tomography and MRI) allows one to measure cerebral blood flow through $H_2{}^{15}O$ PET and cerebral blood volume with $C^{15}O$ PET and merge this with anatomical magnetic resonance imaging [20].

Although computed tomography (CT) shows a less detailed image than MRI, CT angiography is better for assessing the tumor's relationship to the blood vessels and skull bone structure, which can be invaluable to planning the surgical approach. In some cases, CT may substitute MRA and DSA.

8.7 Arterial Reconstruction Strategies

The extracranial–intracranial (EC-IC) bypass was first performed by Professor Yaşargil in 1968 from the superficial temporal artery (STA) to the MCA [21]. This procedure was initially conceived as an augmentative flow method for patients harboring middle cerebral ischemia. Nevertheless, a large prospective study published in 1985 proved the procedure to be of no statistical benefit to such patients [22]. Another prospective trial conducted for the same recommendation was interrupted early for futility [23]. Despite this evidence, revascularization techniques are still considered a prophylactic measure when vascular risk is deemed high during preoperative planning.

Recommendation for bypass during surgeries for skull base tumors [21, 24]:

- Encasing of major vessel in benign recurrent or previously radiated tumor, with high risk of vascular lesion during dissection.
- Need for major vessel sacrifice to achieve complete tumor resection, due to tumor invasion, especially in locally aggressive tumors with surgery being the most effective initial treatment modality (such as chordomas).
- Tumor encasing of invading vessels with high risk of perioperative ischemia, especially if low vascular reserve, ischemic symptoms preoperatively, and previous surgical or radiation treatments.
- Intraoperative vascular lesion without possibility of direct suturing repair, especially in patients with preoperative evidence of intolerance to major vessel sacrifice [5].

The decision to perform a bypass prophylactically before resection of a complex skull base tumor must be individualized during surgical preoperative resection strategy planning, taking into consideration the tumor histology and aggressiveness, encasing of major vessels, prognosis with subtotal versus total resection, the patient's functional level, vascular reserve (ballon test occlusion), the alternative of radiation therapy for residual lesions, and the surgeon's experience with vascular techniques.

8.8 Arterial Reconstruction Techniques

Bypasses can be categorized into two major groups: low-flow and high-flow techniques. Indications for each must take into account the perfusion deficit in the territory to be treated, as estimated by any objective measure, such as PWI/MRI with flow measure, water-PET, or transcranial Doppler with selective vasoactive drugs (Nimodipine).

If the aim is to substitute the internal carotid artery flow, prophylactically or urgently, the high-flow bypass techniques are the best choice, as they provide flow >50 mL/min and up to 100–150 mL/min. The low-flow bypass provides sufficient flow (<50 mL/min) for distal cortical territories, like an M2 branch of the MCA or the PICA, but could be used to augment ICA flow when there is a good circle of Willis in the balloon test occlusion [25].

Low-flow extracranial–intracranial bypass (EC-IC bypass):

- STA-MCA: Superficial temporal artery–Middle cerebral artery
- OA-MCA: Occipital artery–Middle cerebral artery
- OA-PICA: Occipital artery–Middle cerebral artery

Low-flow intracranial–intracranial bypass (IC-IC bypass):

- PICA-PICA: Anastomosing both posterior inferior cerebellar arteries together

Low-flow bypasses usually do not require an interposition graft and consist of dissection, transposition, and preparation for anastomosis of the donor artery, together with exposure and temporary vascular occlusion of proximal and distal recipient arteries, followed by anastomosing by end-to-side or side-to-side, depending on the technique.

High-flow extracranial–intracranial bypass (EC-IC bypass):

- External carotid artery–Internal carotid artery
- External carotid artery–Middle cerebral artery
- IMAX-MCA: Internal maxillary artery–Middle cerebral artery [26]

High-flow bypasses utilize an interposition graft—usually from the saphenous vein or radial artery—to divert flow from a major extracranial artery, such as the external carotid artery or one of its branches (e.g., the internal maxillary artery, IMAX). The technique is initiated by harvesting the graft and preparing it, followed by exposure of the donor vessel, generally by cervical incision to expose the carotid artery bifurcation. Alternatively, to neck dissection, one may opt for the IMAX-MCA technique [26], which requires an extradural middle fossa approach to expose the internal maxillary artery. After exposing the recipient artery (usually the proximal middle cerebral artery or internal carotid artery), the graft is anastomosed end-to-end to the internal carotid or end-to-side to the external carotid artery. Next, the vessel is tunneled through the submandibular pterygoid fossa to the temporal region

using a chest tube, and then anastomosed end-to-end to the siphon- or petrous-ICA or end-to-side to the MCA [27].

High-flow intracranial-to-intracranial bypass (IC-IC bypass):

- Petrous ICA–Cavernous ICA

The high-flow IC-IC technique of anastomosing an interposition graft from the petrous segment to the carotid siphon avoids the use of long grafts and the need for cervical dissection, but there are risks associated with the drilling and dissection, especially for the facial nerve and the optic nerve around the optic canal [27] (Fig. 8.3).

Serious risks are associated with high-flow bypasses. Accordingly, serious morbidity and mortality has been reported to range between 7% and 15% [28, 29]. Most of these complications are related to the temporary flow interruption. To overcome this problem, Tuleken et al. from Utrecht University in the Netherlands developed a different technique over a period of 20 years. This technique is called ELANA—excimer laser-assisted nonocclusive anastomosis [30]—and it allows the surgeon to perform a high-flow EC-IC bypass without arterial occlusion, thus avoiding the risk of cerebral ischemia. In fact, postoperative blood flow MRI studies have demonstrated maintained flows of 199 ± 72 mL/min [31]. In a recent multicentric study on the effectiveness of ELANA [32], 35 patients with complex giant intracranial aneurysms from the USA, Europe, and Canada were treated with ELANA; four of them presented with stroke 30 days after the surgery, all nonrelated to the ELANA procedure. ELANA thus proved to be an acceptable alternative over conventional methods. Considering that the study included a population with a high risk of complications, and that indication for high-flow bypass is rare, a direct comparison between available techniques is practically unfeasible, and indications must primarily be based on the surgeon's experience and the available techniques.

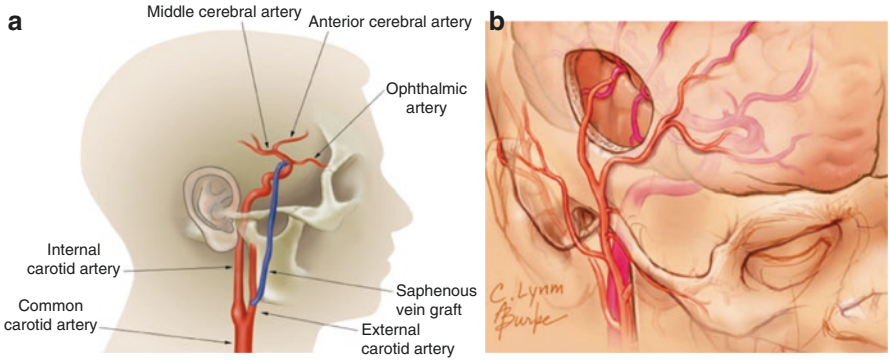

Fig. 8.3 (**a**) High-flow bypass connecting the ICA in the neck and the intracranial ICA at the siphon. (Adapted from Bulsara et al. [27]) (**b**) Low-flow bypass connecting the STA to the M4 segment of the MCA through a small temporal craniotomy. (Adapted from Powers et al. [23])

8.9 Venous Sinus Reconstruction

The risks of injury to a major venous sinus are of venous infarction with consequent edema and intracerebral hemorrhage, potentially leading to significant neurologic deficits, elevation of intracranial pressure, and death. Surgical intervention in the venous sinuses must be carefully considered in light of oncologic benefit, potential secondary thrombosis, patient age and comorbidities, and oncologic alternatives (mainly radiotherapy or radiosurgery) [33]. When an aggressive approach is chosen, with complete tumor removal and involved sinus, reconstructive techniques must be employed. These involve suture of an autologous patch, muscle tissue, or even venous bypass, if total sinus removal is performed [2, 34].

8.10 Venous Sinus Reconstructive Techniques (Fig. 8.4)

The decision to completely resect a tumor involving major sinuses is complex and multifactorial. It involves careful consideration of the patient's life expectancy, estimated tumor-related survival, therapeutic options as well as their efficacy, specific technical difficulty, and the patient's comorbidities. To aid in the decision-making process, Sekhar proposed a three-group classification: (1) marginal and partial sinus involvement (<50% of sinus patency), (2) subtotal sinus involvement (50–99% of sinus patency), and (3) total occlusion [35].

The operating surgeon must keep in mind that in most cases, total sinus occlusion occurred gradually, so that sufficient venous drainage may happen through bridging veins. A diligent study of the venous system must be performed preoperatively, with venous-MRI and often with DSA, in order to assess brain hemodynamics and blood drainage efficiency. If sufficient drainage is being resolved by alternative paths, total sinus resection can be performed safely without the need for reconstruction. In some instances, with advanced sinus involvement in an oligoasymptomatic patient, a watchful waiting approach can be considered, where the surgical intervention is postponed until total sinus occlusion is observed.

8.11 Prognosis

The evaluation of outcomes and prognosis after bypass for brain tumors is highly difficult because of the small number of patients that need it, different tumor types and aggressiveness, as well as different techniques and revascularized territories.

A review of extracranial-to-intracranial bypasses in skull base tumors found 368 reported cases, with most being meningiomas. Greater gross total resection (GTR) occurred after vessel sacrifice with bypass, reaching as high as 72% of tumors. Graft patency varied between 71.5% and 95.4% [36]. Sekhar et al. report the University

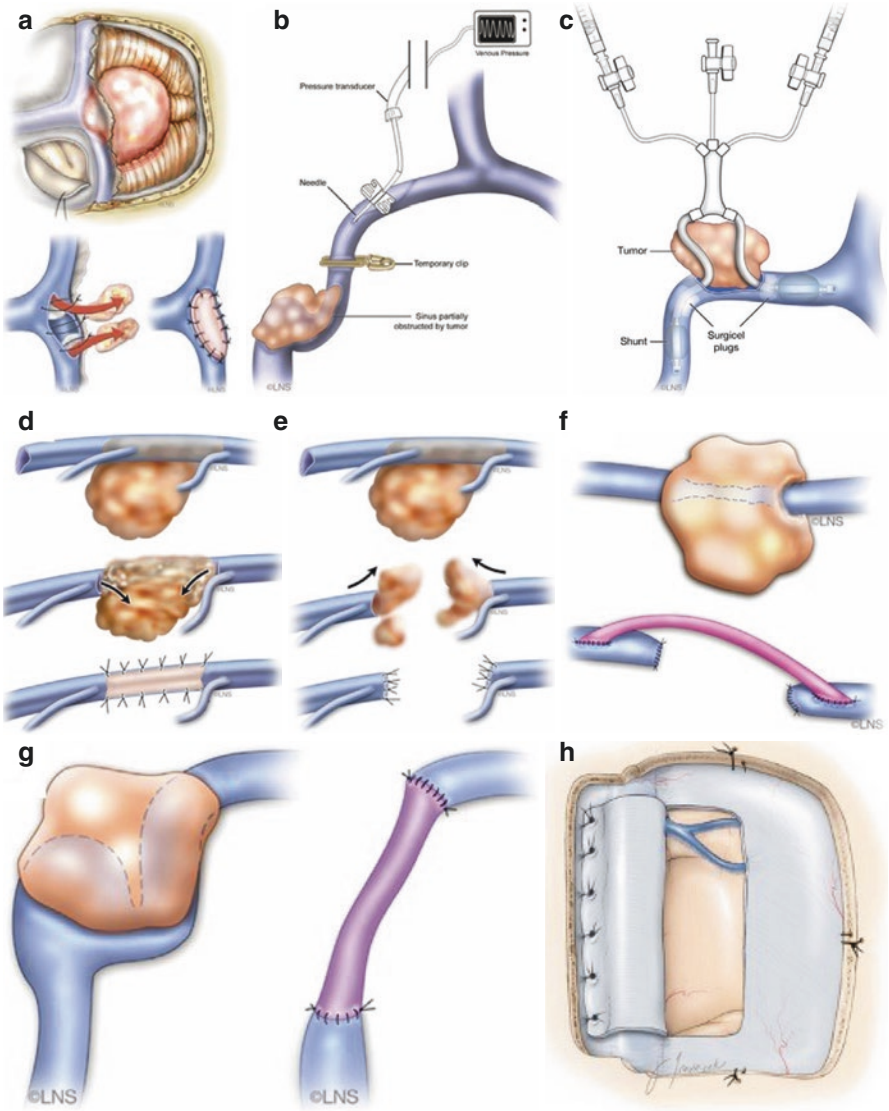

Fig. 8.4 Venous sinus reconstruction techniques. (**a**) An opened sinus after tumor removal can be reconstructed by suturing a dural, temporal fascia, or muscle patch. (**b**) Temporary clip occlusion and intraluminal pressure measure can indicate that the sinus can be transected if the pressure did not elevate beyond 5 mmHg from the baseline. (**c**) Fogarty catheters can be placed proximally and distally to stop bleeding during surgical reconstruction. (**d**) Direct reconstruction using a dural patch. (**e**) Sinus ligation in case of long (>2 cm) sinus occlusion. (**f**) Sinus ligation and interposition of radial artery graft in end-to-side anastomosis. (**g**) Interposition of a saphenous graft in end-to-end anastomosis. (**h**) The dural "swing flap" technique to reconstruct large sinus lacerations. (Adapted from Sekhar and Kalavakonda [29] and Aaron Cohen-Gadol, https://doi.org/10.18791/nsatlas.v2.14.2)

of Washington's results for direct revascularization of 130 tumors from 1988 to 2006, with GTR at 63%, 95.4% of graft patency, mortality from surgery at 1.5%, and mortality from disease progression/recurrence at 13.1% [37].

Yang et al. present a prospectively collected series of 20 high-flow bypasses in 18 patients with skull base tumors, with 72% GTR, no acute stroke of graft occlusions, and only one delayed graft stenosis that was surgically corrected. Their perioperative overall complication rate was 44.4%, with 14 patients obtaining good clinical outcome and 4 patients dying, 1 from aspiration pneumonia related to postoperative cranial nerve deficits, 2 from sarcoma recurrence despite GTR, and 1 from chordoma progression after subtotal resection [24].

In Sindou et al.'s report of 80 meningiomas involving major venous sinuses, GTR was 91% and good outcome was observed in 87.5% of patients. The rate of mortality was 3.6% from edema and venous infarction. The recurrence rate at the mean follow-up of 8 years was of 2.5% [34].

8.12 Venous Thromboembolism and Neuro-Oncology

A common vascular complication in patients with brain tumors is venous thromboembolism (VTE), with 1.5–2% risk per month of survival in high-grade glioma patients and 30% risk of VTE in postoperative meningioma patients [38, 39].

Glioma patients have an incidence of venous thromboembolism of 15–30% [40, 41]. In a meta-analysis [42] including nine retrospective cohort studies, anticoagulation did not increase the risk of intracranial hemorrhage (ICH) in brain metastasis. By contrast, in the case of gliomas, anticoagulation resulted in a 3.8-fold increase in intracranial hemorrhage.

The challenge of treating VTE with therapeutic anticoagulation in these patients is the risk of intracranial hemorrhage (ICH). Furthermore, a study demonstrated that overall survival was significantly shorter for glioma patients who suffered a major ICH on enoxaparin compared with patients not receiving anticoagulation [43].

There are higher risks of spontaneous bleeding in metastatic lesions from melanoma, renal cell carcinoma, choriocarcinoma, thyroid carcinoma, and hepatocellular carcinoma, which makes it reasonable to indicate brain MRI prior to initiating anticoagulation in patients with these primary tumors and delaying anticoagulation. In other primary tumors, if the anticoagulation can be safely delayed, brain imaging should also be acquired.

In metastases of the primary tumors cited above, the placement of an inferior vena cava filter (IVCF) may be appropriate before treatment of the intracranial lesion, although it should be considered that the IVCF has a high rate of complications in patients with brain tumors. Thus, it is advised to remove the IVCF after the acute phase and initiate therapeutic anticoagulation [39, 44].

For treated brain tumors, surgically or with radiotherapy, it is safe to initiate low molecular weight heparin (LMWH) anticoagulation, even in those with high bleeding risk metastatic lesions.

The PANWARDS risk score was described as a good discriminator of major ICH in high-grade glioma patients requiring anticoagulation. It takes into consideration the platelets, albumin, congestive heart failure, warfarin, age, race, diastolic blood pressure, and stroke [25, 27].

Anticoagulation is avoided in patients with low platelets (<50,000/μL), coagulopathy, and a history of previous intracranial bleeding, but even in those patients it is possible to individualize the approach for the patient and carefully use anticoagulation [44].

8.13 Time After Surgery to Start Anticoagulation

Based on multiple studies of pharmacological prophylaxis of VTE in neurosurgery, it is recommended for all neurosurgical patients undergoing craniotomy to start mechanical prophylaxis with compression stockings (CS) and/or intermittent pneumatic compression (IPC) before surgery, to be used continuously (except when the patient is walking). Additionally, chemoprophylaxis should be initiated with LMWH or unfractionated heparin (UFH) 24 h after surgery. For high-risk patients (risk factors include malignancy, motor impairment, prolonged operation time), IPC should be associated with LMWH or UFH 24 h postoperatively, to be continued until discharge [45–47].

The initiation of full therapeutic anticoagulation is more controversial. Still, there are studies that report low rates of ICH compared to the high risk of mortality due to pulmonary thromboembolism in neurosurgical patients [48, 49]. Based on these findings, it is recommended that anticoagulation for high-risk patients be resumed 48 h after surgery, under close neurologic monitoring. High-risk patients include those who suffered a major ischemic event in the previous month (myocardial infarction or stroke), or have a mechanical heart valve or atrial fibrillation. Determining high risk in patients is a matter of strong controversy, since various scoring systems have been published so far [48, 50]. The lack of consensus and individual risks highlight the need for interdisciplinary discussion of when to reinitiate anticoagulation and which bridging strategies and drugs are best.

8.14 Vascular and Endovascular Topics in Oncological Neurosurgery: Editors' Comments

- The most frequent vascular injuries in neurosurgical oncology happen in tumors located in close proximity to important brain vessels, such as the internal carotid artery (ICA) and its branches, the vertebral arteries, and the dural venous sinuses.
- Parasagittal meningiomas are known for venous sinus invasion, due to their origin in the arachnoid granulations, and may lead to their compression or occlusion.

- Surgery for tumors of the craniocervical transition, such as foramen magnum meningiomas, carry a risk of hemorrhage and brainstem stroke due to the tumor's encasement and adhesion to the vertebral artery and its branches, like the posterior inferior cerebellar artery (PICA), and also due to the risk of sigmoid sinus lesions.
- Sellar and parasellar tumors' close relation to the cavernous sinus and carotid artery increases the risk of vascular injury during surgery.
- Iatrogenic pseudoaneurysms are usually caused by direct trauma to the arterial wall during surgical procedures, more often when a transsphenoidal approach is used.
- The surgeon should use advanced imaging to plan the surgery; part of this evaluation is the identification of perfusion deficits and major vascular risk, which suggests the need for a protective bypass prior to tumor resection.
- The surgical approach to invaded venous sinuses must take into consideration the patient's comorbidities, age, life expectancy due to tumor, treatment alternatives, and employed reconstructive technique.
- As a rule, thromboembolism chemoprophylaxis with LMWH or UFH is indicated within 24 h after elective craniotomy for all patients. High-risk patients must be additionally treated with IPC, to be initiated upon admission.

Editor's Comments

The involvement of vascular structures by intracranial tumors is usually treated by neurosurgeons or by interventional neuroradiologists. Thus, in these situations, the vascular surgeon is more involved with treating venous thromboembolism (VTE).

It is well established that cancer patients have a higher risk of developing VTE. In individuals with tumors of the central nervous system (CNS), this risk is even more significant since they often have reduced mobility caused by the disease itself (especially if there is hemiparesis) or as a result of the postoperative neurosurgical period. The treatment of cancer-associated thromboembolism (CAT) is the same as that used in noncancer patients and is based mainly on anticoagulation [52, 53]. If the cancer patient has a higher risk of VTE, the risk of bleeding complications caused by it is also higher due to treatment, a cause of even greater concern in an individual with a tumor located in the CNS.

The management of CAT, both prophylaxis and treatment, is, therefore, a challenge. Some situations are associated with an increased risk of bleeding. For example, it is known that malignant tumors are more prone to hemorrhagic complications than benign ones. Among malignant neoplasms, it is known that brain melanoma metastases, renal cell carcinoma, choriocarcinoma, and thyroid carcinoma are more prone to spontaneous hemorrhagic events [54–58]. Intratumoral microhemorrhage is commonly seen in magnetic resonance imaging of patients with gliomas of high-grade and melanoma metastases. However, there is controversy as to whether this image represents a greater risk of bleeding with anticoagulation. Treatment with antiangiogenics such as bevacizumab increases the risk of hemorrhagic events in

patients undergoing anticoagulation; however, it is not a contraindication in these cases [59, 60].

We consider a contraindication for anticoagulation if the patient has an intracranial hemorrhage in less than 48 h, severe coagulopathy, and a platelet count below 50,000/μL. As discussed in this chapter, patients at high risk for arterial thromboembolic complications (e.g., atrial fibrillation) undergoing invasive procedures may have their anticoagulation restored within 48 h under strict neurological monitoring. Whenever possible, however, we choose to wait 7–14 days in patients at a lower risk [52]. The implantation of the vena cava filter is an alternative in preventing pulmonary thromboembolism in individuals with deep venous thrombosis of the lower limbs [61, 62]. When anticoagulation can be safely resumed, the filter is removed, and medication is restarted.

Choice of Anticoagulant

Low molecular weight heparins (LMWH) are more effective and safer than warfarin in cancer patients' treatment [63]. The emergence of direct oral anticoagulants (DOACs) has made these drugs, especially rivaroxaban, edoxaban, and apixaban, become the first option in patients considered a low hemorrhagic risk (without lesions of the gastrointestinal tract, genito-urinary, and with preserved renal function) [64–67]. However, data in patients with CNS tumors are still scarce to keep LMWH as the first option in these individuals. In cases where the hemorrhagic risk is higher, we prefer the use of unfractionated heparin (UFH), which has a shorter half-life and reversible effect with protamine sulfate, until the clinical condition stabilizes.

Prophylaxis

The frequency of VTE in the perioperative period of patients with CNS tumors is between 10% and 15% [68–70]. As described in the chapter, the immediate use of intermittent pneumatic compression and the prescription of HBMP or UFH 24–48 h after the procedure are measured safe [71–75]. These preventive measures should be maintained until the patient can walk again. For outpatients, chemical prophylaxis is not routinely indicated.

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Chapter 9
Anesthesia for Vascular Surgery

Claudia Marquez Simões

9.1 Preoperative Evaluation

Oncologic patients scheduled for surgical procedures tend to be high-risk patients due to many different underlying conditions. This may be a challenge for the anesthesiologists because all surgical procedures in cancer patients have high priority and should not be delayed [1]. Preanesthetic evaluation is useful to identify any potential risks that can be mitigated. In the vascular surgery patients, the risk may be related to patient medical conditions or to the surgical procedures or even both.

Hypertension, diabetes, coronaropathy, myocardial, valvular heart, renal, respiratory, and cerebral vascular diseases are often conditions present in these patients. So, the preoperative evaluation should be detailed and should identify clearly all risks. Regular preoperative guidelines sometimes do not suit for all situations [2], because sometimes we will not have enough time to make all optimizations that sometimes are possible. That is why anesthesiologists should always consider cancer patients as special patients that are scheduled always for urgent procedures. Time is essential in this specific population.

A very useful and simple classification used by anesthesiologists is the American Society of Anesthesiologists (ASA) physical status classification [3], described in Table 9.1.

The physical status classification refers only to the patient's medical condition and does not consider the surgical procedure. There are many studies showing a great variation in this classification between different physicians, but despite the great variability it is still one of the most used classifications to describe the patient's physical condition and it is pretty accurate [4].

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Table 9.1 ASA physical status classification

[a]ASA physical status classification	Definition	Adult examples, including but not limited to:
ASA I	A normal healthy patient	Healthy; non-smoking; no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; one or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN; COPD; morbid obesity (BMI ≥ 40); active hepatitis; alcohol dependence or abuse; implanted pacemaker; moderate reduction of ejection fraction; ESRD undergoing regularly scheduled dialysis; premature infant PCA < 60 weeks; history (>3 months) of MI, CVA, TIA, or CAD/stents
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (<3 months) MI, CVA, TIA, or CAD/stents; ongoing cardiac ischemia or severe valve dysfunction; severe reduction of ejection fraction; sepsis; DIC, ARD, or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm; massive trauma; intracranial bleed with mass effect; ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

Modified from: Abouleish et al. [3]

[a]The addition of "E" denotes Emergency surgery. (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)

Abbreviations: *BMI*: body mass index; *ESRD*: end stage renal disease; *DM*: diabetes mellitus; *HTN*: hypertension; *COPD*: chronic obstructive pulmonary disease; *PCA*: post conceptual age; *MI*: myocardial infarction; *CVA*, cerebrovascular accident; *TIA*, transient cerebral ischaemic attack; *CAD*, coronary artery disease

Another important aspect of the preoperative evaluation is the previous use of medications, radiotherapy, or chemotherapy. We have to pay attention even to natural herbal supplements that may have important perioperative effects. For instance, ginger inhibits the activity of CYP3A4, CYP2C9, and P-gp enzymes, enzymes responsible for many drugs' metabolism [5]. Another important aspect of the dietary supplements is their interference on coagulation and also hemodynamics. Bleeding

risks of garlic, ginkgo, ginseng, green tea, saw palmetto, St John's wort, and fish oil are reported. Cardiovascular instability was observed with ephedra, ginseng, and kava [6].

Regarding the surgical procedures, there is a wide range of surgeries involving vascular interventions. We can face a complex patient with no more venous access who is going to have a port-a-cath implantation under sedation. This is a good example, because it is a simple surgical procedure but may be very challenging for the anesthesia team due to the lack of peripheral veins that will be necessary to assure patient safety and also to provide sedation for the patient comfort. Sometimes due to the lack of peripheral veins inhalational anesthesia may be an alternative in extreme cases, even in adult patients, and general anesthesia may be necessary even for such a procedure that can be done under local anesthesia. As we can see through these examples, the oncologic patient can be unpredictable and we should keep our minds open and consider all alternatives to make the surgical procedure safely feasible.

For some surgical procedures with vascular interventions, mainly during cancer resections, the anesthesiologist must include as one of its important targets in anesthesia planning to have some large bore catheter for fluid infusion. In cancer resections we can face challenging ressections, with non conventional anatomy and neovascularization, near or even with invasion of great vessels. It is an important aspect to be considered by the whole surgical team, especially if the team does not work very often with such patients. Onco-anesthesia can be considered an emerging subspecialty, and teamwork, communication, and crisis resource management

Fig. 9.1 Key points for crisis resource management

besides the technical skills are some important competencies for these professionals (Fig. 9.1).

9.2 Anesthesia in Cancer Patients

Surgery is associated with neuroendocrine metabolic responses such as inflammatory/immunological responses. Perioperative immune suppression can favor tumor cell proliferation leading to metastases. Some anesthetic agents or techniques may influence immune functions, and recent studies consider that anesthesia may also play an important role in the surgical cancer treatment (Fig. 9.2) [7].

During the perioperative period, some cancer cells may eventually spread and if they find immunosuppression of the essential barriers that protect us against cancer cells they may escape and find a good condition to develop and may be related with long-term cancer recurrence [8].

It might seem unlikely that any aspect of anesthetic management, lasting a few hours, could influence recurrence of cancer many years later. But the perioperative period produces substantial biologic perturbations, such as intense stress, that activate many signaling pathways, with suppression of our major defenses against cancer for some days, so it is really possible that the perioperative period plays a major role in the whole cancer development process [9] (Fig. 9.2).

Preclinical studies found that some anesthetic agents such as propofol may influence specially natural killer (NK) cell function [8], modulate matrix metalloproteinase [10, 11], and may even affect miRNA expression [12]. There are still some conflicting data and we can make several observations that may justify different results from these studies. First of all, tumors are not the same, so ideally these studies should look for specific tumors, in the same TNM classification, with the same previous treatments before surgery, in similar patients, but it is very difficult to control all these factors.

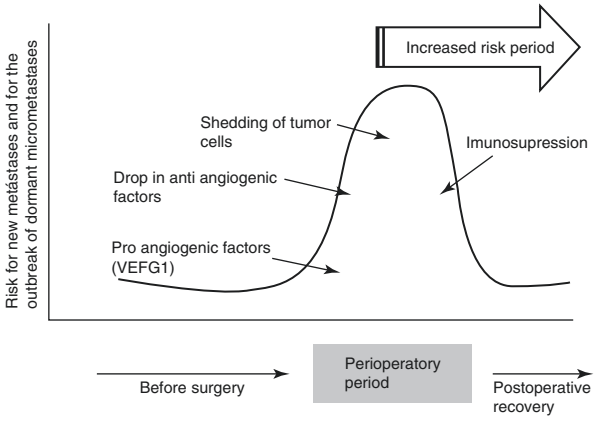

Fig. 9.2 Risk factors for tumor spread in the perioperative period. (Modified from: Ben-Eliyahu et al. [8])

Volatile anesthetics impair many immune functions, so they may play a deleterious role. An important mechanism of action of the inhaled anesthetics is the upregulation of the hypoxia inducible factor 1α and phosphoinositide 3-kinase-Akt pathway signaling and the antiapoptotic properties, all of which may promote proliferation of minimal residual disease as demonstrated previously [13].

In 2020, we already have clinical studies results comparing different anesthesia techniques regarding cancer outcomes. As discussed by many authors, all the results are still questionable due to many study design limitations. Some prospective trials are on their way and may help to clarify the actual role of anesthetic agents in this specific population, but we already know that anesthesia effects are much more important in the whole patient care than it was considered some decades ago. The anesthesiologist must study cancer development basis and understand how their actions may influence it. Available data at this moment suggest that propofol-total intravenous anesthesia reduces cancer recurrence and improves survival, and its benefit is most probable in patients having major surgeries [9].

Opioids also play an important role and are a very frequently used medication during the perioperative period. These drugs have also negative effects regarding tumor development. The improved risk for neoangiogenesis and metastases related to opioid can be justified by immunosuppressive, pro-inflammatory, and pro-angiogenetic effects [14].

On the other hand, despite the used agents, anesthesiologists and surgeons must be concerned with pain control. We must not forget that pain is also an important immunosuppressive mechanism [15].

The complete interaction from opioids and the immune system is not completely understood, but it seems that the immune modulation occurs via a combination of direct actions on the immune cells, via the hypothalamic-pituitary-adrenal (HPA) axis, or even both [15]. These effects can also be peripheral or central as described in Fig. 9.3.

It is important to mention that the central mechanism of action is important and can be confirmed by the observation that opioids that cross the blood–brain barrier exert more immune modulatory effects than opioids that do not cross the blood–brain barrier.

Acute administration of opioids can alter sympathetic system outflow altering immune function, as ganglion stimulants. These sympathetic effects can promote depression of natural killer (NK) cell activity and suppression of peripheral blood

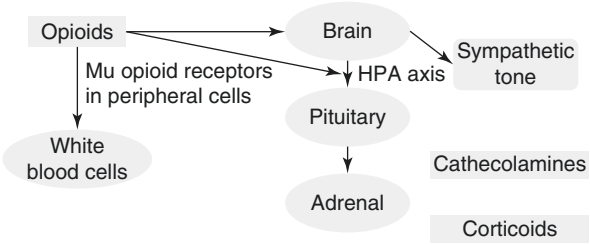

Fig. 9.3 Potential sites of immunomodulatory effects of opioids: both central and peripheral effects. (Modified from Al-Hashimi et al. [15])

lymphocyte proliferation. There are certainly still many questions regarding all these interactions and effects, especially considering the clinical response, but it is a trend to try to avoid at least high opioid doses, and through this strategy we can also avoid other opioid effects such as nausea, vomiting, ileus, somnolence, among others.

9.3 Postoperative Care

The opioid-sparing strategy based on previous presented concept is one of the recent recommendations to the anesthesia in cancer patients. And this strategy may have other benefits, leading us to some current concepts of the postoperative care.

To achieve a successful reduction in opioid use, one important strategy is the multimodal analgesia. The concept is to use different analgesics together, so that we can reduce the total dose of each one, reducing also its adverse effects. Everyone has to keep in mind that using different analgesics, there is synergy, so that is why we can usually reduce the total doses. An important strategy that can also take part in multimodal analgesia is regional anesthesia. Peripheral or neuraxial blockades have an important role in postoperative analgesia and can also reduce or even avoid the use of opioids. There are few side effects of regional anesthesia and respecting the safety issues and excluding the contraindications, it may always be considered in order to compose the multimodal analgesia. Opioid-free or sparing strategies can be feasible, relying on non-opioid adjuncts and regional anesthesia, without negative impact on perioperative pain management [16].

Enhanced surgical recovery programs (ESRPs) or fast-track surgery programs should be our main target considering perioperative care. Through these concepts the postoperative recovery has been changing in the recent years, and for cancer patients this is something very important for many different reasons. The success of this strategy is not only related to intraoperative care, but also related to postoperative care. Good analgesia, rapid emergence from anesthesia, and normothermia are some of the mainstem points of postoperative care that can make possible the early feeding and ambulation. It may seem simple, but believe this is much more complex and goes beyond anesthesia. To have success and have a good postoperative recovery it is essential to have not only good anesthetic care, but also a multidisciplinary team, engaged and working together [17].

An important concept recently described is the time to return to intended oncologic therapy (RIOT). RIOT has been suggested as an outcome measure for perioperative cancer programs and assessing the value of an enhanced recovery, so it is easy to see that there is no place anymore for the old postoperative care, with lots of opioids for analgesia and long postoperative fasting times. Early feeding and ambulation can be started as soon as possible, even in the postanesthesia care unit, a completely new model that must involve all team: surgeons, nurses, and anesthesiologists.

9.4 Conclusion

Anesthesia is having great improvements in the last decades, specially onco-anesthesia as a growing subspecialty that will help surgeons and patients in their cancer treatments, trying to make the whole process always safe and comfortable; and if the initial findings continue to be proved in the forthcoming clinical trials, the anesthetic techniques may play an important role as adjuvant in the perioperative cancer care, allowing a short time to return to oncologic treatment.

Editor's Comments

Cancer patients and patients with peripheral vascular diseases, especially arterial ones, are considered higher surgical and anesthetic risk.

Risk factors for arterial diseases, such as advanced age, systemic arterial hypertension, smoking, and obesity, are also risk factors for several types of cancer, such as lung, colorectal, breast, and prostate cancer [18–20]. Thus, perioperative care are similar for these two clinical situations.

Venous puncture to guarantee central access can be challenging, especially in oncological surgeries in the cervical territory or patients with a history of cervical surgery and/or radiotherapy, in which there may be a distortion of the normal anatomy and thrombosis or ligation of neck veins, such as the internal jugular, in addition to scar changes in the skin and subcutaneous cellular tissue. Cervical lymphadenomegaly can also hinder obtaining central access to veins that drain into the vena cava system. Ultrasound-guided puncture is essential to minimize the risks of the procedure [21].

The invasive monitoring of blood pressure, necessary in more extensive operations, also requires care in cancer patients. Due to the concomitance of risk factors with arterial diseases, calcifications in the arteries can hinder puncture and increase vascular occlusion risk. Prior assessment of the integrity of the palmar arch (e.g., through Allen's test) is essential to avoid the hand's ischemic complications. Puncture of lower limb arteries should also be avoided as much as possible, where the atherosclerotic disease is more frequent. Invasive blood pressure monitoring is usually maintained postoperatively in intensive care units and should be removed as soon as possible.

Vascular Surgeries on Cancer Patient

Even for smaller procedures, such as the implantation of tunneled catheters, there are particularities concerning the anesthetic act. First, monitoring and the anesthesiologist's presence are essential, regardless of the type of anesthesia chosen (the

editors' preference is for sedation associated with local anesthesia in most cases) [22, 23]. The puncture of deep veins, even if eco-guided, is not without risks. Inadvertent arterial puncture, remembering that cancer patients with some frequency have platelet counts below normal levels, can cause cervical hematoma that impairs ventilation. The intravascular navigation of devices such as guidewires, dilators and sheaths, and the catheter itself can trigger cardiac arrhythmias that eventually go unnoticed by the surgeon, concentrated on the surgical act. Thus, even using local anesthesia, monitoring the patient's vital signs by an anesthetist is essential.

Not infrequently, patients referred for tunneled catheter implantation have difficulty in peripheral venous access, and often, as in patients treated for breast cancer, there may be a restriction of a limb for puncture as a result of axillary emptying.

Patients with deep venous thrombosis of lower limbs in the acute phase and who will have to interrupt anticoagulation for a more extended period due to the need for a more extensive oncological operation are usually candidates for the inferior vena cava filter implant. This device is usually implanted in the same anesthetic act as the oncological procedure after anesthetic induction. In these cases, we prefer access by puncture of the internal jugular vein since, after releasing the filter in the infrarenal vena cava, we pass the guidewire and, after removing the filter introducer, we leave a double-lumen catheter in a central position (cavo-atrial junction), saving the patient a new puncture.

The other vascular surgeries are performed with a preparation similar to that of the non-cancer patient, with particular attention to the platelet count, in addition to avoiding invasive procedures in individuals with severe neutropenia (<500/μL).

Oncologic Surgeries

When tumor resection occurs en bloc with large vessels, the patient receives unfractionated heparin 80 IU/kg before vascular clamping. In the case of venous reconstruction, anticoagulation is usually maintained in the postoperative period, and the anesthetist must take the necessary precautions before removing any epidural catheter maintained for postoperative analgesia. Arterial reconstructions do not usually require anticoagulation maintenance, regardless of the use of autologous or synthetic substitutes [24, 25].

Anticoagulated Patient Care

Anticoagulated patients should have their medication suspended before invasive procedures for a period varying according to the hemorrhagic risk (Table 9.2).

Table 9.2 Anticoagulant suspension time for invasive procedures according to hemorrhagic risk

Anticoagulant medication	Anticoagulant suspension time	Type of operation according to hemorrhagic risk
UFH (prophylactic dose)	12 hours (h) 24 h	Minimum/low risk High/very high risk
UFH (therapeutic dose)	6 h (ev); 12 h (sc) 6 h (ev); 24 h (sc)	Minimum/low risk High/very high risk
LMWH HNF (prophylactic dose)	12 h 24 h	Minimum/low risk High/very high risk
LMWH HNF (therapeutic dose)	24 h 48 h	Minimum/low risk High/very high risk
DOAC	24 h 48–72 h	Minimum/low risk High/very high risk
Warfarin	24 h 5 days 7 days	Minimal risk Low risk High/very high risk

Abbreviations: *DOAC* direct oral anticoagulants; *LMWH* low molecular weight heparin; *UFH* unfractionated heparin

Note: DOAC (rivaroxaban, edoxaban, apixaban, dabigatran) ensured via intravenous administration or via subcutaneous administration

Examples of risky procedures are as follows:

- Minimal: small dermatological operations, arthrocentesis, endoscopy without biopsy
- Low: coronary angioplasty, arthroscopy, laparoscopic cholecystectomy, endoscopy/bronchoscopy with biopsy, prostate/bladder/thyroid biopsies, removal of the definitive central venous catheter
- High: major oncological/vascular/thoracic/abdominal/orthopedic surgery, head and neck surgery, reconstructive plastic surgery, colonoscopy polypectomy, liver/kidney biopsy
- Very high: neurosurgery (intracranial or spinal), which includes cerebrospinal fluid (CSF) puncture and neuraxial block, cardiac surgery, urological surgery

In the case of hemorrhagic complications, suspension of the medication is often sufficient. It is worth remembering that the anticoagulant effect depends on the medication's half-life and the patient's renal and hepatic functions (the latter to a lesser extent). We considered a complete resolution of the anticoagulant effect equivalent to five half-lives after the last dose administered. Table 9.3 shows the half-life and the fraction of renal excretion of each drug.

Patients with significant bleeding and immediate risk of life should be kept under intensive monitoring for hemodynamic support with volume replacement and transfusion of blood products as deemed necessary (packed red blood cells, platelets if associated thrombocytopenia), maintenance of body

Table 9.3 Half-life and rate of renal excretion of the principal anticoagulants

Anticoagulant	Half-life/renal excretion
UFH	1 h/50%
LMWH	5–7 h/40%
Apixaban	8–15 h/25%[a]
Edoxaban	6–11 h/50%[a]
Rivaroxaban	5–9 h/35%[a]
Betrixaban	19–27 h/11%[b]
Dabigatran	12–17 h/80–85%
Warfarin	20–60 h/hepatic elimination

Abbreviations: *LMWH* low molecular weight heparin; *UFH* unfractionated heparin
[a] Severe liver failure may increase the serum level of the drug
[b] Not recommended for patients with liver failure

temperature, blood pH, and attention hydroelectrolytic disorders, especially serum calcium.

The anticoagulant action of unfractionated heparin (UFH) is monitored by the activated partial thromboplastin time (aPTT), while the measure of anti-factor X activity (aFXa) assesses low molecular weight heparins (LMWH). Warfarin is monitored for prothrombin time (TP). Anticoagulation with DOAC is not routinely monitored in the laboratory. Concerning dabigatran, a standard measure of thrombin time (TT) can eliminate the possibility of the persistence of the anticoagulant effect of this drug. Due to TT's high sensitivity concerning dabigatran, an altered test can occur even with the smallest amount of the drug circulating. The measurement of aFXa activity for rivaroxaban, edoxaban, apixaban, and betrixaban requires tests precisely calibrated to assess these drugs' actions, which is not always available in an emergency. In any case, regardless of calibration, the absence of aFXa activity indicates no relevant effect of this DOAC—studies with betrixaban are more scarce [26].

An anticoagulated patient with active bleeding can be approached only with the suspension of anticoagulation and clinical observation. Other therapies may be necessary such as removal of the anticoagulant with activated charcoal (in the case of DOAC), and/or hemodialysis (useful only for dabigatran: 50–60% elimination by hemodialysis), use of antifibrinolytic agents (such as tranexamic acid), coagulation factors (prothrombin complex concentrate) or specific antidotes (protamine sulfate for heparins, idarucizumab for dabigatran, andexanet alfa for other DOAC), surgery or some other invasive procedure for direct hemostasis (Table 9.4) [27–31].

There is a lack of literature data for reversing the effects of direct oral anticoagulants (DOAC), which is why some services restrict this option to cases in which there is an imminent risk of life, weighing the hemorrhagic risk with the risk of new

Table 9.4 Alternatives for reversing anticoagulant activity and laboratory control tests for the main anticoagulants

Anticoagulant	Anticoagulation reversal	Laboratory control test
HNF	Protamine 1 mg/100 IU and slow (maximum 50 mg) Tranexamic acid 1 g ev 6/6 h	TTPa
LMWH	Protamine 1 mg/1 mg of enoxaparin or 1 mg/100 UI of dalteparin and slow ev Tranexamic acid 1 g ev 6/6 h	TTPa aFXa
Warfarin	Vitamin K1 10 mg and slow ev CCP (50 IU/kg v bolus) PFC (10–15 mL/kg ev in 4–6 h) Tranexamic acid 1 g ev 6/6 h	TP (INR)
DOAC	Coal 50–100 g vo; repeat every hour CCP (50 IU/kg v bolus) Tranexamic acid 1 g ev 6/6 h Specific antidotes: Idarucizumab: dabigatran Andexanet alfa: apixaban, edoxaban, rivaroxaban, betrixaban	TT (dabigatran) aFXa

Abbreviations: *AFXa* anti-factor X activity; *CCP* non-activated prothrombin complex concentrate with four coagulation factors; *INR* international normalized ratio; *LMWH* low molecular weight heparin; *PFC* fresh frozen plasma; *TP* prothrombin time; *TT* thrombin time; *TTPa* activated partial thromboplastin time; *UFH* unfractionated heparin

thromboembolic episodes, increased by some drugs used for this purpose (such as andexanet alfa and prothrombin complex concentrates—CCP).

The use of protamine sulfate to reverse heparins and vitamin K1 for warfarin is more well established. For patients using DOAC, in cases of an imminent threat to life, we suggest using a product with a prohemostatic action (CCP or specific antidote) or an antifibrinolytic agent (tranexamic acid, epsilon-aminocaproic acid). Due to lack of literature on DOAC anticoagulation, it is recommended to avoid the use of activated recombinant factor VII (rFVIIa), plasma, or cryoprecipitate.

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Part II
Clinical Oncology and Oncohematology

Chapter 10
Vascular Surgery and Medical Oncology

Rubens Copia Sperandio and Gustavo Schvartsman

Abbreviations

ADP	Adenosine diphosphate
ATE	Arterial thromboembolism
CLABSI	Central-line-associated blood stream infection
CNS	Central nervous system
COX-2	Cyclooxygenase 2
CP	Cancer procoagulant
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
EGFR	Epithelial growth factor receptor
FGFR	Fibroblast growth factor receptor
HCC	Hepatocellular carcinoma
HIT	Heparin-induced thrombocytopenia
IL-1	Interleukin-1
IVC	Inferior vena cava
mAbs	Monoclonal antibodies
PAI-1	Plasminogen activator inhibitor type I
PDGFR	Platelet-derived growth factor receptor
PE	Pulmonary embolism
PICC	Peripherally inserted central catheter
polyP	Polyphosphates
RCC	Renal cell carcinoma
SIRT	Selective internal radiation therapy
TF	Tissue factor

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TKIs	Tyrosine-kinase inhibitors
TNF	Tumor necrosis factor
TSP-1	Thrombospondin-1
VCF	Vena cava filter
VEGFR	Vascular endothelial growth factor receptor
VTE	Venous thromboembolism
vWF	von Willebrand factor

10.1 Introduction

Vascular Surgery and Medical Oncology are closely related and often overlapping medical specialties. Cancer pathogenesis and particular aspects of oncological treatment confer unique considerations regarding susceptibility to vascular complications. Examples of this interplay include—but are not limited to—an increased risk and incidence of venous and arterial thromboembolic events and hemorrhagic complications. Also, subjects of interest of both specialties include the placement of centrally positioned endovascular devices, in order to safely deliver irritant and/or vesicant antineoplastic agents and organ-directed therapies, such as chemoembolization and selective internal radiation therapy (SIRT), which are reached by endovascular techniques.

10.2 History of Cancer Treatment

Over the centuries, cancer treatment relied initially on local approaches such as surgical resection of tumors and, more recently, application of radiation therapy to a surrounding field. Since the first procedures, concepts of vascular surgery were applied as strategies to optimize vascular control and to avoid hemorrhagic complications commonly seen in early interventions. It was only in the last century that, by a portion of fortune and after accomplishing the successful development of cancer preclinical models, antineoplastic systemic therapies have begun to be discovered and implemented in clinical practice. World War II was the landmark of this serendipitous finding. After an accidental spill of mustard gas in an Italian harbor, bone marrow and lymph node depletion of victims was observed. Further, preclinical tumor-transplanted models were exposed to this same group of chemical agents, showing a marked regression of lesions. In 1943, scientific progress led to the first clinical trial of a chemical agent—nitrogen mustard—in a single patient with advanced non-Hodgkin's lymphoma complicated with airway obstruction. This intervention had positive results, with a temporary improvement in clinical parameters. Subsequently, larger trials were conducted and ultimately led to the approval and clinical use of several alkylating agents such as cyclophosphamide, which is still an important drug nowadays [1].

The following decades were marked by the discovery of different classes of antineoplastic agents, notable cytotoxic chemotherapy, in order to treat malignancies. The rationale behind it is that these substances act at specific phases of the cell cycle, impairing the process and consequently leading to cell death. These drugs can be classified as alkylating agents, antimetabolites, antitumor antibiotics, topoisomerase inhibitors, mitotic inhibitors, among others [2]. High-proliferative cells such as malignant clones are more prone to the therapeutic effects of chemotherapy, as they go through the cell cycle more rapidly and frequently than normal counterparts. Unfortunately, these agents have low specificity against tumor cells and their action also affect healthy cells. This drawback explains why these treatments are highly toxic and dose-limited [3].

As the knowledge regarding cancer biology advanced, an improved understanding of the molecular characteristics of each type of cancer and the signaling proteins and pathways involved in carcinogenesis led to the discovery of targeted therapies. Drugs were developed aiming at disrupted pathways—usually involved in regulation mechanisms that are related to cell proliferation and tumor growth—and have been under the spotlight since the 1990s. Targeted therapies are mainly consisted of tyrosine-kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) that aim to block one or more of the specific mentioned pathways [4, 5].

The first applications of this class of antineoplastic agents were the Bcr-Abl tyrosine kinase, epithelial growth factor receptor (EGFR), and vascular endothelial growth factor receptor (VEGFR). By blocking the transducing signal, the TKI controls cell proliferation and the growth of neoplastic tissue. However, in contrast to what was previously thought—and similarly to cytotoxic chemotherapy—these treatments also demonstrated a high rate of adverse events and toxicities, as they too have low specificity and interfere with cells and pathways across the whole organism [6].

Additionally, medical knowledge regarding the relationship between cancer development and how the host's immune response reacts has been advancing substantially in the past years. The identification of immune checkpoint proteins and the development of molecules that block the tumors' inhibition of the immune response are revolutionizing the treatment and prognosis of highly aggressive types of cancer, such as melanoma and non-small cell lung cancer, even when diagnosed in advanced stages. Despite the recent major advances in the field, reliable biomarkers to accurately predict response are still lacking and the management of immune-related toxicities can be very challenging, since the hyperactivation of immunity may impair tolerance to self and attack physiological host tissues [7].

10.3 Angiogenesis: A Hallmark of Cancer

A proper understanding of pathogenic features of cancer is important to better select and apply treatment options. The concept of "*hallmarks of cancer*," initially proposed by Hanahan and Weinberg in 2000 and revisited in 2011 [8], is defined as the

set of biological skills that cancer cells acquire in a multistep process in order to become tumorigenic and malignant (Fig. 10.1). These include mechanisms that initiate cell proliferation, sustain proliferative signaling, bypass regulatory processes that would inhibit uncontrolled growth, escape cell death and immune destruction, change the cell metabolism, and enable invasion and spread. Among these, the capability of tumor cells of inducing angiogenesis is a key feature of cancer.

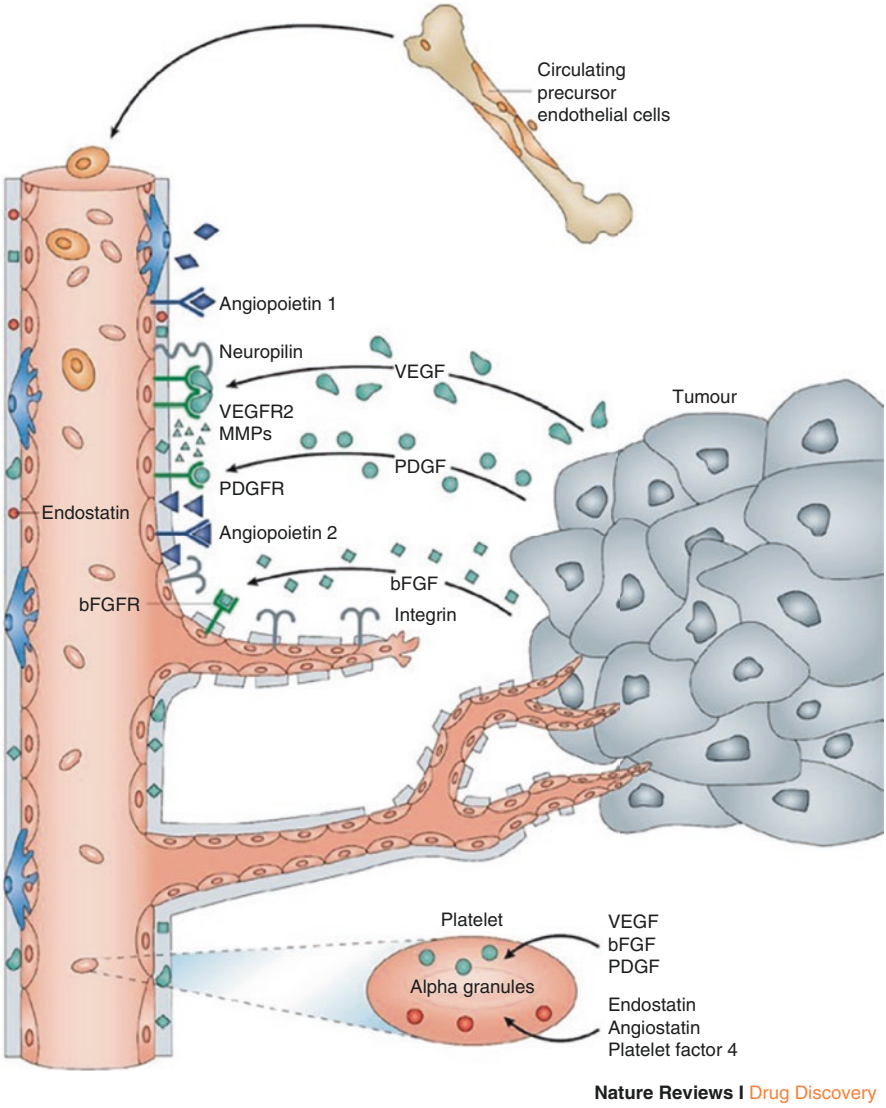

Fig. 10.1 Angiogenesis is a hallmark of cancer. (Reference: Folkman [49])

The formation of new vessels is an early step required for tumor growth, in order to pave the way for nutrients and oxygen to be delivered to highly demanding malignant cells [9]. Early in the embryogenesis, this phenomenon occurs as a physiologic process divided in two main steps: vasculogenesis, defined as the endothelial cells' migration and tubular disposition; and angiogenesis, which is the sprouting of new vessels from previously existing ones. Later, vasculature turns quiescent and undergoes transient activation as needed in situations such as wound healing and female reproductive cycles. However, as part of the carcinogenic process, an event called "*angiogenic switch"* may happen, leading to sustained formation of new vessels as a response to the predominance of angiogenesis-stimulating factors outweighing inhibitory signals.

The stimulatory pathway that has been most extensively studied and is a target for multiple medical treatments is the one encoded by the gene *VEGF-A*, which leads to the expression of VEGFR-1, VEGFR-2, and VEGFR-3 [10]. This family of membrane receptors generates a signal that is regulated at multiple levels, by situations such as hypoxia and oncogene activation, causing upregulation of these receptors and, hence, stimulating the proangiogenic pathway. Besides being an angiogenic stimulatory pathway, vascular endothelial growth factor (VEGF) is also proven to be protective and regulate endothelial function by inhibiting apoptosis and inflammation [11]. Through the production of nitric oxide, it is associated with antiplatelet effect, inhibition of leucocyte adhesion, and diminished proliferation of vascular smooth muscle cells. Many other targetable molecules are involved in proliferation signaling, such as fibroblast growth factor receptor (FGFR). It has been an ongoing field of study, and multiple pathways have been described. In general, their net result is a common inductive signal. On the other hand, inhibitory agents to the angiogenesis process include thrombospondin-1 (TSP-1), fragments of plasmin (angiostatin), and type 18 collagen (endostatin), among a dozen others. However, their clinical use is still experimental.

When the angiogenic switch is permanently activated, the formed vessels are aberrant, with findings of precocious capillary sprouting, excessive vessel branching, distorted and enlarged vessels, erratic blood flow, abnormal levels of endothelial proliferation and apoptosis, and microhemorrhages due to the leakage of plasma into parenchyma. These neovessels play an important role by interacting with normal cells that are recruited to the site of disease and forming the stroma. Altogether, these elements constitute the "tumor microenvironment," a complex scenario where a number of pathogenic processes initiate and perpetuate giving cancer its autonomous and invasive properties. Additionally, it is noteworthy to mention that pericytes, bone-marrow-derived cells that act as vascular progenitor cells, are supportive elements to the endothelium that are also involved in the angiogenic process.

Highly vascularized tumors, such as hepatocellular carcinoma (HCC), renal cell carcinoma (RCC), gliomas, and others—often chemotherapy-refractory tumors—are more prone to responding to agents that target angiogenesis. A summary of the main agents and indications targeting the angiogenic pathway is displayed in Table 10.1.

Table 10.1 Antiangiogenic approvals

Agent	Indications	
Bevacizumab	Metastatic colorectal cancer (mCRC) Non-small cell lung cancer (NSCLC) Renal cell carcinoma (RCC)	Ovarian cancer Cervical cancer Glioblastoma multiforme (not in Europe)
Ramucirumab	Advanced gastric cancer Non-small cell lung cancer (NSCLC) Metastatic colorectal cancer (mCRC)	
Multi-kinase TKIs (sunitinib, sorafenib, pazopanib, vandetanib, cabozantinib, axitinib, Lenvatinib, and regorafenib)	Renal cell carcinoma (RCC) Hepatocellular carcinoma (HCC) Gastrointestinal stromal tumor (GIST) Refractory thyroid cancer	Pancreatic neuroendocrine tumors (pNET) Soft tissue sarcoma (STS) Refractory chronic myeloid leukemia (CML) Refractory metastatic colorectal cancer (mCRC)

10.4 Cancer-Induced Changes in Coagulability

Cancer is largely recognized as a major risk factor for the development of arterial and venous thromboembolism (VTE). The estimated incidence of these complications with clinical manifestations in cancer patients is up to 15% [12]. Temporal relationship between the onset of vascular complications and diagnosis of cancer is variable, and it even may precede the diagnosis of cancer by years [13]. There is a broad spectrum of clinical manifestations, ranging from minor asymptomatic events to life-threatening conditions. For instance, the most common associated types of cancer diagnosed at the time of a VTE event are lung (17%), pancreas (10%), colorectal (8%), kidney (8%), and prostate (7%) [14].

Intrinsic pathogenetic features of cancer patient demographics and comorbidities may contribute to thromboembolic risk in several ways. Cancer type, location, stage, and time since diagnosis influence the incidence of thromboembolic events. Unsurprisingly, advanced cancers are associated with higher risk. Certain types of malignancies, such as pancreatic cancer, central nervous system (CNS) tumors, and multiple myeloma, are more associated with a hypercoagulable state [15, 16]. Additionally, patient characteristics such as age, obesity, history of previous deep vein thrombosis (DVT), use of pacemaker, and medical and surgical interventions may also be contributing factors [17].

The pathophysiological landmark for developing thrombosis is known since the nineteenth century as the Virchow's triad, which is determined by: (1) blood flow stasis, (2) endothelial lesion, and (3) hypercoagulability [18].

First, blood flow stasis is commonly found in cancer patients as a consequence of reduced mobility and bedrest, poor performance status, surgical procedures

leading to prolonged recovery time, direct extrinsic compression of vessels, thrombocytosis, and leukocytosis.

Second, endothelial dysfunction can occur in the context of an infection, secondary to inflammatory cytokines that increase vascular permeability and alter the expression of endothelial surface proteins. Disseminated intravascular coagulation (DIC) is also related to this mechanism. The presence of vascular catheters and administration of antineoplastic agents are other factors that may lead to endothelial changes.

In turn, malignancies are related to hypercoagulability as they can alter the levels and function of coagulation factors. On the one hand, it has been described that tumor cells may produce prothrombotic molecules such as cancer procoagulant (CP) [19] and tissue factor (TF) [20], activating the coagulation cascade and thus leading to thrombin formation. On the other hand, in response to the tumor presence, normal host cells may produce procoagulant molecules such as P-selectin—related to TF exposure—adenosine diphosphate (ADP), and von Willebrand factor (vWF), which also contribute to the prothrombotic state [21–23]. There is also a role for increased platelet reactivity and circulating inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), which are found in up to 50% of cancer patients [24, 25]. These molecules disrupt endothelial function and suppress the endogenous fibrinolytic system activity. Intracellular products and components such as those released by dying neutrophils, as well as the secretion of polyphosphates (polyP)—accentuated negatively charged molecules that activate factor VII and the intrinsic pathway of coagulation)—and expression of *MET*, an oncogene that changes the pattern of expression of plasminogen activator inhibitor type I (PAI-1) and cyclooxygenase-2 (COX-2), also have been implicated in increasing the risk of thromboembolic events [26, 27].

10.5 Treatment-Related Considerations

Besides pathogenic factors of cancer itself, most of antineoplastic treatment options also pose a higher risk of vascular complications. The risk is reported to be higher in the first months after initiating chemotherapy. Both venous thromboembolism—in form of DVT and pulmonary embolism (PE)—and arterial thromboembolism (ATE)—represented by stroke and myocardial infarction—as well as an increased risk of bleeding due to thrombocytopenia and the use of anticoagulants are reported in cancer patients.

Hemostasis components and endothelial function may be affected by cancer treatment in several ways. Coagulation factors, platelet number and function, angiogenic regulatory pathways, and the expression of molecules at the blood–endothelium interface are reported sites of alterations. As it occurs, the fragile balance between pro- and anticoagulant states can become unstable. For example, the antineoplastic interventions can either decrease levels of anticoagulant proteins, for example, antithrombin, protein C, and protein S, or increase prothrombotic activity

via endothelial damage, whether by modifying the expression of proteins in endothelial cells or increasing von Willebrand factor levels. Also, changes in platelet number and function are described, with thrombocytopenia or increased adhesion and aggregation being the most common mechanisms of impaired or exacerbated primary hemostasis, respectively [28].

Agents more commonly associated with these changes include chemotherapeutics such as L-asparaginase, cisplatin, and thalidomide and its analogs; selective estrogen receptor modulators, best represented by tamoxifen; and the antiangiogenic monoclonal antibodies and tyrosine-kinase inhibitors that target VEGFR and EGFR pathways [29].

All TKIs, specially the anti-VEGFR agents, are associated with drug-induced hypertension, which is largely known to be a major risk factor for vascular disease. It is related with a higher incidence of stroke, myocardial infarction, and aortic dissection. Studies also have showed that atherosclerosis, which is another cornerstone of vasculopathy, is reported to be accelerated by anti-VEGFR therapy. This is proposed to be due to a disruption of endothelial cell homeostasis. Structural abnormalities in vessel walls may be induced by the use of antiangiogenic agents and hence render a higher incidence of aneurysms and dissections [30–32].

Bleeding risk is reported to be increased in all VEGFR-targeted agents, since their mechanism of action disturb endothelial function and may lead to poorly formed artery walls, with impaired function of muscular smooth muscle cells and impaired hemostasis. This is of particular concern in shrinking tumors that respond effectively to therapy—related to intracranial bleeding and pulmonary hemorrhage and cavitation, with potential to be life-threatening. As mentioned above, when exploring deeper the angiogenesis process, VEGFR signaling protects and also regulates endothelial function. Therefore, its blockade decreases tumor growth but also causes deleterious effects on normal vessels and cause vascular toxicity.

Treatment-induced myelosuppression decreases platelet count and causes thrombocytopenia, which also increases the risk of bleeding.

Most of available anti-VEGFR agents are not specific to this pathway, targeting multiple different kinases, for example, platelet-derived growth factor receptor (PDGFR), among others. This leads to an effect called "*off-target activity*," altering endothelial function even further, hypothetically causing the surface to switch from a smooth anticoagulant surface with linear blood flow to a prothrombotic structure aggravated by the exposure of phospholipids, collagen, and tissue factor.

When considering the EGFR pathway, an increased risk of bleeding was reported with the monoclonal antibodies cetuximab and panitumumab, but no correlation was made to TKIs erlotinib and osimertinib [33].

Cyclin-kinase-dependent inhibitors—palbociclib, ribociclib, and abemaciclib—used in combination with endocrine therapy for hormone receptor-positive metastatic breast cancer, have also been associated with an increased risk of thromboembolic events [34].

Moreover, supportive measures and other adjuvant interventions commonly used in cancer treatment, such as erythropoiesis-stimulating agents for treating anemia [35] and corticosteroids, [36] are recognized to also play a role in inducing vascular

changes and contribute to the risk of vascular complications. In summary, oncologic treatment may lead to both bleeding and thrombotic events, depending on tumor context and hematological adverse events observed throughout therapy.

10.6 Vascular Accesses and Oncologic Treatment

With the evolution of cancer treatment to a multimodality approach, long-term reliable intravascular access to intermittently deliver irritant and vesicant agents, and parenteral nutrition, as well as to allow frequently blood drawing became a standard requirement. As multiple devices are developed, medical oncologists and vascular surgeons must become familiar with their concepts and indications, manufacturing materials, placement techniques, maintenance care, and possible complications.

Selection of the most appropriated device should take into account the type of antineoplastic regimen, duration, and frequency, as well as patient convenience and comorbidities, advantages, drawbacks, and risks of each option. Catheters are usually inserted into the central venous system, and their extremities can be classified as external or implantable, that is, under the skin, into the subcutaneous tissue.

The external ones can be further separated in tunneled and non-tunneled catheters; the former is used for longer periods and depends on the creation of a subcutaneous tunnel, while the latter is the fastest to insert and its use is recommended for up to 14 days, being removed as soon as it is no longer needed. Peripherally inserted central catheters (PICCs) are a more durable alternative, usually inserted by specialized nurses or interventional radiology teams into the upper limb veins and introduced until the superior vena cava. Despite minimizing the risk of pneumothorax or vascular injuries and having a similar risk of infection, PICCs are more associated with thrombosis than central catheters, demand more routine maintenance, and cause more discomfort to patients [37, 38].

In turn, implantable devices such as medical ports and continuous infusion pumps minimize exposure of the vascular system to the environment as they are fully covered by skin and their access is percutaneous. Their placement is a surgical procedure realized in an operation room or in an interventional radiology suite, with local anesthesia and sedation. After the procedure, a device called port is located in a pocket at the anterior thoracic wall; a special needle is used to gain access to the catheter through the portal device and the device must be heparinized in a periodic manner. This access is commonly used for antineoplastic treatments as many current chemotherapy regimens are offered in an intermittent schedule with few days or weeks apart from one cycle to another. With good maintenance, these devices may remain working and with no complications for several years. Moreover, as cancer patients often need contrast-enhanced scans to stage, assess response, and follow-up, a more resistant device in which is permitted to administer contrast has also been developed. Despite being low, the risk of complications, for example, infection and pneumothorax that may require surgical management, is relevant and must be considered [39].

The general principles when choosing the most appropriated device is to consider the expected length of use; try to select a catheter with the minimum number of lumens possible, as it is directly related to infection rates [40]; assess the vascular anatomy and previous use of devices, and the team's expertise. Catheter types, indications, and notes are summarized in Table 10.2.

Catheter complications can be divided into immediate and delayed. Immediate complications often arise secondary to the procedure itself. The most common is pneumothorax, followed by vascular injury leading to hematomas, and arrhythmias. Thrombosis and infection are the more relevant long-term complications [41].

Up to 50% of cancer patients may develop thrombotic complications, but only 5–10% are clinically relevant. As expected, the risk of clotting is higher due to endothelial damage by the presence of a foreign body and it is aggravated with a concomitant infection, mispositioning of catheter tip, or other patient's contributing factors such as altered anatomy, stenosis, compression, prior clots, or prothrombotic states [42]. Prevention of clot formation with flushes of heparinized saline and treatment with thrombolytics may prevent or reverse the flow obstruction [43]. Phlebitis, deep vein thrombosis, and embolism—pulmonary or paradoxical—are the main

Table 10.2 Overview of centrally intravascular devices (excludes peripheral short-term catheters such as Jelco and Intima)

Length of stay	Type	Subcutaneous manipulation	Catheter	Indications	Notes
Short term (up to 14–21 days)	External	Non-tunneled	CVC	Acute conditions, for example, fluid resuscitation, delivery of vasopressors, and hemodynamic monitoring	Fastest to insert, uses landmark of ultrasound guidance, bedside; poses a higher risk of infections and immediate complications
Long-term (months to years)			PICC	Intermediate duration, patient comfort	Can be inserted by specialized nurses and interventional radiology; lower risk of vascular injury and immediate complications; higher risk of thrombosis, more resistance due to longer course
		Tunneled	High flow	Hemodialysis, apheresis	Higher risk of immediate complications
			Low flow	Parenteral nutrition	
	Implantable	All tunneled	Port	Intermittent or continuous delivery of chemotherapy agents	Convenience, durability; need interventional radiology or operation room for placement

Table 10.3 Most commonly used irritant and vesicant chemotherapy agents

Irritants	Vesicants	
Daunorubicin	Ado-trastuzumab emtansine	Fluorouracil
Doxorubicin	Bendamustine	Gemcitabine
Enfortumab vedotin	Bleomycin	Ifosfamide
Epirubicin	Bortezomib	Irinotecan
Idarubicin	Carboplatin	Liposomal doxorubicin
Mitomycin	Carmustine	Melphalan
Vinblastine	Cisplatin	Mitoxantrone
Vincristine	Cyclophosphamide	Oxaliplatin
Vinorelbine	Cytarabine	Paclitaxel
	Dacarbazine	Nab-paclitaxel
	Docetaxel	Topotecan
	Etoposide	

risks of catheter-related thrombosis, but prophylactic anticoagulation has not been well established and is not routinely recommended [44].

Catheter-related infections, which encompass central-line-associated blood stream infections (CLABSI), are less frequent than thrombotic complications but may be critical to a point of requiring removal or exchange of the device. Microbiological studies are mandatory, as resistant microorganisms may be isolated and a course of broad-spectrum systemic antibiotics, usually involving Gram-positive bacteria coverage, with or without antibiotic lock therapy may be necessary [45].

Many chemotherapeutic agents are irritant and/or vesicants. There is a special concern about the potential of extravasation of these drugs, causing severe vascular and soft tissue lesions. Protocols have been developed and, when feasible, antidotes must be used [46]. Table 10.3 summarizes the most used irritant and vesicant chemotherapy agents.

10.7 Other Applications

There is a growing number of distinct scenarios in which the specialties of Vascular Surgery and Medical Oncology have been working together. An emerging field of Interventional Oncology has been lining up to the consolidated modalities of cancer treatment: medical, surgical, and radiation oncology [47]. Also, a novel nomenclature is being proposed for the field of cancer surgeries that require ligation or reconstruction of major vascular structures: oncovascular surgery [48].

As surgical techniques and technology progress, a trend toward minimally invasive procedures is witnessed, aiming to reduce morbidity and improve outcomes, such as shorter length of stay, quicker recovery, and less postoperative pain. Organ-directed therapies often use endovascular approaches as means to achieve the target

location, like transarterial chemoembolization or radioembolization—also known as selective internal radiation therapy (SIRT)—of hepatocellular carcinomas for patients who have localized disease not amenable to surgery or liver transplantation. For renal cell carcinoma, nephron-sparing procedures include embolization as a management option. Other examples include preoperative embolization of head and neck and brain vascularized tumors, such as paragangliomas, meningeomas, hemangioblastomas, and central nervous system metastases; this adjunct intervention is applied with the intention of reducing the risk of bleeding, shortening the operative times, and facilitating the surgical act itself.

Another specialties' overlapping situation relates to those cancer patients who present with VTE in which therapeutic anticoagulation is contraindicated. Moreover, complications of anticoagulation, such as bleeding and heparin-induced thrombocytopenia (HIT), and failure of anticoagulation, through a new episode or worsening of previous DVT or PE under therapeutic anticoagulation, also may require the placement of a vena cava filter (VCF). In special circumstances, insertion of a VCF as a prophylactic measure may also be considered. The procedure is undertaken in an interventional suite and complications include DVT at the insertion site; inferior vena cava (IVC) thrombosis; and filter erosion, fracture, or migration.

Finally, the concept of oncovascular surgery as a medical specialty has been recently proposed. As surgical *en bloc* resection is the cornerstone of several localized but locally invasive tumors, still amenable to a curative approach, tumors that are closely related to major vessels and need vascular ligation or reconstruction at the same time are commonly seen. Malignancies in such massive surgeries in which benefit has been demonstrated include retroperitoneal masses (soft tissue sarcomas, germ cell tumors), tumors arising from vascular structures (angiosarcoma, leiomyosarcoma of the vena cava, paraganglioma), and limb tumors with intention of avoiding amputation.

10.8 Conclusion

This chapter summarized the main aspects by which the medical specialties of Vascular Surgery and Medical Oncology are interrelated. Along the last century, scientific advances in medical knowledge regarding the biology of cancer led to the development of multiple modalities of treatment that have been capable of changing the natural history of this recalcitrant and heterogeneous group of diseases. A better understanding of pathogenic mechanisms put angiogenesis under the spotlight as a hallmark of cancer, and various therapies were developed targeting this pathway. Moreover, cancer as a disease and its treatment options are associated with an increased risk of thromboembolic and hemorrhagic events, sometimes life-threatening and demanding immediate intervention by both medical professionals and surgeons. Moreover, most of cancer patients require a long-term implantable device to safely deliver antineoplastic agents and there are a number of special considerations regarding this intervention, from selecting the best catheter regarding

material, anatomic site, duration, to the inherent risks of procedure and cautions. Other scenarios that both specialties are connected include performing organ-directed local therapies through endovascular procedures, placement of vena cava filters, and developing techniques to resect and reconstruct major vessels during cancer surgery.

Editor's Comments

Cancer, cardiovascular events, and peripheral vascular events are associated in several ways. As pointed out in the comments referring to Chap. 9, several factors that contribute to the appearance of some types of cancer are also associated with the development and worsening of circulatory diseases [50–56].

This chapter details the role of angiogenesis in cancer's pathogenesis and the relationship between the neoplasm itself and the different types of treatment with venous and arterial events, the latter capable of affecting both the cardiovascular and peripheral vascular systems. This topic is also detailed in Chap. 12.

In the arterial territory, complications associated with cancer or its treatment can manifest themselves more severely in a patient with previous atherosclerotic disease, and treatment can also be problematic in these circumstances. Not infrequently, such acute arterial events occur in a patient with abnormal nutritional status (some degree of malnutrition or even cachexia), in addition to immune weakness and coagulation disorders, conditions that increase the risk of eventual surgical treatment. For decision-making concerning some type of more invasive treatment, in addition to the usual clinical parameters, issues directly related to cancer take on importance. Any delay in cancer treatment and its impact on disease control and even considerations regarding the patient's prognosis must be carefully evaluated, influencing vascular therapeutic planning. The treatment of chronic arterial disease in an oncology patient is also decided considering the same considerations, with the advantage that patients outside of an acute event can have their vascular treatment performed at a more convenient time from the oncological point of view.

As for aneurysmal diseases, many scientists believe a greater risk of expansion of aortic aneurysms caused by some chemotherapeutic agents, but it is still a controversial subject [57]. The less invasiveness provided by the endovascular technique may be necessary for patients with less favorable clinical conditions or in individuals with previous abdominal operations that may represent more significant morbidity in open surgery [58–60].

The prognosis of patients with aortic aneurysms and cancer is more linked to oncological disease than to aneurysmal disease [61]. Concomitant surgical treatment of cancer and aneurysm is described; however, we must consider the sum of the risks associated with 2 major surgeries and the risk of infection of the vascular prosthesis used in the treatment of the aneurysm, either via the endovascular approach or, to a greater extent, via the open approach [60, 61]. Thus, unless the patient has an aortic aneurysm with a diameter excessively increased or

symptomatic concerning the aneurysm, the authors indicate cancer treatment before surgical correction of the aneurysm.

Classically, cancer and its treatment are more associated with venous vascular events, especially venous thromboembolism. This relationship is detailed in Chap. 14. In any case, it is important to remember that the cancer patient is at greater risk both of suffering a venous thromboembolic event and of presenting the main complication attributed to the treatment, that is, bleeding. This hemorrhagic risk is related to malnutrition, renal dysfunction, liver failure, and drug interactions. Several of these parameters have dynamic evolution and, therefore, they must be reassessed frequently, being essential the proximity of the vascular surgeon to the oncologist throughout the treatment.

This multidisciplinary interaction is also beneficial when indicating vascular access for intravenous chemotherapy. This decision is made based on the schedule of antineoplastic therapy (type of drugs, frequency of application, interval between applications, estimated time for infusional treatment), besides, of course, on the patient's conditions as to the adequacy of the individual's peripheral veins.

The treatment of cancer patients is multidisciplinary, but it should be centered on the oncologist's figure, responsible for therapeutic planning and everything that involves it, such as side effects, complications, and drug interactions, and generally being the professional with the closest proximity to the patient.

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Chapter 11
Oncohematology

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11.1 General Principles

11.1.1 Introduction

Hematological neoplasms (HN) are a category of cancers that originate from hematopoietic cells [1]. Clinically, HN can be classified as leukemias, lymphomas, plasma cell neoplasms and myelodysplastic syndromes (MDS) [1, 2]. The main classification is based on the cell types that are primarily affected in each group. Neoplasms originating from bone marrow cells are mainly called myeloid neoplasms. This group is composed of acute (AML) and chronic (CML) myeloid

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leukemia and MDS. Those derived from the lymphatic system are called lymphoid neoplasms and comprise Hodgkin's (HL) lymphoma, non-Hodgkin's (NHL) lymphoma and acute (ALL) and chronic lymphocytic leukemia (CLL), in addition to multiple myeloma (MM) [3].

Brazilian data show that HN corresponds to 5% of all new cases of all neoplasms and 7% of all deaths from cancer [4]. Despite that, there has been a reduction in mortality rates due to HN, with a tendency to chronicle some diseases. Based on that, we tend to have more elderly patients being treated with antineoplastic therapies than was previously seen. Although many treatments have evolved, monoclonal antibodies have been developed, tendencies toward therapy with oral drugs and with less toxicity have emerged, we are dealing with a different population, often with multiple comorbidities that can impact the therapeutic choice, as well as the profile of adverse events associated with treatment [4].

As mentioned, in the recent years, cancer patient treatment has improved. Many therapies are given with curative intent, but others focused on disease control and quality of life or on palliative care. Despite the multiple new drugs available, the old chemotherapy drugs are still widely used. The traditional cytotoxic agents act damaging cell DNA and although their activity against cancer cells, they also end up damaging normal, healthy cells. Examples of these drugs are antimetabolites, such as methotrexate and alkylating agents, such as cyclophosphamide. Also, immunotherapy, like monoclonal antibodies and immune checkpoint inhibitors, has been used to treat HN. Target cancer therapies, which interfere with specific molecules necessary for tumor growth and progression, are another class of drugs used. Small molecules can penetrate the cell membrane to interact with target proteins. This group is composed of bortezomib and imatinib [5–8].

All of these drugs and their mechanisms of action can cause toxicity and lead to irreversible damage to patients. Acute toxic vascular effects of chemotherapeutic agents are common and such vascular complications of chemotherapy might occur as a result of "off-target" drug effects or, importantly, as a result of the significant overlap between signaling pathways required for normal vascular function and those required for tumor growth. Vascular toxicity of chemotherapy often reflects endothelial dysfunction, with loss of vasorelaxant effects and suppressed anti-inflammatory and vascular reparative functions. These effects might serve to initiate and further perpetuate the development of hypertension, thrombosis, and atherogenesis. In addition to the procoagulant effect of cancer per se, platelet activity is further enhanced by decreased endothelial nitric oxide (NO) bioavailability [9, 10].

Baseline comorbidities, preexisting vascular disease, hypertension, diabetes, and other cardiovascular risk factor influence in the propensity to develop cardiovascular complications of cancer therapy [11]. Nowadays, many cardiovascular risk scores have been used to predict the risk of cardiovascular disease and select the most appropriate chemotherapy. Although most of the times aggressive therapeutic approaches to control risk factors are used, sometimes it may contra-indicate some types of therapies. This resembles the importance of multidisciplinary approaches to cancer patients.

11.1.2 Complications of Anticancer Therapy

11.1.2.1 Chemotherapy-Related Complications

Vascular Endothelial Growth Factor Inhibitors

The vascular endothelial growth factor (VEGF) is among the most important of growth factors involved in angiogenesis and this process of new blood vessels formation is central to many tumor growth. Chemotherapy agents might influence VEGF effects directly, as is the case for VEGF inhibitors (VEGFIs), or as a secondary effect as occurs with the "classical" cytotoxic drugs, including antimetabolites, taxanes, anthracyclines, and alkylating agents [12–14]. Examples of this are small-molecule inhibitors of intracellular tyrosine kinases like Sorafenib, a not VEGFR2-specific drug used in hematological neoplasms. In addition, it also inhibits other receptor tyrosine kinases, including platelet-derived growth factor and c-Kit signaling [15]. The interruption of VEGF signaling is associated with the development of vascular toxicity and clinical sequelae such as hypertension, acute coronary syndromes, stroke, venous thrombosis, and thromboembolism [12, 16–19].

Hypertension is the most common complication and almost all patients will have an absolute increase in their blood pressure, sometimes severe and difficult to treat, but manageable with the appropriate antihypertensives and constant monitoring. Yet, although hemorrhagic complications are mentioned, prothrombotic effects appear to predominate and VEGFIs are associated with an absolute increase in risk of arterial and venous thrombosis and thromboembolism of 1.5–4%. The risk of arterial thrombosis appears to be greater than that of venous thrombosis [11, 20–22].

Besides its clinical relevance, the absolute risk increase is small and it does not justify prophylactic antithrombotic therapy. Despite this, it is important to pay attention to patients with previous cardiovascular risk factors because in those, might be a role for antiplatelet therapy. But, concerns over coexisting propensity to hemorrhage have limited the applicability of this strategy. Also, the potential cardioprotective effects of statin therapy in this context remains to be evaluated [11].

Tyrosine Kinase Inhibitors

The tyrosine kinase inhibitors (TKIs) were developed for the use in hematological malignancies, targeting the oncogenic fusion gene, Bcr-Abl. They are mainly used to treat chronic myeloid leukemia (CML) and their development changed this disease prognosis. But some of them are particularly associated with high incidence of acute arterial thrombosis (e.g., nilotinib and ponatinib) or pulmonary hypertension (e.g.,. dasatinib). The first TKI developed was Imatinib, called a first generation TKI. It has less impact in venous and arterial complications. The second generation TKIs (mostly dasatinib and nilotinib) are related to cardiovascular toxicities as mentioned above as well as third generation TKI (ponatinib). As TKIs' potency

increases, the adverse reactions can also increase, leading to many treatment dose reductions or discontinuations.

Ponatinib is associated with an almost 12% incidence of arterial thrombotic events at 2 years, with relatively high rates of venous thrombosis, with an incidence of 2.2% at 1 year and 2.9% at 2 years. Due to that, ponatinib was initially withdrawn from market but then, considering its clinical benefit, reintroduced in 2014 with a US Food and Drug Administration "black box" warning. Nilotinib is also associated with high rates of arterial thrombosis, with 25% of patients experiencing an acute arterial event in the initial study [23]. The 2-year incidence of acute arterial event is almost 15% with a 33% predicted 10-year risk of progressive peripheral arterial disease [24]. The risk appears to remain high regardless of baseline cardiovascular status [25]. Mechanisms underpinning such events remain unclear, although not all anti-Bcr-Abl TKIs are associated with such risk and hence the most appropriate approaches to manage this situation remain unclear. Scores were provided to predict the risk of initiating such agents and it is recommended patients with cardiovascular risk factors to be evaluated and have all those factors controlled before its initiation as a main goal to avoid therapy-related complications [26].

Alkylating Agents

In hematological malignancies, two alkylating agents are the most used ones: cyclophosphamide and cisplatin. Cyclophosphamide is associated with hypertension, myocardial ischemia (MI), stroke, Raynaud phenomenon and hepatic veno-occlusion and cisplatin is associated with hypertension, MI and infarction, thromboembolism and cerebrovascular disease [10]. Cisplatin-based chemotherapy is associated with a 9% risk of thromboembolic complications with endothelial cell damage and dysfunction provoking a hypercoagulable state with platelet activation, adhesion, and aggregation, increased von Willebrand factor, and reduced NO bioavailability being the potential mechanisms for that [27, 28]. Differently, cyclophosphamide administered at continuous low doses may reduce the circulating concentrations of VEGF, which might underpin some of the observed vascular toxicity. Despite that, there are not known standard therapies that can prevent or treat such complications, risk factors control seems to be the best approach.

Antimetabolites

5-Fluorouracil (5-FU) and its prodrug, capecitabine, are mainly associated with myocardial ischemia, which might be due to primary coronary artery spasm, thrombosis, or endothelial dysfunction [19, 29, 30]. These drugs are not commonly used for hematological malignancies. Belonging to this class, cytarabine, 6-Mercaptopurine (6-MP), fludarabine, gemcitabine, and methotrexate are more used but, are less related to cardiovascular toxicities.

Anticancer Antibiotics

This class is composed of anthracyclines such as doxorubicin, which is associated with profound cardiotoxicity and has a marked long-term effect on cardiac structure and function. The principal side effect is a cumulative, permanent, and dose-related cardiotoxicity with consequent left ventricular dysfunction and heart failure [31, 32]. This appears to occur through direct pathophysiological mechanisms rather than as a secondary consequence of systemic hypertension, or arterial or venous thrombosis [32, 33]. Bleomycin also belongs to this class of anticancer drugs and is widely used in the setting of hematological neoplasms. Its effects are seen through the damage of DNA and cytoskeleton disruption. It may cause a dose-dependent reduction in endothelial cell growth and induction of apoptosis. These vascular toxic effects, at least in part, explain associated cardiovascular complications including myocardial ischemia and infarction, thrombosis and thromboembolism, pulmonary fibrosis, and Raynaud phenomenon [12].

Microtubule-targeted agents like the vinca alkaloids, vincristine, and vinblastine are also known. They are tubulin binders that precipitate cell death and are primarily used in the treatment of leukemia and lymphoma. Their main cardiovascular side effects are MI and infarction, which tend to occur during or shortly after therapy and might therefore be related to coronary artery vasospasm as a result of cellular hypoxia [19].

11.1.2.2 Tumor-Related Complications

Disseminated Intravascular Coagulation

Occurrence of decompensated disseminated intravascular coagulation (DIC) is a major management challenge posed by cancer patients, particularly in the case of those suffering from hematological malignancies. It may occur as the first sign of an underlying malignant disease, and in fact for hematological malignancies it tends to appear in early stage, or as a late complication of a previously diagnosed and heavily treated cancer [34, 35]. There is undoubted evidence that an interaction among coagulation/fibrinolysis pathways and cancer tissues exists [36–38]. The interaction is mediated by an amount of molecules/enzymes such as cancer procoagulant (CP), tumor cell surface tissue factor (TF), microparticles carrying tissue factor, urokinase plasminogen activators (uPAs), plasminogen activator inhibitor-1 (PAI-1) [38–41]. Thus, cancer cells possess prothrombotic and fibrinolytic properties at once, and a thrombophilic state is present in almost all cancer patients. Accordingly, thromboembolic events and DIC, or coagulation consumption coagulopathy, can occur as a result of the cancer-related prothrombotic tendency.

In most cases of hematologic malignancies, decompensated DIC presents itself as an acute consumption coagulopathy with rapid platelet count drop and coagulation factors exhaustion potentially leading to dramatic and fatal bleeding [42]. However, bleeding is not the only life-threatening complication affecting DIC

patients. Furthermore, widespread deposition of fibrin-rich thrombi in microvasculature and subsequent ischemia are both factors able to cause a fatal multiple organ dysfunction syndrome (MODS) [43–45]. Despite presenting with thrombocytopenia, the above type of thrombotic microangiopathy (TMA) observed in DIC course has a different pathogenesis in comparison with other TMAs, which are usually not associated with coagulation factors consumption at least in their early stage [46].

The approach to decompensated DIC varies from watchful waiting to active treatment according to the severity of clinical presentation. The treatment of the trigger causes at once with restoring (as necessary) coagulation factors and platelet count has a pivotal role in influencing the course of decompensated DIC [47]. For monitoring patients, some markers as elevated leukocyte counts, decreased hemoglobin and elevated D-dimer can be considered as potentially useful even as platelet count decrease. It is important to note that the prothrombin time (PT) and partial thromboplastin time (PTT) may not be prolonged in patients with cancer-associated DIC, especially with the subclinical form, when coagulation factor levels are only moderately decreased. In a similar fashion, serum fibrinogen levels are very rarely decreased in the procoagulant type of DIC, although in hyperfibrinolytic form, the levels can decrease dramatically. An abrupt decrease in fibrinogen can be a strong risk factor for bleeding in any type of DIC and threshold values (1.5–2.0 g L^{-1}) have been suggested for replacing fibrinogen to prevent this complication [48]. It may be useful to monitor the D-dimer values as a surrogate marker for excess thrombin generation and fibrinolysis in DIC. The hyperfibrinolytic type is likely to have very high D-dimer values, which can be reduced by appropriate treatment, while the procoagulant type and subclinical forms can have elevation of D-dimers to varying levels [49]. Once again, worsening D-dimers rather than absolute values are crucial for the diagnosis of DIC.

The treatment is based in guidelines recommendations, and it is suggested that DIC associated with cancer should be categorized into three subtypes: procoagulant, hyperfibrinolytic, and subclinical. Associated with that, all patients should be risk-assessed for the likelihood of thrombosis and bleeding. For DIC with active bleeding, platelet transfusion aiming platelets count above 50×10^9/L is mandatory. Also, fresh frozen plasma (15–30 mL/kg) or prothrombin complex concentrates (to avoid volume overload) must be necessary. If low fibrinogen values (<1.5 g/L) are noted, cryoprecipitate (~1–1.5 bag for each 10 kg) or fibrinogen concentrate is indicated. For DIC with high risk of bleeding it is suggested platelet transfusion if platelets count is below 30×10^9/L for acute promyelocytic leukemia (APL) or below 20×10^9/L if other tumors [48, 50].

Two additional caveats are to be kept in mind in this context. First, the lifespan of transfused platelets and fibrinogen may be very short, especially in patients with vigorous coagulation activation and fibrinolysis [51]. These patients require frequent blood monitoring to determine the thresholds and need for (further) replacement therapy. In addition, organ impairment such as liver failure can cause decreased platelet and fibrinogen production and function. Also, thrombin excess inhibition is always thought, but the risk of bleeding has prompted some recommendations to limit its use in highly prothrombotic forms of DIC, especially those associated with

solid cancers [52]. In these cases, heparin should be considered as prophylactic therapy in the absence of contraindications such as low platelets count (less than 20×10^9/L) or active bleeding. Subclinical types of DIC will also benefit from heparin prophylaxis, although it is best avoided in hyperfibrinolytic DIC [53].

Randomized controlled studies have not specifically addressed the issue of treatment of a new thromboembolic episode in patients with acute leukemia. In view of the high risk of bleeding in patients with hematologic malignancies such as APL, treatment doses of LMWH with frequent monitoring of peak anti-Xa levels have been suggested [42]. Abnormalities in the clotting screen by themselves should not be considered an absolute contraindication in these circumstances, especially in the absence of bleeding. And about choice of heparin, UFH is chosen due to its easier reversibility, while in all other cases, LMWH should be given [50]. Other approaches like antifibrinolytic agents such as tranexamic acid or epsilon aminocaproic acid have not been demonstrated as significant beneficial, including for the incidence of early hemorrhagic deaths [54]. For these reasons, its routine use cannot be recommended and may be deleterious; however, if therapy-resistant bleeding dominates the picture in hyperfibrinolytic DIC, tranexamic acid may be considered. The role of recombinant FVIIa in the management of cancer-related DIC remains uncertain and it is not recommended [50].

Unfortunately, most of the therapeutic measures are surprisingly not based on high levels of evidence. Because DIC is an intermediary mechanism of disease and is always secondary to an underlying process, appropriate management of the underlying malignancy is the key goal of treatment.

Acute Massive Venous Thromboembolic Disease

The majority of patients who die from this disorder do so within the first 30 min of a massive pulmonary embolus. The therapy of choice in this disorder is the use of fibrinolytic agents to induce rapid lysis, thereby resuming flow through the obstructed pulmonary circulation. The widespread availability of tissue-type plasminogen activator, which has advantages over currently available agents such as streptokinase and urokinase, should in the future alter the approach to the management of deep vein thrombi of the lower limbs, which are the main source of pulmonary emboli [55].

Superior Vena Cava Syndrome Secondary to a Large Mediastinal Tumor

Superior vena cava syndrome (SVCS) occurs in the setting of an extrinsic compression or other occlusion of the superior vena cava (SVC), mainly due to thoracic tumors growth. Also, the presence of indwelling venous lines can lead to SVC. It occurs due to tumor external compression of the vessels resulting in impaired venous drainage from the head, neck, and upper extremities. The compressing tumors are frequently in the middle or anterior mediastinum and the right

paratracheal and precranial nodal regions. The compression results in the formation of venous collaterals, including the azygos vein. Superior vena cava syndrome secondary to a compression below the azygos vein can result in more severe symptoms, highlighting the importance of the azygos vein as a collateral vessel [56].

The SVC can be acute, subacute, or more insidious. Very highly proliferative tumors and SVC thrombosis can result in a rapid onset of symptoms like dyspnea, orthopnea, cough, sensation of fullness in the head and face, and headache, often exacerbated by stooping. Less common symptoms are chest pain, hemoptysis, hoarseness, dizziness, light-headedness, and even syncope. We frequently see facial and neck swelling, arm swelling, and dilated veins in the chest, neck, and proximal part of the arms. Stridor and mental status changes are worrisome signs and indicate laryngeal edema and increased intracranial pressure, respectively [57]. A plain chest radiograph may suggest SVCS, but the best method to diagnose is computed tomography with IV contrast. Nonetheless, magnetic resonance imaging is particularly helpful in cases in which the administration of IV contrast is contraindicated. For the treatment, graduating SVC can be helpful. Yu and collaborators, in 2008, created a grading system which classifies patients according to its symptoms in 0–5 categories and defines its treatment urgency [58]. Symptoms and signs concerning for cerebral and/or airway edema and circulatory instability need urgent initiation of therapy. If the etiology is not yet known, endovascular stenting of the SVC can promptly relieve symptoms of SVCS and is the treatment of choice in very symptomatic patients [59, 60]. Radiation therapy is effective for many patients, but tissue diagnosis with biopsy needs to be established before its initiation and also, the relief of symptoms may be slow. Radiation is sometimes most used for solid tumors, since hematological malignancies tend to respond to glucocorticoids. As well, cytoreductive chemotherapy with cyclophosphamide, vincristine, and prednisone may be used if lymphoma diagnosis is known, at least until immunohistochemistry tumor definition. Supportive care with supplemental oxygen must be given as needed. Anticoagulation should be reserved for patients with evidence of an SVC thrombus or other venous thromboembolic complications and considered for patients who undergo a stent placement. Catheter-directed thrombolysis can be useful in SVCS secondary to a thrombus [61]. The definitive therapy is dictated by the underlying cancer, which also is the primary determinant of the patient's prognosis and the final best approach for the resolution of the syndrome.

11.1.3 Choosing the Best Option of Vascular Access

Choosing the best way to deliver chemotherapy is still a challenge. Optimal practices for intravenous (IV) access remain unknown. Despite changes in its nature (that is, less anthracycline use) and duration, for example, administration every 3 weeks for 3–6 cycles, subcutaneous presentations for maintenance, many times intravenous devices are still required and are the best option [62, 63].

Broadly, IV therapies can be administered through a peripheral IV access inserted into a vein in the arm during each visit to the chemotherapy unit and removed before the patient returns home, or through central venous access devices (CVADs) such as peripherally inserted central catheters (PICCs) and implanted vascular access devices ("PORTS"). A PICC is a percutaneous central line that is inserted into the upper arm and that stays in the arm for the entire duration of the chemotherapy. It is easily removed after chemotherapy treatment is complete. A port is a reservoir that is surgically placed under the skin in the chest. Its removal after systemic therapy is finished is more complex [64]. These intravenous access techniques differ significantly in terms of morbidity and cost to the health-care system. Each of the IV administration routes has its own merits and complications that have to be weighed for each individual patient and systemic regimen being delivered. Thus, although peripheral IV access means that minimal follow-up care is required, risks for peripheral phlebitis and chemotherapy extravasation (that is, accidental leakage into surrounding tissues rather than containment in the blood vessel) are increased. On the other hand, the use of a PICC or port is thought to reduce the risk of extravasation, to ensure reliable access for infusion, to improve patient satisfaction, and to eliminate the long-term effects on peripheral veins that can be damaged by the administration of vesicant drugs [65]. However, CVADs are also associated with an increased risk of thrombotic and infectious complications [66–69].

The most common factors associated with CVADs decision are prior difficult IV access, reports from chemotherapy nurses if peripheral access was deemed problematic, risk of extravasation with chemotherapy regimen, type of chemotherapy (e.g., anthracycline administration), factor related to the patient like prior thromboembolic disease or history of IV drug use and also, patient personal preference [70]. Besides that, we lack prospective clinical trial data directly comparing various forms of vascular access for chemotherapy administration in cancer patients. Although CVADs are not only expensive, but that all types of vascular access are associated with complications and affect the patient's quality of life, having retrospective literature demonstrating that the risk of thrombotic and infectious complications might be increased with central access devices, but those data are prone to many biases and confounders [66–68]. To date, no clear consensus about best practice for the use of vascular access routes has been reached. Very few trials have compared the various strategies and the use of those methods is also associated with considerable clinical equipoise [70].

It is of utmost importance to weigh the benefit of each type of access with its possible complications, added to the patient's will to define the best strategy. Often, the type of access to be used does not need to be defined in the first consultation or in the first application of chemotherapy. Most chemotherapeutic drugs, despite the risks of leakage, can be performed through peripheral access with subsequent definition of a definitive access route depending on the difficulties during the chemotherapy process, as well as based on the opinion of the chemotherapy nurses and the patient himself. A joint decision is usually the best strategy.

11.1.4 Conclusion

In tandem, with the improved survival from cancer, there has been increasing focus on cardiovascular actions of chemotherapeutic agents. In addition to acute toxic vascular effects of chemotherapeutic agents, the latent effects of direct and indirect cardiovascular toxicity become more relevant. Patients survive long enough to allow these effects manifest and more focus is now being given for quality of life. Nonetheless, smaller evidence base and mechanistic insight to the vascular complications associated with cancer chemotherapeutics are known. Despite this, it is extremely important that we bear in mind the various complications caused by the various therapeutic modalities used today. Although for the most part they do not have defined therapeutic strategies or based on strong evidence, the control of risk factors and the multiprofessional approaches are fundamental for the success of the therapy and the preservation of the physical integrity and quality of life of our patients.

11.2 Lymphomas

11.2.1 Hodgkin's Lymphoma

Hodgkin's lymphoma is a lymphoid neoplasm of B lymphocyte origin, composed of Reed-Sternberg cells in an inflammatory microenvironment. It has a higher incidence in young adults and a second peak after 50, with a slight preference for males [71]. It represents about 30% of all lymphomas and can be considered curable in 90% of cases, especially when the disease is not in an advanced stage [72].

Clinically it manifests with lymphadenopathy, which may be associated with constitutional symptoms, fatigue, and itching. Most patients have painless lymph node enlargement with a firm and elastic consistency, affecting the cervical region in approximately 60–80% of cases. It may also present with large mediastinal masses capable of causing chest discomfort, respiratory symptoms, and even more urgent complications related to vessel and airway compression. Constitutional symptoms or also called B symptoms (fever, night sweats, and weight loss) are present in approximately 40% of cases. In the minority, the clinical presentation is relatively nonspecific or atypical [73].

An excisional biopsy makes the diagnosis of the suspected lymph node. The pathological evaluation identifies RS cells in an inflammatory microenvironment composed of non-neoplastic cells. RS cells are B lymphocytes that express immunohistochemical markers CD30 and CD15. HL can be subclassified into classic HL, the most common, and LH with nodular lymphocytic predominance [73].

For therapeutic planning, it is essential to staging the disease with imaging tests, preferably PET-CT (positron emission tomography), and its classification according to prognostic factors such as advanced age, male gender, presence of large

mediastinal mass, involvement of more than three lymph node regions, elevated VHS, anemia, leukocytosis, or lymphopenia [74].

The treatment of classic HL consists of chemotherapy-associated or not with radiotherapy. The most used chemotherapy regimen is the ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). For cases of relapse or refractoriness, patients receive salvage chemotherapy followed by autologous hematopoietic cell transplantation (BMT). Allogeneic BMT is reserved for cases of degeneration after autologous transplant [75].

New drugs were recently introduced in the treatment of HL, allowing to achieve excellent results even in relapsed/refractory disease. Brentuximab vedotin is an anti-CD30 antibody indicated for relapsed post-BMT disease, relapse cases in patients' ineligible for BMT, and as maintenance treatment after autologous BMT in high-risk patients. It may also be shown in the first line for cases of advanced staging in combination with chemotherapy. The checkpoint inhibitors, nivolumab, and pembrolizumab have also been inserted in this context of post-BMT recurrence, representing a significant advance in the treatment of HL [75].

11.2.2 Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphomas comprise a diverse and heterogeneous group of more than 50 subtypes of neoplasms, which may, more rarely, originate from B lymphocytes, T lymphocytes, or natural killer cells. They comprise about 4% of neoplasms and affect patients of all ages, races, and socioeconomic levels. Diagnosis and classification of NHL require an adequate biopsy specimen as clinical manifestations, prognosis, and clinical management vary widely according to the type of lymphoma [76].

This lymphoma group can result from chromosomal translocations, infections, environmental factors (exposure to chemical agents, for example), immunodeficiency states, and chronic inflammation. However, in most cases, the disease is of unknown cause.

NHL can be classified according to clinical behavior in indolent and aggressive lymphomas. Indolent lymphomas grow slowly, with lymphadenopathy increasing and decreasing over months or years, and may also present with hepatomegaly, splenomegaly, and cytopenias. In this subgroup, the most common type is follicular lymphoma, which preferentially affects the elderly and accounts for 20% of all lymphomas. They usually have low-grade anatomopathological characteristics, with a low proliferative index and cells with more mature characteristics.

On the other hand, aggressive lymphomas show faster growth, most often related to exuberant symptoms and immediate need for treatment. The most common aggressive lymphoma is Diffuse Large B-Cell Lymphoma (LDGCB), morphologically with an increased proliferative index and cells with more immature characteristics. The LDGCB corresponds to about 30% of NHL in adults [76].

The clinical presentation of NHL varies with the histological subtype and sites of involvement. Aggressive or highly aggressive lymphomas, such as Burkitt's Lymphoma, commonly present subacutely or acutely with a rapidly growing mass, constitutional symptoms of fever, night sweats, or weight loss, and may present with tumor lysis syndrome.

A minority of patients initially present with extranodal involvement (primary extranodal NHL), but many other patients develop the extranodal disease in the course of their illness. Primary extranodal lymphoma of the gastrointestinal tract, primary CNS lymphoma, and cutaneous lymphoma is the most common examples of these cases, and the clinical manifestations are related to the affected organ.

Some patients present with atypical findings such as pruritus, exaggerated reactions (hypersensitivity) to insect stings or stings, generalized fatigue, malaise, fever of unknown origin, ascites, or strokes that may accompany nodal or extranodal NHL or, rarely, maybe the only manifestation of lymphoma [77].

There are emergencies and life-threatening oncological complications that can be recognized at the NHL presentation or can develop during the disease or its treatment. Especially for highly aggressive subtypes such as Burkitt's lymphoma, prompt recognition and management are critical as these complications can be fatal or delay treatment. Examples of oncological complications of NHL include spinal cord compression from expansive injury, lymphomatous meningitis and/or mass lesions of the central nervous system, airway obstruction, pericardial tamponade, superior vena cava obstruction, venous thromboembolic disease, gastrointestinal obstruction or failure liver, tumor lysis syndrome, hyperviscosity syndrome, among others [78].

Diagnosis is made through biopsy, preferably excisional of the ganglion. Fine needle aspiration puncture (FNAP) is contraindicated due to the high chance of diagnostic confusion. In addition to morphology and immunohistochemical characteristics, the pathologist can search for genetic alterations that define lymphoma subtypes.

The prognosis of NHL is generally individualized to each lymphoma subtype, as is the therapeutic approach. For indolent lymphomas, it is often possible not to immediately treat the patient by adopting the watch and wait for strategy, with careful monitoring of symptoms that can last for months and even years. The leading indicators of the need for treatment are grouped in the GELF criteria (bulky mass > 7 cm, more than three affected lymph node groups, cytopenias, and constitutional symptoms). When there is an indication for treatment in these cases, it is based on immunological and/or chemotherapy protocols, and the objective is not curative. The natural history of indolent NHL is one of the multiple relapses, which become progressively more chemorefractory and with a shorter period between them [77].

For aggressive NHL, treatment should be immediate and based on a combination of monoclonal antibodies and chemotherapy. The R-CHOP protocol (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is the first-line treatment for LDGCB, associated with radiotherapy according to the stage. Relapse cases are treated with salvage chemotherapy followed by autologous transplantation

when there is adequate performance status. New options have been introduced in this context, including CAR T-cell therapy (chimeric antigen receptor T-cell therapy), which consists of personalized treatment of the patient's T lymphocytes, genetically modified to target the death of lymphoma cells. Studies have shown promising results with this therapy, recently approved in the United States [79].

11.3 Acute Leukemia

11.3.1 Acute Myeloid Leukemia

11.3.1.1 Introduction

Acute myeloid leukemia (AML) consists of hematopoietic neoplasms characterized by clonal expansion of progenitor cells (blasts) in the bone marrow, peripheral blood, and other organs. In AML, these committed precursor cells are of the developmental myeloid lineage (i.e., those that give rise to granulocytic, monocytic, erythroid, or megakaryocytic cells).

The accumulation of leukemic blasts or immature forms in bone marrow, peripheral blood, and occasionally in other tissues causes a variable reduction in the production of normal red blood cells, platelets, and mature granulocytes. The increased production of malignant cells, together with the decrease in these mature elements, results in various systemic consequences, including anemia, bleeding, increased risk of infection, and other symptoms and complications [80].

A particular subtype of acute myeloid leukemia called acute promyelocytic leukemia (APL) comprises approximately 10% of AML cases. ALI has a different morphology, clinical presentation, and treatment than AML, so that it will be explained separately.

11.3.1.2 Incidence

AML is the most common acute leukemia in adults and accounts for approximately 80% of cases in this age group [80, 81].

In the United States and Europe, the incidence is reported as 3–5 cases per 100,000 population [82, 83].

In adults, the average age at diagnosis is approximately 65 years. Incidence increases with age, with around 2 and 20 cases per 100,000 population for those aged 65 and under, respectively [84]. The male: female ratio is approximately 5:3. This incidence is similar among people of different races. In one study, non-Hispanic whites had the highest incidence (4 cases per 100,000 population), while Hispanic whites, blacks, and Asian-Pacific islanders had a slightly lower incidence (3 cases per 100,000 population) [84].

11.3.1.3 Risk Factors

Exposure to solvents, smoking, ionizing radiation, chemotherapy (mainly alkylating agents and topoisomerase II inhibitors), in addition to other drugs such as chloramphenicol and phenylbutazone [85].

The increased risk of acute leukemia in people with a family history is unclear in the literature, and no Mendelian inheritance pattern has been identified.

Some congenital genetic syndromes (Down's Syndrome, Klinefelter's Syndrome, Turner's Syndrome, Neurofibromatosis, among others) are associated with a higher risk of AML, as well as spinal cord failure syndromes such as Fanconi's anemia, dyskeratosis congenita, Schwachman-Diamond syndrome, Blackfan-Diamond syndrome, amegakaryocytic thrombocytopenia, and malignant diseases (myelodysplastic syndrome and myeloproliferative diseases) [85, 86].

11.3.1.4 Clinical Presentation

- Symptoms related to cytopenias include fatigue, infections, fever, and bleeding (bruises, gingival bleeding, epistaxis, metrorrhagia).
- Visceromegaly occurs in around 10% of cases.
- Neurological symptoms may indicate infiltration of the central nervous system.
- Gingival hypertrophy is common in cases with a monocytic component.
- Extramedullary disease (granulocytic sarcoma or chloroma) occurs in less than 1% of cases and may precede or accompany the medullary disease. The most common sites are bones, periosteum, soft tissue, and lymph nodes, and the least common are the orbit, intestine, mediastinum, epidural region, uterus, and ovaries.
- Metabolic and electrolyte abnormalities may be associated with tumor lysis syndrome, a cancer emergency. Suspect in patients with hyperphosphatemia, hyperuricemia, hypocalcemia, and hyperkalemia.

11.3.1.5 Diagnosis

A complete anamnesis and physical examination, including age, ethnicity, family history, previous exposure to toxic agents, personal history of cancer and its treatment (class of chemotherapy, radiotherapy), previous diseases, comorbidities, and performance status (ECOG) [85].

Complementary tests: blood count with reticulocytes, electrolytes, uric acid, renal and liver functions, coagulogram, DHL, beta 2 serum microglobulin, serology for HIV, Hepatitis A, B, C, HTLV I and II beta HCG (women of childbearing age), chest X-ray, ECG, echocardiogram, HLA typing of the patient and siblings, and CSF puncture if neurological symptoms.

The myelogram is essential for the diagnosis of AML; bone marrow biopsy is not mandatory, except in cases with "dry aspiration." Morphological, immunophenotypic, cytogenetic, and molecular genetic studies must be performed in all cases.

Information derived from these studies is necessary for correct diagnosis and proper classification. The selection of treatment modality and accurate prognosis strongly depend on information derived from these studies.

The diagnosis of acute leukemia is made by more than 20% of blasts in the peripheral blood or bone marrow.

In the presence of some genetic abnormalities, the diagnosis of AML is considered without the need for 20% of blasts:

- LMA with t(8;21)(q22;q22); RUNX1-RUNX1T1
- LMA with inv(16) (p13.1q22) or t (16;16)(p13.1;q22);(CBFB-MYH11
- APL with t(15;17)(q24.1;q21.1)PML-RARA

The presence of granulocytic sarcoma also confirms the diagnosis of AML, regardless of the blast count [87].

Leukemic cells must have their myeloid origin confirmed by the presence of Auer rods in the morphology, positive myeloperoxidase in cytochemical reactions, or the presence of myeloid/monocytic markers recognized by immunophenotyping [88].

11.3.1.6 Prognostic Factors in AML

Response to treatment and overall survival of patients with AML are heterogeneous. The main associated factors are as follows:

- Advanced age
- Cytogenetic and/or molecular findings in tumor cells with poor prognosis
- Bad performance status
- History of prior exposure to cytotoxic agents or radiotherapy
- Previous myelodysplasia or other selected hematological disorders

11.3.1.7 Treatment

Treatment goals should be determined by shared decision-making by physicians and patients, with input from loved ones. The discussion should recognize that AML will be an end-of-life disease for most patients and emphasize the benefits of treatment for short-term and long-term outcomes. Goals are influenced by medical fitness, age, personal values and preferences, and prognostic characteristics of the leukemic cells [89].

Achieving complete remission (CR; <5% blast cells in blood or bone marrow) is an appropriate goal for most AML patients, as achieving CR is associated with prolonged survival, improved quality of life, and it is necessary for AML cure. For some patients, treatment to achieve CR (or even modifying the course of the disease) may be inadvisable due to old age, frailty, coexisting medical problems, and/or previous treatment [89].

The lesser intensity of targeted therapies may be an option for some frail patients. We consider frail patients whose debility or comorbid conditions would not allow treatment with the objective of modifying the course of the AML disease.

Induction chemotherapy for patients not eligible for intensive care:

- Low-intensity therapy with Azacitidine, intravenously or subcutaneously applied, 75 mg/m^2 for 7 days in a row associated with oral drug venetoclax 100 mg on D1, 200 mg D2, 400 mg on D3 onward, daily, cycles every 28 days.
- Decitabine 20 mg/m^2 intravenously on days 1–5, associated with oral drug venetoclax 100 mg on D1, 200 mg D2, 400 mg on D3 onward, daily, cycles every 28 days.
- Low dose of Cytarabine SC
- Control therapy with oral hydroxyurea, transfusion therapy.

Supportive care Treatment of the frail patient should focus primarily on supportive care to improve quality of life by decreasing the symptoms caused by AML. Supportive care for AML patients includes red blood cell and platelet transfusions, antibiotics to treat infections, growth factor support, and correction of coagulopathies.

Induction chemotherapy for patients eligible for intensive care:

There are several protocols used in oncohematology practice for these patients, including the following:

- Cytarabine 200 mg/m^2 in continuous infusion for 7 days with Daunorubicin 60 mg/m^2 for 3 days.
- Cytarabine 100 or 200 mg/m^2 in continuous infusion for 7 days with Daunorubicin 60–90 mg/m^2 or Idarubicin 12 mg/m^2 or Mitoxantrone 12 mg/m^2 for 3 days.
- With FLT3 mutation: Cytarabine 200 mg/m^2 in continuous infusion for 7 days with Daunorubicin 60 mg/m^2 for 3 days and oral Midostaurin 50 mg every 12 h, days 8–21.

Bone marrow collection collected 14–21 days after initiation of induction chemotherapy, mainly for patients eligible for intensive care.

Patients considered candidates for bone marrow transplantation should be transplanted in the first remission.

11.3.2 Acute Promyelocytic Leukemia

11.3.2.1 Introduction

Acute promyelocytic leukemia (ALP) is a subtype of AML and comprises approximately 10% of AML. It is characterized by the presence of t(15;17)(q22;q12) / PML-RARA.

11.3.2.2 Clinical Presentation

It is often associated with disseminated intravascular coagulation, with changes in the coagulogram and bleeding. Coagulopathy is responsible for the high rate of early mortality in this disease [90].

If ALI is suspected, treatment with trans-retinoic acid (ATRA) should be started, which has the unique ability to promote blast differentiation and reverse coagulopathy. There is no need to wait for the results of cytogenetic and molecular tests to start the drug.

11.3.2.3 Diagnosis

The initial approach and diagnosis follow the same principles as for AML. The morphology may indicate that it is an ALI, which can be classified as typical, abnormal promyelocytes and hyper granular blasts in the bone marrow and hypogranular variant, with blasts with few granules. The diagnosis must be confirmed by molecular detection of PML-RARA fusion [91].

11.3.2.4 Treatment

As mentioned above, when the disease is suspected, treatment with ATRA should be started immediately.

Main induction protocols used are as follows:

- ATRA with arsenic trioxide (ATO): ATRA 45 mg/m^2 orally divided twice a day + ATO 0.15 mg/kg iv daily. Re-evaluate bone marrow on day 28 before starting consolidation.
- ATRA and chemotherapy with anthracycline: ATRA 45 mg/m^2 orally divided into twice a day + Idarubicin 12 mg/m^2 on days 2, 4, 6, and 8.

Most used consolidation protocol:

- ATRA 45 mg/m^2/day orally, for 2 weeks, every 4 weeks, for seven cycles, +ATO 0.15 mg/kg intravenously, 5 days a week, every 8 weeks, for a total of 4 cycles.

Maintenance It is not necessary for patients classified as low-risk treated with ATRA and ATO. It should be performed in high-risk patients and those at low risk treated with the combination of ATRA and chemotherapy.

11.3.2.5 Final LPA Considerations

The evaluation of molecular remission must be performed in a bone marrow sample using the RT-PCR method, which is crucial for determining the risk of relapse.

Invasive procedures should be avoided before and during induction therapy due to the risk of bleeding complications.

For patients considered at high risk at diagnosis, steroids should be administered to prevent differentiation syndrome [91].

Central nervous system prophylaxis is only considered for high-risk patients or those with some CNS manifestation.

11.3.3 Acute Lymphoblastic Leukemia

11.3.3.1 Introduction

Lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, or other organs.

They are classified based on the lineage of B cells versus T cells:

- Leukemia / lymphoblastic lymphoma B (B-ALL / LBL)
- Leukemia / lymphoblastic T lymphoma (T-ALL / LBL)

11.3.3.2 Epidemiology

The incidence rate in the United States is 1.5 per 100,000 individuals per year, with approximately 6000 new cases and 1440 deaths per year. The average age at diagnosis is 15 years, with 60% of diagnoses before 20 years, 26% from 45 to 64 years, and 11% after 65.

The cause of B-ALL/ LBL is unknown, but it may be associated with ionizing radiation and/or infectious agents not yet identified [92]. True familial ALL is rare, although it has been associated with inherited mutations of PAX5, ETV6, and TP53 [93]. There is an increased incidence of B-ALL in children with Down syndrome and other constitutional disorders [94]. B-ALL is also associated with certain single nucleotide polymorphisms in specific genes, including GATA3, ARID5B, IKZF1, CEBPE, and CDKN2A/B [95].

11.3.3.3 Clinical Presentation

Clinical presentation is varied, similar to AML, fatigue, lethargy, constitutional symptoms, dyspnea, infections, and spontaneous bleeding. The presence of lymphadenopathy, splenomegaly, and/or hepatomegaly on physical examination occurs in approximately 20% of cases.

11.3.3.4 Diagnosis

The diagnosis of ALL is made by more than 20% of lymphoblasts in the blood or bone marrow. Cases involving nodal or extranodal sites with less than 20% of blasts are called lymphoblastic lymphoma.

Immunophenotype and cytogenetic/molecular findings are needed to distinguish LLA-B/LBL from other leukemias and lymphomas because morphology alone is not diagnostic.

B-cell antigens B-ALL/LBL lymphoblasts are almost always positive for CD19, cytoplasmic CD79a, and cytoplasmic CD22; none of these markers alone is diagnostic-specific their positivity in combination or at high intensity strongly supports the diagnosis [96].

- T-cell antigens (e.g., CD3) are negative.
- Myeloid antigens such as CD13 and CD33 can be expressed and do not exclude the diagnosis of B-ALL/ LBL [90]. However, myeloperoxidase (MPO) expression is considered to define the myeloid lineage, and the co-expression of MPO with B lineage antigens excludes the diagnosis of B-ALL/ LBL [97].

ALL can be classified according to its morphological, immunophenotypic, and cytogenetic characteristics. This classification will allow us to design a therapeutic plan that is more suitable for the patient.

11.3.3.5 Treatment

ALL—young adults (15–39 years) Philadelphia chromosome-positive:

- Induction therapy with chemotherapy + tyrosine kinase inhibitor (ITK) or corticosteroids + ITK. If complete response, proceed with consolidation with allogeneic bone marrow transplantation (HSCT) and maintain post-HSCT ITK for at least 1 year. In the absence of a donor, follow the chemotherapy protocol (consolidation and maintenance).

ALL—adults (>40 years) Philadelphia chromosome-positive:

- Induction therapy with chemotherapy + tyrosine kinase inhibitor (ITK) or corticosteroids + ITK. If complete response, proceed with consolidation with allogeneic bone marrow transplantation (HSCT) and maintain post-HSCT ITK for at least 1 year.

ALL—young adults (15–39 years) Philadelphia chromosome-negative:

- Induction therapy with chemotherapy or clinical research. If complete response, follow with consolidation with allogeneic HSCT. In the absence of a donor, follow the chemotherapy protocol (consolidation and maintenance).

ALL—adults (>40 years) Philadelphia chromosome-negative:

- Induction therapy with chemotherapy or clinical research. If complete response, follow with consolidation with allogeneic HSCT. In the absence of a donor, comorbidities that contraindicate HSCT follow the chemotherapy protocol (consolidation and maintenance).

11.3.3.6 Leukemia Outcome

Very little is known about leukemia; one should be aware of possible signs and symptoms related to it and seek immediate medical attention. Therapeutic options have been improving every year and should be carried out by a multidisciplinary team, providing the most appropriate treatment for each case, aiming to achieve a cure for the disease when possible.

11.4 Multiple Myeloma

11.4.1 Introduction

Plasma cell neoplasms are characterized by the clonal expansion of differentiated B cells secreting a monoclonal immunoglobulin, also called monoclonal protein (M protein). However, this chapter emphasizes clonal plasma cell disease symptomatic multiple myeloma. According to the WHO 2017 classification, plasma cell dyscrasias can be divided into the following:

11.4.1.1 Non-IgM Monoclonal Gammopathy of Undetermined Significance (GMSI)

Patients with GMSI are asymptomatic. The prevalence of GMSI in the white population is 3.2% in those over 50 years old [98].

Defined by the presence of M protein IGG, IGA or rarely IGD at a concentration of <3 g/dL; clonal plasmacytosis in bone marrow less than 10%, absence of target organ damage unrelated to monoclonal protein deposition (hypercalcemia, renal failure, anemia, bone lesions) and lack of B-cell lymphomas or other M-protein-producing diseases.

11.4.1.2 Asymptomatic or Indolent Multiple Myeloma

Patients are asymptomatic but in a stage already considered premalignant, with a high risk of progression to symptomatic or active multiple myeloma.

Non-IGM monoclonal protein greater than or equal to 3 g/dL or urinary greater than or equal to 500 mg/24 h, and/or clonal plasma cells in bone marrow 10–60%, absence of disease-defining events or Amyloidosis.

Asymptomatic MM can progress to active multiple myeloma at a rate of 10% per year within the first 5 years of diagnosis, 3% per year for subsequent years, and 1.5% per year onward [99].

11.4.1.3 Symptomatic or Active Multiple Myeloma (MM)

Diagnosis requires the presence of one or more disease-defining events in association with evidence of greater than or equal to 10% clonal plasma cells in bone marrow or a biopsy demonstrating plasmacytoma. In 2014, The International Myeloma Working Group (IMWG) complemented with three specific biomarkers that also determine active multiple myeloma: clonal plasma cells greater than or equal to 60% in bone marrow, light chain ratio (Kappa or Lambda) greater than or equal to 100 (free light chain involved over non-involved) and presence of more than one focal lesion on magnetic resonance imaging [100].

This topic will be better addressed during the chapter description.

11.4.1.4 Solitary Plasmacytoma (Bone or Extraosseous)

Defined as plasmacytoma at a single bone site or a single extramedullary site, bone marrow with no evidence of clonal plasma cells.

Normal skeletal X-ray, MRI, and/or low voltage whole-body tomography (except for the primary lesion).

11.4.1.5 Immunoglobulin Storage Disease (Primary Amyloidosis)

Amyloidosis is the general term used to refer to extracellular tissue deposition of fibrils composed of low molecular weight subunits of a variety of proteins, many of which circulate as constituents of plasma [101].

The immunoglobulin deposit disease-related subtype is AL amyloidosis, which is related to the deposition of protein derived from immunoglobulin light chain fragments. It is a complication of plasma cell dyscrasia in which a monoclonal protein is detectable in urine and/or serum in >95% of patients affected if serum and urinary immunofixation [101].

It is a systemic disorder that can present with various symptoms or signs, including intense proteinuria (usually in the nephrotic range), edema, hepatosplenomegaly, otherwise unexplained heart failure, and carpal tunnel syndrome.

They are usually related to low-grade plasma cell clones but may occur in association with multiple myeloma or, much less frequently, Waldenström's macroglobulinemia or non-Hodgkin's lymphoma. Light chain deposition disease has similar

pathogenesis and shares some clinical manifestations with AL amyloidosis; the main difference is that the deposited light chain fragments generally do not form fibrils and do not generate deposition of amyloid cofactors. In rare cases, amyloidosis can be derived from immunoglobulin heavy chain fragments, in which case it is called AH amyloidosis [102].

11.4.1.6 Plasma Cell Neoplasm Associated with the Paraneoplastic Syndrome (POEMS Syndromes)

POEMS syndrome is a rare paraneoplastic syndrome marked by a polyneuropathy and a monoclonal plasma cell disorder. The pathogenesis is not well understood, and its incidence is poorly measured.

Diagnosis depends on major and minor criteria. The major mandatory standards are polyneuropathy, typically demyelinating, and monoclonal disorder. There are also three major secondary criteria, in which only one of them needs to be present: Castleman's disease, sclerotic bone lesions, or elevated VEGF.

There are six minor criteria, and one is enough to complete the diagnostic triad: organomegaly, extravascular volume increase, endocrinopathy, skin changes, papilledema, and thrombocytosis/erythrocytosis.

After the POEMS syndrome has been confirmed, the therapy must be evaluated. The basis of the treatment is the suppression of the proliferation of monoclonal cells [103].

Epidemiology

Despite being considered an infrequent cancer, it is the second most diagnosed hematologic neoplasm, with an incidence of 6.2 cases per 100,000 inhabitants, more common in men than in women and more prevalent in individuals of African-American descent [104].

It is a disease of elderly patients, with a median age of 65–75 years; only 2–10% of patients are younger than 40 and 50 years, respectively [104, 105].

The incidence varies with ethnicity, being two to three times higher in African descendants and African-Americans than whites [106]. On the other hand, the risk is lower in Asians, mainly in Japan. The genetic and/or behavioral reasons for such a difference in incidence need to be better clarified [107].

Official data on the incidence and prevalence of MM in Brazil are imprecise and included in the National Cancer Institute (INCA) statistics in the classification "other tumors."

Risk factors for the development of MM are not well established yet. However, numerous viruses and other infectious agents have been linked to the pathogenesis of the disease and exposure to toxic substances and radiation.

A small fraction of cases are considered familial, with an estimated three familial cases for every 1000 patients with multiple myeloma [108].

Pathogenesis

The development of MM is an oncogenic process with several steps, arising with the proliferation of pre-neoplastic clonal plasma cells.

In the initial phase, up to 60% of acquired genetic mutations occur, such as translocations involving the immunoglobulin heavy chain gene (14q32) and, in a later stage, additional new genetic alterations are found, such as MYC (8q24), K-RAS, and TP 53 (17p); confirming the neoplastic clonal evolution described in the introduction. Additionally, in disease progression, there is an abnormal interaction between neoplastic plasma cells and the bone marrow microenvironment, in addition to increased angiogenesis.

Diagnosis

Most patients with Multiple Myeloma present signs and symptoms related to infiltration of plasma cell cells in the bone marrow or other organs or renal damage related to immunoglobulin deposition [109].

Diagnosis requires the presence of one or more disease-defining events in association with evidence of greater than or equal to 10% clonal plasma cells in bone marrow or a biopsy demonstrating plasmacytoma. Disease-defining events consist of the acronym's signs and symptoms derived from the English CRAB (C calcium elevated—hypercalcemia, R renal failure—renal failure, A for anemia—anemia, B bone lesion—lytic lesions). In 2014, The International Myeloma Working Group (IMWG) complemented with three specific biomarkers that also determine active multiple myeloma: clonal plasma cells greater than or equal to 60% in bone marrow, light chain ratio (Kappa or Lambda) greater than or equal to 100 (free light chain involved over non-involved), and presence of more than one focal lesion on MRI. The update of the criteria in 2014 represented a paradigm shift, as it allowed an earlier diagnosis of active MM and initiation of drug therapy before target-organ damage [99].

Treatment

Once active multiple myeloma is identified, the patient should be treated. The introduction of high-dose chemotherapies followed by autologous hematopoietic bone marrow transplantation and the availability of new drugs has transformed the treatment of Multiple Myeloma in the last 20 years. The main objective is to increase survival and to improve the quality of life of these patients.

The treatment choice is based on eligibility to perform autologous marrow transplantation (HSCT) and risk stratification, as shown in Table 11.1 [99].

Table 11.1 International Staging System (R-ISS) in multiple myeloma

Stage	Risk factors	Median overall survival (months)	5-year overall survival rate[a](%)
I	All factors: serum albumin ≥3.5 g/dL, B2microglobulin <3.5 mg/L, no high cytogenetic risk factor, serum DHL below the upper limit of normality	Not reached	82
II	Does not fit either stage I or III	83	62
III	B2 serum microglobulin ≥5.5 mg/dL E high-risk cytogenetic t(4;14); t(14,16) or del 17p or high DHL	43	40

Source: Elaborated from Palumbo et al. [110]
DHL lactic dehydrogenase
[a]After a median follow-up of 46 months

The need to pass a long-term catheter for chemotherapy infusion in treating multiple myeloma will depend on the type of drug protocol chosen, the number of scheduled chemotherapy sessions, and the patient's peripheral access conditions.

Currently, a vast majority of protocols for multiple myeloma provide the option of drug treatment with subcutaneous application associated with the oral route, eliminating the need for a long-term catheter. Still, when necessary, the port-a-cath catheter is preferred.

11.4.1.7 Patient Eligible for Autologous HSCT

HSCT eligibility depends on patients' age and comorbidities. Despite new perspectives on drug combinations, triple combinations are still recommended by international guidelines as induction options [100].

Induction therapy can be performed with a chemotherapy protocol containing at least one proteasome inhibitor (bortezomib) or an immunomodulator (thalidomide or lenalidomide) associated with other chemotherapeutic agents (average of 4–6 cycles).

Recently, the anti-CD38 monoclonal antibody Daratumumab is a drug option available to be used in combination with bortezomib, thalidomide, and dexamethasone as a first-line drug induction in MM in eligible patients [111].

All of these treatments are followed by high-dose melphalan chemotherapy and autologous HSCT. The main triple and/or quadruple therapeutic options currently used in Brazil in patients eligible for BMT are listed below:

- Bortezomib, Lenalidomide, Dexamethasone
- Bortezomib, Thalidomide, Dexamethasone
- Daratumumab, Bortezomib, Thalidomide, Dexamethasone
- Carfilzomib, Lenalidomide, Dexamethasone
- Cyclophosphamide, Thalidomide, Dexamethasone

11.4.1.8 Patients Not Eligible for Bone Marrow Transplantation

Around 60% of patients with MM fall into this situation of non-eligibility. There was an increase in response rates associated with better survival after the use of new chemotherapeutics, such as immunomodulators (thalidomide, lenalidomide), proteasome inhibitors (bortezomib), and monoclonal antibodies (such as daratumumab). The possibility of therapy until progression and for a limited time has also been discussed, but it is always important to remember that, in the treatment of older patients, we must balance efficacy and toxicity [99].

The main therapeutic options currently used in Brazil, on average for 9–12 cycles for patients not eligible for BMT, are listed below:

- Bortezomib, Melphalan, Prednisone
- Bortezomib, Lenalidomide, Dexamethasone
- Bortezomib, Dexamethasone
- Daratumumab, Bortezomib, Melphalan, Prednisone
- Daratumumab, Lenalidomide, Dexamethasone
- Daratumumab, Bortezomib, Dexamethasone
- Melphalan, Prednisone, Thalidomide

Treatment Response Criteria

The response criteria developed for multiple myeloma were essential to standardize the assessment of the various therapies used in the MM; for this, we used the IMWG criteria described below:

- Strict Complete Response (sRC): Complete response associated with standard Kappa/Lambda ratio in freelight and absence of monoclonal plasma cells in bone marrow biopsy immunohistochemistry.
- Complete Response (CR): Negative immunofixation in serum and urine, the disappearance of plasmacytoma, less than or equal to 5% of plasma cells in the bone marrow.
- Very Good Partial Response (VGPR): M-protein in serum and/or urine detectable by immunofixation but with normal protein electrophoresis, or greater than or equal to 90% reduction in serum M-protein and urinary M-protein level less than 100 mg in 24 h.
- Partial Response (PR): Reduction of greater than or equal to 50% of serum M-protein and reduction of 24-h urinary M-protein greater than or equal to 90% or less than 200 mg in 24 h. If the M-protein is not measurable: greater than or equal to 50% reduction in the difference between the involved and uninvolved light chain or greater than or equal to 50% reduction in plasma cells in the bone marrow. If plasmacytoma at diagnosis: greater than or equal to 50% reduction in tumor size.
- Stable Disease: No criteria for RCs, RC, RPMB, RP, or disease progression.

Currently, several studies demonstrate that obtaining profound responses, such as strict complete response and minimal negative residual disease, characterized by the complete answer and clonal infiltration of plasma cells in the bone marrow of <1/10 5, after treatment has led to an increase in free survival of progression (SLP) and overall survival (OS).

Maintenance Therapy

A still controversial topic in the treatment of Multiple Myeloma, strategies to define maintenance in eligible patients can be performed based on the risks and quality of the therapeutic response obtained after HSCT [112].

In patients ineligible for HSCT, a clinical study in phase III demonstrated an advantage of (SLP) and (SG) for patients who used the regimen of lenalidomide associated with dexamethasone, with the maintenance of lenalidomide until progression [99].

In patients eligible for HSCT, maintenance with an immunomodulator (thalidomide or lenalidomide), in association or not with corticosteroids, showed an advantage in PFS, but not in SG [113]. However, caution should be exercised since thalidomide has shown many adverse events, especially peripheral neuropathy, affecting the quality of life of these patients.

Regarding only the drug lenalidomide, which is used until disease progression, two studies showed advantages in PFS, one of which also demonstrated a benefit in GS [114].

Relapse and Refractoriness

Relapse refers to a disease that progresses after a period of remission. Classic relapse is the appearance of clinical change related to MM activity or defined as an increase of at least 25% of the serum or urinary monoclonal component of a nadir, absolute increase ≥0.5 g/dL and ≥200 mg/24 h, or free involved/uninvolved light chain ratio >100 mg/L. [115]

Refractory patients progress while they are in therapy or within 60 days of the end of their last treatment. Patients who do not obtain at least minimal response are defined as primary refractory [115].

Most patients with MM will eventually evolve with relapses, needing different rescue treatments, thus becoming an arduous task for your hematologist. In addition, as patients experience relapses, the effectiveness of the regimens is reduced, as it is related to the genomic complexity of tumor cells and the acquisition of mutations and/or epigenetic alterations, requiring new drug classes with different mechanisms of action.

Numerous and effective therapies are available, and the choice depends on several factors, such as response to previous treatment, drug availability, the aggressiveness of the relapse, eligibility for a new bone marrow transplant, and whether the relapse occurred while the patient was or was not receiving therapy (two).

In addition to the new drug classes that are being approved worldwide, we must remember the allogeneic bone marrow transplant, which, although currently little used, must be remembered in some selected cases. In addition, some patients may also benefit from clinical trial treatments.

The main therapeutic options available in Brazil suggested by the National Comprehensive Cancer Network (NCCN) for MM relapse are listed below:

- Bortezomib, Lenalidomide Dexamethasone
- Carfilzomib, Lenalidomide, Dexamethasone
- Carfilzomib, Thalidomide, Dexamethasone
- Daratumumab, Bortezomib, Dexamethasone
- Daratumumab, Lenalidomide, Dexamethasone
- Ixazomib, Lenalidomide, Dexamethasone
- Elotuzumab, Bortezomib, Dexamethasone
- Elotuzumab, Lenalidomide, Dexamethasone
- Polychemotherapy (selected cases)

Main Complications

Hyperviscosity syndrome is a classically known oncological emergency in multiple myeloma characterized by neurological deficit, visual changes, and mucosal bleeding. The pathophysiology of the syndrome involves slow blood flow with impaired microvascular circulation and tissue hypoperfusion. Therefore, the treatment must be immediate, with clinical measures and therapeutic plasmapheresis [109].

Infectious conditions are frequent complications related to the underlying disease itself, given its damage to the humoral immune system. In addition, immunosuppressive therapy potentiates infections by encapsulated agents. Therefore, prophylactic antibiotics are recommended in certain situations.

Thrombotic events are also noteworthy in patients with multiple myeloma. Again, there are factors related to the patient, such as cardiovascular diseases, surgical procedures, obesity, smoking, and selected drug therapy factors.

The option of using chemotherapy drugs known as immunomodulators, especially lenalidomide and thalidomide, are drugs considered pro-thrombotic and, therefore, favor the appearance of thrombotic events.

Depending on the identified risk factors of the patient with multiple myeloma, prophylactic therapy with aspirin (100 mg/day) or even full anticoagulation (especially warfarin or low molecular weight heparin) should be discussed with your hematologist.

Support Care

- Bone Disease

  A common manifestation in MM that causes significant morbidity in patients. Bisphosphonates, such as zoledronic acid and pamidronate, remain the main treatment and reduce skeletal events, hypercalcemia, bone pain, vertebral fractures, spinal compression, among others. It must be used for 2 years.

  Other treatments include radiotherapy, orthopedic surgery, and drug analgesia, remembering to avoid the use of non-steroidal anti-inflammatory drugs due to the potential risk of associated kidney damage.

  The use of the drug Denosumab for the treatment of MM bone injury was recently incorporated. An anti-RANK binding monoclonal antibody that can be used without dose adjustment in patients with renal failure.
- Anemia

  Anemia in MM is a frequent complication, and its cause is multifactorial. It can be caused by medullary plasma cell invasion in the MM, drug toxicity, and even overlapping of more than one disease. As an example, we have deficiency anemia associated with anemia by neoplastic infiltration.

  As supportive therapy in these cases, transfusion support with packed red blood cells and the subcutaneous use of the drug erythropoietin stand out.
- Infections

  Infectious surveillance in these patients is essential given their increased risk of severe infectious conditions. Indication for prophylactic antibiotic therapy will depend on the treatment used, associated comorbidities, and the joint decision of your hematologist.
- Thrombotic events

  A topic already discussed above, surveillance of thrombotic events, is necessary for the treatment of MM at all stages of the disease, especially if the patient will use immunomodulating drugs (especially thalidomide and lenalidomide).
- Renal insufficiency

  On many occasions, a nephrologist is needed for the proper management of kidney damage in these patients. They range from oral drug therapies to renal replacement therapy (hemodialysis).

Outcome

Despite being considered a complex hematologic neoplastic disease, still considered incurable, the outcome of patients with multiple myeloma has improved significantly in recent years, which is due both to the development of new drugs and to greater knowledge of the biology of the disease.

11.5 Bone Marrow Transplantation

11.5.1 Introduction

Hematopoietic stem cell transplantation (HSCT) is a treatment modality that consists of the intravenous infusion of hematopoietic stem cells (HCTH) to reestablish the medullary and immune function since these cells can multiply and differentiate into all mature blood cells. HSCT can be obtained from the patient himself (autologous) or from a donor of the same species (allogeneic), whether related or unrelated. These cells can be taken directly from the bone marrow. They can be collected from the peripheral blood circulation and also from the umbilical cord [116].

It is used primarily to treat hematologic diseases, although other conditions are also treated (Table 11.2).

Today, Brazil has 87 bone marrow transplant centers to carry out these procedures. And, per year, it is estimated that more than 3000 procedures are performed, including autologous (1827) and allogeneic (1235)—according to data presented by the Brazilian Association of Organ Transplantation (ABTO) in 2018.

Given the morbidity and mortality of the procedure, its indication is formalized after the patient's assessment, taking into account age and comorbidities and the calculation of risk scores related to the transplant.

Table 11.2 Main indications for hematopoietic stem cell transplantation

Autologous transplant	Allogeneic transplant
Neoplastic diseases Multiple myeloma Hodgkin's and non-Hodgkin's Lymphomas Acute Myeloid Leukemia Neuroblastoma Ovary cancer	Neoplastic diseases Acute myeloid leukemia Acute lymphoid leukemia Chronic myeloid leukemia Myelodysplastic syndromes Myeloproliferative diseases Hodgkin's and non-Hodgkin's Lymphomas Chronic lymphoid leukemia Multiple myeloma
Other diseases Germ cell tumors Autoimmune diseases	*Other diseases* Aplastic anemia Paroxysmal nocturnal hemoglobinuria Fanconi's anemia Blackfan-Diamond anemia Thalassemia major anemia Sickle cell anemia Combined severe immunodeficiency Wiskott-Aldrich syndrome Inborn errors of metabolism

11.5.2 Types of Transplant

There are three types of bone marrow transplants [116]:

Autologous The donor is the patient himself, in which he is stimulated using medication so that the cells are collected, frozen, and stored until the day of infusion.

Allogeneic The patient receives marrow from another person, which may be a family member or not. The unrelated donor can be found in the national donor bank present in the Bone Marrow Donor Registry (REDOME) or any international donor registry.

Syngenic The donor is an identical twin brother. It is the rarest modality of transplantation due to the low frequency of identical twins in the population.

11.5.3 Sources of Hematopoietic Stem Cells

Hematopoietic stem cells (HSC) are found in different concentrations in bone marrow, peripheral blood, and umbilical cord blood. These cells are obtained through multiple punctures of the posterior iliac crests in the bone marrow, with a donor under general anesthesia. Several nucleated cells greater than 2.0×10^8/kg are recommended for allogeneic transplants to ensure medullary engraftment [117].

Another source is peripheral cells that can be used both in autologous and allogeneic transplants and can be infused fresh or frozen. To obtain it, since the amount of HSC in peripheral blood is lower, two strategies are used: (1) Submit the patient to a course of chemotherapy, combined with administration of growth factor (the most used is granulokine) at the beginning of spinal cord recovery. (2) Use only the growth factor at a dose of 10 mcg/kg/day for 5 days. The ideal time for collection is defined by the number of CD34+ cells in peripheral blood above 10, with a collection objective of 2.0×10^6/kg. To collect these cells by the apheresis procedure, it is necessary to evaluate the peripheral venous network by the blood bank. If this network is terrible, it is mandatory to pass a larger central venous catheter, such as the Schiller catheter. Apheresis is a procedure used to remove a particular component of the blood—in our case, the HSC; it is performed in bed, without the need for anesthesia, with a variable duration according to the number of plasmatic volemia required for the collection target [117].

Umbilical cord blood cells are destined exclusively for allogeneic transplants. It contains a high concentration of HSC, but its volume is limited (50–200 mL), enabling transplants mainly in children and adults with low weight. The collection and freezing are done right after birth, without any risk to the donor and the parturient. It is recommended that 4×10^7/kg be infused to avoid spinal cord attachment failure. Immune reconstitution is usually slow. Umbilical cord blood transplantation has been widely used in patients without a family donor who urgently needs transplants [118].

Another source is haploidentical donor HSC, in which the use of cyclophosphamide after transplantation is one of the techniques that have been used the most to reduce the possibility of rejection and the high rates of GVHD were commonly found in this type of transplant with HLA incompatibility. Recent publications have shown that haploidentical transplantation with cyclophosphamide-post can lead to survival rates similar to transplantation with unrelated HLA-compatible donors, making it another treatment option for patients without HLA-compatible family donors [119].

11.5.4 Autologous Transplant

Autologous transplantation is one in which the bone marrow precursor cells come from the transplanted individual (recipient). This type of transplant is used for diseases that do not affect the quality of the bone marrow, that is, those that do not originate directly in the marrow or when the disease has already decreased to the point where it is no longer detected in the marrow (state of remission). The most common is multiple myeloma and Hodgkin's and non-Hodgkin's lymphomas.

The patient undergoes pre-transplant general clinical assessment to assess possible risks and contraindications—disease status (complete remission, partial remission), age, performance status, and comorbidities are taken into account. Afterward, it is mobilized with growth factor in high doses, associated or not with chemotherapy, followed by a collection of cells by apheresis. HSC can be frozen for later use or fresh infused (most common in multiple myeloma transplantation).

Then, we subject the patient to conditioning (high-dose chemotherapy), which is performed by intravenous infusion through a central venous catheter (double or triple lumen). It varies according to the underlying disease, the most used being: for lymphoma, the BEAM (Carmustine, Etoposide, Cytarabine, and Melphalan) and BeEAM (Bendamustine, Etoposide, Cytarabine, and Melphalan) protocols; for multiple myeloma, high-dose melphalan; and, for acute myeloid leukemia, the BuCy (Busulfan and Cyclophosphamide) and BuMel (Busulfan and Melphalan) protocols. Afterward, HSC infusion is performed on D0. The patient remains hospitalized for clinical and transfusional support and control of the main collection effects—febrile neutropenia and mucositis—until spinal cord engraftment [119].

11.5.5 Allogeneic Transplant

Allogeneic transplants are those in which HSC comes from another individual (donor), according to the level of compatibility of the blood material. This modality takes place in several stages, starting with the decision on the need for this transplant —is the indication well done? Does the patient's age and comorbidities allow its performance without adding high risk for him? The diseases in which it is more

indicated are acute leukemias, severe aplastic anemia, Fanconi anemia, and immunodeficiencies [120].

Once the need is defined, the next step is the search for the best donor, who is preferably family; when it does not exist, the search begins in the registry of voluntary donors (REDOME). These are also evaluated for health, venous access, and willingness to donate.

The next step consists of the conditioning regimen that aims to reduce and even eradicate the underlying residual disease and induce immunosuppression in the donor to accept the graft. A central venous catheter (Hickmann, double or triple lumen) is inserted for chemotherapy administration due to the risk of extravasation of chemotherapy in peripheral access and its complications. Conditioning can be at high doses (myeloablative), at reduced doses (non-myeloablative), or reduced-intensity (RIC). The main conditioning regimens are as follows: (1) Myeloablative: cyclophosphamide + anti-thymocyte globulin associated or not with total body irradiation (TBI) for aplastic anemia; Busulfan + Cyclophosphamide or Cyclophosphamide + TBI for acute leukemia and myelodysplasia. (2) Non-myeloablative: Fludarabine + Busulfan associated or not with TBI, Fludarabine + Melphalan, Fludarabine + TBI [120].

The next step is the infusion of HSC through the central venous catheter. It is also essential to use immunosuppressive agents (e.g., tacrolimus, mycophenolate, cyclosporine, and methotrexate) for a variable period for prophylaxis of Graft Against Host Disease (GVHD). The patient remains hospitalized for side effects control—mucositis, febrile neutropenia, acute GVHD, Hepatic Sinusoidal Obstruction Syndrome (SOS)—clinical and transfusional support until spinal graft.

The donor's immune system can recognize the recipient patient's cells, including tumor cells, as foreign and reject them. This beneficial reaction is called the graft versus tumor effect. In many types of cancer, the immune response caused by the transplanted cells improves the overall effectiveness of the treatment. This immune response helps kill any residual cancer cells. However, in the same way, an immune response against the recipient's normal tissues, called graft-versus-host disease, can occur.

11.5.6 Complications

Mucositis It is one of the most frequent complications in BMT, especially in those who use myeloablative conditioning regimens. It is characterized by lesions, usually ulcerated, in the oral cavity, associated with pain and low food intake. In addition to general oral health care, a laser can be helpful in prophylaxis and treatment. Mucositis can affect any mucosa-lined region; consequently, nausea, vomiting, and diarrhea may also be present [120].

Febrile neutropenia The transplant patient is intensely immunosuppressed, therefore, very vulnerable to opportunistic infections, especially during the period of aplasia. The most common is infection with Gram-negative bacteria translocated

from the gastrointestinal tract. However, viral (cytomegalovirus reactivation, hemorrhagic cystitis by BK virus or adenovirus) and fungal (candidemia, aspergillosis) infections may also occur [120].

Hepatic sinusoidal obstruction syndrome (SOS) Also known as a hepatic venous-occlusive disease (VOD), it is characterized by painful hepatomegaly, jaundice, and fluid retention. It results from damage to sinusoidal endothelial cells, obstructing the hepatic circulation and hepatocellular injury. It is potentially fatal. The use of total body irradiation, Busulfan, and cyclophosphamide are some drugs that can cause SOS. Some risk factors such as chronic liver disease and specific hemochromatosis gene polymorphisms are well established. Prophylaxis through careful selection of the conditioning regimen should be recommended and the use of ursacol and anticoagulant until permissive platelet count. The use of defibrotide is indicated in severe cases [120].

Acute graft versus host disease (GVHD) It is the most critical complication of allogeneic BMT and is triggered by cytotoxic T lymphocytes from the donor. Acute GVHD can affect the skin, liver, and gastrointestinal tract (GIT). It affects about 50% of patients despite prophylaxis, and the main risk factor is the incompatibility of the HLA system. The initial treatment for patients with an acute GVHD grade greater than or equal to II is immunosuppression performed with corticosteroids [121].

Chronic graft versus host disease (GVHD) Occurs later, and the main risk factors are: older age, source of peripherally collected HSC, unrelated donors, and presence of acute GVHD. It results from loss of self-tolerance and often resembles autoimmune diseases such as scleroderma and Sjogren's syndrome. It can affect one or more organs such as skin, eyes, salivary glands, mouth, TGI, liver, and lungs. Patients with extensive disease require prolonged use of immunosuppression, leading to secondary chronic complications such as diabetes, osteoporosis, and infections. It is associated with the effect known as graft-versus-tumor since patients affected by chronic GVHD have a lower recurrence rate of the underlying disease [121].

Secondary neoplasms The type and intensity of the conditioning regimen used, as well as the prolonged use of immunosuppressants, may lead to a higher risk of developing skin tumors, oral mucosa, central nervous system, thyroid, and bones in those who underwent allogeneic BMT. On the other hand, patients treated with autologous BMT are at increased risk of secondary hematologic malignancies such as myelodysplastic syndromes and acute leukemias.

11.5.7 Support

Venous access The central venous catheter (CVC) is a fundamental tool for patients undergoing an HSCT, it is necessary for HSC collection and infusion, administration of chemotherapy to minimize the risk of leakage, and support throughout the

process (hydration, antibiotic therapy, transfusion of blood components, vasoactive drug, and hemodialysis in more severe cases). However, a CVC requires correct handling to avoid malfunction due to complete occlusion, displacement, bending, rupture, thrombosis, or life-threatening complications such as catheter-related bloodstream infection [122].

Transfusion support Transfusions are an essential part of care in the context of HSCT, with platelets and red blood cells being the most transfused blood components. These should be filtered to reduce febrile non-hemolytic reactions, in addition to decreasing the incidence of alloimmunization for leukocyte antigens and the risk of cytomegalovirus transmission; and should be irradiated to reduce the risk of transfusion-associated graft-versus-host disease, which is a rare and severe complication in which viable T lymphocytes in the donated pouch mount an immune response against the recipient. In case of ABO incompatibility between donor and recipient, attention must be paid to which stage of the transplant the patient is in to adjust the blood type of the blood component to be transfused [122].

Nutrition Transplant patients, particularly allogeneic, are at risk of malnutrition, which is associated with poor clinical outcome, decreased overall survival, increased risk of infectious and immunological complications, delayed neutrophil grafting, and prolonged hospital stay. Nutritional support must be individually adapted and reduce the caloric deficit and reduce the risk of negative metabolic effects [122].

Vaccination It should be considered a routine practice for all HSCT recipients, whether autologous or allogeneic, adults or children, and must include those who live with the patient. The recommendations of the international consensus can be found in Table 11.3 [123].

Follow-up Transplant patients should be consulted periodically to evaluate complications such as relapse of the underlying disease, chronic GVHD, cardiovascular diseases, secondary neoplasms.

Editor's Comments

Bone marrow transplantation is applied to patients with hematological neoplasms, solid neoplasms, and autoimmune diseases. The patient's bone marrow is replaced by new stem cells, capable of populating it and regenerating new blood cells.

Autologous and allogeneic hematopoietic stem cell transplantation of cytokine-mobilized peripheral blood stem cells (PBSCs) is increasingly used to treat patients with hematologic disorders.

Stem cells can be obtained from the umbilical cord, bone marrow, or blood (apheresis). Blood collection can be performed through peripheral access in the upper limb or a double-lumen catheter, requiring a flow of between 50 and 100 mL/

Table 11.3 International consensus recommendations (Ljungman et al. [123])

Vaccine	No. of doses	Time post-HSCT to initiate vaccine
Influenza (inactivated)	1 2 for children <9 years, or if <6 m from HSCT	4–6 months, yearly, lifelong seasonal vaccination
Measles[a] Mumps Rubella (in adults for sero(-) females with pregnancy potential)	1 (2 in children)	24 months
Hepatitis B virus (HBV) (follow country recommendations for general population)[b]	3	6–12 months
Human papillomavirus follow recommendations for general population in each country	Follow recommendations for general population in each country	
Inactivated polio	3	6–12 months
Pneumococcal conjugate (PCV) Polysaccharide pneumococcal vaccine (PPS) In case of GVHD, use PCV instead of PPS for this 4th dose	3 1 1	3–6 months 6 months after last PCV
Meningococcal conjugate (follow country recommend for general population)	1	6–12 months
Haemophilusinfluenzae conjugate	3	6–12 months
Diphtheria-tetanus (DT preferred over Td)	3	6–12 months
Pertussis (acellular) (DTaP preferred over Tdap)	3	6–12 months

[a]MMR. These vaccines are contraindicated (EIII) before 24 months post-HSCT or in case of active GVHD or IS. These vaccines are usually given together as a combination vaccine

[b]VHB. Vaccination is recommended for HBV surface Ag-negative or HBV core Ab-positive patients, as vaccination can reduce the risk of reverse seroconversion (BII). For HBV surface Ag-negative or HBV core Ab-negative HSCT patients, recommendations for the general population in their country of residence should be followed

min [124]. The collection from peripheral veins can be performed through a venous access (intermittent flow) or two accesses (continuous flow) [125].

The 2007 international registry [126] showed that the main access routes used in apheresis were as follows:

- The non-implantable central venous catheter
- Peripheral veins
- The femoral vein (through a catheter)

The catheter was the preferred route in Asia and the Americas, while the peripheral venous in Europe and Australia. Femoral access was the second route of choice in Asia.

The advantages of using the catheter are the guarantee of constant flow during collection and the absence of punctures in the limbs. Among the disadvantages are

the procedures' costs and the (low, but not null) rates of complications [127] such as thrombosis, infection, and pneumothorax, especially considering if any of them occur in a healthy donor.

In the study by Couzin et al. [128] 617 apheresis sessions were performed in 273 patients and 128 healthy donors for allogeneic or autologous transplantation. The main indications were multiple myeloma and lymphoma. Apheresis was performed through peripheral venous access in 380 patients (94.8%), accounting for 584 sessions (94.7%). The central venous catheter was used in 21 patients (5.2%), accounting for 33 sessions (5.3%). Only four donors (0.9%) for allogeneic transplantation needed a catheter. There was no difference between the groups regarding the quality of the collection product, assessed through CD34+ count and neutrophil contamination.

During bone marrow transplantation, the patient will always need a central catheter during some treatment stage, whether for the administration of chemotherapy, cell infusion, transfusion of blood products, collection of blood tests, administration of antibiotics, or other types of intravenous support.

An interdisciplinary discussion is essential for deciding the venous accesses to be employed, as they involve issues of costs and complications in patients who are temporarily transiently immunocompromised. Factors such as using another central catheter, conditioning for bone marrow transplantation, leukopenia, and acute myeloid leukemia are independent risk factors for the occurrence of central venous catheter-related infection in patients with neoplasms [129].

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General Principles

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Chapter 12
Vascular Toxicity and Cardiotoxicity of Cancer Treatment

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12.1 Introduction

Recent advances and the increase in the therapeutic arsenal against cancer have impacted on the reduction of mortality from this disease, with an important increase in survival in the last three decades. Concomitantly, the spectrum of toxicities related to cancer treatment has also been expanded through new presentations and with a new level of clinical significance, given the increase in the number of patients with morbidity and mortality related to adverse effects. Thus, the impact of the toxicity of these therapies has gained greater importance and concern for the involvement in the various systems, especially the cardiovascular system [1, 2].

In addition to the direct cardiovascular changes caused by chemotherapy, there may also be decompensation and worsening of pre-existing cardiovascular diseases (especially when not properly treated), in some cases impacting the course of cancer treatment [1, 2].

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12.1.1 Cardiotoxicity

Cardiotoxicity is defined as any evidence of cardiac injury secondary to cancer treatment, leading to a decline in cardiac function. Acute cardiotoxicity is defined as that which occurs within 1 week of starting treatment. The chronic form, on the other hand, can start early or late (that is, within or after 1 year after the completion of cancer treatment). This decline in cardiac function caused by cardiotoxicity is usually triggered by more than one mechanism and can present with several changes in the cardiovascular system. These damages can be caused by direct injury to cardiomyocytes, changes in perfusion and innervation, hormonal disruptions and by infiltration of inflammatory cells in the myocardium. The result of this aggression leads to direct effects on the cardiac structure (myocardial fibrosis)—impacting on systolic and diastolic function, conduction disorders, systemic and pulmonary vascular effects, and also on the myocardial response to stress. As a final result of this process, cardiotoxicity can present with cardiomyopathies, arrhythmias, venous thromboembolism, acute vasospasm, arterial thrombosis, and accelerated atherosclerosis [2, 3]. A decline in cardiac function in patients with cancer can occur as a consequence of direct toxic effects of cancer therapies on the myocardium or secondary to other alterations that translate into a reduction in cardiac function. Nontoxic or nonreactive primary inflammatory myocarditis is a unique subtype of cancer therapy-related cardiomyopathy, and requires immunosuppressive treatment.

Treatment of the underlying or contributing abnormality is crucial to the restoration of cardiac function, and also, heart failure therapy is essential. Table 12.1 shows the cancer therapies that have been associated with each type of cardiomyopathy, as well as the diagnosis and management strategies.

12.1.2 Conventional Chemotherapy, Target Therapy, and Immunotherapy

Conventional chemotherapy drugs are chemical compounds designed to attack tumor cells, acting on their high metabolic demand and mitotic activity. However, the action of these drugs is not specific and, therefore, the potential for adverse effects due to damage to normal cells is quite high. One of the most effective and prominent examples of this class of drugs is anthracyclines, which between their actions intercalate between base pairs of DNA or RNA strands and thus inhibit the synthesis of DNA or RNA. As with other conventional chemotherapeutics, cardiotoxicity is an adverse dose-limiting effect of anthracycline therapy. Like anthracyclines, there are a range of other drugs belonging to this class [2, 3].

Target therapy is a newer class of drugs in the treatment of cancer. Unlike conventional drugs, these chemotherapy drugs are more specific and were designed with the objective of obtaining higher success rates with lower complication rates.

Table 12.1 Cancer therapy-related cardiomyopathy

	Direct effect on the myocardium	Indirect effect on the myocardium	Effect related to myocarditis
Therapy			
Doxorubicin	Yes	Yes	Yes (toxic or reactive)
Cyclophosphamide	Yes	Yes	Yes (toxic or reactive)
5-Fluorouracil	Yes	Yes	NR
HER2 inhibitors	Yes	Yes	NR
VEGF inhibitors	Yes (related to TKIs)	Yes	Unclear
ICIs	Possible	Possible	Yes (immuno-mediated)
Radiation therapy	Yes (at high dose)	Yes	Yes (toxic or reactive)
Diagnosis			
Imaging	Echocardiography, cardiac MRI, MUGA scan	Echocardiography, (stress) cardiac MRI, nuclear stress test, CT coronary angiography, vasoreactivity studies	Cardiac MRI, PET, echocardiography
Biomarkers	Consider using cardiac troponins, natriuretic peptides (especially long term)	Catecholamines ECG abnormalities (e.g., ST-segment shifts, T-wave inversions)	Cardiac troponins, natriuretic peptides, ECG abnormalities (e.g., heart block, ectopy)
Management			
Treatment	Consider holding cancer treatment, β-blocker (carvedilol), ACE inhibitor, ARB, spironolactone	Consider holding cancer treatment, treat the underlying cause (e.g., correction of myocardial ischemia or valve disease)	Consider holding cancer treatment; for ICI therapy, anti-inflammatory, and immunosuppressive therapy, supportive care

ACE angiotensin-converting enzyme, *ARB* angiotensin-receptor blocker, *ECG* electrocardiogram, *ECMO* extracorporeal membrane oxygenation, *ICI* immune checkpoint inhibitor, *MUGA* multi-gated acquisition, *NR* not reported, *PET* positron emission tomography, *TKI* tyrosine kinase inhibitor, *VEGF* vascular endothelial growth factor

They are drugs that target the molecular action of malignant cells. A classic example is trastuzumab, a humanized antibody directed against HER2, which is overexpressed in 15–20% of breast cancers. HER2 inhibition, therefore, has resulted in revolutionary clinical success. However, even though it is a targeted medication, studies have revealed an incidence of trastuzumab-related cardiotoxicity of 15–20% and HF <5%. However, when therapy with trastuzumab was discontinued, cardiac function was recovered close to baseline in most patients. Table 12.2 lists other drugs in this therapeutic class [2].

More recently, treatment with immunotherapy appeared. These drugs are even more specific and were developed with the aim of training the host's immune cells to recognize, target, and destroy cancer cells. Although less cardiotoxic, they also have adverse cardiovascular effects (Table 12.2) [2].

Table 12.2 Cardiovascular toxic effects of cancer immunotherapies

Immune checkpoint inhibitors	Cancer therapy indications (label and off label)	Toxicity	Arrhythmia	Vascular toxicity
Ipilimumab (anti-CTLA4)	Colorectal cancer, melanoma, RCC, SCLC	+	+	+
Nivolumab (anti-PD1)	Colorectal cancer, HNSCC, hepatocellular carcinoma, HL, melanoma, NSCLC, RCC, SCLC, urothelial carcinoma	+	+	++
Pembrolizumab (anti-PD1)	Cervical cancer, gastric cancer, HNSCC, hepatocellular carcinoma, HL, melanoma, Merkel cell carcinoma, NSCLC, primary mediastinal large B cell lymphoma, urothelial carcinoma	+	+	+
Atezolizumab (anti-PDL1)	Breast cancer (triple negative), NSCLC, SCLC, urothelial carcinoma	+	–	+
Avelumab (anti-PDL1)	Merkel cell carcinoma, urothelial carcinoma	+	–	–
Durvalumab (anti-PDL1)	Nonsmall-cell carcinoma, urothelial carcinoma	+	–	–
Tisagenlecleucel (anti-CD19)	ALL, diffuse large B-cell lymphoma	++	+++	++

Frequency of cardiovascular toxic effects: – not reported, + uncommon (<1%), ++ common (1–10%), +++ very common (>10%). *ALL* acute lymphoblastic leukemia, *CAR* chimeric antigen receptor, *CTLA4* cytotoxic T lymphocyte antigen 4, *HL* Hodgkin lymphoma, *HNSCC* head and neck squamous cell carcinoma, *NSCLC* non-small-cell lung cancer, *PD1* programmed cell death 1, *PDL1* programmed cell death 1 ligand 1, *RCC* renal cell carcinoma, *SCLC* small-cell lung cancer

12.2 Vascular Toxicity

Cardiomyopathy is the most common cardiovascular toxicity related to cancer treatment. Nonetheless, vascular toxicity stands for the second most common cancer therapy-related cardiovascular complication. Vascular events include not only venous thromboembolism (a well-known and deeply discussed disease), but also arterial thromboembolic events (ATEs). Although less discussed, ATEs are frequent in cancer population: in these patients, rates are more than double compared to healthy population [1].

ATEs can be defined as any thromboembolic event that affects arterial beds, including coronary arteries, cerebrovascular system, and peripheral arteries. According to Herrmann J [2], ATEs can be categorized into three main types: acute vasospasm, acute thrombosis, and accelerated atherosclerosis. These groups will be briefly discussed in the following sections.

12.2.1 Acute Vasospasm

Acute vasospasm is a recognized complication related to 5-fluorouracil (5- FU) and capecitabine (5-FU oral prodrug), and has been discussed since the 80thies [3]. Vascular smooth cell hyperreactivity and endothelial dysfunction (direct 5-FU toxic effect) are some of the proposed mechanisms of these events [4]. As a consequence, patients with baseline endothelial dysfunction (i.e., any atherosclerotic disease—clinical or subclinical) are at high risk for 5-FU-related vasospasm [5]. Clinical presentation includes angina in almost half of cases (45% of patients) [6]. Less common presentations are: myocardial infarction (22%) and arrythmias (23%), and rarely cardiogenic shock, heart failure, Takotsubo cardiomyopathy, cardiac arrest (<5%) [6].

Other cancer therapies less frequently related to vasospasm are paclitaxel (might be associated with myocardial ischemia) and cisplatin/vinca alkaloids (related to endothelial dysfunction and eventually coronary events) [7].

Management of acute vasospasm should follow available guidelines for each clinical syndrome presented. Limited evidence is available regarding the safety of cancer therapy re-exposure after vasospasm occurrence. In this scenario, vasodilators can be offered, although its efficacy against new vasospasm episodes remains unknown [8].

12.2.2 Acute Arterial Thromboembolic Events (ATEs)

Acute thrombosis in cancer patients results from the prothrombotic state promoted by cancer cells, especially in the case of pancreatic, lung, and gastric cancer, as well as undifferentiated and advanced cases [9]. ATE's risk was shown to be highest in the month before and after cancer diagnosis; however, it remains elevated during the first year following diagnosis [1]. Regarding the relationship between cancer therapies and ATEs, cisplatin has been extensively related to these events. The classic clinical presentation is acute arterial thrombosis (i.e., coronary thrombosis) in the absence of significant atherosclerosis or plaque rupture. The proposed pathophysiologic mechanism is superficial endothelial erosion, due to direct cytotoxic effect on endothelial cells [10]. Bevacizumab can induce both venous or arterial events, due to its VEGF-inhibitor activity [11]. Nilotinib and ponatinib are tyrosine kinase inhibitors used by chronic myeloid leukemia patients. These drugs have been associated with ATEs like MI and stroke due to a prothrombotic effect [12], in addition to accelerated atherosclerosis (which will be explored below).

12.2.3 Accelerated Atherosclerosis

Beyond its association with vasospasm and acute thrombosis, cisplatin may also result in chronic endothelial dysfunction and accelerated atherosclerosis. Metabolic disorders (like hypertension and dyslipidemia) can affect up to 30% of testicular cancer survivors formerly treated with cisplatin [13], and can play an additive role on the genesis of CV events in this population. Pre-existing atherosclerotic disease and mediastinal radiation therapy might act as co-factors that increase even more the rates of cardiovascular events among these patients. Cisplatin-related general toxicities are related to cumulative dose. Similarly, CV events can start at doses around 850 mg [13].

Anti-BCR-ABL TKIs like nilotinib and ponatinib are also related to accelerated atherosclerosis. Interestingly, progressive peripheral artery disease was described with nilotinib and ponatinib soon after TKIs initiation, in the absence of plaques in other territories [14]. Acute peripheric arterial events were observed with ponatinib, leading to a temporary suspension of sales [15]. The pathophysiology of this effect is not fully understood, but involves mainly chronic endothelial dysfunction and increases on plaque instability [2].

Radiation therapy is another classical factor related to accelerated atherosclerosis, especially when thoracic/mediastinal dose exceeds 30 Gy [16]. Typically, plaques affect proximal segments of large arteries within radiation field [17]. Given the high CV risk profile of cancer survivors due to late cardiotoxic effects of chemotherapy agents and higher incidence of classical CV risk factors, radiation therapy seems to play an additive role in the atherosclerotic process [18]. This issue will be deeply discussed in the specific section of this chapter.

Management of accelerated atherosclerosis should follow available guidelines for each clinical syndrome presented. Since the majority of patients present a chronic course, medical therapy typically is the mainstay of treatment. Serial ankle–brachial indices (ABI) have been suggested as a possible surveillance method during anti-BCR-ABL TKIs treatment [8]. However, screening schedules and cut-off points to trigger treatment modifications/interventions have not been defined.

Prognosis

Navi et al. [1] were able to show that ATEs are associated with increased mortality, even after matching for other factors and the stage of cancer. In this study, 30-day cumulative death rates after ATEs among cancer patients versus controls were presented as 17.6% and 11.6%, respectively [1]. Such high numbers are consistent with other publications that present vascular toxicities as the second most common cause of death in cancer patients undergoing outpatient therapies [2]. Despite this extensive impact on prognosis, ATEs are still poorly studied. More well-designed and well-conducted clinical trials are imperative in this field.

Editor's Comments

Progress in cancer treatment has been responsible for a greater chance of curing patients and, when a cure is no longer possible, greater survival is achieved, with cancer behaving like a chronic disease. However, the treatment of cancer may be responsible for the appearance of new diseases or the worsening of previous diseases, with an impact on mortality and the quality of life of these individuals. Children undergoing cancer treatment have a higher risk of developing cardiovascular diseases in adulthood, such as systemic arterial hypertension, coronary heart disease, carotid disease, and a higher incidence of metabolic disorders, such as dyslipidemia [19].

This chapter deals with the toxic effects of antineoplastic treatment on the heart muscle and the vascular system. The peripheral vascular system is not free of similar complications.

As already discussed in Chap. 9, cancer and atherosclerosis have common risk factors, such as age, smoking, obesity, and physical inactivity. The prevalence of degenerative abdominal aortic aneurysm, related to risk factors for atherosclerosis, was 2.5% among patients with solid tumors over 50 years treated at the Cancer Institute of the State of São Paulo (Icesp), Brazil. Ischemic events occur between 1.5% and 3.1% of cancer patients [20, 21]. Some factors are associated with an increased risk of these ischemic events, such as chronic obstructive pulmonary disease, chemotherapy, kidney disease, blood transfusion, infection, in addition to the state of hypercoagulability caused by cancer and its treatment [22].

Some chemotherapeutic drugs are associated with certain ischemic events, as shown in Table 12.3.

Radiotherapy is known to accelerate the atherosclerotic process, making the disease more severe and extensive in arterial segments in the radiation field [23–25]. This phenomenon is probably the result of microcirculatory damage with consequent endothelial dysfunction, inflammation of the arterial wall, and oxidative

Table 12.3 Chemotherapy and related ischemic events [22]

Chemotherapy	Ischemic event
L-asparaginase	Cerebrovascular events
Cisplatin	Cerebrovascular, peripheral events, aortic thrombosis
Fluorouracil	Cardiac ischemia (coronary vasospasm)
Bevacizumab	Cardiac ischemia (coronary thrombosis), cerebrovascular
Gemcitabine	Digital ischemia, thrombotic microangiopathy
Thalidomide	Arterial thrombosis (rare)
Sorafenib/Sunitinib	Myocardial infarction, cerebrovascular
Bleomycin	Raynaud's syndrome

stress. Radiotherapy treatment is associated with an increased risk of coronary heart disease, especially in patients treated for breast cancer, non-Hodgkin's lymphoma, lung, and carotid, in those treated for head and neck tumors [26–34].

Prevention of ischemic events is based on strict control of blood pressure and blood glucose. The use of antiplatelet agents and statins is prescribed whenever possible. Anticoagulants are not routinely used. Changes in lifestyle, with better eating habits and regular physical activity, are also apparent measures. In an acute arterial thromboembolic event with no apparent cause, full systemic anticoagulation, as long as there is no contraindication at the moment, is prescribed. Revascularization depends on the patient's clinical condition and limb viability. Endovascular procedures are preferred due to less surgical aggression. Open surgery in a previously operated and/or irradiated area can be technically quite challenging.

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Part III
Vascular and Endovascular Surgery

Chapter 13
Vascular Reconstruction in Oncologic Surgery

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13.1 Introduction

The invasion of truncal arteries and veins by malignant neoplasms is rare. Vessel involvement may occur as a result of tumors originating in the vascular wall itself or by contiguous growth of tumor masses. This second condition is the most frequent, leading to direct infiltration or incarceration of the vascular wall.

Conley JJ published in 1953 the first case series addressing arterial reconstructions associated with malignant tumors [1]. The study outlined ten patients who underwent carotid reconstruction, eight due to malignant tumors. There was a high rate of vascular complications, with three graft occlusions and one rupture, resulting in three deaths.

At that time, surgical treatment of patients with malignant tumors presenting vascular, nerve, and bone invasion was restricted. Technical and therapeutic limitations made tumor resection extremely difficult in these situations. For a long time, these cases were considered unresectable and for almost two decades publications were rare and limited to case reports.

In the end of the 1970s, advances occurred in the treatment of tumors with vascular invasion. The approach to this disease became multidisciplinary, advances occurred in reconstruction, and revascularization techniques and effective adjuvant therapies developed. These technical refinements and growing expertise made the concept of tumor unresectability due to vascular invasion to be practically abandoned.

More recently, for some specific tumors such as soft tissue sarcomas, evidence shows that long-term survival outcomes are not affected by the need for vascular resection and reconstruction, suggesting that vascular involvement is not necessarily a predictor of an aggressive biology [2].

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13.2 Surgical Management in Cases of Vascular Invasion

Vascular involvement is suspected and investigated in the preoperative period by means of imaging studies; however, the need for vascular resection is determined according to intraoperative findings. When adequate safety margins for tumor resection cannot be obtained due to the proximity with vascular structures, three approaches are possible:

1. Subadventitial Vascular Dissection

Subadventitial vascular dissection consists of the release of the vessel that is surrounded by the tumor mass through the dissection of a plane between the vessel adventitia and the tumor. The dissection plane is not always well defined, and in most cases parietal thinning of the vessel wall may occur after resection of the adjacent tumor.

Advantages of this technique include reduced surgical morbidity due to the absence of ischemia and tissue congestion caused by vascular clamping.

The disadvantages include higher chance of local recurrence due to microscopic tumor invasion of the vascular wall, and increased risk of rupture or fistulization to other structures in consequence of the parietal thinning.

In 1977, Kennedy et al. reported 28 patients with cervical carcinomas and carotid invasion [3]. Subadventitial resection was performed in 20 of these patients. Five cases of arterial rupture and 10 cases of local disease recurrence were observed, suggesting the limitations of the technique.

Similarly, in the abdominal region, Jaeger et al. and Donohue et al. reported serious postoperative complications such as aortic rupture and aortoenteric fistula after subadventitial dissection of the aorta for resection of retroperitoneal tumors [4].

2. Vascular Resection and Ligation of the Stumps

This is the fastest technical option, however, associated with varying risks of tissue ischemia and congestion, due to resection of the trunk vessel along with collateral circulation.

Moore and Baker published in 1955 a case series of 88 patients submitted to carotid ligation, most of which were associated with tumor resection [5]. Extremely high morbidity and mortality rates of 45% and 31%, respectively, were observed resulting from cerebral ischemia [5].

Tests used to quantify cerebral collateral circulation, such as arteriography [6], measurement of carotid stump retrograde pressure [7], balloon occlusion test [8], and gradual carotid clamping tolerance test [9], are not entirely reliable to rule out neurological events after carotid ligation.

In the extremities, there are also no useful tests to evaluate collateral circulation status. Fortner et al., in 1977, performed arterial ligatures in three out of the seven patients who underwent tumor resection in lower limbs, and none of them presented

severe ischemia [10]. On the other hand, Paulson [11], in 1975, and Wright et al. [12], in 1987, described cases of arterial ligatures that resulted in severe ischemia and upper limb amputation.

The impact of venous ligation depends on the affected territory. In cervical territory, unilateral internal jugular vein ligation is frequently performed, without significant clinical consequences [13]. In the abdominal segment and extremities, however, the ligation of truncal veins, such as the inferior vena cava, iliac, femoral, and popliteal veins, may lead to acute and chronic venous hypertension, usually with significant symptoms [14]. The joint resection of collateral veins and lymphatic vessels are aggravating factors and generators of edema. Whenever there are intraoperative clinical conditions and technical feasibility, we choose to perform venous reconstruction in all body segments with the exception of the cervical region.

3. Vascular Resection with Reconstruction

This is the preferred technique, recommended for restoring arterial flow and venous return, avoiding ischemia or tissue congestion and their complications. Furthermore, this technique is the most appropriate to enable *en bloc* resection with adequate margins respecting ideal oncological principles.

13.3 Preoperative Evaluation

The surgical oncology team initially assesses all patients. Vascular involvement is suspected when imaging studies such as computed tomography or magnetic resonance fail to demonstrate a well-defined cleavage plane between the tumor and the vascular bundle.

The vascular surgeon's clinical evaluation consists of a thorough medical history and clinical examination. Arterial stenosis or occlusion caused by the tumor mass are rare; however, edema of the extremities resulting from venous compression or occlusion is more frequent.

Duplex scan is important to evaluate the caliber and patency of autologous substitutes (saphenous veins, internal jugular, femoral vessels).

In cases of cervical tumors, contralateral carotid and vertebral artery patency must be carefully assessed by means of duplex scan.

Computed tomography angiography (CTA) is useful to evaluate with greater precision vessels that are not easily accessible with duplex scan, such as abdominal or thoracic vessels. When vascular occlusion is observed in a duplex scan, CTA may be important to complement the findings.

At this point, the vascular substitutes to be used are determined and details such as vessel diameter and extension of vessel resection are taken into consideration to elect the ideal substitute.

13.4 Arterial and Venous Reconstructions

An important aspect of concern in reconstructions associated to malignancies is major trunk and collateral vessel resection leading to tissue ischemia and congestion. Surgical technique should always aim to minimize clamping time. For this, several tactics may be used:

- Clamping and sectioning of the vessels are performed in the last stage of the en bloc resection, after selection of the vascular substitute to be used for reconstruction.
- When the saphenous vein is chosen as substitute, it should be excised and prepared before tumor resection.
- In carotid or extremities reconstructions, temporary shunts (such as the Pruitt-Inahara) can be used to secure distal perfusion. In these cases proximal termino-lateral anastomosis is necessary.
- In tumors invading abdominal vessels such as the aorta or vena cava, temporary bypasses may be performed using polytetrafluoroethylene (PTFE) or dacron grafts (Fig. 13.1).

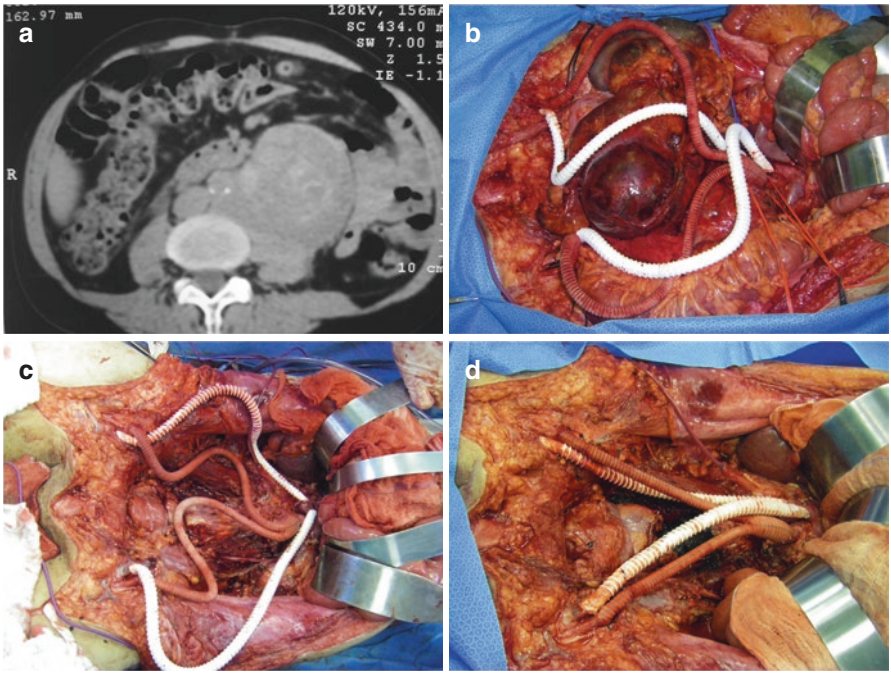

Fig. 13.1 Temporary aorto-bifemoral and bifemoral vein to inferior vena cava derivation for treatment of a germ cell tumor invading the infra-renal aorta: (**a**) CT scan of the tumor showing aortic invasion. (**b**) Temporary aorto-bifemoral (Dacron) and bifemoral vein to inferior vena cava (ringed PTFE) grafts prior to tumor resection. (**c**) Redundant grafts after tumor resection. (**d**) Final appearance after graft adjustments

13.5 Vascular Substitutes

Vascular substitutes for vessel reconstruction can be autologous, synthetic, or homologous. Whenever possible, autologous grafts are preferably used, due to the higher patency rates and lower risk of contamination.

Specific scenarios where autologous materials are highly recommended include vascular reconstruction of the extremities, carotid artery [10], and in surgeries with potentially contaminated fields.

13.6 Autologous Substitutes

The autologous substitute most frequently used for bypasses or patches is the great saphenous vein. Other examples are the small saphenous vein, internal jugular vein, femoral vein, renal vein, peritoneum graft, upper limb veins, and the superficial femoral artery.

13.7 Synthetic Substitutes

The synthetic materials available for vascular reconstruction include Dacron or PTFE grafts. PTFE grafts may or may not have external rings for reinforcement and increased patency. When vascular resection is noncircumferential and primary closure would lead to significant stenosis (greater than 30–40% of vessel diameter) reconstruction can be performed with a patch of bovine pericardium, PTFE or Dacron. Figure 13.2 shows examples of reconstructions using synthetic grafts.

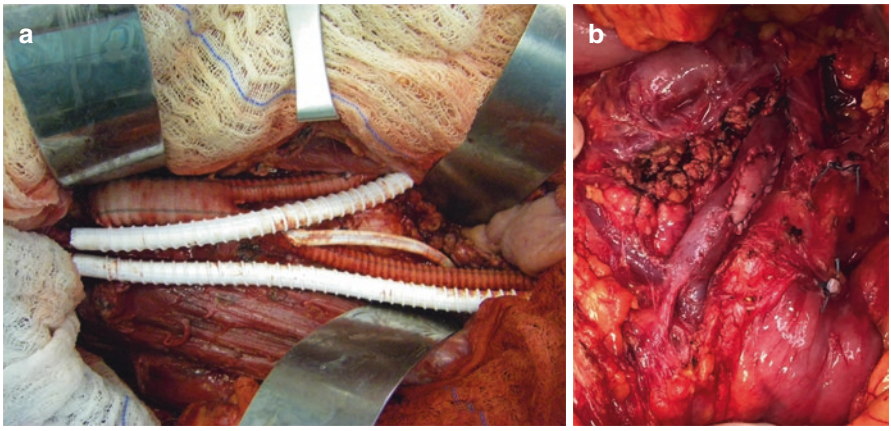

Fig. 13.2 (**a**) Reconstruction of the infra-renal aorta with Dacron and right internal iliac artery with PTFE grafts. Reconstruction of a "neocava" using a ringed PTFE graft. (**b**) Bovine pericardium patch in a portal vein reconstruction

13.8 Homologous Substitutes

Homologous substitutes depend on the existence of a bank of cryopreserved homografts (usually iliac veins and inferior vena cava or aorta) and are used mainly in the reconstruction of iliac veins and inferior vena cava [15].

13.9 Postoperative Care and Follow-Up

In patients undergoing major tumor resections, computed tomography or magnetic resonance are routinely performed every 3 or 4 months in the first 2 years after surgery and become less frequent after the third year of follow-up.

Postoperative follow-up is performed in outpatient visits, with a vascular physical examination and complementary imaging tests. In the cervical territory and in the extremities, duplex scan mapping is performed every 6 months for the first 2 years and then annually.

In the thoracic and abdominal regions, CTA may be necessary if the clinical examination and routine imaging tests used for oncological follow-up are insufficient to confirm the patency and absence of complications of the reconstructions.

In case of suspected complications (stenosis, occlusion, or dilation), a complementary imaging exam should be performed immediately.

13.10 Antithrombotic Therapy After Vascular Reconstruction in Surgical Oncology

The role of antithrombotic therapy in the postoperative care of patients submitted to vascular reconstruction procedures frequently arises discussion and information obtained in the present literature is confusing. Due to the wide range of surgical scenarios and broad variety of anticoagulation and antiplatelet treatments available, management options are diverse and far from a consensus [16–20]. Furthermore, the absence of a standardized protocol allows surgeons to adopt the most varied antithrombotic schemes according to their individual preference.

Evidence does not support routine anticoagulation for reconstructions (arterial or venous) performed with autologous grafts [17–19]. The same idea applies to arterial reconstructions using synthetic substitutes [17, 18].

For venous revascularizations, available evidence is nonconsensual, although most author agree that full anticoagulation with warfarin can be used to increase patency outcomes [16, 17, 20].

Until the present moment there is no clear evidence to support the postoperative use of DOACs to increase patency outcomes after vascular reconstruction in surgical oncology. Extra attention should be taken in cases with associated major

gastrointestinal tract resections since DOACs absorption can be impaired, reducing efficacy for thrombosis prevention [21].

13.11 Singularities of Vascular Reconstructions in Different Body Segments

Tumor invasion of vascular structures can occur in all body segments and in consequence of an enormous variety of tumor subtypes. Each surgical intervention is unique and programmed according to the caliber, extension of invasion, and body segment of the vascular structure involved.

For the purpose of study, an attempt to standardize these countless variables and enable group comparison is to subdivide the revascularization procedures into body segments: head and neck, thorax, abdomen, and extremities.

13.12 Head and Neck

In the head and neck region, squamous cell carcinoma originating in different tissues (skin, tongue, pharynx, and larynx) is the most frequent tumor subtype with vascular invasion. Most patients have local disease recurrence with previous treatment strategies such as surgical resection, chemotherapy, and radiotherapy.

Until the 1990s, both autologous (great saphenous and femoral veins) and synthetic (PTFE, Teflon and nylon) substitutes were employed for head and neck vascular reconstructions. However, high rates of infection were observed in consequence of the nature of surgical interventions in this territory. Exposure and manipulation of the aero-digestive tract mucosa, presence of tracheostomy, manipulation of previously irradiated tissues and salivary fistula are the main predisposing factors for surgical site infections.

Autologous substitutes therefore became the preferred option since the 90s. Sessa et al. published in 1998 a series of 30 patients submitted to carotid reconstruction using the superficial femoral artery, considered by the authors more resistant than the saphenous vein [22]. Even so, complications such as ruptured anastomosis and late asymptomatic occlusions were observed.

Nowadays, almost all reconstructions in this segment involve the carotid artery and are performed using saphenous vein grafts [23, 24]. The saphenous vein presents good caliber compatibility in this territory, with low infection and high patency rates—93% of primary patency in 5 years [24]. However, long-term patency analysis is limited due to the low survival (19.4% in 2 years), resulting from the poor prognosis of the underlying condition [24]. Adequate coverage of the graft with myocutaneous flaps is of extreme importance in this region to reduce infectious complications.

Central neurological complications occur in consequence of graft losses. Early losses (<30 days) are more frequent, usually symptomatic and related to technical failure in surgery resulting in acute thrombosis. Graft infection resulting in arterial rupture and ligation is another cause for early graft loss, leading to hemispheric cerebral ischemia in up to 30% of the cases. Late graft occlusions are often oligosymptomatic.

Other neurological complications result from cranial nerve lesion or resection and include hoarseness (recurrent laryngeal nerve), dysphagia (glossopharyngeal and vagus), and atelectasis (phrenic nerve).

Carvalho A et al. [25] published a series containing 224 patients with advanced cervical neoplasia, without any previous treatment. These patients underwent three different treatment modalities: clinical support (33), radiation therapy (137), and surgery (54). The 3-year survival rates were 7.9%, 7%, and 17.9%, respectively, ($p < 0.001$). Although the prognosis of these patients was poor, the best results were obtained in those treated surgically [25].

Figure 13.3 shows a complex case of multiple vessel revascularizations in the head and neck territory after resection of a recurrent squamous cell carcinoma.

13.13 Thorax

In the thoracic region, vascular reconstructions are associated with a variety of tumors and the most frequent originate in the thyroid, thymus, breast, and lung.

In the largest series containing graft reconstruction in this territory, the synthetic substitute was most frequently used.

Sekine Y et al. published in 2010 a series of 20 patients with tumors invading the superior vena cava that underwent 31 reconstruction procedures with ringed PTFE (8 to 12 mm) grafts [26]. In nine cases, tumors originated in the lung, eight in the thymus, two were germ cells tumors, and one thyroid. No deaths were observed in

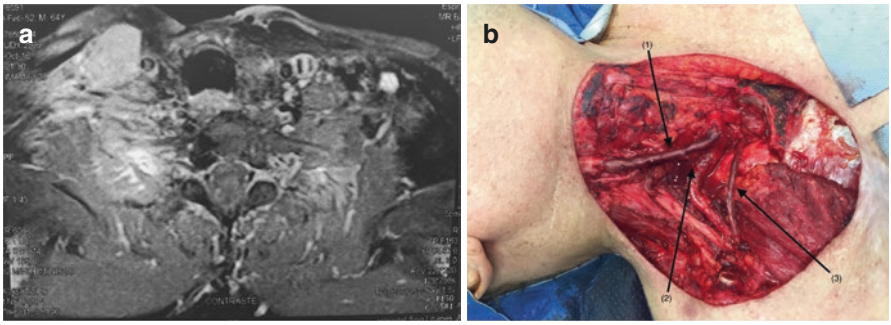

Fig. 13.3 (**a**) Magnetic resonance of a recurrent squamous cell carcinoma in the head and neck segment with multiple vessel invasion. (**b**) (1) Common carotid interposition saphenous vein graft; (2) bovine pericardium patch in the subclavian artery; (3) innominate-subclavian vein interposition with saphenous vein graft

30 days. Seven patients had no postoperative complications. Nonvascular complications were: arrhythmia (5), atelectasis (3), extensive pleural effusion (2), pneumonia (2), respiratory failure (1), bronchial fistula (1), phrenic nerve paresis (4), gastric ulcer (1), paralytic ileus (1) and myasthenia gravis crisis (1).

Single graft reconstruction was performed in nine patients, bilateral grafts in ten patients and bilateral graft associated with pulmonary artery reconstruction in one case. Full anticoagulant therapy with warfarin for 3 to 6 months was used in all patients. No graft occlusions were observed in the initial 4 weeks after surgery. The average follow-up was 45 months and the 1-year primary patency was 70%, which is consistent with primary patency rates observed in the literature that may vary from 62% to 100%. Patients that presented occlusion had symptoms lasting up to 12 months.

In 2015, Mercier O et al. described reconstruction procedures of the subclavian artery in 85 patients [27]. There were 69 cases of nonsmall cell lung cancer, 11 sarcomas, 3 breast, and 2 thyroid tumors. There were no deaths, neurological sequelae, prosthesis infection, or limb ischemia. Nonvascular complications were: pneumonia (16), nerve paresis (6), bleeding (4), pulmonary embolism (1), cerebrospinal fluid leakage (1), chylothorax (1), and wound infection (2).

The reconstruction techniques employed were: end-to-end anastomosis in 48 cases, polytetrafluoroethylene (PTFE) graft interposition in 21 cases, subclavian-to-common carotid artery transposition in 8 cases, and superficial femoral artery graft in 1 case. No deaths, neurological deficits, occlusions, or graft infections were noted. After a median follow-up of 44 months, two asymptomatic PTFE occlusions were observed, occurring 12 and 31 months after surgery, resulting in a 78% primary patency in 5 years. There were no cases of stenosis or occlusion in primary anastomoses reconstructions.

Figure 13.4 illustrates a case of thymoma with superior vena cava invasion.

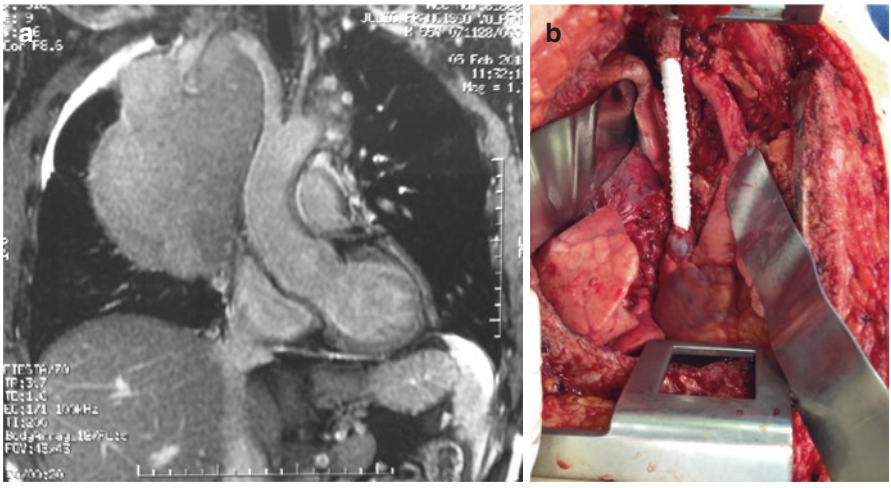

Fig. 13.4 (**a**) CT scan of a thymoma with invasion of the superior vena cava. (**b**) Revascularization of the right innominate vein/superior vena cava using a ringed PTFE graft

13.14 Abdomen

In the abdominal segment, the most frequent tumor types requiring vascular reconstruction are retroperitoneal (sarcomas), kidney, liver, and pancreatic tumors. Due to the large caliber of the vessels in this region, most reconstructions are performed using prosthetic grafts.

In 2006, Schwarzbach MH et al. [28] published a series of 141 patients with retroperitoneal sarcomas and proposed a classification according to the type of vascular involvement: type I, involving arteries and veins (4 patients); type II, involving only arteries (5 patients), type III, involving only veins (16 patients); type IV, without vascular involvement (116 patients). Eight arterial reconstructions with synthetic interposition grafts and one replantation were performed. The venous reconstructions were performed in six cases with synthetic interposition grafts, four patches, two primary closures, and one replantation. Only one case of graft infection associated with arterial and venous graft thrombosis was observed in consequence of a perforated diverticulitis. This complication was treated with graft explanation and extra-anatomical arterial bypass. The median follow-up time was 19.3 months and the primary arterial and venous patencies were 88.9% and 93.8%, respectively.

In 2017, Wortmann M et al. described 20 patients who underwent reconstruction of the abdominal aorta (6) and iliac arteries (14) due to invasion of retroperitoneal soft-tissue sarcomas. Synthetic substitutes were used in 14 patients and autologous in 6, with no complications from aortic reconstructions (all synthetic). Considering the iliac reconstructions, there were two cases of synthetic graft infection requiring explants and two asymptomatic autologous graft occlusions. Disease-free survival at 1 and 2 years were 84% and 46%, respectively.

In 2019, Ferraris M et al. published a series of venous reconstructions associated with retroperitoneal sarcomas. Of the 741 operated patients, 67 (9%) underwent venous resection concurrently, with the iliac veins in 24 patients, inferior vena cava in 39, and inferior cava associated with the iliac vein in 4. All patients received low-molecular-weight heparin in a prophylactic dose for 30–90 days. Primary closure was performed in partial resections when the residual vessel stenosis did not exceed 50% of the original diameter. If residual stenosis exceeded 50% of the original vessel, reconstruction with patch was performed. In cases of circumferential resections, interposition grafts or vessel ligation was performed (when evidence of adequate collateral circulation was observed in preoperative CT scans and intraoperative findings). Regarding the inferior vena cava, 38 circumferential resections (88.4%) and 5 (11.6%) partial resections were performed. Of the patients who underwent circumferential resections, 32 required graft reconstructions (22 with homograft and 10 PTFE grafts) and 6 were treated with ligation. The renal vein was reimplanted in 17 patients. In the patients submitted to graft reconstructions, five presented thrombosis in a median period of 1 month after surgery—all with homografts. Five-year inferior vena cava graft primary patency was 100% for PTFE grafts and 76.7% for homografts.

In the iliac cases, 21 circumferential and 3 partial resections were performed. Considering the patients submitted to circumferential resections, 9 underwent graft reconstructions—1 with homograft, 7 with PTFE grafts, and 1 with contralateral femoral vein—and 12 with ligation. Five patients submitted to graft reconstructions presented thrombosis (one with homograft, three with PTFE grafts, and one with femoral vein) after a median period of 3 months after surgery. All inferior vena cava and iliac vein graft occlusions were treated conservatively. Persistent limb edema occurred in two patients with inferior vena cava involvement (an occluded homograft and a patent PTFE graft) and in five cases of the iliac vein involvement (four ligations and one occluded autologous graft). No graft infections were observed, despite concomitant intestinal resection in some cases.

Figure 13.5 illustrates a case of a retroperitoneal sarcoma with infra-renal aortic and vena cava invasion.

Vascular resection and reconstruction associated with pancreatic surgery is increasingly more common. The procedure is currently considered standard of care for patients with pancreatic head tumors with limited involvement of the superior mesenteric and portal vein [29]. A classification proposed by Jiqiao Zhu et al. include the main surgical tactics for vascular resection and reconstruction according

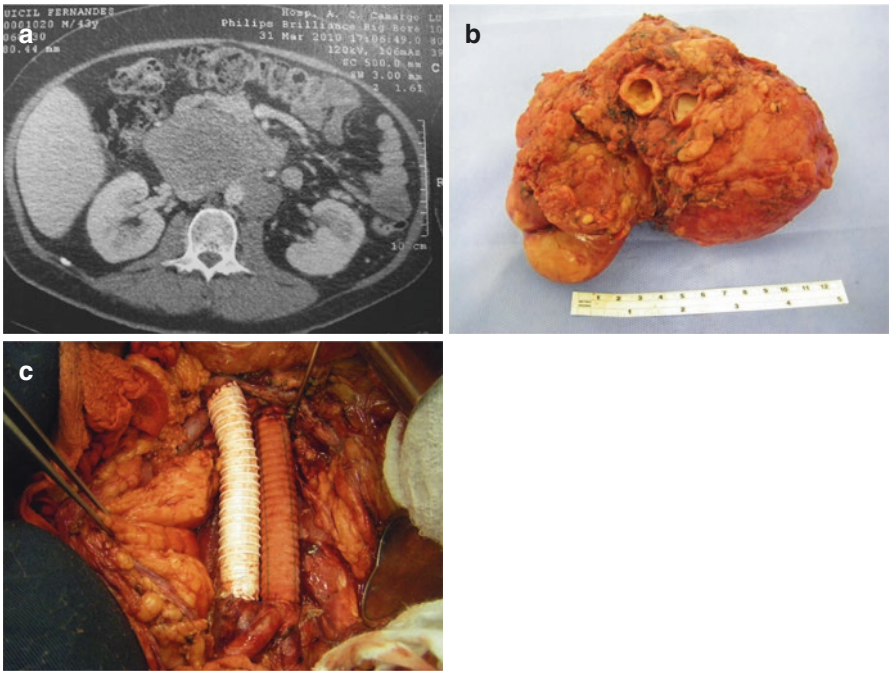

Fig. 13.5 (**a**) CT scan of a retroperitoneal sarcoma with infra-renal aortic and vena cava invasion. (**b**) Macroscopic appearance of excised tumor mass with transverse section of the aorta an inferior vena cava. (**c**) Reconstruction of the aorta and inferior vena cava with Dacron and ringed PTFE grafts

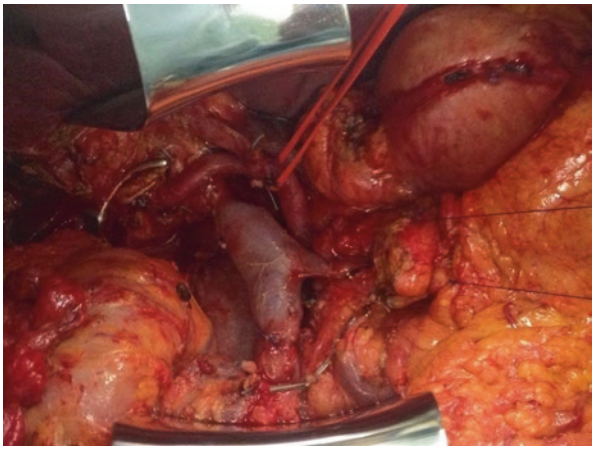

Fig. 13.6 Reconstruction of the spleno-mesenteric confluence using a jugular vein graft. The external jugular vein was used for reimplantation of the splenic vein

to the location and extension of pancreatic tumor invasion [30]. The possibilities include: partial venous excision with direct closure, segmental resection with direct end-to-end venous anastomosis, segmental resection with interposed venous conduit, segmental resection with phleboplasty of the branches of superior mesenteric vein, and interposed venous conduit. The patency noted by Jiqiao Zhu et al. in all of the reconstruction methods exposed above was similar although the sample size was limited [30].

Song W et al. published in 2017 a meta-analysis of 14 studies on superior-mesenteric and portal reconstruction associated with pancreatic tumors [31]. The analysis included 257 patients with graft reconstructions and 570 patients in which reconstructions were performed without grafts (i.e., end-to-end anastomosis or lateral wedge). Mortality and morbidity outcomes related to reoperation, pancreatic fistulas, gastroparesis, hemorrhage, and biliary fistula were similar in both groups.

Perioperative and long-term analysis of the reconstructions was performed. In the perioperative period, thrombosis rates were similar in the two groups (with or without a graft) and were independent of the type of graft used for reconstruction. In the long term (≥6 months) the graft group was associated with a higher rate of thrombosis. The sub-analysis according to the type of graft used (autologous vein or prosthesis) showed a higher incidence of thrombosis for the autologous substitute when compared to the group without a graft. There was no statistical difference when the substitute was prosthetic.

Figure 13.6 illustrates a reconstruction of the spleno-mesenteric junction using the jugular vein as a conduit.

13.15 Extremities

In the extremities, soft tissue sarcomas and osteosarcomas are the tumors most frequently associated with vascular invasion. They present unfavorable outcomes if not aggressively treated with adequate surgical margins. Considering that this type of

tumor generally affects young adults, limb preservation is important since rehabilitation is highly successful despite extensive resections.

For arterial reconstructions in lower extremities, there is a balance between the use of autologous or synthetic substitutes [32]. The internal saphenous vein and synthetic Dacron or PTFE grafts present high patency outcomes [33–35], although results are superior when the autologous substitute is used [36, 37]. Infection is more frequent with synthetic grafts [38]. Due to the greater caliber compatibility and lower infection rates, the saphenous vein is the best option for reconstructions in this territory (Figs. 13.7 and 13.8).

The benefits of venous reconstructions after the resection of tumors in the extremities are controversial. Authors who support venous ligation report that occlusion rates are high and patients present satisfactory control of edema over time with clinical measures (18, 19). On the other hand, routine reconstruction of the lower limbs is performed because the development of disabling chronic venous hypertension symptoms is unpredictable after ligation and may significantly limit

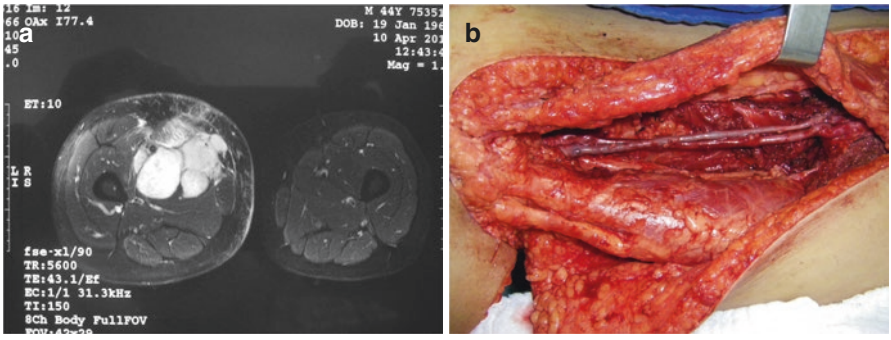

Fig. 13.7 (**a**) Magnetic resonance of a sarcoma with invasion of the femoral vessels. (**b**) Arterial and venous femoral interposition graft using ipsilateral internal saphenous vein grafts

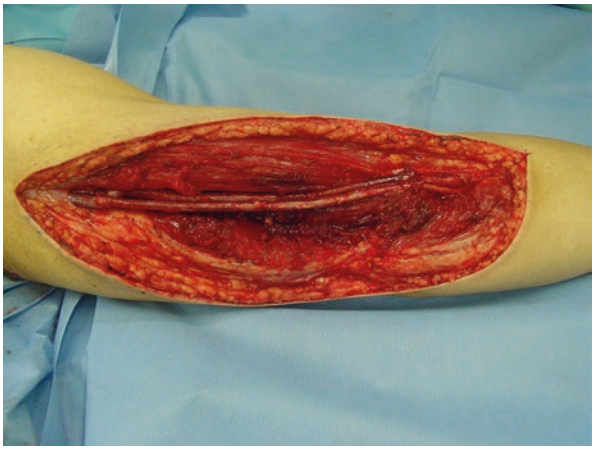

Fig. 13.8 Arterial and venous brachial reconstructions using saphenous vein grafts

quality of life (5). Furthermore, the inevitable resection of lymphatic vessels along with the tumor mass contributes to exacerbation of the edema.

In venous reconstructions of the extremities, studies show a predominance of PTFE over autologous grafts [34, 39]. However, there is also clear evidence supporting the superiority of autologous grafts in terms of lower infection and higher patency [36, 37].

The main neurological complications relate to femoral and fibular nerve injury, requiring physical therapy and the use of orthoses or arthrodesis.

13.16 Experience in Vascular Reconstructions in a Single Cancer Center

In our 20-year single-center experience in vascular reconstructions associated with malignancies, 91 patients were submitted to 139 revascularization procedures with interposition grafts (92 arterial and 47 venous) [23]. Tumors involved all body segments and were distributed as follows: 23 head and neck, 6 upper limb, 3 thorax, 30 abdomen, and 29 lower limbs.

In a median follow-up time of 134 months, the overall arterial patency rates in 24 and 60 months were 96.7% and 84.9%, respectively. The venous patency rates were 71.4% and 64.2% in 24 and 60 months, respectively. The arterial and venous patency curves are presented in Fig. 13.9.

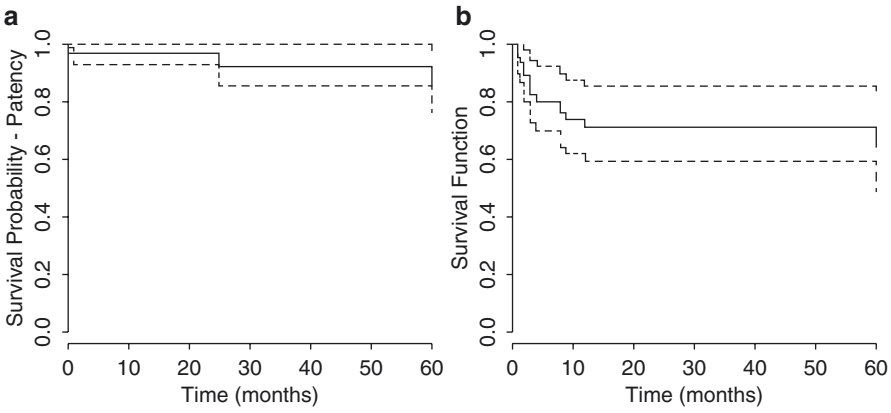

Fig. 13.9 Arterial (**a**) and venous (**b**) patency curves for revascularizations in a single cancer center. (Extracted from *Krutman* et al*, J Vasc Surg, 2018*)

13.17 Conclusion

The treatment of patients with malignant tumors with vascular invasion is complex. Advances in preoperative imaging tests are essential for early diagnosis and definition of treatment strategies. The combination of effective adjuvant therapies and advances in surgical technique enables *en bloc* resection without tumor violation, allowing progressive improvements in survival and cure.

Editors Comments

The suspicion of vascular invasion by tumor cells occurs during the preoperative evaluation through imaging exams. Thus, it is an elective procedure with the vascular surgeon participating in the therapeutic programming from the beginning.

When tumor resection surgery generates inadvertent vascular lesions, revascularizations performed on an "urgent" basis are generally necessary. In these situations, vascular complications and morbidity and mortality rates increase.

Morin et al. [40] underwent retroperitoneal lymphadenectomy in 78 patients, with 17 (22%) requiring vascular intervention. In nine patients, the repair occurred due to inadvertent lesions during resection of the tumor block (aorta = 1, inferior vena cava = 2, renal artery = 6). The evolution of patients who underwent repair of the aorta (aortic-biiliac graft) and the inferior vena cava was satisfactory, but three patients with renal artery lesions required nephrectomy.

Palfalvi L et al. [41] performed 184 radical gynecological interventions, the majority of which were associated with lymphadenectomy. There was a vascular injury in 13 patients, occurring in the external iliac artery (4), inferior vena cava (3), external iliac vein (5), and femoral vein (1). All patients needed only primary raffia. There were complications in four of these patients, two femoral venous thrombosis and two iliac artery occlusions. Patients with arterial occlusions evolved with intermittent claudication in the lower limb.

In the case series of Bianchi et al., [42] 39 patients underwent vascular reconstruction, 6 of them due to inadvertent injuries (aorta = 1, internal carotid = 1, superior mesenteric artery = 1, subclavian vein = 1, axillary vein = 1, and portal vein = 1). The patient who underwent upper mesenteric reconstruction evolved with intestinal ischemia and death.

Importance of Collateral Circulation

Collateral circulation is of great importance in tumor resections associated with trunk vessels' resection in the venous and arterial territory. During block resection, many collateral vessels are removed next to the tumor block to allow free margins for cancer safety.

In the study by Machado MA et al. in 2004 [43] three patients underwent resection of pancreatic tumors. Two of them presented occlusion of the celiac trunk and ostial stenosis of the superior mesenteric artery, all asymptomatic from the clinical point of view. Immediately after tumor resection, there was a critical intestinal or visceral ischemia in all three cases, requiring immediate arterial revascularization leading to regression of the condition and good evolution.

We believe that trunk vessels and collateral circulation's associated resection can eventually decompose the tissues downstream, making the trunk reconstruction fundamental.

All teams must be prepared for this type of procedure, with vascular surgeons making up the group.

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Chapter 14
Venous thromboembolism and Cancer

Guilherme Yazbek and Bruno Soriano Pignataro

14.1 Introduction

Venous thromboembolism (VTE), composed of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in cancer patients. Since Armand Trousseau first described thrombophlebitis as a sign of visceral malignancy more than 150 years ago, the effect of cancer on blood coagulation has remained a major challenge for health-care providers. Derangements in the coagulation cascade, which can manifest as thrombosis, bleeding, and disseminated intravascular coagulation, are common in patients with cancer and have significant ramifications on treatment, prognosis, and quality of life [1].

Oncological patients are 4.1 times more likely to develop VTE compared to individuals without cancer; during chemotherapy this risk reaches 6.5 times [2]. This high incidence of VTE reflects an increase in morbidity and is a major cause of mortality in this group [3]. The risk of VTE comprises cancer-related, patient-related, and treatment-related causes (Table 14.1). Cancer-related causes are associated with active cancer, types of cancer, and extrinsic compression. In some types of cancer, the risk of VTE is greater, such as pancreas, bladder, colon, ovary, lung, and stomach.

Active cancer patients have a multifactorial cause of hypercoagulability. Biological factors, including tumor cell-specific prothrombotic properties and the host cell inflammatory response to the tumor, play a central role in the pathogenesis of cancer-associated thrombosis. Cancer cells produce and release procoagulant and fibrinolytic proteins, as well as inflammatory cytokines. In addition, they are capable of directly adhering to host cells (i.e., endothelial cells, monocytes, platelets,

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Table 14.1 Risk factors for VTE divided into three groups, related to the patient, related to cancer, and related to treatment

Patient-related	Old age
	Hereditary or acquired thrombophilia (pregnancy)
	Comorbidities (infection, kidney disease, lung disease, CHF, arterial thromboembolism)
	Obesity BMI >35 kg/m^2
	Platelets>350,000/μL (before chemotherapy)
	Leukocytosis>11,000/μL (before chemotherapy)
	Anemia <10 g/dL (before chemotherapy)
	Previous history of VTE
	Hospitalization
	Prolonged immobilization
	Low performance
Cancer-related	Active cancer
	Primary high-risk sites (CNS, pancreas, stomach, bladder, gynecological, lung, kidney lymphoma, myeloproliferative neoplasia)
	Extrinsic vascular compression
Treatment-related	Prolonged surgery
	Central venous catheter insertion
	Use of high doses of dexamethasone + thalidomide/lenalidomide/pomalidomide
	Use of hormone therapy (hormone replacement therapy, contraceptives, tamoxifen/raloxifene, DES)
	Use of erythropoietin-stimulating agents

and neutrophils), thereby stimulating additional prothrombotic properties of the host effector cells. Tumor-shed procoagulant microparticles also contribute to the patient hypercoagulable state. Finally, tissue factor promotes changes of stromal cells of the tumor "niche" altering hemostasis [4].

There is evidence of structural changes in tumor cells that start to not only expressing procoagulant proteins (tissue factor, procoagulant cancer, and factor VII), but also show structural changes such as EGFR mutation that make them more responsive to these same procoagulants. This self-feeding relationship promotes the development and proliferation of the tumor [5].

Patient-related and treatment-related risk factors also contribute to the development of VTE (Table 14.1). Old age, cardiovascular risk, and prolonged immobilization are some examples of patient-related risks factors; and chemotherapy, prolonged surgery, and the presence of central catheters are examples of treatment-related risk factors. The end result is a procoagulant, anti-fibrinolytic, proaggregating state, in addition to the release of proinflammatory and proangiogenic cytokines as already described.

14.2 Diagnosis—Laboratory, Image

Clinical Signs and symptoms:

- Deep venous thrombosis: pain, swelling of the calf and edema of the affected area are common symptoms but nonspecific. Only 1/4 of the patients with these symptoms are confirmed with DVT. Semiological maneuvers such as Homans and the Flag signal could be performed when lower limbs DVT is suspected. In some cases, the diagnosis is easy to establish due to the evident signs of DVT (Fig. 14.1).
- Pulmonary embolism: There is no classic or pathognomonic clinical sign. Young, healthy individuals may develop PTE without overt clinical evidence, while elderly individuals with comorbidities may have PTE symptoms and signs masked by an underlying disease. Most frequent signs and symptoms are dyspnea, cough, pleuritic pain, tachypnea (RF >20) and hemoptysis.

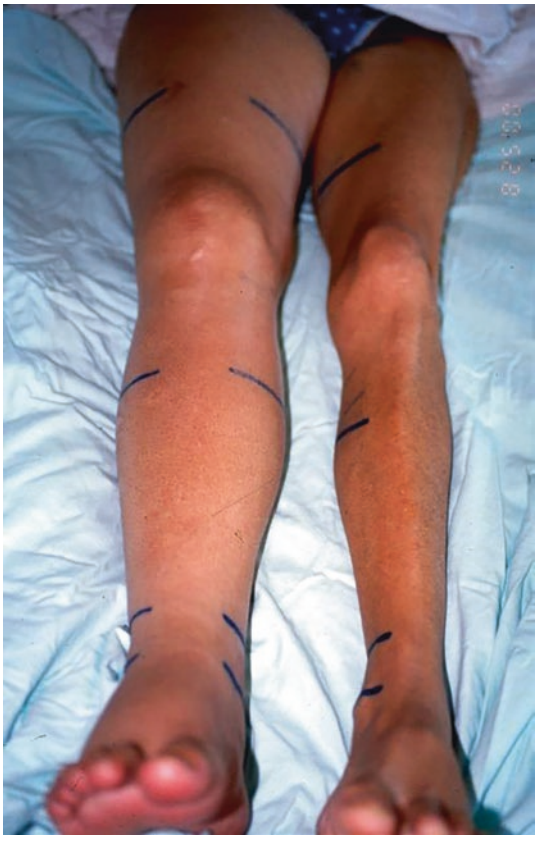

Fig. 14.1 Iliofemoral deep venous thrombosis

Laboratory:

- D-dimer (DD): Product of fibrinolysis degradation. It has high sensitivity and low specificity, especially in the cancer group, where patients are chronically inflamed. DD dosage should be used only in patients with low clinical probability for DVT, since they do not have 100% sensitivity. There is strong evidence that the use of DD alone, that is, without the combination of pre-test scores, has a high negative predictive value in a specific population: outpatients, nonrecurring, adults (nonelderly), and with a short duration of treatment. Symptoms: In patients with high pre-test probability for DVT or PE, the usefulness of DD is questionable and limited usefulness.

Image:

- Doppler ultrasound of lower limbs (Eco-doppler color): Noninvasive and easily accessible exam, excellent for the diagnosis of DVT, with sensitivity of 96% and specificity of 98–100%. Its accuracy in diagnosing asymptomatic DVT is lower compared to symptomatic DVT. The patient who has a high probability according to the Wells score, negative EDC and positive DD, the EDC should be repeated in 3–7 days. For the diagnosis of PE, it has limited utility, since only about 50% have concomitant DVT. However, once DVT is confirmed and there is clinical suspicion of PE, there is no need for additional tests, and the diagnosis has been confirmed.
- Echocardiogram: Noninvasive, low sensitivity test for PE. It is especially useful when excluding cardiac pathologies in the differential diagnosis such as congestive heart failure and coronary artery disease. Its greatest relevance for PE is in patients with hemodynamic instability to view acute RV dilation and the presence of pulmonary artery hypertension. In these situations, the transesophageal echocardiogram is more sensitive and reliable than the transthoracic one.
- Angiotomography: Considered gold standard exams due to high sensitivity and specificity around 95% for PE (Fig. 14.2).

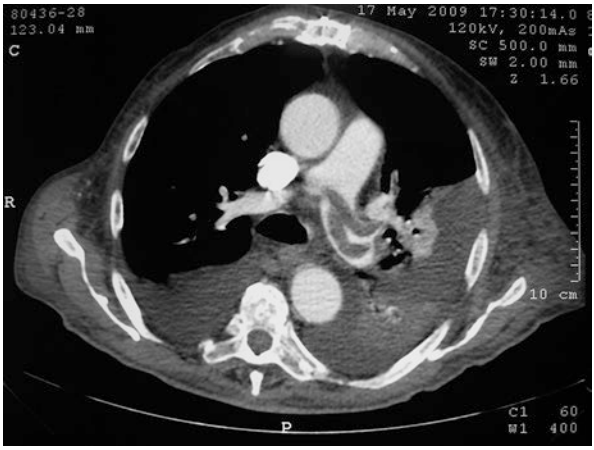

Fig. 14.2 Angiotomography with a massive pulmonary embolism

14.3 Epidemiology

Cancer-related thrombosis is responsible for almost 20% of all incident VTE. Despite the burden, VTE associated with cancer is not decreasing probably due to a higher sensitivity of diagnostic methods and suboptimal treatment [6]. The incidence is higher in cancer of the brain, pancreas, ovary, colon, stomach, lung, kidney, and bone and also in the presence of distant metastases [7].

After the first VTE episode those patients have an increase incidence of recurrence almost 10 per 100 person-years, with a peak of 22.1 in the first 6 months. There is no difference in terms of recurrence after initial DVT or PE. The mortality rate is approximately 65% after 1 year and almost 90% after 10 years [8]. Among patients with cancer VTE is the second leading cause of death [9]. For those patients with spontaneous VTE, approximately 10% is associated with further diagnose of malignant disease [10].

14.4 Prophylaxis

14.4.1 Clinical Patient—Hospitalized Patients

Patients hospitalized for acute medical illnesses, such as heart failure, respiratory insufficiency, stroke, and infectious or inflammatory diseases, are at increased risk for venous thromboembolism [11]. Primary VTE prophylaxis can reduce deep vein thrombosis (DVT), pulmonary embolism (PE), and fatal PE in several high-risk populations such as hospitalized patients or in the postoperative setting. In the cancer population, identification of patients most at risk for VTE followed by institution of effective prophylaxis could improve morbidity, mortality, delivery of cancer therapy, cancer-related outcomes, quality of life, and use of health-care resources [5]. Validated risk scores that include additional factors, such as a lack of mobility, advanced age, cancer, previous venous thromboembolism, and elevated d-dimer levels, aid in the identification of patients who are at risk for symptomatic venous thromboembolism.

The administration of anticoagulant thromboprophylaxis for all patients with cancer who are hospitalized for acute medical illness is considered standard practice and strongly recommended in clinical guidelines [12]. These recommendations are extrapolated from randomized controlled prophylaxis trials not specifically conducted in cancer cohorts. One of them, The Medenox trial, that was a prospective, double-blind, randomized, placebo-controlled trial, which enrolled 1102 hospitalized and acutely ill medical patients to receive 40 mg of enoxaparin, 20 mg of enoxaparin, or placebo, for 6–14 days. At the 40-mg dose, the risk of venous thromboembolism was significantly reduced in patients with heart failure, as well as in patients with other medical illnesses, including respiratory failure, infectious disease, or rheumatic disorders. The incidence of venous thromboembolism was 5.5%

in the group that received 40 mg of enoxaparin as compared with 14.9% in the group that received placebo ($p < 0.001$), a benefit that was maintained at 3-month follow-up [13].

Because hospitalized patients with cancer constitute a unique population with increased risk of venous thromboembolic events and major hemorrhage, validation of the efficacy and safety of primary thromboprophylaxis in this population is critical. One meta-analysis tries to prove it and could be selected only three placebo-controlled randomized trials included venous thromboembolic events as a primary outcome and were analyzed according to cancer subgroups. Anticoagulation did not significantly reduce the risk of VTE in hospitalized patients with cancer (The pooled relative risk of venous thromboembolic events was 0.91 (95% confidence interval, 0.21–4.0; I(2): 68%)) who were receiving thromboprophylaxis compared with placebo [14]. It is necessary to emphasize that included patients with cancer were heterogeneous with respect to VTE risk, and the sample size of patients with cancer was small and bleeding information for the cancer subgroup was not available.

To date, no controlled randomized trials have evaluated inpatient thromboprophylaxis in a cancer-only population. The generalizability of these data to all hospitalized patients with cancer is unclear, especially to those who are only admitted for scheduled chemotherapy and are otherwise ambulatory and close to their baseline health status. However, hospitalization is associated with an increased risk of VTE in patients with cancer. Many hospitalized patients with cancer have additional risk factors for VTE what can greatly increase the risk requiring the use of risk assessment models may enhance the appropriate use of thromboprophylaxis. Therefore, American Society Clinical Oncology (ASCO) recommend the use of pharmacologic thromboprophylaxis in hospitalized patients who have active malignancy and acute medical illness or reduced mobility in the absence of bleeding or other contraindications and accept the use in hospitalized patients who have active malignancy without additional risk factors [7]. Admission for minor procedures or chemotherapy infusion the pharmacologic thromboprophylaxis is not necessary even if undergoing stem-cell/bone marrow transplantation. Important to note that there are no controlled randomized trials with direct oral anticoagulants (DOACs) for impatient patients. The use of unfractionated heparin, low molecular weight heparin (Enoxaparin and Dalteparin) and Fondaparinux are acceptable options for pharmacologic thromboprophylaxis.

14.4.2 Clinical Patient—Ambulatory Patients Under Anticancer Therapy

The VTE occurs primarily in the outpatient setting and is a significant cause of death. The risk of CAT is highly variable (2–20%) and depends on some variables [15]. Some types of tumors are associated with a higher risk of VTE, such as those of the pancreas, stomach, kidneys, and brain. Currently, there has been an increased

Table 14.2 The Khorana score

Predictive model of Khorana—VTE associated with chemotherapy	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count 350×10^9/L or more	1
Prechemotherapy leukocyte count more than 11×10^9/L	1
Hemoglobin level less than 100 g/L or use of red cell growth factors	1
BMI 35 kg/m^2 or more	1

Total score	Risk category	Risk of symptomatic VTE
0	Low	0.3–1.5%
1–2	Intermediate	1.8–4.8%
≥3	High	6.7–12.9%

risk in patients with lymphomas and lung cancer. The search for predictive models in the literature culminated in the publication of the Khorana Score (range, 0–6, with higher scores indicating a higher risk of venous thromboembolism) in order to identify the most susceptible patients who may benefit from pharmacological prophylaxis (Table 14.2) [16]. From the diagnosis of pancreatic tumor, the patient is already classified as of intermediate risk, being able to attain high risk depending on the existence of other factors (platelet count, hemoglobin level, leukocyte count, and body mass index) [17].

In order to increase the effectiveness of the Khorana score, some modifications were proposed, with the addition of two biomarkers, P-selectin and D-dimer. Another group proposed modifying the score, adding chemotherapeutic agents, such as platinum-based antineoplastic therapy and gemcitabine (Protecht score) [18].

The benefit–risk profile of antithrombotic prophylaxis among ambulatory patients with cancer is hard to establish. Some studies evaluating anticoagulants in this setting using low molecular weight heparin (LMWH) or DOACs. In the SAVE-ONCO, they compared the use of low molecular weight heparin or placebo in 3212 patients with metastatic or locally advanced solid tumors who were beginning to receive a course of chemotherapy. Despite a short duration of treatment (3.5 months), they observed a significant risk reduction in patients treated with semuloparin (hazard ratio, 0.36; 95% confidence interval [CI], 0.21 to 0.60; $p < 0.001$) without increase in major bleeding (hazard ratio, 1.05; 95% CI, 0.55–1.99) [19] and in a subgroup of high-risk patients (Khorana ≥3) the number needed to treat (NNT) of 25 in compared to 333 for low risk patients. Another study, The PROTECTH trial, also after a short period of treatment (4 months), described a significant reduction in the incidence of thromboembolic events when the Nadroparin was used in ambulatory patients with metastatic or locally advanced cancer who are receiving chemotherapy (2.0% Nadroparin × 3.9% Placebo, $p = 0.02$) with same bleeding incidence [20]. In a subgroup analysis (Khorana score ≥3) was found a VTE rate of 11.1% with placebo and 4.5% with nadroparin. Thus, the number needed to treat (NNT) was 15 for high-risk patients, as compared to 77 for combined low/intermediate-risk patients [12].

Some meta-analyses focused primarily on thromboprophylaxis with LMWH demonstrated a risk reduction of VTE in the prophylaxis group with LMWH, specially in some specific populations, as pancreas tumor (RR 0.31, 95% CI 0.18–0.55) and lung tumor (RR 0.42, 95% CI 0.25–0.71) when compared with placebo [21] and multiple myeloma when compared with the vitamin K antagonist warfarin (RR 0.33, 95% CI 0.14–0.83), while the difference between LMWH and aspirin was not statistically significant (RR 0.51, 95% CI 0.22 to 1.17) [22].

Two trials, CASSINI [23] and AVERT [24] described the use of direct oral anticoagulants (DOACs) as a prophylaxis regimen in ambulatory patients under chemotherapy analyzing specific population, with a high or intermediate-to-high risk of VTE using the Khorana score (≥2).

The AVERT study compared the use of Apixaban 2.5 mg twice daily and placebo with the primary efficacy outcome the objective and documented VTE over a 180-day follow-up period and the main safety outcome, major bleeding. From 574 randomized patients, 563 were included in intention-to-treat analysis. There was a significant reduction of VTE in apixaban group (4.2% × 10.2%, hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.26–0.65; $p < 0.001$) and in a subgroup of on-treatment analysis the results also significant (1% × 7.3%, hazard ratio [HR], 0.14; 95% CI, 0.05–0.42). About the safety outcome, 10 patients (3.5%) in the apixaban group and 5 patients (1.8%) in the placebo group experienced major bleeding (HR, 2.00; 95% CI, 1.01–3.95; $p = 0.046$). During the treatment period, 6 patients (2.1%) in the apixaban group and 3 patients (1.1%) in the placebo group experienced major bleeding (HR, 1.89; 95% CI, 0.39–9.24).

The CASSINI trail was similar to AVERT, but with differences as the thromboprophylaxis with Rivaroxaban 10 mg versus placebo and mandated lower-extremity ultrasonography at baseline (thus excluding any inapparent deep vein thrombosis [DVT] at baseline) and serial time points during the study (screen-detected VTE as an end point—841 patients randomized). Over 50% of study participants had a diagnosis of very high-risk tumor types (pancreatic or gastro-esophageal cancers), and only 7% were patients with lymphoma. Among the VTE-screened patients with a Khorana score of 2 or higher, 4.5% were found to have a thrombosis on baseline screening imaging and were not eligible for randomization. The VTE reduction in the primary end point did not achieve significance over placebo (6% × 8.8%; hazard ratio [HR], 0.66; 95% CI, 0.4–1.09; $p = 0.10$), with the majority of events in the rivaroxaban group occurring after drug discontinuation. When on-treatment was analyzed, there was a significant reduction of VTE (2.6% × 6.4%; hazard ratio [HR], 0.40; 95% CI, 0.2–0.80). Major bleeding occurred in 2.0% in rivaroxaban arm versus 1.0% in placebo arm (HR, 1.96; 95% CI, 0.59–6.49; $p = 0.26$).

In the trials with unselected patients, the absolute benefit was modest, meaning that many patients required prophylaxis to prevent a single event of VTE, therefore the greatest absolute reduction in VTE risk was observed in trials of patients with advanced pancreatic cancer or selected high risk populations [6, 9]. Consequently, guidelines do not recommend routine thromboprophylaxis for ambulatory patients with cancer [6, 25, 26].

Studies focused in high risk population, including pancreatic cancer, multiple myeloma, described reduce risk of VTE in a thromboprophylaxis arm using LMWH higher-than-standard prophylactic dosing: dalteparin 200 IU/kg once daily for 4 weeks followed by a stepdown to 150 IU/kg for a further 8 weeks in FRAGEM study [27] and enoxaparin 1 mg/kg once daily in CONKO-004 [28]. Based on such data presented, guidelines endorse the use of the Khorana score to identify patients who may benefit from thromboprophylaxis with apixaban, rivaroxaban, or low molecular weight heparin (LMWH) provided there are no significant risk factors for bleeding and no drug interactions in ambulatory cancer patients under chemotherapy. Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting. In a multiple myeloma receiving thalidomide or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients [6].

14.4.3 Surgical Patient

After oncologic surgery, VTE risk is elevated post-discharge in patients with cancer. The incidence of clinically overt VTE in patients with cancer after surgery was approximately 1–3% depending on the type of surgery and 40% of VTE occurred after 21 days post-surgery and is responsible for 46% of deaths [29].

It is well known that in cancer surgical patients, the prolonged durations of thromboprophylaxis reduce the VTE incidence as described in ENOXACAN II trial. After 1 week with enoxaparin 40 mg in surgical patients undergone abdominal or pelvic surgery, two groups were randomized to continued prophylaxis with enoxaparin or placebo for an additional 19–21 days. The incidence of VTE was significantly lower in patients with continued enoxaparin versus placebo (4.8% vs. 12.0%, respectively; $p = 0.02$) [30]. Rasmussen et al. compared the incidence of VTE in 427 patients who underwent abdominal surgery for cancer and were randomized to receive dalteparin 5000 IU for 7 or 21 days. They also found a reduction of incidence of VTE in the prolonged thromboprophylaxis group (7.3 vs. 16.3%, respectively; RR reduction 55%, 95% CI 15–76%, $p = 0.012$), without increase of and major bleeding (0.5% vs.1.8%, respectively) [31].

Also laparoscopic cancer procedures are associated to increase risk of VTE, as described by Vedovati et al. who enrolled 225 patients with colorectal cancer undergoing to laparoscopy. They compare short to long time prophylaxis (1 week × 4 weeks) and found a VTE reduction in the extended group after 3 months (28 days [SD 2]); 9.7% in group A versus 0.0% in group B; $p = 0.001$) with no difference in bleeding concluding that after laparoscopic surgery for colorectal cancer, extended antithrombotic prophylaxis is safe and reduces the risk for VTE as compared with 1-week prophylaxis [32].

In view of the wide variety of prophylaxis modalities including pharmacological agents and mechanical devices, some studies have evaluated what would be the best method to be used. In a meta-analysis of clinical trials evaluating the efficacy and safety of LMWH (once a day) and unfractionated heparin (UFH) (3 times a day) for thromboprophylaxis following cancer surgery, no differences were found in mortality with LMWH versus UFH treatment (RR 0.89, 95% CI 0.61–1.28) or in the risk of clinically suspected DVT (RR 0.73, 95% CI 0.23–2.28). However, the use of UFH 2 times a day was associated with a reduction in the effectiveness in preventing VTE. The unfractionated heparin (UFH) appears to be as efficacious as LMWH in preventing VTE.

Most of the guidelines recommend that mechanical methods may be added to pharmacologic thromboprophylaxis but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated for one of the above-noted reasons [20, 33]. A Korean study, conducted in Asian populations, where there is a lower incidence of thromboembolic events due to the probable low prevalence of thrombophilic factors (the Factor V Leiden and prothrombin G20210A mutations), compared two types of prophylaxis, the use of intermittent pneumatic compression (IPC) only or an IPC plus enoxaparin in gastrectomy for cancer. Among the 666 patients included in the analysis, the overall incidence of VTE was 2.1%. The incidence of VTE was statistically significantly higher in the IPC-only group compared with the IPC + LMW heparin group (3.6%; 95% CI, 2.05–6.14% vs. 0.6%; 95% CI, 0.17–2.18%; p = 0.008) but with higher incidence of bleeding in the IPC + LMW heparin group (9.1% vs. 1.2%; $p < 0.001$) [34].

In summary, in a high risk VTE cancer surgical patients is recommended offered pharmacologic thromboprophylaxis with either unfractionated heparin (UFH) 3 times a day or LMWH commenced preoperatively, in association with mechanical methods, in extended duration for up to 4 weeks postoperatively in patients undergoing major open or laparoscopic abdominal or pelvic surgery who have high-risk features, such as restricted mobility, obesity, history of VTE, or with additional risk factors [7, 14, 35].

In Table 14.3, we describe some thromboprophylaxis regimen [36].

14.5 Treatment

The treatment of VTE is full anticoagulation, which must be effective in reducing the recurrence of VTE, and at the same time safe to minimize the risk of bleeding. A minimum of 6 months of treatment is recommended and discontinuation depends on the status of the disease and the risk of bleeding.

For approximately 20 years, low molecular weight heparin (LMWH) prevailed as the treatment for cancer-associated thrombosis (CAT). Recently, direct oral anticoagulants (DOACs), inhibitors of factor Xa and thrombin, have gained grounds in CAT treatment. The advantages of DOACs over LMWH are lower costs and oral administration.

Table 14.3 Dosing regimens for prophylaxis of VTE in patients with cancer from ASCO guidelines [7]

Pharmacologic (anticoagulant) prophylaxis		
Hospitalized medical patients	UFH	5000 U every 8 hours
	Dalteparin	5000 U once daily
	Enoxaparin	40 mg once daily
	Fondaparinux	2.5 mg once daily
Surgical patients	UFH	5000 U 2–4 hours preoperatively and every 8 hours thereafter
	Dalteparin	2500 U 2–4 hours preoperatively and 5000 U once daily thereafter
		Or 5000 U 2–4 hours preoperatively or 10–12 hours preoperatively and 5000 U once daily thereafter
	Enoxaparin	40 mg 2–4 hours preoperatively or 10–12 hours preoperatively and 40 mg once daily thereafter.
	Fondaparinux	2.5 mg once daily beginning 6–8 hours postoperatively
Outpatients	Dalteparin	5000 U once daily
	Enoxaparin	40 mg once daily
	Fondaparinux	2.5 mg once daily
	Apixaban	2.5 mg orally twice daily
	Rivaroxaban	10 mg orally once daily

The choice of LMWH is due to clinical trials that compared LMWH with vitamin K antagonist (VKA) such as warfarin and acenocoumarol. In these trials LMWH was more effective lowering the risk of recurrent venous thromboembolism without increasing bleeding risk when compared to VKA [37]. CLOT was a prospective and randomized and the study with the greater statistical power; a total of 654 patients, 336 in LWWH (dalteparin) arm and 336 in VKA arm (acenocoumarol). In VKA arm recurrence occurred in 53/336 compared to 27/336 in dalteparin group. The relative risk was 0.51 (95% CI 0.33–0.79). Other clinical trials showed the same tendency of LMWH to be more effective compared to VKA, but with less statistical power [38–40].

DOACs such as apixaban, dabigatran, edoxaban, and rivaroxaban became first the treatment choice for TEV in a non-cancer population [41, 42]. Later came randomized clinical trials specific for oncologic patients, which compared DOACs with LMWH. Select-D studied rivaroxaban, HOKUSAI-Cancer edoxaban, and Caravaggio apixaban. These trials showed DOACS as effective as LMWH but increasing bleeding risk in gastrointestinal cancer [43–45].

The HOKUSAI-Cancer that included 1046 patients as first published. Primary outcome was the association of recurrent venous thromboembolism and major bleeding. Edoxaban 60 mg once daily after 5 days of LMWM was compared with dalteparin. If creatinine clearance was between 30 and 50 ml/dL or patient weight

<60 kg, edoxaban dosage was 30 mg once. Primary outcome occurred in 12.8% in the edoxaban group compared to 13.5% in the dalteparin group (relative risk 0.97, $p = 0.006$, noninferiority). Less recurrence was found in the edoxaban group, relative risk 0.71 (95% CI 0.48–1.06), but a tendency to higher risk of bleeding, relative risk 1.77 (95% CI 1.03–3.04). Gastrointestinal tumor had higher chance of bleeding [44].

The study Select-D compared rivaroxaban 15 mg twice for the first 21 days followed by 20 mg once daily, with dalteparin. Each arm included 203 patients. Symptomatic and asymptomatic incidental pulmonary embolism (PE) were studied. Only symptomatic and proximal deep vein thrombose (DVT) were included. Metastatic disease was found in 53% of the population. Lower recurrences were found in the rivaroxaban group, relative risk 0.43 (95% CI 0.19–0.99). A tendency to more bleeding in the rivaroxaban group; relative risk 1.83 (95% CI 0.68–4.96) for major bleeding and 3.76 (95% CI 1.63–8.69) for clinically relevant nonmajor bleeding. The authors highlighted major bleeding occurred predominantly in gastrointestinal tumor presumably due to local and systemic effect of rivaroxaban [43].

After SELECT-D and HOKUSAI-Cancer, Caravaggio trial was published. Despite the increase of GI bleeding, they included patients with GI neoplasia, but they did not include patients with CNS neoplasia, CNS metastasis or acute hematological disease. Caravaggio trial compared apixaban 10 mg twice daily for the first 7 days, followed by 5 mg twice daily with dalteparin. Primary outcome was recurrent venous thromboembolism, which occurred in 32 of 576 (5.6%) in the apixaban group and in 46 of 579 (7.9%) in the dalteparin group, hazard ratio 0.63 (CI 95% 0.37–1.07; $p < 0.001$ for noninferiority). Major bleeding occurred in 22 patients (3.8%) in the apixaban group compared to 23 patients (4.0%) in the dalteparin group, hazard ratio 0.82 (CI 95% 0.4–1.69; $p = 0.60$). The chance of bleeding did not increase in Caravaggio trial [46].

Real-world studies have been congruent with these clinical trials with acceptable recurrence rate, but with caution related to bleeding rates. In a cohort with 400 patients and diagnostic of venous thromboembolism treated with rivaroxaban, the incidence of recurrent venous thromboembolism was 3.25%, major bleeding 5.5%, and clinically relevant nonmajor bleeding 15.2% [47]. In another cohort with 296 patients, 118 had active malignancy. The recurrence between malignant (3.3%) and nonmalignant (2.8%) group was equivalent ($p = 0.53$) [48].

As a consequence, some guidelines had their recommendations updated, and DOACs have gained some grounds in CAT treatment. The guideline of International Society on Thrombosis and Haemostasis (ISTH) has recommended DOACs (Rivaroxaban and Edoxaban) for CAT since there is low risk of bleeding and no drug interaction. LMWH is preferable in cases of gastrointestinal and bladder cancer and in cases of mucosal abnormality (gastritis, esophagitis, colitis, and duodenal ulcer) [49]. Congruent with the guideline of ISTH, the American Society Clinical Oncology (ASCO) recommends LMWH, DOACS (Rivaroxaban and Edoxaban), Fondaparinux, and unfractionated heparin (UFH), and when these drugs are not available, VKA is an alternative. When parenteral therapy is needed, LMWH is preferable over UFH, which is indicated when creatinine clearance <30 ml/min. In addition to ISTH, ASCO recommends a careful evaluation of bleeding risk before prescribing DOACs. Both guidelines agree that the patient should engage in the

treatment decision [12]. These guidelines were published prior to the Caravaggio study, which is why apixaban had not yet been cited.

14.5.1 Drugs

14.5.1.1 Low Molecular Weight Heparin (LMWH)

The standard treatment for acute DVT and PTE episodes in cancer patients is anticoagulation with LMWH, according to the main guidelines [35, 50]. This recommendation is based on the superiority in reducing the incidence of new thromboembolic events when compared to vitamin K antagonists (VKA) [39, 40, 51, 52]. Another advantage is a predictable pharmacokinetics and low drug interaction [53].

The main disadvantages are the cost, in our environment making most outpatient treatments impossible and the fact that administration is subcutaneous. In addition, although less frequent than unfractionated heparin, it can also cause heparin-induced thrombocytopenia [53].

14.5.1.2 Direct Oral Anticoagulant (DOAC)

The advantage of using NOACs—Activated factor × inhibitors (Rivaroxaban, Edoxaban, and Apixaban) in relation to vitamin K antagonists lies in the posology (without the need for dose adjustment based on RNI) and in the lower amount of drug interactions. In relation to LMWH, the advantage lies in the ease of administration (oral) and the cost. Disadvantages are drug interactions, especially drugs that act on the metabolism of protein P and cytochrome P-450, such as some antifungal, antiretroviral, antimitotic (Paclitaxel), immunomodulatory drugs (dexamethasone), and tyrosine inhibiting drugs (Imatinib) (Fig. 14.3). They are also of limited use in patients with thrombocytopenia and renal failure [54]. Nausea or vomiting may also impact adherence with use of DOACs given their oral route of administration.

Inhibitors

Azole antifungals	*Protease inhibitors*	*Immunosuppressive drugs*[a]	*Other*
Ketoconazole	Ritonavir	Cyclosporine	Clarithromycin
Itraconazole	Lopinavir/ritonavir	Tacrolimus	Conivaptan
Voriconazole	Indinavir/ritonavir		
Posaconazole			
Fluconazole			

Inducers

Anti-epileptic drugs	*Other*
Phenytoin	Rifampin
Carbamazepine	St.John's wort

Fig. 14.3 Lists strong inhibitors and inducers of CYP3A4 and/or P-glycoprotein. (Figure from Ref. [54])

Particular caution for DOAC use is warranted in settings associated with an increased risk for bleeding. Patients with additional risk factors for bleeding, such as use of antiplatelet agents, renal or hepatic impairment, thrombocytopenia, or prior history of GI bleeding, should be appropriately counseled. Patients with unresected mucosal tumors or active mucosal lesions may experience more bleeding with DOACs than with LMWH. This situation with high risk of bleeding the LMWHs are currently preferred [12].

Dabigatran do not have published data in comparison with LMWH in the therapeutic setting and are not recommended in the cancer setting until efficacy and safety data are available.

14.5.1.3 Vitamin K Antagonists (VKA)

The main advantages of VKAs are oral administration and a lower cost than NOACs and LMWH. They act by inhibiting the synthesis of vitamin K-dependent clotting factors: II, VII, IX, X and anticoagulant proteins C and S.

The antithrombotic effect starts when the clotting factors are inhibited and depleted. This takes time, for example, prothrombin (factor II) has a half-life of approximately 65 hours. On the other hand, by depleting protein C which is a natural anticoagulant more quickly (half-life of 6 hours) can induce an initial procoagulant state; it is essential to use some anticoagulant in the first days until reaching an adequate level of anticoagulation (INR between 2 and 3).

The major disadvantage of this treatment modality is the amount of drug and food interactions, as well as dependence on organic integrity, which becomes a challenge in cancer patients, given the multiple medications administered, malnutrition, nausea, and vomiting triggered by chemotherapy in addition to organic disorders (e.g., liver and kidney). This time, on many occasions, anticoagulation with vitamin K antagonists becomes unpredictable.

In Tables 14.4 and 14.5 we described the dosing regimen options to patients with cancer from ASCO guidelines.

Treatment extension (full dose, reduced dose, criteria for suspension/reduction) and follow-up.

The choice to extend the anticoagulation is based on the recurrence risk. We should divide patients into different subgroups according to the risk of recurrence of VTE patients after stopping anticoagulant therapy: (1) VTE provoked by surgery (a major transient risk factor; 3% recurrence at 5 years); (2) VTE provoked by a nonsurgical transient risk factor (e.g., estrogen therapy, pregnancy, leg injury, flight of >8 hours; 15% recurrence at 5 years); (3) unprovoked (also termed “idiopathic”) VTE; not meeting criteria for provoked by a transient risk factor or by cancer (30% recurrence at 5 years); and (4) VTE associated with cancer (15% annualized risk of recurrence; recurrence at 5 years not estimated because of high mortality from cancer) [50].

There is limited information about the risks and benefits of anticoagulation beyond 6 months in patients with cancer. Such data gathering is complicated by the

Table 14.4 Dosing regimens for initial treatment of VTE in patients with cancer

Treatment VTE		
Initial	UFH	80 U/kg IV bolus, then 18 U/kg/h IV and adjust dose based on aPTT
	Dalteparin	100 U/kg every 12 hours
		200 U/kg once daily
	Enoxaparin	1 mg/kg every 12 hours
		1.5 mg/kg once daily
	Tinzaparin	175 U/kg once daily
	Fondaparinux	< 50 kg: 5.0 mg once daily
		50–100 kg: 7.5 mg once daily
		>100 kg: 10 mg once daily
	Rivaroxaban	15 mg orally every 12 hours for 21 days

Table 14.5 Dosing regimens for long-term treatment of VTE in patients with cancer

Treatment VTE		
Long term	Dalteparin	200 U/kg once daily for 1 month, then 150 U/kg once daily
	Enoxaparin	1.5 mg/kg once daily
		1 mg/kg every 12 hours
	Tinzaparin	175 U/kg once daily
	Warfarin	Adjust dose to maintain INR 2–3
	Rivaroxaban	15 mg orally every 12 hours for 21 days, followed by 20 mg once daily thereafter (both doses with food)
	Edoxaban	Needs at least 5 days of parenteral anticoagulation prior to its start, the switch to 60 mg orally once daily in those weighing ≤60 kg, who have creatinine clearance between 30 and 50 ml/min, or who need concomitant use of a P-glycoprotein inhibitor

recruitment and retention of patients in extended treatment trials (i.e., because of high mortality and a general reluctance to continue treatment beyond 6 months). In Daltecan trial, patients with cancer with VTE received extended treatment with dalteparin. Of 334 patients enrolled, 109 completed 12 months of dalteparin (116 patients died during the 12-month study). Risk of major bleeding was greatest during the first month of treatment (3.6%), declining to 1.1% per patient-month during months 2–6 and 0.7% during months 7–12. Similarly, the risk of recurrent VTE was highest in the first month, at 5.7%, 3.4% during months 2–6, and 4.1% during months 7–12 [55]. Also, Hokusai-VTE-Cancer study had 38% patients died during the trial period (12 months) [44].

The optimal duration of anticoagulation for CAT treatment is particularly challenging. There is a consensus based on extrapolation from patients with unprovoked VTE as described, that continuing anticoagulation beyond 6 months should be considered for selected patients because of the persistent high risk of recurrence in those with active cancer.

Most guidelines for CAT support extended anticoagulation therapy (≥6 months) for the secondary prevention of VTE, or the continuation of therapy for as long the patient harbors active malignancy (with no scheduled stop date) [56]. The decision to anticoagulation must be balanced against the risk of bleeding, cost of therapy, quality of life, life expectancy, and patient preference. Further studies regarding extended-duration CAT treatment would be beneficial but will likely continue to be challenging to obtain.

14.5.2 Vena Cava Filter

The first percutaneous interruption of the inferior vena cava—with a vena cava filter—was described by Mobin-Uddin in 1967 [57]. There has been an exponential increase in the number of vena cava filter placements, going from 2000 procedures in the late 1970s to more than 140,000 in 2003 [58]. Vena cava filter placement was considered, back in the early 1990s, to be a possible solution regarding deep vein thrombosis care in cancer patients. But recent studies show a change in medical practice, with more reflection concerning the decision to place these filters or not [59].

The PREPIC1 study the only RCT with permanent IVC filters during 8-year follow-up, demonstrated that addition of IVC filters to standard anticoagulation for at least 3 months compared with anticoagulation alone reduced (although it did not nullify) the occurrence of new pulmonary embolism, at the expense of a higher frequency of venous thrombosis. Patients with cancer constituted 16% and 12% of those with and without filters, respectively [60]. The recently published PREPIC 2 randomized trial found that placement of an IVC filter for 3 months did not reduce recurrent PE, including fatal PE, in anticoagulated patients with PE and DVT who had additional risk factors for recurrent VTE [61]. This evidence was according some guidelines that in patients with acute DVT or PE who are treated with anticoagulants, they recommend against the use of an IVC filter [50].

Later, in clinical practice, it became *relatively* consensual that the filter would play a role in patients who were not qualified for anticoagulation, or had complications associated with it, thus requiring mechanical protection from pulmonary embolism. Despite of this consensus, in patients with contraindications to anticoagulant therapy, there are no randomized clinical trial data to guide therapy, but there is mounting evidence of long-term harm from filters in nonrandomized studies. Cohort studies in patients with cancer suggest much higher long-term rates of recurrent VTE and the absence of a survival advantage with filters [12].

Increased mortality among IVC filter recipients was reported in some studies of hospitalized patients with VTE and a contraindication to anticoagulation. In a retrospective analysis of 247 oncologic patients with acute proximal venous thrombosis that compared survival between 100 consecutive patients who needed vena cava filter (FILTER group) versus a control group of 147 patients in whom anticoagulation was possible (ANTICOAGULATION group), they found that IVC filter in a

patient with cancer is a marker that indicates patient's disease severity and worse prognosis (risk of death was 8.83-fold higher) [62]. Another retrospective study with 250 patients with cancer who had undergone placement of vena cava filter, 59.2% had metastatic disease at the time of filter placement and about 31.2% fulfilled criteria for early death. Patients with a greater chance of survival at a 3 or 5 years interval seem to be those whose filters were placed in the perioperative context of other surgeries (especially elective and curative), who were not undernourished, and whose disease was not metastatic at that time [59].

Questions regarding filters are whether permanent or retrievable filters are preferable in the cancer setting. It is reasonable to select a retrievable filter when the contraindication to anticoagulation is expected to be transient, and an active investigation protocol for filter removal should be implemented [12, 59].

In the absence of RCT, uncertain short-term benefit, and mounting evidence of long-term harm from filters, the ASCO guidelines recommend the insertion of a vena cava filter should not be offered to patients with established or chronic thrombosis (VTE diagnosis more than 4 weeks ago), nor to patients with temporary contraindications to anticoagulant therapy (e.g., surgery). There also is no role for filter insertion for primary prevention or prophylaxis of PE or DVT due to its long-term harm concerns. It may be offered to patients with absolute contraindications to anticoagulant therapy in the acute treatment setting (VTE diagnosis within the past 4 weeks) if the thrombus burden was considered life-threatening [12]. According to NCCN, vena cava filter (retrievable is preferable) placement should be considered if venous thromboembolism (e.g., lower-extremity DVP ± PE) occurred within 1 month of surgery [63].

Some situations were challenging and a case-by-case decision have to be made, multidisciplinary decision involving not only medical personnel (oncologist, surgeon) but patient and the family were undertaken. For severe oncologic cases, multidisciplinary evaluation (and possibly consideration for palliation) should take place before the decision to insert a vena cava filter depending on overall status.

14.5.3 Thrombectomy

Anticoagulation prevents clot extension and recurrence, but does not actively dissolve clot. If in all cases the organism performed the spontaneous lysis of all thrombi effectively, there would be a restoration of the flow of the venous system and the preservation of the function of the valves. Full recanalization can occur in up to 90% of veins with DVT in popliteal-distal territory after 1 year [64], however, with a lower incidence in the iliac-femoral territory.

During this thrombus absorption of thrombi, destruction of the valves commonly occurs. Consequently, the result of DVT is post-thrombotic valve dysfunction, which can cause chronic venous hypertension in the affected lower limb causing signs and symptoms characteristic of post-thrombotic syndrome.

Clinical signs and symptoms may be mild, such as hyperpigmentation of the skin, dilation of the veins of the lower limb, discomfort and edema; even more severe cases where manifestations impair quality of life, with chronic pain, edema, and development of stasis ulcers. Its incidence is variable, with studies showing low incidence (13%) [65] and others with more than 60% of cases [66]. About 40–50% of these patients develop venous claudication, defined as pain in the thigh or calf when walking, with improvement at rest [67]. About 5–10% develop ulcers within 5 years [66]. In addition to aesthetic-functional changes, we verified economic consequences related to the need to leave the individual's job to treat the ulcer.

A real treatment option is fibrinolysis for cases of proximal DVT. The desired objectives of performing fibrinolysis in a patient with DVT are to improve symptoms, save the limb in a state of phlegmasia and to decrease the incidence of post-thrombotic syndrome.

The first reports of active removal of the thrombus relate to patients with massive PTE where pulmonary artery embolectomy was indicated. Only in the early 1960s, better results were achieved with the use of "cardio-pulmonary bypass." In 1969, Greenfield et al. describe the first mechanical fibrinolysis devices for aspiration of thrombi (Fig. 14.4) [68].

The fibrinolytic action began to be studied in the late 1950s with scientific works such as Astrup's that describes the dynamic balance between coagulation and the fibrinolytic system [69]. From these studies, clinical applicability began with its use in coronary arteries. The first study on the use of a drug with fibrinolytic action in patients with DVT was published by Kakkar et al. in 1969 [70]. He compared the use of streptokinase in relation to unfractionated heparin, showing a higher rate of recanalization in those treated with fibrinolytic (70% × 30% recanalization).

The process of transforming plasminogen into plasmin seems to be the most important in triggering fibrinolysis. This key enzyme leads to the cleavage of fibrin and fibrinogen with the consequent destruction of the thrombus [71]. The maintenance of the organism's homeostasis occurs due to the balance between fibrinolysis inhibitors (plasmin) and plasminogen activators. The fibrinolytic drugs used in our clinical practice are plasminogen activators. We can mention streptokinase,

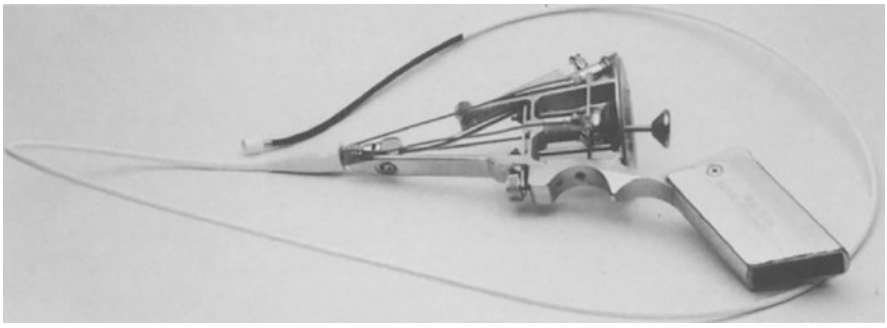

Fig. 14.4 Greenfield device for thrombus aspiration

urokinase, and rt-PA (recombinant tissue plasminogen activators, alteplase, reteplase, and tenecteplase).

The use of selective fibrinolysis through the use of a catheter for intra-thrombus infusion seems to be more effective than systemic treatment because it reduces the presence of residual thrombus. It improves the patency of the deep venous system, decreases the incidence of post-thrombotic syndrome and the recurrence of DVT in addition to improving QOL [72]. Laiho et al. demonstrated competence of the deep venous system after fibrinolysis in 44% of patients treated with the use of a catheter compared to competence in only 13% of patients treated with systemic use of fibrinolytic [73]. The limitation of this treatment is related to the impossibility of more comprehensive use, especially when the patient has some contraindication to the use of the fibrinolytic agent due to the risk of bleeding, something common in cancer patients.

The development of catheters in which pharmacological fibrinolysis is associated with a mechanical device has further increased the efficacy and safety of fibrinolysis and appears to be a major differential in the treatment for thrombus removal [74]. The devices are characterized as rotational, rheolytic, and ultrasound. The best time for its use is the period of up to 14 days, that is associated with attractive success rates. After this period, recanalization rates worsen significantly [75].

There is still a lack of scientific data on its applicability in patients with DVT, especially in cancer patients. The Cavent trial, a Norwegian, multicenter RCT study, without cancer patients, demonstrated a significant reduction in PTS after 24 months in patients treated with fibrinolysis with catheter treated compared to anticoagulation (41.1 vs. 55.6% $p = 0.047$) [76]. Another RCT trial, The TORPEDO trial, compared the efficacy and safety in addition to the incidence of recurrence and post-thrombotic syndrome at 6 months of follow-up among patients treated with pharmacomechanical fibrinolysis and anticoagulation or anticoagulation only. They found a significant reduction in recurrence (2.3% vs. 14.8% $p = 0.003$) and in post-thrombotic syndrome (3.4% vs. 27.2% $p < 0.001$) without an increased bleeding [77].

The ATTRACT trial (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis) was a multicenter, controlled, and randomized study that randomly assigned 692 patients with acute proximal deep-vein thrombosis to receive either anticoagulation alone (control group) or anticoagulation plus pharmacomechanical thrombolysis (catheter-mediated or device-mediated intra-thrombus delivery of recombinant tissue plasminogen activator and thrombus aspiration or maceration, with or without stenting). After 24 months of follow-up, 24 months, there was no significant between-group difference in the percentage of patients with the post-thrombotic syndrome (PTS) (47% in the pharmacomechanical-thrombolysis group and 48% in the control group; risk ratio, 0.96; 95% confidence interval [CI], 0.82 to 1.11; $p = 0.56$), with increase of major bleeding within 10 days (1.7% vs. 0.3% of patients, $p = 0.049$) [78]. According the authors: "The results suggest that pharmacomechanical catheter-directed thrombolysis (PCDT) should not be routinely used to prevent post-thrombotic syndrome in patients with

symptomatic proximal deep vein thrombosis above the popliteal vein as there is no added benefit to exposing them to the risks and costs of additional catheter-based thrombolysis" but some considerations was made about the iliofemoral subgroup.

In 391 patients with acute deep vein thrombosis involving the iliac or common femoral veins from ATTRACT trial, PCDT did not influence the occurrence of PTS (Villalta scale ≥5 or ulcer: 49% PCDT vs. 51% No-PCDT; risk ratio, 0.95; 95% CI, 0.78–1.15; $p = 0.59$) or recurrent venous thromboembolism, but PCDT significantly reduced early leg symptoms ($p < 0.01$) and, over 24 months, reduced PTS severity scores, reduced the proportion of patients who developed moderate-or-severe PTS (Villalta scale ≥10 or ulcer: 18% vs. 28%; risk ratio, 0.65; 95% CI, 0.45–0.94; $p = 0.021$), and resulted in greater improvement in venous disease specific quality of life ($p = 0.029$). These findings support early use of PCDT in patients with acute iliofemoral DVT who have severe symptoms, low bleeding risk, and who attach greater importance to a reduction in early and late symptoms than to the risks, cost, and inconvenience of PCDT [79].

Retrospective patient series have demonstrated that cancer patients can benefit from PCDT [80, 81]. The 2012 ACCP guidelines do not recommend routine use of CDT over anticoagulation alone, but suggest that patients with the following factors are most likely to benefit from PCDT: iliofemoral DVT; symptom durations less than 14 days; good functional status; life expectancy of at least 1 year; and low risk of bleeding [82]. The NCCN panel believes that PCDT and thrombectomy can be considered a therapeutic option for select patients with large symptomatic extremity DVT, particularly when they are not responding to conventional anticoagulation [83, 84]. In our experience, the cases in which we observed the greatest benefit were in the treatment of the superior vena cava syndrome frequently associated with the presence of a fully implantable catheter, with a greater probability of survival in the treated cases compared to those of the lower limb ($p = 0.063$) (Figs. 14.5, 14.6, nd 14.7).

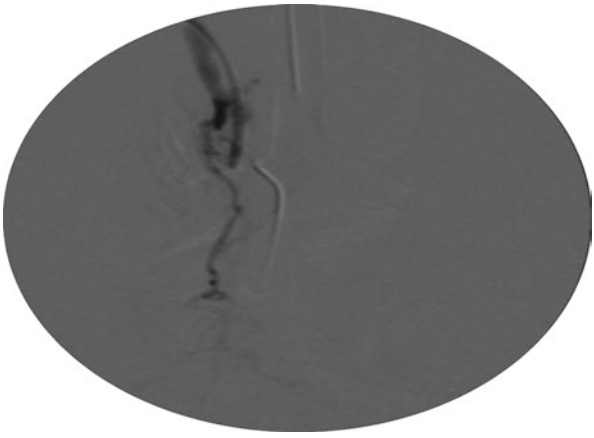

Fig. 14.5 Angiographic image of the superior vena cava syndrome (named vein obstruction and superior cava)

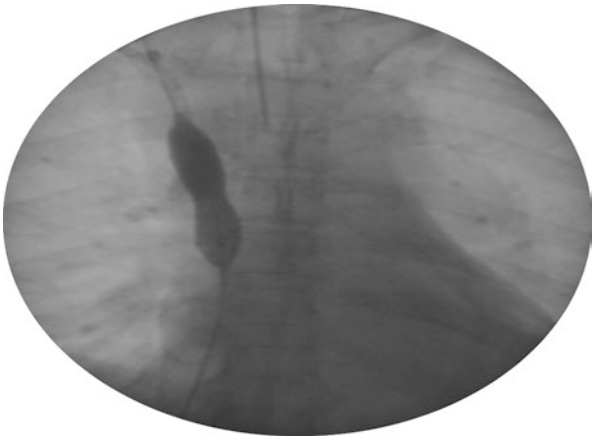

Fig. 14.6 PCDT, angioplasty and stenting in the superior vena cava

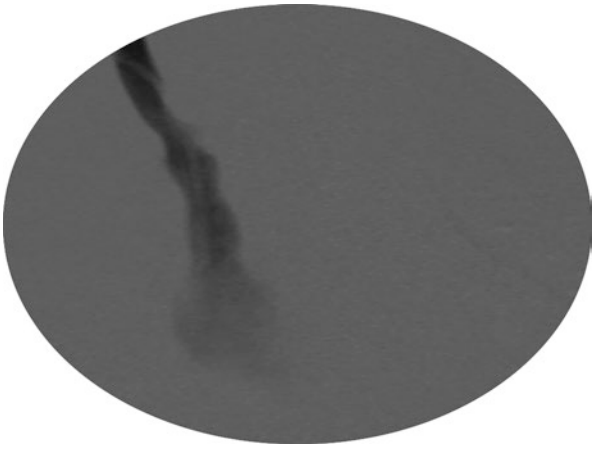

Fig. 14.7 Final result after endovascular treatment

Editors Comments

Perhaps the main event that brings cancer closer to peripheral vascular disease is venous thromboembolism (VTE). The relationship between the two has been known since the nineteenth century when Armand Trousseau (1801–1867) described the association between thrombosis and malignant disease 2 years before his death [85]. The diagnosis of cancer-associated migratory spontaneous venous thrombosis has the name of Trousseau syndrome, himself a victim of gastric cancer diagnosed after the emergence of a thrombophlebitis [85, 86].

"Je suis perdu; une phlegmatia qui vient de se déclarer cette nuit, ne me laisse aucun doute sur nature de mon mal."

["I am lost; a phlebitis which has declared itself this night leaves me no doubt about the nature of my illness."] —Armand Trousseau [86]

Since then, as stated in this chapter, VTE has been the second leading cause of death in individuals with cancer, behind only the oncological disease itself. The clinical presentation of DVT ranges from the absence of symptoms to more dramatic conditions, with severe pain and pallor (phlegmasia alba dolens) or cyanosis (phlegmasia cerulea dolens). Symptoms are often vague and familiar to several other clinical conditions, especially in the individual with cancer. The clinical picture depends on which veins were affected, the degree of obstruction, and collateral circulation development. The most common signs and symptoms are pain and edema, hyperemia, prominence of superficial veins, low fever, cyanosis, pain on passive foot dorsiflexion (Homans sign), muscle swelling, cyanosis, pallor [87]. About 70% of patients with characteristic DVT symptoms do not have a confirmed diagnosis, while 50% of those with confirmed DVT do not show typical symptoms, which makes evident the need for the complementary tests described in the chapter for diagnostic confirmation [87].

As the cancer patient is frequently submitted to imaging tests, either for tumor staging or to investigate other complications, such tests may reveal the presence of venous thrombosis and/or pulmonary embolism as an incidental finding. Incidental VTE accounts for half of VTE cases associated with cancer and should be treated in the same way as the symptomatic one since its risks are comparable to those of the symptomatic VTE. A more careful investigation can reveal a sign or a symptom that the patient or his doctor may have attributed to another cause. As imaging tests for cancer staging are not necessarily standardized in the same way as those performed for VTE research, it may be necessary to continue the investigation with tests targeted explicitly for this purpose.

The need for prophylaxis in hospitalized patients for clinical treatment is well established, as well as in high-risk surgical patients. More recent studies have shown benefit in the prophylaxis of high-risk patients undergoing outpatient antineoplastic treatment.

As in non-cancer patients, treatment is based on anticoagulation, and the risk of bleeding should be considered. The dissemination of studies of efficacy and safety of direct oral anticoagulants (DOAC) in cancer patients has led to changes in guidelines of significant medical associations, as exposed in this chapter, admitting rivaroxaban use, edoxaban, and apixaban in individuals with lower hemorrhagic risk. Alternative treatments using fibrinolytic and drug-mechanical thrombectomy should be considered as an exception and evaluated very rigorously in this population.

In the patient with pulmonary embolism, the risk estimate based on classifications such as the pulmonary embolism severity index (PESI) can be used to determine long-term mortality and morbidity (Table 14.6) [88].

For patients with high-risk PTE, fibrinolytic treatment is indicated in an intensive care setting, as long as there is no contraindication, followed by full anticoagulation. In intermediate or high-risk cases, the patient is treated with full anticoagulation with unfractionated heparin or low molecular weight heparin under

Table 14.6 Pulmonary embolism severity index—original and simplified versions [88]

Parameter	Original version	Simplified version
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate >110 b.p.m.	+20 points	1 point
Systolic blood pressure <100 mmHg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	–
Temperature <36°	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhemoglobin saturation <90%	+20 points	1 point
	Risk strata (based on the sum of points)	
	Class I: ≤65 points Very low 30-day mortality risk (0–1.6%) *Class II: 66–85 points* Low mortality risk (1.7–3.5%) *Class III: 86–105 points* Moderate mortality risk (3.2–7.1%) *Class IV: 106–125 points* High mortality risk (4.0–11.4%) *Class V: >125 points* Very high mortality risk (10.0–24.5%)	*0 point* = 30-day mortality risk 1.0% (95% CI 0.0–2.1%) *≥1 point* = 30-day mortality risk 10.9% (95% CI 8.5–13.2%)

b.p.m. beats per minute, *PESI* pulmonary embolism severity index

monitoring in an intensive care unit due to the risk of clinical deterioration. Patients classified as intermediate risk and low risk are treated with full anticoagulation, considering the hemorrhagic risk and the drug interaction for choosing the anticoagulant drug.

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Chapter 15
Endovascular Procedures in Cancer Patients

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15.1 Embolization of Tumors and Vascular Malformations

Vascular anomalies, according to the classification universally adopted by the International Society for the Study of Vascular Anomalies (ISSVA) [1], are divided into two major groups: the vascular tumors, characterized by proliferation of cells of the vascular endothelium and subdivided into benign, locally aggressive or borderline, and malignant, and the vascular malformations, whose endothelial cells present a normal cell cycle and arise as a result of focal embryological failure, the vascular differentiation that occurs in intra-uterine life, leading to an abnormal development of the vascular system (Fig. 15.1).

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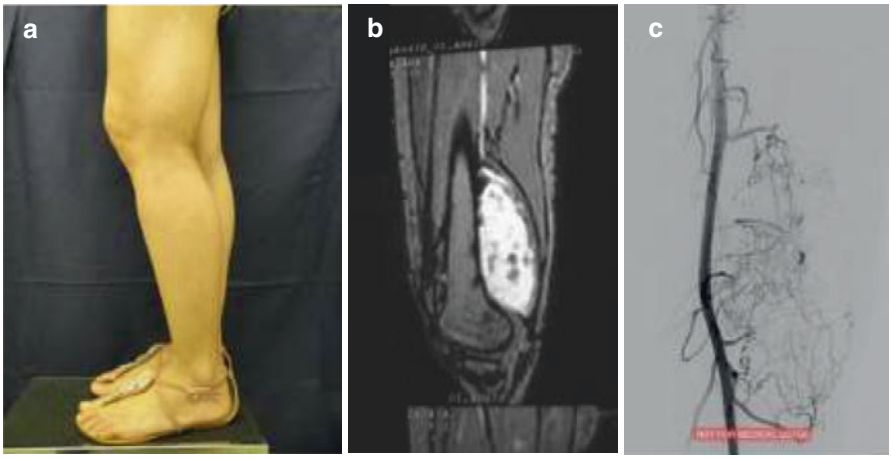

Fig. 15.1 (**a**) A.A.T. Female, 27 years old. Non-pulsatile tumor on lateral and posterior sides of left thigh beginning in adolescence. (**b**) MRI of left thigh: coarsely oval image of lobulated margins with intima counted with the biceps femoral muscle presenting intermediate signal at T1 and high signal intensity in the STIR sequence with intense impregnation and homogeny by the paramagnetic agent. (**c**) Left femoral arteriography: several arterial pedicles from the superficial femoral artery irrigating with high-flow the vascular malformation associated with multiple smaller size arterial branches (arterio-arterial anastomosis) as a consequence of previous embolizations

15.2 Vascular Tumors

15.2.1 Benign Vascular Tumors

They are characterized by the proliferation of endothelial cells. Infantile Hemangioma (IH) represents about 70% of childhood tumors, being the only one in this group to present positivity for the immunohistochemical marker GLUT1 [2, 3].

The IH appear in the first month of life, presenting bright red coloration and firm consistency in superficial lesions, grow rapidly during the first year of life (proliferative phase), and slowly regress until 10 or 12 years of age (involutive phase), when in the great majority of cases they regress completely.

The hemangiomas occur in any part of the organism with predominance at the cephalic segment, and can be single or multiple, superficial or deep. Their diagnosis is essentially clinical, and in the presence of lesions located in deeper planes, they can be easily confused with high-flow vascular malformations (VAMs) or with other types of tumors. In this case they should be better investigated through imaging examinations such as Doppler ultrasound and eventually magnetic resonance, which will be very useful in diagnostic differentiation. The treatment of IH, in general, is clinical and propranolol (beta-blocker) is the drug of choice. This drug acts by refraining the proliferation of endothelial cells, accelerating cellular apoptosis, and should be used early in order to reduce local sequelae and complications, once checked that there is no cardiological contraindication.

15.2.1.1 Hepatic Hemangioma

Hepatic hemangioma (HH) is considered the most frequent benign tumor of this organ. In general, they are asymptomatic, multiple, and of reduced size being treated conservatively [4]. However, in about 10% of cases, these lesions can reach larger sizes exceeding 5 cm in diameter, causing different and non-specific symptoms, in addition to presenting hemorrhagic risk due to rupture that usually occurs due to local trauma. In these circumstances, surgical treatment and embolization by selective catheterization must be considered, the latter being especially indicated in more complex cases, when the hepatic hilum is involved by the tumor occurs or in those that present extension to the thorax or pelvis [5, 6].

Catheter embolization for hemangioma was reactivated for the first time in 1917 and few reports succeeded this [7, 8]. In an original article published in 2015 by Szejnfeld et al. [9], the authors used an association of ethanol and lipiodol for selective embolization in the treatment of symptomatic giant hemangiomas, with satisfactory results, complete regression of symptoms and significant improvement in quality of life in all patients. The authors based their experience on a published experiment using the same strategy of hepatic embolization used in oncologic treatment [10]. A good argument of the authors regarding the result obtained is due to the adequate choice of the liquid embolic agent, which due to its good diffusion and intimate contact with the vascular endothelium allowed an effective occlusion of the tumor without complications related to the treatment.

15.2.1.2 Congenital Hemangiomas

They are completely formed tumors at birth and represent about 30% of hemangioma cases [11].

Congenital hemangiomas are GLUT1 negative, despite their histological similarity to childhood hemangioma [12, 13]. They can also be classified according to their involutive capacity as:

1. Rapidly Involuting Congenital Hemangioma (RICH): These are rare tumors, present at birth and totally regressing in the first year of life. They might leave sequelae such as skin and subcutaneous atrophy due to rapid involution. This type of hemangioma can evolve with transient thrombocytopenia in the neonatal period and more rarely with coagulopathy of consumption—the Kassabach-Merritt syndrome (KMS). In these cases, the treatment must be instituted immediately, under risk of evolving to death.
2. Non-invasive Congenital Hemangioma (NICH): Also described as a variant of proliferative hemangioma, unlike RICH, it does not present spontaneous involution. It has more common prevalence in males and the best treatment is surgical removal.
3. Partially Involuting Congenital Hemangioma (PICH): Also described as a variant of proliferative hemangioma, unlike RICH and NICH, it presents partial

spontaneous involution and is equally prevalent between sexes. The best treatment is surgical removal of the residual lesion.

Congenital cases of NICH and PICH can be confused with vascular malformations, and the complementation of imaging studies associated with biopsy can define the diagnosis and therapeutic conduct.

15.2.2 Locally Aggressive or Borderline Vascular Tumors

In this group, we will highlight the Kaposiform Hemangioendothelioma (KHE) which is a rare pediatric vascular tumor, negative for GLUT1 gene, that invades skin, subcutaneous fat, and muscles, being characterized as a blue-purple tone lesion, of firm consistency, sometimes equimotic and painful to palpation. Local lymph nodes may be involved, but metastases are not observed. From the histological point of view, it presents as an irregular nodular lesion, similar to the morphological pattern of hemangiomas, but more infiltrative. This lesion is often associated with thrombocytopenia and can also evolve into KMS. In this case, there would be an accentuated thrombocytopenia due to the kidnapping of platelets by the lesion, triggering hemolytic anemia and consumption coagulopathy, with a possible cardiac decompensation and hepatic involvement associated with a high mortality rate.

KHE is often clinically confused with vascular malformation or other vascular tumors. Its diagnosis should be based on a combination of clinical, histological findings, and complementary imaging examinations, in addition to a hematological investigation into changes related to the KMS.

Magnetic resonance imaging is preferably indicated among imaging exams, with T1-weighted sequences typically showing a poorly circumscribed soft tissue mass, with thickening of the dermis and subcutaneous tissue and diffuse enhancement with gadolinium. T2-weighted sequences show a diffuse increased signal, with subcutaneous fat entanglement. The gradient sequences show discretely dilated vessels in and around the soft tissue mass.

Whenever possible, histological confirmation should be obtained to direct the specific therapy. However, if the clinical and imaging findings are highly suggestive of the diagnosis, the biopsy may be postponed to avoid possible bleeding complications during the procedure.

The recommended treatment is performed with the use of corticosteroids in pulses. In the presence of persistent cell proliferation associated with the KMS, the drug Vincristine should be used.

The recent introduction of the drug Sirolimus, which acts as an inhibitor of the cellular receptor M-TOR preventing neoangiogenesis, can be considered as a drug of first choice in the treatment of KHE, stabilizing the progression of the disease and

contributing to the hematological control. It is also worth mentioning that transfusion of platelets and red blood cells, due to their consumption (kidnapping) in the intimacy of the tumor mass, is formally contraindicated for worsening the self-consumption of blood elements. In extreme cases with risk of death the blood transfusion must be performed with strict monitoring, in intensive care unit due to the high risk of complications.

Even with the introduction of appropriate therapy, KHE lesions may not completely regress and recurrence may occur with age progression, especially at puberty. The symptomatology in general is aggravated with inflammation and pain. Long-term effects include chronic pain, lymphedema, heart failure, and orthopedic problems [14].

15.2.3 Malignant Vascular Tumors

15.2.3.1 Angiosarcoma

These are highly malignant tumors that represent 2% of sarcomas, and can appear in any part of the body, being more common in soft tissues. It presents distinct biological behavior and depends on the initial location, being less aggressive and metastatic in children and, therefore, with better prognosis. There are reports of its occurrence in newborns and in childhood, with presentation of multiple skin lesions and hepatic lesions, some of which are positive for GLUT1.

It affects preferentially bones, muscles, liver, spleen, breast, subcutaneous tissue and retroperitoneum, and when it reaches the skin, it is characterized as dark red nodular elevations. Bone involvement is rare. It may be associated with chemical carcinogenesis, exposure to radiotherapy and chronic lymphedema. They are highly hemorrhagic, due to invasion of deep planes and with poor delimitation of neighboring structures. In addition to aggressive local growth, metastases occur frequently.

The treatment for the localized disease is initially surgical. Radiotherapy is indicated for localized skin disease in adults, and a combination of surgery, chemotherapy, and radiotherapy is indicated for cases of metastatic disease. Biological agents that inhibit angiogenesis have shown activity in adults with angiosarcoma, but are still under study [15].

Differential diagnosis of malignant vascular tumors can often be quite challenging, both at the lower end of the spectrum, distinguishing an epithelial hemangioendothelioma from an epithelial hemangioma, or at the high end of the spectrum, between an angiosarcoma and a malignant epithelial hemangioendothelioma. In this differential diagnosis, both clinical-radiological aspects (size and multifocality) and immunohistochemical markers (expression of endothelial markers) are often similar and, therefore, it may not be possible to distinguish between benign and malignant vascular lesions.

15.3 Vascular Malformations (VVMs)

Vascular malformations arise from dysplastic vascular channels. In general, they are present at birth, grow proportionally to the individual's development and never present involution [16]. This evolutionary aspect differs completely from the history of a hemangioma, which can present rapid growth in a short period of time.

VAMs are subdivided according to the predominance of vascular channels into venous, lymphatic, capillary, arterial or combined forms and according to the flow characteristics, high and low.

15.3.1 Venous Malformation (VM)

The VM is characterized as a bluish tumor in superficial lesions or with normal looking skin in muscular lesions. They present softened consistency and are depressible upon palpation, without fremitus or blow.

The VM is characterized by Doppler ultrasound as anomalous venous spaces, compressible, superficial or intramuscular, with slow flow and presenting an echogenic or hypoechogenic content. Thrombi or phleboliths (calcified thrombi) can also be identified inside these lesions.

In the presence of large lesions or those affecting the muscle compartment, a diagnostic complementation with magnetic resonance imaging (MRI) is recommended for better differentiation in vascularized tumors. VMs are characterized by MRI as hyperintense lesions on T2-weighted sequences and variable intensity signal on T1-weighted sequences often associated with areas of flow voids indicating the presence of phleboliths and regional fat hypertrophy.

The treatment of choice is performed through a percutaneous approach, with the use of injections of liquid sclerosing agents [17] such as absolute ethanol (95–98% ethanol), at the maximum recommended dose of 1 mL/kg per session [18], or the use of 3% polidocanol in the form of foam (Tessari technique) without exceeding 10 mL of foam in each session.

15.3.2 Lymphatic Malformation (LM)

The LMs predominate in the cephalic segment and may occur in any region of the body. They manifest as microcystic lesions, present in the skin or mucous membranes, in the form of vesicles with clear content, isolated or associated with capillary malformations, or as macrocystic lesions located in the subcutaneous cellular tissue or deep tissues, and may cause bulging of the skin, without changes in underlying color. They present fibroelastic consistency and may often evolve with inflammation signs due to an inflammatory or infectious process.

The diagnosis should be complemented by ultrasound, which shows cystic lesions of varying sizes, that is, microcystic (<0.5 cm) or macrocystic (>0.5 cm), incompressible and with no flow inside and still containing septa between the larger cysts. The content can also vary from an echogenic (purely lymphatic) to hypoechogenic (mixed: lymphatic-venous).

MRI can confirm the diagnosis by differentiating venous lesions by finding liquid level in macrocysts, in addition to hypersignal in T2-weighted sequences and septa identified in T1-weighted sequences.

Treatment should be early instituted, with the use of liquid sclerosing agents such as OK-432, Bleomycin, and Doxycycline, after direct puncture of the lesion, guided by ultrasonography. After puncturing the cyst, it is emptied of its lymphatic content and then the intralesional infusion of the liquid agents already mentioned is performed.

15.3.3 Arteriovenous Malformations (AVMs)

They are characterized by the presence of a pulsatile and little compressible tumor, with a firm consistency, with fremitus or blow resulting from turbulent blood flow [19]. Other characteristic findings of these lesions are an increase in the proximal arterial pulse and the presence of prominent venous drainage, usually elongated and tortuous. Secondary changes caused by distal ischemia and venous hypertension, such as edema, skin pigmentation, stasis eczema, ulcerations, and gangrene can also occur [20, 21].

In most cases, the lesions of the extremities are easily diagnosed by the clinical findings; however in the face and trunk, including the pelvis, the diagnosis should be complemented by imaging exams for a better differentiation between other vascular anomalies and between these and soft tissue tumors.

US Doppler is considered the exam of choice for an initial evaluation of patients with soft tissue lesions of probable vascular origin [22, 23] and makes it possible to characterize vascular malformations from a morphological and hemodynamic point of view.

MRI allows evaluating the extent of lesions and their relationship with adjacent anatomical structures, being useful in differentiating between high and low-flow lesions [24, 25]. AVMs are characterized as areas of absence of signal (flow-void) in T1- and T2-weighted sequences, corresponding to the nutritional arteries and malformation nidus [26–28].

MRI can also contribute to the differential diagnosis of soft tissue tumors such as hemangiomas, which are characterized as well-defined and lobulated lesions, characterized by hyperintense signal on T2-weighted sequences and intermediate signal on T1-weighted sequences, besides areas of flow voids in their contour [15, 23, 29]. Other tumors such as sarcoma, neuroblastoma, hemangiopericytoma, fibrosarcoma, rhabdomyosarcoma present characteristics of tissue invasion associated with perilesional edema [23, 30–32].

The development of new embolic agents and the introduction of smaller caliber catheters (microcatheters) allowed greater selectivity of the nutritional vessels, making the embolization technique the treatment of choice for AVMs [20, 33, 34].

The goal of embolotherapy in AVM is the occlusion of the primitive nutritional vessels of the vascular nidus, avoiding the embolization of non-target areas, and the choice of material to be used should be based on this angioarchitecture, that is, the caliber, length, and quantity of vessels involved; their flow characteristics; and their venous drainage [35, 36]. Therefore, in these conditions, the embolic agents of liquid nature are the most appropriate.

Two types of liquid embolic agents are used: adhesives such as glue (N-butyl cyanoacrylate—NBCA) with two products available Histoacryl® (B. Braun, Melsungen, Germany) and Glubran 2® (GEM Srl, Viareggio, Italy) and non-adhesive liquid embolic agents such as Onyx® (Onyx System, MTI—Micro Therapeutics Inc., San Clemente, CA, USA), Squid®, and Phill® (precipitating hydrophobic injectable liquid).

The glues (tissue adhesive) present great versatility of use, and can be used in several types of AVM with different dilutions [37]. The liquid nature of this agent allows its passage through microcatheters, and when released very close to or inside the nidus region, it starts the process of polymerization forming a framework around it and occluding the blood circulation. Its association with iodized poppy-seed oil (Lipiodol ® UF -Guerbet) makes the material radiopaque and delays the time of polymerization, facilitating its handling [38]. Thus, dilutions of cyanoacrylate with lipiodol are performed in proportions that vary from 1:1 to 1:8 according to the flow characteristics of the lesion to be treated. The injection technique of cyanoacrylate can vary from slow to fast depending on the dilution chosen and the intralesional flow pattern. For plexiform vascular malformations, bulky or low-flow lesions, diluted cyanoacrylate in low concentrations (15–20%) is indicated. For high-flow lesions of the fistular type, concentrated cyanoacrylate solutions, ranging from 33% to 50%, allow satisfactory occlusion of the lesion.

The risk of embolization with the use of cyanoacrylate implies the possibility of the microcatheter getting stuck to the vessel, making its removal impossible. Maneuvers to minimize this risk include the use of solutions with lower concentration of cyanoacrylate as well as its heating to reduce viscosity.

Non-adhesive liquid agents, such as Onix, Squid, and Phill, use DMSO as a solvent and therefore should use microcatheters resistant to this solvent, avoiding the deterioration of the material during the injection. These agents present good applicability in the treatment of AVMs in general, especially in bulky lesions with plexiform nidus or nourished by multiple branches. The high or low flow does not interfere or contraindicate their use. However, it is not used in the presence of direct high-flow arteriovenous fistula, where cyanoacrylate is indicated.

From a technical point of view, the injection pressure in the microcatheter during embolization should be sufficient to promote the progression of the material in the vessel, avoiding reflux towards the microcatheter. Refluxes are acceptable as long as they involve only 1.0–1.5 cm from the distal end of the microcatheter. Although these agents have no adhesive property, a prolonged injection of this material associated to a reflux will make it difficult to remove the microcatheter. After the embolization is over, the removal of the microcatheter should occur in a smooth and progressive way. Abrupt maneuvers when removing it increase the risk of rupture of the artery or catheter, increasing the morbidity related to the treatment.

Control angiography is necessary to verify the effectiveness of the procedure and the need for extra treatments.

There is no consensus in literature as to the ideal way to perform AVM embolization. The treatment can be performed in a single session, with occlusion of the entire injury or in several sessions. Multiple sessions are indicated, especially in large lesions, because they reduce the side effects related to hemodynamic alterations, responsible for the appearance of edema or bleeding [39].

Embolotherapy, although less invasive and relatively safer, is not entirely free of complications. For this reason, patients should be informed of the potential risk of the treatment. Possible complications include skin lesions such as bedsores, sometimes aggravated by infections and bleeding. Other potentially more serious complications include organ and tissue ischemia resulting from migration of embolic agents to normal vascular branches [40].

15.4 Final Considerations

The diagnosis of vascular tumors in general is clinical, but in doubtful cases it should be complemented by histological examination associated with immunohistochemical markers. In most cases, the treatment of benign vascular tumors is drug treatment. As for other vascular tumors, it is essential to make the differential diagnosis between locally aggressive vascular tumors and malignant vascular tumors, so that appropriate oncologic treatment is quickly instituted.

The diagnosis and treatment of vascular malformations is still considered a challenge, given the wide variety of lesions, often of great complexity. Low-flow lesions are treated by percutaneous sclerosis and high-flow lesions are treated by catheter embolization.

Of note, high-flow lesions (AVMs) with peculiar angiographic characteristics and considered as false tumours should be biopsied for pathological and immunohistochemical analysis as a precaution. After having the diagnosis confirmed as a benign lesion they can be treated by embolization and followed up with imaging methods.

15.5 Chemoembolization of the Liver

15.5.1 Introduction

In 1977, Yamada et al. performed transarterial chemoembolization (TACE) of 120 patients with hepatocarcinoma that received embolization therapy with gelatin sponge [41]. However, only since the 2000s the studies comparing TACE versus transcatheter arterial embolization (TAE), in which no chemotherapeutic agent is used, were effective in demonstrating the superiority of TACE [42].

The liver has a double circulation, from both the portal vein and hepatic artery. The portal vein is responsible for two-thirds of the hepatic blood flow and nutrition of hepatocytes. The hepatic artery preferably nourishes the bile ducts due to its one-third of flow to the liver. Most hypervascular tumors, such as hepatocarcinoma (HCC), metastases of colorectal cancer (CCR), neuroendocrine tumors (NET), among others, have preferentially arterial nutrition.

The rationale of hepatic tumors embolization technique is to occlude the arterial circulation, which feeds the tumor, maintaining normal hepatocyte circulation (portal flow) [43]. The association of a chemotherapy with an embolization agent provides ischemic action on the tumor and local chemosaturation, which acts directly on the tumor and inhibits the neoangiogenesis, with a low serum concentration of the chemotherapy [44].

15.5.2 cTACE X DEB-TACE

The conventional TACE (cTACE) is performed with a solution of lipiodol and chemotherapy. Lipiodol is an iodized poppy oil that serves as a contrast medium, a temporary embolizing agent, and a chemotherapy carrier. The HCC has tropism for the lipiodol, being able to actively capture and retain it for prolonged periods. These characteristics allow that after injecting the emulsification, by selective catheterization of the feeding artery of the lesion, the anti-cancer effect is potentialized.

In DEB-TACE, biocompatible spherical microparticles capable of carrying some chemotherapeutic agents are used. There are several companies in the market today, each one with particularities of material, size, and preparation. The preparation of the particles, either by absorption and/or by adsorption, makes that after its controlled and selective injection of the hepatic artery, it occludes the circulation by impaction and gradually releases the drug (Fig. 15.2).

After the embolization the beads release the drug for 14 days, with action of up to 1.2 mm in diameter, keeping the serum concentration low [45].

The first multicenter, international, prospective randomized study, PRECISION V, evaluated the safety and efficacy of DEB-TACE compared to cTACE for HCCs after 6 months of treatment. The results showed significant reduction in liver toxicity and doxorubicin-linked side effects even at the high doses delivered, and it was

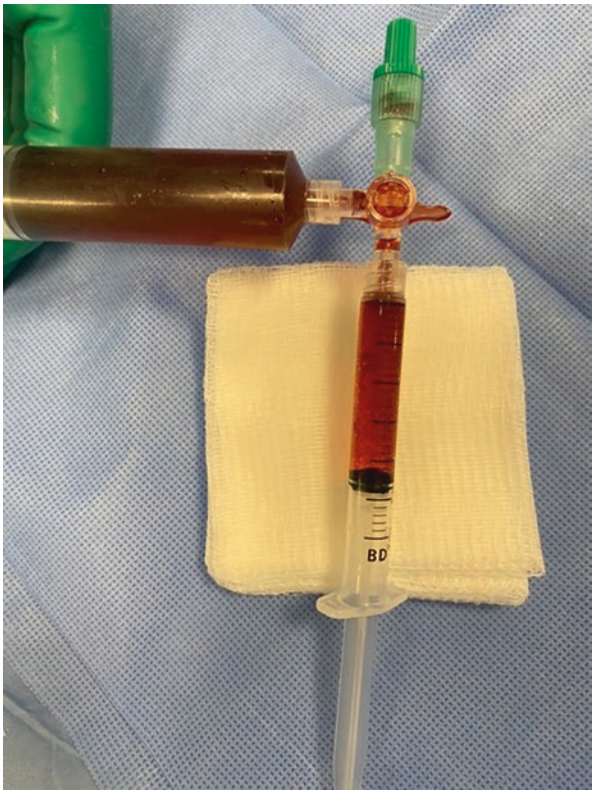

Fig. 15.2 DB-beads with doxorubicin

also effective in demonstrating benefit of DEB-TACE for Child-Pugh B and ECOG 1 patients. For the other patients there were improved rates in favor of DEB-TACE for complete response (27% vs. 24%), objective response (52% vs. 44%), and stable disease (63% vs. 52%), but this difference was not significant [46].

Two meta-analyses identified better overall survival and complete response rates, and lower rates of adverse effects in favor of DEB-TACE, suggesting the superiority of this technique compared to cTACE. However, these results should be interpreted with caution since there is a need for more multicenter randomized and well-structured studies comparing the two methods [47, 48].

15.5.3 Hepatocarcinoma (HCC)

The HCC is the most common primary cancer of the liver, sixth most common type of cancer in the world and fourth in number of deaths. The Barcelona Clinic Liver Cancer (BCLC) staging system classifies according to number and size of lesions, tumor invasion, liver function, and performance status (ECOG). According to

BCLC patients with intermediate stage disease (B), that is, multinodular disease who have preserved liver function and ECOG, TACE is the standard treatment in palliative treatment, with positive impact on 2-year survival [49].

In patients listed for liver transplantation the use of TACE or DEB-TACE is positive for local control of the disease, either to keep the patient within the Milan criteria while waiting for the availability of an organ (bridge treatment) or to reduce the size of the tumor and reframe it within the transplant criteria (downstage).

However, the use of chemoembolization has been expanded to BCLC 0 to C. In patients Stage 0 and A the procedure may be indicated as an alternative in the impossibility of resection or ablation by radiofrequency (RFA), or in association with RFA for better local control of nodules of 3–5 cm compared to isolated RFA. In cases with advanced disease (BCLC C), studies have shown benefit in better local control when associated with systemic therapy [50].

15.5.4 Metastasis

The liver is a common destination for the migration and development of metastatic cells of the most diverse types of neoplasias. Among these, the hepatic metastases of colorectal carcinoma are the most frequent.

At the time of diagnosis, approximately 20–30% of patients already present metastasis, and during the course of the disease, 60% of patients will present hepatic metastasis. Only about 25% of patients with colorectal metastases are candidates for curative therapy [51, 52], and even patients who have undergone a successful resection, present up to 60%, develop recurrence.

Systemic chemotherapy is the standard approach for these patients with increased survival, but it may present limiting results beyond systemic effects.

Liver chemoembolization is indicated for symptom palliation or increased survival in selected patients with non-resectable metastases (or no indication for ablation) and refractory to systemic chemotherapy [53]. These patients should have at least predominant or exclusively hepatic disease, life expectancy greater than 3 months, performance status (ECOG) less than 2 [54].

Ranieri et al. demonstrated that there is improvement overall survival and disease-free survival when the DEBTACE is performed in patients in the third line of chemotherapy, for patients refractory to the first lines of systemic treatment (complete response 21.8%, partial response 13%, stable disease 52.2%, and progressive disease 13%; mean 37 months) [55].

Due to the safety and effectiveness proven in previous studies, new study protocols include liver chemoembolization with DEB-TACE for metastases of colorectal tumor as the first treatment line, in association with FOLFOX/Bevacizumab, showing increased success in downstage for subsequent resection and improved survival.

TACE based on Mitomycin C and Cisplatin or Doxorubicin regimens offers an average survival of 11–14 months after the beginning of the salvage treatment.

However, two-thirds of the patients present post-embolization syndrome with this technique. The DEBTACE technique associated with doxorubicin or irinotecan reduces the plasma concentration of the chemotherapy and may increase tolerance to side effects after treatment [53].

Other hepatic metastases can also be treated with therapy, among them, metastases of neuroendocrine tumors (NET). Carcinoid tumors response rates to systemic chemotherapy are as low as 20%, so locoregional therapy is satisfactorily applied to control tumor progression and control hormone-related symptoms. The absence of prospective randomized studies for treatment of NET metastases results in heterogeneous results as radiological response rate between 25% and 95% and 5-year survival of 13.7–83%. Moreover, there is no consensus regarding the scheme used in TACE and whether the best responses are associated with early or late indication [56].

15.5.5 Procedure

Before the procedure, it is essential to evaluate the patient as well as his or her previous history of oncologic treatment—chemotherapy lines, which chemotherapy agent was used, previous surgeries—it is necessary to have an image examination (CT or MRI) with contrast, tumor marker, liver function tests, and physical examination. The patient must be within the indication criteria according to BCLC or for metastases.

Patients with liver dysfunction (bilirubin greater than 3 mg/dL or Child-Pugh C), encephalopathy, bleeding or active infection, leukopenia, and low life expectancy are against chemoembolization criteria. Portal thrombosis is a matter that might contraindicate the procedure; however, it is possible to perform it if there is a superselective catheterization of the feeding branch of the lesion, preserving the normal hepatic parenchyma.

The procedure can be performed under general or local anesthesia with sedation; the catheterization of the celiac trunk with 5Fr diagnostic catheter allows panoramic angiography for identification of anatomical variations and nutritional branches. Large nodules located preferably on the hepatic surface, and that do not respond to the TACE sessions that were properly performed, must have investigated the presence of extra-hepatic collaterals. Especially in hypervascular tumors, associated with neoangiogenesis, tumor nutrition from non-hepatic branches (phrenic artery, left gastric artery, gastroduodenal artery, and intercostal arteries) may justify the absence of necrosis after the chemotherapy session.

By coaxial system, superselective catheterization of the hepatic arteries is performed, followed by angiography confirming the feeding of the lesion. When possible, it is recommended that the embolization (with emulsion of lipiodol and doxorubicin or carrier particles) is performed in the sub-segmentary branches, so that there is preservation of the irrigation of healthy hepatic parenchyma.

The angiographic control should show the absence of the hypervascular enhancement and the disappearance of the lesion, reduced vascularization of the embolized segment and preservation of vascular trunks.

The follow-up of the patient is performed with image examination (tomography or three-phase magnetic resonance imaging) within 45–60 days for evaluation of locoregional oncologic response.

15.5.6 Side Effects and Complications

The most common adverse effect associated with TACE/ DEB-TACE is the post-embolization syndrome occurring in about 2–36% of cases. It is defined by fever, pain in the right hypochondrium, nausea, and vomiting, due to an inflammatory syndrome by tumor necrosis and hepatocyte injury. It has a benign and self-limited evolution usually within 14 days, being controlled with oral analgesia, antiemetics, and antipyretic [57, 58].

Complications may be digestive bleeding, gastrointestinal ulcers, ascites, tumor bleeding, cholecystitis, non-target embolization, dissection, hepatic abscess, and infection; this is associated with repeated and non-selective necrosis [59, 60].

Major complications are rare events, from 0.84% to 2.7% per procedure; however, when they occur, the death risk is 16.7%. In cases of hepatic abscess, it is suggested by Arslan that the necrosed area does not receive adequate substrate and antibiotic therapy due to the arterial branches occlusion and consequent progression of infection [61].

Acute liver failure and hepatic infarction are the most serious complications after TACE (conventional or DEB) and are associated with risk factors such as portal thrombosis, high levels of AST, bilirubin and alpha-fetoprotein, and low serum levels of albumin and sodium [62].

15.5.7 Hemostatic Embolization in Oncology

Clinically relevant bleeding occurs in approximately 10% of patients with advanced neoplasms [63]. Survival rates have improved over the years. However, approximately 600,000 people die annually from cancer in the United States. Cancer surpasses cardiovascular diseases as the leading cause of death in the United States in people under the age of 80 [64].

In the oncologic context, the evolution of the disease to multiple organ failure can occur spontaneously due to disease progression, by the extension of malignancy or by acute conditions such as infection, bleeding or thromboembolic complications [65].

There are several and often concomitant causes for these patients to bleed. Namely, (1) tumor invasion: by a combination of mechanical invasion and local

inflammatory reaction, the tumor can locally infiltrate the blood and lymphatic vessels, eroding large or small vessels. In head and neck tumors, for example, bleeding has a catastrophic potential, with a mortality rate of 40%, and in those that survive, there is a high rate of neurological sequelae [66]. In addition, angiogenic factors produced by some tumor types promote a hypervascularization of the tumor, predisposing the patient to bleeding. A hepatocarcinoma, typically hypervascular, when ruptured, can cause hemoperitoneum difficult to manage [67].

(2) Systemic factors: (A) Thrombocytopenia is the most prevalent hemostatic alteration in oncologic patients and occurs independently of chemotherapy [68]. Spontaneous bleeding does not usually occur with platelets above 20 thousand/μL. (B) Coagulopathy may result from disseminated intravascular coagulation, primary fibrinolysis, and liver disease. It is established as the most common cause of bleeding in oncologic patients [69]. The disseminated intravascular coagulation (DIC) is more common in mucin-producing tumors, such as prostatic carcinoma, pancreas, gastrointestinal tract (GI), lung, breast, and ovary. (C) Use of medication: anticoagulants are associated with increased bleeding, especially in patients with advanced tumors. In some patients, the risk of anticoagulation may even outweigh the benefits, even with the adequacy of therapeutic doses. In addition, anti-platelet drugs, such as aspirin and non-steroidal anti-inflammatory drugs, can induce or exacerbate bleeding, especially in patients with thrombocytopenia [70].

(3) Bleeding associated with treatment: mucositis is a cause of bleeding in patients receiving radiotherapy and chemotherapy; extensive mucositis is a common cause of GI bleeding in patients who will be submitted to trunk cell transplantation. In addition, bone marrow transplantation is associated with bleeding, even in the absence of mucositis [71].

15.5.8 Management of Hemorrhagic Diathesis in the Oncologic Patient

Due to the unavailability of large studies that guide therapy in cancer patients with bleeding, management is commonly based on personal preferences, available resources, and cost. In Table 15.1, there is a summary of treatment options available for these patients [66].

The systemic treatment, aiming the correction of hemostatic defects, is indispensable in the treatment of these bleeding patients. If the blood dyscrasias are not minimally corrected, most of the other available treatments will be futile.

The vascular surgeon is an important part in the treatment of oncologic patients. He or she may be needed primarily when scheduling a surgical resection that might need vascular reconstruction, as a rescue surgeon in a complication during oncologic surgery or after a bleeding intercurrence not related to the surgery and/or as a surgeon part of a multidisciplinary oncology team that makes decisions about the best treatment for the patient [72].

Table 15.1 Bleeding control in patients with cancer

Local measures
Surgical packing
Compression dressings
Topical hemostatics
Radiation therapy
Endoscopy
Palliative embolization
Systemic interventions
Transfusion therapy
Platelet
Plasma products (fresh frozen plasma, cryoprecipitates)
Administration of vitamin K
Desmopressin
Antifibrinolytic agents
Recombinant factor VIIa
Prothrombin complex concentrate

Together with these roles and the constant evolution of endovascular surgery, the vascular surgeon and the interventionist are an important milestone in palliative oncologic treatment. The arterial and venous network provides a fast and accessible route for most tumors. The advance in catheters, guides, and above all in imaging technologies has substantially increased the scope of what can be obtained by percutaneous access, minimally invasive [73].

Percutaneous arterial embolization (PAE) is a technique used to reduce blood flow in certain vessels after the use of hemostatic agents. The procedure is commonly performed via the femoral or brachial/axillary artery and is restricted to territories where the vessels are accessible and whose interruption of blood flow will not cause ischemia of a vital organ. It has been used for management of bleeding in various types of neoplasms, such as head and neck, bladder, prostate, cervix, lung, liver, kidneys, and for metastatic disease [66]. In addition, it can be used prophylactically, before a scheduled surgery of a hypervascular tumor, whose bleeding may be difficult to control—urgently during or after a surgery that evolves with major bleeding, or in spontaneous bleeding in advanced tumors.

The procedure can be performed under sedation, using iodinated contrast media, but also carbon dioxide or gadolinium if necessary. The tumor and its vascularization can be derived from the largest artery that vascularizes that organ (e.g., renal artery) or it can recruit from nearby territories, as in cases of hepatic tumors and TGI.

High-quality angiographies can outline the arterial supply of the tumors, but more recently the endovascular surgeon can count on angiographies obtained by the cone-beam CT, which can show the arterial tree in submilimetric resolution. In addition, workstations can create 3D plans to schedule the intervention. VesselNavigator™—Philips, Amsterdam, NE—is a software that allows the use of 3D information from the vascular anatomy coming from computerized tomography or magnetic resonance imaging previously performed, creating a 3D roadmap that overlaps the live image of fluoroscopy. In addition, there are software such as

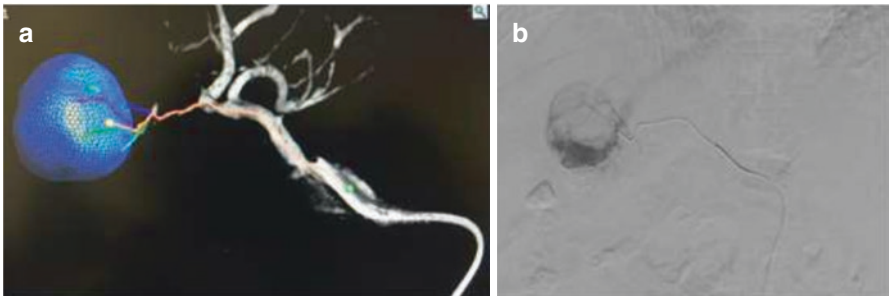

Fig. 15.3 (**a**) Reconstructed image through the software EmboGuide,™ Philips, Amsterdam, NE, after selective angiography of the proper hepatic artery, with identification of the tumor fed by the right hepatic artery, branch of the segment V, with automatic creation of a "path" to the lesion as a roadmap. (**b**) Superselective angiography of the segment V branch, in the right hepatic, showing the previously identified hypervascular area of the tumor, after assistance from the software

EmboGuide™—Philips, Amsterdam, NE, which detect the tumors and their suppressing vessels, creating a roadmap over the fluoroscopy image to guide the catheterization, increasing by up to 50% the detection of vessels that arrive in the tumor [74] (Fig. 15.3).

The embolization technique involves placing the catheter as superselective as possible in relation to the target, to reduce collateral damage as much as possible. Ideally, the catheter should be free floating in the artery to allow the blood flow to take the embolizing agents and not be forced by pressure on the syringe. After all, when this occurs, there is an increase in reflux and non-target embolization as a consequence.

The most commonly used embolizing agents are as follows: (1) Gelatin sponge: a low-cost, temporary effect method. Vessel recanalization occurs within a few weeks (Fig. 15.4) (2). Particles and spheres (Fig. 15.5): they are permanent agents, commonly made from polyvinyl alcohol (PVA) and graduated in size. The small particles (45–150 μm) can cause obliteration of the capillary bed, causing necrosis. The spheres are precisely calibrated, deformable, compatible with small catheters without forming lumps, but have a higher cost (3). Metallic coils: available in several sizes, shapes, and materials. Some have Nylon or Dacron fibers adhered to induce coagulation. They can be free or controlled release (Fig. 15.6) (4). Absolute alcohol induces effective necrosis, but is painful and requires general anesthesia [73].

15.5.9 Situations Requiring Endovascular Intervention

15.5.9.1 Hemoptysis

Malignant tumors are responsible for 30% of hemoptysis; 30% of lung cancer patients will manifest hemoptysis and 10% of these will be massive. In cases of hemoptysis that require intervention, the bronchial arteries are responsible for over 90% of cases [75].

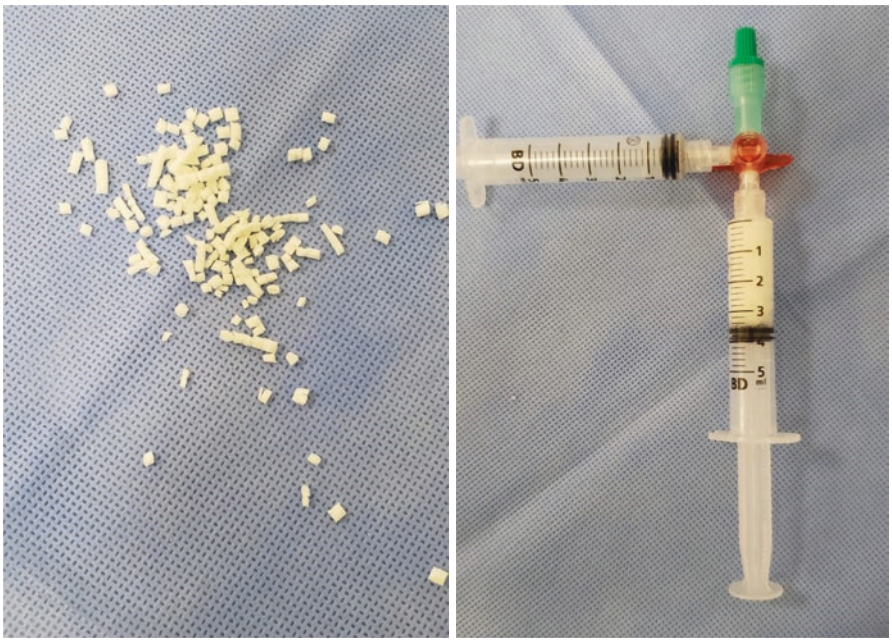

Fig. 15.4 Gelatin sponge Gelfoam,™ Pfizer, New York, United States, after preparation for embolization use

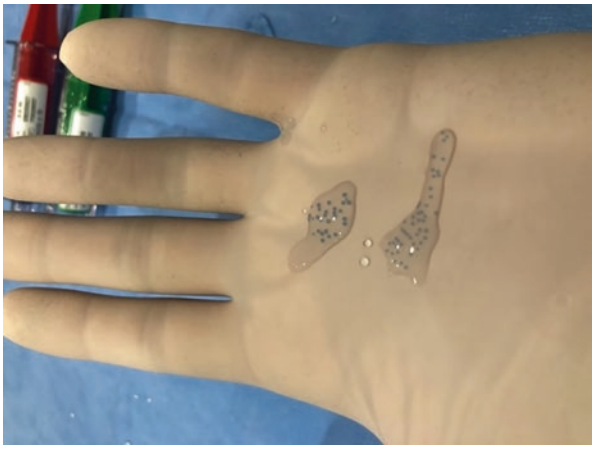

Fig. 15.5 Bead Block™ Spheres, Boston Scientific, Massachusetts, Estados Unidos

The vascularization of the pulmonary parenchyma is extremely variable and consists of bronchial and non-bronchial arteries. The most common type of vascularization only occurs in 25% of patients and consists of a right bronchial artery emerging from a right bronchial–intercostal trunk and two left bronchial arteries emerging directly from the descending aorta between T5 and T6. In patients with pleural disease (suggested by pleural thickening >3 mm), it is suggested that there is a

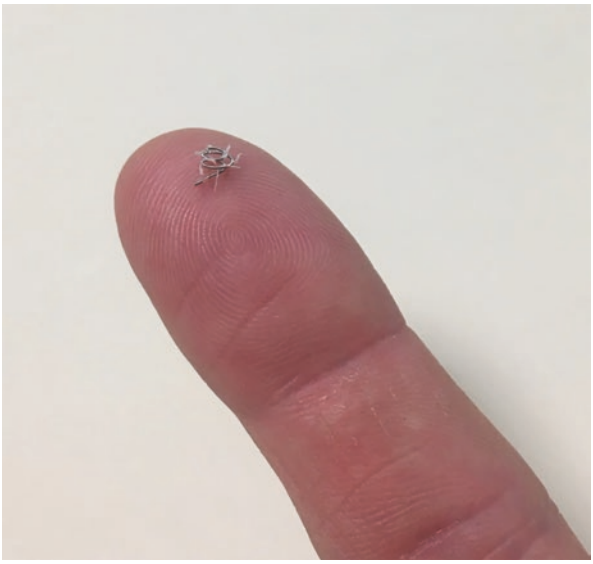

Fig. 15.6 Fibered Coil, Interlock™, Boston Scientific, Massachusetts, United States

recruitment of the thoracic wall arteries. Therefore, occasionally there may be involvement of the inferior phrenic, internal thoracic, and thyrocervical trunk arteries. Multiple bronchial–mediastinal anastomoses may also exist, especially in patients who present with hemoptysis. These anastomoses, when hypertrophied, represent a risk factor for recurrence and should be treated, such as interbronchial anastomoses [76].

This entire interconnected vascular network is also concerned with ischemic complications, the most feared of which is medullary ischemia, resulting from the embolization of intercostal branches that contribute to the formation of the great anterior radiculomedullary artery, whose anatomy also varies. In 75% of the cases, it is between T9 and T12, at the left side (65–80%) [77]. Besides, it is important that the vascular surgeon is able to recognize it in angiography, and to pay attention to its retrograde refilling by collaterals, avoiding the embolization of these branches.

Chest CTA plays a very important role in the investigation of hemoptysis and treatment planning. The findings that suggest pathological blood vessels irrigating the lung and potentially responsible for hemoptysis are a combination of: (1) vessels of larger diameter (greater than 2 mm); (2) excessive tortuosity; (3) systemic pulmonary shunt, and, very rarely, (4) contrast overflow.

Treatment with embolization often requires the use of microcatheters due to the small size of the target vessels. Embolization should be selective enough to avoid reestablishment of flow by arterial anastomosis. However, the embolization site cannot be too peripheral to avoid the risks of ischemic complications. Access to the proximal region of the embolized arterial trunk should be kept patent, considering the risk of recurrence. The most commonly used agents are non-absorbable microparticles (with diameters greater than 200 μm) and Onyx® (Medtronic, Dublin, Ireland). Coils should be avoided, especially if used alone, as they do not

completely stop the flow and may prevent further access to the bleeding site. Recent studies show clinical success rates close to 90% in oncologic patients, but the prognosis is poor, with a mortality rate of 64% in 1 year [78, 79].

15.5.9.2 Upper Gastrointestinal Bleeding

Gastric carcinomas are responsible for 1–8% of upper gastrointestinal bleeding. Digestive endoscopy is considered a first-line modality for evaluation and treatment in these cases and is effective, with initial hemostasis in 67–100% of the cases. However, 41–80% of the patients bleed again and tumors larger than 20 mm in maximum diameter are associated with treatment failure. Palliative radiotherapy is an alternative for patients with non-surgical tumors, but for patients with resectable tumors with sudden bleeding causing hemodynamic instability, transarterial embolization (TAE) is an option (Fig. 15.7).

In the study published by Part et al., the technical success rates with TAE reach up to 85% and clinical success 65%, but patients who needed embolization had a worse prognosis, with a mean survival of 85 days after the procedure. The most commonly performed treatment was the TAE of the left gastric artery alone, followed by the left gastric artery with other vessels such as the right gastroepiploic. Despite the lack of consensus in literature, the choice of the target vessel, in the absence of active overflow images, should be based on the location of the tumor, namely, right gastroepiploic if the tumor is located in the great curvature; short gastric arteries for tumors in the stomach fundus. Although there is no consensus regarding the choice of the embolizing agent, temporary agents such as gelatin

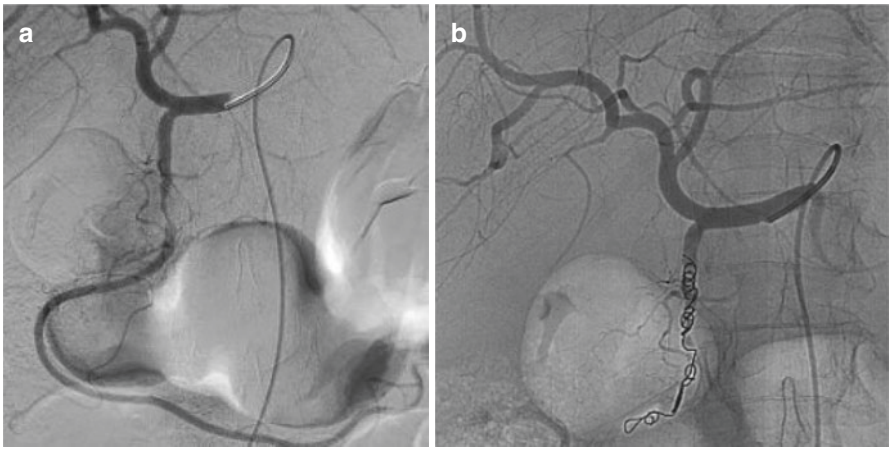

Fig. 15.7 Patient with small intestine tumor, presenting high digestive hemorrhage. (**a**) Angiographic study of the gastroduodenal artery showing involvement of the gastroduodenal artery by the tumor. (**b**) Angiography after embolization of the gastroduodenal artery with coils

sponge were related to higher rates of recanalization, suggesting benefit with definitive agents. No major complications were described in the 40 patients treated. However, two splenic infarcts were described, with no need for surgical approach [80].

Koo et al. published results of 20 patients with stromal tumors with ADH submitted to TAE. All patients were previously evaluated by abdominal CTA. Embolization was performed based on the identification of vessels with signs of overflow or by tumor "shadow." The choice of embolizing agents was based on the experience and preference of the interventionist and involved agents such as N-butyl cyanoacrylate mixed with lipiodol, particles of various sizes, coils, and gelatin sponge. The technical success was described in 95% of the patients and the clinical in 90%. Only one patient manifested recurrent bleeding and 75% of the patients were operated with curative resection after bleeding control. No major complication related to TAE was described in this study [81].

15.5.9.3 Lower Gastrointestinal Bleeding

Neoplasms are responsible for about 12% of lower gastrointestinal bleeding. The most common symptom is hematochezia, present in 55.5%. Melena is found in only 11% of patients. Colorectal carcinoma is the third most common type of cancer in the United States and is the predominant cause of oncological bleeding. At least 10% of hematochezia in patients over 50 years of age is caused by tumor bleeding.

Nowadays, TAE already replaces surgery in patients with lower gastrointestinal bleeding nonresponsive to endoscopic treatment or in patients where colonoscopy cannot be performed for technical reasons or because the patient presents contraindications. Once the target vessel has been characterized, treatment includes injection of vasopressors (with high recurrence after ceasing the infusion of the drug) or superselective embolization. TAE can be performed in high-risk patients, not candidates for surgery or as a bridge for patients who will undergo tumor resection after clinical stabilization. The success rates described with TAE reach up to 98% in relation to immediate hemostasis, but it is not a complication-free procedure. The most feared and significant complication is bowel ischemia, with rates as high as 20% at the beginning of this therapeutic modality [82]. However, with the advent of microcatheters, superselective catheterization techniques, in a study that demonstrated the use of microcoils as an embolizing agent, the rates reduced to close to 4.5% (Fig. 15.8) [83].

15.5.9.4 Ruptured Hepatocarcinoma (HCC)

The HCC can be an indirect cause of bleeding due to decompensation of hepatic cirrhosis, and also directly from tumor rupture. Although this complication is not common, if left untreated it can be fatal. The clinical presentation is a combination

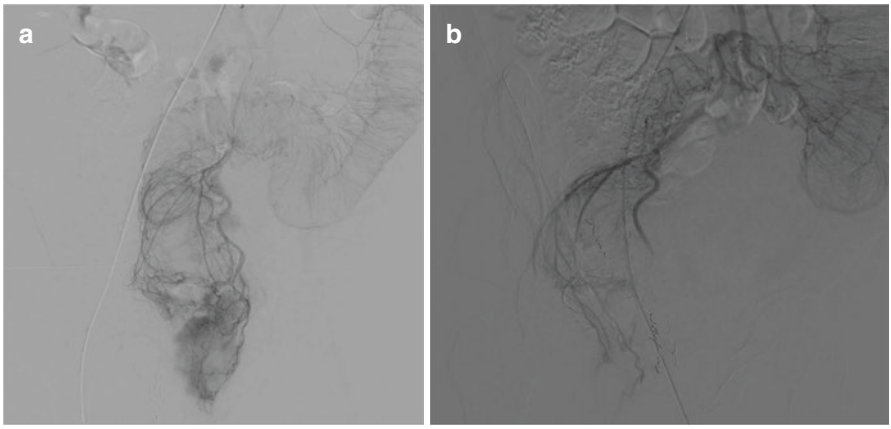

Fig. 15.8 A 44-year-old female patient with squamous cell carcinoma of the anal canal presented with low digestive hemorrhage. (**a**) Superselective angiography of the upper rectal arteries identifying an area of arterial blush, suggestive of bleeding. (**b**) Control angiography after embolization of the upper rectal arteries with metallic spikes and microspheres, demonstrating preservation of the truncal branches, with bleeding control

of sudden epigastric pain, cardiovascular shock, and abdominal distension. Occasionally, the tumor may rupture into the bile duct, causing cholestatic jaundice, epigastric pain, and melena/hematochezia.

The most accepted mechanism for this complication is the invasion of the hepatic veins by the tumor, which prevents its drainage, resulting in a sudden increase in intratumoral pressure and hemorrhage, initially inside the tumor, until there is rupture and extravasation to the abdominal cavity. The risk factors are hypertension, cirrhosis, tumors larger than 5 cm, tumors that insinuate into the hepatic capsule, vascular thrombosis, and extrahepatic extension.

Treatment with embolization is effective and causes less damage than surgical treatment in those patients who are fragile and vulnerable. The agent of choice is gelatin microspheres, but chemoembolization can also be performed if the patient is not hemodynamically unstable and if the chemotherapy drug is available (Figs. 15.9 and 15.10). Thrombotic portal obstruction is an absolute contraindication and dilation of the biliary tract is a relative contraindication because the risk of ischemia and cholangitis must be weighed against the severity of bleeding. As this is an emergency situation, it is difficult to apply the BCLC [84] guidelines to these patients, so there is no consensus on treatment. Still, embolization is effective in controlling bleeding in 94% of cases [85]. The poor prognosis related to ruptured HCCs is in association with several factors such as the fact that bleeding suggests locally or remotely advanced disease and decompensation of cirrhosis. In addition, rupture of the tumor to the cavity represents risk for peritoneal metastasis and contraindicates transplantation, at least temporarily [86].

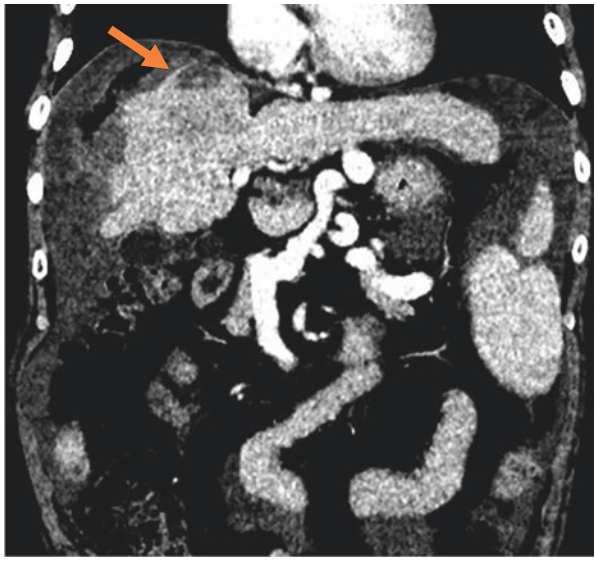

Fig. 15.9 Coronal section of abdominal CTA in portal phase: orange arrow indicating nodule with washout, pseudocapsule, and fat component, located in the periphery of the IVa hepatic segment, measuring 5.6 cm, compatible with hepatocarcinoma. There is a focus of discontinuity of the contours at the upper edge of the lesion, suggestive of bleeding. In the midst of the ascites, hyperattenuating areas are noted, suggestive of hemoperitoneum

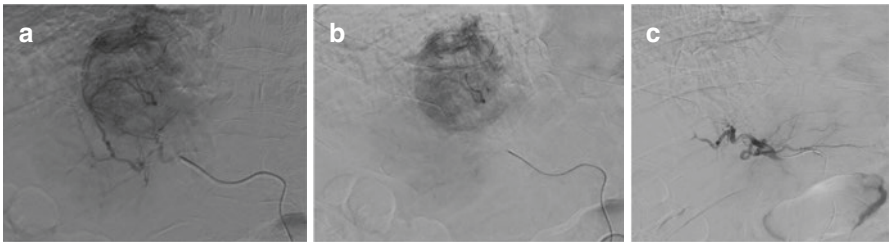

Fig. 15.10 (**a**, **b**) Angiographic image with superselective microcateterization of a IVa segment branch with image of a hypervascular lesion, compatible with hepatocarcinoma previously identified by abdominal tomography. There is an area of discontinuity of the left side of the lesion with iodinated contrast overflow, suggested by rupture. (**c**) Control angiography identifying the lesion devascularization after embolization with 300–500 μm microspheres

15.5.9.5 Bleeding from Breast Cancer

Breast tumors, especially those locally advanced, may rarely present with acute bleeding that is difficult to control, especially if they are ulcerated. This complication can have a difficult surgical management with little result. Attempts of external compression, with complex dressing, have also resulted in frustration. In this scenario, TAE has played an increasingly important role in the treatment of these patients. There are some case reports in the literature demonstrating the adequate bleeding control by embolization technique, with technical success obtained with the use of PVA and microspheres [87, 88]. The costocervical trunk and the internal mammary artery are the most frequently treated, and there may also be involvement of pectoral, intercostal branches and supreme intercostal artery (Fig. 15.11).

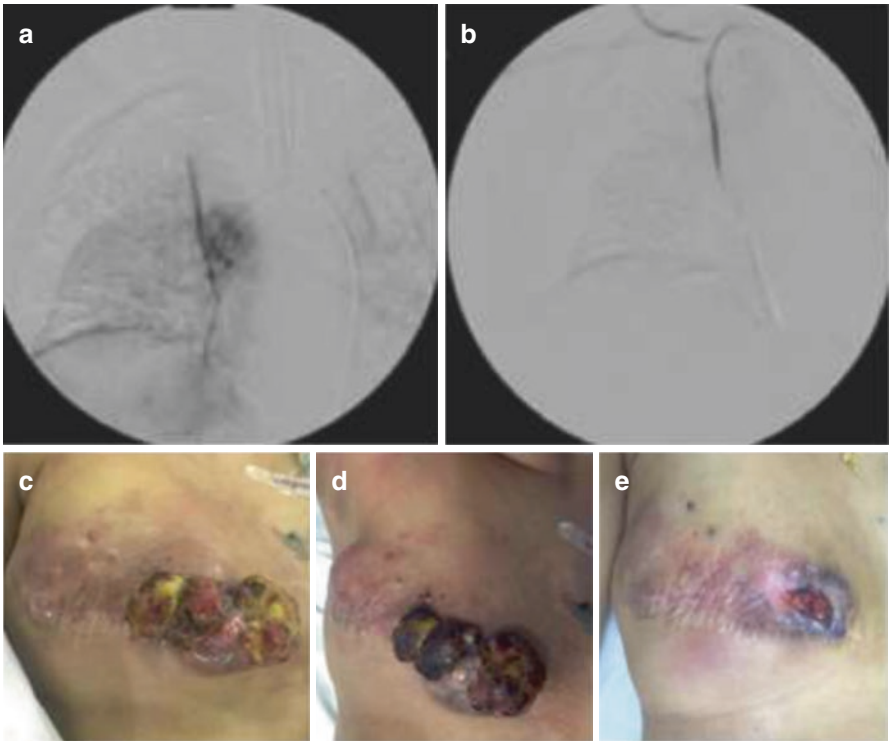

Fig. 15.11 Patient with local recurrence of right breast neoplasia, with local ulceration and bleeding, refractory to systemic therapy. DEBDOX was performed, a 100–300 μm microspheres with doxorubicin 75 mg/vial. (**a**) Right internal thoracic arteriography in the parenchymal phase showing hypervascular lesion in right breast topography. (**b**) Control angiography after proximal chemoembolization of the right internal thoracic artery to vascular stasis. (**c**) External aspect of the right breast before chemoembolization. (**d**) External aspect of the right breast on the first day after DEBDOX. (**e**) External aspect of the right breast on the 34th day post-procedure. Note the improvement of the appearance of the lesion, as well as the decrease in its volume

15.5.9.6 Ruptured Retroperitoneal Tumor

This is a rare condition, most frequently caused by renal tumors, with nonspecific symptoms, which may include the Lenk triad in 50% of cases: sudden unilateral lumbar pain, lumbar edema and hemodynamic changes. Hematuria is commonly absent [89]. Angiomyolipomas and renal cell carcinomas are usually richly vascularized, which is a risk factor for bleeding. The priority imaging exam for these cases is tomography of the abdomen [90]. The identification of the tumor can be difficult due to the presence of perirenal hematoma and also in those patients who present multiple cysts. Regardless of the cause of bleeding, embolization is the first-line treatment. Often it is effective and can identify the responsible lesion.

After emergency treatment, it is important to identify and treat the cause. If no cause is found, it is important to pay attention to the high probability of the presence of a malignant tumor and even the need for nephrectomy should be carefully considered [91].

Spontaneous rupture of a pheochromocytoma is also rare, but mortality reaches 32%. This is explained not only by bleeding but also by the systemic release of catecholamines with fatal potential. Embolization, therefore, is also the treatment of choice because it allows bleeding control and gives time to prepare patient to undergo surgical correction, with administration of an alpha-adrenergic blocker, to stabilize blood pressure and reduce the risk of arrhythmia [92].

15.5.9.7 Hematuria and Bladder Cancer

Macroscopic hematuria, typically at the end of urination and painless, is the symptom present in 80% of bladder cancer cases. The causes are multiple and often related: primary tumor bleeding, actinic or drug cystitis, severe infection, or coexistence of other pelvic tumors. The bleeding is perpetuated by the anticoagulant effect of urokinase [93]. The consequences of hematuria may be palpable bladder, obstructive kidney injury, or hemorrhagic shock. Multiple approaches can be performed for these cases, including oral drug therapy, intra-vesical irrigation, radiotherapy, and endoscopic or surgical resection.

Embolization and intra-arterial injection of chemotherapy are alternative treatments, which do not require general anesthesia. The anterior division of the internal iliac artery must be accessed, allowing superselective embolization with spheres or particles, preferably. The most common complications are gluteal pain and passing urinary alterations (Fig. 15.12).

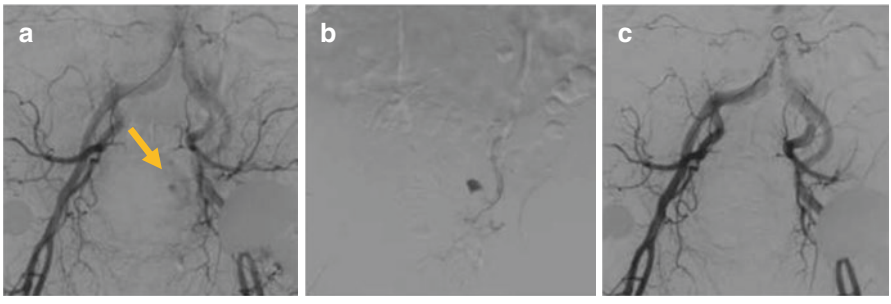

Fig. 15.12 An 82-year-old male, with diagnosis of bladder cancer, evolved with hematuria. (**a**) Pelvic angiography with identification of blush on the left vesical wall, suggestive of bleeding focus (yellow arrow). (**b**) Superselective catheterization of the left upper bladder artery with contrast overflow. (**c**) Control pelvic angiography after bladder branch embolization with 500–700 microns particles and coils, showing bleeding control

15.5.9.8 Arterial–Ureteral Fistulas

The incidence of this situation is underestimated and is growing. The risk factors for this are: history of abdominal or pelvic oncologic surgery, urinary derivations, prolonged use of bladder probe, previous radiotherapy, or presence of vascular stent. The most common site is the crossing point between the iliac artery and the ureter, due to the proximity of these structures and the vulnerability of their walls to inflammatory and fibrotic reactions. Its mortality is 58%, if untreated, and the delay in diagnosis is a factor of worse prognosis. The predominant symptom is hematuria, which occurs in all patients and can be micro- or macroscopic. Hematuria is the unique symptom in 74% of cases and is combined with low back pain and signs of infection in approximately 10% of cases. The diagnostic examination of choice is angiography as only 42% of diagnoses are given by tomography and 4% by cystoscopy. Once the treatment is diagnosed, it should be done with the use of coated stents [94].

Editors Comments

This chapter dealt with the procedures for embolization of tumors and vascular malformations.

In these comments, we intend to address the possibilities of endovascular treatment of peripheral vascular complications caused directly by cancer, in addition to the treatment of common vascular diseases in cancer patients.

Pharmaco-mechanical thrombectomy for the treatment of venous thromboembolism (VTE) was the subject of Chap. 14. Patients with large tumors may complain of symptoms resulting from vascular structures' compression, notably veins in the chest, abdomen, and pelvis. The superior vena cava syndrome was discussed in the comments referring to Chap. 2. In the abdominal and pelvic territory, the iliac veins' compression is not uncommon, leading to symptoms of corresponding lower limb venous hypertension and increased risk of venous thrombosis. The resection of the tumor en bloc with the iliac veins requires, whenever possible, the reconstruction of the venous flow (see Chap. 13) even in cases of oligosymptomatic patients in the preoperative period, since the removal of the tumor usually sacrifices a significant part of the collateral circulation developed from the compression of the trunk vein, in addition to also affecting the lymphatic flow, increasing eventual edema in the post-surgical period. If there is no planning for surgical resection of the tumor, the treatment of venous compression aims to relieve symptoms and improve quality of life. In the patient with more limiting symptoms of venous hypertension, stent angioplasty is a resource to be considered, despite the limited data in the literature [95–97].

Tumors of the carotid body were discussed in Chap. 1. The treatment of carotid body tumors is eminently surgical, but it is a procedure with a higher risk of massive hemorrhage, either due to an injury to the arterial wall or a type of highly vascularized tumor addition to cranial nerve damage. Thus, to reduce the frequency of

hemorrhagic complications, there are reports of endovascular procedures preceding surgical resection, such as tumor embolization and coverage of the internal common-carotid segment with coated stents; however, the benefit of these measures has not yet been confirmed in the literature [98–101].

The resection of head and neck tumors adhered to the carotid artery may require a careful dissection to prevent recurrence due to the permanence of a tumor lesion in the vascular wall or a more extensive operation en bloc resection of the artery with the tumor. Thinning of the wall can lead to rupture of the carotid artery and massive hemorrhage in the postoperative period. This event, called carotid blowout syndrome, can also occur due to erosion of the arterial wall due to tumor invasion or post-radiotherapy complication and is also amenable to endovascular treatment by embolization covered stent implant [102–105]. Arterial erosion by tumor invasion can occur in other territories, causing complications such as aortoesophageal fistulas (in tumors of the upper digestive tract) and femoral hemorrhage in patients with inguinal lymph node metastases originating in genital cancers (femoral blowout syndrome) [106–108].

As we saw in Chaps. 9 and 12, cancer and atherosclerotic disease share similar risk factors, so the coexistence of neoplasia with the peripheral arterial disease is not a rare event. Often, arterial disease treatment, whether obstructive or aneurysmatic, is indicated during cancer treatment or in territories with sequelae from antineoplastic treatment (surgery, radiotherapy). Therefore, less invasive procedures, already widely adopted as the first choice in non-cancer patients, are also preferred in treating individuals with a history of cancer or active cancer. The endovascular technique brings the same good results from the general population in cancer patients in treating an abdominal aortic aneurysm [109, 110]. When the aortic aneurysm has a huge diameter, especially if the patient will undergo a significant cancer operation, its treatment must precede oncology or, in selected cases, it can occur jointly [109]. The effect of chemotherapy treatment on the growth rate of aortic aneurysms is still an object of study.

Carotid stenosis in patients with head and neck tumors is expected not only because of the common risk factors but also because radiotherapy accelerates and aggravates the atherosclerotic process (see comments in Chap. 12). Thus, the carotid artery's critical and/or symptomatic stenosis in the hostile neck due to extensive oncological surgery and/or sequelae of radiotherapy may be an obvious indication for endovascular treatment [111–113].

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Chapter 16
Lymphedema in Cancer Patients

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16.1 Lymphedema in Cancer Patients

Basically, the lymphatic system is responsible for tissue homeostasis by regulating the interstitial space. Excess leaked fluids from the microcirculation, macromolecules, extravascular blood cells, and cell products are managed by the lymphatic system through a complex network of capillaries, lymph vessels, and lymph nodes.

When the lymphatic system fails the interstitial homeostasis is disrupted; extracellular fluid accumulates, lymphocyte trafficking and regional immune response are impaired and tissue overgrowth, mainly caused by fibrosis and fat tissue deposition, occurs. Clinically, lymphedema follows conditions of low lymphatic output, either caused by congenital abnormalities or, as in our current interest in this chapter, provoked by tumor obstruction and therapeutic interventions onto lymphatic pathways which damage a previously normal lymphatic system.

Swelling due to lymph stasis can occur in the arms, legs, genitalia, face, neck, and torso, depending on the tumor location or the site of lymphatic intervention.

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The most common conditions associated with lymphedema development are breast cancer, urological and gynecological malignancies, melanoma, soft tissue sarcomas, and head and neck cancers.

As we are still confronted against different diagnostic standards to define clinical lymphedema, it is difficult to estimate the real prevalence of lymphedema. It is likely that lymphedema burden is largely underestimated after staging or therapeutic procedures on lymph nodes in cancer patients.

Lymphedema following breast cancer treatment has an extensive literature. Reported incidence of lymphedema related to breast cancer treatment ranges from 11% to 57%, pooled incidences estimate that at least one among four breast cancer survivors will develop lymphedema during follow-up. Although less invasive approaches to the axilla as sentinel lymph node biopsy decrease the risk, lymphedema still affects around 6% of patients. Gynecological malignancies (cervical, endometrial, and vulvar cancer) also present a significant risk of lower limb lymphedema. An incidence of 27% is reported after cervical cancer treatment, endometrial and vulvar cancer, about 1% to 16% and 30% [1]. Risk of lymphedema of the upper or lower limbs in patients undergoing lymph node dissection for melanoma is estimated in 3% and 18%, respectively. Considering sentinel lymph node biopsy in these patients, risk falls to 4% [2]. Data on head and neck cancer treatment are scarce.

16.2 General Aspects of the Lymphatic System Anatomy

From the interstitium to the end of the thoracic duct (and the right lymphatic duct) at the confluence of the internal jugular and subclavian veins in the neck, the lymphatic system is formed by a number of progressively larger vascular structures interspersed by series of lymph nodes, sophisticated filters that regulate lymph flow and immune responses. Actually, the lymphatic system is not a circulatory one like the blood circulation; lymph flows unidirectionally from the interstitium to the central venous system.

The lymphatic system begins as lymph capillaries whose prime function is absorption of fluid and macromolecules. Structurally, they differ from blood capillaries: their format resembles glove fingers; they have incomplete basal membrane and are larger than the correspondent blood capillary vessels [3]. Their endothelial cells have open junctions, not found in blood vessels (except for sinusoidal capillaries and injured vessels). In some areas, adjacent endothelial cells partially overlap, allowing interstitial fluid inside the lumen and at the same time preventing lymph reflux to the interstitium. Additionally, these endothelial cells present extensions which originate on the outer surface of the intercellular contact area between two adjacent cells and fix onto elastic and collagen fibers of the interstitium, the anchoring filaments. They are a unique anatomical feature presented by lymph capillaries; whenever the interstitial volume increases, these fibers pull and open the intercellular space, allowing more interstitial fluid to enter the capillary.

More recently, a model of active lymph absorption by the initial lymphatics has been proposed, suggesting that the passive flow driven by hydraulic forces described by Starling's law might not be the only way lymph is formed [4].

Collector vessels and trunks present structure similar to veins, even though their three layers—intimae, media, and adventitia—are thinner and less conspicuous than those observed in the venous system. The muscular layer, unlike that of the blood vascular system, presents spontaneous contractions that promote centripetal flow. Semilunar valves inside the lumen are found throughout the system, more numerous but similar to the vein valves. They are folds of endothelium, smooth muscle, and connective tissue. There is also a valve at the lymphatic confluence at the jugulosubclavian junction, thus avoiding blood reflux to the major lymphatic ducts [5].

Lymph nodes are clusters of lymphoid tissue surrounded by a fibrous capsule and are arranged as groups of variable number of lymph nodes found in reasonably constant areas of the body. Their number is estimated to be around 600 to 700 [6] throughout the body. They are spherical or round in shape and their size may vary considerably. Afferent collectors reach their convex surface and drain lymph into a sub capsular space that is subsequently filtered in the network formed by the trabecular and medullar sinuses into the lymph follicles and exit as efferent collectors by the hilus, a depressed area which also contains blood vessels and nerves [7].

The lymphatic system, according to its topography, can be divided into superficial, deep and visceral. The superficial system drains skin and subcutaneous tissue whereas the deep lymphatic system is responsible for the subfascial tissue drainage. The visceral system can also be considered a part of the deep system. Perforating vessels cross the fascia and connect the superficial and deep systems. Some authors consider another group of vessels: the communicating vessels, which communicate areas drained by different bundles. Lymphatic collectors of the limbs, both superficial and deep, accompany neighboring vessels [8]; drained volume through the superficial system being far more important to the lymphatic drainage of the extremities.

The same as in lymph vessels, lymph node groups, or chains can be classified according to their location as superficial, when they are embedded into the subcutaneous tissue or deep, situated under the muscular fascia or inside abdominal or thoracic cavities [8].

16.3 Anatomy of the Lymphatics of the Upper Limbs

The superficial lymphatic drainage of the upper limbs is made almost exclusively to the homolateral axilla. Lymph from the skin and subcutaneous tissue reaches the axillary lymph nodes through collectors located at the subcutaneous area; ten bundles may be identified and they frequently anastomose between them.

These bundles comprise one or many collectors that accompany superficial veins. Six of them are located in the arm and four in the forearm and hand [9].

In the arm there are three anterior bundles (cephalic, basilica, and prebicipital) and three posterior ones (posteromedial, posterior, and posterolateral). The four bundles which drain the distal regions are divided in two anterior (anterior radial and anterior ulnar) and two posterior (posterior radial and posterior ulnar).

The deep lymphatic system accounts for a lesser amount of lymph drainage of the upper limb. The deep lymphatic collectors comprise six bundles containing few vessels which run close to the main arteries (brachial, deep brachial, radial, ulnar, and interossei).

The most important group of lymph nodes of the upper limb is located at the axilla. The axillary lymph nodes receive lymph from both the arm and the homolateral torso and are arranged in five chains around the axillary vessels:

(a) Anterior group (also pectoral or external mammary or lateral thoracic): These lymph nodes are located laterally to the pectoralis minor muscle at the inferior border of the pectoralis major muscle. They are related to the lateral thoracic vessels and drain lymph from most of the breast and supra umbilical region.
(b) Lateral group (or axillary): This chain lies close to the axillary vessels, still laterally situated to the pectoralis minor muscle and drains most of the lymph from the upper limb.
(c) Posterior group (also subscapular): Situated anterior to the subscapular muscle and lateral to the pectoralis minor muscle all along the subscapular vessels and receives lymph from the dorsum.
(d) Intermediate group (or central): Is also located following the axillary vessels but it lies behind the pectoralis minor muscle and is immediately medial to the previous group, receiving lymph from efferent vessels of the anterior, posterior, and lateral chains.
(e) Medial group (or apical): This last group is situated medial to the pectoralis minor muscle, receives efferent vessels from the intermediate group and from this group, efferent vessels form the subclavian trunk that flows to the lymphatic duct on the right side and thoracic duct on the left.

These groups may be also categorized according to their relation to the pectoralis minor muscle as in Berg's levels I, II, and III, which are very useful to access surgical intervention at the axilla. Anterior, lateral, and posterior chains are referred as level I, intermediate as II, and apical as III.

Although lateral group mostly receives lymph from the upper limb and the anterior group is closely related to breast lymph drainage, an anatomical study failed to demonstrate that those body areas drain to independent lymph nodes. Those lymph nodes are not only close to each other but also overlapping drainage is common [10].

Also, part of the lymph from the upper limbs does not reach the axillary nodes; these vessels are denominated derivative or accessory pathways. Two derivative pathways are important in the upper limbs: the cephalic (Mascagni's pathway) that

run to the supraclavicular nodes and the posterior bundles of the arm that reach posterior scapular nodes [9]. These derivative pathways are among the possible explanations why some patients are spared from lymphedema after axillary dissection and radiation for breast cancer treatment.

16.4 Anatomy of the Lymphatics of the Lower Limbs

As for the upper limb, the lymphatic drainage of the lower limbs also consists of a more important superficial and a deep system [8, 12].

The superficial system comprises six different bundles [11], two distal in the foot and in the leg, named according to the main vein they follow: great saphenous bundle (or ventromedial) and lesser saphenous (or posterolateral) bundle and four bundles in the thigh. The anterior bundles are the anteromedial (or greater saphenous) and anterolateral of the thigh. The posterior bundles of the thigh are denominated posteromedial and posterolateral.

The greater saphenous bundle of the leg extends upward and continues as the anteromedial bundle of the thigh. These lymphatic vessels converge posterior to the medial condilum of the femur to reach the thigh and receives anastomotic vessels from the lesser saphenous bundle. The anterolateral bundle of the thigh, also called accessory saphenous bundle originates in the thigh so there is no direct connection between this bundle and the lymphatics of the leg. These collectors are closely related to the greater saphenous vein, especially at the knee, making them susceptible to trauma during saphenous vein harvest [8].

The superficial inguinal lymph nodes are found in the subcutaneous of the inguinal and popliteal regions and are named according to their anatomical relationship with the neighboring vein. There are seven superficial nodal chains: six of them are located near to the saphenous femoral junction and the last one at the saphenous popliteal junction. In the popliteal region, the superficial popliteal node is commonly unique and receives lymph from the posterolateral bundle of the leg.

Three of the inguinal chains lie inferiorly to the saphenous arch and contain one or few bean-shaped lymph nodes: greater saphenous, lateral accessory saphenous and intersaphenous chains. The remaining three are cranial to the saphenofemoral junction, usually contain several small round nodes (superficial circumflex iliac, superficial epigastric, and external pudenda chains).

Usually, the lymphatic drainage of the lower limbs reaches the inferior inguinal lymph nodes (greater saphenous, lateral accessory saphenous, and intersaphenous) whereas superior ones receive lymph from infra umbilical abdominal area, gluteus, external genitalia, and part of the uterus. The major labia of pudendum have both homolateral and contralateral drainage.

After the inguinal lymph nodes, lymph of the lower limbs reaches external iliac and common iliac lymph nodes. Subsequently, it passes through lumbar aortic lymph nodes that form the lumbar trunks and finally drain into the thoracic duct.

16.5 Diagnosis and Staging

Patients presenting clinical symptoms of lymphedema or baseline volume changes need to have the lymphatic function checked in order to plan the treatment. The presence of dermal backflow in imaging tests such as lymphoscintigraphy, lymph magnetic resonance imaging (MRI) or indocyanine green lymphography is diagnostic for lymphedema. Lymphoscintigraphy allows the evaluation of the deep vessels and the transport level. The anatomy of the lymphatic system is better studied with the aid of the lymph MRI, while indocyanine green lymphography only allows the analysis of superficial lymphatic channels and is a powerful tool for surgical planning of lymphovenous bypass surgery.

16.6 Conservative Treatment of Lymphedema

16.6.1 Complex Decongestive Therapy (CDT)

Among conservative treatments, Complex Decongestive Therapy (CDT) is noteworthy as the best approach for reducing upper limb lymphedema volume the after breast cancer and lower limb lymphedema volume after gynecological cancer, as well as lymphedema in other etiologies [13–15].

CDT is a two-phase treatment and consists of four components: skin care, manual lymphatic drainage (MLD), compression therapy, and exercises. The first phase (decongestive phase) aims at the maximum reduction of limb volume and comprises skin care, MLD, multilayer bandaging, and exercises performed in daily sessions and usually lasts from 4 to 6 weeks. The maintenance phase (second phase) begins immediately after and its objective is to conserve and optimize the results obtained in the initial phase, consisting of the adaptation of elastic garments, exercises, skin care, and MLD when necessary [16].

Studies carried out with different lymphedema etiologies have shown that CDT reduces limb volume and symptoms, improves quality of life and patients report satisfaction with the received treatment, so this therapy is currently considered the gold standard treatment [17–20].

In women with breast cancer-related lymphedema (BCRL), adequate response to CDT is associated with weight control, lymphedema grade, physical activity, and adherence to the use of compression therapy [21–23].

16.6.1.1 Manual Lymph Drainage

MLD consists of a specific manual therapy performed on the superficial lymphatic system, by means of precise, light, smooth, slow, and rhythmic maneuvers, which obey lymphatic system anatomy and physiology.

Its main objectives are to increase the absorption of liquid and proteins from the interstitium by the lymphatic capillaries, increase the contractility of the lymphatic collectors and increase lymph transport, thus increasing the amount of liquid that returns to the venous system through the lymphatic system [24]. In addition, because they are maneuvers that involve superficial touch, MLD can also promote quality of life improvement, sleep improvement and reduction of pain, anxiety, and other symptoms [25].

However, the effectiveness of manual lymphatic drainage in reducing lymphedema is not yet clear. Studies have reported similar results in reducing limb volume when performing CDT with or without MLD. A clinical trial was conducted in Brazilian women presenting BCRL who underwent CDT and were randomized into two groups: with or without MLD. Both groups displayed reduction in limb volume at the end of the first treatment phase, but with no difference between them [26]. Other randomized clinical trials have reported similar results, with no difference in response to CDT with or without MLD [27, 28].

16.6.1.2 Compression Therapy

Compression therapy is performed using multilayer bandage, adjustable compression devices, and elastic garments. It is considered the main resource for lymphedema treatment, both in the volume reduction phase and in the maintenance phase [16].

The effects of compression therapy on the lymphatic system include the reduction of excess interstitial fluid due to decreased blood ultrafiltration, enhanced resorption, and improved muscle pumping. Improvement of pain, functionality, and quality of life has been reported with compression therapy [29].

Multilayer bandaging has the best clinical response in reducing limb volume. The pressure exerted on the limb during muscle contraction (working pressure) will depend on the type of material, the degree of extensibility or stretching (tension imposed during the bandaging), the force exerted by the bandage (the number of layers), and material conditions (usage time, washing method). Concerning lymphedema treatment, the use of short stretch bandages is recommended, as they promote higher working pressures favoring interstitial fluid absorption by increasing interstitial pressure. However, excessive pressure may result in pain and skin damage. The determination of the ideal pressure must take into account lymphedema type and severity, the presence of fibrosis and skin conditions [30].

During the maintenance phase, the use of elastic garments is indicated. For each clinical situation, it is necessary to assess the appropriate compression class that depends on the physical and dynamic aspects of the fabric (elasticity and stiffness) and also the specific characteristics of each patient (skin texture, limb size, edema location, presence of fibrosis and functionality of the affected limb) [29].

Another possibility of compression therapy that can be used both in the reduction and in the maintenance phase of limb volume are adjustable compression devices. These consist of a garment made of low elasticity fabric that wraps around the limb

with lymphedema, being attached with adjustable Velcro. These self-adjusting devices allow the patients to maintain great compression as the limb volume decreases [31]. Although Velcro devices are not better than bandage wrapping, they may be an alternative possibility for patients who do not adhere to other forms of compression, those with important wounds or skin changes or for financial reasons [32–36].

16.6.1.3 Exercises

Active exercises are indicated for patients with lymphedema to increase venous return and lymph absorption through muscle pumping. Results are better when performed with some form of external compression [16, 37, 38].

Different types of exercises have been deemed safe in patients with lymphedema, including water exercises, stretching, Pilates, swimming, walking, resistance exercises, yoga, weight training, and aerobic exercises [39, 40]. A study that evaluated the performance of passive exercises in combination with the CDT showed no difference in the analyzed outcomes [41].

The choice of exercise should take into account the patient's preference. Whenever possible, patients should be instructed to perform daily living activities as a form of exercise, prioritizing activities with greater energy expenditure.

16.6.1.4 Skin Care

Patients with lymphatic insufficiency may present skin changes such as thickening, hyperkeratosis, papillomatosis, skin fold deepening, skin fissures, dermal fibrosis, and lymphorrhea, among others. These complications are associated with a higher risk of infection, worsening grade of lymphedema, functionality, and quality of life [42, 43].

Therefore, skin care is essential in the treatment of lymphedema and must be performed during all phases of CDT. Patients should be instructed to perform daily hygiene measures with careful washing, daily moisturizing, and avoid skin damage or trauma [43, 44].

16.7 Complementary Conservative Treatments

16.7.1 Kinesio Taping

Several studies have been published using taping in lymphedema treatment, mostly after breast cancer, but without standardization as to its form of application. Usually, taping follows anatomical lymphatic pathways**,** to facilitate interstitial fluid absorption by skin stretching during muscle contraction [45].

Meta-analyses of clinical trials showed that taping is not more effective than bandaging in reducing limb volume, although a better quality of life, comfort and convenience was observed and may be an alternative technique for patients who have contraindication to compressive therapy [46, 47]. Despite being considered a safe technique patients may have skin lesions resulting from taping application [48].

16.7.2 Intermittent Pneumatic Compression (IPC)

Intermittent pneumatic compression pump (IPC) devices are pneumatic cuffs connected to pumps that mimic the naturally occurring pump effect of muscles contracting around peripheral lymphatics**.** It has been developed to replicate manual techniques of a therapist's hands, utilizing low pressure with short repetitive application moving progressively along a limb to simulate manual lymph drainage (MLD) and garments that incorporate the root of the limb to clear the pathway for drainage [49].

A variety of pumps are available. Pneumatic compression device product classification list includes nonsegmental and segmental, home or professional models for half or full limb without or with calibrated gradient pressure. The devices differ with respect to the number of chambers, time of inflation, deflation, regulation of inflation pressure, and calibrated gradient pressure, as well as garment shapes [50].

Regarding the parameters on IPC machine, older studies used higher pressures (100–150 mmHg), while recent studies applied pressure between 30 and 60 mmHg. There is limited low to moderate quality evidence for the application of 45–60 minutes of 30–60 mmHg using multi cell, sequential IPC programs for the management of upper and lower limb lymphedema [51, 52].

Previous systematic review indicated that IPC devices are well-tolerated in low to moderate pressure ranges, and the device enables compression application in the patient's home. IPC is also a safe and effective intervention and may provide an acceptable home-based treatment modality in addition to wearing compression garments [50]. The IPC for the management of BCRL lead to a significant alleviation of edema and subjective symptoms, but the addition of IPC failed to show superiority compared to CDT alone [53].

A series of clinical trials and systematic reviews have tried to investigate benefits of IPC. However, the results have been controversial and no final conclusion on the influence of IPC on lymphedema has been reached [54–56].

16.8 Surgical Treatment

Surgical treatment for lymphedema can be divided into two categories: physiological and debulking procedures. The first ones aim to restore lymphatic flow, while debulking procedures have no impact on function and intend to minimize consequences of later stage lymphedema [57–59].

Resection techniques have been long used in lymphedema patients and limb volume reduction can be achieved without lymphatic function improvement in different ways. They are currently reserved for advanced stages, since not only the lymphatic function is not improved but can be even worsened due to scar tissue and fibrosis [16]. Their effectiveness resides on limb functional improvement and ideally should allow the patient to don adequate compression garments. Charles procedure consists of complete excision of the skin and subcutaneous tissue and subsequent skin grafting [58]. It is indicated for late-stage cases and has poor aesthetic outcomes. Partial resection may be indicated for localized or redundant bulks after previous volume reduction with conservative treatment. Liposuction has been increasingly reported and may be indicated for patients who present no pitting edema and excessive fat deposition. Liposuction is extremely effective in reducing limb volume, but requires strict compliance with postoperative compression to maintain the results. Once compression is interrupted fluid accumulation causes the recurrence of lymphedema.

Physiological operations are represented by lymphaticovenular bypass (LVB) and vascularized lymph node transfers (VLNT). LVB is a technically challenging procedure that requires not only supermicrosurgical skills from the surgeon, but special sutures and surgical sets (Fig. 16.1). The availability of lymphangiography

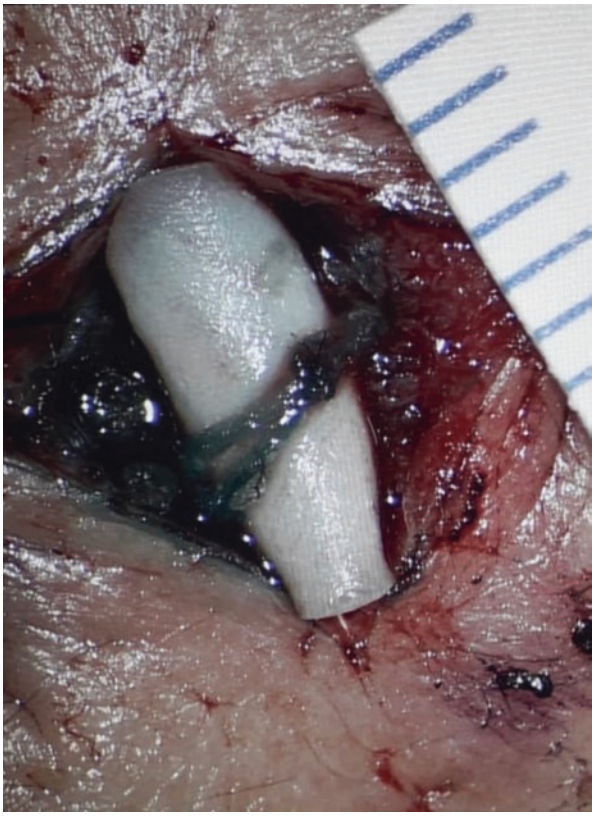

Fig. 16.1 Lymphovenous bypass. Image shows 2 lymphatic vessels anastomosed to a single vein

with green indocyanine is of paramount importance for the diagnosis and correct positioning of the bypasses in regions close to the areas of dermal back-flow (Fig. 16.2) [60–67]. LVB has little morbidity, can be performed under local anesthesia and is normally indicated for patients presenting with initial stages of lymphedema. Advanced stages have little to no response to this technique due to the fibrosis of the lymph vessels and reduced lymph transport present in this kind of patient [61, 65, 68].

VLNT is another option for patients with lymphedema secondary to cancer treatment. Lymph nodes are transplanted from healthy regions to the affected limbs to improve lymphatic transport (Figs. 16.3 and 16.4).

There are two proposed mechanisms for VLNT. Lymphatic pathways can be restored when a flap containing lymph nodes is placed between the stumps of lymphatic vessels. Lymph nodes are known to contain VEGF-C, which promotes the anastomosis between the transplanted lymph nodes and the remaining lymphatic vessels after cancer ablation [68–70]. The second one is a "sponge like" effect. The lymph nodes can absorb the fluid excess due to a pressure gradient between the affected limb and the flap. Fluid is then drained to the venous system by means of

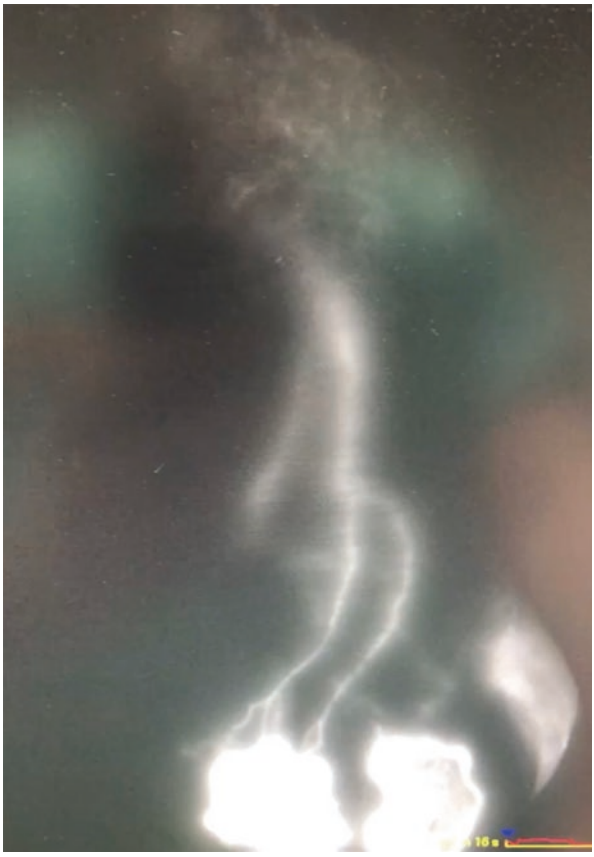

Fig. 16.2 Preoperative indocyanine green (ICG) fluorescence assessment of the right hand using the SPY Elite Fluorescence machine. Three interdigital injections. Lymphatic channels with upward flow on the back of the hand and area of dermal back flow at the level of the forearm

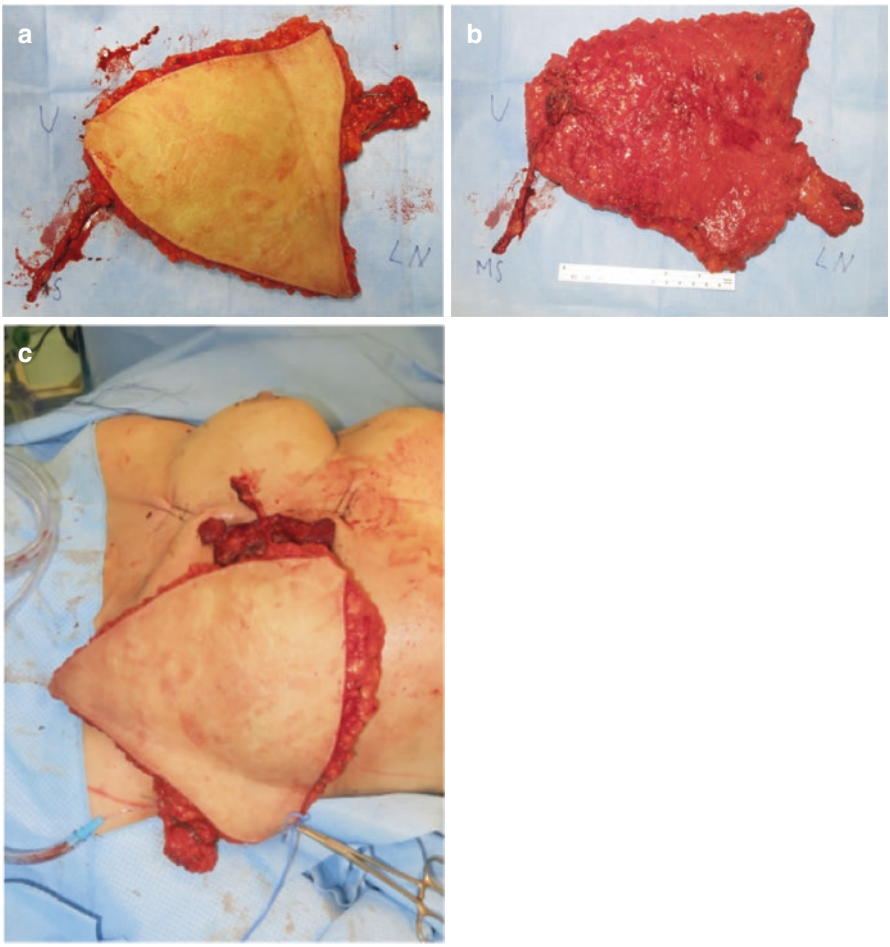

Fig. 16.3 DIEP (deep inferior epigastric perforator) flap with lymph nodes positioned in the armpit. (**a**) Anterior view of the flap—vascular pedicle on the left, inguinal lymph nodes on the right; (**b**) Posterior view of the flap; (**c**) Lymph modes positioned in the axilla

intra flap shunts between the lymphatic and venous systems. This mechanism is also known as the lymphatic pump [71–73].

In patients with lymphedema related to breast cancer VLNT can be performed in one of two ways. Isolated flaps containing lymph nodes can be used in patients without desire to have their breasts reconstructed or in patients with prior breast reconstruction. Patients without reconstruction or with previous failed attempts can have simultaneous treatments by means of a composite abdominal flap containing lymph nodes, which allows the reconstruction of the breast mound and lymphedema treatment at the same operation.

Lymph node can be harvested from several donor areas such as the groin, lateral thoracic wall, supraclavicular fossa, and submental region. Intra-abdominal lymph

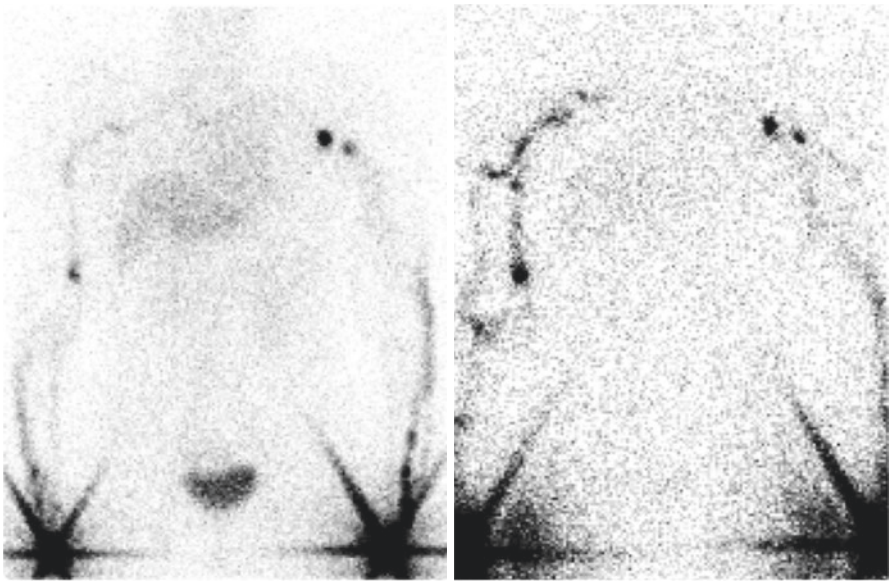

Fig. 16.4 Lymphoscintigraphy of the patient showed in Fig. 16.3. Before VLNT (left) and 6 months post-VLNT (right)

nodes such as the omental and mesenteric can also be used. The main concern when harvesting a lymph node flap is to avoid secondary iatrogenic lymphedema. Intra-abdominal lymph node harvesting eliminates the potential for secondary lymphedema but has other disadvantages such as the need to open the abdominal cavity.

Although rare, iatrogenic lymphedema is a feared complication of lymph node harvesting specially when dealing with the groin and axillary regions. There are reports of lymphedema and reduced lymph transport even without clinical symptoms [74, 75]. To reduce the chance of secondary lymphedema, one can utilize a technique called reverse mapping in which two different contrast types are injected allowing the identification of the essential lymph nodes draining the limb [76].

Another question is VLNT flap positioning. Proximal inset at the site of the surgical ablation is the logic solution, but for this approach to work we need a functioning lymphatic system with lymph flowing towards the axilla. This approach was originally described by Becker [77], working with breast cancer-related lymphedema. Groin VLNT flap was placed in the axilla after scar release. Other authors reported good clinical outcomes combining the inguinal lymph nodes with the abdominal flap for total breast reconstruction and lymphedema treatment simultaneously [70, 78]. Patients suffering from late-stage lymphedema with extensive scarring of the lymphatic system and little to no upward lymphatic flow are poor candidates for proximal VLNT positioning. Those patients can be submitted to distal flap positioning and benefit from the catchment effect that relies on gravity to transport lymph distally [73].

Since there are few evidences on where the lymph node transplant should be placed we conducted a prospective study to compare the clinical outcomes of patients submitted to VLNT for breast cancer-related lymphedema. Lymph node flap was positioned either in the axilla or the wrist. After 12-month follow-up period, an average 20% volume reduction was observed in both groups. The number of episodes of cellulites and erysipelas was also reduced in both groups. No differences were observed between the groups regarding volume reduction or infectious episodes [79].

Surgical treatment has a small, but growing role for a group of patients. Future perspectives include better understanding of risk factors for lymphedema development, prophylactic surgery, drug treatment, and nanotechnology use [80].

Editors Comments

The drainage of the lymph begins in the lymphatic capillaries and precollectors existing in the interstitial space, which take this material to the lymphatic vessels. Valves of the lymphatic collectors prevent reflux of lymph. The lymph moves toward the systemic circulation through peristaltic movements promoted by the smooth muscle present in the lymphatic vessels' wall. The drainage into the deep venous system occurs through the thoracic duct, which drains lymph from the lower limbs, the gastrointestinal tract, the left upper limb, and the left side of the anterior and posterior chest wall, including the left breast. The lymph from the right upper limb and the right side of the chest wall is drained through the right lymphatic duct. The thoracic duct drains its content into the left subclavian vein, close to the junction with the internal jugular vein, while the right lymphatic duct does so in the right subclavian vein, also close to the intersection with the right internal jugular vein (Fig. 16.5). The limbs' superficial lymphatic system drains lymph from the skin and subcutaneous cell tissue into the deep lymphatic system, from which it drains into axillary or pelvic lymph nodes [81, 82].

Lymphedema results from a difficulty in draining the lymph caused by congenital malformation or injury to lymph vessels/lymph nodes, which causes lymph accumulation in the interstitial space [83]. The chronic accumulation of lymph fluid promotes adipocyte proliferation and the deposition of collagen in the extracellular matrix.

In cancer patients, lymphedema can settle by compressing the tumor on lymph vessels and/or lymph nodes, by neoplastic infiltration of the lymphatic system (carcinomatous lymphangitis), or by lymphatic damage secondary to radiotherapy or caused by cancer operations (especially those that include lymphadenectomy). Lymphadenectomy is the leading cause of lymphedema in patients treated for cancer of the breast, prostate, endometrium, and melanoma [81, 84–86]. Other factors associated with lymphedema after cancer surgery are high body mass index (BMI), the extent of primary tumor resection, tumor location, and infection [87].

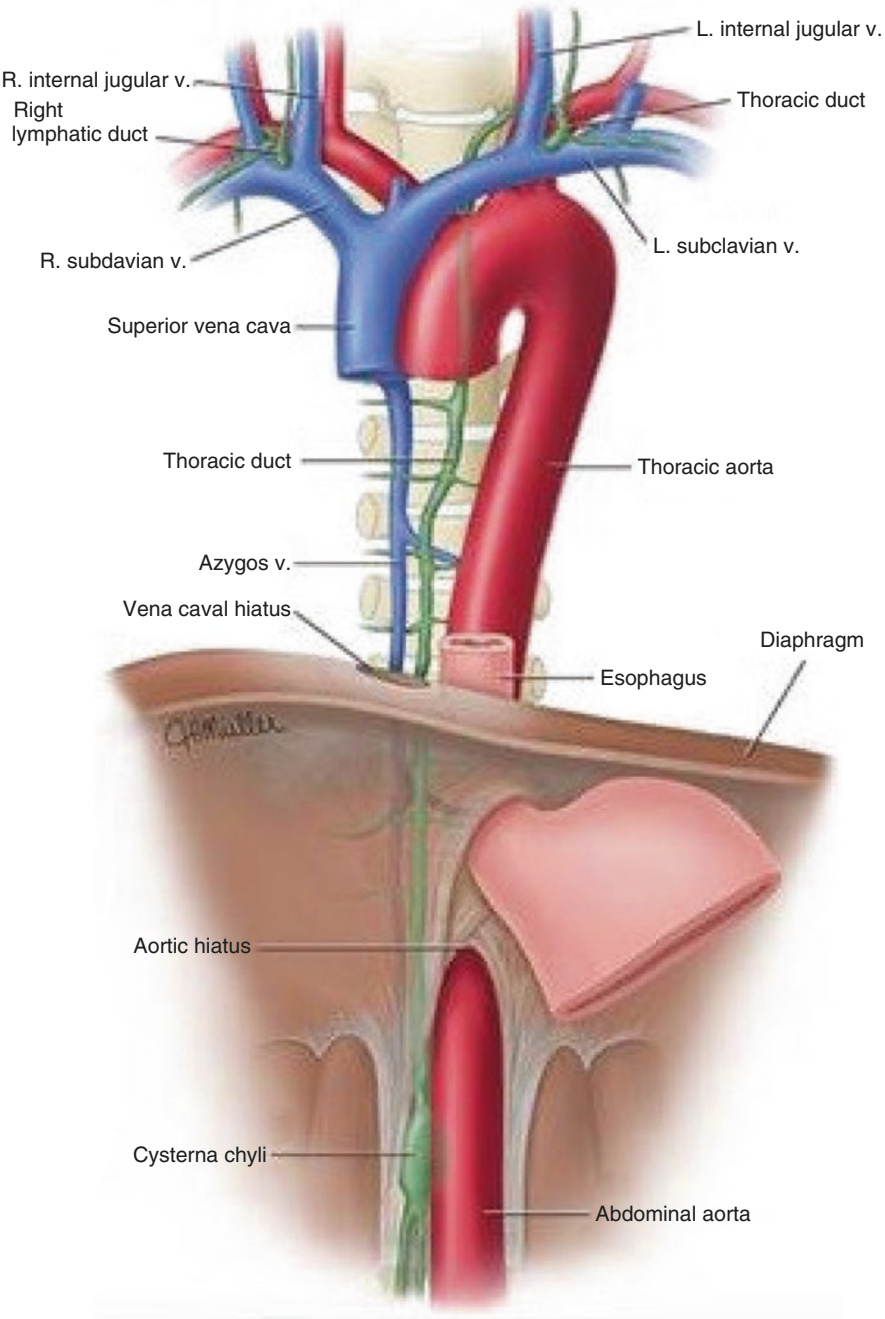

Fig. 16.5 Anatomy of the thoracic duct and the right lymphatic duct

Lymphedema associated with breast cancer treatment is the most frequent, although the adoption of more conservative surgeries, with less extensive breast resections and less indication of axillary emptying, has reduced the risk of lymphatic drainage disorders. The dissection of axillary lymph nodes has been restricted to patients with clinically identified positive lymph nodes, patients with locally advanced tumors, or in cases of inflammatory breast cancer, while patients without positive lymph nodes in the preoperative evaluation are submitted to sentinel lymph node biopsy [88–91].

Other tumors frequently associated with lymphedema are sarcoma, melanoma in the lower limbs, gynecological neoplasms, and those of the urinary, genital tract [87].

Although conservative treatment of lymphedema remains of great importance, surgical treatment (techniques have been described in this chapter) has gained ground in large cancer treatment centers.

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Chapter 17
Vascular Access

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17.1 Introduction

Harvey, in the seventeenth century, was a pioneer in the study of the physiology of the blood vessels describing the circulatory system in *Excercitatio Anatomica de Moto Cordis et Sanguinus in Animalbus* [1, 2]. After a few decades, interventions through blood vessels began to be described, as the first blood transfusion between two animals made by Folly in 1654, using a silver tube connecting a donor artery to a bone cannula inserted in the receptor's vein [3].

The first blood transfusion between humans occurred in 1818 thanks to Blundell, who transfused to a woman in a postpartum hemorrhagic shock the blood drawn from another individual [4]. The first polyethylene catheter introduced by venipuncture through the lumen of a needle was created in 1945, commercialized under the name Intracath® (BD Worldwide, Franklin Lakes, New Jersey) [5]. The puncture of the deep venous system by puncture described by French military surgeon Robert Aubaniac, who described the technique in 1952 [6]. Puncture for accessing the

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subclavian vein made it possible to infuse larger volumes of fluid more quickly in the treatment of individuals in hypovolemic shock on the battlefield. In 1952, Seldinger described the insertion of intravascular catheters advancing them by navigation through a flexible guide wire introduced by puncture, which is the basis for the modern endovascular procedures [7].

The progress on long-term catheters development was driven by Broviac, who, in 1973, created a device that was externalized by the anterior thorax wall after subcutaneous tunneling from the puncture site. This device was synthesized in silicone and carried a polyester ring that provide better catheter fixation due to the adherence of this ring to the subcutaneous tissue [8]. In 1979, Hickman adapted the Broviac device, creating a new, thicker model that allowed plasmapheresis and bone marrow transplantation (BMT) [9]. Another major step in the evolution of vascular access devices is the creation of the totally implantable venous catheter in the beginning of the 1970s, when Belin et al. described the implantation of a central venous catheter (CVC) with subcutaneous chamber for parenteral nutrition infusion [10]. In 1982, Niederhuber et al. showed the results of 30 totally implantable devices in cancer patients [11]. These fully implantable catheters are now widely used, mainly in the treatment of cancer, constituting the topic of this chapter.

17.2 Indications and Types of Catheters

Patients undergoing cancer treatment have a constant need to access the venous system for a variety of reasons, ranging from allowing the collection of blood for laboratory tests to the infusion of chemotherapy drugs or to treat clinical complications that arise relatively frequently.

The choice of vascular access, so that it is able to provide comfort and safety to the patient, must consider several factors, such as the definition of which drugs will be administered, the expected duration of treatment, the frequency of use of the access, the need of blood products transfusion and its frequency, and the availability of the patient's peripheral veins (Table 17.1).

Short-term peripheral catheters are made of Teflon or silicone, are about 35–52 mm long and are inserted by peripheral veins puncture, in a very low-risk procedure. They have low cost and very short durability, being the most used in daily clinical practice in hospitalized patients.

Short-term central venous catheters are polyurethane devices 20–30 cm long and gauge up to 8 French, passed through the puncture of a central vein (internal jugular, subclavian, axillary, or femoral) and with the tip positioned close to the cavoatrial junction. There are single or multiple lumen versions, always for continuous use exclusively in hospitalized patients. Its use at home is inadvisable due to the greater risk of infection and displacement of the device. The thicker model (12 French), known as "Schiley," allows high blood flow, necessary in hemodialysis or apheresis sessions, for short-term, since it is not tunneled.

Table 17.1 Main venous catheter devices and the criteria of choice for implantation

Device	Needle cannulas	Long cannulas	Midline	PICC	Nontunneled CVC	Tunneled CVC	Port
Main indications	Immediate venous access, general infusions	Immediate venous access, general infusions	Immediate venous access, general infusions	Chemotherapy Infusion of blood components Parenteral nutrition	Hemodynamic monitoring Chemotherapy Apheresis (auto-transplant) Dialysis Infusion of blood components Parenteral nutrition	Chemotherapy Apheresis (auto-transplant) Dialysis Infusion of blood components Parenteral nutrition	Chemotherapy
Type of medication	Compatible with periphery infusion	Compatible with periphery infusion	Compatible with periphery infusion	Compatible or not with peripheral infusion	Compatible or not with peripheral infusion	Compatible or not with peripheral infusion	Compatible or not with peripheral infusion
Duration	≤5 days	6–14 days	6–14 days	> 15–30	6–14 days	> 15–30	> 15–30
Contraindication	Neurological, circulatory or fistula alteration to dialysis in the limb	Neurological, circulatory or fistula alteration to dialysis in the limb	Neurological, circulatory or fistula alteration to dialysis in the limb. DVT history in the upper limb	Neurological, circulatory or fistula alteration to dialysis in the limb. DVT history in the upper limb	Coagulopathy	Coagulopathy	Morbid obesity Coagulopathy
Risk of infection	0.2–0.5/1000 catheter days	0.2–0.5/1000 catheter days	0.2–0.8/1000 catheter days	2.1/1000 catheter days	2–5/1000 catheter days	1.6/1000 catheter days	0–0.4/1000 catheter days

PICC peripherally inserted central catheter, *CVC* central venous catheter, *DVT* deep venous thrombosis

The peripherally inserted central catheters, known as PICC, are inserted by puncture of superficial veins usually of the upper limb (antecubital, basilica, cephalic), or, with the support of ultrasound, also by puncture of the brachial vein. They are nontunneled catheters, but of long duration, whose tip is kept in a central position. Its use can be continuous or intermittent in hospitalized or homecare patients. Because it is long (50–65 cm in length) and little gauge (up to 5 Fr), the catheter does not allow high-flow infusions. It has the advantage of being easily removable, but it has disadvantages in relation to aesthetic and comfort issues.

Tunneled catheters have greater durability, since the subcutaneous path provides a protective factor against infections, in addition to providing better fixation of the device [12, 13]. Semi-implantable catheters are introduced from an entry orifice in the skin (usually from the anterior chest wall) and passed through a subcutaneous path to the venous puncture site—the tip is positioned in the cavoatrial junction. There are two main types of semi-implantable catheters: a more malleable model with a symmetrical lumen tip (usually 2), known as "Hickman" and another of greater rigidity, capable of allowing an average flow of 350–450 mL/min and with tips capable of minimizing blood recirculation (lumens with symmetrical tips—for example, Palindrome™, Covidien®; asymmetrical tips—for example, Mahurkar™, Covidien®; separated tips—Splitcath®, Medcomp®), generically named as "permcath." Both Hickman and permcath have a Dacron® ring that is positioned inside the subcutaneous tunnel, ideally 2 cm from the skin orifice. This ring causes an inflammatory reaction and consequent adherence, providing better fixation of the device after about 1 month of the implant.

Another long-term catheter model is the totally implantable catheter, known as "portocath" or "port." It is a catheter with a less than 10 Fr diameter, which can be implanted through a peripheral or central vein, and which, after a subcutaneous path, is connected to a reservoir implanted generally on the muscular fascia. As no segment of the device is externalized, it has a lower risk of infection and greater durability compared to semi-implantable ones [12]. The reservoir is made of titanium or plastic with a single or double chamber. Likewise, there are valved and nonvalved devices. In some models, the valve is positioned in the reservoir and, in others, at the tip of the catheter. The advantage of valved catheters would be to reduce the occurrence of malfunction caused by intracatheter thrombi, as they prevent inadvertent blood reflux. The superiority of valved catheters, however, has not been proven [14, 15].

Some of the new catheter models are more resistant and allow the infusion of fluids with higher pressure (up to 5 mL/s, 300 psi)—for example, Dignity®—Medcomp; PowerPort®—Bard.

Long-term catheters (PICC, semi-implantable, and fully implantable) are made of silicone or polyurethane, with different characteristics. If the silicone shows better biocompatibility and less risk of causing thrombosis, the polyurethane catheter has thinner walls, allowing a larger diameter of internal light compared to a catheter of the same external diameter made of silicone, which results in a lower risk of obstruction [13, 16].

17.3 Surgical Technique

17.3.1 Implant of Tunneled Catheters

The implant of tunneled catheters must be performed in a proper environment, with the patient under monitoring of vital signs and with image support, especially of a radioscopy equipment. This structure is usually offered in surgical rooms or interventional radiology rooms.

The type of anesthesia will depend on the patient's clinical condition and the preference of the surgical team. Generally, local anesthesia associated with sedation is sufficient. In spite of classified as a clean operation, our team provide antibiotic prophylaxis since cancer patients are usually immunosuppressed.

The choice of implant site should consider the vein through which the catheter will be inserted and the location where the reservoir store will be created. Since cancer patients usually have imaging of the thorax for cancer staging, those images are analyzed in order to identify conditions such as venous thrombosis and/or compression, as well as laboratory tests, especially platelet and neutrophils levels. The patient will not have the tunneled catheter implanted if neutrophil level is below 500/μL. Patients with platelet counts below 50,000/μL should receive platelet transfusion immediately before surgery.

Venous puncture site The main access routes are the internal jugular, subclavian, external jugular, cephalic, basilic, saphenous, and femoral veins. Despite the good results for catheters implanted through veins of the lower limbs, the preference is of vessels that drain into the superior vena cava system [17, 18].

The access technique depends on the vessel selected. As a rule, superficial veins (external jugular, cephalic, basilic, and saphenous veins) are accessed by dissection, while deep veins (internal jugular, subclavian, and femoral) are approached by puncture. The refinement of materials (needles, guidewires) combined with the dissemination of the ultrasound-guided technique turned the puncture of the deep veins the procedure of choice in most centers.

When the option falls on superficial vein dissection, venotomy is performed so that the catheter is inserted until the tip reaches a central position. The vessel is ligated distally, with a new proximal ligature surrounding the catheter, taking care not to constrict it. In the case of larger caliber veins, a suture around the incision, in place of the ligature, allows blood flow to be maintained, preventing phlebitis.

The venous path to the atrium is more straight on the right, which is why the preference is for the introduction on this side. In the case of tumors with laterality (e.g., breast tumors), the preference is for the implant contralateral to the tumor.

The tip of the catheter is positioned at the cavoatrial junction. During the procedure, we must pay attention to arrhythmias caused by the device. In many cases, the tip of the catheter can be inside the right atrium, without prejudice to the patient.

Thrombosis or significant compression of the superior vena cava is an indication for implantation in the inferior vena cava system (femoral or internal saphenous vein).

After introducing the catheter into the venous system, we made the port pocket on the anterior chest wall just above de fascia of the pectoral muscle. In obese patients, the pocket is made more superficially. The catheter is then passed subcutaneously from the site of introduction in the vein to the newly made pocket. The reservoir is connected to the catheter and positioned inside the pocket and fixed in the inferior limit of the pocket [2]. When the catheter is placed through the femoral vein or the internal saphenous vein, the tip of the catheter is positioned in the same place (cavoatrial junction) and the reservoir is deployed in the abdomen (medially to the antero-superior iliac crest) or on the anterolateral surface of the thigh [2].

Ultrasound-Guided Venipuncture

The use of intraoperative ultrasound allows the precise location of the vessel and the detection of venous thrombosis or anatomic variations, leading to greater safety of the procedure (Fig. 17.1).

Excessive rotation of the head to the contralateral side can cause anatomic distortion by overlaying the internal jugular vein over the carotid artery, shortening the distance between them, and increasing the risk of inadvertent arterial puncture.

Puncture of the Internal Jugular Vein

- Patient positioned at de Trendelenburg at 15°, with a slight elevation of the head (supported on a small cushion) and keeping the head in a position close to the midline, with a slight counter-lateral rotation. Care should be taken with the pressure applied on the ultrasound probe, in order to avoid the collapse of the internal jugular vein.
- Trendelenburg and/or Valsalva (hyperinflation if intubated) can increase the cross-sectional area of the internal jugular vein by almost 40%.
- The color-Doppler tool is rarely necessary, since research on compressibility of the vein is sufficient to certify its patency (Fig. 17.2).

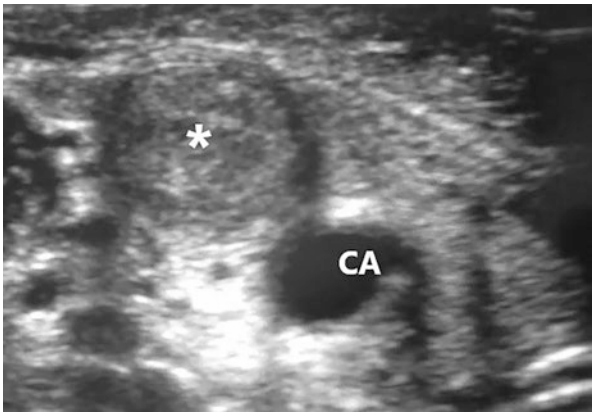

Fig. 17.1 Ultrasound cross-sectional image of the cervical vessels. CA—carotid artery; (*)—thrombus within the internal jugular vein

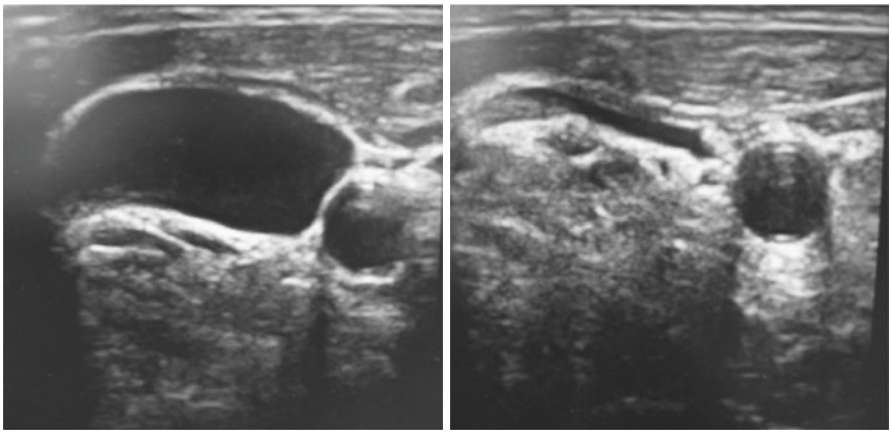

Fig. 17.2 Ultrasound image. Compressible internal jugular vein

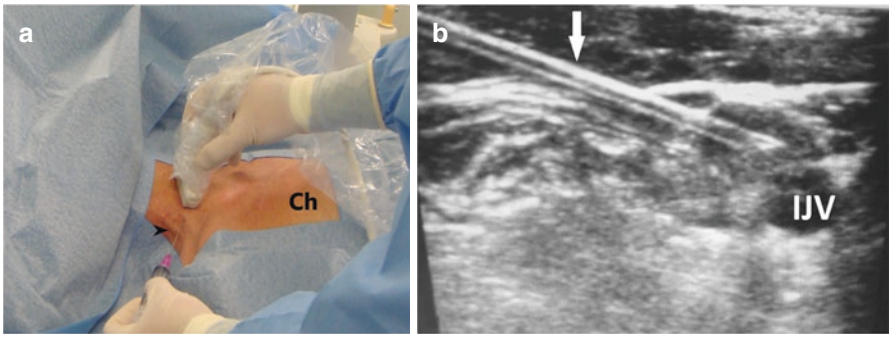

Fig. 17.3 Posterior puncture of the internal jugular vein. (**a**) Needle introduced between external jugular vein (arrow head) and sternocleidomastoid muscle; Ch—patient's chest; (**b**) corresponding ultrasound image; IJV—internal jugular vein; white arrow—puncture needle

The posterior puncture of the internal jugular vein (IJV) allows the ultrasound probe to be parallel to the needle, providing an image of the entire needle. It is the ideal technique especially when the access is aimed at the implantation of a long-term catheter, since it allows a lower puncture and a smoother curve after the subcutaneous pathway is made (Fig. 17.3).

In the anterior puncture of the IJV, with the probe positioned transversely to the vessels, the puncture site is higher (Fig. 17 .4). In a tunneled catheter, this higher puncture site can cause an excessive catheter angulation when passing it through the subcutaneous path towards the chest. As we will see later, this excessive angulation can impair the functioning of the device.

The medial puncture of the IJV is a less used technique, but has the advantage of removing the carotid artery from behind the jugular vein, decreasing the risk of an accidental arterial puncture (Fig. 17.5).

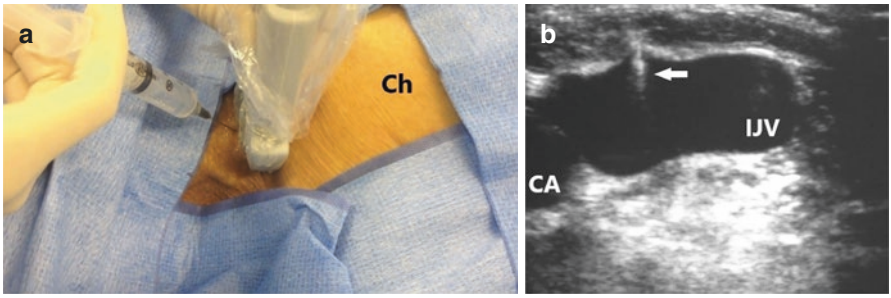

Fig. 17.4 Anterior puncture of the internal jugular vein. (**a**) Ch-patient's chest; (**b**) corresponding ultrasound image; CA—carotid artery; IJV—internal jugular vein; white arrow—puncture needle

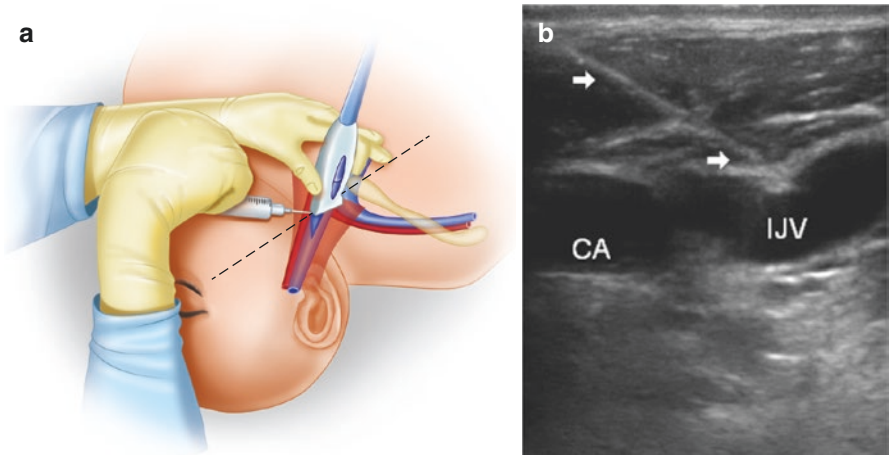

Fig. 17.5 (**a**) Medial puncture of the jugular vein with the probe in a position oblique to the vein and parallel to the needle. (**b**) Corresponding ultrasound image. CA—carotid artery; IJV—internal jugular vein; white arrows—puncture needle

The longitudinal puncture of the IJV can be made taking care to avoid a very cephalic puncture that would lead to a sharp angulation of the catheter after the subcutaneous path (Fig. 17.6).

Some patients with cervical lymph node enlargement, which can impair anterior or lateral/posterior puncture, may benefit from this technique, as long as there is no medial lymph node compression of the jugular vein.

Puncture of the Subclavian Vein

When accessing the subclavian vein, it is important to avoid a more medial puncture, where the space between the clavicle and the first rib is narrower, which can cause compression of the catheter and its consequent fracture. Subclavian access for long-term catheters requires a more lateral puncture (Fig. 17 .7).

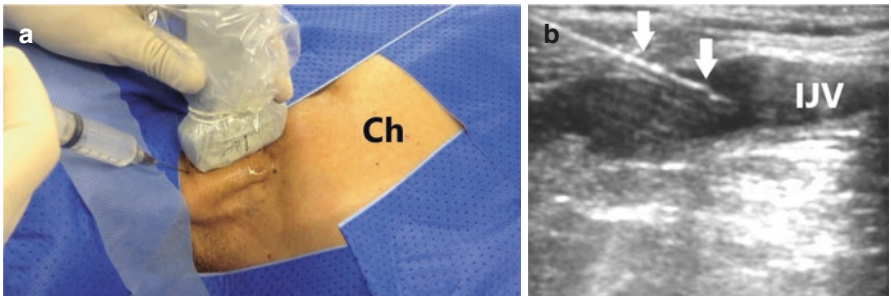

Fig. 17.6 Longitudinal puncture of the internal jugular vein. (**a**) Ch-patient's chest. (**b**) Corresponding ultrasound image. IJV—internal jugular vein; white arrows—puncture needle

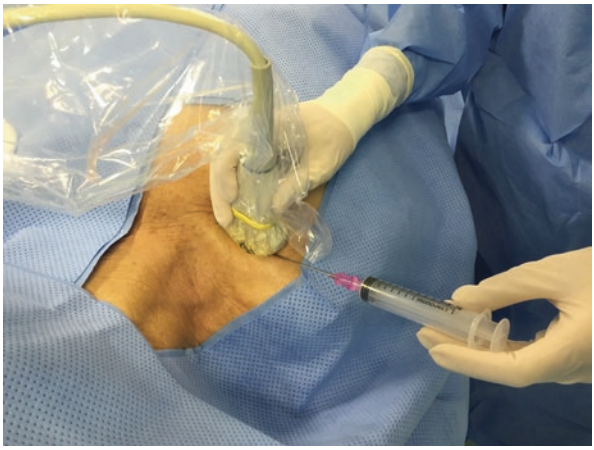

Fig. 17.7 Puncture of the subclavian vein with ultrasound guidance

Port—Pocket

The pocket must be made in a firm location and away from areas where the skin is not healthy, such as areas with radiodermatitis or near ulcerated tumor lesions or stomata. Whenever possible, the reservoir is implanted in the anterior chest wall, just above the fascia of the pectoralis major muscle. In obese patients, with very thick subcutaneous tissue, the positioning of the reservoir on the muscular fascia can make it very deep and hinder its puncture. In such cases, the pocket should be made more superficially, respecting a minimum thickness of 2 cm of subcutaneous tissue.

In subjects with inadequate chest wall (e.g., extensive radiodermatitis), the alternatives are to implant the reservoir in the arm (introducing the catheter through a peripheral vein or through a central vein) or implanting the catheter in veins of the inferior vena cava system (femoral or saphenous veins) to place the pocket in the abdominal wall or the thigh (Fig. 17.8) [19]. If the superior vena cava is thrombosed, the option is to implant the device through the femoral or saphenous veins.

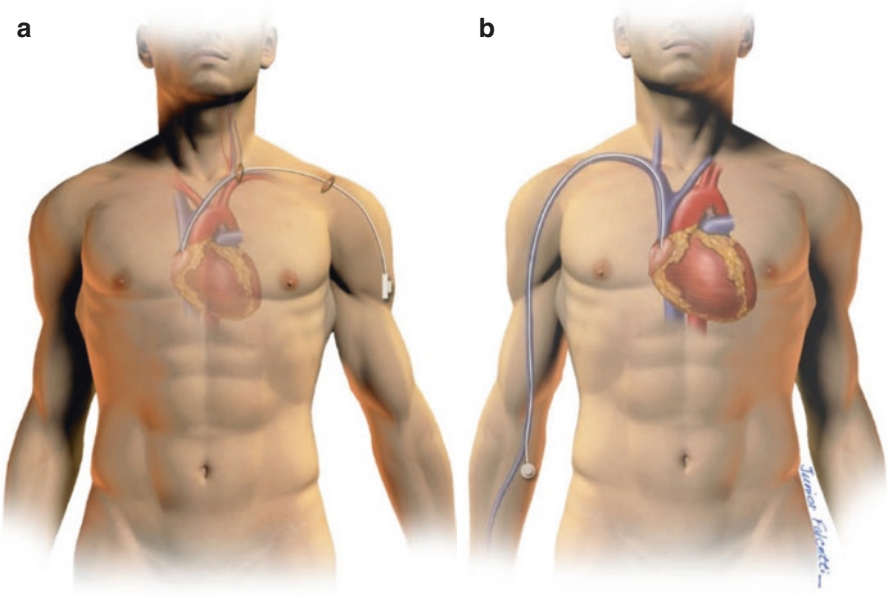

Fig. 17.8 Alternatives for the preparation of the reservoir pocket when the anterior chest wall is inadequate. Reservoir implantation in the arm. (**a**) Central vein catheterization. (**b**) Peripheral vein catheterization

17.4 Complications of Tunneled Catheters

17.4.1 Infectious Complications

Infectious complications are the most frequent ones related to long-term catheters and the main cause of early (before the end of treatment) withdrawal. The main risk factors for the development of infection are: neutropenia (<500 neutrophils) at the time of the device implantation, onco-hematological disease, infection from another site at the time of placement of the device, use of the catheter for a purpose other than chemotherapy, catheter implantation in hospitalized patients [20].

The infection can be located in the catheter implant bed (pocket/subcutaneous tunnel) or in the bloodstream.

17.4.1.1 Pocket/Tunnel Infection

Diagnosis is made by clinical examination when there are signs of inflammation (pain, hyperemia, increased local heat) in the region of the reservoir or the subcutaneous path. There may be an abscess in the pocket, sometimes accompanied by dehiscence with drainage of purulent secretion.

Conservative treatment does not usually bring good results, leading to catheter removal in most cases, associated with systemic antibiotic therapy.

17.4.1.2 Catheter-Related Bloodstream Infection (CR-BI)

Diagnosis of CRBI is still a major challenge in patients with long-term catheters. Fever and chills are usually associated with CRBI, but are nonspecific symptoms. When suspected, paired blood cultures (BC) should be obtained (aerobic and anaerobic) from the long-term catheter and from peripheral vascular access. The diagnosis of BI is established in the following situations:

- Growth of the same microorganism (species and antibiotype) in catheter and peripheral BC:
  - Differential time to positivity (DTP): CRBI is diagnosed when the cultures from the catheter and the peripheral vein are positive for the same microorganism and the sample collected from the catheter turns positive ≥120 min when compared to the sample collected from the peripheral vein (DTP ≥120 min).
  - Quantitative HMC: The number of colony-forming units per mL (CFU/mL) isolated from blood drawn from any lumen of the patient's IVC(s) was ≥fourfold the number isolated from peripheral blood.
- Positive central HMC and negative peripheral HMC.
- When there is sepsis, without any other presumable infectious focus.

While awaiting the results of blood cultures, empiric treatment should include coverage for Gram-positive and Gram-negative microbial agents. After the identification of the infectious agent, the therapy should be adjusted according to the result of the cultures, maintaining systemic antibiotics associated with seal therapy (lock-therapy) for 7–14 days [2]. After 72 hours of effective antibiotic therapy combined with lock-therapy, a new pair of blood cultures from the central catheter should be collected, regardless of the clinical response. In case of persistence of positivity for the same infection agent, the catheter must be removed.

Situations that require immediate removal of the catheter, without attempting preservation, are shown in Table 17.2.

Prevention Prefer an outpatient regimen for catheter implantation, do not implant the catheter in neutropenic patients (neutrophil count 500/μL) or with active infec-

Table 17.2 Indications for long-term catheter removal

Hemodynamic instability
Blood culture positive for *S. aureus, Candida* spp.
Sepsis or persistent bacteremia after 48 hours of appropriate antibiotic therapy
Systemic complications (e.g., septic embolism, osteomyelitis, endocarditis)

tion until the end of antibiotic therapy, avoid using the catheter for other purposes than chemotherapy or apheresis/hemodialysis.

17.4.2 Noninfectious Complications

17.4.2.1 Deep Venous Thrombosis (DVT)

In addition to other risk factors associated with DVT in cancer patients, such as hypercoagulability, endothelial injury by chemotherapy, and venous compression by the tumor, the presence of the catheter can be considered another risk factor.

Catheter-associated DVT can provoke signs and symptoms, such as pain in the venous path, limb edema, face edema, and the presence of collateral venous circulation in the chest wall. The diagnosis is made through imaging exams such as the venous duplex-scan for the cervical, upper and lower limbs, and abdominal territories. If thrombosis of the venous brachiocephalic trunk or superior vena cava is suspected, computed tomography or nuclear magnetic resonance angiography is more appropriate. Often, however, the patient is asymptomatic and his diagnosis is made in routine tests performed during cancer treatment or staging.

Once the diagnosis of DVT is made, full anticoagulation starts immediately (provided there is no clinical contraindication). Very symptomatic patients with extensive thrombosis, as in cases of superior vena cava syndrome, may be candidates for fibrinolytic treatment, weighing the risks of hemorrhagic complications.

Catheters that maintain good functioning should be preserved, since there is no benefit in removing it, in addition to the risk of new venous thrombosis caused by a new catheter elsewhere. Catheter removal is restricted to patients in whom the device is malfunctioning, as we see when DVT is extensive and involves the catheter's tip.

Prevention Keep the tip of the catheter at the cavoatrial junction or inside the right atrium, even in cases where the implant is done by femoral or saphenous access.

17.4.2.2 Malfunction

The catheter may have reflux dysfunction only, or deficiency in both reflux and flux (drug infusion). The malfunction may be due to technical failure in surgical implant, such as improper positioning of the catheter tip or excessive angulation or catheter constriction (Fig. 17.9). The latter situation is more frequent when the catheter is passed through a subclavian vein puncture, since the space between the first rib and the clavicle is narrow. Malfunction since the first use is indicative of technical failure of the surgical implant.

The presence of the catheter in the intravascular space can cause the formation of fibrin around the tip, preventing reflux by acting as a valve mechanism when

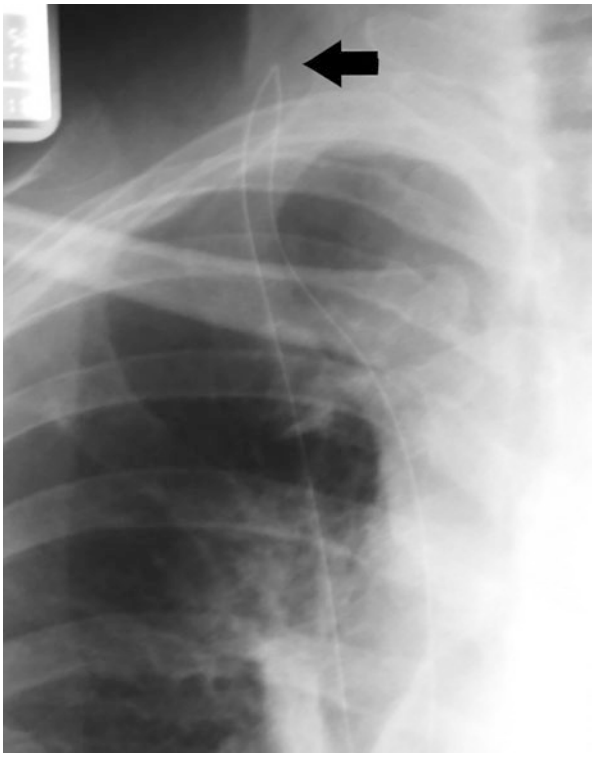

Fig. 17.9 X-ray of a malfunctioning totally implantable venous catheter. Note the sharp angulation of the catheter segment near the entry into the jugular vein (black arrow)

negative pressure is applied during aspiration. In catheters with the slotted valve at the end, the fibrin layer can prevent not only reflux, but also the infusion of fluids.

Another condition that impairs the functioning of the device is the formation of thrombus in the catheter lumen, as a result of blood reflux that can occur, for example, with the negative pressure generated when the puncture needle is removed from the reservoir.

The evaluation of a malfunctioning catheter begins by checking the reservoir puncture. Flow deficiency is often due to inadequate puncture of the reservoir. The next step is to perform a simple chest X-ray, in order to evaluate the catheter position. The catheter tip may be misplaced due to technical failure at the time of implantation, or due to tip migration (Fig. 17.10). If the catheter is properly positioned, without excessive angulation and without signs of fracture or clamping, fibrinolytic therapy can be tried, with better results if the eventual thrombosis occurred less than 15 days earlier.

DVT, as discussed above, can cause malfunction if it involves the tip of the catheter.

Prevention Technical care during implantation and handling of the catheter.

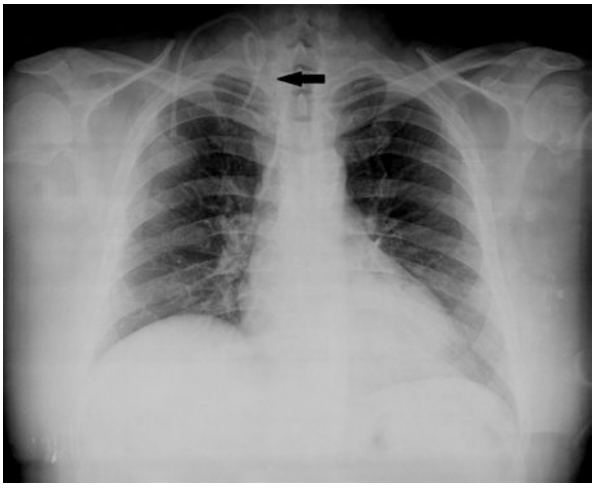

Fig. 17.10 X-ray of a malfunctioning totally implantable venous catheter. Late migration of the catheter tip (black arrow)

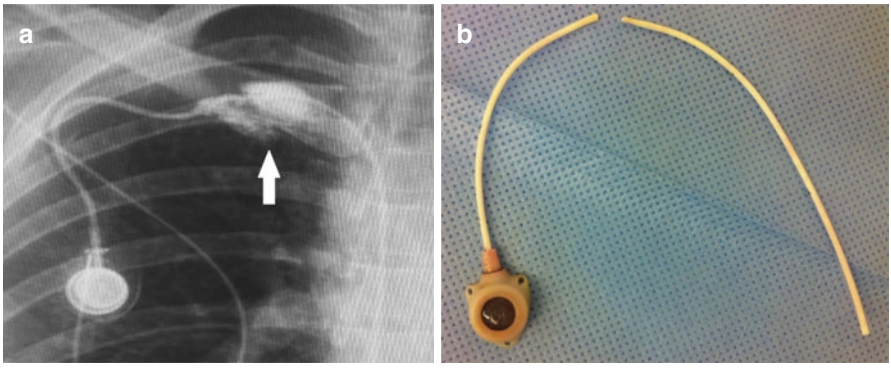

Fig. 17.11 Fracture of a totally implantable catheter inserted by puncture of the right subclavian vein. (**a**) Contrast radiography shows contrast leakage at the level of the space between the clavicle and the first rib (white arrow). (**b**) The two pieces of the fractured catheter

17.4.2.3 Catheter Fracture

It is a complication that occurs more frequently when the catheter is implanted by puncture of the subclavian vein.

Suspicion is raised when the catheter does not show reflux and the patient complains of pain when infusing medication. A simple chest X-ray can show a complete fracture and possible migration of the catheter. Partial lesions in the catheter are diagnosed with a contrast exam, showing a contrast leak point (Fig. 17.11).

In such cases, removal of the device is mandatory. If there was a complete fracture, removal of the catheter can be achieved by endovascular access.

Prevention If the option is for subclavian access, perform the puncture as laterally as possible.

17.4.2.4 Port Rotation

The rotation of the reservoir on its own axis prevents it from being punctured.

Lateral chest radiography shows the rotation of metallic reservoirs—the posteroanterior view may not be conclusive (Fig. 17.12). If the reservoir is radiolucent (e.g., plastic devices), palpation may be sufficient for diagnosis. Even the impossibility of the needle to penetrate the reservoir can raise the possibility of its rotation.

Treatment requires surgical repositioning and reservoir fixation.

Prevention Reservoir fixation to the muscular fascia with two points of nonabsorbable threads.

17.4.2.5 Port Extrusion

The dehiscence of the skin with exposure of the port may be due to an infectious process, but it also occurs through skin necrosis, which can occur when the reservoir is implanted too superficially, under insufficient subcutaneous thickness (Fig. 17.13).

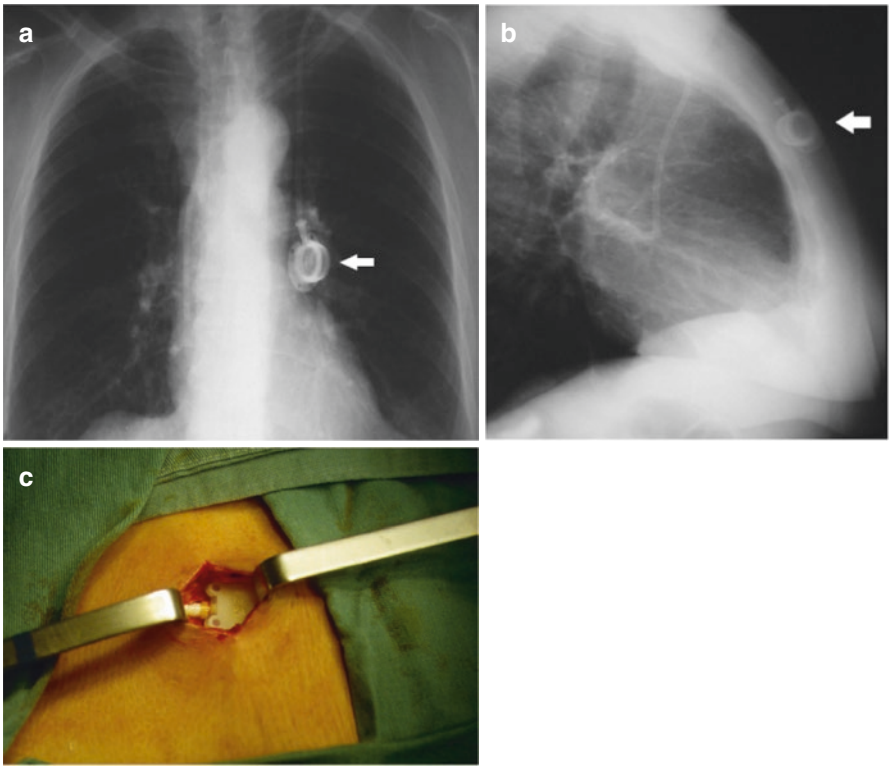

Fig. 17.12 Reservoir rotation. Posteroanterior (**a**) and lateral chest radiography (**b**). Note that the rotation of the reservoir (white arrow) is more evident in the lateral view. (**c**) Surgical image of the reservoir rotation

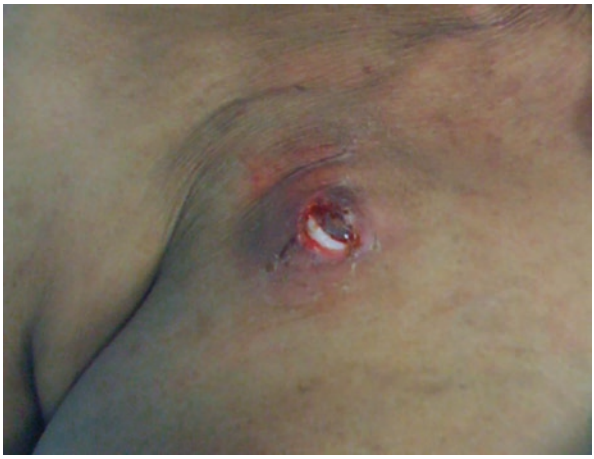

Fig. 17.13 Reservoir extrusion

Prevention Choose the best place for making the port pocket, avoiding areas with little adipose tissue, such as close to the sternal manubrium. Prefer low-profile port in cachectic patients, in whom the reservoir can be implanted below the muscle fascia.

17.5 Vascular Access—Nursing Care

17.5.1 PICC—Peripheral Insertion Central Catheter

The use of central venous catheters (CVCs) is essential for the treatment of patients with various pathologies in a hospital environment. These catheters can be tunneled, nontunneled, or fully implanted [21]. The placement of these catheters can result in risks and complications for the patient, such as pneumothorax, arterial puncture, hemothorax, and arrhythmias. When in use, catheters can cause complications, such as blood stream infection, deep vein thrombosis, and (DVT), or be prone to catheter displacement [21, 22].

17.5.1.1 What Is a PICC?

One of the advanced techniques available for patients requiring prolonged intravenous therapy is the peripherally inserted central catheter (PICC), an intravenous device inserted through a superficial or deep vein, in most cases in the upper limbs, until reaching a central position, that is, the transition point between the superior vena cava and the right or proximal atrium of the inferior vena cava [23–25].

The main indications for PICC are as follows: intravenous therapy for 14 days or more; clinically stable patient requiring intravenous therapy with peripheral venous

access incompatibility; critically ill patients with bleeding disorders; continuous vesicant infusions, such as parenteral nutrition or irritant solutions incompatible with peripheral venous access for any duration in cyclic chemotherapy treatment with active cancer for more than 3 months, considering PICC discontinuation when therapy is complete; burn patients, since the early use of PICC decreases the risk of bacteremia; chronic anemia; cystic fibrosis or short intestine; patients hospitalized more than six times a year; and palliative care patients requiring intravenous therapy [23].

PICCs can have one to three lumens and be valved (proximal or distal) or nonvalved. They are biocompatible; flexible; radiopaque; and can be made of silicone, polyethylene, polyurethane, Carbothane, or an integral polymer and noneluting material mixed with polyurethane with the Endexo technology [23–25].

17.5.1.2 Puncture Technique

PICCs can be inserted in three techniques: (1) "Direct" venipuncture under visual or palpatory control, known as "blind technique"; (2) ultrasound-guided venipuncture using the modified Seldinger technique, which has numerous benefits compared to direct venous puncture; or (3) tunneled PICC [23].

1. Direct Venipuncture

The direct puncture model uses the superficial veins of the antecubital fossa (usually the cephalic vein or the communication vein between the cephalic or basilica vein) accessible and identifiable by palpation. The insertion technique is based on the introduction of the catheter into a short cannula placed in the vein using a direct percutaneous puncture needle. This type of puncture is not recommended for an uncomfortable area characterized by great mobility and is feasible only in superficial veins that are visible or palpable. This technique has a high risk of thrombotic complications and infectious diseases [23].

2. Ultrasound-Guided Venipuncture Using the Modified Seldinger Technique

The availability of micro-introduction kits and new biocompatible materials such as third-generation polyurethanes facilitates advanced insertion techniques. The modified Seldinger technique is based on the use of the micro-introduction kit associated with ultrasound, which increases procedure quality. Ultrasound-guided puncture increases the success rate, minimizes the rates of failure and accidental brachial artery or median nerve damage, and eliminates the risks of hemorrhagic complications [23].

3. Tunneled PICC

In some situations, it is advisable that the PICC insertion site does not coincide with the venipuncture site, usually when the only appropriate size vein is available in the proximal third part of the arm or in cases of allergies at the puncture site for catheter insertion. In these situations, a short area of the PICC can be

subcutaneously tunneled. This tunneling is done anteriorly, that is, the PICC is slid into the subcutaneous area from the insertion site to the venipuncture site and then implanted into the vein through the introducer [23].

17.5.1.3 Catheter Tip Position

The intracavitary electrocardiogram (ECG) method is currently the best cost-benefit option to evaluate distal PICC tip position. Intracavitary ECG is performed during PICC insertion, considered beneficial in terms of cost, catheter agility, and noninvasiveness, besides preventing chest radiography, which exposes the patient to radiation [23].

There is currently a broad consensus that the ideal tip position is the cavoatrial junction level for PICCs inserted in the upper limbs. The ideal position is extremely important, since incorrect placement is associated with a high risk of malfunction, DVT, arrhythmia, and vessel damage [23].

17.5.1.4 General Principles for Inserting a PICC

Antibiotic therapy is not indicated as pre- and postinsertion prophylaxis. It is advisable to perform a pre-procedure ultrasound examination to evaluate all veins in the arm and select the most appropriate vein in terms of caliber, position, and the most appropriate insertion site [23].

The correct asepsis technique requires hand washing by the operator and the use of maximum barrier measures such as sterile gloves, nonsterile masks, nonsterile cap, wide patient covering, and sterile ultrasound probe cover. The skin should be disinfected with 2% chlorhexidine [23].

After local anesthesia, out-of-plane ultrasound-guided venipuncture is performed on the transversal axis of the selected vein. After puncture, the cannulation maneuver is performed using the modified Seldinger technique. The ideal insertion site is located, on average, at one-third of the arm's length, midway between the elbow and the axilla, which is called the green zone or zone insertion method area [26].

Catheter stabilization with suture should be avoided to prevent chronic skin granuloma that increases extraluminal contamination of the venous access. It should be fixed with adhesive on the skin or by subcutaneous system [23].

Maximum barrier protection for operator and patient:

- Nonsterile cap
- Clean, unsterilized mask
- Surgical degermation with 2% chlorhexidine
- Sterile gloves
- Sterile ultrasound probe cover
- Large sterile field (80% patient covering or more)
- Use of 2% chlorhexidine on the patient skin [23]

17.5.1.5 PICC Maintenance

The procedures mentioned below are followed to maintain the vascular access device and ensure patient safety:

1. The connectors to be used should be disinfected before drug administration with 70% alcohol for 5–60 seconds.
2. Connectors must be accessed without a needle.
3. The use of passive disinfection caps containing agents such as isopropyl alcohol decreases the risk of microbial and intraluminal contamination and bloodstream infection.
4. Connector change interval must be 96 hours.
5. PICC stabilization with adhesive tape or subcutaneous tissue anchors is indicated.
6. Vascular access devices are washed and aspirated before and after each infusion to evaluate the infusion and prevent complications.
7. The vascular access device is blocked after the final flush to decrease the risk of intraluminal occlusion and catheter-related bloodstream infection.
8. Catheter should be flushed with 0.9% saline solution with pulsatile flush.
9. Chlorhexidine-impregnated dressings are recommended for use during catheter insertion.

Overall, the use of PICC in modern medicine has grown rapidly for several reasons: practical bedside insertion, more cost-effective than other CVCs, and expansion of intravenous therapy teams formed by specialized nurses [27].

17.5.2 Fully Implanted Catheter—Port-a-Cath

17.5.2.1 Proper Handling

After insertion, the catheter continues to be handled by many subjects, including the patient, so everyone should know the risks involved in incorrectly touching the catheter. Institutions should follow the guidelines and fulfill the set norms and routines to ensure standardized catheter handling in all healthcare departments [28].

In addition, a permanent education structure is required for professional training and recycling, updating the routines according to new information based on scientific evidence. It is beneficial to include the patient in this process as an ally in catheter self-care and not only as a vigilant subject.

17.5.2.2 Fully Implanted Catheter

Fully implanted catheters, known as port-a-cath or Ports, are surgically inserted in subcutaneous tissue, where a dome-shaped reservoir or port with a silicone septum is punctured. This port structure is made of titanium, plastic, or stainless steel,

preferably placed over a bone prominence. The tip of the catheter is freely located in a large-caliber vein, preferably at the atrial cava junction [28].

At the end of the surgical procedure, it is advisable to puncture the catheter with the patient still under anesthesia when there is need for immediate use of the device. Subsequently, when the patient is receiving in- or outpatient chemotherapy, the punctures will be made by a nurse. After making the puncture, the port should have excellent blood flow and reflux, allowing full and safe use [28].

17.5.2.3 Port-a-Cath Puncture

Skin Antisepsis

Taking antisepsis precautions is necessary before puncturing the patient's skin on the port-a-cath site, given that opening this protective barrier of the skin opens the door for infections. Antiseptic solutions with chlorhexidine are generally used to clean the skin and recent products recommend applying the solution from one side to the other with friction to agitate the skin surface layers [29]. After applying the antiseptic, the skin should be allowed to dry completely. Inadequate drying can lead to complications such as contact dermatitis, decreased or inactive dressing adhesion to the skin, or, in certain circumstances, increased risk of infection due to moisture trapped under the dressing [29].

17.5.2.4 Needle Insertion

A skin puncture on the chamber with a specific Huber point needle is necessary to access the catheter reservoir. This needle reduces silicone membrane damage or cracks, allowing a large number of punctures and increasing catheter durability. It is important to rotate the puncture sites on the silicone with the Huber point needle to allow the skin to heal and to avoid exposing the silicone septum [30].

Needle size should be chosen by the nurse by palpating the entire skin on the catheter, taking care to insert the whole needle into the reservoir, touching the bottom of the chamber. This care is important to prevent overflow due to incomplete needle insertion into the port [31].

17.5.2.5 Port-a-Cath Dressing

Port dressing should be considered to fix the needle into the skin and to protect the device, to prevent the needle from moving when the patient moves and when it is handled, and to avoid traction of the infusion line connected to the catheter [32]. The use of chlorhexidine gluconate-impregnated dressings on central catheters is recommended to reduce the risk of infection from extra luminal sources [33].

17.5.2.6 Catheter Maintenance

The port-a-cath can be used safely after the catheter is punctured and the dressing is well positioned. The hands should be sanitized before and after handling the patient, following the guidelines for five hand hygiene moments. The catheter connector, valve, and plug should be vigorously disinfected with friction for at least 5 seconds [34].

The catheter should be flushed with a 10 mL syringe prefilled with saline solution before and after drug, chemotherapy, and parenteral nutrition administration. The catheter should be flushed with 20 mL saline solution before blood collection [35].

Heparin or saline solution is used to maintain catheter patency. When the chemotherapy cycle is over, the Gripper® needle is drawn, but before that the catheter must be salinized or heparinized, depending on the institution's protocol. Heparin is widely used, but many studies show that heparin is not better than saline solution when considering catheter occlusion, or that this difference is not statistically significant [35, 36].

17.5.3 Dialysis Catheter—Permcath

There has been a steady increase in the prevalence of renal disease worldwide in the last decade, with more than two million patients under renal replacement therapy (RRT). Hemodialysis is the main RRT modality, used in 70–90% of patients requiring vascular access for hemodialysis [37].

Chronic diseases are associated with aging. Among these pathologies, chronic kidney disease is characterized by high morbidity and low quality of life. Hemodialysis, peritoneal dialysis, and renal transplantation are some popular RRT options. The survival and quality of life of chronic nephropathy patients depend on the quality of vascular accesses to perform treatment. There are three catheter options for this type of treatment: [38]

- Short-term catheters
- Long-term catheters
- Arteriovenous fistula

17.5.3.1 Short-Term Venous Access

Venous access catheters, such as the Shilley®, are indicated for acute conditions and for percutaneous bedside insertion. Most dialysis patients have comorbidities associated with kidney disease that increase their risk of infection with the use of catheters. Temporary access is recommended for a maximum of 1 week [39, 40].

17.5.3.2 Long-Term Venous Access

There are two types of long-term catheters: fully implantable and semi-implantable (permcath®), which are indicated for patients under dialysis therapy for a period longer than 1 week with no arteriovenous fistula, for patients with comorbidities, older patients, and for those with unfavorable vascular anatomy. Permcath® has a lower infection risk and better flow for dialysis than short-term catheters.

17.5.3.3 Basic Principles

Hemodialysis catheters are usually made of silicone with two main lumens connected to two holes (blue and red). A third lumen may be present for blood collection and medication administration [39, 40]. The red port denotes the arterial lumen that draws blood from the body, and the blue port, the venous lumen for venous return from the dialysis machine to the blood. [39, 40]

Surface-coated catheters, for example, with heparin, silver, chlorhexidine, rifampicin, and minocycline, prevent thrombosis in hemodialysis catheters and hemodialysis catheter-related infection. Although other types of catheters with antithrombotic or antimicrobial coatings have been found to be effective, very few studies have focused on them, providing only short-term results [40].

17.5.3.4 Catheter Position

The tip of the catheter in the hemodialysis tunnel should be positioned inside the right upper atrium when the patient is in the dorsal decubitus position. As the patient moves to the vertical position, the catheter tends to retract by 2–4 cm. Catheter retraction is increased when the placement is on the left side. If the catheter is placed using another measurement it may end up being positioned in the superior vena cava or brachiocephalic vein, which may lead to catheter malfunction [40].

17.5.3.5 Puncture Technique

The implant must be performed in an appropriate environment and by a qualified professional, like a nephrologist or vascular surgeon. The procedure is performed under local anesthesia using imaging examination for optimal positioning. It is recommended not to insert it on the same side of the arteriovenous fistula. The recommended veins for this implant are the right internal jugular vein, left internal and external jugular vein, subclavian, and femoral vein. The use of ultrasonography to access the vessel is gold standard in this procedure and reduces complications [39].

17.5.3.6 Maintenance

Catheter insertion and exit sites take about 2–3 weeks to heal. It is recommended to use sutures to fix the catheter, to keep it stable with an adhesive tape on the skin while the site is healing, and to ensure the catheter cuff is fixed. Before starting hemodialysis, the blocking solution should be aspirated from each catheter route and each lumen should be vigorously washed with saline solution. After disinfecting the site with chlorhexidine, the catheter hubs should be immediately connected to the dialysis machine to avoid exposure to air [40].

17.5.3.7 Catheter Washing and Blocking After Dialysis

At the end of dialysis, the catheter should be disconnected from the machine, 10 mL of saline must be injected into each catheter lumen, and a blocking solution must be used in the lumen. Proper washing and use of blocking solution decrease the risk of catheter-related thrombosis. Washing is the most crucial factor in preventing catheter malfunction [40].

- Heparin: It is the traditional and most commonly used blocking solution to minimize catheter dysfunction, given its easy use, availability, and relatively low cost [40].
- Citrate: It prevents hemorrhagic complications associated with heparin and provides an effective alternative for patients with thrombocytopenia, besides being economical. Citrate also has the advantage of antimicrobial activity. There is evidence that at a concentration of 4%, it prevents catheter-related bloodstream infections [40].
- rt-PA: Alteplase instillation can improve blood flow and decrease the incidence of catheter clotting but it is expensive and cannot be routinely stored. [40]

At the end of the dialysis session, each catheter lumen should be filled with the exact amount specified by the manufacturer since this volume is different for both sides, with the venous volume usually being higher than the arterial volume [40].

To minimize the incidence of infection associated with dialysis catheters, the use of the catheter should be avoided when it is not indicated. It is important to use sterile techniques to handle the catheter. [40] The patient should have access to basic information about the catheter, including the correct way to maintain catheter hygiene at home [40].

17.5.4 What Is an Adequate Access? Nursing Point of View

Vascular access is very important in the treatment of several pathologies, from bloodstream infections to complex and long-term conditions, such as cancer, besides being important in surgery, diagnostic exam, and outpatient therapy. The ideal

vascular access provides good blood flow, long survival time, and low rate of complications.

In 1973, the first central catheter was used for parenteral nutrition by Broviac, who created a silicone catheter with a Dacron ring for subcutaneous tract fixation. In 1979, the Hickman catheter was used for the first time for chemotherapy patients, which is larger diameter catheter. The fully implanted catheter port-a-cath was first introduced in the early 1980s [41].

Vascular access is very important for the treatment of several pathologies, from infections, dehydration, and malnutrition, to more complex and lasting states, such as renal failure and cancer. The constant use of the superficial venous network to inject solutions and drugs invariably leads to its exhaustion, which can cause peripheral phlebitis and medication overflow. Such problems are worsened when vesicant solutions are used, such as in chemotherapy [23].

The ideal vascular access provides good blood flow, long survival time, and low rate of complications [42]. A device is considered effective when it achieves the clinical goal for which it is designed and used, is considered efficient when it achieves the goals without wasting resources, and is considered cost-effective when it has a cost advantage over other resources used [23].

The development and dissemination of procedures for venous access management developed by a multidisciplinary group of hospital specialists must be based on specific guidelines published in both national and international literature. Each operating unit should implement local protocols based on its specific requirements and device availability. Some venous access flow techniques in the literature minimize the risks of intravenous therapy [23].

The presence of a nursing or multidisciplinary team allows the full and systematic implementation of a program and of the best device at hospital, clinical, and outpatient levels. Technical insertion by experienced and trained professionals can reduce the complications and costs associated with the use of catheters [23]. The implementation of a vascular access team increases patient safety and reduces complications and costs associated with maintaining hospital infusion therapies through the following mechanisms:

- Cost reduction in purchasing the materials and devices used
- Material waste reduction due to increased insertion success rate
- Rational use of devices due to prevention measures and effective treatment of mechanical and infectious complications that would normally lead to device removal
- Implementation of vascular access planning through careful selection of the vascular access device
- Reduction in mean length of stay
- Reduction in nursing work time related to repeated venous punctures for peripheral venous access

To conclude, owing to its cost-effectiveness, PICC is a valid and viable option for improving nursing care quality and patient safety and patient well-being. The choice of vascular device should be based on the clinical judgment and skills of the nurse,

scientific evidence on indications and contraindications, patient characteristics, intravenous drugs prescribed, vein availability for puncture, time of intravenous therapy, patient preferences, and risks and benefits for the patient [43].

Editors Comments

Echo-Guided Venous Access

Adequate venous access is essential for many patients, especially those admitted to hospitals. The choice of the best access route and the type of catheter are mainly related to the type of substance to be infused, the duration of therapy, and the existence of an adequate peripheral venous network.

Venous access should preferably be obtained through puncture rather than dissection, as it generates less tissue manipulation and lower morbidity rates.

Except for puncture of visible superficial veins and adequate caliber, the accesses must be eco-guided. In addition to the objectives mentioned, one of the applications of ultrasound is to verify the correct direction of the guidewire's progression, especially in procedures performed at the bedside. As an example, when performing a puncture of the axillary/subclavian vein and with the transducer at the base of the neck at the height of the sternoclavicular junction, it is possible to quickly identify whether the guidewire traveled the wrong path to the ipsilateral internal jugular or had the appropriate path for the ipsilateral innominate venous trunk. If the guidewire has progressed to the internal jugular and with visualization concomitant with ultrasound, the guidewire is initially pulled until its "J" end exits the jugular. The "J" is rotated in the central direction, followed by compression of the transducer with one hand and concomitant progression of the guidewire with the other hand to direct the extremity to the innominate vein. Similarly, it is possible to check the internal or jugular access to the cranial or caudal direction of the guidewire and eventual repositioning.

There are two techniques for visualizing the needle: in-plane or out-of-plane. In the in-plane technique, there is a perfect alignment between the needle and the ultrasound beam during its entire path, which is visualized entirely from its entry into the skin until it reaches the target vessel. In the out-of-plane technique, there is no alignment, just an intersection of the ultrasound beam with the needle, so during the progression of the needle, there is no visualization of it. Visualization of its extremity occurs only when this crossing occurs in the center of the target vessel.

There is no superiority of one technique over another concerning venous access [44, 45].

There are two ways of visualizing the vessel: transverse axis (transducer perpendicular to the vascular bundle) or longitudinal axis (transducer parallel to the bundle).

The echo-guided puncture technique is a combination of the needle view and the vessel view. The best combination choice depends on the type of catheter,

anatomical location of the target vessel, and professional experience: as an example, the in-plane puncture of the internal jugular on the longitudinal axis. The only advantage is the almost zero possibility of pneumothorax, as it is an extremely cranial puncture. For short-term catheters, there is a clear disadvantage of the discomfort caused by the catheter externalized far above the neck's base, and for long-term catheters, the curvature necessary to perform the subcutaneous course is inadequate. Another example is the in-plane puncture of the axillary vein. There is the advantage of comfort in the exterior of the catheter for short-term catheters, but for long-term catheters, there is the disadvantage of curvature.

Positioning the Catheter Tip

Some imaging methods must be performed concomitantly or immediately after obtaining central venous access for proper positioning of its extremity, the most used being: fluoroscopy, intra-cavity electrocardiogram, and radiography.

The central catheters' tip must be located in the cavoatrial junction or the right atrium [46, 47], especially in long-term accesses. Significant complications such as device dysfunction and deep venous thrombosis are correlated with poor positioning of the extremity (innominate vein or proximal superior vena cava), being attributed to factors such as the diameter of the vessel/catheter, blood flow speed, and the caustic/hypertonic nature of the solutions (chemotherapy, parenteral nutrition).

Prophylactic Anticoagulation

It is known that patients with malignant neoplasia have higher rates of thromboembolic events, with the presence of a central venous catheter among the various factors that cause it.

Chemoprophylaxis in these patients with catheters is controversial as to the results, type of anticoagulant (oral or parenteral), dose, and duration. Some studies show a decrease in the number of symptomatic and asymptomatic events [48, 49], others show no advantage, and routine use is not recommended [50, 51].

Maintenance of Ports

At the end of the use of all central venous catheters, a flush with saline solution is performed, followed by filling with a solution (lock) until further handling, aiming to avoid the deposit of crystals and blood in the lumen leading to dysfunction and/or occlusion.

In ports, heparin lock is classically used between chemotherapy sessions, however, with varying dilutions and time intervals. The use of heparin is based on the fact that it is an anticoagulant substance; therefore, it would minimize the mentioned complications.

Few studies compare maintenance with a heparin lock or saline solution, none of them showing the advantage of using heparin.

A retrospective study comparing occlusion rates with heparin lock (50 IU/mL) versus saline solution showed no difference [52].

A randomized study comparing the reflux dysfunction indices between heparin lock (100 IU/mL) versus saline solution showed no difference [53].

Another retrospective study comparing the reflux dysfunction rates, flow dysfunction, and occlusion between heparin lock (100 IU/mL) versus saline solution also showed no difference [54].

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Chapter 18
Diagnostic Imaging Assessment of Tumor Vascular Involvement

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18.1 Imaging Methods

18.1.1 Ultrasonography

18.1.1.1 Strong Points

Ultrasonography (US) has a wide spectrum of resources, from B-mode and Doppler (color flow, pulsed wave, and amplitude flow), to the association with microbubble contrast medium, which creates several alternatives for the use of the method. US stands out for being an inexpensive and widely available method and also because of their real-time dynamic evaluation. The method has a relevant role in children, as it is free from ionizing radiation and because this population usually needs sedation to perform magnetic resonance (MR) and computed tomography (CT). In patients with limited mobility, US may represent the only viable imaging method because of its portability.

In the diagnosis or monitoring of several tumors, US is often the first imaging method used to detect the presence or absence of vascular thrombosis (whether hematic or tumor) and the invasion of a vessel wall.

Contrast-enhanced US (CEUS) consists of microbubbles that increase the reflectivity of sound echoes. Thus, CEUS improves the detection of blood flow even in very small vessels (microcirculation/vasa vasorum). The microbubbles contrast agent has, in practice, no serious adverse reactions. In patients with renal failure, a known contraindication to CT and MR contrast agents, CEUS can be safely used, as microbubbles contrast agent is not related to nephrotoxicity and their excretion is not carried out by the kidneys, but by the lungs and liver [1, 2]. Because of that, patients with underlying cardiopulmonary disorders may represent a contraindication to CEUS.

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Published data show that CEUS has sometimes a performance comparable to that of CT and MR [1, 3], has excellent accuracy in the differential diagnosis between tumor and hematic thrombi, and helps in the assessment of tumor invasion of the vessel wall [2, 3].

Endoscopic US (EUS) is an alternative form of sonographic imaging method that has a relevant role in the assessment of pancreatobiliary disease, including vascular evaluation due to neoplasia.

Laparoscopic US (LUS), also known as intraoperative US, has the advantage of scanning lesions with maximum proximity, which improves substantially the sonographic evaluation. LUS may represent an important complementary tool to the surgeon in the dynamic assessment of tumor vascular invasion. Tumor thrombus within inferior vena cava (IVC) by locally advanced renal cell carcinoma and borderline pancreatic adenocarcinoma are good examples where LUS might have a relevant role [4, 5].

18.1.1.2 Weak Points

One of the main limitations of US is the evaluation of structures or regions with gaseous content. The air acts as a barrier to US waves, which prevents the formation of images posterior to the place where the gas is accumulated. Therefore, intestinal loops, especially when greatly distended by gaseous content, and subcutaneous emphysema, for example, may limit the performance of the method. It should be remembered, however, that pulmonary US uses exactly the artifacts generated by gas for the evaluation of the parenchyma, which, when aerated, does not allow the evaluation of its deeper portions. Another condition that imposes limitations to US is patient's obesity. Thick subcutaneous fat layer limits the assessment of deeper structures. The fact that US is an operator-dependent method influences the performance of the method.

18.1.2 Computed Tomography and Computed Tomography Angiography

Advances in surgical resection of tumors have demanded more precise and detailed morphologic preoperative evaluations that rely mostly on imaging exams.

CT has become the imaging method of choice for tumor evaluation because of its widespread availability and diagnostic value. Images from CT are obtained in a more fast and reproducible way than MR and most of the time with better spatial resolution. The exam is also simpler to evaluate than MR since it usually has only one phase (CT) or two phases (arterial and venous phases in CT angiography [CTA]). Furthermore, the set of images created by CT can be more easily manipulated by different software platforms allowing better quality of three-dimensional

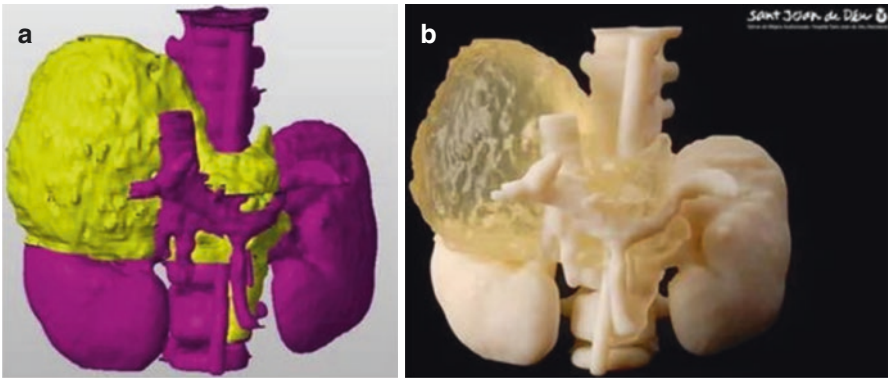

Fig. 18.1 (**a**) 3D virtual reconstruction of a tumor encasing major vessels from CT and MR fusion images. (**b**) 3D-printed prototype. Tumor is represented in a semitransparent, "operable" consistency. (With permission from Krauel et al. License Number 4841070538391)

(3D) reconstructions and also 3D printing, which can contribute to improve surgical management of complex tumors [6] (Fig. 18.1).

Major arteries and their relation to tumors can be easily evaluated by CTA with a good contrast between lesion and artery, also reliably evaluating tumor vessel encasement [7]. Veins can be evaluated as well, but once they are analyzed in a venous return phase of the contrast, the delineation of the vein and tumor is not so clear.

The relationship of the tumor with bone structures is a definite advantage of CT. The high bone attenuation of X-rays, in which CT relies to construct images, results in an easily recognized structure with high contrast to soft tissue and vessels [8]. However, when a medullary invasion is suspected, an MR is the image of choice because of its better tissue contrast.

Tumor margins can be delineated by CT especially in contrast-enhanced phase, providing enough information to surgical resection planning. Compared with MR, CT has a lower capacity of margin delineation for most of the tumors, especially soft tissue tumors because of the inherent high contrast that can be obtained by MR imaging (MRI) with multiple sequences with different weighting.

In the context of suspected active bleeding of a tumor, CTA plays an important role in showing the site of bleeding [9] by depicting contrast extravasation during the angiographic (in cases of active arterial bleeding) or late phase (slow arterial or venous hemorrhage). Furthermore, CTA can usually demonstrate the artery branch responsible for the bleeding, helping guide appropriate vascular intervention or surgery.

Advances in image analysis brought by artificial intelligence (AI) can help extract more information faster and with little or even no human interference from CTA. Initial experiences show that AI could provide comprehensive data for surgical planning like tumor localization, delineation, and vascular relationship that can improve process efficiency [10].

Technical issues of concern for performing contrast-enhanced CT or CTA are mainly related to radiation and the use of iodinated intravenous contrast. In the oncologic context, the benefit of performing a CT generally exceeds the risks (that are minimum) if the exam is well indicated. Pediatric patients and young adults with curable or benign diseases need special attention with repeated exams and MR should be preferred in these cases.

Allergic-like reactions can be mild to life-threatening. Severe acute reactions to currently used intravenous iodinated contrast (low-osmolar, non-ionic) are very rare, with an estimated rate of approximately 4 in 10,000 (0.04%) [11, 12].

Another concern for CTA is the risk of contrast-induced nephropathy (CIN) with the use of iodinated intravenous contrast. Recent studies showed that CIN is much less common than previously announced: in patients with an estimated stable basal glomerular filtration rate (eGFR) ≥45 m/min/1.73 m^2, intravenous injection of iodinated contrast medium was not an independent risk factor for nephrotoxicity, and in patients with a stable basal eGFR at 30–44 mL/min/1.73 m^2, intravenous iodinated contrast medium did not or rarely presented nephrotoxicity. Therefore, CTA can be safely indicated for patients with a stable eGFR of more than 30 mL/min/1.73 m^2 [13–15].

18.1.3 Magnetic Resonance Imaging

MR imaging (MRI) involves the interaction between the strong magnetic field of the MR scanner and the hydrogen protons of water molecules in human tissue. The images are generated through the processing of radiofrequency pulses emitted and collected by a receiving coil [16].

The use of a strong magnetic field imposes some restrictions on the examination, to ensure patient safety. Some absolute contraindications are notorious (such as traditional pacemakers and metallic hearing implants), while other relative contraindications are constantly reviewed, and are published in magazines and made available on websites dedicated to the topic of MR safety [17]. Thus, before indicating an MR in patients who have some type of implant or other metallic artifacts, the referring physician should discuss the case with a radiologist or with the department responsible for the examination.

When properly used, MR is considered a safe method, which does not use ionizing radiation, iodinated contrast, or intra-arterial injections for vascular studies. It has the advantage of more intrinsic contrast resolution between different tissues as compared to CT, also allowing direct acquisition in multiple planes (factors that might help in the evaluation of neoplastic conditions). It is important to emphasize that the relation of neoplastic lesions with surrounding vascular structures can be performed on MRI even on standard acquisitions, usually not requiring a dedicated, "vascular" study [18].

18.1.3.1 Diffusion-Weighted Imaging

Besides the use of anatomical images (usually weighted on T1 and T2), MR has the possibility of using diffusion-weighted imaging (DWI), a technique sensitive to the normal disorganized microscopic motion of water molecules (Brownian movement). Diffusion provides morphofunctional information about tissues, including cellular density, extracellular space characteristics, cell membrane interfaces, and grade of glandular organization. For instance, in tumors with a higher cellular density, the motion of water molecules is more restricted. Therefore, besides its use for tumor detection and characterization, DWI can aid in the definition of tumor aggressiveness [18].

18.1.3.2 MR-Angiography and Dynamic Contrast-Enhanced (DCE) Studies

MR-angiography (MRA) was developed for non-invasive assessment of vascular pathologies and can provide information on vascular anatomy and hemodynamic data (such as blood flow and speed). Three-dimensional acquisitions allow reformatting on any axis, and the examination can be associated with sequences dedicated to the joint evaluation of target organs [19].

The method has limitations, such as susceptibility to various artifacts, the most common ones related to patient movement, cardiac pulsatility, and some types of vascular endoprostheses. There are still some disadvantages in relation to CT angiography, such as less availability, longer total exam time, greater susceptibility to movement artifacts—very common in unstable patients—and difficulty in demonstrating parietal calcifications [19].

Non-contrast MRA techniques explore the natural dynamics of blood flow; although very useful in patients with contraindications to gadolinium (Gd), they require longer acquisition time and can generally overestimate stenosis, especially in cases of complex anatomy, tortuous vessels, or abnormal blood flow [20].

Dynamic contrast-enhanced (DCE) studies are commonly performed for a variety of oncologic conditions throughout the body. It uses the different enhancing characteristics of different tumors (usually based on different degrees of neovascularization) to detect and characterize lesions [21].

18.1.3.3 Gadolinium-Based MR Contrast Agents

Gadolinium (Gd) is a metal in the lanthanide series, and its chelates are widely used as paramagnetic contrast agents in MRI. It is important to note that MRI does not show Gd itself, but its paramagnetic effect, which consists of altering the signal intensity of the tissues around it. There are different types of Gd-based compounds, macrocyclic ones being considered safer and preferable.

Serious acute adverse reactions to Gd, such as laryngospasm, are rare (incidence of 0.01%, whereas with ionic iodine contrast they reach 0.17%) [22]. The most common mild adverse effects include nausea, headache, and vomiting.

In the last two decades, adverse effects related to the use of gadolinium-based contrasts have been described. In 2006, authors revealed the link between nephrogenic systemic fibrosis (NSF), a progressive disease with high lethality, and the previous use of Gd in patients with severe renal dysfunction [23]. It is nowadays generally accepted that careful screening and a consensual decision-making should be taken before the injection of Gd-based contrast agents in dialysis patients with hepatorenal syndrome or with a glomerular filtration rate below 30 mL/min/1.73 m^2 (preferentially, those agents should not be used in these conditions; if needed, macrocyclic agents should be used) [24]. Also, Gd-based contrast agents are contraindicated in pregnant patients, regardless of gestational period [25]. More recently, studies have shown that free Gd can deposit in the body tissues, especially the brain, usually in patients with renal function impairment and multiple lifelong injections. The clinical significance of this condition is still unknown, but it is well established that macrocyclic Gd-based contrast agents are also safer to minimize the risk of tissue deposition [26].

18.1.4 Positron Emission Tomography CT and MR

Positron emission tomography (PET) is a nuclear medicine functional imaging technique with proven clinical value, primarily in oncology. The most commonly used tracer is 18F-fluorodeoxyglucose (FDG), which competes with glucose and accumulates in cancer cells. FDG-PET provides unique information regarding tumor metabolism in cancer patients, which cannot be determined by conventional imaging modalities like CT or MRI alone. PET has improved the management of oncologic patients by providing information regarding tumor staging and prognosis. The integration of PET with CT (PET/CT) or, more recently, with MRI (PET/MRI) has resulted in its widespread use in cancer imaging by enabling simultaneous acquisition of images for quantification of metabolic activity together with morphology and anatomic correlation images [27, 28].

Nowadays, the vast majority of PET/MRI systems are installed in academic or tertiary care centers, most of them dedicated to research; however, the number of clinical PET/MRI systems is increasing gradually. Compared with PET/CT, the standard hybrid imaging system, PET/MRI offers reduced radiation exposure and higher soft tissue contrast (an intrinsic advantage of MRI over CT) [29].

Depending on the type of cancer, body region, and the choice of PET radiotracer, studies have reported that PET/CT and PET/MRI perform similarly, or that PET/MRI has minor to moderate advantages. However, many other variables should be

taken into account before deciding which exam is more suitable to one specific oncologic patient, such as availability, price (usually lower for PET/CT), duration (longer on PET/MRI), need for contrast media, and possibility of artifacts (more common on MRI), among others [30]. For both modalities, there is the possibility of adding a complete, contrast-enhanced CT or MR (including CTA and MRA) to the study, with the same reconstruction capabilities of dedicated exams (for vascular and tumor relations analysis).

A proposed strategy for imaging assessment of tumors according to their location is shown in Table 18.1.

Table 18.1 Proposed strategy for imaging assessment of tumors according to their location; intravenous contrast medium is usually recommended

Tumor location	Imaging method			Comments
	US	CT	MR	
CNS	0	+	+++	
Head and neck	+	++	+++	Thyroid's best initial evaluation is usually with US
Lung	0	+++	0	
Mediastinum	0	+++	++	Best initial evaluation is usually with CT
Liver	++	++	+++	
Biliary tract	+	++	+++	Gallbladder best initial evaluation is usually with US
Pancreas	+	++	+++	
Spleen	+	++	+++	
GI tract	+	+++	+	For rectal cancer, MR is the best option
Kidney	++	+++	+++	
Urinary tract	+	+++	++	US is appropriate for bladder evaluation
Prostate	0	0	+++	
Adrenal	+	+++	+++	
Retroperitoneum	+	+++	+++	
Soft tissue	+	++	+++	
Bone	0	+	++	Radiography is usually the first option; MR is the best option after radiography

Note: This table is intended to propose a generalization that works well for most cases. However, unusual situations may deviate from the proposed rule, and must be analyzed individually. In these cases, a prior discussion with a radiologist is recommended. Contraindication to a particular imaging method and/or to a determinate contrast medium should be investigated before choosing the imaging strategy

Score decoding: 0, Usually not appropriate; +, May be appropriate; ++, Usually appropriate; +++, Usually appropriate (probably the best option)

Abbreviations: *CNS* central nervous system; *CT* computed tomography; *GI* gastrointestinal; *MR* magnetic resonance; *US* ultrasonography

18.2 Relevant Aspects on Imaging Interpretation in Oncologic Patients

The reading process of an oncologic (confirmed or suspected case) imaging study by a diagnostic radiologist could be described as putting together patient information (e.g., signs and symptoms), disease knowledge (e.g., biological behavior, pattern of spread), and imaging findings (e.g., mass within an organ) to form an interpretation of the patient condition. This is one didactic way of decomposing the reasoning behind the radiologist practice (not excluding other approaches to the subject), and it is no different in oncologic cases in which tumor vascular invasion is under evaluation. In the next topics, we are going to clarify this argument and highlight the most important parts of each step. It seems reasonable that spreading this knowledge might improve communication between health professionals and patient care.

18.2.1 Communication of Patient Information and Diagnostic Imaging Interpretation

The excellence of diagnostic imaging interpretation depends on several aspects, and covering the whole complexity of this issue is beyond the scope of this chapter. However, we want to approach here a few aspects from the perspective of a diagnostic radiologist. In order to achieve quality patient care, health care professionals must have effective communication. From the diagnostic radiologist's perspective, this communication could be divided into two parts: first, information provided to the interpreting physician; and second, information provided by this professional, which is influenced by the first.

Regarding the first part, the American College of Radiology (ACR) comments that a reciprocal duty of information exchange between interpreting physician and ordering physician/health care provider is critical to achieve excellence [31]. The quality of information provided to the interpreting physician is a crucial step in achieving a state-of-the-art diagnostic imaging findings interpretation. This issue is of special relevance in oncologic patients, from diagnosis to treatment and follow-up. Here we suggest a checklist of relevant information that should be provided, whenever possible, to the interpreting physician in order to optimize patient care:

- Relevant clinical (e.g., pertinent clinical signs and symptoms, family and personal disease history, past surgical procedures) and laboratory information.
- Confirmed or most probable diagnosis, as well as important differential diagnosis to be considered (e.g., neoplasia, infectious/inflammatory disease).
- Previous reports and images for review and comparison with the current study.
- Intended surgical treatment for the patient, if possible (e.g., restaging study after neoadjuvant therapy).

- Previous surgical or other manipulation of the lesion under evaluation (e.g., biopsy, radiotherapy, chemotherapy, immunotherapy, radioembolization, chemoembolization, among others).

Regarding the second part, the ACR, in its document of orientation for communication of diagnostic imaging findings [31], states that an effective method of communication should: (1) promote optimal patient care and support the ordering physician/health care provider in this endeavor; (2) be tailored to satisfy the need for timeliness; and (3) minimize the risk of communication errors. Besides the content of the communication, a timely receipt through an adequate method of its delivery is also a determinant to achieve effectiveness. The radiology report is a written document that represents the most commonly used method of communicating diagnostic imaging findings. Although there is a constant effort to improve communication through radiology report [32–34], it has limitations. Radiologists and non-radiologists involved in patient care should always leave an open channel for oral communication to transpose these limitations. Even ensuring implementation of all of these premises, the quality of an imaging exam interpretation might be strongly influenced by the patient information provided to the interpreting physician.

18.2.2 Tumor Characteristics

The assessment of vascular involvement by neoplasia is part of the reading routine in oncologic studies. The interpretation of tumoral extension to adjacent structures is influenced to varying degrees by the knowledge of the disease, whether it is confirmed or under suspicion. In other words, there are tumor characteristics, such as biological behavior, spreading pattern, delimitation in imaging studies, among others, that compose the pre-test probability of tumor invasion in a given case. The interpreting physician's final opinion on a radiology report is in part influenced by this pre-test probability of tumor local invasion, especially in borderline cases, as well as their level of confidence that his or her opinion might be right or wrong in face of the disease under evaluation.

The importance of knowing the characteristics of the disease under evaluation can be exemplified in cases of cholangiocarcinoma. This malignant neoplasia has basically three distinct types in its morphologic classification: mass-forming, periductal-infiltrating, and intraductal-growing [35]. This means that cholangiocarcinoma can present itself as an intrahepatic mass, as a stenosing parietal thickening of the bile duct confluence (e.g., Klatskin tumor), or as a biliary duct dilation with a solid and mucoid tissue inside. Each one of these presentation patterns has a different prognosis, could arise in several locations within the biliary tract, and is usually associated with different risks of relevant vascular involvement. This knowledge is crucial for adequate study interpretation.

Another interesting observation is how tumor characteristics influence the probability of a given contact between a tumor and a vessel representing infiltration or

only proximity. Pancreatic adenocarcinoma, for instance, is frequently poorly defined in imaging exams, and in 10% of the cases no pancreatic mass is visualized [36]. Besides that, its infiltrative behavior, demonstrated by surgical resectability of less than 20% of cases at diagnosis and largely related to involvement of major abdominal vessels [37], has great influence in favoring invasion when there is contact between the mass (that sometimes it is barely seen) and the adjacent vessel. On the other hand, in lymphoma there is a known discordance between the volume of the mass and repercussions on adjacent structures [38]. This fact can be typically observed in mediastinal and retroperitoneal lymphoma masses that promote vascular encasement without invasion [39]. In conclusion, the knowledge of the different behavior of tumors directly affects the radiologist's interpretation of whether or not there is invasion in a given contact between a tumor and a vessel.

18.2.3 Imaging Findings Analysis

After discussing the importance of patient information and tumor characteristics, attention should be taken regarding imaging characteristics. With the technological evolution of computer processing and the development of artificial intelligence algorithms, it is becoming increasingly more evident that there are overwhelming amount of data that can be extracted from medical imaging examinations. Morphological analysis, tissue evaluation, and methods of quantification are great examples of data arising from medical imaging studies. The field under investigation is vast and the major effort now is to extract data that have value as a disease-relevant biomarker.

18.2.3.1 Tumor Vascular Involvement

The accurate judgment of vascular involvement represents a crucial step in cancer diagnosis and staging. It represents one of the most important components of determining the resectability of borderline or locally advanced tumors.

Some tumors clearly do not present vascular infiltration. In these cases, we can see a defined cleavage plane between the tumor and the vessel in imaging examinations, usually of adipose tissue. On the other hand, there are tumors that surround the vessels circumferentially, deforming and/or infiltrating them. These two situations present objective findings easily recognizable and more uniformly interpreted by radiologists. However, it is usually challenging to determine the resectability of tumors that have contact (in minor or major degrees) with a vessel.

Some tumors demand a definition of whether or not there is vessel infiltration to proceed to adequate treatment. Once again, pancreatic adenocarcinoma is a good example. In order to try to improve the agreement between the radiological opinion and the surgical definition of vascular involvement by the tumor, several radiological classifications were published [40]. According to these classifications,

morphological imaging patterns can be used, which are related to different degrees of residual tumor (R classification) [41]:

- Presence of a border of normal tissue (adipose tissue) at the vessel–tumor interface determines the absence of involvement of such vessel by tumor (Fig. 18.2a).
- When a tumor presents contact with the vessel (the adipose cleavage plane has been infiltrated), but without deforming or narrowing/occluding this vessel, we are facing a borderline case (possibly resectable). In these cases, studies suggest that a tumor-to-vessel contiguity of 50% or less (contact of 180° of vessel circumference or less) has high probability of surgical resectability (borderline resectable tumor) [42] (Fig. 18.2b).
- Change of normal vessel shape, vascular contour irregularities, and tumor encasement (defined as more than 180° of circumferential contact between the tumor and the vessel) are signs associated with locally advanced tumor/unresectable disease [43] (Fig. 18.2c). Another finding that strongly suggests the presence of a locally advanced disease is the presence of a tumor mass infiltrating the vessel lumen, which characterizes tumor thrombosis (a topic that will be explored in the next section).

The above-mentioned findings regarding tumor contact or involvement/infiltration of a vessel are based in publications of pancreatic adenocarcinoma, which is known for its infiltrative behavior. However, we believe that these patterns can be used as a guidance for the evaluation of other tumor-to-vessel relations, in conjunction with the tumor characteristics (such as biological behavior, spreading pattern, and delimitation in imaging examinations).

18.2.3.2 Malignant Versus Bland Thrombosis

Tumor staging and treatment are significantly impacted if there is presence of a tumor thrombus. A vessel thrombus is defined as a filling defect, partially or completely occluding the vessel lumen. The radiological evaluation of the presence of a

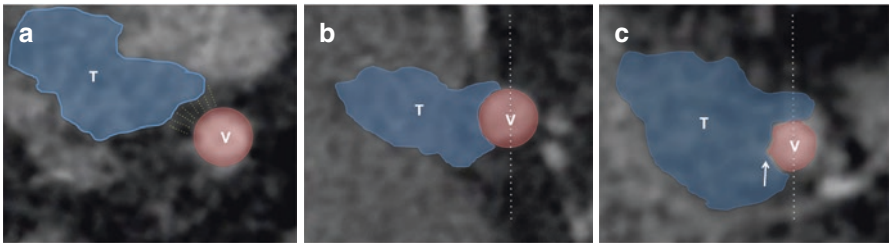

Fig. 18.2 Vessel tumor contact. (**a**) Presence of an adipose tissue at the vessel–tumor interface. (**b**) Less than or equal to 180° tumor contact without deformity. (**c**) More than 180° tumor contact with deformity (arrow)

vessel thrombosis cannot be limited to defining the presence and location of the thrombus in cancer patients. It is fundamental to attempt to differentiate whether the thrombus consists of a tumor (tumor thrombus) or a blood clot (bland thrombus).

The main difference between them is that the tumor thrombus, as well as the tumor itself, is vascularized (at least in part) and the blood clot is usually non-vascularized. In imaging studies, we document vascularization within a mass (including a thrombus) by observing enhancement, defined as attenuation increment of ≥20 Hounsfield unit (HU) on CT or signal intensity increment of ≥15% on MRI from pre-contrast phase to post-contrast phase [44]. Another finding that allows characterization of tumor thrombosis in imaging studies is continuity between the tumor mass and the vessel thrombus. These two findings when presented together are highly indicative of tumor thrombus, with specificity of 100% and sensitivity of 86% [44, 45].

Some tumors are more commonly associated with tumor thrombosis, such as renal cell carcinoma, since up to 10% of patients with advanced renal tumors might develop a thrombus in the inferior vena cava [46]. In these cases, inferior vena cava segmental resection or even prosthetic replacement may be necessary to prevent recurrence or positive resection margins [47]. Hepatocellular carcinoma is another tumor that illustrates the importance of defining the presence of tumor thrombosis in imaging methods. The therapeutic approach may be drastically changed by the presence of tumor thrombus instead of a bland thrombus. Patients with tumor thrombosis are no longer eligible for the main curative treatment for liver cirrhosis and hepatocellular carcinoma, that is, liver transplantation [48].

Therefore, imaging methods are frequently able to differentiate between tumor and bland thrombus, and this definition has usually major influence in management.

18.3 Illustrated Radiological Report

*18.3.1 **Head and Neck*** (Fig. 18.3)

*18.3.2 **Mediastinum*** (Fig. 18.4)

*18.3.3 **Chest*** (Fig. 18.5)

*18.3.4 **Gastrointestinal*** (Figs. 18.6, 18.7, 18.8, 18.9, 18.10, and 18.11)

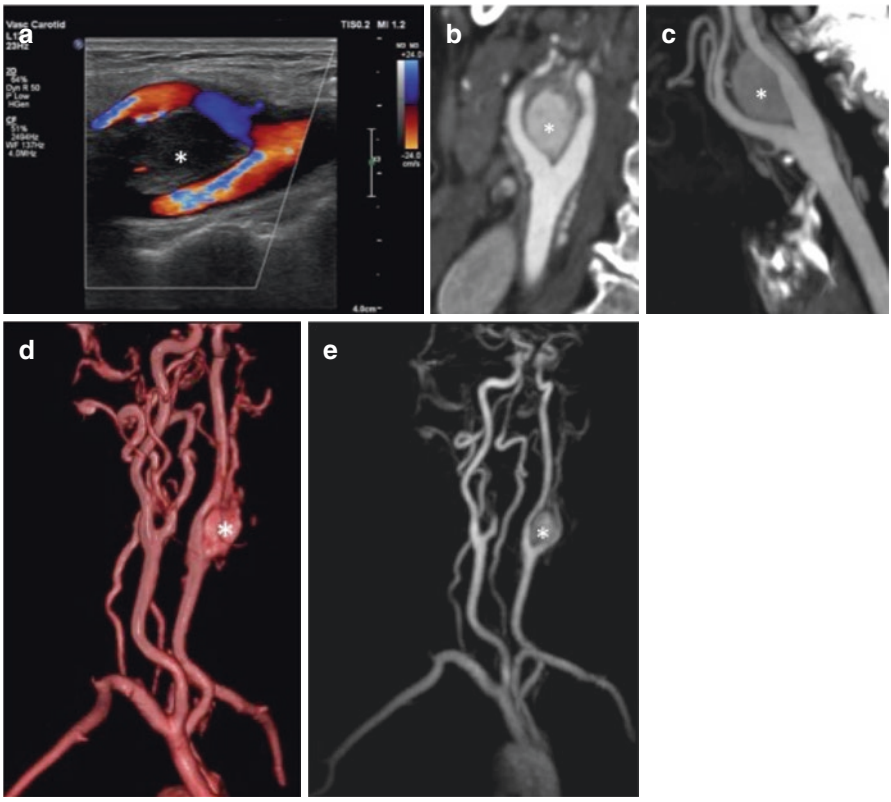

Fig. 18.3 Paraganglioma of the carotid bifurcation. Solid oval neoplastic lesion at the level of the left carotid bulb bifurcation (*), hypoechogenic on Doppler-US (**a**), hypervascular on CTA with oblique (**b**) and 3D MIP (**c**) reconstructions, and also on MRA with 3D VR (**d**) and 3D MIP (**e**). The lesion widens the space between the internal and external carotid arteries' origins and displaces posteriorly the internal jugular vein (that remains patent)

18.3.5 Genitourinary (Figs. 18.12, 18.13, and 18.14)

18.3.6 Retroperitoneum (Figs. 18.15 and 18.16)

18.3.7 Musculoskeletal (Figs. 18.17 and 18.18)

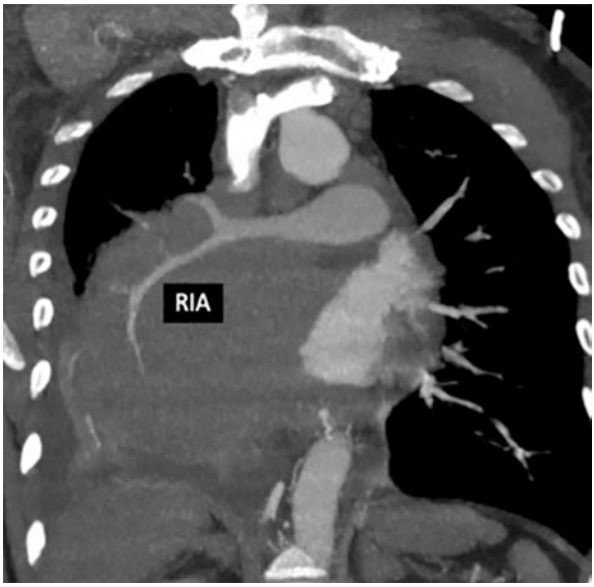

Fig. 18.4 Chest CTA of an HIV-positive patient with Burkitt's lymphoma. Right interlobar artery (RIA) circumscribed and stretched but not infiltrated by the tumor. This is a typical appearance of this type of lesion

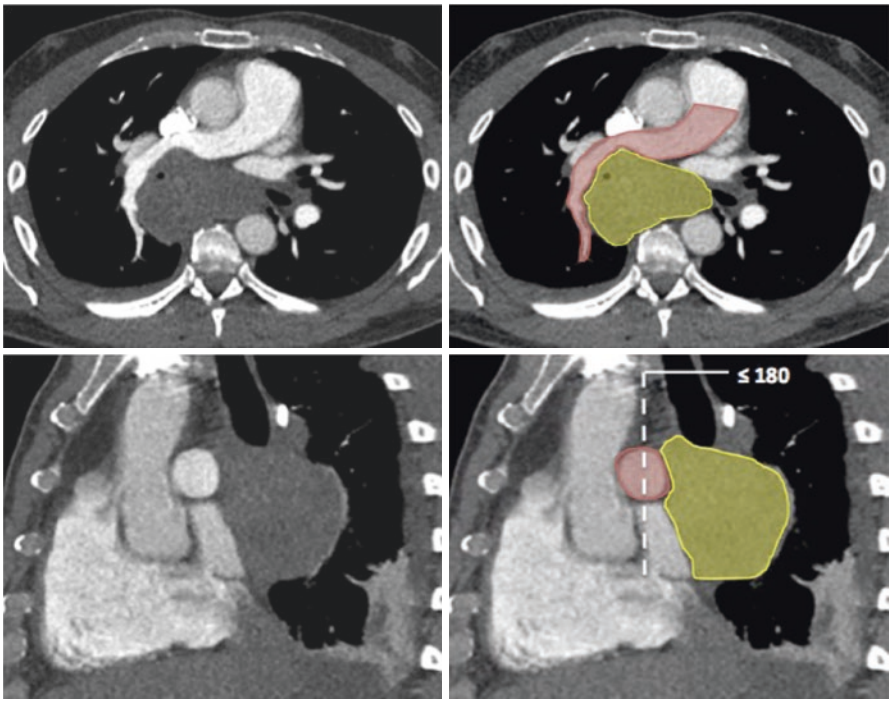

Fig. 18.5 Chest CTA of a patient with non-small-cell lung cancer. Right hilar lesion with lobulated contour that presents wide contact with the main pulmonary artery, displacing it anteriorly, but without definitive signs of vascular invasion by the tumor

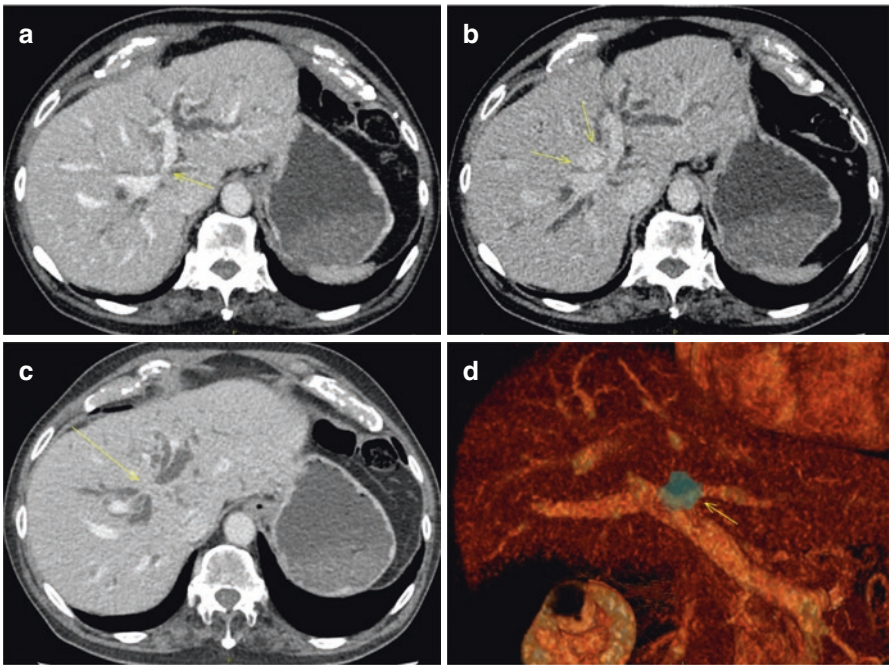

Fig. 18.6 CT of a patient with a central cholangiocarcinoma. (**a**) Infiltration causing narrowing of the left portal vein (arrow). (**b**) Late enhancement of the tumor (arrows). (**c**) Lesion causing obstruction of the main bile ducts (arrow). (**d**) 3D reconstruction showing the relation of the tumor with the portal vein

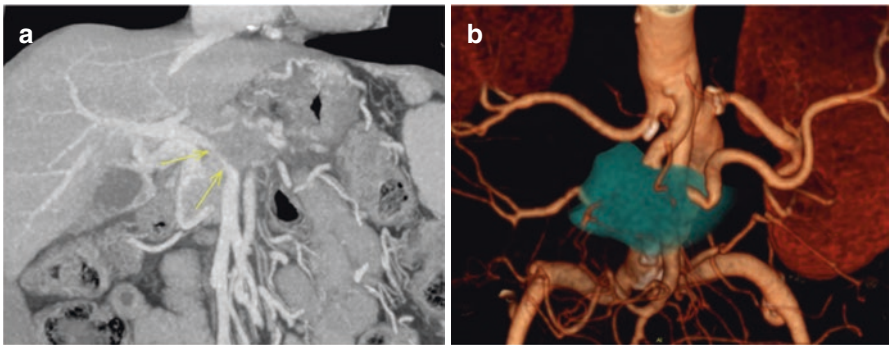

Fig. 18.7 MR exam showing a diffuse hepatocarcinoma with tumoral thrombosis of a portal vein branch (arrows). (**a**) Portal phase demonstrating a filling defect of the vein. (**b**) Corresponding image of the arterial phase showing vascularization of the tumoral thrombus

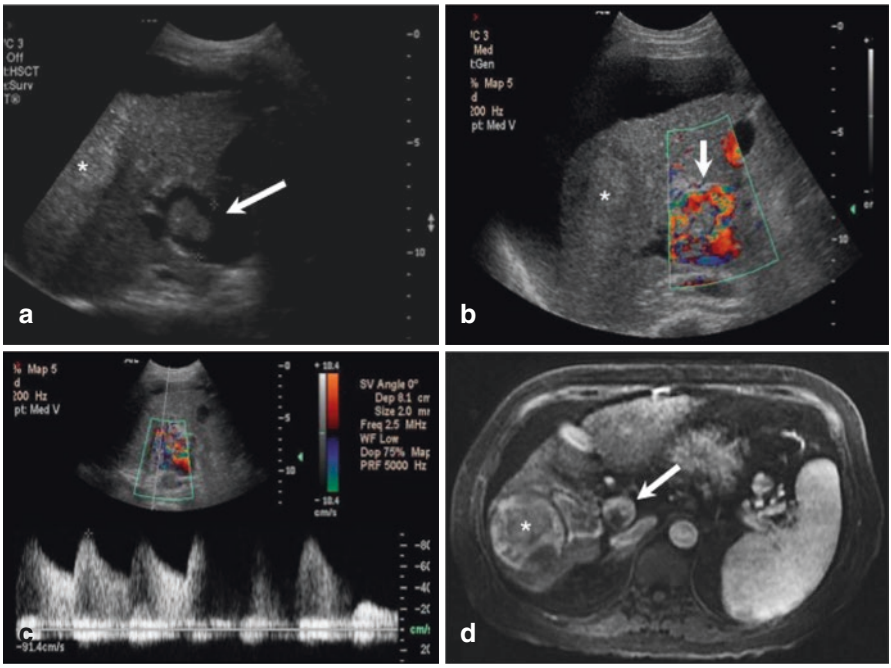

Fig. 18.8 Tumor thrombus of the portal vein (arrows) on B-mode US (**a**), color Doppler (**b**), and pulsed Doppler (**c**), which show isoechogenic content partially filling the lumen of the vein, with arterial low-resistance flow within. Post-contrast MRI phase (**d**) shows the same findings: hepatocarcinoma (*) and the tumor thrombus (arrow) in the portal vein

Editors' Comments

Vascular reconstruction can transform unresectable tumors into resectable ones. Although the importance of vascular reconstruction is defined before the cancer surgery, this definition often occurs during the intraoperative period, when the real relationship between the tumor and large vessels becomes more evident.

Preoperative imaging exams are of fundamental importance for planning eventual vascular reconstruction, as they show whether the vessels in question are patent or occluded, what is the extent of the relationship between the tumor and vascular structures, and what is the condition of other vessels that may participate in the perfusion or drainage of the organs/tissues served by the arteries and veins affected by the tumor.

This chapter dealt with the leading imaging exams to evaluate vascular involvement by tumors, including the radiological characteristics that allow a tumor thrombus to be differentiated from a hematic thrombus.

Ultrasonography, computed tomography, nuclear magnetic resonance, and positron emission tomography/resonance have advantages or disadvantages in evaluating some aspects in certain situations, which were also covered in this chapter.

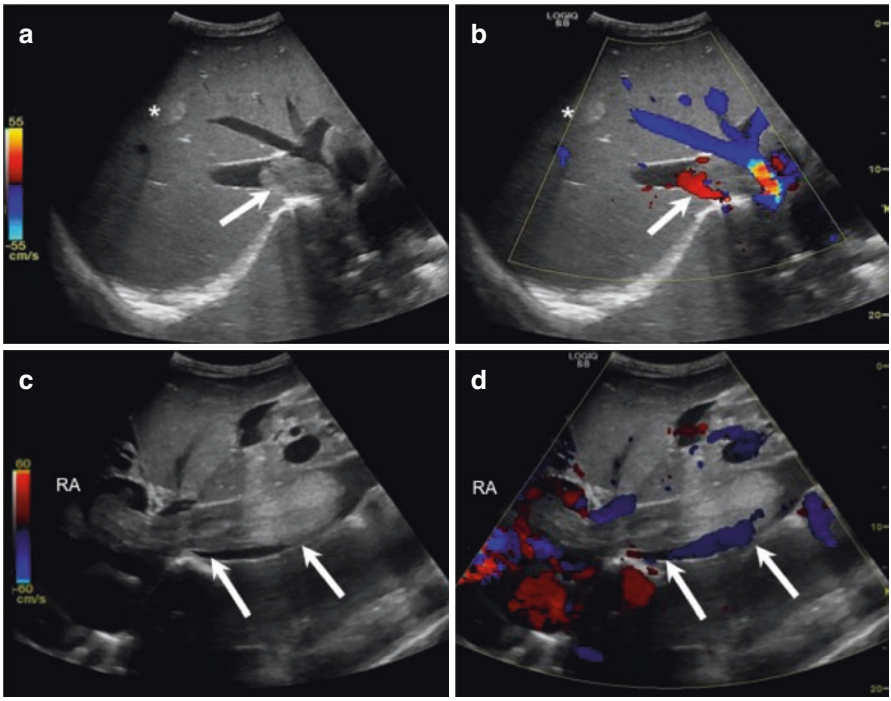

Fig. 18.9 Hepatic metastasis (*) associated with hematic thrombosis of the intrahepatic inferior vena cava (arrows) with cranial extension to the right atrium. B-mode US (**a**, **c**) and color Doppler US (**b**, **d**) images

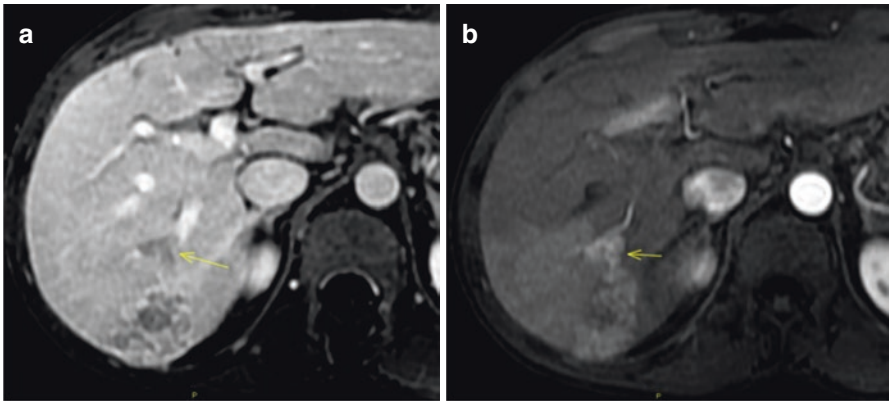

Fig. 18.10 CTA of a pancreatic carcinoma. (**a**) The lesion is infiltrating the portal vein (arrows). Collateral perigastric veins are evident. (**b**) 3D reconstruction showing the invasion of the celiac trunk and its branches by the tumor (in green)

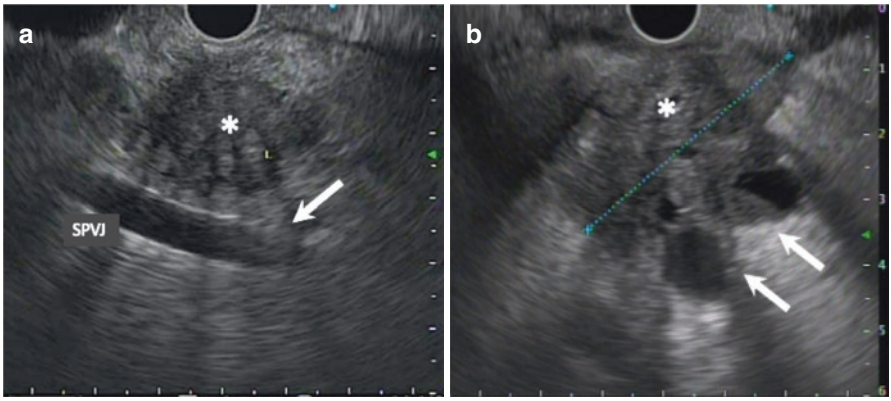

Fig. 18.11 Pancreatic head adenocarcinoma (* on **a** and **b**) evaluated by endoscopic US. (**a**) Signs of incarceration of the splenoportal venous junction (SPVJ) characterized by the loss of the interface between the tumor and the vein (arrow). (**b**) Splenic vein invasion (arrows)

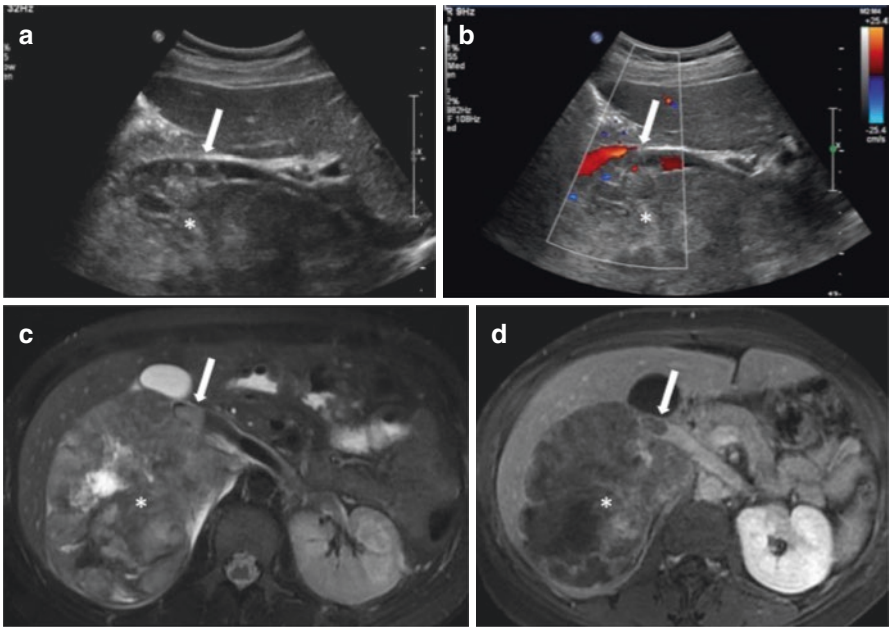

Fig. 18.12 Right adrenal carcinoma. Large heterogeneous neoplastic lesion at the right adrenal gland region (*), hypoechogenic on US (**a**), compressing the IVC on Doppler-US, with thrombus within the venous lumen (arrow on **b**). The mass shows heterogeneous signal intensity on T2WI (**c**) and enhancement on T1WI (**d**), with tumor thrombus in the right adrenal vein extending into the inferior vena cava (arrows)

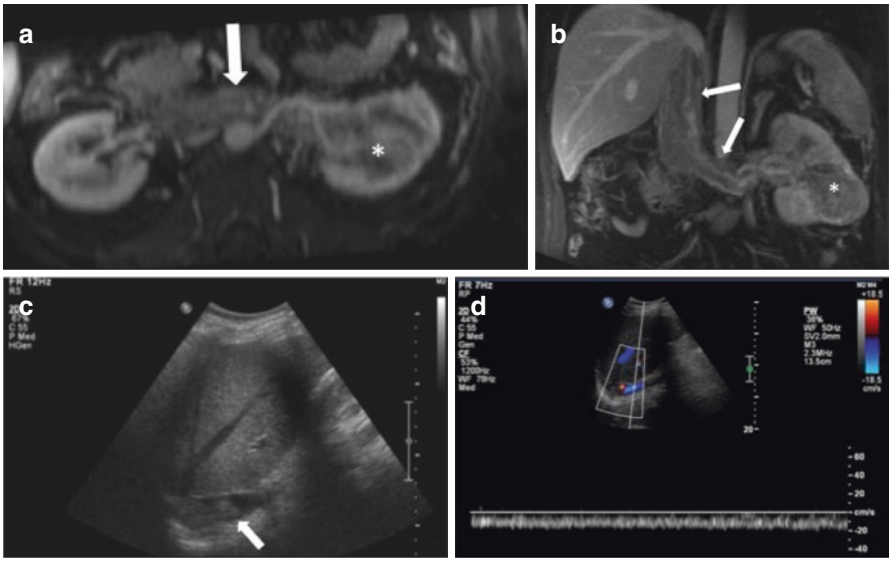

Fig. 18.13 Clear cell renal cell carcinoma. Hypervascular infiltrative solid mass in the middle-third of the left kidney (*), with renal sinus invasion and enhancing tumor thrombus in the renal vein extending into the inferior vena cava until the level of the diaphragm (arrows), on volumetric axial (**a**) and coronal (**b**) post-contrast MR images. US confirmed the presence of a thrombus inside the IVC (arrow in **c**), with presence of flow on Doppler (**d**), conforming its tumor nature

In addition to these modalities, performed and interpreted by radiologists, others are usually performed by vascular surgeons: endovascular ultrasound, intravascular ultrasound (IVUS), and angiography. In some situations, IVUS can increase the accuracy of vascular invasion diagnosis, as in assessing the extent of pancreatic cancer concerning the portal vein, celiac trunk, and superior mesenteric artery [49, 50].

As it is an invasive image exam, the IVUS is especially useful when diagnosing vascular invasion can change the management. If vascular invasion contraindicates immediate surgical treatment, making neoadjuvant treatment more appropriate, the greater invasiveness of IVUS becomes acceptable.

Angiography has been increasingly restricted to intraoperative and may be useful to assess both the conditions of the newly implanted bridges and possible complications inherent to surgical manipulation and the need for vascular clamping, such as distal thromboembolism, arterial dissection, and low-flow thrombosis.

In addition to the issue directly related to large vessels' relationship to tumors, imaging studies are also important in vascular surgical planning concerning the evaluation of the conditions of vessels that are candidates for arterial substitutes. Perviousness and caliber of saphenous veins, jugular veins, and veins of the upper limb—the duplication of femoral veins, for example—can be assessed with a pre-operative duplex-scan.

The rapid and continuous advancement in image quality has been a great ally in cancer patients' best therapeutic planning.

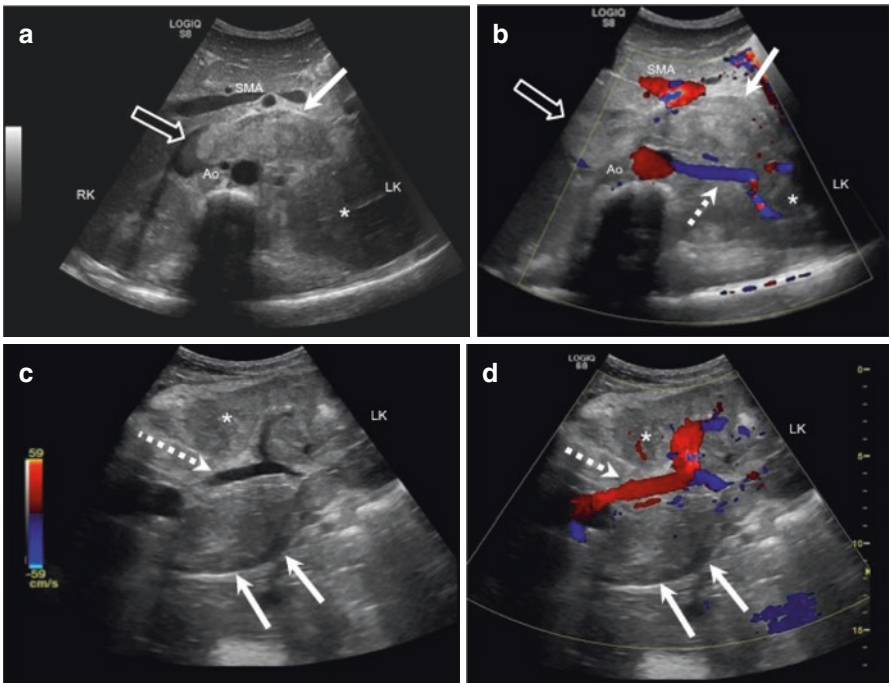

Fig. 18.14 Left renal tumor (*) associated with occlusive hematic thrombosis of the entire left renal vein (white arrows) with extension to the inferior vena cava (black arrows). B-mode US (**a**, **c**) and color Doppler US (**b**, **d**) images. Axial section of the upper abdomen on (**a**) and (**b**), and left renal hilum via lumbar access on (**c**) and (**d**). *LK* left kidney; *RK* right kidney

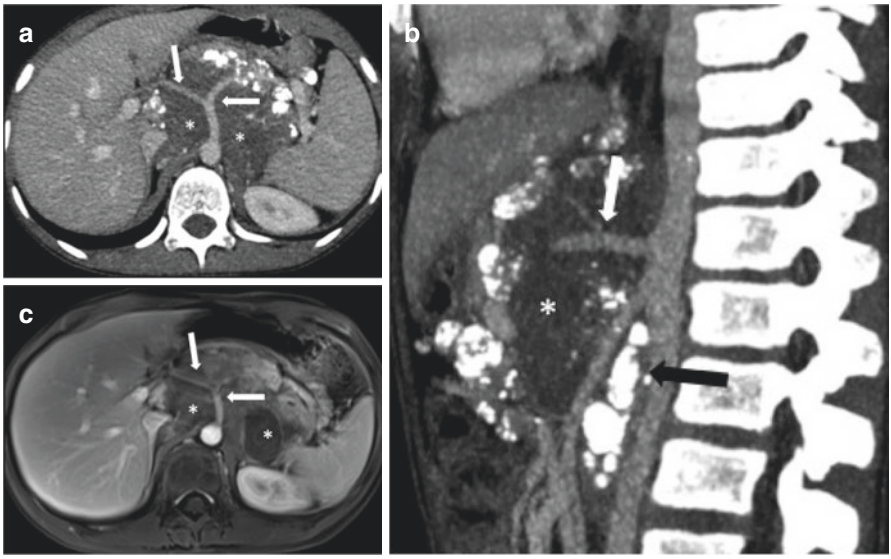

Fig. 18.15 Neuroblastoma. Large retroperitoneal mass with calcifications, centered in the epigastric/mesogastric region (*), involving the celiac trunk and its branches (white arrows) on CT (**a**, **b**) and MRI (**c**) and widening the space between the aorta and the superior mesenteric artery (black arrow in **b**)

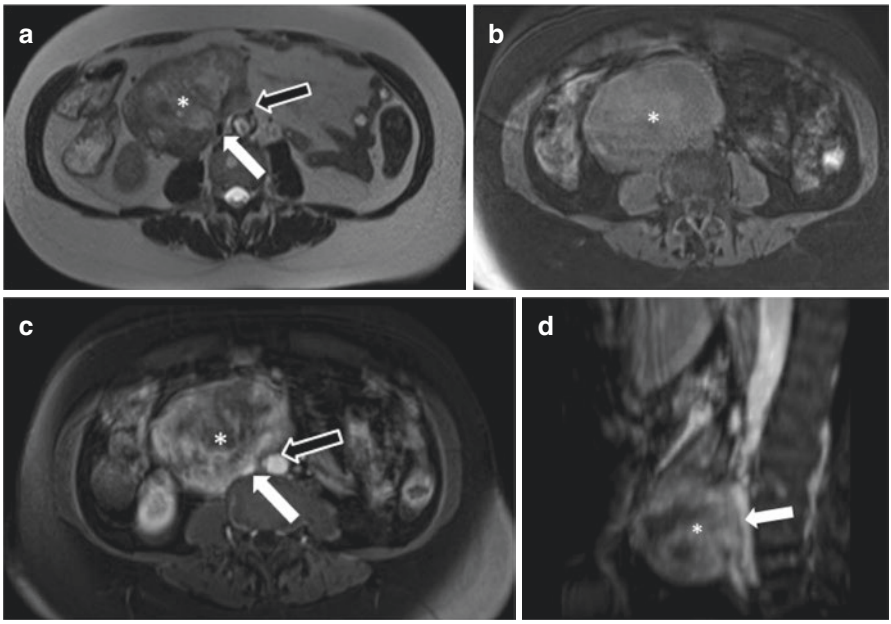

Fig. 18.16 Retroperitoneal leiomyosarcoma. Solid mass in the right infrarenal retroperitoneum (*), with heterogeneous signal intensity on axial T2WI (**a**), T1WI (**b**), and sagittal post-contrast T1WI (**d**), compressing and possibly originating from the inferior vena cava (**a**), (**c**) (white arrows), which remains patent. There is contact with the distal abdominal aorta, with no definite signs of invasion (**a**), (**c**) (black arrows)

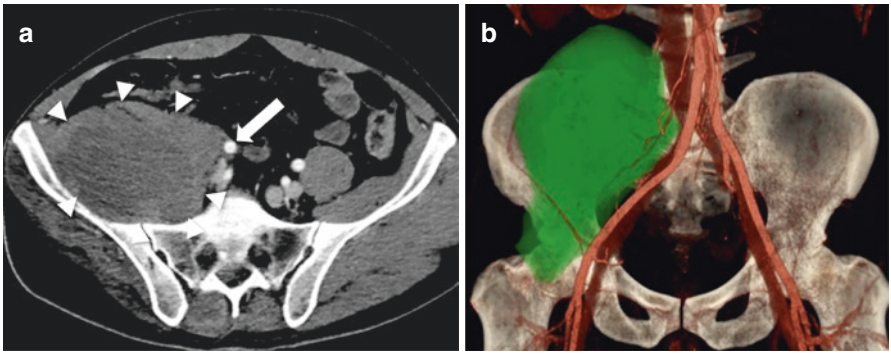

Fig. 18.17 CTA of a patient with a pelvic malignant peripheral nerve sheath tumor (arrowheads). (**a**) The proximity of the tumor with the external iliac artery is well demonstrated (arrow). (**b**) 3D reconstruction showing the relation of the tumor with iliac veins and arteries important for surgical planning

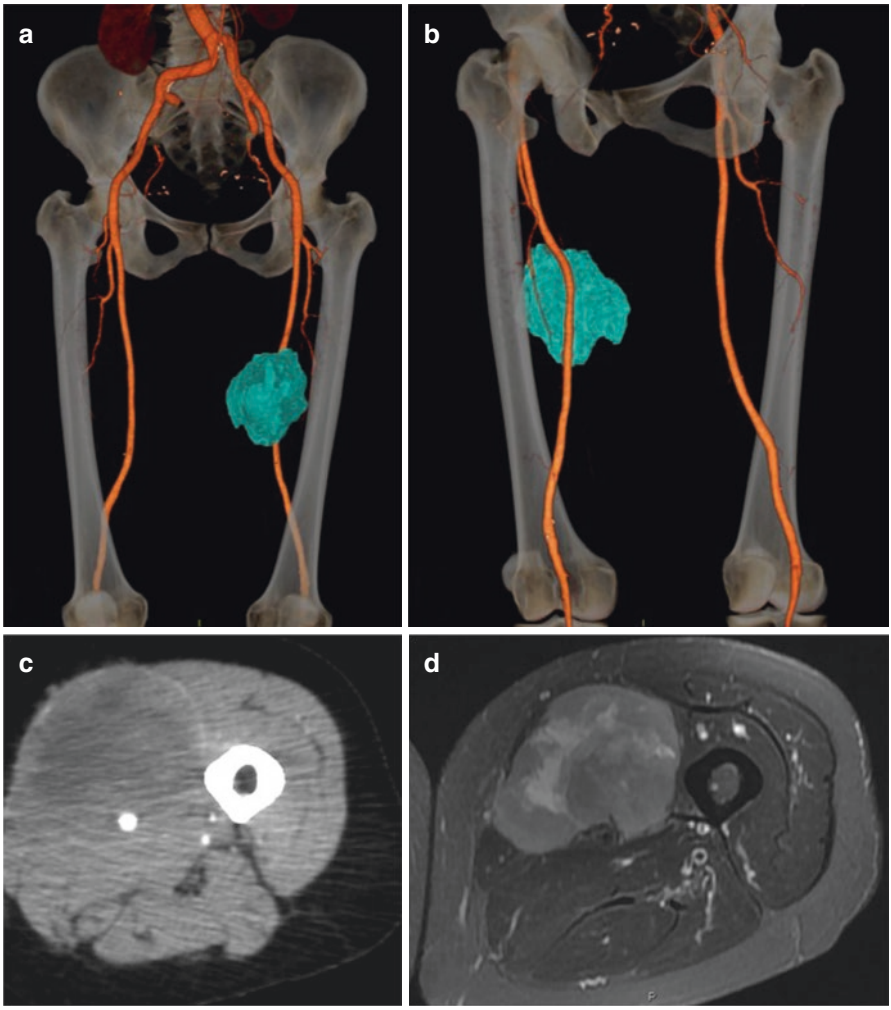

Fig. 18.18 3D volume rendering of a CTA showing a high-grade spindle-cell sarcoma in the left thigh and its relationship with the femoral artery (**a**, **b**). Axial view of the same CTA demonstrates tumor vessel contact of approximately 180°. (**c**) MR axial T2-weighted image with fat saturation (**d**) characterize tumor limits more precisely than the CTA due to high tissue contrast of the method

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