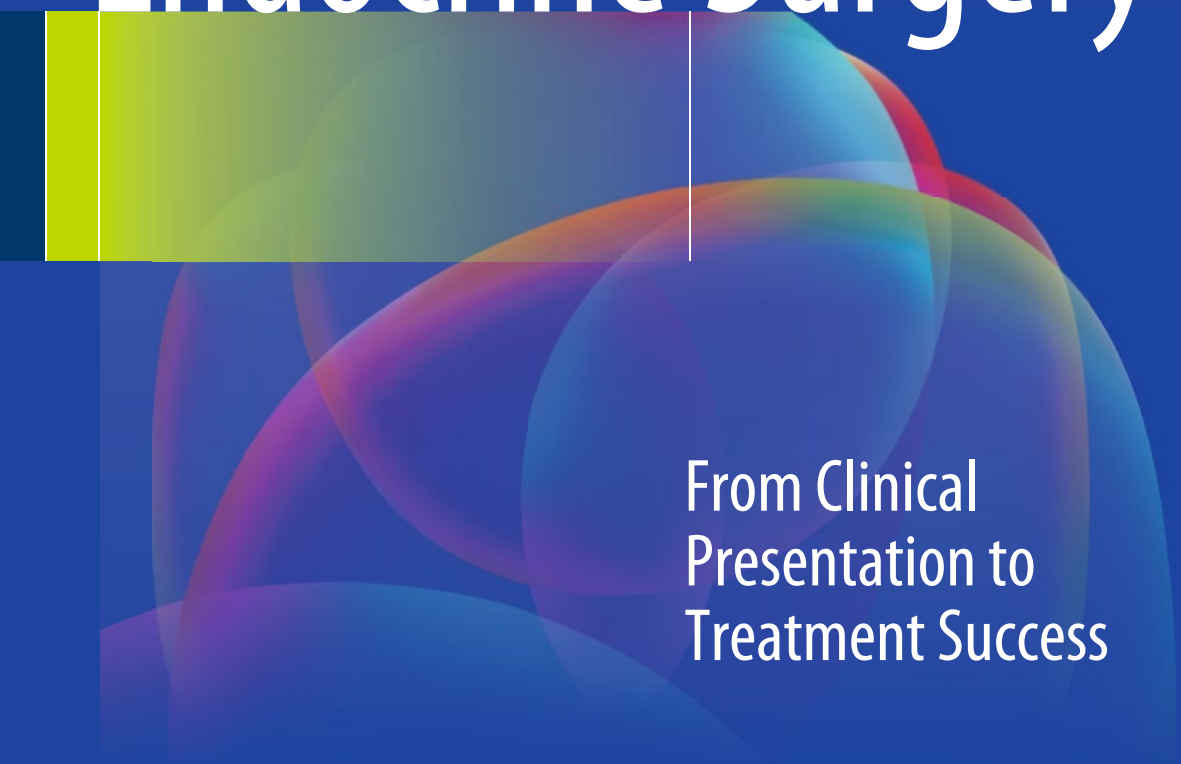
Mahmoud Sakr
Editor

Head and Neck and Endocrine Surgery



From Clinical Presentation to Treatment Success

Springer

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To my wife

Preface

Head and neck and endocrine surgery has now become a major specialty within the surgical domain. We have endeavored to give some rein to the new developments, which are evidence based and widely supported in the literature.

The purpose of this book is to provide a comprehensive review of the current knowledge of the pathophysiology, clinical-diagnostic techniques, and therapeutic strategies of surgical disorders of head and neck and endocrine glands. This book addresses a wide range of topics including maxillofacial injuries; surgery of the scalp, jaw, oral cavity, and salivary glands; tumors of the pharynx; cervical lymphadenopathy; neck swellings; and deep space infections. In addition, endocrine surgery included diverse conditions of the thyroid, parathyroid, and adrenal glands as well as the endocrine pancreas. The last chapter involves also the newer developments and recent advances in minimally invasive surgery of the head and neck.

This book has been structured in such a way as to facilitate quick reference. We believe it will be a useful tool for clinicians to provide timely and up-to-date therapy of the head and neck and endocrine problems of their patients.

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Last but not least, I would like to express my deepest gratitude to my family for their unlimited support and unconditioned love.

Contents

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Maxillofacial Injuries

1

Mahmoud Sakr and Ibrahim Fathi

1.1 Introduction

Trauma to the maxillofacial (MF) region is a common category of injuries in the field of emergency medicine. This type of injuries usually requires a multidisciplinary approach for proper management (a team composed of an emergency medicine specialist, an oral and maxillofacial surgeon, otolaryngologist, ophthalmologist, and a plastic surgeon). In almost 50 % of cases, MF injuries are associated with other multisystem injuries, requiring coordination between other surgical specialties, rather than being an isolated injury [1].

Variable modes of trauma can lead to MF injuries. Assault is the most common form in developed countries followed by road traffic accidents (RTA), while in underdeveloped regions, RTAs are the leading cause. Other etiologies include sport injuries, stumbling, pedestrian collisions, and warfare [2–4].

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1.1.1 Classification

Maxillofacial injuries include (1) soft tissue injury (with or without skin loss), (2) injury of specialized structures (e.g., facial nerve, parotid gland/duct, and lacrimal duct), and (3) facial bone fractures.

1.1.2 General Principles of Management

Principles of Advanced Trauma Life Support (ATLS) should apply to all cases of facial trauma. Only after the primary and secondary surveys are concluded, the definitive treatment of facial injury can proceed safely [5].

1.1.2.1 First Aid Treatment

A patent *airway* should be secured. A compromised airway is the leading cause of death in MF injuries, most commonly caused by falling back of the tongue or soft tissues of the neck or hemorrhage flooding the airway. Maintenance of a patent airway can be achieved through putting the patient in the prone position to avoid the obstruction of the oropharynx by the tongue and removal of blood clots. A jaw thrust or a chin lift can help in unblocking the airway. Impacted maxillary fracture should be dis-impacted, thus regaining the patency of the airway.

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Oropharyngeal airway can be used. A laryngoscope should be used to assess the laryngeal inlet, foreign bodies (FBs) are removed, and an appropriate cuffed endotracheal tube can be placed. If the vocal cords cannot be visualized or if a blocking FB removal is not feasible, a cricothyroidotomy can be made and an appropriate cuffed tracheostomy tube is advanced.

Tracheostomy may still be needed in some cases.

Hemorrhage should be controlled by pressure using a sterile dressing and clamping of bleeders. Deep sutures can be placed in the scalp or the tongue if the bleeding is profuse and cannot be controlled by simple pressure [5].

1.1.2.2 Hospital Evaluation

Upon reaching the hospital, proper evaluation should be done before starting the systematic plan of definitive treatment. This includes (1) examination of the head, chest, and abdomen for associated injuries that may need urgent interference, especially if there is shock, which is rare in MF injuries, as well as determination of the extent of facial injury by (1) thorough physical examination (facial nerve integrity, presence of diplopia, sensory loss, parotid and lacrimal duct examination, etc.), (2) assessment of *intracranial hemorrhage* (level of consciousness, usually using the Glasgow Coma Scale [GCS]), pupil size, and reaction to light), (3) plain radiography (may show a fracture or FB), (4) CT scan (the investigation of choice if intracranial damage is suspected), and (5) examination under anesthesia (EUA) (offers better evaluation).

1.1.2.3 Primary Care

If the patient has not been previously immunized, *tetanus* immunoglobulin, 250 units IM, and tetanus toxoid, 0.5 ml, should be given. Two additional toxoid boosters at monthly intervals are necessary. For previously immunized patients who received their last booster more than 10 years ago (or more than 5 years in tetanus prone wounds), a single dose of tetanus toxoid should be given. Perioperative *antibiotic* coverage is required for patients with rheumatic or valvular heart disease, human and animal bites, extensive injuries, associated skeletal trauma, and grossly contaminated wounds. *Pain control* should be achieved. Simple temporary immobilization of fractures including the mandible will reduce pain. Narcotic analgesics should be avoided, but when essential, codeine phosphate is a good choice. *Primary wound care* includes arresting hemorrhage, cleansing, and appropriate dressing.

1.1.2.4 Anesthesia

The choice of anesthesia is determined by several factors, which include the extent of soft tissue injury, the presence or absence of associated bony injuries, and the age and general condition of the patient. *Local infiltration* is used for small lacerations. *Regional nerve blockade* is useful in extensive injuries. *General anesthesia* is necessary for extensive soft tissue injuries with associated facial fractures, in small children, and noncooperative patients.

However, many debates exist regarding the optimum modality of anesthesia. Airway patency and the risk of aspiration should be kept in mind while taking the decision.

1.2 Soft Tissue Injuries

Although soft tissue injuries in the facial region may not be of fatal outcome, they may have a devastating psychological impact necessitating special attention. In 25 % of the cases, facial lacerations are associated with bony facial fractures. Such fractures should be recognized first.

Several types of soft tissue injuries can result from MF trauma including contusions, abrasions, lacerations, and puncture wounds with or without retained FBs. In most of the cases, hemorrhage resulting from isolated facial lacerations can be controlled with compression.

1.2.1 General Principles

Extensive blood supply to the facial region decreases the incidence of devitalization of tissues. However, the incidence of hematoma formation is exaggerated. Several layers

constitute the soft tissue covering of the MF region: skin, SC tissue, and superficial muscular +/– mucosa.

Photographing facial lacerations and contusions is essential for postoperative evaluation and follow-up as well as for medicolegal aspects. Repair of facial soft tissue injuries can be safely delayed up to 24 h without compromise of the cosmetic outcomes. Care to the associated multisystem injuries in poly-trauma patients and the stabilization of the hemodynamic status may necessitate such delay.

Absorbable suture material should be used to repair the mucosa and SC tissues, while nonabsorbable sutures should be used for skin repair and removed after 4–6 days. For infected facial lacerations, it is not advisable to attempt primary closure. Instead, frequent dressings are applied allowing for free drainage. Systemic antibiotics are administered, and delayed primary closure is planned after 3–10 days [6].

1.2.1.1 Preoperative Care

The wounds should be adequately assessed. Any affection of the neural or muscular function should be noted. Parotid or lacrimal duct injury should be assessed. Associated fractures and retained FB should be excluded through radiology. Shaving of the facial hair may be required for adequate visualization and approximation. It should be noted though that eyebrows should never be shaved even if lacerated for their significance in cosmetic outcome. Tetanus prophylaxis is administered according to the immunization history of the patient.

1.2.1.2 Anesthesia

Local anesthesia can be used for small facial lacerations, while general anesthesia is reserved for extensive injuries or the ones with coexisting facial skeleton fractures.

1.2.2 Wound Preparation

Gentle cleansing and irrigation with saline solution or aqueous chlorhexidine, removal of blood clots, and protection of eyes are essential. *Debridement* should be minimal. Skin is preserved, even if it appears doubtfully viable to avoid loss of cosmesis. Only ragged skin ends are trimmed.

1.2.3 Principles of Repair

1.2.3.1 Surgical Repair According to the Type of Injury

Abrasions

Cleansing of the wound and moist dressings are applied to promote healing.

Contusions and Hematomas

Mostly they get absorbed uneventfully, and warm fomentation will speed up the absorption process. Large hematomas may require incision and evacuation.

Lacerations

These can vary widely regarding the mode of trauma and extent and depth of injury (Fig. 1.1a, b). Lacerations should be repaired through meticulous approximation of the transected tissues in layers. Proper alignment is essential for good cosmetic results. Evidently devitalized tissues and irregular skin edges should be trimmed out for better re-approximation.

Avulsions

Owing to the abundant blood supply to the facial region, even the narrow-based avulsion flaps can survive if carefully re-approximated. Small insignificant avulsion flaps can be removed, but larger ones should be preserved with limited excision of the thinned out leading part. Compression dressing can help in decreasing the resulting edema.

Special Types of Injury

Human and animal bites: Copious irrigation should be done together with sharp debridement of infected and devitalized tissues. Prophylactic systemic antibiotics should be administered, and the wound should be planned for delayed reconstruction. It should be noted that human bites are more liable to

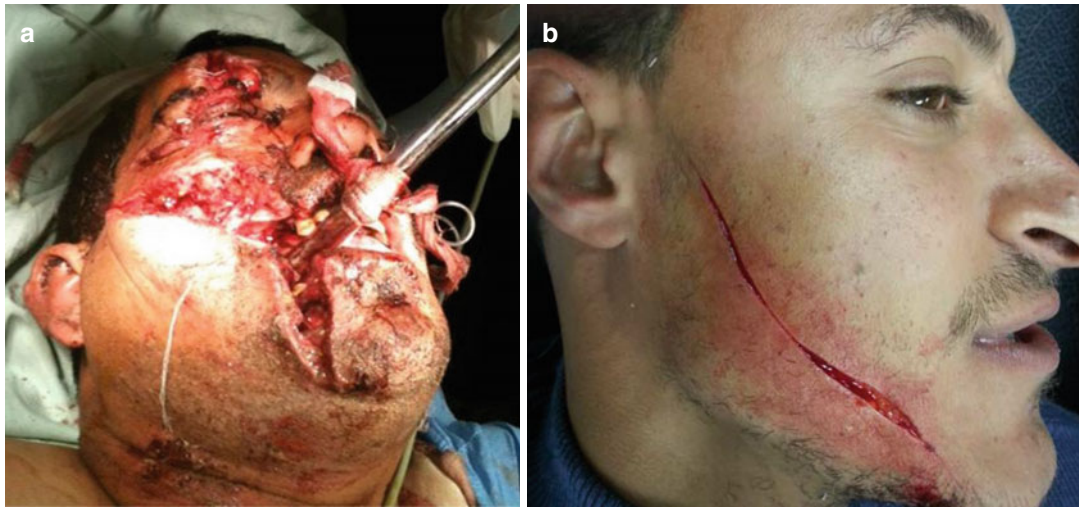

Fig. 1.1 (**a**) Severe lacerations due to blunt facial trauma associated with facial fractures. (**b**) A linear cut wound of the cheek caused by assault with a sharp object

become infected as they carry greater contamination than animal bites.

Facial burns: The modern principle of early excision and grafting of burns has a very limited application in the face; only circumscribed contact full-thickness burns benefit from this approach.

Soft tissue loss: The defect is covered by a full-thickness graft (Wolf graft), local flaps (rarely used especially in the young because of the scar they leave), or distant flaps from the forehead or neck, if the defect is too large for local repair.

1.2.3.2 According to the Location of Injury

Fig. 1.2 A full-thickness lower lip laceration extending to the chin

Lip Injuries

If these lacerations are planned to be repaired under local anesthesia, alignment should be done before injection of the local anesthetic solution through marking, tattooing, or suturing. Orbicularis oris muscle injury should be carefully assessed and repaired. Alignment of the vermillion border is necessary for good cosmetic results to preserve what is known as "Cupid's bow" [7] (Fig. 1.2).

Nasal Injuries

Proper alignment is necessary for sound esthetic reconstruction especially around the nasal rims. Speculum examination of the nasal septum should be performed to detect septal hematomas that—if left untreated—can end up in erosion and loss of septal cartilage. Such hematomas can be evacuated through small incisions. Repair of full-thickness nasal lacerations should proceed from deep to superficial layers starting from the nasal mucosa, cartilage, and finally the skin. Various algorithms have been described for reconstruction of nasal defects [8–10]. In "avulsion injuries," the missed segment is cleansed and re-sutured as a composite graft, but if lost, a "composite graft" from the auricle may be used.

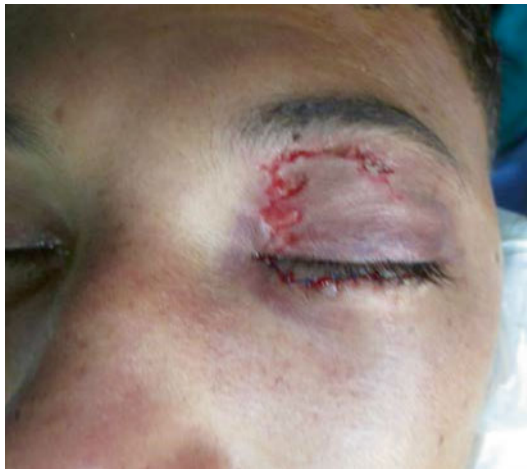

Fig. 1.3 Left eyelid laceration

Eyebrow Injuries
No shaving of the eyebrow should be attempted. Tissues of questionable vitality should also be preserved. Proper anatomical alignment is required to achieve the best cosmetic results. In case of tissue loss in the eyebrow region, primary repair with interval hair graft harvested from the posterior scalp region should be sought.

Eyelid Injuries (Fig. 1.3)
The lower eyelid is usually more involved than the upper. Exclusion of any associated lacrimal or globe injury is mandatory at the time of wound assessment. Debridement should be minimal, and careful layer by layer repair should be done. Knots should be directed away from the eye globe. If the eyelid margin is involved by the injury, proper alignment of the cilia is required for optimum repair. An eyelid tissue defect may require lateral canthoplasty to allow for medial mobilization of the whole lid to close the defect [11].

1.2.4 Postoperative Care

Postoperative management of traumatic facial lacerations is rarely discussed in the literature. Many conflicting data regarding the optimum type of dressing, the use of topical antimicrobials, and the need for systemic antimicrobials in certain types of wounds exist. At other instances, the data are not strong enough to provide enough evidence.

In 2010, Nicholas Medel et al. [12] reviewed the literature for postoperative management options for facial lacerations. The authors came up with certain recommendations for the postoperative period, stating however that not all of them are based on randomized trials. These recommendations included applying Steri-Strips plus Mastisol until suture removal or preferably for few weeks to decrease the tension. They also recommended the use of topical antimicrobials for the first 2 days and encouraged showering after the first night. Sutures should be removed after 4–5 days of suturing.

1.2.5 Complications

Scars An unsightly scar results from hypertrophic scarring, poor wound characteristics, or poor surgical technique. The patient should be consulted regarding the possibility of developing scars, in spite of meticulous surgical technique, before the repair process is pursued. Patients with tendencies to develop *keloid* have higher probability of such complications. Some topical agents can be used after removal of sutures to promote proper healing and achieve better cosmetic results with variable success rates. Scar revision can be done after complete healing of the wounds (6–12 months) via different surgical modalities.

Infection Abundant blood supply to the face region decreases the incidence of infection. Therefore, routine use of topical or systemic antibiotics in facial wounds is not advised. In certain scenarios, including human and animal bites, severely contaminated wounds, and retained FBs, use of prophylactic antibiotics seems reasonable. Most of facial wound infections are, however, superficial and respond well to antibiotic therapy. Studies show that wound infection occurs maximally in the first 48 h after repair, though these results are not specific to facial lacerations.

1.3 Injury of Specialized Structures

1.3.1 Parotid Gland and Duct Injury

Although traumatic salivary gland injury is rare, the parotid gland and duct location makes it more prone to traumatic injury compared to other salivary glands. It occurs in around 0.21 % of trauma cases, being far more commonly associated with penetrating modes of trauma [13, 14]. Unfortunately, half of these injuries pass unnoticed during the initial evaluation and management, which results in the development of sialoceles and salivary fistulas [15].

1.3.1.1 Evaluation

The key to proper management of parotid gland and duct injuries is early recognition at the time of primary assessment. Detailed history of the mechanism and timing of injury is required. Whenever an injury to the parotid gland or duct is suspected, the patient should be asked about the timing of the last meal since a recent meal will result in increased salivation with pouring of saliva into the wound [16]. On examination, an injury to the parotid gland or duct should be suspected whenever the wound affects the region extending from the tragus of the ear to the upper lip (imaginary line). When suspicious, massaging of the gland region can express saliva from the injured region. In many cases, cannulation of the parotid duct orifice with injection of saline and/or methylene blue (MB) is required to confirm or exclude parotid duct injury. Care should be taken not to stain the surrounding tissue when using MB, making detection of facial nerve injury and its repair troublesome.

Penetrating injuries to the parotid gland and duct region are usually associated with injuries to surrounding structures including:

- *Facial nerve*: Injury of the facial nerve is associated with 20 % of gland injuries and more than half of parotid duct injuries. Facial nerve assessment should therefore be done as part of the initial evaluation. The buccal branch is the most commonly affected one due to its intimate relation to the parotid duct [17].
- *External auditory canal (EAC)*: Otorrhagia should raise suspicion of EAC injury.
- *Temporomandibular joint (TMJ)*: Occlusion and jaw opening should be evaluated.
- *Vascular injury*: Injury to the intraglandular vasculature can be troublesome. In such conditions, only proper compression should be applied until appropriate intraoperative evaluation and management is pursued. No blind attempts to control bleeding should be done for fear of facial nerve injury [18].

1.3.1.2 Treatment

Isolated Gland Injury The wound should be properly cleansed. The gland capsule is simply sutured using absorbable sutures. Pressure dressing is used for 2 days to prevent development of sialoceles. Cannulation of the duct for 2 weeks maybe required to prevent obstruction of the salivary outflow due to associated edema. Close follow-up is required to recognize any complications as early as possible [19, 20].

Parotid Duct Injury According to Van Sieckel's classification [21], parotid duct injury of the intraglandular portion (site A) requires no repair; repairing the parotid duct capsule is sufficient in this location. Injury of the part overlying the masseter muscle (site B) is the most commonly affected portion and should be treated by direct anastomosis whenever possible. Injury to the portion distal to masseter muscle (site C) is optimally treated by direct anastomosis, but this is usually difficult, so oral reimplantation can be done in this situation.

Anastomosis is better done over a catheter introduced through the duct orifice. Injection of saline or MB facilitates recognition of the distal stump. The proximal stump is found through fine exploration of the wound. Massaging of the gland may aid the identification of the proximal stump through expression of saliva. At least 3 stitches with fine nylon sutures (9-0 or 10-0) are used to repair the duct. Alternatively, 7-0 or 8-0 silk sutures can be used. If a segment is lost, an autologous venous graft can be used for the repair [22]. Pressure dressing is required for 2 days, and the intraductal catheter should

be left in place for 2 weeks postoperatively. Antisialogogues and antibiotics should be prescribed. Observation of the postoperative course is mandatory [18, 21].

In case of badly lacerated parotid duct, ligation of the proximal stump can be done aiming at atrophy of the parotid gland. This can be aided by the use of anticholinergic drugs. Alternatively, oral reimplantation of the proximal stump into the oral mucosa can be done [18].

1.3.1.3 Complications

Sialoceles These result due to unrecognized injury to the parotid gland or duct or improperly treated injuries. They present as soft cystic swellings. Aspiration will confirm the diagnosis (amylase content can be done when doubtful and is diagnostic if >100,000 IU/L) [20]. If they develop few days following surgery, the wound should be re-explored and the underlying injury should be properly managed. On the other hand, if they develop as a delayed complication, repeated aspiration and pressure dressings are usually effective [14]. This can be aided by the use of anticholinergics to decrease salivary secretion. Some authors advocate nasogastric feeding to limit the stimuli for salivary secretion [16]. Intraglandular low-dose botulinum toxin injection can block the parasympathetic impulses and result in decreasing the salivary secretion [23, 24]. In resistant cases, parotidectomy can be performed [20]. Radiotherapy is now abandoned for fear of risk of malignancy.

Salivary Fistulas They present as a communication with the skin surface pouring salivary secretions. They may follow spontaneous rupture of sialoceles. Again, if they are detected early postoperatively, the wound should be re-explored and properly managed. If delayed, compression dressing and anticholinergics are used [20]. Tympanic neurectomy aiming at destruction of tympanic nerve carrying parasympathetic supply to the gland is better not done due to its limited short-term success (probably due to reinnervation). Parotidectomy remains the last resort for resistant cases [25, 26].

1.3.2 Facial Nerve Injury

Facial nerve injuries can result from either blunt or penetrating trauma. An injury can occur at any part along the course of the nerve; thus, it can be classified according to the site of injury into five different types as follows [27]:

1.3.2.1

Type	Description
I	Involves the portion inside the facial canal in the internal auditory canal (IAC)
II	Involves the horizontal course of the facial nerve through the middle ear
III	Involves the vertical course of the facial nerve through the mastoid
IV	Involves the facial nerve through its course in the parotid tissue
V	A combination of the above types of injuries

1.3.2.2 Evaluation and Treatment

Facial nerve integrity should be evaluated in any patient presenting with craniofacial injury through exclusion of motor facial deficits. If facial nerve affection is present, grading of the injury is essential as it can help in estimating the magnitude of the injury and the probable recovery potential. The "*House-Brackmann*" grading system is the most commonly used for this purpose [28]. A computed tomography can help in delineating the site of injury in cases of temporal bone fractures. Electroneurography aids in the identification of the degree of injury and in follow-up. Deteriorating results warrant nerve exploration [29].

For intratemporal injuries, a simple mastoidectomy is done for approaching the injured site. Only decompression is required if the nerve is not severed. If the nerve is severed, mobilization may be required to attain tension-free repair.

Injuries distal to the stylomastoid foramen should be suspected in any deeply seated wound along the course of the nerve as in case of deep cheek lacerations. A motor deficit should promote meticulous nerve exploration with the target being primary repair. The utilization of nerve

monitor and surgical microscope is greatly helpful in this situation. It is well established that injuries distal to a line connecting the lateral canthus and gonial notch of the mandible do not require repair due to the distal branching of the facial nerve [18]. Otherwise, more proximal injuries require primary repair. Identification of the cut ends is the first concern, sometimes requiring a classic superficial parotidectomy to identify and trace the branches.

Crushed ends should be carefully trimmed and approximated without tension. Two or three nonabsorbable 8-0–10-0 monofilament sutures are placed through the epineurium with the help of surgical microscope (although several debates exist regarding the time and technique of repair). Mobilization may be required to attain such tension-free repair. If such approximation is not feasible, cable nerve grafting is done using either the great auricular nerve or sural nerve. Inferior to direct anastomosis and nerve grafting are the nerve substitution techniques involving either a hypoglossal-facial or a cross-facial anastomosis [30].

Recovery of motor functions usually requires at least 6 months following the injury. However, extent of recovery and the duration required vary widely according to the extent of nerve affection, site of trauma, and the methodology of the repair process. A certain degree of synkinesis almost always results.

In case of failure of primary treatment, a variety of secondary facial reanimation techniques exist with variable success rates. These techniques include the nerve substitution techniques, dynamic muscle slings, or static procedures [29].

1.3.3 Ear Injuries

The *cartilage* should have the primary priority. Any exposed cartilage should be covered by skin to avoid secondary infection that may result in a painful chondritis, which is very difficult to treat. After debridement and suturing, if cartilage is still exposed, local postauricular or mastoid skin flaps can be used for cover. If the ear is totally avulsed, microsurgical reimplantation can be considered.

1.4 Fractures of Facial Bones

1.4.1 Surgical Anatomy

Anatomically, the MF region is divided into three zones as demonstrated in Fig. 1.4:

1. *The upper face*: Fractures involve the frontal bone and the frontal sinus.
2. *The middle face*: This is again divided into upper and lower zones. The upper midface consists of the zygoma, nasal bones, ethmoid bone, and non-tooth-bearing segment of the maxilla. This is where maxillary Le Fort II and Le Fort III fractures occur. Also, it is where nasal bones, naso-ethmoidal complex (NEC), or zygomaticomaxillary complex (ZMC) and the orbital floor fractures occur. The lower midface includes the maxillary alveolus, teeth, and palate and is the site of Le Fort I fractures.
3. *The lower face*: This is the site where mandibular fractures occur.

1.4.2 Nasal Fractures

Nasal fractures represent the most common type of facial fractures due to the prominence of the

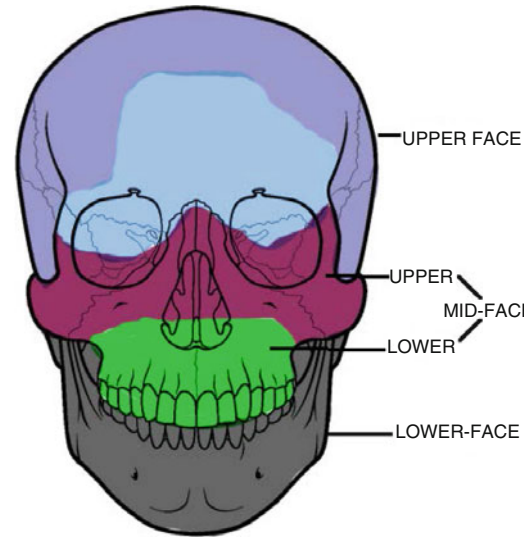

Fig. 1.4 The three anatomical zones of the maxillofacial (MF) region

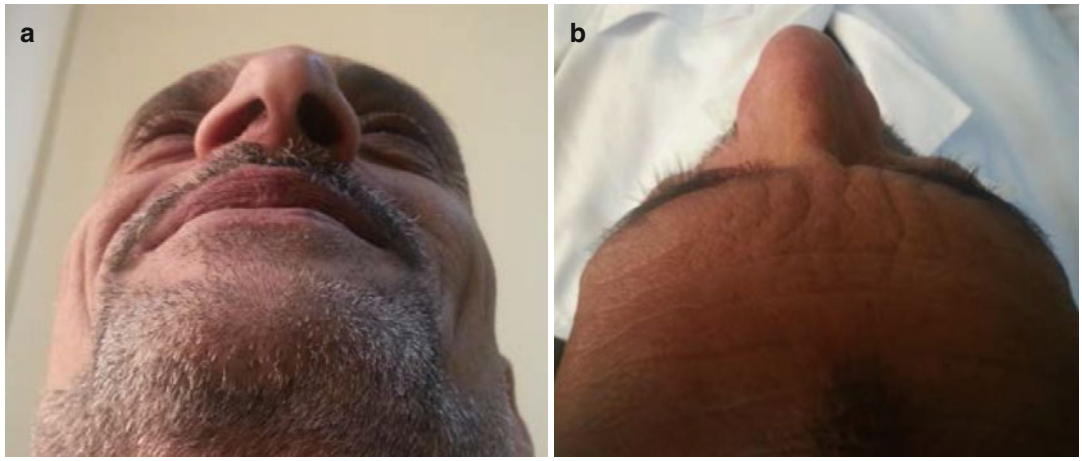

Fig. 1.5 (**a**) Worm's eye view, (**b**) bird's eye view for nasal deformity evaluation

nose placing it at a higher risk of attaining trauma together with the relatively lower force required to cause such injury [31]. The nose shape and contour represent some of the main aesthetic aspects of the face. Also, nasal trauma can affect one of its functions related to air humidification, smell sensation, and respiration. Therefore, nasal fractures should be dealt with great care to restore both of its aesthetic and functional properties.

Nasal fractures can result from a variable cascade of injuries; sport injuries are of the most recognized causes especially in the adolescent population. Males attain nasal fractures twice as females as reported by several reports [32–34].

1.4.2.1 Assessment of Nasal Fractures

Detailed history regarding the mechanism of trauma should be taken to assess the possible extent of injury. Any accompanying manifestations including loss of consciousness, dizziness, or headache should be noted and dealt with carefully as they may reflect concussions with associated intracranial injuries. It should be noted that almost half of the assault injuries to the MF region are associated with high alcohol levels, which can lead to a variable degree of confusion. This, however, should not be assumed as the causative factor until both intracranial injury and hypoxia are excluded [5].

Inspection of the nasal region can reveal variable degrees of external deformity, the detection of which can be facilitated by examination through the different views (frontal, worm's eye, bird's eye views) (Fig. 1.5). However, such deformity can be obscured by the resulting edema. *Palpation* may reveal nasal or septal deviations; a step deformity or crepitus can also be felt. Good lighting and proper nasal speculum are required to detect the integrity of septal cartilage and bone together with the development of septal hematoma. If the physician is familiar with fiberoptic naso-endoscopy, it will be a valuable tool to assess the nasopharyngeal cavity and the posterior nasal complex. Epistaxis and cerebrospinal fluid (CSF) rhinorrhea can be present; the latter should raise suspicion of an associated skull base injury. Thorough examination of the whole facial region is required to rule out associated MF injuries with special focus on the naso-orbital-ethmoid varieties [35].

Imaging Although imaging is not required in all cases of nasal trauma and plain X-rays can be sufficient in isolated nasal injuries, CT scan represents a very informative tool in case of nasal fractures especially in the setting of suspected associated MF or intracranial injuries.

1.4.2.2 Treatment of Nasal Fractures

Closed Reduction

Indication Closed reduction is commonly used and is suitable for most isolated nasal fractures. It

can be coupled with external stabilization and nasal packing to restore the functional and aesthetic aspects of the nose.

Time Frame Nasal fractures are optimally reduced during the first week of injury. Although immediate reduction is sometimes feasible, the associated edema usually masks the nasal contour, thus hindering optimal assessment, reduction, and fixation. Therefore, delaying the intervention is reasonable to allow such edema to subside. It should be noted, however, that unjustified delaying for more than 1 week may result in difficult and more painful manipulation due to the resulting fibrosis.

Preparation Many debates exist regarding the best anesthesia modality. Several reports confirm the suitability and patient's preference of local compared to general anesthesia where both can be used to reach comparable cosmetic outcomes [36]. Some reports confirm also the superiority of external infiltration when compared to nerve block techniques regarding the patient convenience. However, the risk of bleeding that may endanger the patient airway should be recognized, making a brief general anesthesia with endotracheal intubation or placement of laryngeal mask a reasonable option. Local anesthesia is mostly not suitable for the pediatric population [35, 37]. After the application of anesthesia, a throat pack may be placed (in case of general anesthesia with endotracheal tube or laryngeal mask). Careful reassessment of the nasal injury should follow aided by continuous suction and the proper nasal speculum. Care should be taken to protect the eye during the application of vasoconstricting agents (e.g., oxymetazoline), which are used to obtain mucosal vasoconstriction. In case of general anesthesia, local anesthetics are applied for postoperative analgesia.

Technique Digital manipulation is used to reduce displaced nasal fragments. Frontal and maxillary bones are used as anchors for this process. The reduction is guided by careful inspection from different views and palpation to achieve a symmetrical smooth contour. The use of Goldman elevator maybe required for septal reduction. Care should be taken if Asch forceps is used for septal reduction for fear of mucosal injuries. The use of septal splints and nasal packing is sometimes required to maintain the reduction. Nasal packing also provides the advantage of bleeding control. Some commercial forms soaked in antibacterial solutions are available. Bleeding may require posterior nasal packing. Intraoperatively bleeding sites can be controlled through the use of electrocautery. External nasal splints are required to support the fracture site until healing is achieved. Such splints should be tailored and molded maintaining a smooth contour. Care should be taken not to encroach on the nasal alae, tip, or canthi [35].

Open Reduction

Bicoronal incision is the common approach for open reduction in nasal fractures, which is usually required in case of significant comminution or with associated fractures of the frontal sinus or the naso-orbital-ethmoid complex. The fixation can be achieved by low profile fixation devices. In some special modes of trauma where unusual forms of comminution or avulsions exist as in animal bites and ballistic injuries, primary bony grafting may be required. Partial-thickness grafts from parietal bone are commonly used in these situations. Direct approaches to the fracture site for reduction and fixation may be used if the laceration site permits enough access [38, 39].

Postoperative Management and Complications

After closed reduction, nasal packs should be removed within 3–4 days. Septal splints can be left for 1 week or more. Nasal massaging is encouraged 2–4 weeks postoperatively aiming at reducing any minor deviations and obtaining a smoother contour. In the pediatric population, such maneuvers may require additional anesthesia or sedation [35].

In spite of proper closed or open reduction and fixation techniques, up to 50 % can end up with posttraumatic *deformities* requiring secondary interventions, which are usually delayed for at least 6 months postoperatively to obtain accurate

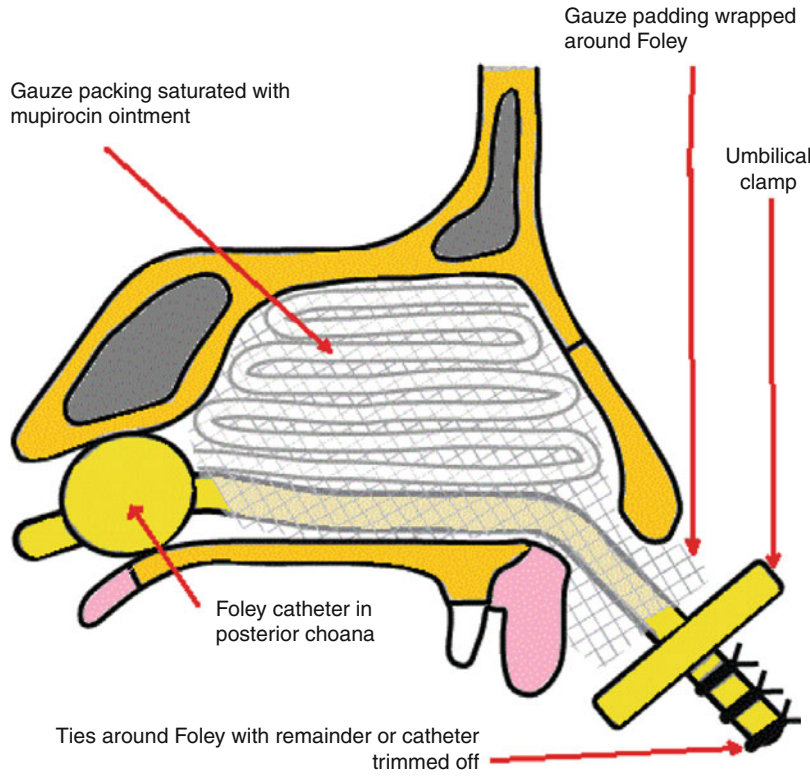

Fig. 1.6 Technique of posterior nasal packing using Foley's catheter where the balloon is inflated against the posterior concha

assessment [40]. In children, secondary interventions should be postponed due to the growth of nasal bones unless significant respiratory affection or psychological impact exists. Secondary interventions include a diverse magnitude of rhinoplasty and septoplasty techniques to achieve optimum symmetry, contour, and nasal projection.

Obstruction of airflow after nasal trauma can result from septal hematoma, septal deviation, or collapse of the internal nasal valve. Detailed examination of the nasal cavity is required to determine the exact cause. Positive *Cottle test* (outward stretching of the cheeks resulting in improved airflow) may require using spreader grafts which should be placed between the septum and upper later cartilages, thus increasing the internal nasal valve angle [35].

Postoperative epistaxis is common and results from either anterior or posterior nasal bleeding. Good nasal inspection and suction are required to assess the site of bleeding. Posterior nasal packing is done through various techniques including introduction of tied cotton gauzes transorally or using nasally introduced balloon catheters to be inflated at the site of bleeding (Fig. 1.6). The patient should be kept upright with slight head flexion to prevent blood from going into the nasopharynx. Bleeding can also be controlled via direct pressure, chemical cautery with silver nitrate, and local hemostatic agents.

One of the rare complications of nasal trauma is development of *septal hematoma*. This can be either unilateral or bilateral and usually presents with airway obstruction or pain. It can be detected on nasal examination in the form of a bulge at the region of Kiesselbach's plexus. This hematoma develops between the septal cartilage and perichondrium and if left untreated may result in septal erosion leading to septal perforation, saddle-shaped nasal deformity, or abscess formation with intracranial extension of infection. It should be treated through incision and drainage with placement of nasal packs to prevent re-accumulation of the hematoma. Antibiotic coverage is also required to prevent infection.

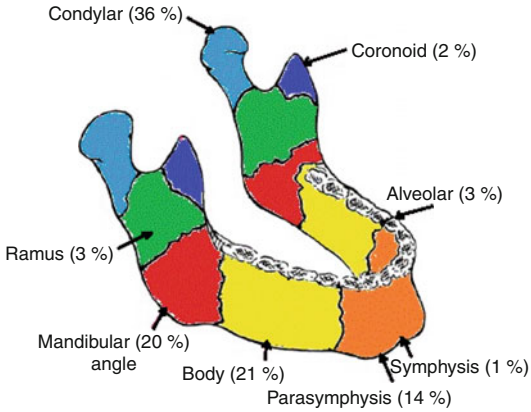

Fig. 1.7 The different anatomical regions of the mandible with the percentages of their traumatic injury

Sometimes, septal splinting with transseptal mattress sutures is required to compress the perichondrium against the septal cartilage.

1.4.3 Mandibular Fractures

1.4.3.1 Anatomical Considerations

The mandible shares directly or provides support required for several functions including mastication, deglutition, speech, and airway maintenance. Anatomically, the mandible is formed of 7 distinct regions: the symphysis, para-symphysis, body, angle, ramus, condyle, and coronoid process. The different regions of the mandible together with the approximate percentages of their traumatic injuries are demonstrated in Fig. 1.7 [41].

Teeth anchored to the mandible can be a source of infection together with the intraoral flora.

Several muscles have their insertion in the mandible. These muscles can either support or cause displacement of the fracture site; muscles of mastication and suprahyoid muscles can cause displacement of mandibular fractures, while the masseter and medial pterygoids cause splinting of fractures of the mandibular ramus. An injury disturbing attachments of genioglossus and geniohyoid muscles will also impair the support of the tongue with airway affection. Intimate relation of the inferior alveolar and mental nerves to the mandible places them at risk of injury in the course of mandibular injuries [41].

1.4.3.2 Assessment of Mandibular Fractures

Airway assessment is the first priority when dealing with a polytrauma patient according to ATLS guidelines. Injury to the mandible or the attached muscles may lead to airway compromise [5]; therefore, initial assessment of the airway is mandatory. If a neck collar is in place, it should be loosened during mandibular examinations while maintaining immobilization of the neck as long as cervical injury is not excluded. Endotracheal intubation may be required in facial trauma if vomiting is anticipated to prevent against aspiration.

Signs of mandibular fracture include changes in occlusion (the hallmark of mandibular fracture), drooling, swelling, pain during swallowing or talking, loose teeth, mobile fracture segments, bleeding periodontium, numbness of lower lip, trismus, and sublingual hematoma. Occasionally, ipsilateral facial weakness due to facial nerve affection can result from a direct blow on the mandibular ramus. Ipsilateral facial weakness may also result from trigeminal nerve injury as a result of medial displacement of mandibular condyle. However, it should be noted that normal occlusion doesn't rule out mandibular fracture.

1.4.3.3 Classification (According to Site)

A. *Ramus of the mandible*
   1. Condylar region fractures
   2. Coracoid process fractures
   3. Ramus fractures

B. *Body of the mandible*
   1. Fracture of the angle
   2. Midbody fracture
   3. Midline fracture (symphysis)
   4. Fracture lateral to the midline
   5. Alveolar fracture

1.4.3.4 Management of Mandibular Fractures

Treatment of mandibular fractures ranges from a conservative approach with soft diet only to closed reduction, or in some cases, open reduction and internal fixation (ORIF). Conservative

treatment may be appropriate in case of nondisplaced fractures of the ramus, or in the subcondylar region, and in the absence of malocclusion.

The aim of the management strategy should be restoration of the pre-injury occlusion, reduction of displaced fractures, stabilization and fixation of fractures maximizing the potential bone healing process, and, finally, repair of soft tissue lacerations.

Fractures of the Ramus

Usually, these are "closed" fractures. The most common site is the condylar fracture.

Condylar Fractures

Most fractures are extracapsular with or without dislocation of the condylar head. The patient presents with local pain and tenderness on palpation. There will be edema over the temporomandibular joint (TMJ), deviation of the mandibular midline (deformity), and limitation of mandibular movements, especially lateral excursion away from the injured site. Condylar fractures may be bilateral (e.g., anterior open bite). Plain radiography is diagnostic.

Unilateral or bilateral fractures with no open bite are treated by encouraging early movements of the joint. Bilateral fracture with an open bite is treated by gagging the occlusion in the molar area by interposing a 6 mm thickness of black "gutta-percha" between the upper and lower molar teeth and then closing the anterior open bite with elastic traction and wiring. Splint is maintained for 5–6 weeks.

Dislocation of the Temporomandibular Joint (TMJ)

Dislocation of the TMJ occurs when the muscles of mastication contract at the time when the mouth is open to its greatest extent, also due to a blow to the mouth or chin with the mouth widely open. The patient presents with pain and locked jaw in an open bite position. There is a condyle movement to a point beyond and above the lowest point on the eminantis, and the jaw is controlled by the balanced pull of muscles, which brings the condyle back into the glenoid fossa. It is treated, under sedation and local anesthesia, with reduction by downward and backward pressure with padded thumb in the premolar area.

Temporomandibular Ankylosis

Ankylosis of the TMJ is the most common complication of fracture neck of the mandible. It may be intra- or extracapsular, partial or complete, fibrous or bony, and unilateral or bilateral. The most common cause is trauma due to birth injury, or chin trauma, in which the condyle is impacted against the glenoid fossa and results in hemarthrosis and malunion of the fracture. It may also result from primary or secondary inflammation. The patient will be unable to open his mouth. If the fracture involves the growth center, it interferes with growth of the corresponding side of the mandible. If bilateral, it will lead to "*bird face.*" It is treated with excision of the condyle (condylectomy).

Factures of the Body of the Mandible

The *clinical presentation* is with local pain, swelling, crepitus, and imperfect dental occlusion. Displacement depends on the site of the fracture, its direction, and pull of the muscles. *Treatment* is by reduction under endotracheal anesthesia with a throat pack. The normal dental occlusion is restored, and intermaxillary fixation (IMF), for 6 weeks, is performed, using arch bars, or interdental wires. Rarely, open reduction and wiring or plating is resorted to.

Fixation methods include direct wiring, interdigital wiring, arch bar wiring, transosseous wiring, gunning-type splint, and cap splinting. The period of immobilization is 5 weeks for children, 3–4 weeks for adults, and 6 weeks for the elderly. Good oral hygiene should be achieved (toothbrushing after every meal and irrigation with normal saline by Higginson syringe), and fluids or semisolid diet should be provided every 2 h.

Dentoalveolar Fracture

With fracture of the alveolus, the teeth may be avulsed, subluxed, dislocated, or fractured. The alveolar fracture should be reduced rapidly and the teeth splinted to normal ones in the upper teeth. If a segment is infected, it should be removed and the defect closed.

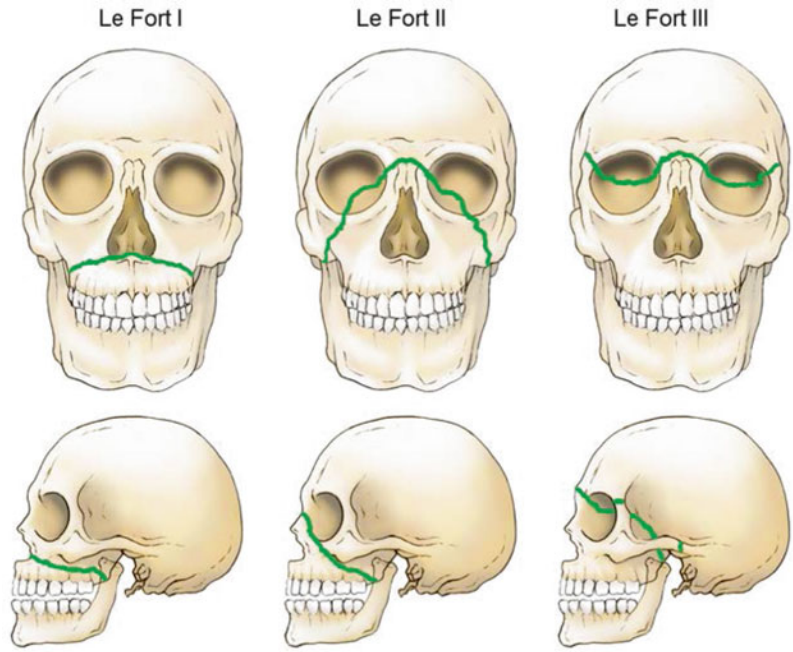

Fig. 1.8 Le Fort classification of midfacial injuries

1.4.4 Middle Third Fractures

1.4.4.1 Classification

Midfacial injuries are classified into lateral midfacial injuries (zygomatico-orbital) and central midfacial injuries, which are further anatomically classified as Le Fort I, II, and III fractures after the French surgeon *Rene Le Fort* who originally studied them in 1901 (Fig. 1.8).

- *Le Fort I*: The fracture involves only the tooth-bearing maxilla and alveolar process. The fracture line includes the alveolar process, portions of the walls of the maxillary sinuses, the palatine bone, and the lower portions of the pterygoid processes of the sphenoid bone.
- *Le Fort II*: The fracture runs from the thin middle area of the nasal and lacrimal bones and then downward, forward, and laterally crossing the inferior orbital margin. The posterior wall of the orbit is not fractured.
- *Le Fort III* (craniofacial disjunction): Nasal bones are separated from the frontal bone. There is complete separation of the maxilla, nose, ethmoids, and palatal bone from the base of the skull. The fracture line runs through the zygomatic arch, lateral orbital wall, orbital floor, medial orbital wall, and nasofrontal junction [42].

It should be noted, however, that this classification represents an oversimplification of the complex nature of such fractures, where combinations, unilateral and unusual patterns, exist. It should also be noted that some patterns of localized isolated injuries fall out of this classification (e.g., direct blow with a hammer to the maxilla causing focused fracture of the anterior maxillary sinus wall).

1.4.4.2 Assessment of Midfacial Injuries

A detailed history regarding the mechanism of trauma (high velocity versus low velocity) is required to predict the extent of injury. Associated manifestations including double vision and loss of consciousness should be taken into consideration. Assessment of the facial fractures in this type of injury usually yields overlapping and complex patterns with

facial edema and tenderness hindering accurate clinical assessment. Detection of associated injuries at this stage is also crucial, including intracranial injuries, medial canthal ligament injury (widened inter-canthal distance should raise suspicion), nasal injuries with CSF rhinorrhea, and orbital damage. At many instances, consultation of different specialties including ophthalmologists, otolaryngologists, and neurosurgeons is required. Due to the complex nature of these injuries and the high probability of associated injuries, three-dimensional CT scans represent the most accurate way to assess the injury providing excellent details for planning surgical interventions.

- *Le Fort I*: Usually, there is mobility and downward derangement of the palate and alveolus. Only a slight deformity can exist in isolated Le Forte I fractures. An element of Le Forte I injury commonly exists with the higher levels of injury. There may be only derangement of occlusion. Lengthening of the face can occur due to downward and backward movement of the maxilla. An impacted maxillary fracture can be confirmed by tapping on the teeth resulting in a dull note (known as cracked cup sign).
- *Le Fort II*: It is commonly associated with injury to the adjacent structures, and this should be meticulously looked for. This mandates exclusion of orbital injury, nasal deformity, medial canthal ligament injury, and frontal sinus fracture. Lengthening of the face is common, usually masked by marked edema.
- *Le Fort III*: Associated injury of adjacent structures is more common. Scanning for intracranial injuries is mandatory. This type is usually associated with change of facial dimensions (horizontal, anteroposterior, or vertical dimensions).

1.4.4.3 Treatment

Emergency Management

Management should follow the principles of ATLS with great concern to securing the airway, which can be easily compromised in such injuries. The mobile face is pulled upward and forward, and then, the nasal airway is cleared by suction. Indications of tracheostomy are (1) gross retroposition of the middle 1/3, which is impacted and *cannot* be corrected manually, (2) severe edema of the face, (3) uncontrollable postnasal hemorrhage, and (4) gunshot injuries of the face and jaws with extensive soft and/or hard tissue loss.

Patient Position The patient with severe MF injuries should be placed on his front with the face down. The unconscious patient is nursed on his side, while the conscious patient is nursed sitting with his head forward. Parenteral antibiotics should be considered to avoid infection.

Definitive Treatment

Preparations and Planning

Definitive treatment for midfacial fractures is usually delayed (7–10 days) after injury to allow for brain edema to subside and to stabilize the general condition of the patient. Proper preoperative investigations including CT scanning are crucial for optimum surgical planning and management of the associated injuries. In many instances, organized coordination between different specialties (ophthalmologists, neurosurgeons, otolaryngologists, and maxillofacial surgeons) is required to manage the complex nature of these injuries. Preoperative dental casts and facial photographs are valuable tools for both the surgical planning and follow-up.

Anatomical Considerations (Facial Pillars)

Two sets of supportive pillars for the midfacial skeleton exist; vertical pillars include the paired frontonasal maxillary pillars, the zygomaticomaxillary pillars, and the pterygoid processes. However, those pillars are mostly inaccessible for direct repair in case of facial fractures. The second set is the horizontal pillars, including superiorly the frontal bar, inferiorly the maxillary alveolus, and the palatal processes. In between those two levels is another horizontal pillar represented in the zygomatic arches, bodies, and the infraorbital rims [43] (Fig. 1.9).

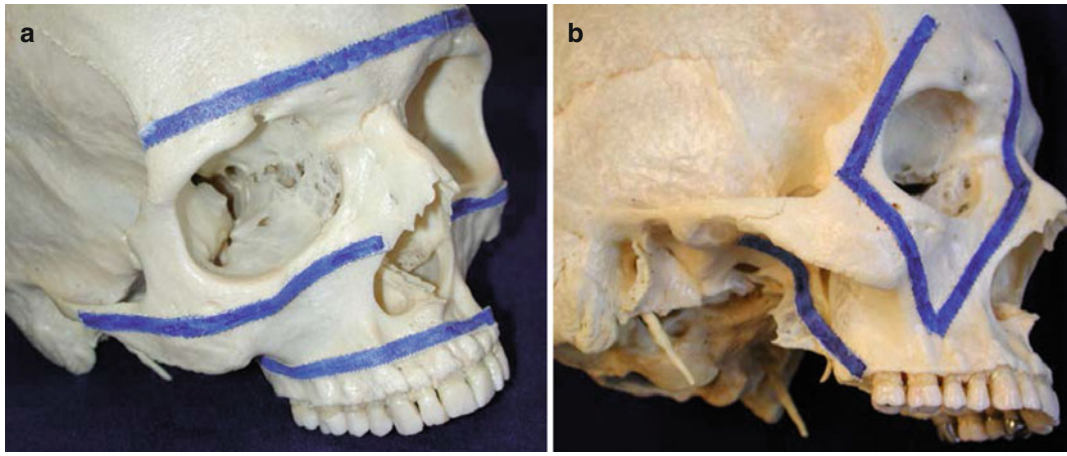

Fig. 1.9 (**a**) Horizontal pillars, (**b**) vertical pillars of the midfacial skeleton

Reduction and Fixation

As previously mentioned, repair of facial fractures and associated injuries of adjacent structures should proceed in a well-tailored multidisciplinary approach. For the facial fractures, usually sequencing of reduction and fixation is required to achieve good results with multi-level fractures. Such sequence should be tailored to every individual case.

Most midfacial fractures require open reduction and internal fixation. Conservative treatment can only be advised in certain situations where occlusion is not affected, facial contour is preserved, and no major function impairment is present.

Access for open reduction and internal fixation (ORIF) is chosen according to the site of fracture:

- Scalp: A bicoronal incision is optimum for high-level mid-zonal fractures allowing adequate access to the orbits, naso-orbital-ethmoid complex (NOE), frontonasal regions, and the skull.
- Facial: A facial incision provides exposure for orbital, NOE, and zygomatic fractures.
- Buccal: It is optimum for low-level midfacial fractures.

The broad lines for reduction and fixation of some common midfacial fractures are listed below:

- Depressed zygomatic bone fractures are elevated before dis-impaction of the central part of the face.
- The tooth-bearing portion of the upper jaw is reduced to its proper position.
- For Le Fort I, reduction of the tooth-bearing area only is performed.
- For Le Fort II, the central part of the face including the nasal complex is reduced and fixed.
- For Le Fort III, the fracture sites around the *skull base* are exposed, and various bony fragments are reduced and fixed with plates and screws (any dural defect is closed). The *orbital floor* is reconstituted, and the bony fragments, which are providing attachment for the medial canthal ligaments, are restored by transfixion wires passing through the glabellar bone. The *lower maxilla* is restored to proper occlusion with the mandible and fixed also with plates and screws.

Care should be taken not to increase the intracranial damage during manipulation of the fracture site. After achieving good anatomic reduction, postoperative elastic IMF is usually required. Placement of arch bars will also help in correcting minor occlusal issues postoperatively.

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Surgery of the Scalp

2

Mahmoud Sakr

2.1 Scalp Swellings

2.1.1 Etiology

Swellings of the scalp could be either of congenital origin or acquired in nature. The main causes of scalp swellings are summarized in Table 2.1.

2.2 Congenital Swellings

2.2.1 Inclusion (Sequestration) Dermoid Cyst

These cysts are due to inclusion of some of the surface epithelial cells (ectoderm) into the subcutaneous (SC) tissue at the lines of embryonal fusion of skin dermatomes. Although it presents later in life (childhood and adolescence), still it is considered "congenital" because it results from a congenital defect that develops between 3 to 5 weeks of intrauterine life [1–3]. The secretions of the skin (sweat and sebaceous) accumulate inside these cysts, and by time they grow slowly, forming a small cyst. In the scalp, very rarely, it may have an *intracranial extension* through a defect in the underlying bone, forming a dumbbell-shaped swelling, often called "hourglass dermoid."

Pathologically, dermoid cysts have been c1assified in three groups: (1) congenital (teratorna type), (2) congenital inclusion cysts (due to desquamation, proliferation, and edema of dermoid cells), and (3) acquired (by implantation) [2, 4]. Microscopically, dermoid cysts are different from epidermoid cysts as they contain all the skin appendages, such as hair follicles, sebaceous glands, and sweat glands [5].

Clinically, an inclusion dermoid cyst may be seen at birth but usually a few years later when it begins to fill up. There is a preponderance for females in the anterior fontanel dermoid cysts [1, 5]. The main concerns are paternal distress at the cosmetic disfigurement and definite diagnosis. Dermoid cysts rarely become big enough to cause disability and rarely become infected [1, 5–7].

The anterior fontanel is the most common site [1, 6], but other midline or paramedian locations have also been reported [1, 8]. Different sites in the body including the head, neck, and trunk are summarized in Table 2.2. Congenital dermoid cysts are usually single, small in size (1–2 cm), and ovoid or spherical in shape, with a smooth surface and well-defined borders. Consistency is cystic or soft. The cyst may fluctuate but will *not* transilluminate (*opaque*). It is *not* pulsatile, compressible, or reducible and is non-tender. The skin overlying is normal unless it is inflamed [1, 4, 7, 8]. Dermoid cysts lie deep to the skin, in the SC tissue. Unlike

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Table 2.1 Etiological classification of scalp swellings

I. Congenital	1. Inclusion (sequestration) dermoid cyst		
	2. Meningocele/encephalocele		
	3. Cirsoid aneurysm		
II. Acquired			
A. Traumatic	1. Caput succedaneum		
	2. Hematoma (subcutaneous, subgaleal [subaponeurotic], subperiosteal)		
B. Inflammatory	1. Infected granuloma		
	2. Osteomyelitis		
	3. Cock's peculiar tumor		
	4. Suppuration (abscess)		
	5. Cellulitis and erysipelas		
C. Sebaceous Cyst	Single – multiple – Cock's peculiar tumor		
D. Neoplastic	*Benign tumors*	*Malignant tumors*	
	1. Papilloma 2. Hemangioma 3. Lymphangioma 4. Cirsoid aneurysm 5. Plexiform neurofibroma 6. Lipoma 7. Osteoma 8. Chondroma	*Primary tumors* 1. Squamous cell carcinoma 2. Basal cell carcinoma 3. Malignant melanoma 4. Multiple myeloma 5. Fibrosarcoma	*Secondary tumors from:* 1. Thyroid 2. Breast 3. Bronchogenic carcinoma 4. Kidneys 5. Suprarenal glands 6. Prostate
E. Pott's puffy tumor			

Table 2.2 Different sites of inclusion dermoid cysts in the body

1. *Head*
Midline of the scalp (most common site)
Postauricular region
Preauricular (temporal) region
Inner and outer canthus
At the fusion of the mandibular and maxillary processes
Midline of the chin
2. *Neck*, (midline, anteriorly, and posteriorly):
Upper part (sublingual)
Lower part (suprasternal)
3. *Trunk:*
Midline anteriorly (presternal dermoid)
Midline posteriorly (pilonidal sinus)

sebaceous cysts, they are not attached to the overlying skin (*you can pinch the skin over it*), but like sebaceous cysts, they are *not* attached to deep structures.

Plain X-ray (PXR) of the skull may show a soft tissue mass and flattering, indentation, or pitting of the outer table of the skull. Sometimes bone defects extending up to the inner table are noted [1, 5, 7, 9]. Computed tomography (CT) scan is valuable in showing extracranial localization of the cyst and excluding the intracranial extension [9] (Fig. 2.1). Diagnostic aspiration of the cyst is *never* recommended because it increases the risk of contamination and secondary infection [1].

The differential diagnosis of inclusion dermoid cysts of the scalp inc1udes encephalocele, sebaceous cyst, lymphangioma, hemangioma, melanoma, cephalhematoma, and lipoma [1, 8, 9].

Complications include infection (abscess formation) and depression of the underlying bone resulting in increased intracranial tension. It may have an intracranial extension causing cerebral compression, intracranial infection, or recurrence (after partial excision).

Treatment of congenital inclusion dermoid cysts is complete excision with careful dissection from the underlying bone and periosteum. This provides definitive diagnosis, prevents infection, and serves cosmetic reasons [2, 5]. If there is an *intracranial connection*, it is advisable to leave it until adulthood as the bones will fuse (close) and

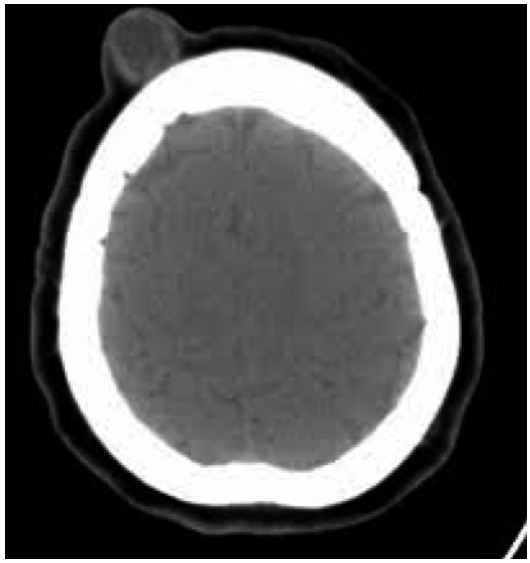

Fig. 2.1 CT scan of the skull showing no intracranial extension of the dermoid cyst in the scalp

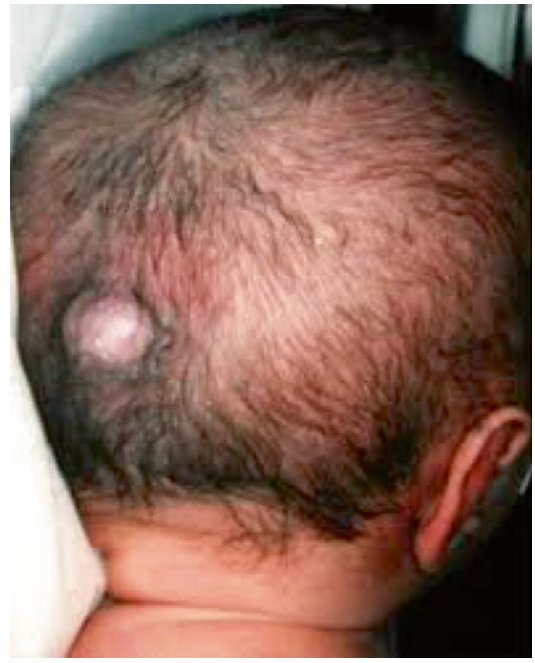

Fig. 2.2 A small encephalocele in the occipital region of the skull

obliterate the stalk. The subcutaneous part can then be excised completely. *If infected*, forming an abscess, incision and drainage should be performed. This is followed later on by excision of the wall of the cyst, to avoid recurrence.

2.2.2 Meningocele/Encephalocele

Encephalocele is sometimes known by its Latin name "cranium bifidum." It is a neural tube defect (NTD) that results in a saclike protrusion of the brain and the membranes that cover it through openings in the skull, most commonly in the occipital region. If the bulging portion contains only cerebrospinal fluid (CSF) and the overlaying membrane, it may be called a *meningocele*. If it also contains brain tissue, it may be referred to as a *meningoencephalocele* [10]. There are various types depending on location, which also has an impact on severity of the condition: occipital, frontoethmoidal, nasofrontal, and naso-orbital.

Although the exact cause is still unknown, there are several factors that have been reported to influence the risk of development of encephaloceles These include low levels of folic acid, vitamin C, and riboflavin during the first trimester of pregnancy; exposure to teratogens, trypan blue, or arsenic during early pregnancy; family history of NTDs; viral infections such as rubella or cytomegalovirus (CMV); diabetes mellitus; and maternal obesity and smoking [11, 12].

Encephaloceles are often associated with other craniofacial abnormalities or cerebral malformations [13]. The child may present with neurological deficits, hydrocephalus, spastic quadriplegia, microcephaly, ataxia, visual problems, seizures, as well as mental and growth retardation.

Usually encephaloceles are noticeable deformities and are diagnosed immediately after birth. The swelling itself is fixed to the skull and not adherent to the skin. It is tense, rounded, fluctuant, and translucent and yields an impulse on straining (crying). It may be small (Fig. 2.2) or huge in size. Prenatally these defects can be diagnosed by following tests: serum alpha-fetoprotein (AFP) levels, quadruple/triple screen, US, and amniocentesis [14, 15].

Currently, the only effective treatment of encephalocele is reparative surgery that can be carried out pre- or postnatally. Prenatal surgery

has a better outcome than that of postnatal. Prenatal fetal surgeries may include open fetal surgery and minimal invasive fetal surgery [16].

Postnatal surgery is usually performed during infancy. The extent of surgical correction depends on the location and size of the protrusion. The goals of surgical treatment include (1) closure of open skin defects to prevent infection and desiccation of brain tissue, (2) removal of nonfunctional extracranial cerebral tissue, (3) total craniofacial reconstruction, and (4) relief of intracranial pressure that may delay normal brain development. Occasionally, shunts are placed to drain excess CSF from the brain [12].

Prognosis is difficult to predict preoperatively and depends on the type of brain tissue involved and location of the encephalocele. In general, when the bulging material consists of primarily CSF, a complete recovery can occur. When a large amount of brain tissue is present in the encephalocele, there is a higher chance of perioperative complications. If surgery is successful and developmental delays have not occurred, a child can develop normally.

2.2.3 Cirsoid Aneurysm

Cirsoid aneurysms are rare arteriovenous fistulas of the scalp that are usually congenital though traumatic fistulas have also been reported [17]. In approximately 90 % of the patients, the superficial temporal artery (STA) is the main supply to the fistula, and in the remaining cases, there is usually involvement of both the STA and the occipital artery [17, 18]. It presents as an elongated, pulsating, tender mass, not attached to the skin or the skull (Fig. 2.3).

The swelling empties easily on pressure and refills very rapidly on releasing the pressure. A thrill may be felt and a loud continuous bruit may be heard. There may be throbbing headache and hemorrhage. Untreated patients can develop progressive cosmetic deformity from the markedly tortuous subcutaneous vessels and, in severe cases, scalp necrosis [18].

The skull may show a bone defect, and angiography is the investigation of choice as it can show the feeding artery. Aneurysm of the STA and metastatic deposits from follicular carcinoma of the thyroid should be ruled out prior to the diagnosis of cirsoid aneurysm. Clinical examination with imaging confirms the diagnosis.

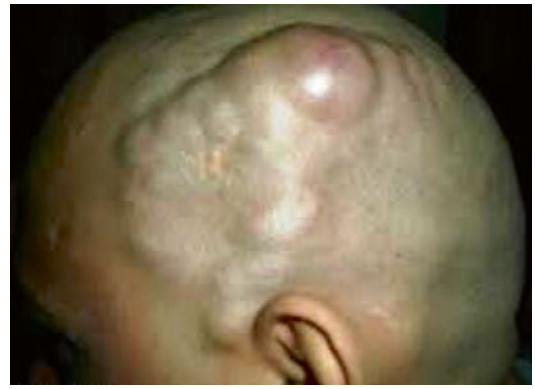

Fig. 2.3 Cirsoid aneurysm in the scalp with marked tortuous dilated vessels in a 23-year-old gentleman

Simple elective ligation and complete excision of the cirsoid aneurysm are curative [19], without significant blood loss or scalp necrosis [20]. Alternative techniques for nonsurgical closure include intra-arterial embolization, transcatheter coagulation, injection of sclerosing solutions, and irradiation; however, results have been variable [21].

2.3 Acquired Swellings

2.3.1 Traumatic

2.3.1.1 Caput Succedaneum

Caput succedaneum is an edema of the scalp at the neonate's presenting part of the head. It often appears over the vertex of the newborn's head (Fig. 2.4) due to pressure against the mother's cervix during labor. Edema in caput succedaneum crosses the suture lines and may involve wide areas of the head or it may just be a size of a large egg.

Causes of caput succedaneum include mechanical trauma of the initial portion of scalp pushing through a narrowed cervix, prolonged or difficult delivery, and vacuum extraction. It is

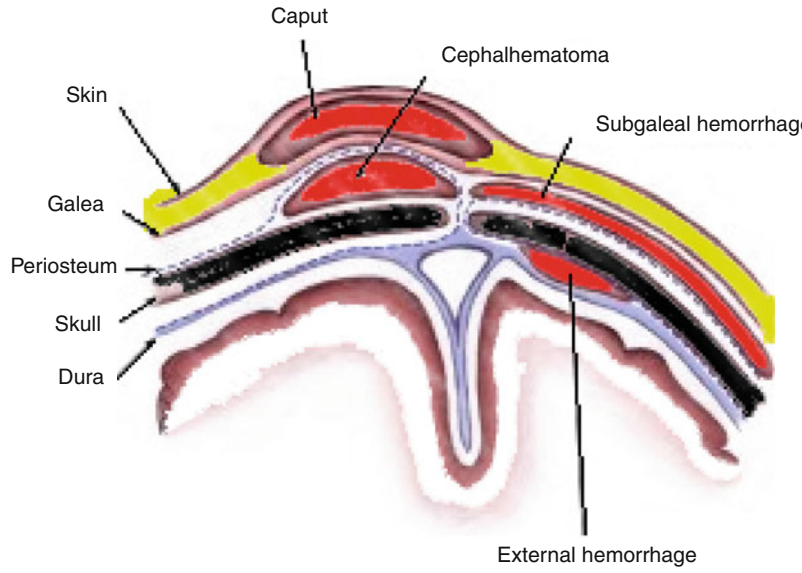

Fig. 2.4 Diagram showing the anatomical sites of caput succedaneum and cephalhematoma

more common after rupture of the membranes or in presence of too little amniotic fluid such that there is no longer a "cushion" for the baby's head. Vacuum extraction done during a difficult birth can also increase the chances of a caput succedaneum. The caput corresponds to the area where the extractor is used to hasten the second stage of labor [21].

A caput succedaneum may be detected by prenatal ultrasound (US) before labor begins. It has been reported as early as 31 weeks of pregnancy. The newborn presents with a soft and puffy scalp swelling that extends across the midline and over suture lines. It may or may not have some degree of discoloration or bruising. Jaundice may result as the bruise breaks down into bilirubin. Caput succedaneum needs no treatment as the edema is gradually absorbed and disappears on the third day of life [22].

2.3.1.2 Cephalhematoma

A cephalhematoma is a collection of blood between the skull and the periosteum of a newborn baby secondary to rupture of blood vessels crossing the periosteum. Because the swelling is subperiosteal, its boundaries are limited by the individual bones, in contrast to a caput succedaneum.

Cephalhematoma occurs in approximately 0.2–2.5 % of live births, usually due to prolonged second stage of labor or instrumental delivery, particularly ventouse. Vitamin C deficiency has been reported to possibly be associated with development of cephalhematomas [23].

The baby presents with a well-demarcated, fluctuant swelling that most commonly occurs over the parietal bone and occasionally over the occipital bone. It does not cross suture lines and there is no overlying skin discoloration. A cephalhematoma is not present at birth but appears by day 2–3 of life. It may worsen over the first few days and may take a few months to resolve as the blood clot is slowly absorbed from the periphery toward the center. In time the swelling hardens (calcification), leaving a relatively softer center that may be mistaken for a "depressed fracture," but the lip is above the level of the rest of the skull.

If severe, a cephalhematoma may be complicated with jaundice, anemia, hypotension, or infection such as osteomyelitis or meningitis. In some cases, it may be an indication of an underlying linear skull fracture.

No laboratory studies usually are necessary. Plain X-ray (PXR) of the skull or CT scanning is used if neurological symptoms appear. It will show a homogenous soft tissue density with a

sharply demarcated convex outer border that may develop a fine calcified rim over time. A skull fracture may be an associated finding.

Cephalhematoma should be differentiated from subgaleal (subaponeurotic) hematoma (collection of blood between the scalp and the periosteum), which is more extensive and more liable to complications, particularly anemia and bruising. An occipital cephalhematoma should also be distinguished from cranial meningocele, which pulsates and increases in pressure on crying. The presence of a bleeding disorder should be considered but is rare [23].

Management of cephalhematoma is mainly observation. Phototherapy may be necessary if blood accumulation is significant, leading to jaundice. Rarely, anemia can develop necessitating blood transfusion. Aspiration of accumulated blood should not be attempted because of the risk of infection and abscess formation. It may take weeks and months to resolve and disappear completely [24].

2.3.2 Inflammatory

2.3.2.1 Infected Granuloma

Repeated injury of the scalp by a sharp comb or scratching by a nail causes abrasions and results in infection and a reaction in the skin with granulation tissue and fibrous tissue formation. The lesion thus becomes more subjected to trauma, ending in a small swelling which is soft, strawberry colored, and covered by clots and dirty crusts. Diagnosis is confirmed by biopsy. It shrinks and disappears by painting with silver nitrate solution.

2.3.2.2 Osteomyelitis of Skull Bones

Osteomyelitis of the skull is common in the mastoid region, from the middle ear due to otitis media. It is also common in skull bones close to sinuses where infection occurs and at any site of trauma (e.g., fracture which causes bone infection).

2.3.2.3 Cock's Peculiar Tumor

It is *not* actually a tumor but a big sebaceous cyst in the scalp, which has been traumatized by a sharp comb causing injury and infection, thus forming "an ulcer on top of the sebaceous cyst" (Fig. 2.5). Repeated injury and infection causes elevation and the overlying skin ulcerates, simulating a malignant ulcer (epithelioma). The edges are *raised* and not everted, and there is dry sebaceous material, necrotic tissue, and pus. It may reach up to 25 cm in diameter. It is more common in women and occurs at a mean age of 65 years. Treatment is excision and skin closure.

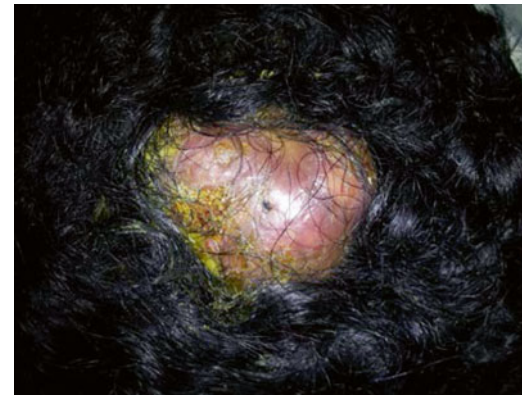

Fig. 2.5 Cock's peculiar tumor (large ulcerated sebaceous cyst)

2.3.2.4 Suppuration (Abscess)

According to location, a scalp abscess may be subcutaneous (SC), subaponeurotic, or subperiosteal. An SC abscess is usually small and tense because of the dense fibrous tissue septae in the SC layer of the scalp. A subaponeurotic (subgaleal) abscess may extend from the forehead to the occiput. It may also extend to the intracranial contents via the emissary veins. A subperiosteal (subepicranial) abscess usually results from infection of the cranial bone (osteomyelitis).

2.3.3 Sebaceous Cyst (Trichilemmal or Pilar Cyst)

Trichilemmal or pilar cysts are the commonest swellings in the scalp, occurring in approximately 5–10 % of the population [25]. Sebaceous cysts are intradermal acquired retention cysts caused by obstruction of the duct of a sebaceous gland

by dried sebum or inflammatory scarring. They may be *sporadic* or they may be autosomal dominantly (AD) *inherited* [26, 27]. Despite attempts at gene mapping, a specific disease locus and the responsible genes are not known.

Sebaceous cysts occur in all age groups, but as they are slow growing, they rarely present before adolescence. They mostly present in adulthood and middle age and have a slight male preponderance but no racial predilection [25]. The commonest sites are the scalp (90 % due to condensed hair follicle concentration) and face, followed by the scrotum, shoulders (chest), back, and abdomen [28, 29]. It never affects the palms of hands or soles of feet as they do *not* contain sebaceous glands.

A family history (Hx) may be present. Proposed clinical criteria for recognizing these autosomal dominant (AD) hereditary cases include (1) diagnosis of trichilemmal cyst in 2 or more 1st- or 2nd-degree relatives, (2) age of the patient at diagnosis less than 45 years, diagnosis of multiple or large (>5 cm) cysts, and diagnosis of the rare histologic features such as proliferating and ossifying cysts [30].

Trichilemmal cysts are solitary in 30 % and multiple in 70 % of patients [31]. The patient complains of a painless skin-colored swelling (unless there is infection) (Fig. 2.6), which is smooth, mobile, well defined, and cystic or firm in consistency [25]. There is a *punctum*, which is the opening of the occluded sebaceous duct. The swelling may be indented due to its doughy sebaceous material inside. The skin over the cyst *cannot* be pinched because of its intradermal nature. Squeezing causes the sebaceous material to come out via the punctum. Sometimes a cyst will discharge its contents spontaneously and then regress or even disappear.

A sebaceous cyst may present by any of its complications, which include (1) infection, which results in abscess formation, (2) Cock's peculiar tumor (proliferating trichilemmal cyst), (3) sebaceous horn (a sebaceous cyst with repeated leak of sebaceous material and its dryness and hornification due to friction and lack of cleanliness) (Fig. 2.7), and (4) malignant transformation into a sebaceous adenocarcinoma, which is exceedingly rare but can occur. Rapid growth is unusual and may be a sign of malignancy. Other suspicious features include non-scalp location, size larger than 5 cm, an infiltrative growth pattern, and (5) atrophy of the hair follicles and baldness of the scalp due to the presence of many cysts [25].

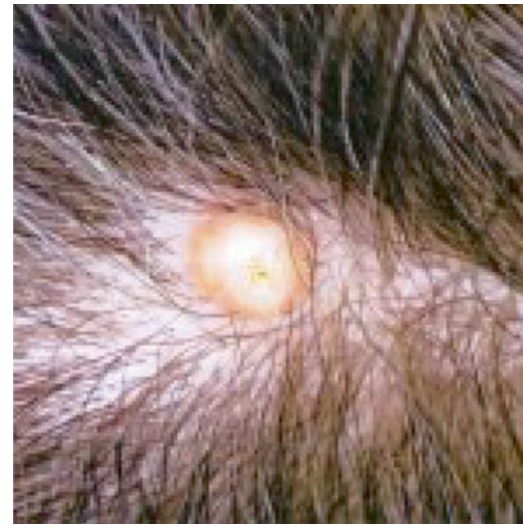

Fig. 2.6 Sebaceous cyst in the scalp; firm and smooth

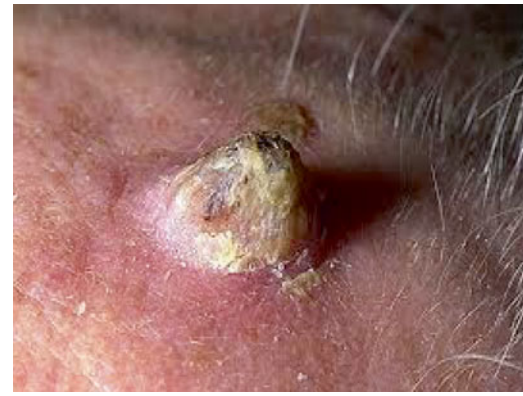

Fig. 2.7 Sebaceous horn in the scalp

Radiography of the head, CT scanning, and MRI may be needed to differentiate midline scalp lesions that may have a connection to the meninges or the central nervous system. Inflamed, ruptured cysts may have an infectious etiology. Wound culture can elucidate infection and guide therapy if necessary. However, the cyst should be excised and submitted for histopathology in order

to exclude carcinoma, particularly nodular or nodulocystic basal cell carcinomas [32].

A sebaceous cyst should be differentiated from other diseases of the sebaceous gland (sebaceous adenoma or adenocarcinoma), dermoid cyst, acne keloidalis nuchae, lipoma, pilomatrixoma, and steatocystoma multiplex. Its cyst is treated by excision under local or general anesthesia through an elliptical incision around the punctum [33]. If infected, treatment is by incision and drainage to be followed later (after 4–6 weeks) by excision of the walls of the cyst to avoid recurrence. Systemic antibiotics are usually *not* necessary. Most proliferating trichilemmal cysts are cured with complete surgical removal [28]. In the very occasional instances when multiple proliferating trichilemmal cysts require several local excisions [34], additional radiotherapy and/or chemotherapy may be considered [35].

2.3.4 Neoplastic

2.3.4.1 Soft Tissue Swellings

Lipoma: It may be subcutaneous, subaponeurotic, or subperiosteal.

Turban tumor: It presents as irregular masses, which may cover the whole scalp, looking like a "turban." It is a descriptive term and may be caused by:

(a) *Multiple cylindromata:* Turban tumor is most often used to describe multiple cylindromata, which present as multiple, firm, pink nodules in the scalp (Fig. 2.8).

(b) *Nodular multiple basal cell carcinoma:* Firm and retain their pearly white appearance and covering of fine blood vessels.

(c) *Multiple hidradenomata:* Multiple sweat gland tumors form soft boggy swellings in the scalp. Although soft, they are not fluctuant and cannot be compressed or indented.

(d) *Plexiform neurofibroma:* It is the rarest of all and is usually associated with neurofibromata in other sites and "cafe au lait" patches.

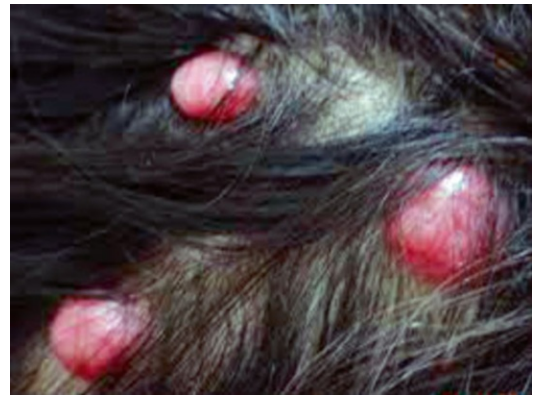

Fig. 2.8 *Turban tumor.* Note the multiple pink nodules scattered in the scalp

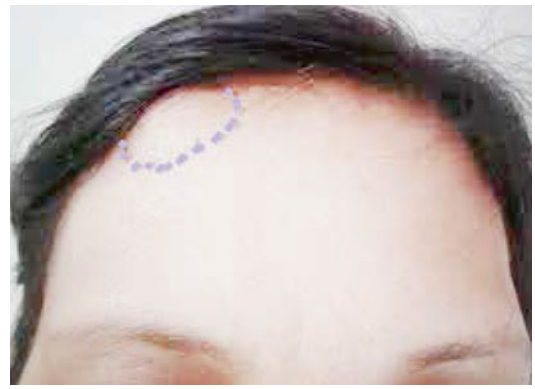

Fig. 2.9 Ivory osteoma of the skull. Note the small rounded swelling

2.3.4.2 Bony Swellings

Ivory Osteoma of the Skull (Calvaria)

This is an osteoma of the cortical bone that forms the outer table of the skull, particularly the frontal, parietal, or occipital bones. The inner table is only rarely involved by itself, and this suggests some protection by the dura mater. Osteomas are the most common primary benign tumors of the calvaria, affecting approximately 0.4 % of the general population and occurring more often in females than in males (2:1).

Osteomas of the skull appear during adolescence and young adult life as a small (<2 cm) hard swelling (Fig. 2.9) but may occasionally attain enormous dimensions. They are most often

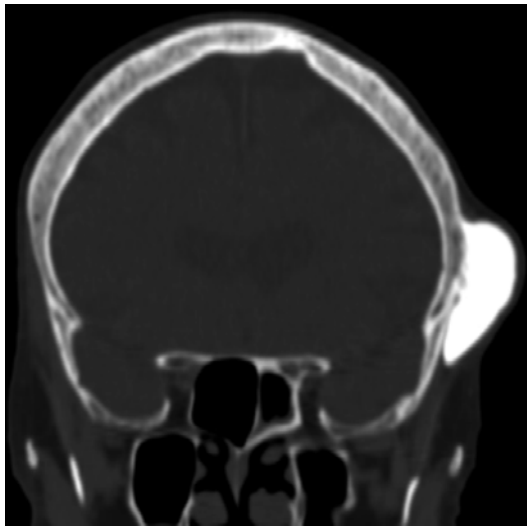

Fig. 2.10 CT scan showing an osteoma of the skull

asymptomatic masses found incidentally; however, a palpable protrusion or cosmetic deformity may occur if a calvarial osteoma is large.

The radiographic study and the CT scan (Fig. 2.10) presentation of an osteoma are usually diagnostic. Typically, they will show an eburnated (ivory-like) smooth round mass of bone arising from the periosteum of the outer table of the skull. Osteomas are sharply marginated and homogeneously dense but may occasionally show lobulation [36].

No treatment is required for asymptomatic lesions. Complete surgical excision is possible for symptomatic relief, cosmetic reasons, or cranial nerve decompression.

Multiple Myeloma

In multiple myeloma, the plain X-ray is diagnostic. It shows multiple radiolucent bone defects without reaction around (Fig. 2.11). Other characteristic clinical features of multiple myeloma should be also present.

In 2003, the International Myeloma Working Group [37] agreed on diagnostic criteria for symptomatic myeloma, asymptomatic myeloma and monoclonal gammopathy of undetermined significance (MGUS), which was updated in 2009 [38].

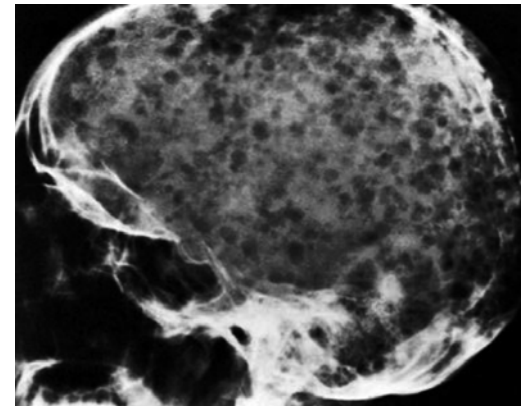

Fig. 2.11 PXR of the skull showing multiple radiolucent shadows with no reaction around, characteristic of multiple myeloma

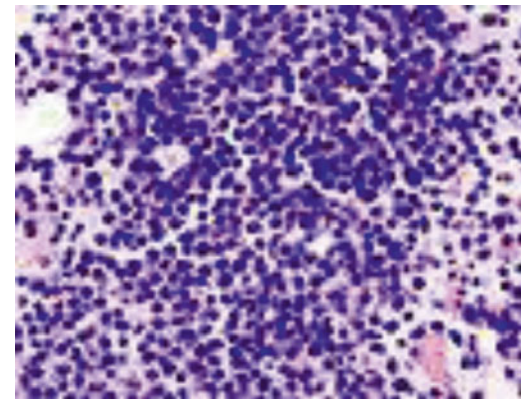

Fig. 2.12 Bone marrow aspirate showing the histologic correlate of multiple myeloma under the microscope (H&E stain)

Symptomatic Myeloma

1. Clonal plasma cells >10 % on bone marrow biopsy (Fig. 2.12) or (in any quantity) in a biopsy from other tissues (plasmacytoma)
2. A monoclonal protein (paraprotein) in serum or urine
3. Evidence of end-organ damage felt related to the plasma cell disorder commonly referred to by the acronym "CRAB": calcium (elevated calcium >2.75 mmol/L), renal insufficiency attributable to myeloma, anemia (hemoglobin <10 g/dL), and bone lesions (lytic lesions or osteoporosis with compression fractures).

Asymptomatic/Smoldering Myeloma

1. Serum paraprotein >30 g/L
2. Clonal plasma cells >10 % on bone marrow biopsy
3. No myeloma-related organ or tissue impairment

Monoclonal Gammopathy of Undetermined Significance (MGUS)

1. Serum paraprotein <30 g/L
2. Clonal plasma cells <10 % on bone marrow biopsy
3. No myeloma-related organ or tissue impairment

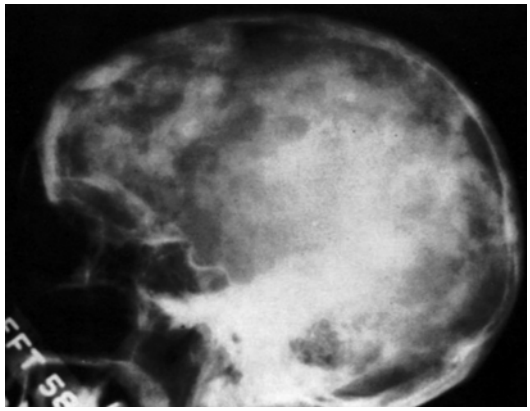

Fig. 2.13 Osteoblastic (osteosclerotic) secondaries from primary prostatic cancer

Secondaries (Metastases)

They are the most common tumors of the skull. The primary tumors, which give bone metastases (blood-borne and start in the diploe) are those of the thyroid, breast, bronchi, kidneys, adrenal glands, and the prostate. Metastases from the prostate are usually osteoblastic (steosclerotic) (Fig. 2.13) and not osteolytic. The swellings are painful and tender, with ill-defined edges and hard consistency (or soft depending on vascularity). Some extremely vascular metastases show pulsations.

2.3.5 Pott's Puffy Tumor

It is *not* actually a tumor. It is simply "*edema*" of the overlying skin and SC tissue, over an area of *osteomyelitis* of the skull, or in front of an intracranial lesion such as a chronic intracranial abscess in a "silent" area so that it presents only on the outside of the skull. In the frontal region, it is due to imperfectly treated acute frontal sinusitis. About 10 days after the onset, considerable pyrexia with severe pain and tenderness over the sinus strongly suggests osteomyelitis.

A useful approach for diagnosis of a scalp swelling is to determine whether it is *cystic, pulsating, or solid*.

Cystic swellings	Pulsating swellings	Solid swellings
1. Sebaceous cyst 2. Inclusion dermoid cyst 3. Cephalhematoma 4. Meningocele 5. Hemangioma 6. Lymphangioma	1. Cirsoid aneurysm 2. Sarcoma of the skull 3. Encephalocele	*A. Soft tissue swellings:* 1. Lipoma 2. Turban tumor *B. Bony swellings:* 1. Ivory osteoma 2. Multiple myeloma 3. Secondaries

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Surgery of the Salivary Glands

3

Mahmoud Sakr and Tarek Koraitim

3.1 Introduction

The human salivary gland system can be divided into two distinct exocrine groups. The *major salivary glands*, which include the paired parotid, submandibular, and sublingual glands, and *the minor salivary glands*, which are hundreds of small glands lining the mucosa of the upper aerodigestive tract. The major function of the salivary glands is to secrete saliva, which plays a major role in lubrication, digestion, immunity, and the overall maintenance of homeostasis within the human body.

3.2 Embryology and Developmental Disorders

Development of the major salivary glands is thought to consist of three main stages [1, 2]. The *first stage* is marked by the presence of a primordial anlage (from the German verb *anlagen*, to set a foundation) and the formation of branched duct buds due to repeated epithelial cleft and bud development (Fig. 3.1). Ciliated epithelial cells form the luminal lining, while external surfaces are lined by ectodermal myoepithelial cells [3]. During the *second stage*, the early appearance of lobules and duct canalization take place resulting in the appearance of primitive acini and distal duct regions.

The *third stage* is marked by maturation of acini and intercalated ducts and reduced prominence of interstitial connective tissue.

The primordial *parotid gland* is the first to appear, during the sixth gestational week, when oral ectodermal outpouchings extend into the adjacent mesoderm and serve as the site of origin for growth of glands. After a short journey of

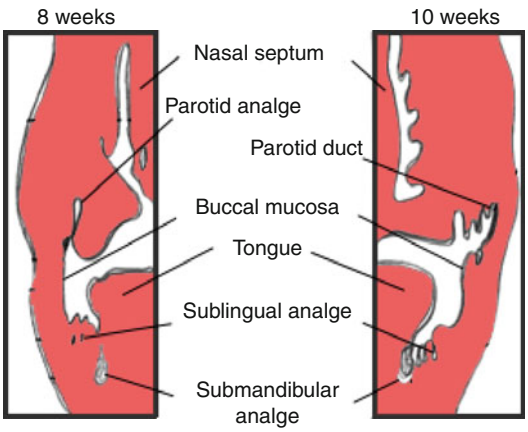

Fig. 3.1 Embryological development of the salivary glands

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dorsal and lateral migration, the parotid gland resides in the preauricular region. The facial nerve arbitrarily divides the gland into superficial and deep lobes by the 10th week of gestation. A fully developed capsule from the nearby mesenchyme surrounds the gland by the 12th week [1].

During the sixth week of embryonic life, small buds appear in the floor of the mouth lateral to the tongue and extend posteriorly around the mylohyoid muscle into the submandibular triangle. These buds eventually develop into the *submandibular glands*. A capsule from the surrounding mesenchyme is fully formed around the gland by the third-gestational month [2].

During the ninth embryonic month, the *sublingual gland* anlage is formed from multiple endodermal epithelial buds in the paralingual sulcus of the floor of the mouth. Absence of a capsule is due to infiltration of the glands by sublingual connective tissue. Intraglandular lymph nodes (LNs) and major ducts also do not generally develop within sublingual glands. Upper respiratory ectoderm gives rise to simple tubuloacinar units. They develop into the *minor salivary glands* during the 12th intrauterine week [4].

Aside from heterotopic salivary glands, developmental disorders of these glands are rare. Reported congenital anomalies include aplasia (absence) [5–8], gland duplication [9], as well as congenitally atretic, imperforate, ectatic, and duplicated ducts [10, 11]. Agenesis may be associated with abnormalities of the lacrimal apparatus and may also be genetically transmitted [7]. Agenesis may be partial or total or unilateral or bilateral and may involve more than one salivary gland. Association with specific syndromes such as Levy-Hollister syndrome, Down syndrome, or Klinefelter syndrome has been reported. The true incidence of parotid agenesis is unknown since most of the cases are asymptomatic. Symptoms include dental caries, thirst, xerostomia, and gingival infections. Oral examination reveals absence of the papilla of Stensen's duct. When suspected, magnetic resonance imaging (MRI) is the imaging tool of choice to demonstrate glandular bed being replaced by fat. Congenital parotid fistula is another developmental disorder.

Tumorlike presentations of maldevelopment include rare hamartomas of the hard palate [12] and unusual cystic choristomas of the submandibular gland [13], which appear to be a mixture of epithelium of both ectodermal and endodermal derivation. The congenital salivary gland anlage tumor or congenital pleomorphic adenoma (PA) is thought to represent a hamartoma of minor salivary gland origin [14].

3.3 Histology

All glands in general are derived from epithelial cells and consist of *parenchyma* (secretory unit and associated ducts) and *stroma* (surrounding connective tissue that penetrates and divides the gland into lobules). Salivary glands are exocrine glands that secrete saliva through ducts from a flask-like, blind-ended secretory structure called *the salivary acinus*.

The acini of the *parotid gland* are lined exclusively by *serous* cells. The acini of the *submandibular gland* are also mainly serous (90 %) but also contain mucous as well as mixed acini. The *sublingual gland* is composed primarily of mucous acini. *Minor salivary glands* are either mucinous or seromucinous except for the serous *Ebner's glands* on the posterior aspect of the tongue. This histological description results in parotid thin watery, devoid of mucins, saliva; submandibular mixed saliva; and sublingual more viscous, mucin-rich, saliva [15].

The acini are drained by a series of ducts, the smallest of which are the intralobular intercalated ducts, which are comprised of an irregular myoepithelial cell layer lined with squamous or low cuboidal epithelium and in turn drain into the striated ducts. The striated ducts are also intralobular but lined by a different epithelial arrangement. Striated ducts drain into the interlobular ducts. In the major salivary glands, these ducts drain into major excretory ducts (*Stensen's* duct in the parotid gland, *Wharton's* duct in the submandibular gland, and *Bartholin's* duct in the sublingual gland), and the epithelium of these ducts changes to squamous as they exit through the oral mucosa. The *minor salivary gland* duct

system is simpler than that of the major salivary glands, where the intercalated ducts are longer and the striated ducts are either less developed or not present [15].

3.4 Physiology

The major function of the salivary glands is the production of saliva, which performs many functions including lubrication of the food bolus, maintaining the pH of the oral cavity within 6–7, maintaining the teeth integrity, fighting bacteria, aiding taste and digestion, as well as providing a continuous lavaging biofilm for the oral cavity [4].

The amount of saliva is affected by the total body fluid volume, and so dehydration decreases its amount and so one feels thirsty. Many agents and viruses are actively excreted in saliva. Mercury poisoning can manifest as stomatitis and lead poisoning by the gingival deposition of lead. The rabies and poliomyelitis viruses are excreted into saliva and can be transmitted in this manner. The two main triggers for salivary production are mastication and gustatory stimuli. Acidic foods are the best stimulus and sweet tastes the least. Olfaction is surprisingly a poor secretory stimulus.

3.4.1 Salivary Flow Rates

In normal circumstances the minimal total unstimulated salivary flow rate is defined as 0.1 mL per minute, and the minimal stimulated flow rate is 0.2 mL per minute. Maximal stimulated flow rate is 7 mL per minute. The 24-h volume of salivary secretion has been estimated to be 500–1,500 mL. Salivary flow in the unstimulated glands is produced primarily by the submandibular glands (65 %), with the parotid, sublingual, and minor glands providing 20 % and 7–8 % of the flow, respectively. Once stimulated, the relative contributions of the parotid and submandibular glands are reversed, with the parotid gland supplying greater than 50 % of the flow. The minor salivary glands, independent of stimulation, produce less than 10 % of the total flow.

Bilateral tympanic neurectomies (bilateral parasympathetic denervation) have been used for patients with ptyalism (drooling) with good initial results. Others, however, advocate bilateral parotid duct rerouting with or without bilateral submandibular gland excision for long-term management of drooling. Intraglandular botulinum toxin has been reported to have good results for patients with hyper-sialorrhea. Most resting salivary gland flow arises from the submandibular glands, and surgery should be focused on this gland to control uncontrolled sialorrhea. Salivary flow rates are independent of age. Xerostomia in the elderly is probably the result of systemic disease or medication side effects. Salivary gland hypofunction is defined as an unstimulated flow rate less than 0.1 mL per minute or a 50 % reduction below basal rates if they have been determined. Basal flow rates should be recorded after 15 years of age [4, 16].

3.5 Parotid Glands

The parotid gland is the largest of the major salivary glands and consists of two lobes: superficial and deep with regard to its relation with the facial nerve. It is wrapped around the mandibular ramus and secretes saliva through the parotid (*Stensen's*) duct and the oral cavity. The word "parotid" (*paraotic*) literally means around the ear.

3.5.1 Surgical Anatomy

The parotid gland is a paired organ, weighing about 15–30 g each. Its superficial lobe overlies the lateral surface of the masseter muscle and is bounded superiorly by the zygomatic arch, while its deep lobe is located in the pre-styloid compartment of the parapharyngeal space between the mastoid process posteriorly, the ramus of the mandible anteriorly, and the external auditory meatus (EAM) superiorly. Medially, the gland reaches to the styloid process. Inferiorly, the parotid tail extends down to about the anteromedial margin of the sternocleidomastoid (SCM) muscle.

Several structures run through the parotid gland. These are (1) the terminal segment of the external carotid artery (ECA), which gives the posterior auricular artery just before entering the gland and terminates by dividing into the superficial temporal artery and the maxillary artery; (2) retromandibular vein; (3) facial nerve which soon gives 5 branches inside the gland radiating forward superficial to the vein and artery; and (4) parotid lymph nodes (LNs).

3.5.1.1 Parotid Fascia

The deep cervical fascia continues superiorly to form the parotid fascia which is split into superficial and deep layers to enclose the parotid gland. The thicker superficial fascia extends up to the zygomatic arch, while the deep one extends to the stylomandibular ligament, which separates the superficial and deep parotid lobes. The parotid fascia forms a dense inelastic capsule.

3.5.1.2 Parotid Duct (Stensen's Duct)

The parotid gland drains its serous secretions through a long duct (Stensen's duct) that arises from the most anterior superficial portion of the gland and travels parallel and 1 cm below the zygoma, running on the lateral surface of the masseter, just deep to the skin, and then it finally dives at an angle of about 90° at the anterior border of the masseter to pierce the buccal pad of fat and the buccinator muscle and opens in the oral vestibule opposite the 2nd maxillary molar over the summit of a papilla [4, 17].

3.5.1.3 Accessory Parotid Gland

Accessory parotid tissue (lobe or gland) may sometimes exist and come to reside over the masseter muscle between the zygomatic arch and Stensen's duct. As proved histologically, this accessory glandular tissue secretes mucous in addition to serous secretions drained through a single short duct that joins the main duct [18].

3.5.1.4 Surface Anatomy of the Parotid Gland

The *anterior* border of the gland corresponds to a line that extends from the ear tragus to the posterior border of the masseter opposite the angle of the mouth, the *inferior* border from there to below and behind the angle of the mandible, the *posterior* border from there to the mastoid process, and the *superior* border from the mastoid process to the ear tragus. Surface anatomy of the *parotid duct* corresponds to the middle third of an imaginary line that extends from the tragus of the ear to the midportion of the upper lip.

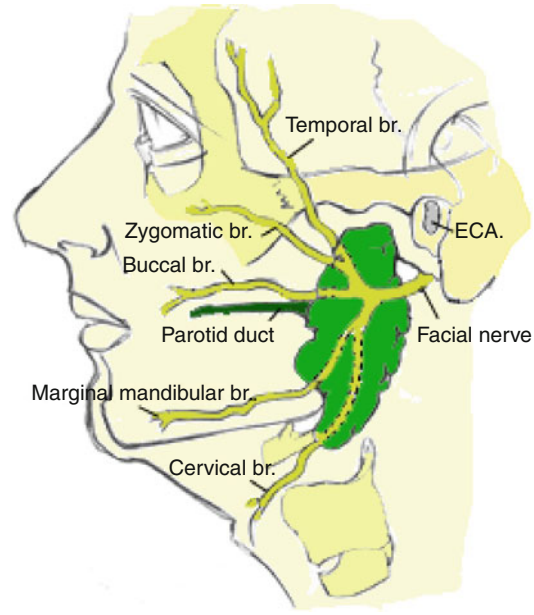

Fig. 3.2 Anatomy of the facial nerve. It divides first into two divisions: upper temporofacial and lower cervicofacial. The upper division gives off the temporal, zygomatic, and buccal branches, while the lower gives off the marginal mandibular and cervical branches

3.5.1.5 Nerve Supply

The facial nerve (CN VII) exits the skull base through the stylomastoid foramen, which is slightly posterolateral to the styloid process and anteromedial to the mastoid process. The nerve immediately gives off three motor branches for the posterior belly of the digastric, the stylohyoid, and the postauricular muscles. Its main trunk then enters the posterior portion of the gland. Inside the gland, at the pesanserinus (*Latin*: goose's foot), it divides into upper temporofacial and lower cervicofacial division approximately 1.3 cm from the stylomastoid foramen (Fig. 3.2). The temporofacial division gives off the temporal, zygomatic, and buccal branches, while the cervicofacial gives off the marginal mandibular and cervical branches.

The *temporal branch* passes with the superficial temporal vessels over the zygoma to supply the frontal belly of occipitofrontalis, orbicularis oculi, corrugator supercilii, and anterior and superior auricular muscles. The *zygomatic branch* passes over the periosteum of the zygomatic arch to supply the zygomatic, orbital, and infraorbital muscles. The *buccal branch* travels with the Stensen's duct to supply the buccinator, upper lip, and nostril muscles. The *marginal mandibular branch* travels along the inferior border of the parotid gland just deep to the platysma muscle but superficial to the posterior facial and retromandibular veins, to supply the lower lip and chin muscles. Running in the same plane is the *cervical branch*, which supplies the platysma muscle. All the muscles supplied by the facial nerve are muscles of facial expression.

The *great auricular nerve* (C2, C3) is a sensory branch of the cervical plexus that provides general sensation to the parotid gland and the skin of the posterior portion of the ear pinna and the ear lobule. It accompanies the external jugular vein along the lateral surface of the SCM muscle toward the tail of the parotid gland, and there it splits into anterior and posterior branches. It is often injured during parotidectomy leaving the ear lobule senseless. Its harvesting for facial nerve grafting may be needed when the latter is injured or sacrificed.

The *auriculotemporal nerve* (ATN) is a branch of the mandibular division of the trigeminal nerve (CN V). After exiting the foramen ovale, it runs parallel to the superficial temporal vessels and anterior to the external auditory canal to innervate the skin and scalp immediately anterior to the ear.

The *glossopharyngeal nerve* (CN IX) provides visceral secretory innervation to the parotid gland. The nerve carries preganglionic parasympathetic fibers from the inferior salivatory nucleus in the medulla through the jugular foramen. Then, a small branch of the CN IX (Jacobsen's nerve) reenters the skull through the inferior tympanic canaliculus and into the middle ear to form the tympanic plexus.

The preganglionic fibers then travel as the lesser petrosal nerve into the middle cranial fossa and out through the foramen ovale to synapse in the otic ganglion. Postganglionic parasympathetic fibers exit the otic ganglion to join the ATN in the infratemporal fossa. The ATN enters the substance of the gland from its deep aspect along the neck of the mandible and emerges from the gland just inferior to the root of the zygomatic arch. The ATN carries fibers that innervate the parotid gland for secretion of saliva (Fig. 3.3).

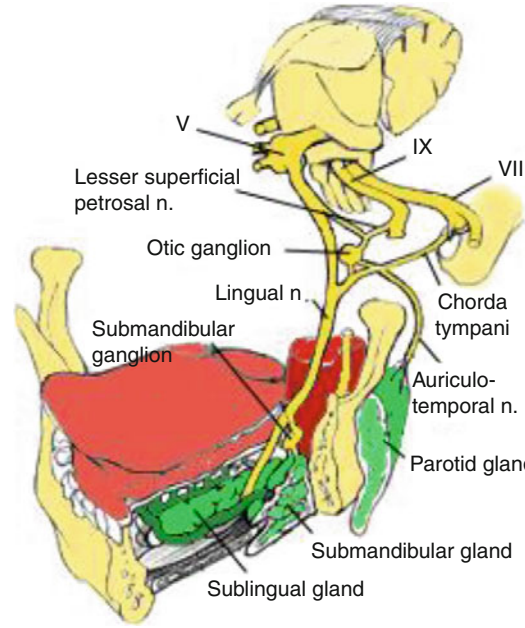

Fig. 3.3 Parasympathetic innervations of the salivary glands

Postganglionic sympathetic fibers innervate the salivary glands, sweat glands, and cutaneous blood vessels, mediating vasoconstriction, through the external carotid plexus from the superior cervical ganglion. Acetylcholine serves as the neurotransmitter for both postganglionic sympathetic and parasympathetic fibers. This physiologic coincidence allows for the occasional development of "gustatory sweating," also known as *Frey's syndrome*, following parotidectomy [19].

3.5.1.6 Arterial Supply

The parotid gland receives its blood supply through branches of the external carotid artery (ECA), mainly through the *posterior auricular artery*. The ECA travels parallel to the mandible under the posterior belly of digastric muscle. It then travels medial to the gland and splits into its two terminal branches: the superficial temporal

artery that leaves the superior portion of the gland and the maxillary artery that leaves the medial portion of the gland. The *transverse facial artery* is a branch of the superficial temporal artery that runs anteriorly between the zygoma and parotid duct to supply it together with the parotid gland and the masseter muscle.

3.5.1.7 Venous Drainage

The *retromandibular vein*, formed by the union of the maxillary and the superficial temporal veins, runs through the parotid gland just deep to the facial nerve. It drains into the external jugular vein. There are many variations as regards the surgical anatomy of the retromandibular vein.

3.5.1.8 Lymphatic Drainage

As a result of late encapsulation during embryological development, the parotid gland, unlike the submandibular and sublingual glands, contains intraparenchymal lymph nodes (LNs), with salivary gland structures, usually ducts and less frequency acini, in the intra- and peri-parotid LNs. Ninety percent of the nodes draining the parotid gland are located in the superficial layer between the gland and its capsule (3–20 nodes). These drain the parotid gland, external auditory canal, pinna, scalp, eyelids, and lacrimal glands. Deep LNs, residing on the lateral wall of the pharynx, drain the gland, external auditory canal, middle ear, nasopharynx, and soft palate. Both groups drain into level II of cervical LNs.

3.5.1.9 Parapharyngeal Space (PPS)

Tumors of the deep lobe of the parotid gland often extend medially into the PPS, which is shaped like an inverted pyramid, where the greater cornu of the hyoid bone serves as the *apex* and the petrous bone of the skull base as the *base*. The PPS is bound *medially* by the lateral pharyngeal wall, which consists of the superior constrictor muscles, buccopharyngeal fascia and tensor veli palatine. It is bounded *laterally* by the ramus of the mandible and the medial pterygoid muscle, *anteriorly* by the pterygoid fascia and the pterygomandibular raphe, and *posteriorly* by the carotid sheath and prevertebral fascia.

A line from the styloid process to the medial portion of the medial pterygoid plate divides the PPS into pre- and post-styloid compartments. The *pre-styloid* one contains the deep parotid lobe, internal maxillary and ascending pharyngeal arteries, and inferior alveolar, lingual, and ATNs. The *post-styloid* compartment contains the internal jugular vein (IJV), carotid artery, vagus nerve (tenth cranial nerve, CN X) all within the carotid sheath, as well as the cranial nerves IX, XI, and XII and the cervical sympathetic chain. Thus, neurogenic tumors or paragangliomas arising from these nerves lie in this post-styloid compartment [20].

Hints and Tips

- The parotid bed is an irregular space located between the ramus of the mandible, the EAM, the mastoid and styloid processes, the digastric, and SCM muscles.
- Structures entering the parotid gland exit from its posterior, superior, inferior, and anterior surfaces. The posterior auricular artery exits from the posterior aspect of the gland. The superficial temporal artery and vein, ATN, and temporal branches of the facial nerve are seen at the superior margin of the gland. Inferiorly, the retromandibular vein exits the parotid gland. Emanating from the entire facial margin of the gland are the terminal branches of the facial nerve, grouped into five major branches: the temporal, zygomatic, buccal, mandibular, and cervical branches.
- General sensation to the parotid gland is provided by the great auricular nerve of the cervical plexus. Sympathetic innervation is supplied by the carotid plexus, whereas secretomotor innervation is supplied by the glossopharyngeal nerve and delivered to the gland by the ATN.
- The gland cannot be moved over the deep structures and becomes more prominent when the patient clenches his teeth by contracting the masseter muscles.

3.5.2 Evaluation of the Parotid Gland

3.5.2.1 Clinical Evaluation

Despite the availability of modern technology in diagnosis of parotid gland disorders, great care should be taken during history taking and thorough physical examination as they still play important roles in the clinical diagnosis of the patient.

History Taking

Patients with parotid gland disorders usually complain of swelling, pain, *xerostomia* (dry mouth), foul taste, and occasionally *sialorrhea* (excessive salivation). Swelling and pain during meals followed by reduction in symptoms after meals may indicate partial stenosis of the duct. *Demographic data* (age and gender) are of considerable importance. The autoimmune disorder known as Sjogren's syndrome, for example, is common in menopausal women, while *mumps* usually occurs in children.

The *medical profile* of the patient may provide helpful clues to diagnosis. Dysfunction of the gland is often associated with certain systemic disorders such as diabetes mellitus (DM), atherosclerosis, hormonal imbalances, and neurologic disorders [21, 22]. A careful *dietary and nutrition* history should not be neglected, for patients who suffer from chronic dehydration due to bulimia or anorexia or during chemotherapy are at risk for parotitis.

Drug history of the patient should also be considered, for salivary function is often affected by certain drugs such as diuretics and other antihypertensive drugs, which may cause xerostomia [21, 22]. Since xerostomia is also a debilitating consequence of radiation therapy to the head and neck, history of *prior irradiation* should be sought.

Physical Examination

Initial clinical evaluation involves careful examination of the head and neck regions. Both extraoral and intraoral examinations should be carried out in a systematic way to avoid missing any crucial signs. Bimanual palpation (extraoral with one hand and intraoral with the palmar aspects of the fingertips of the other) must be also performed to properly examine the submandibular glands.

Inspection *Extraoral inspection* is performed with the patient facing in front of the examiner, three to four feet away. The examiner should inspect symmetry, color, pulsations, and discharging sinuses on both sides of the patient. Enlargement of the parotid gland may be unilateral or bilateral. *Parotitis* typically presents as preauricular swelling, but may not be visible if deep in the parotid tail or within the substance of the gland. Neurologic deficits should also be examined. Facial nerve paralysis in conjunction with a parotid mass, for example, should raise the suspicion of a *malignant* parotid neoplasm. *Intraoral inspection* is done using a torch or headlight. The orifices of the parotid (Stensen's) ducts are inspected opposite the second upper molar tooth and the two sides compared. Saliva may be seen pouring from the non-affected side only.

Palpation With the examiner standing in front of or behind the patient, the patient's head is inclined forward to maximally expose the parotid gland region. Size, tenderness, consistency, mobility, and other features of the parotid gland and associated masses can be easily evaluated with *extraoral and intraoral palpation* owing to the superficial anatomical location of the gland.

Auscultation Rare clinical entities, such as *hemangiomas* and other vascular anomalies, may be identified by auscultation.

3.5.2.2 Imaging

For patients with no specific symptoms (swelling and pain) and unclear physical signs, imaging studies can play an important role in clarifying the etiology of the gland disorder and assist in treatment selection and planning.

Sialography

Sialography is used to evaluate sialolithiasis (or other obstructive disorders) and inflammatory and neoplastic diseases. In this technique, 0.5 to 2 mL of a suitable radiopaque liquid such as

Hypaque (sodium diatrizoate) or Lipiodol is introduced into the duct system through a fine polythene catheter, or a blunt metal cannula, and a plain-film radiograph is taken. Sialography is contraindicated in case of iodine allergy and acute sialadenitis. Any filling defect (e.g., stone), retained sections (e.g., chronic sialadenitis), stricture (e.g., inflammation), extravasation (e.g., Sjogren's syndrome), or irregular borders (e.g., tumor) are noted. Fistulae and abscesses cavities can also be displayed with this technique.

Computed Tomography (CT)

The parotid gland has low attenuation due to its high fat content and is therefore easily discernible by CT scanning. The advantage of CT imaging is the two-dimensional view of the salivary gland, which can elucidate relationships to adjacent vital structures, differentiate intrinsic from extrinsic disease, and assess the draining cervical LNs. It is also extremely valuable in defining abscess formation versus phlegmon. However, it is limited in evaluating the ductal system unless combined with simultaneous sialography (CT sialography) [23]. Differences between intrinsic and extrinsic parotid gland masses, however, are often difficult to assess especially when present in the parapharyngeal space (PPS) [24].

Magnetic Resonance Imaging (MRI)

Compared with CT, MRI provides better contrast resolution, exposes the patient to less harmful radiation, and yields detailed images on several different planes without patient repositioning. It is more often used for assessment of parapharyngeal space abnormalities especially in discriminating between deep lobe parotid tumors and other lesions, such as schwannoma and/or glomus vagale. However, MRI is inferior to CT scanning for the detection of calcification and early bone erosion. Chronic inflammation of the salivary glands and calculi are *not* indications for MRI.

3.5.2.3 Endoscopic Examination (Sialendoscopy)

Sialendoscopy is a minimally invasive technique that inspects the salivary glands using narrow-diameter, rigid fiber optic endoscopes, introduced under direct vision through the ductal orifice after its dilatation with a lacrimal probe [25]. It is well tolerated, with minimal complications, and has thus opened up a new frontier for evaluation and treatment of salivary gland disorders [26]. Direct inspection of the glandular duct and hilum is performed during lavage of the duct. Thus, in one setting, at the time of diagnosis, treatment of benign lesions can be performed [27]. Through a CO_2-laser papillotomy, sialolithectomy can be easily performed. Pharmacotherapy and laser ablation can also be performed. This relatively new technique has shown much promise in the diagnosis and treatment of chronic obstructive sialadenitis (COS) and sialolithiasis.

3.5.2.4 Biopsy

Fine-needle aspiration cytology (FNAC) is an accurate investigation for the diagnosis of a parotid mass in up to 93 % of cases [25–27]. It allows for improved patient selection for surgery since it can identify disorders such as reactive lymph nodes that might mimic parotid tumors clinically. The information gained by FNAC is thus useful for patient counseling and for surgical timing and planning. Open biopsy of the lip should be considered when the diagnosis of Sjogren's disease is contemplated.

3.5.3 Parotid Injuries and Fistulae

Successful treatment of parotid injuries depends on early recognition and appropriate early intervention. Sequelae of inadequate diagnosis and treatment include parotid fistula and sialocele formation, which are inconvenient for the patient and more difficult to treat than the initial injury.

A parotid fistula is a communication between the parotid gland (*glandular fistula*) or duct (*ductal fistula*) and the skin externally (*external fistula*) or the oral cavity internally (*internal fistula*). A sialocele is a collection of saliva beneath the skin that occurs if the duct leaks but no fistula forms or when the glandular substance, but not the duct, is disrupted.

3.5.3.1 Etiology

Causes of the fistula include: (1) penetrating or blunt injury in the region of the parotid gland, (2)

improper incision and drainage or spontaneous rupture of a parotid abscess (or sialocele), (3) intraoperative iatrogenic injury, (4) complication of parotid duct cannulation for sialography, and (5) malignant tumors invading the surface [28].

3.5.3.2 Clinical Presentation

Males are twice as likely to experience parotid duct injury as females, and the mean age of patients with parotid duct injury is approximately 30 years.

History

Important aspects of history of the wound include the circumstances surrounding the injury, precipitating cause, exact mechanism and site of injury, time of occurrence, and treatment initiated prior to presentation.

Other important aspects of the history include tobacco, alcohol, or drug use; tetanus immune status; and comorbid conditions that may place the patient at a higher risk for infection such as diabetes mellitus and immunosuppression.

Physical Examination

An internal fistula constitutes no consequences and requires *no treatment*. However, an external fistula connected with large ducts causes extreme discomfort every time the patient has a meal, smells, or even thinks of food, due to excessive outpouring of saliva on the cheek causing skin excoriation. A sialogram will determine whether the fistula is ductal or glandular.

A thorough clinical examination is necessary for proper evaluation of the overall state of health, comorbidities, nutritional status, and mental status of the patient. Important signs or symptoms related to the wound include pain, fever, edema, discharge, and/or odor. Important aspects of wound assessment include location, shape, size, type (blunt or penetrating), depth, drainage (quality, character, odor), presence of a foreign body (e.g., glass, tooth fragments), loss of tissue, tenderness, asymmetry, surrounding skin (erythema, edema, crepitus), and status of the facial nerve.

An injury classification system that divides the parotid duct into 3 regions has been devised for parotid duct injuries.

- Site A: Posterior to the masseter muscle or intraglandular (*glandular*)
- Site B: Overlying the masseter muscle (*masseteric*)
- Site C: Anterior to the masseter muscle (*pre-masseteric*)

3.5.3.3 Treatment

Various treatment modalities to treat the parotid fistula have been advocated, if *conservative measures* fail. *Tympanic neurectomy* involves drilling into the temporal bone and disruption of the tympanic nerve, which carries parasympathetic secretory nerve fibers to the parotid gland [29, 30]. This technique aims at reducing salivary flow and causing spontaneous fistula resolution. Although popular in the past, this method tends to be abandoned due to short-term and poor results due to reinnervation of the gland with time [31].

Radiation has been used in the past to suppress the gland, but use of radiation for benign disease is now avoided. Some authors advocate use of *anticholinergics* to suppress glandular function during healing, but this is not a frequently used modality. *Three operative techniques* have been popularized over time. These include repair of the duct over a stent, ligation of the duct, and fistulization of the duct into the oral cavity.

Medical Therapy

Wound care is the cornerstone of therapy. Prophylactic antibiotics should be administered and continued for 5–7 days, but it should be noted that antibiotics cannot avert or cure infections in the setting of poor wound care. In rare cases, human saliva contains and occasionally transmits *Clostridium tetani.* Accordingly, all patients should be assessed for their tetanus immune status and immunization should be updated as appropriate.

Some authors choose to use anticholinergic agents to suppress glandular function during healing or in an attempt to close a fistula or resolve a sialocele spontaneously. A commonly used agent is propantheline bromide (Pro-Banthine), which inhibits the action of acetylcholine at the postganglionic nerve endings of the parasympathetic nervous system (adult dose 15 mg PO qid half an hour prior to meals).

Sialocele and salivary fistula can frequently be managed nonoperatively with antibiotics, pressure dressings, and serial aspiration. Anticholinergic medications and the injection of botulinum toxin represent additional measures before resorting to surgical therapies such as tympanic neurectomy or parotidectomy [32].

Surgical Therapy

Copious irrigation of the wound with normal saline solution has been shown to decrease the incidence of wound infection. *Careful debridement* of devitalized tissue, particulate matter, and clot is necessary to reduce the infection risk and to improve the cosmetic result. Clean, surgically created wound margins allow for faster wound healing and better scarring.

Head and neck wounds, less than 12 h old and not obviously infected, being in a cosmetically sensitive area, may be *closed directly* with a low incidence of infection. The low infection rate is probably related to the excellent regional blood supply and infrequency of edema in these areas. For a good cosmetic result, closure is performed in a simple interrupted fashion, using fine stitches and avoiding layered closure with buried sutures.

The most important initial step for proper surgical repair is the identification of key structures, namely, the buccal branches of the facial nerve (with the aid of a nerve stimulator intraoperatively if available) and the parotid duct itself. If the buccal branch was transected, repair it with fine sutures (8–0 to 10–0 monofilament is appropriate) under microscopic aid. The distal end of the parotid duct is identified by a Silastic tube, placed via cannulation of the intraoral papilla. The proximal parotid duct can usually be identified by the flow of saliva into the wound, with gentle pressure over the gland if necessary. Once all key structures are identified, a decision is made regarding which repair technique to employ.

Distal lacerations, occurring at site C, may be treated in several ways. If the *papilla is uninjured*, the proximal portion may be dissected free and reimplanted into the papilla. If the *papilla is injured* or if the proximal duct does not reach the papilla, the duct may be reimplanted (under magnification) into the oral mucosa posterior to the papilla, using fine interrupted absorbable sutures with meticulous approximation of duct epithelium to oral mucosa. If the distal injury is too short to be reimplanted into the oral mucosa without undue tension, then the best decision is to ligate the proximal duct.

Injuries occurring over the masseter muscle, at site B, are the most common injuries to the parotid duct and may be treated by *repair or ligation*. If enough *length remains*, primary anastomosis over a Silastic stent, using a single layer of interrupted fine sutures (8–0 to 10–0 monofilament) is performed under magnification. If a portion of the duct is *damaged* beyond repair or is missing, the proximal and distal duct should be ligated. Reports of attempts to use a vein graft (saphenous) in such cases have generally found such attempts unsuccessful. Sialendoscopy-assisted repair of a transected Stensen's duct in zone B has been reported [33].

Injuries of the proximal duct near the parotid substance, at site A, are usually best treated by duct *ligation* as the amount of proximal duct remaining is usually insufficient to result in a useful repair. Laceration of the gland itself without disruption of the parotid duct may be repaired with fine absorbable sutures (5–0 or 6–0 Vicryl).

A drain in the wound bed is recommended to drain any residual salivary leak and prevent early sialocele formation. Drains are removed once drainage is minimal and the skin has become adherent to the operative site. *Postoperatively*, a compression dressing is placed over the operative field postoperatively for several days. If ductal injury required ligation of the proximal duct, marked temporary swelling of the gland followed by rapid glandular atrophy is expected. If leaking of saliva occurs as in the development of a fistula or sialocele, the pressure dressing should be continued or reinstituted. Intermittent aspiration of sialoceles has led to resolution in many cases. Anticholinergics may be used to temporarily decrease salivary flow in order to effect wound healing. In the case of a *chronic* parotid duct fistula, an intraoral diversion technique to reestablish salivary flow in case of a nonfunctional parotid duct punctum has been described. The fistula tract and the surrounding ellipse of skin are passed in the oral cavity and sutured to the buccal mucosa with 4–0 chromic sutures without

need for stenting [34]. Alternatively, chronic fistula and sialocele have been medically managed with botulinum toxin [35].

3.5.3.4 Complications

Persistent Salivary Fistula If the fistula occurs in the oral cavity, it is of no consequence and requires no further therapy. If the fistula occurs to the overlying skin, the patient experiences saliva dripping down the cheek. Initial expectant management, with or without anticholinergic medications, has led to resolution in many cases. Other cases have required surgical excision of the fistula tract with repair of the duct or superficial parotidectomy. *Sialocele* usually resolves with intermittent aspiration and compression and rarely requires drain placement. Anticholinergics may be beneficial in the treatment of sialoceles. Duct ligation may lead to early edema of the gland with accompanying pain from stretching of the capsule. This usually subsides spontaneously within 1–2 weeks as atrophy of the gland occurs. Infection of the remaining glandular substance may occur as a late complication of duct ligation. *Sialadenitis* may result from manipulation of the intraoral papilla or from sialography and may require drainage and antibiotics. *Facial nerve injury* and sensory nerve injury may occur when surgery is conducted in the region of the parotid duct, particularly in cases where trauma and blood extravasation have discolored the tissues and disrupted tissue planes.

3.5.4 Parotid Calculus

Parotid stones are much less common than submandibular stones (20 % versus 80 %, respectively). However, recent studies showed some rapprochement between these figures. This is attributed to a number of factors such as the difference in the composition of the saliva produced by each gland and the dependence of the submandibular (Wharton's) duct, which hinders easy drainage of its viscid secretions. Parotid stones are composed of organic substances such as cellular debris, mucopolysaccharides and glycoproteins, and inorganic substances such as different calcium and magnesium salts. The organic substances are mainly found as the core of the stone, while the inorganic substances are in its periphery. Apatite is the most frequent component present throughout the calculus. The annual growth rate of an established stone is about 1 mm per year. Their shape is either rounded or irregular and the average size is about 3.2 mm. Clinical presentations of a parotid stone vary from being *asymptomatic*, to intermittent obstructive parotitis, to an acute abscess. Parotid stones are usually imaged through sialography being mostly radiolucent [36].

Stones present in the gland or within the collecting ducts are treated with parotidectomy, while those present near the papilla may be treated with longitudinal incision of the duct releasing the stone. The advent of external lithotripsy in the early 1990s [37] paved the way for conservative treatment of all calculi, with a success rate of 40 % in the submandibular gland and 75 % in the parotid. Unfortunately, results were discouraging, specifically in patients with large calculi [38–41].

Interventional sialendoscopy, first described in the 1990s, offered much less invasive therapeutic options and became popular with technological improvements in the years after 2000 [42–47]. It can be used to retrieve stones from the ducts (Fig. 3.4) as well as dilating strictures.

Nevertheless, success rates of interventional sialendoscopy with intraductal laser fragmentation and basket extraction of calculi remained possible in only 80 % of patients [42]. Unsuccessful treatment of the remaining 20 % of patients was attributed not only to large-sized calculi (6 mm and larger) but also due to associated ductal stenosis [48]. In such cases, the only solution was to remove the gland, with its associated significant morbidity [38–40].

3.5.5 Inflammatory Disorders (Sialadenitis)

3.5.5.1 Viral Infections

Mumps [49]

Mumps is a specific acute viral infection due to a paramyxovirus, an RNA virus that belongs to the influenza and parainfluenza family. In 85 % of cases, it affects the school-age children under the

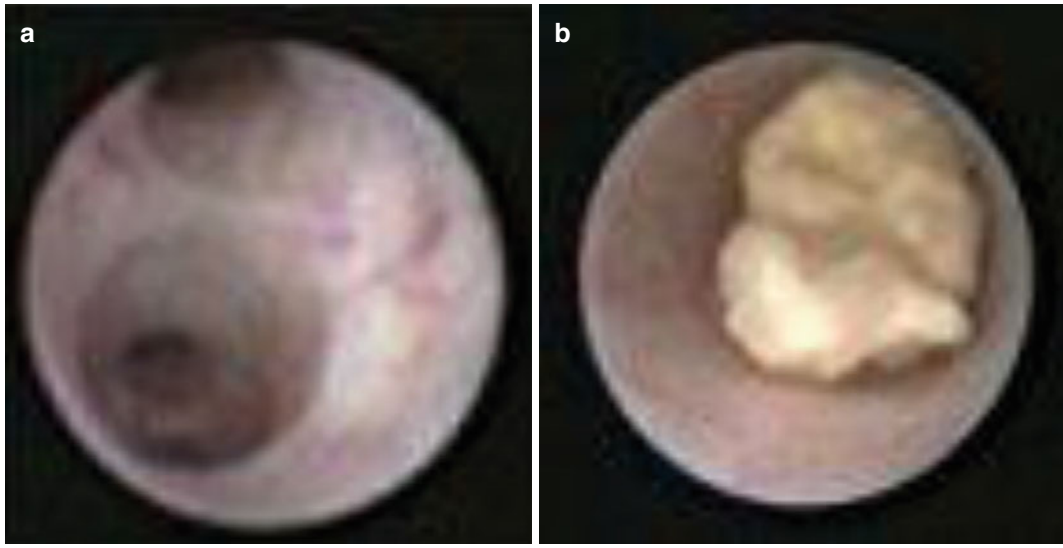

Fig. 3.4 Sialendoscopy showing interior of the parotid (Stensen's) duct (**a**) and intraductal stones (**b**)

age of 15 years, with an incubation period of 2–3 weeks. The illness starts by 1–2 days of prodromal influenza-like syndrome (discomfort, loss of appetite, nausea, chills, fever, sore throat, and headache), followed by the appearance of the characteristic face swelling. The patient is infectious from 3 days before the onset of salivary swellings to 7 days after, through airborne droplets of infected saliva. A single episode of infection confers lifelong immunity. Fortunately, this condition has been mostly eradicated as a result of vaccination.

The swelling, which usually starts unilateral and in a few days becomes bilateral, lasts from a couple of days to 1 week (Fig. 3.5). The virus causes fever and is considered the most common cause of acute painful profuse swelling of the parotid gland.

The gland is soft and tender, but never suppurates. Impingement on the auriculotemporal and great auricular nerves causes much pain as the gland is pressured during mastication. Symptoms usually resolve within 5–10 days.

Mumps may be complicated by pancreatitis, orchitis, and oophoritis. It might be a cause of abortion during the first trimester of pregnancy because of fetal endocardial fibroelastosis. Sensorineural deafness (1/20,000) and meningoencephalitis are rare but are more likely to occur in adults.

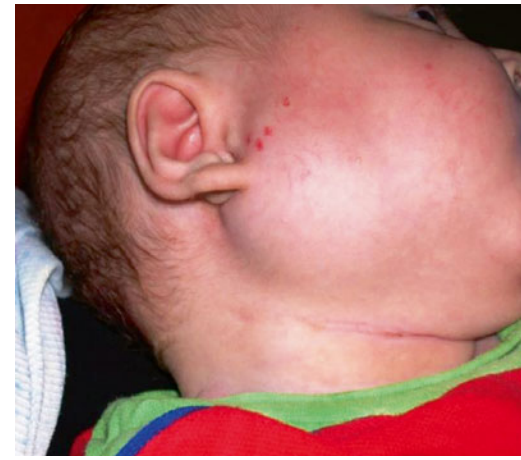

Fig. 3.5 Mumps in a 10-month child with a smooth enlargement of the right parotid gland

Laboratory findings include leukocytopenia with relative lymphocytosis. Serum amylase peaks in the 1st week and normalizes by the 2nd or 3rd week. Soluble antibodies directed against the nucleoprotein core of the virus appear within the final week of infection and disappear within 8 months. Antibodies directed against the outer surface appear several weeks after soluble antibodies, and persist for 5 years. Mumps is a self-limited disease that requires rest and symptomatic treatment only, which includes antibiotics, sialagogues, and rehydration.

Non-Mumps

Parotitis with the same clinical picture as that described for mumps can be caused by other viral agents, namely, Coxsackie A and B, parainfluenza types 1 and 3, echovirus, and lymphocytic choriomeningitis virus.

Human Immunodeficiency Virus (HIV)-Associated Sialadenitis [50, 51]

The presentation of HIV-associated sialadenitis is in the form of chronic, bilateral enlargement of parotid glands where the glands are painless, hard, and nodular. The disease is more common among children than among adults. The condition may be associated with xerostomia and xerophthalmia, being so similar to the classical Sjogren's syndrome in adulthood. Although both conditions share similar histological characteristics, HIV-associated sialadenitis is usually associated with a negative autoantibody screen. Multiple glandular cysts causing gross parotid swelling and facial disfigurement are another pattern of presentation. Thirty percent of HIV-infected children have been reported to have enlargement of their parotid glands. In addition, patients with HIV are more susceptible to infection with cytomegalovirus (CMV) and adenoviruses as causative agents for non-mumps parotitis.

Useful imaging tools include ultrasound (US), computed tomography (CT), and MRI. The latter two demonstrate the characteristic "Swiss cheese" appearance of multiple large cystic lesions (Fig. 3.6). They can also guide fine-needle aspiration, which reveals serous fluid with the presence of lymphocytes and macrophages. As the parotid gland contains many LNs at different levels, they might be enlarged as the HIV virus mainly affects the lymphoid tissue. The sole indication of surgery might be to improve the appearance.

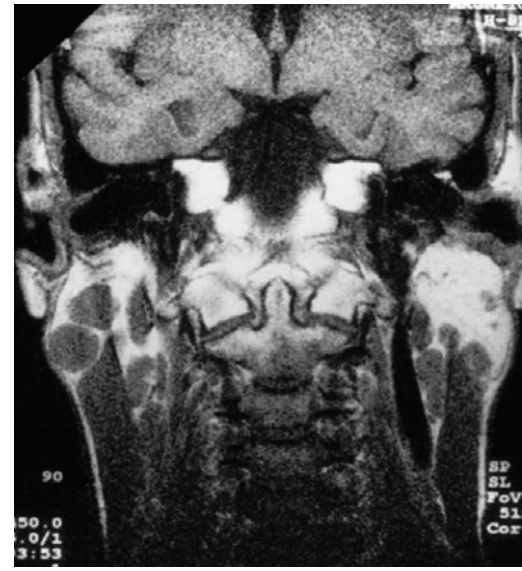

Fig. 3.6 MRI showing the characteristic Swiss cheese appearance of multiple large cystic lesions

3.5.5.2 Bacterial Infections

Acute Suppurative Parotitis (Abscess) [52]

The infective organism can be any of the following bacteria: *Staphylococcus aureus*, *Streptococcus viridans*, Penicillin-resistant coagulase-positive staphylococcus, *Streptococcus pneumoniae*, beta-hemolytic streptococcus, methicillin-resistant *Staphylococcus aureus* (MRSA), or gram-negative germs, such as *E. coli*. Studies have shown the presence of 30–40 % of anaerobic bacteria: bacteroides, peptostreptococcus, and fusobacteria. In Southeast Asia, *Pseudomonas pseudomallei* has been reported. In many cases the infection is a mixed one.

Ascending retrograde infection spreads from an infected dry mouth through the duct into the gland, or it may be blood-borne. One or more of the following factors that cause dehydration and/or electrolyte imbalance are usually evident: septicemia, obstruction of Stensen's duct by a stone, after major surgery, or bad oral hygiene. However, sometimes the condition is totally idiopathic. Parotids are affected more frequently than submandibular glands. One of the possible reasons is that the bacteriostatic activity of the saliva secreted by the parotid gland is inferior to that secreted by the submandibular gland as the former is predominantly serous and thus lacks the protective constituents (IgA, sialic acid, and lysosomes) seen in mucinous secretions of the other salivary glands.

The patient generally complains of anorexia, fever, tachycardia, and malaise. Over several

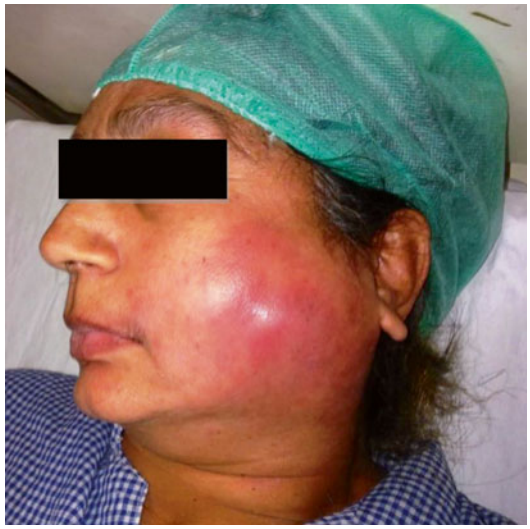

Fig. 3.7 Large left parotid abscess with erythematous, edematous, and tethered overlying skin

hours, the local condition starts with a swelling which is very tender, hot, and with throbbing pain that is exacerbated by mastication. The gland size may reach 3–4 times larger than that of the normal gland, which is usually diffuse but may localize to the lower pole. The skin overlying the gland is red, edematous, and tethered (Fig. 3.7). Movements of the ipsilateral temporomandibular joint (TMJ) are restricted and painful. The upper deep cervical LNs are enlarged and tender.

The parotid gland, being enclosed in a dense capsule, is liable to fulminating inflammation and necrosis due to increased tension within this tightly closed fascial compartment. Fluctuation is difficult to elicit and is never waited for. Pus may exude from the duct orifice on massage of the gland, which is in spite of being painful at the moment; it relieves the pressure inside the ductal system and thence the pain. Diseases of the parotid gland cause pain to be referred to the ear, the TMJ, and the external auditory meatus. This is due to the overlapping of sensory branches of various nerves serving the regions of the parotid bed, ear, and TMJ. Infections of the parotid gland may be confused with toothache as a result of trigeminal nerve (CN V) involvement. An inflamed parotid papilla (parotid duct orifice in the oral cavity) provides clue to diagnosis.

A parotid abscess may be complicated by local spread in the form of cellulitis, chronicity due to inadequate management, development of a fistula, septicemia, and rupture into the external auditory meatus or along the carotid sheath. The patient shows increased white blood cell count, and culture and sensitivity should be done from the pus. Sialography is contraindicated during acute infection and US may be needed; however, the diagnosis is mostly done on clinical grounds.

Prophylaxis against the development of such suppuration is considered much safer through adopting good oral hygiene, preventing dehydration, and early adequate correction of electrolyte imbalance. As an early treatment of any inflammatory condition affecting the parotid gland, one should use warm local fomentations, intravenous antibiotics, anti-inflammatory agents, and analgesics. When suppuration ensues (known by throbbing pain, hectic fever, aspirated pus, or US-identified abscess formation), formal drainage under general anesthesia becomes necessary.

Decompression of the Parotid (Hilton's Method) Do not wait for fluctuation. Under general anesthesia, a *vertical* incision is done in the skin down to the parotid capsule. The capsule in then incised *transversely* along the course of the branches of the facial nerve to avoid their injury. Pus is evacuated, a drain is put in the lower part of the incision for 24–72 h, and then closure is achieved. Complications of this procedure include parotid fistula and facial nerve injury. Alternatively, the skin incision may be made low to avoid damage to the lower branch of the facial nerve.

Chronic Pyogenic Parotitis

Chronic bacterial sialadenitis is rare in the parotid gland. It may result from improper treatment of acute parotitis, presence of stones in the duct, or stenosis of the Stensen's duct [53].

Actinomycosis

Actinomycosis affects LNs adjacent to salivary glands, mimicking a salivary gland infection. The pathogen is *Actinomyces israelii*, *A. propionica*, *A. viscosus*, or *A. odontolyticus*. Infection may be acute, subacute, or chronic. The *acute* form is

associated with suppuration, the *subacute* with a slightly tender and tumorlike mass attached to the mandible, and the *chronic* with marked induration that may be misdiagnosed as a neoplasm. The finding of pollen grain like "sulfur granules" on clinical examination or "sulfur grounds" on pathological evaluation is pathognomonic of this condition. Treatment of the acute phase is surgical, with eventual drainage of the exudates and administration of broad-spectrum antibiotics [54].

Cat-Scratch Disease

A disease caused by infection with a gram-negative bacillus called *Bartonella henselae*. The disease originally involves LNs adjacent to salivary glands, which may be secondarily involved by continuous spread. The disease is due to contact with cats, and children or young adults are the most often involved. Laboratory tests include specific PCR or serology. Antibiotics do not seem to shorten the course of the disease but may be given as prophylaxis against secondary bacterial infection. The affected LNs disappear spontaneously within a few months [55, 56].

3.5.5.3 Recurrent Parotitis of Childhood

This is a distinct clinical entity of unknown etiology and unsure prognosis. It is the most frequent nonviral disorder of salivary glands in children [57]. Suggested etiologies include congenital malformation of the parotid ducts, primary or secondary infections, and local manifestations of systemic immunological disease.

The clinical picture comprises fever, malaise, rapid swelling of one or both parotid glands, and pain which is made worse by mastication. This usually lasts from 3 to 7 days followed by a quiescent period of weeks to several months. The condition may rarely start as early as 4 months of age, but usually children present between the ages of 3 and 6 years and usually resolve around puberty. The diagnosis is made by obtaining typical history and findings of the clinical examination. Sialography may be confirmatory. It shows a characteristic punctate sialectasis likened to a "snowstorm" (Fig. 3.8) which persists until adult life. Sialendoscopy may show diffuse

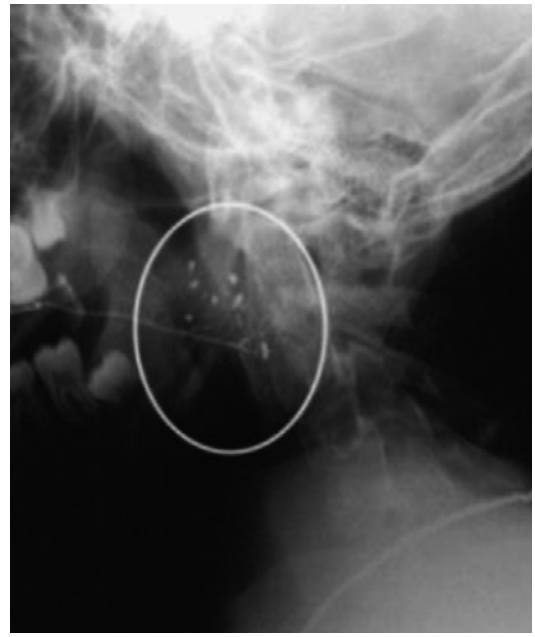

Fig. 3.8 Sialography showing a characteristic punctate sialectasis (snowstorm appearance)

reduction of the caliber of Stensen's duct, associated sometimes with multiple localized stenosis and may be salivary calculi. Endoscopy may also show sialectasia (dilated ductules and acini). Sialendoscopy has proven recently to be effective therapeutically through injection of antiseptic solutions in some cases [57].

No specific treatment is available; however, therapeutic options include good oral hygiene, prophylactic low-dose antibiotics for several months or even years especially if recurrence is frequent, anti-inflammatory agents, sialendoscopy, and total conservative parotidectomy [58].

3.5.5.4 Papillary Obstructive Parotitis

Although there are many recognized causes of obstructive parotitis, however, papillary obstruction due to trauma to the parotid papilla through either an overextended upper denture flange or a fractured upper molar tooth is merely the most common of all. Subsequent edema and then fibrosis of the papilla obstruct salivary flow, especially at mealtimes, in intermittent and then chronic forms, respectively. Thus, the patient suffers from an intermittent painful swelling of the

parotid, accumulating over minutes after the start of his meal. If stenosis ensues, the symptoms will not resolve except by a papillotomy. Obstructive parotitis is less common than obstructive submandibular sialadenitis.

3.5.5.5 Granulomatous Sialadenitis

Granulomatous sialadenitis can result from tuberculosis, mycosis, sarcoidosis, or duct obstruction from calculi or malignant tumors. In the latter instance, the granulomas result from rupture of ducts and may contain small pools of mucin.

Tuberculosis (TB)

Mycobacterium tuberculosis and atypical mycobacterium both affect LNs adjacent to salivary glands or intraglandular LNs. The patient may suffer from one or more of the systemic manifestations of TB such as low-grade fever, night sweating, and anemia. The gland is firm and nodular but may become cystic with sinuses and little pain. Polymerase chain reaction (PCR) is the best preoperative laboratory diagnostic tool, but diagnosis is only confirmed with histopathology following parotidectomy, if needed. Specific treatment of this condition includes multidrug therapy for an average of 1 year together with exposure to direct sunlight, good aeration, and well-balanced nutrition to enhance general health and immunity [59, 60].

Sarcoidosis

Sarcoidosis is a systemic disease involving multiple organs. Its etiology remains unclear, but several hypotheses have been made, including autoantigens and infectious organisms. It resembles TB but with no caseation. Salivary glands are usually affected and specifically the parotid glands. Symptoms include swellings and xerostomia. Sometimes, the disease my present as a mass, and the diagnosis is only made after surgical excision of the presumed tumor: the *sarcoid pseudotumor*. Laboratory diagnosis is made through amylase, kallikrein, and the ACE test. Radiological and histological evidences of noncaseous epithelial granulomas are confirmatory. Corticosteroids are the best therapeutic option. *Heerfordt's syndrome* is a rare form of sarcoidosis that involves parotid swelling, anterior uveitis, facial palsy, and fever (uveoparotid fever). It affects young patients in their third decade [61].

3.5.5.6 Autoimmune Sialadenitis

Mikulicz Disease (MD)

It is an autoimmune disease, which is characterized by chronic, symmetrical, bilateral enlargement of all salivary and lacrimal glands. The disease almost always occurs in association with another underlying disease such as TB, leukemia, syphilis, or systemic lupus erythematosus (SLE). Sometimes patients may experience recurring fever. Patients with MD are at higher risk of developing lymphomas. Some believe that it should be considered a form of Sjogren's syndrome (SS). Actually the main clinical difference between MD and SS is the preservation of the lacrimation and salivation in MD due to much less gland cell apoptosis than that found in SS [62].

Sjogren's Syndrome (SS)

This disease is an autoimmune one involving the parotid glands more frequently than the submandibular glands. Females are affected more than males (10:1). It leads to xerostomia and keratoconjunctivitis sicca due to progressive destruction of both salivary and lacrimal glands. The diseased gland is occasionally enlarged and is occasionally painful. Secondary bacterial ascending infection may occur as a result of dry mouth. Histologically, SS is characterized by massive progressive lymphocytic infiltration, acinar cell destruction, and ductal epithelial cell proliferation affecting all salivary and lacrimal glands. This is the *primary* SS. *Secondary* SS differs in that it is associated with a connective tissue disorder, symptoms are less severe, and the incidence of lymphomatous transformation (most commonly monocytoid B-cell lymphoma) is also less [62].

There is no known specific treatment available to stop Sjogren's syndrome, and thus management is totally symptomatic. Artificial tears and periodic ophthalmological examination is mandatory to avoid corneal ulcerations. Artificial salivary substitutes are available and their importance

increases in the dentate patient where fluoride should be added as well. Usually the patient consumes a large amount of water daily carrying a bottle of water with him all the time [63].

3.5.5.7 Benign Lymphoepithelial Lesion (Myoepithelial Sialadenitis, MESA)

This disease mostly affects females over 50 years of age. Patients present with a diffusely enlarged, firm, and often painful parotid gland, which is bilateral in 20 % of cases. Sialography shows sialectasia, which ranges from punctuate to cavitary. Management is usually parotidectomy to establish a final diagnosis. Histopathological examination of the excised gland carries the very same previously described histopathological features of Sjogren's syndrome, and so the differentiation between both is only done on clinical grounds. Prolonged follow-up of such patients is mandatory as 20 % of them will develop lymphoma at a certain time [64].

3.5.5.8 Other Autoimmune Sialadenitis

Wegener's granulomatosis is an autoimmune disease characterized by upper and lower respiratory and renal disease. The most common salivary gland to be involved is the parotid gland [61]; however, this occurs in less than 1 % of the cases [65]. *Kimura's disease* occurs typically in young Asian males and is characterized clinically by painless lymphadenopathy of the head and neck region, including peri-parotid and intra-parotid LNs [61, 64, 66]. *Chronic sclerosing sialadenitis* presents as a firm localized swelling of the salivary gland mimicking a neoplasm, most commonly involving the submandibular gland. It may be associated with autoimmune extra-salivary disease such as primary sclerosing cholangitis and idiopathic retroperitoneal fibrosis [64].

3.5.6 Sialadenosis (Sialosis)

Sialadenosis is a noninflammatory disorder causing diffuse enlargement of salivary glands, usually the parotid glands and less commonly the submandibular [64, 67, 68], and minor salivary glands [69].

3.5.6.1 Clinical Presentation

Sialadenosis is frequently bilateral and has an equal sex distribution. Most of the patients are between 40 and 70 years of age. There is a painless, soft, and diffuse enlargement of both parotid glands giving the patient a striking facial feature, known as the "*hamster-like appearance*".

3.5.6.2 Etiology

Causes of sialadenosis can be categorized as: (1) *nutritional* (alcoholism, cirrhosis, bulimia, kwashiorkor, and pellagra), (2) *endocrine* (DM, thyroid disorders, gonadal dysfunction), and (3) *neurochemical* (vegetative state, lead and mercury poisoning, iodine, thiouracil, isoproterenol) [64, 68]. However, in many cases no underlying disorder can be detected.

3.5.6.3 Pathogenesis

The proposed pathogeneses include prolonged malnutrition with resultant glandular atrophy and fatty replacement. Sialadenosis is also thought to be a neurosecretory disorder. Diabetic neuropathy may be the clue causing acinar cell atrophy, in some cases. Ultrastructural and animal experimental studies point to a disturbance in the autonomic innervation of salivary glands. This is considered to be the initiating factor for sialadenosis [67, 68, 70–72].

3.5.6.4 Pathology

Grossly, there is only diffuse enlargement of the affected gland. Histologically, the condition is characterized by acinar hypertrophy and fatty infiltration [73]. Zymogen granules are increased in size and number by light and electron microscopy [71]. No inflammation or fibrosis can be detected, which differentiates sialadenosis from sialadenitis. While amyloidosis may also present with diffuse enlargement of the salivary glands, histologically, there will be interstitial fibrosis as well as the characteristic pale amyloid deposition that can be demonstrated with a Congo red stain [74].

3.5.6.5 Treatment

Treatment is in the form of controlling the underlying disorder or withdrawing the incriminated drug. There is usually little morbidity

Table 3.1 Cystic parotid lesions

Bilateral
Warthin's tumor
Benign lymphoepithelial lesions of HIV
Sjogren's syndrome
Sialocele
Unilateral
Warthin's tumor
Sialocele
First branchial cleft cyst: parotid lymphoepithelial cyst
Necrotic LN(s) especially SCC
Infected LN(s)

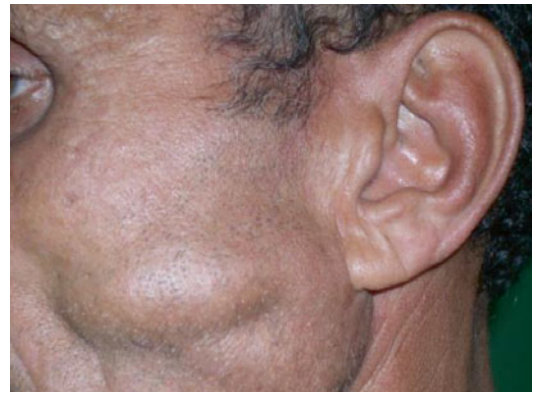

Fig. 3.9 Left parotid duct ectasia

associated with the condition itself, and surgery is resorted to only in case of significant cosmetic complaint.

3.5.7 Cystic Parotid Lesions

Cysts of the parotid gland represent a clinical dilemma. The differential for cystic parotid lesions is summarized in Table 3.1. Apart from the cystic forms of benign and malignant neoplasms, cysts of the parotid gland may be the presentation of a variety of diseases. Such nonneoplastic cysts are uncommon and represent 2–5 % of all salivary gland lesions [75]. A first branchial arch anomaly must be considered when one encounters a case of parotid cyst [76].

Disruption of the parotid duct or parenchyma results in extravasation of saliva into the glandular or peri-glandular tissues forming what is known by *sialocele*. The cause might be either facial trauma or surgery especially when Surgicel is used.

Parotid duct cysts are also known as sialocysts, simple cysts, and retention cysts and result from obstruction due to various causes [74, 77, 78]. They are true cysts lined by epithelium, unlike *mucocele*, which is lined by granulation tissue [77]. Parotid duct cysts should not be confused with duct ectasia (Fig. 3.9).

Duct cysts are unilocular and may grossly contain mucoid material or sialoliths in long-standing cases. Histologically, they are lined by a cuboidal, columnar, or squamous epithelium, though oncocytic metaplasia may be seen in older patients. However, these cysts are not associated with lymphoid elements [64]. Prognosis is excellent. Complications are rare and include superimposed infections. Recurrence is also rare and results from incomplete excision [64].

Dermoid cysts [78] and *hydatid* cysts [79] have also been reported in the parotid, yet they are exceptionally rare.

3.5.8 Tumors of the Parotid Glands

3.5.8.1 WHO Histological Classification of Tumors of Salivary Glands

Benign Epithelial Tumors

- Pleomorphic adenoma (PA) (mixed salivary tumor)
- Myoepithelioma
- Basal cell adenoma
- Warthin's tumor (adenolymphoma, papillary cystadenoma lymphomatosum)
- Oncocytoma
- Canalicular adenoma
- Sebaceous adenoma
- Lymphadenoma
  - Sebaceous
  - Non-sebaceous
- Duct papilloma
  - Inverted duct papilloma
  - Intraductal papilloma
  - Sialadenoma papilliferum
- Cystadenoma

Malignant Epithelial Tumors
- Acinic cell carcinoma
- Mucoepidermoid carcinoma (MEP)
- Adenoid cystic carcinoma (ACC)
- Polymorphous low-grade adenocarcinoma (PLGA)
- Epithelial-myoepithelial carcinoma
- Clear-cell carcinoma, not otherwise specified
- Basal cell adenocarcinoma
- Sebaceous carcinoma
- Sebaceous lymphadenocarcinoma
- Cystadenocarcinoma
- Low-grade cribriform cystadenocarcinoma
- Mucinous adenocarcinoma
- Oncocytic carcinoma
- Salivary duct carcinoma
- Adenocarcinoma, not otherwise specified
- Myoepithelial carcinoma
- Carcinoma ex-pleomorphic adenoma (CEPA)
- Carcinosarcoma (malignant mixed salivary tumor)
- Metastasizing pleomorphic adenoma
- Squamous cell carcinoma
- Small cell carcinoma (SCC)
- Large cell carcinoma
- Lymphoepithelial carcinoma
- Sialoblastoma

Soft Tissue Tumors
- Hemangioma

Hematolymphoid Tumors
- Hodgkin's lymphoma
- Diffuse large B-cell lymphoma
- Extra-nodal marginal zone B-cell lymphoma

Secondary Tumors

Tumors of the salivary glands are relatively uncommon and represent less than 2 % of all head and neck neoplasms.

3.5.8.2 Benign Tumors (BTs)

Salivary gland BTs occur mostly in the parotid gland, and most of them are pleomorphic adenomas. The BT usually presents as a slowly growing painless mass in front of the tragus of the ear, below the ear lobule, or in upper part of the neck, arising from the superficial lobe of the gland which represents 80 % of the cases. Less commonly, the mass presents as a cheek mass overlying the masseter, arising from the accessory parotid lobe. If the tumor arises from the deep lobe, it presents as a parapharyngeal mass with completely different clinical presentation. In this instance, the patient will complain of difficultly in swallowing and snoring, and physical examination will reveal a soft palate and tonsillar firm, diffuse bulge.

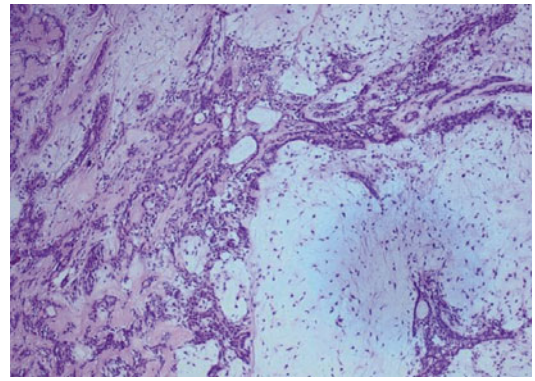

Fig. 3.10 Pleomorphic adenoma: biphasic population of epithelial and mesenchymal cells. Epithelial cells assume tubular profiles, cords, or nests. Stroma is myxoid (H&E, ×100)

Pleomorphic Adenoma (PA)

This *mixed salivary tumor* represents 75–80 % of all benign parotid tumors. It may affect as well the submandibular and minor salivary glands. Its incidence is slightly higher in females and affects most commonly patients between 30 and 50 years of age [80–82]. It is uncommon to be bilateral [78, 83]. It is usually a solitary lesion, although synchronous or metachronous involvement of two or more salivary glands can occur. It may also occur in combination with other tumors, mostly Warthin's tumor.

It is a well-defined tumor, but with small extensions into the adjacent normal tissue through an incomplete capsule, which explains the recurrence after enucleation. It has a pleomorphic matrix, with a non-cystic cut section that may show some islets of cartilage. Microscopically, it is formed of epithelial cells intermingled with a pleomorphic stroma: fibrous, myxomatous, and pseudo-cartilaginous (Fig. 3.10). It is categorized into four types: (1) principally myxoid, (2)

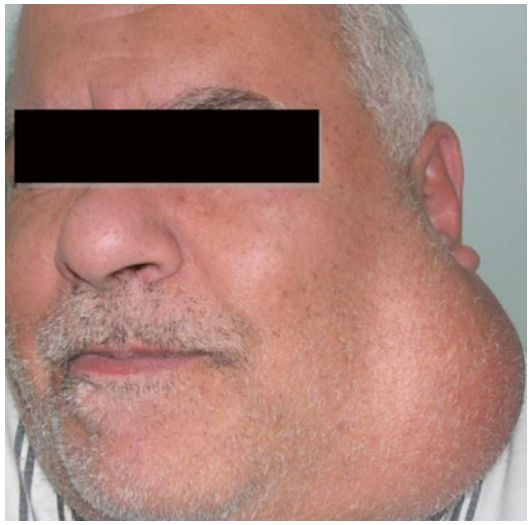

Fig. 3.11 A large left pleomorphic adenoma (PA) of the parotid gland in a 56-year-old male patient

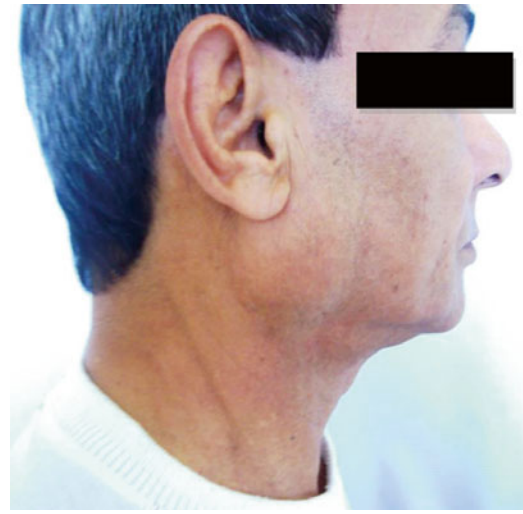

Fig. 3.12 Pleomorphic adenoma in its typical position over the angle of the mandible and below the lobule of the ear

mixed myxoid and cellular components in equal proportions, (3) predominantly cellular, and (4) extremely cellular [84].

It carries a malignant potential of 5–10 %. The presence of hyalinized stroma is the most predictive histological parameter for malignant transformation. The tumor may rarely metastasize without having the histological features of malignancy, but this almost always occurs after inadequate surgical excision, possibly due to altered anatomy secondary to surgery, which gave access to vascular and lymphatic channels.

Roughly 70 % of PAs have cytogenetic alterations that likely play a major role in pathogenesis (tumorigenesis) and can be categorized into 4 groups: those with 8q12 rearrangements, those with 12q13-15 rearrangements, those with miscellaneous clonal changes, and those that are karyotypically normal [85, 86].

The patient presents with a painless, slowly growing, spherical mass, of variable size ranging from pea-size to a large mass, 20–50 cm across [87–89] (Fig. 3.11). The mass usually lies over the angle of the mandible and below the lobule of the ear (Fig. 3.12). However, a swelling of the lower pole of the parotid gland may present in the lateral side of the neck, below and behind the angle of the mandible, giving rise to clinical diagnostic difficulty (Fig. 3.13). The patient's complaint is usually disfigurement. The mass is of heterogonous consistency and mobile, being neither attached to the skin nor to the deep structures. Bosselation of the tumor is demonstrable if it is bigger than 3 cm.

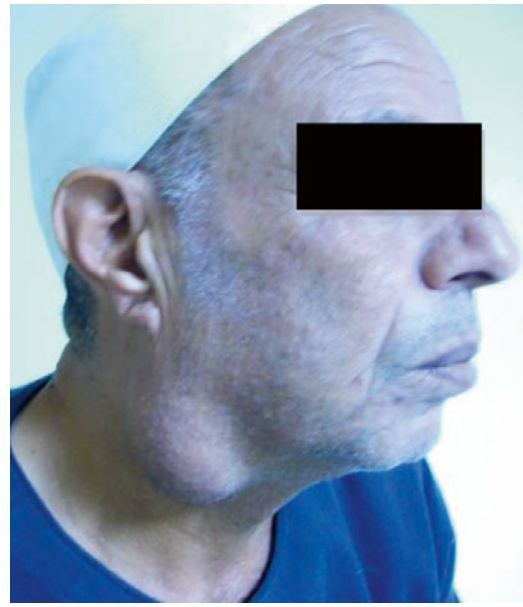

Fig. 3.13 Pleomorphic adenoma arising below and behind the angle of the mandible. Not related to the ear lobule

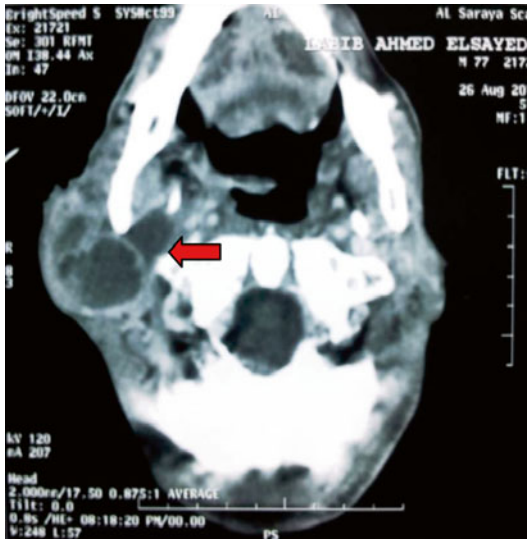

Fig. 3.14 CT scan showing extension of the PA to involve the deep lobe of the parotid gland (*red arrow*)

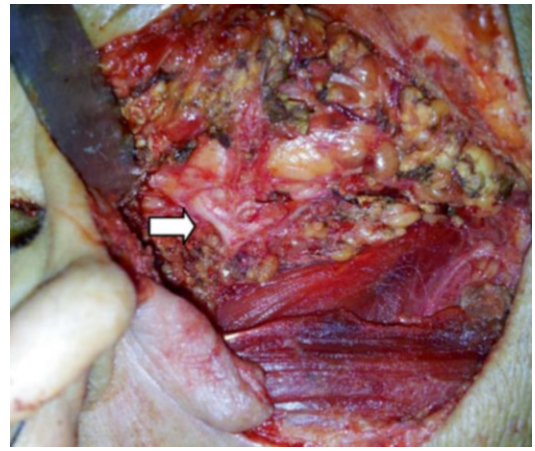

Fig. 3.15 Dissection of the main trunk and only one division, related to the parotid mass (*white arrow*)

While most PAs occur in the superficial lobe of the parotid gland (80 %) [90–92], the deep lobe can be involved (20 %) and is clearly demonstrable by CT scan (Fig. 3.14). Extensions of deep lobe PAs are the most common tumors of the parapharyngeal space constituting 40 % of tumors in this region [83, 92]. The draining LNs are not enlarged and the facial nerve is always intact.

As for any parotid mass, US, CT, and MRI (preferably with diffusion-weighted and perfusion sequences) are the best imaging tools. Fine-needle aspiration cytology (FNAC) is a recognized method for obtaining preoperative diagnosis and is advised to be done after imaging for the fear of hemorrhage. Many studies showed that the use of flow cytometry as a biological parameter for the prediction of recurrence in PAs should be considered. Tumors of a larger size showed a higher percentage of cells in the S-phase fraction and probably a greater tendency for recurrence [93].

Treatment is through surgical excision. Superficial or total conservative parotidectomy with preservation of the facial nerve is done. Partial superficial parotidectomy and extracapsular dissection are other recognized options of resection [94–96]. Partial superficial parotidectomy entails dissection of the main trunk of the facial nerve and only one division with its terminal branches (Fig. 3.15). Enucleation is never done for its high recurrence rate. The skin incision can be the classical lazy-S incision, or recently one can resort to the cosmetically better face-lift incision.

The flaps are raised and the facial nerve trunk is exposed at the stylomastoid foramen, and all its five terminal branches are followed to the muscles to avoid their injury. The incidence of recurrence following surgery varies depending on the surgical technique used, the experience of the surgeon, and the duration of patient's follow-up [97]. Whatever the series and its duration of patient follow-up, a recurrence rate of less than 1 % is considered acceptable. Recurrent PAs have a higher likelihood for second recurrence of about 6–15 % [98]. Uninodular recurrences have a better outcome than multinodular recurrences [99, 100].

Warthin's Tumor (Adenolymphoma)

Warthin's tumor represents about 5 % of all benign parotid tumors and is bilateral in 5–10 % of cases. It occurs almost exclusively in the parotid gland, affecting males more than females. The ratio has decreased drastically during the past 50 years to 2:1 [101, 102]. This gender predilection shift is referred to that it is highly linked to smoking. Smokers have an 8 times higher incidence of developing Warthin's tumors than nonsmokers [103]. The mean age is 62 years. Patients are rarely below 40 years [104, 105].

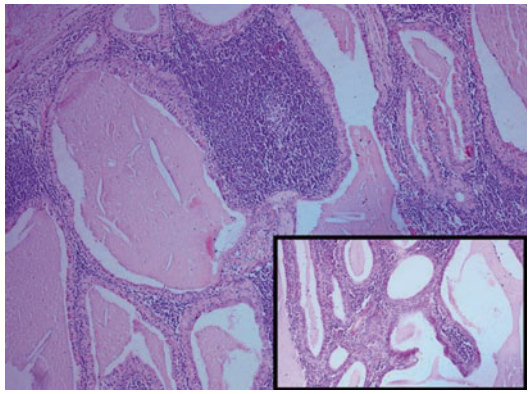

Fig. 3.16 Warthin's tumor: cystic spaces lined by double layer of epithelial cells resting on dense lymphoid stroma. *Inset* depicts intracystic polypoid projections with lymphoid stroma (H&E, ×100)

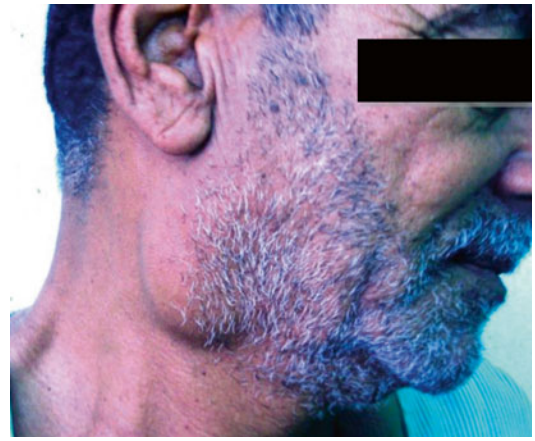

Fig. 3.17 Right adenolymphoma presenting as a small (3-cm), smooth, mass in a 61-year-old gentleman

Macroscopically, it is a reddish-brown mass with a true capsule. Its cut section has many cystic spaces, and the fluid content is characteristically granular brown resembling "motor oil". Under the microscope, it is comprised of a papillary proliferation lined by a double layer composed of surface columnar oncocytic epithelium and a smaller basal layer of small cuboidal cells with myoepithelial characteristics. The surrounding stroma contains a highly ordered lymphoid architecture similar to an actual LN (Fig. 3.16). When Warthin's tumor arises in a cervical LN, it may be mistaken for metastatic carcinoma, particularly from a papillary thyroid carcinoma. Malignant transformation is extremely rare where MEC is the most common histology. The lymphoid component may lead to lymphoma.

The mass is painless, slowly growing, soft, freely mobile, and usually 1–3 cm in diameter. It does not attain a huge size (Fig. 3.17). It has a smooth surface and homogenous consistency and is sometimes cystic. It is often multifocal and may be fixed to the overlying skin [106]. Rarely, infarcted Warthin's tumors may cause pain [102]. Adenolymphoma is the only parotid tumor that can give a hot spot in Tc^{99} scan. If the preoperative diagnosis is certain, then enucleation can be added to the operative options of the surgeon as the tumor is well capsulated and does not recur.

Basal Cell Adenoma (BCA)

Basal cell adenoma tends to occur over the age of 50 years with a female-to-male ratio of 2:1 [107]. It usually occurs in the parotid gland (75 %), much less commonly in the submandibular gland (5 %) [108], and rarely in the minor salivary glands with the exclusion of canalicular adenomas, which were previously categorized with BCA [109, 110]. It typically presents as a slowly growing solitary painless mass [64]. A special variant of BCA, the membranous type (dermal analog tumor) has a propensity for multifocality and can be associated with multiple trichoepitheliomas and cylindromas (*Brooke-Spiegler syndrome*) [111]. Prognosis of BCA is generally excellent. Recurrence rate is low, except for the membranous subtype, which may recur in about 25 % of cases. Malignant transformation is rare, again favoring the membranous subtype [101, 112, 113].

Canalicular Adenoma

Canalicular adenoma, previously categorized with BCA, is a rare tumor comprising <1 % of all salivary tumors [101, 112, 113]. The mean age is 65 years with a female-to-male ratio of 1.8:1 [101, 114]. It rarely affects the parotid glands [101]. The minor salivary glands of the upper lip are the ones most commonly involved (80 %) followed by the buccal mucosa [113] and palate [115]. It typically presents as painless, slowly growing submucosal nodule. Rarely, multiple/

multifocal canalicular adenomas may occur and present clinically with multiple discrete masses, typically occurring in the upper lip and buccal mucosa [64]. The prognosis is excellent and recurrences are extremely rare. Some of these recurrences may be considered as separate tumors [101, 116].

Myoepithelioma

Myoepitheliomas account for about 1.5 % of all salivary tumors. This tumor primarily affects adults with a peak incidence in the third to fourth decades (range 8–82 years) [117, 118]. The parotid gland is the most common site affected (40–50 %), followed by the minor salivary glands in the palate [64]. It usually presents as a slow-growing painless mass. Prognosis is generally favorable; recurrences are relatively rare and are usually the result of incomplete excision [119]. Malignant transformation is uncommon [120].

Cystadenoma

Cystadenoma is a rare benign cystic salivary tumor that resembles Warthin's tumor, though with different clinicopathologic features. Unlike Warthin's tumor, there is a slight female predilection, there is no association with smoking [101, 121], and it is not exclusive for the parotid gland, though it is affected in nearly half of the cases. Other sites include the lip and buccal mucosa [122] and rarely the supraglottic larynx [123]. It affects adults with a mean age of 57 years [124]. Prognosis of cystadenoma is excellent; complete excision is curative.

3.5.8.3 Malignant Tumors

Parotid cancer represents <1 % of all body cancer and about 20 % of all parotid tumors. It is either de novo or on top of PA. There is no sex predilection or males are slightly more affected. Age of developing this cancer is usually above 50 years.

Signs of malignant transformation in a preexisting BT include rapid rate of growth, harder consistency, or fixation to the underlying muscles or the overlying skin, which may be severe enough to show fungation (Fig. 3.18). The patient may develop pain and tenderness which are usually due infiltration of the auriculotemporal nerve with the pain being referred to the ipsilateral ear. Trismus due to invasion of the masseter or pterygoid muscles or due to restricted movements of the temporomandibular joint (TMJ) is another finding.

In 10–15 % of the cases, the facial nerve will be paralyzed. Unequal pulsations of superficial temporal artery may as well be noticed. Manifestations of metastases to regional LNs or distant organs such as the lungs or the liver may ensue. On the first suspicion of any change in the behavior of the preexisting tumor, FNAC should be done immediately after MRI preferably with a diffusion-weighted and perfusion sequences.

Spread of parotid malignancy occurs through the well-established routes of metastases, where the first echelon LN is the intra- and peri-glandular nodes. The next echelon is level II LNs. Local spread can affect any of the critical nearby organs. Hematogenous spread occurs very late and is mainly to the lungs and bones particularly the vertebral column. However, adenoid cystic carcinoma (ACC) tends to grow through perineural lymphatics with increased risk of nerve affection and intracranial extension, as well as increased rate of recurrence.

Mucoepidermoid Carcinoma (MEC)

This is the most common malignancy of the salivary glands [125] and that of the parotid gland (80 % of cases) seems to be less aggressive than that of the submandibular gland (8–13 % of cases) and of better prognosis [126]. It mostly occurs around an age of 50 years, but still, it is the most common salivary malignancy of the pediatric age group [126, 127].

Low-grade and high-grade variants are recognized, where the low-grade one very rarely metastasizes [128–130]. It usually presents as a slowly growing painless mass; however, rapid growth, pain, and tenderness may be seen with the high-grade variant [131, 132] (Fig. 3.19). Metastases occur to LNs, lungs, and bones [126]. Treatment is surgical resection. Neck dissection is needed in high-grade variants [128].

Prognosis is influenced by the grade and stage of the tumor and patient's age and gender. Overall 5-year survival rates range from 92 to 100 % for low-grade tumors and 0 to 43 % for high-grade tumors [133].

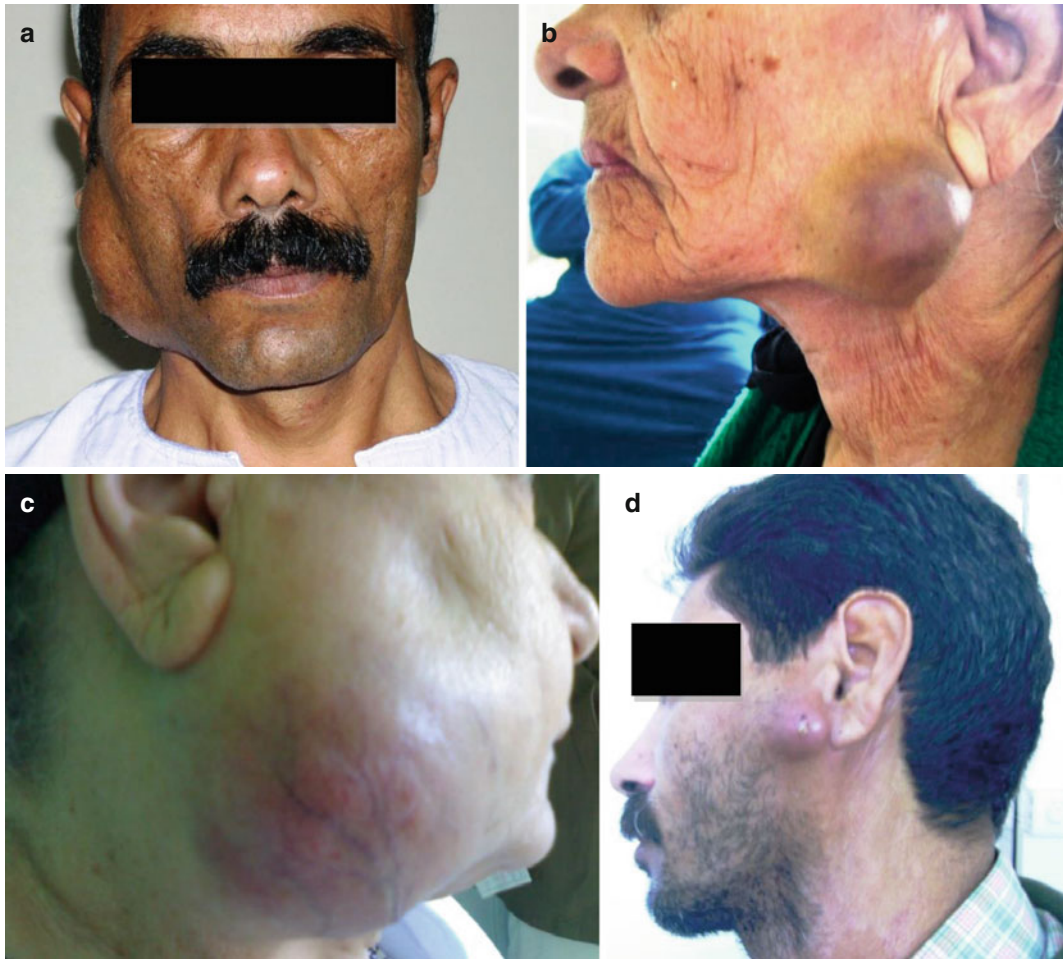

Fig. 3.18 Malignant tumors of the parotid gland present with a hard, rapidly growing mass (**a**) that may become fixed to the overlying skin (**b**) and with erythema and increased vascularity (**c**) miming an abscess and may be severe enough to show fungation (**d**)

Adenoid Cystic Carcinoma (ACC)

This tumor has been given many names since it was first described by *Robin and colleagues* in 1853. From these names, "cylindroma" was particularly discouraged to avoid confusion with the benign cutaneous appendage tumor carrying the same name. This tumor arises not only from major and minor salivary glands but also from seromucous glands throughout the body [134, 135]. It is the second most common salivary malignancy and affects patients between 40 and 60 years of age. It is a slowly growing tumor frequently presenting as a painless mass giving a false sense of security. Lymph node metastases are uncommon, but distant metastases occur in up to 60 % of the cases, mainly to the liver, lung, bones, and brain [135, 136]. It has a high affinity to perineural invasion, which results in paresthesia or paralysis of the nerve affected.

Histologically, low-grade (Fig. 3.20) and high-grade (Fig. 3.21) variants are recognized. Best results of treatment are obtained through radical surgery and postoperative radiotherapy. The tumor is radiosensitive but not radiocurable. Although controversial, neck dissection may be reserved for patients with clinically positive LNs [136–138]. Some studies showed that age over 45 years, advanced clinical stage, paresthesia, as

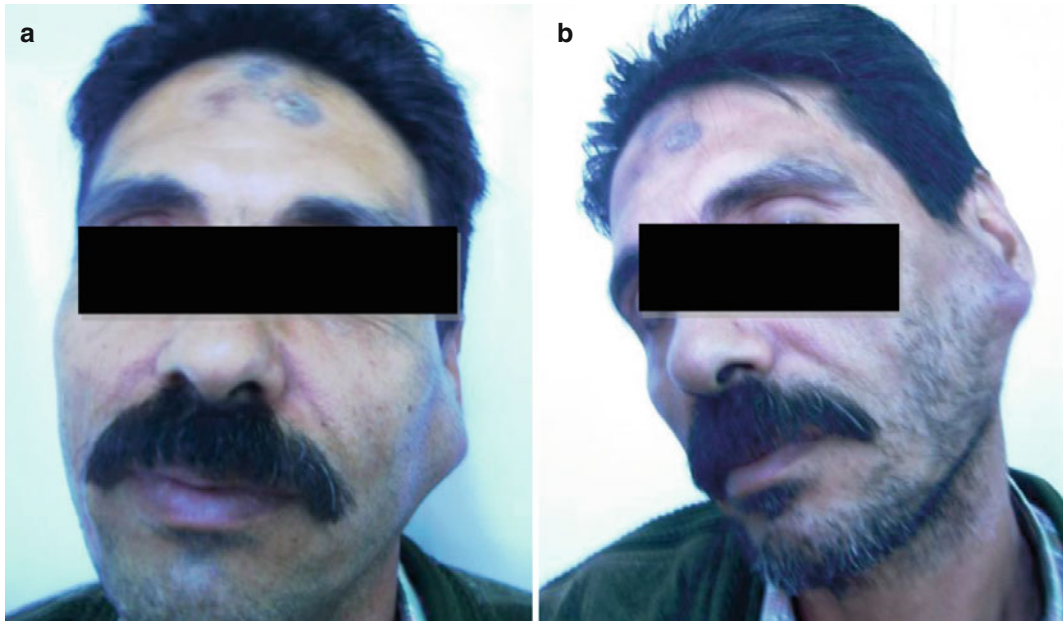

Fig. 3.19 A rapidly growing (high-grade) mucoepidermoid carcinoma (MEC) in a 51-year-old gentleman (**a**) that became fixed to the overlying skin (**b**) within 2 weeks of presentation

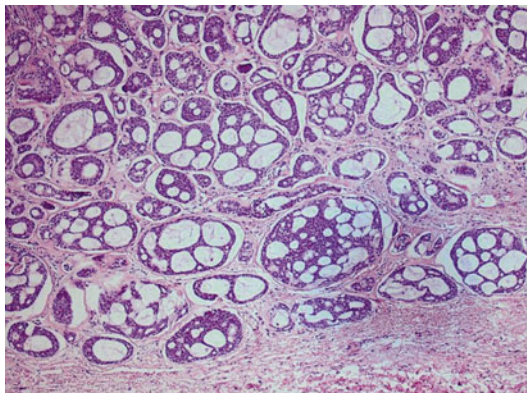

Fig. 3.20 Low-grade adenoid cystic carcinoma (ACC) with a notable cribriform pattern (H&E, ×100)

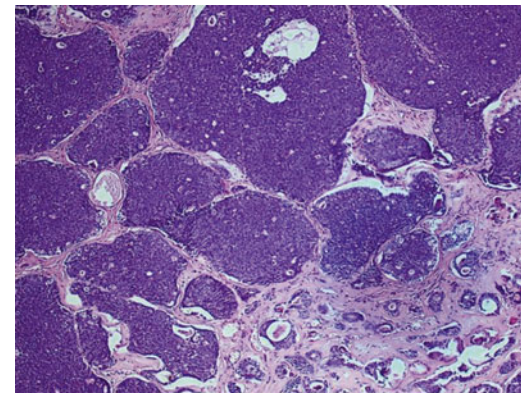

Fig. 3.21 High-grade adenoid cystic carcinoma (ACC) with a predominant (>70 %) solid pattern. The lower right corner still depicts tubular structures (H&E, ×100)

well as increased expression of p53 are associated with poor prognosis [135, 136].

Carcinoma Ex-pleomorphic Adenoma (CEPA)

This is by definition the malignant transformation of a long-standing PA, which occurs in about 25 % of such cases [138–140]. Clinical features predictive of malignant transformation are age, tumor size, long history, and submandibular location. Histologically, the presence of hyalinized stroma is the most predictive parameter for malignant transformation [64, 108]. The carcinoma is usually a high-grade adenocarcinoma or an undifferentiated carcinoma although numerous other types including SCC, MEC, ACC, myoepithelial carcinoma, clear-cell carcinoma, papillary carcinoma, and terminal duct carcinoma

have been reported. Carcinoma ex-pleomorphic adenoma (CEPA) occurs in the major salivary glands in 80 % of the cases, from which again 80 % occurs in the parotid gland. The average age at diagnosis is 50–60 years, which is approximately 10 years older than most individuals with PA. It is extremely uncommon in individuals below the age of 20 years [138, 141]. In 12–55 % of cases, rapid enlargement will be painful and often associated with facial nerve palsy and fixation to the surrounding soft tissues [142].

This carcinoma metastasizes in up to 70 % of the cases to distant sites rather than regionally, with special affinity to the lungs and the vertebral column. Treatment is surgical resection usually with neck dissection. In situ variant is that tumor which did not invade the capsule of a PA and thence was diagnosed postoperatively. In this case, the performed standard resection of a PA is considered curative.

True Malignant Mixed Tumor (TMMT)

True malignant mixed tumor is a very rare neoplasm that may be regarded as carcinosarcoma since both epithelial and stromal components are histologically malignant and both can metastasize. Such metastases are more commonly via a hematogenous rather than lymphatic route, with the lungs and bones being the most frequent sites [143, 144]. There is a wide range of age affection (14–87 years) and there is no sex predilection [144, 145]. Clinical presentation is similar to that of CEPA. Treatment is surgical resection, combined with radiation and chemotherapy. Even with such radical treatment, most patients die within 5 years [141].

Acinic Cell Carcinoma

It is a rare tumor, which is indistinguishable clinically from benign parotid neoplasms being of low-grade malignancy [146, 147]. Yet, it can rarely dedifferentiate into an aggressive high-grade tumor. The parotid gland is the most common site (80 %) followed by the minor salivary glands (16 %) and the submandibular gland (4 %). It is second to Warthin's tumor in bilateral incidence [148], and second to MEC in pediatric age group involvement [149]. Patients typically present with a slowly enlarging painless mass that is not fixed to the surrounding soft tissue or skin. Pain occurs in approximately 22 % of patients and facial nerve palsy in nearly 3–8 % [146, 150].

Treatment is complete surgical resection. Neck dissection is usually not recommended because of the relatively low incidence of metastases to regional LNs [146]. It is usually radioresistant; however, radiotherapy is resorted to when complete resection is not achieved, in case of perineural invasion and if LNs are affected [151, 152]. The recurrence rate averages 10–35 % and the distant metastatic rate 13–16 % [146, 148]. The 5-year survival rate ranges from 78 to 90 % [153, 154].

Basal Cell Adenocarcinoma

Basal cell adenocarcinoma is the malignant counterpart of basal cell adenoma (BCA). It is an uncommon low-grade malignancy that accounts for approximately 1.5 % of all salivary gland tumors and 3 % of all salivary gland malignancies [155]. There is no sex predilection [156], and most patients are in their sixth or seventh decade, although cases have been reported in individuals as young as 2 months and as old as 92 years [155–160]. Most of these tumors arise de novo, as origin in a preexisting BCA is uncommon and usually involves the membranous subtype [156, 157, 160]. Approximately 90 % of the tumors arise in the major salivary glands with the vast majority involving the parotid gland [161]. Patients usually present with a slowly growing asymptomatic mass. Pain and tenderness are uncommon [162]. In 10–15 % of cases, it occurs in conjunction with dermal cylindromas and trichoepitheliomas. This association is lower than the 40 % association of BCA with these dermal tumors [163]. Treatment is complete surgical excision, with neck dissection being reserved for patients with clinically positive LNs [119, 164, 165].

Myoepithelial Carcinoma (Malignant Myoepithelioma)

Myoepithelial carcinoma is the malignant counterpart of myoepithelioma. By definition it is composed of myoepithelial cells with an infiltrative growth pattern. It is a rare tumor accounting for

only 0.2 % of all epithelial salivary gland tumors [119] and involving the parotid glands in 75 % of cases [119, 163, 164]. Approximately 50 % of cases arise in a preexisting BT, usually a PA or a myoepithelioma. Myoepithelial carcinoma is most common in the sixth and seventh decades and occurs with no sex predilection [119]. A painless mass is usually the only clinical complaint. Treatment is complete surgical excision. The clinical behavior of this tumor is unpredictable and unrelated to histological features [165].

Cystadenocarcinoma

Cystadenocarcinomas of the salivary glands are low-grade cystic neoplasms, which are twice as common in the major salivary glands as in the minor salivary glands, and most frequently occur in the parotid [166]. The majority of patients (75 %) are over the age of 50 years [166]. Recognizing these tumors as carcinomas is predicated by finding areas of infiltrative growth. Perineural invasion is not a feature of this neoplasm. Complete surgical excision is usually curative as these tumors are of low-grade malignancy [167].

3.5.9 Parotidectomy

3.5.9.1 Superficial Parotidectomy

The operation is performed under *general anesthesia* with endotracheal intubation with the patient lying supine with the neck hyperextended and the neck turned to the opposite side. If facial nerve monitoring is to be used intraoperatively, nerve electrodes are placed in the ipsilateral facial muscles and tested for electrical integrity.

A modified *Blair (lazy-S) incision* is planned in the preauricular skin crease just in front of the external auditory meatus (EAM), coursing around the ear lobule to the base of the mastoid process and then into an upper neck crease. An alternative incision is a *modified face-lift incision*, which starts behind the tragus down to the lobule of the ear and then behind the ear in the crease and then curved in the hairline for a short distance as indicated.

The skin incision is carried down through the subcutaneous (SC) tissues and platysma muscle. Care is taken to avoid division of the greater auricular nerve. An anterior thick flap is elevated superficial to the greater auricular nerve (which is preserved whenever possible) and the parotid fascia. A posterior, inferior flap is also elevated to expose the tail of the parotid gland. The flaps are retracted with silk sutures or self-retaining hooks.

The tail of the parotid gland is dissected off of the sternocleidomastoid (SCM) muscle and is then elevated to expose the posterior belly of the digastric muscle, which serves as a landmark for the facial nerve. The preauricular space is opened by division of the attachments of the parotid gland to the cartilaginous external auditory canal to expose the tragal cartilage *pointer*, which serves as another landmark for the facial nerve. Thus, identification of the facial nerve is guided by certain anatomic landmarks that include the posterior belly of the digastric muscle, the mastoid tip, the tragal cartilage pointer, and the tympanomastoid suture. If the proximal segment of the facial nerve is obscured, retrograde dissection of one or more of the peripheral facial nerve branches may be necessary to identify the main trunk.

Once the facial nerve is identified, the parotid gland superficial to the facial nerve is divided carefully, preserving the integrity of the nerve. Any bleeding that occurs related to division of the gland is carefully controlled under vision. The facial nerve is followed peripherally, the desired portion of the gland is dissected from successive facial nerve branches and the specimen removed (Fig. 3.22). The facial nerve is preserved except in cases when confirmed malignancy is found invading the nerve. Immediate nerve reconstruction by a nerve interposition graft is usually indicated if resection of the nerve is performed.

A neck dissection is performed for clinically positive LNs. For the clinically negative neck, the first echelon nodes are inspected. Enlarged or suspicious LNs are examined, and a neck dissection is performed if metastatic disease is confirmed by frozen section.

The wound is irrigated with normal saline solution and closed in layers over a closed suction drain, which is usually removed on the first

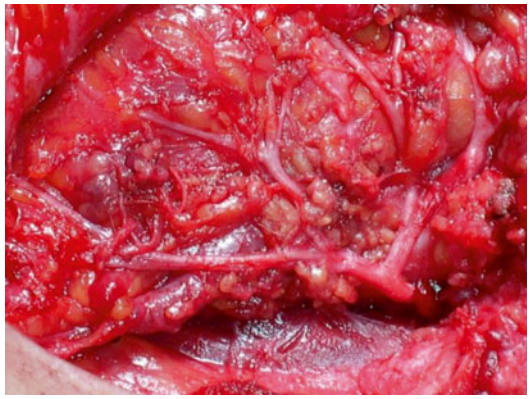

Fig. 3.22 The facial trunk is dissected and followed peripherally to expose and preserve the two divisions and terminal branches before removing the specimen

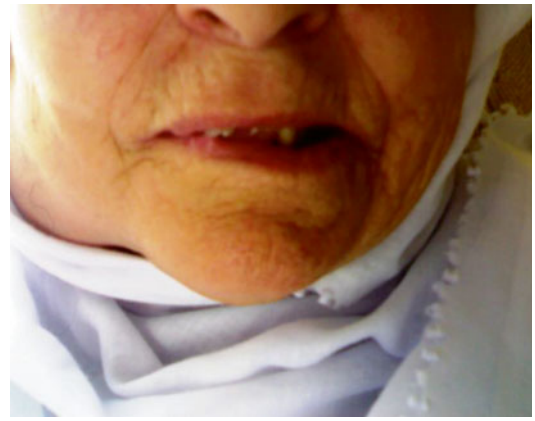

Fig. 3.23 Deviation of the angle of the mouth toward the sound side

Table 3.2 Complications following parotidectomy

Early complications	Late complications
Facial nerve palsy	Frey's syndrome
Bleeding/hematoma	Hypertrophic scar/ keloid
Surgical site infection (SSI)	Recurrence
Skin flap necrosis	Unsightly scar
Salivary fistula/sialocele	Soft tissue defect
Seroma	
External otitis	
Trismus	

postoperative day and the skin sutures are removed within 1 week.

Adjuvant radiation therapy is recommended for selected malignancies including metastatic cutaneous SCC and high-grade and advanced parotid malignancies.

Complications

Early and late complications of superficial parotidectomy are summarized in Table 3.2.

Temporary facial nerve paralysis involving all or any of the branches of the nerve occurs in 10–30 % of superficial parotidectomies [168–172], while *permanent paralysis* occurs in <1 % [171, 172]. The nerve at most risk for injury is the marginal mandibular branch resulting in deviation of the angle of the mouth toward the normal (sound) side (Fig. 3.23) [170–172]. Temporary paresis usually resolves from weeks to months postoperatively. Nerve transection requires immediate microsurgical repair.

Hemorrhage or hematoma is uncommon after superficial parotidectomy and is usually related to incomplete hemostasis during the procedure. Treatment consists of evacuation of the hematoma and surgical control of any identified bleeding vessels under general anesthesia.

Infection is also an uncommon complication after superficial parotidectomy due to the rich vascular supply to the parotid region. It is avoided by the use of aseptic techniques and careful handling of tissues. Perioperative antibiotics are generally not used. Treatment of infection consists of appropriate antibiotics. Abscess formation is rare and requires surgical incision and drainage together with the appropriate antibiotics. *External otitis* can occur postoperatively and can be related to intraoperative blood collection in the external auditory canal. Treatment consists of cleaning the auditory canal and instillation of antibiotic eardrops.

Skin flap necrosis is an uncommon complication. The distal tip of the postauricular skin flap is the most common location of flap necrosis. Smoking, prior radiation therapy, and DM may contribute to this complication by impairing the blood supply to the flap. Treatment entails conservative debridement of necrotic tissue and local wound care.

Salivary fistula or sialocele can occur after superficial parotidectomy in nearly10 % of cases [173] and results from leakage of saliva from

remaining salivary gland tissue. It is usually mild and self-limited. A sialocele is usually treated with repeated needle aspirations. A salivary fistula is managed with local wound care. A chronic salivary fistula is rare following superficial parotidectomy.

Mild trismus may occur following superficial parotidectomy and may be related to inflammation and fibrosis of the masseter muscle. This complication usually resolves with range of motion exercises of the jaw.

Frey's Syndrome (Gustatory Sweating)

Frey's syndrome is now considered an inevitable long-term complication following parotidectomy unless preventive measures are taken [174]. It results from aberrant reinnervation of cholinergic sympathetic sweat glands in the skin with postganglionic fibers from the auriculotemporal nerve that have been exposed following parotidectomy. Thus, a stimulus intended for saliva stimulation evokes hyperesthesia and sweating. The patient complains of facial sweating and hotness on smell or taste of food, which might sometimes be associated with pain. Diagnosis can be confirmed with starch-iodine test.

Preventive measures include SCM flap, temporalis fascial flap, and insertion of an artificial membrane between the skin and the parotid bed. Treatment options include auriculotemporal nerve avulsion and/or tympanic neurectomy. Medical treatment of symptomatic Frey's syndrome includes topical application of antiperspirant and topical anticholinergics (1 % glycopyrrolate); however, recently, local intradermal injection of botulinum toxin has yielded good results. Botulinum toxin blocks the release of acetylcholine from presynaptic neurons. It is postulated to provide long-term results due to poor reinnervation of the skin's cholinergic sweat glands. It is performed as an outpatient.

3.5.9.2 Total Parotidectomy

While superficial parotidectomy entails removal of the lateral portion of the parotid gland with preservation of the facial nerve, total parotidectomy is complete removal of the superficial and deep lobes of the parotid. It should be performed for MTs in the following situations: (1) metastasis to a superficial parotid LN from a primary parotid tumor or an extra-parotid malignancy, (2) any parotid malignancy with metastatic involvement of cervical LNs, (3) any high-grade parotid MT with a high risk of metastasis, (4) primary parotid MT originating in the deep lobe, and (5) primary malignancies that extend outside the parotid gland. Total parotidectomy is also performed for multifocal tumors, such as oncocytomas, to ensure complete resection. The operation may involve sparing or sacrificing the facial nerve branches or trunk depending on tumor extent to the nerve.

3.5.9.3 Extended Total Parotidectomy

Excision of the superficial and deep lobes of the parotid gland (total parotidectomy) may also be extended to involve adjacent structures such as the overlying skin, the underlying mandible, the temporal bone and external auditory canal, or the deep musculature of the parapharyngeal space. Such extensions are dictated by tumor growth and behavior. Patients with extensive parotid malignancies should be counseled regarding the possibility of extended resections and the resulting functional and cosmetic morbidity. The head and neck surgeon needs to anticipate the extent of defect and incorporate plans for reconstruction into the overall surgical plan.

3.6 Submandibular Glands

The submandibular gland is the second largest major salivary gland and weighs approximately 10 g. It is classified *as mixed gland* that is predominantly serous with tubular acini. Approximately 90 % of acinar cells are serous and only 10 % are mucinous.

3.6.1 Surgical Anatomy

The submandibular gland is located in the submandibular triangle, which is bounded superiorly by the inferior edge of the mandible and inferiorly by the anterior and posterior bellies of the

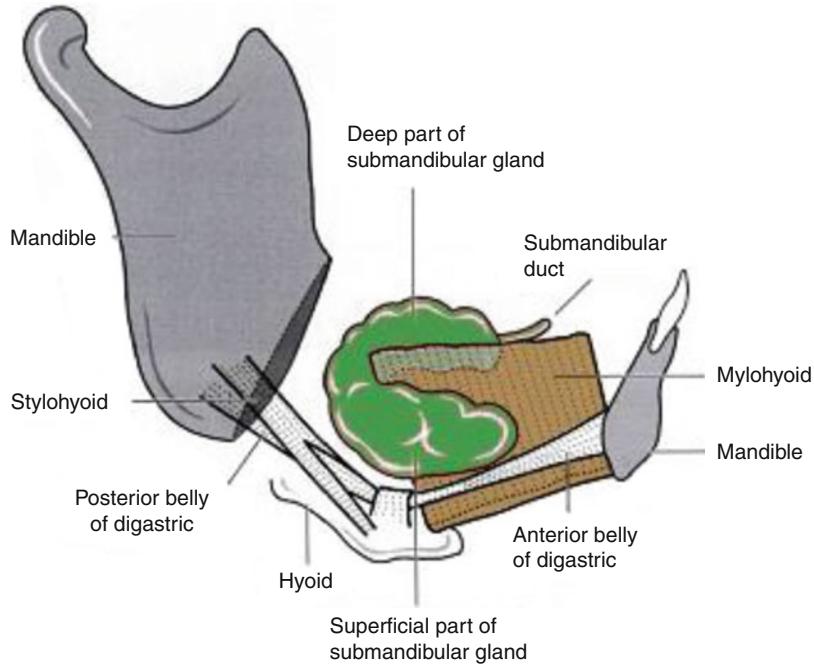

Fig. 3.24 Relationship of the superficial and deep parts of the submandibular gland with the mylohyoid muscle

digastrics muscle. It contains several important neurovascular structures, in addition to the submandibular gland, namely, the marginal mandibular branch of facial nerve, the lingual nerve, the hypoglossal nerve, and the facial artery, as well as lymph nodes (LNs) that can harbor regional metastases from oral and oropharyngeal primary tumors [4, 16, 17].

The submandibular gland lies on the hyoglossus muscle, superficial to the hypoglossal and lingual nerves, and can be arbitrarily divided into superficial and deep parts or lobes according to its relationship with the mylohyoid muscle (Fig. 3.24). The superficial lobe lies superficial to the muscle, reaching upward under cover of the mandible, and is separated posteriorly from the parotid gland by the stylomandibular ligament (Fig. 3.25).

The smaller deep lobe wraps around the posterior aspect of the mylohyoid muscle, and its anterior end reaches as far as the sublingual gland (Fig. 3.26). During submandibular sialoadenectomy or neck dissection, the mylohyoid muscle must be gently retracted anteriorly to expose the lingual nerve and the submandibular ganglion.

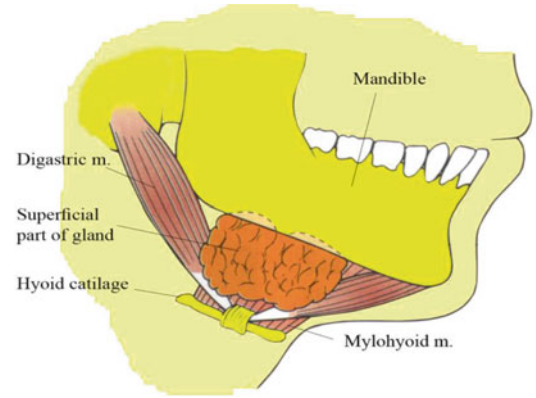

Fig. 3.25 The superficial part of the submandibular gland lying on the mylohyoid muscle and reaching up under cover of the mandible

3.6.1.1 Fascia

The submandibular gland is covered by a capsule derived from the middle layer of the deep cervical fascia. The marginal mandibular branch of the facial nerve lies superficial to this fascia. Thus, division of the submandibular gland fascia, when oncologically appropriate, is a reliable method for preserving the nerve during neck dissection and/or gland resection.

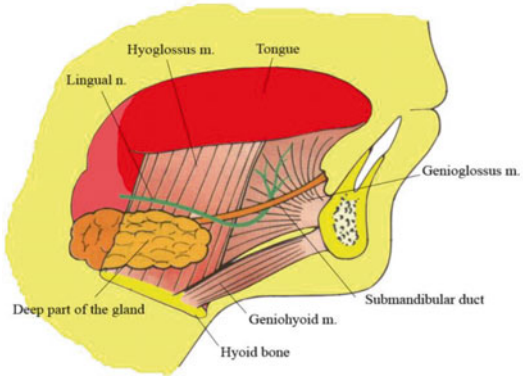

Fig. 3.26 The deep part of the submandibular gland lying on the hyoglossus muscle and the submandibular duct emerges from its anterior end. At the anterior edge of the muscle, the duct is crossed laterally by the lingual nerve

3.6.1.2 Submandibular Duct (Wharton's Duct)

The submandibular gland has both mucous and serous cells that empty into ductules, which in turn empty into the submandibular duct (Wharton's duct) (*Thomas Wharton, 1616–1675, Physician, St. Thomas's Hospital, London, UK*), which is about 4–5 cm long. It emerges from the anterior end of the deep part of the gland, runs anteriorly between the hyoglossus and mylohyoid muscles on the genioglossus muscle, and opens in the oral cavity on the summit of a small papilla, near the frenulum of the tongue behind the lower incisor tooth. On the hyoglossus muscle, it lies between the hypoglossal and lingual nerves, but at the anterior border of the muscle, it is crossed laterally by the lingual nerve (Fig. 3.26), which then ascends medial to the duct. The sublingual veins lie lateral and the sublingual artery medial to the duct, more anteriorly.

3.6.1.3 Lingual Nerve

The lingual nerve, a branch of the marginal mandibular branch of the fifth cranial nerve (CN V), supplies the gland with parasympathetic innervation by means of the chorda tympani nerve (from the seventh cranial nerve, CN VII) and the submandibular ganglion. The lingual nerve passes forward and downward between the duct and the deep part of the gland before passing medially under the duct opposite the first lower molar. While still lateral to the duct, it gives off its sublingual branch, which runs close to the mandible, lateral to the sublingual glands. During submandibular sialoadenectomy, care should be taken to preserve the lingual nerve as it supplies the general sensation and taste to the anterior two-thirds of the tongue.

3.6.1.4 Facial Artery

The submandibular gland is supplied by branches of the facial (main supply) and lingual arteries, branches of the external carotid artery (ECA). The facial artery emerges from under the stylohyoid muscle, runs medial to the posterior belly of the digastric muscle, and then hooks over to pass upward deep to the gland. The artery exits the superior border of the gland at the lower border of the mandible (facial notch), around which it curls to enter the face. During resection of the submandibular gland, the facial artery must be sacrificed twice, first at the inferior border of the mandible and again just superior to the posterior belly of the digastric muscle. The lingual artery runs deep to the digastric muscle along the lateral surface of the middle constrictor muscle and then courses anterior and medial to the hyoglossus muscle and gives off braches to the submandibular gland.

3.6.1.5 Venous Drainage

The submandibular gland is mainly drained by the anterior facial vein (AFV) and to a lesser extent by the venae comitantes of the lingual artery. The anterior facial vein is in close approximation to the facial artery as it runs posteriorly and inferiorly from the face to the lower aspect of the mandible. Since it lies deep to the marginal (mandibular) branch of the facial nerve (CN VII), ligation and superior retraction of the AFV can help preserve this important nerve during surgery of the submandibular gland.

3.6.1.6 Lymphatic Drainage

Lymph nodes draining the submandibular gland are not embedded in the glandular tissue. They are located between the gland and its fascia, in close relation to the facial artery and vein at the superior aspect of the gland, and drain into the deep cervical and jugular chains. These lymph nodes are frequently associated with cancers in

the oral cavity. Thus, care should be taken during ligation of the facial vessels and dissection of the lympho-adipose tissue, to preserve the marginal mandibular branch of the facial nerve, which runs in close proximity to these structures.

3.6.2 Evaluation of the Submandibular Gland

3.6.2.1 Clinical Evaluation

History Taking

Patients with submandibular gland disorders usually complain of swelling and pain during meals followed by reduction in symptoms after meals, which may indicate partial stenosis of Wharton's duct. As with parotid gland disorders, *demographic* data, *medical and nutritional profile* of the patient, as well as history of *medications* and *radiation* can provide helpful clues to the diagnosis of submandibular gland diseases [21, 22].

Physical Examination

Extraoral, intraoral, and bimanual examinations (extraoral with one hand and intraoral with the palmar aspects of the fingertips of the other) should be performed to properly evaluate the submandibular glands clinically.

Extraoral Examination

Extraoral Inspection With the patient facing in front of the examiner, three to four feet away, the examiner should inspect symmetry, color, pulsations, and discharging sinuses on both sides of the patient. Enlargement of the submandibular gland may be unilateral or bilateral. A submandibular swelling presents just medial and inferior to the angle of the mandible. It is often confused with enlargement of LNs, but a submandibular gland swelling is single and generally larger and smoother. Palpation and bimanual examination are necessary to differentiate between both conditions. Significant neurologic deficits should be examined as well. Paralysis of the marginal mandibular branch of the facial nerve with deviation of the angle of the mouth to the sound opposite side should alert the examiner to a malignant submandibular neoplasm.

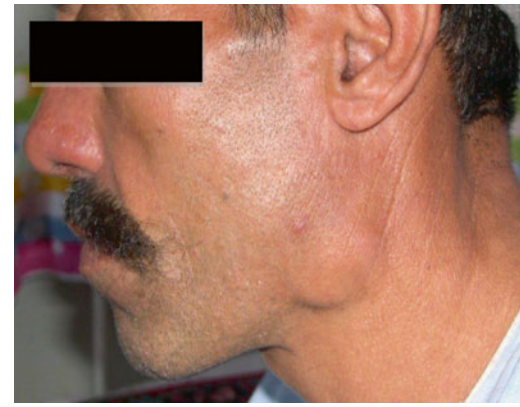

Fig. 3.27 A 43-year-old gentleman with an enlarged left submandibular LN (could be rolled over the mandible contrary to a submandibular gland swelling)

Extraoral Palpation Owing to the superficial anatomical location of the submandibular gland, the size, tenderness, consistency, mobility, and surface of the gland and associated masses can be easily assessed. If the swelling can be rolled over the lower border of the mandible, it is an enlarged LN (Fig. 3.27) and not a submandibular gland swelling since the latter's mobility is restricted by its fascial covering and attachment.

Intraoral Examination

Intraoral Inspection Using a torch or headlight, the orifices of the submandibular ducts are inspected and compared using a light source. They lie on either side of the frenulum of the tongue. A stone (*sialolithiasis*) may be seen exuding from the orifice with edema and redness. Saliva may be seen pouring from the non-affected side only. A *swelling* may be seen in the floor of the mouth, and its characters are recorded. For example, a *ranula* is bluish and transparent, whereas a *dermoid cyst* is yellow and opaque. Dental hygiene and the presence of periodontal disease should also be noted during intraoral inspection.

Intraoral Palpation The gloved index finger is inserted into the mouth, and palpation is started from behind at the end of the alveolus anteriorly. The gland and duct are palpated. A stone may be felt.

Bimanual Examination

With one or two gloved fingers palpating the floor of the mouth and the fingers of the other hand palpating beneath the jaw, a salivary gland swelling is felt to have two components, buccal and cervical. It becomes fixed when the patient contracts the mylohyoid muscle. This is done by asking the patient to open the mouth against resistance by the examiner. If a submandibular gland swelling is felt bimanually, its consistency must be noted. A hard swelling may be a stone or carcinoma, while a firm mass may be due to mixed salivary tumor or chronic sialadenitis. Increased salivation from the duct orifice due to external pressure applied to the gland may indicate inflammation [21, 22].

3.6.2.2 Imaging

Imaging studies can aid in reaching the etiology of the submandibular gland disorders and assist in selection and planning of proper management.

Plain-Film Radiographs

Since the majority (approximately 70 %) of submandibular gland stones (sialolithiasis) is radiopaque, plain X-ray (PXR) using the anteroposterior (AP), lateral, and oblique lateral occlusal views will be valuable in evaluating the presence of such calculi. Conventional plain radiography may also help in detection of infiltration of the mandible by a malignant neoplasm. A plain chest X-ray (CXR) may also be helpful in cases of suspected pulmonary metastases.

Sialography

Sialography can be used to evaluate sialolithiasis (filling defect) and other obstructive disorders (stricture), inflammatory disease (retained secretions), and neoplastic lesions (irregular borders of the submandibular gland). Fistulae and abscesses cavities can also be displayed with this technique. It is, however, contraindicated in cases of acute sialadenitis and presence of iodine allergy.

Computed Tomography (CT)

Imaging with CT can differentiate intrinsic from extrinsic disease, elucidate relationships to adjacent vital structures, assess the draining cervical LNs, and define abscess formation versus phlegmon. However, it is limited in evaluating the ductal system unless combined with simultaneous sialography [23]. Although stones can be identified with CT scanning, submandibular sialadenitis is not generally an indication for CT.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging provides better contrast resolution than CT, exposes the patient to less harmful radiation, and yields detailed images on several different planes without patient repositioning. However, it is inferior to CT scanning for the detection of calcification and early bone erosion. Chronic inflammation of the submandibular gland and calculi are not indications for MRI.

3.6.2.3 Endoscopic Examination (Sialendoscopy)

Sialendoscopy, a recent well-tolerated minimally invasive technique, allows direct inspection of the glandular duct and hilum [25]. Through a CO_2-laser papillotomy, sialolithectomy can be easily performed. Pharmacotherapy and laser ablation can also be carried out [26]. This relatively new technique has shown much promise in the diagnosis and treatment of chronic obstructive sialadenitis (COS) and sialolithiasis [27].

3.6.2.4 Biopsy

Fine-needle aspiration cytology (FNAC) should be undertaken if a solid neoplasm masquerading as sialadenitis is suspected. Open biopsy of the lip should be considered when the diagnosis of Sjogren's disease is contemplated.

3.6.3 Submandibular Sialadenitis/ Sialadenosis

3.6.3.1 Acute Submandibular Sialadenitis

Etiology

Acute submandibular sialadenitis is acute inflammation of the submandibular salivary gland. It is usually secondary to obstruction of Wharton's duct and is often recurrent. The most common

organism is *Staphylococcus aureus*. Other *bacterial* organisms include *Streptococcus viridans*, *Haemophilus influenzae*, *Streptococcus pyogenes*, and *Escherichia coli*. Infection is often the result of dehydration with overgrowth of the oral flora. The most common causes are postoperative dehydration, radiation therapy, and immunosuppression. Though rare in the neonate and prepubescent child, infection of the submandibular gland can result from other pathogens such as *Pseudomona aeruginosa* and group B streptococci.

Though less common than bacteria, several *viruses* have been implicated in acute submandibular sialadenitis including mumps virus (typically affects the parotid gland), HIV, Coxsackie virus, parainfluenza types I and II, influenza, and herpes.

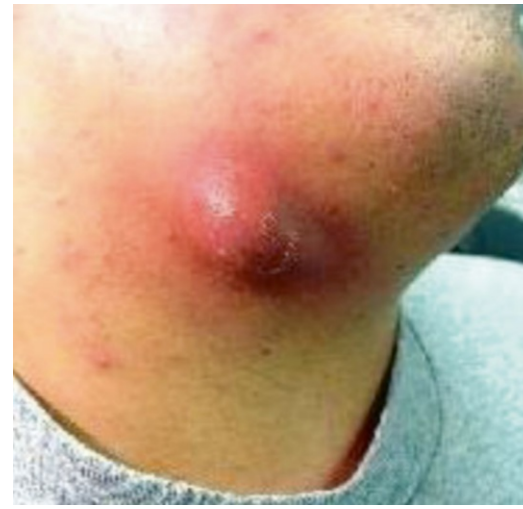

Fig. 3.28 A 33-year-old gentleman with a right submandibular gland abscess with overlying erythema and edema

Clinical Picture

There is no *age* predilection; however, sialadenitis in general tends to occur in older, debilitated or dehydrated patients [175]. No *race or sex* predilection per se exists.

The patient usually *complains* of a painful swelling in the submandibular region and salivary colic, i.e., pain and swelling of the gland with meals. Pain may be referred to teeth or tongue. Infection of the submandibular gland can result in the formation of a submandibular *abscess* (Fig. 3.28). In such cases, the patient may appear toxic with feature similar to acute sialadenitis and, sometimes, spiking fever. The infection may spread to other deep spaces of the neck. *Trismus* may be indicative of parapharyngeal space involvement. Progression to *Ludwig angina*, a life-threatening infection of the submental and sublingual spaces, although rare, may occur.

Physical examination should begin with the gland itself. A tender swelling is felt bimanually. A stone in the duct may also be felt. The orifice of the duct will appear congested and edematous. It may pour drops of purulent saliva on squeezing the duct. Palpation should extend to include the floor of the mouth, tongue, cheek, and neck. All of the major salivary glands should be examined for masses, symmetry, and the presence of discharge. Cervical lymphadenopathy should also be noted. Both eyes should be examined for interstitial keratitis and a cranial nerve examination should be conducted with particular attention to cranial nerves VII and XII.

Investigations (Workup of the Patient)

Laboratory investigations should begin with culture of the offending gland prior to administration of antibiotics, in addition to blood cultures in presence of bacteremia or sepsis. As a rule, needle aspiration of a suspected abscess is not indicated. Electrolytes and complete blood count (CBC) with differential should be obtained to assess for any evidence of dehydration or systemic infection.

Imaging studies should begin with conventional PXR, which is particularly valuable in evaluating the presence of calculi. Sialography is contraindicated in acute sialadenitis. Ultrasonography (US) can differentiate between solid versus cystic lesions of the gland and is helpful in the identification of abscess formation. Computed tomography (CT) scanning is an excellent modality not only in differentiating intrinsic versus extrinsic glandular disease but also in defining abscess formation versus phlegmon. Magnetic resonance imaging (MRI) is of little utility in sialadenitis or sialadenosis.

Treatment

Management of acute submandibular sialadenitis involves a wide range of approaches, from conservative medical treatment to more aggressive surgical intervention.

Medical management focuses on eliminating the causative factor, and the goals of pharmacotherapy are to eradicate the infection, reduce morbidity, and prevent complications. Adequate *hydration* should be ensured and electrolyte imbalances corrected. *Sialogogues* may temporarily increase salivary flow, but this frequently is short lived and better results are obtained by an overall increased fluid intake [176]. Patients are most often treated on an outpatient basis, with the administration of a single dose of parenteral *antibiotics* in an emergency department, followed by oral antibiotics for a period of 7–10 days. Clindamycin (900 mg IV q8h or 300 mg PO q8h) is an excellent choice and provides good coverage against typical organisms. In patients refractory to antibiotics, viral and atypical bacterial causes should be considered. In addition to antibiotics, patients may be treated with *non-steroidal anti-inflammatory* medications, and *narcotics* may be needed in severe cases. When possible, patients are instructed to empty the gland by *external massage*. The submandibular gland is best emptied by a constant compressive motion, starting below the mandible near the angle, with the hand sliding upward toward the chin. A short course of high-dose *steroids* reduces the peri-ductal inflammation and facilitates massage. Patients who are septic, severely dehydrated, or exhibiting significant morbidity should be admitted to hospital, and CT scanning of the affected area should be performed. Small abscesses usually respond to conservative methods; however, if a large abscess is noted, incision and drainage should be considered. Patients with sialolithiasis are initially treated with hydration, warm compresses, and gland massage, as well as antibiotics for the infected gland.

Surgical management includes incision and drainage in case of abscess formation, and excision of the gland, during a period of *quiescence*, in patients with recurrent acute sialadenitis. *Endoscopic management* of sialadenitis frequently obviates the need for gland excision. Results follow a learning curve [177].

Prognosis

The prognosis of acute sialadenitis is very good. Most cases are easily treated with conservative medical measures, and admission is the exception, not the rule. Acute symptoms usually resolve within 5–7 days; however, edema in the area may last several weeks. Patients with sialolithiasis require definitive surgical treatment in most cases, which results in an excellent prognosis.

3.6.3.2 Chronic Submandibular Sialadenitis/Sialolithiasis

Chronic Sialadenitis

Chronic sialadenitis is typically less painful than acute sialadenitis and is associated with recurrent enlargement of the gland (often following meals) typically without erythema (Fig. 3.29). It is associated with conditions linked to decreased salivary flow, rather than dehydration. These conditions include salivary stasis, a change in the fluid and electrolyte composition of the gland, and mechanical obstruction of Wharton's duct. Proximal to the site of chronic obstruction, the duct will be dilated with retention of secretions and chronic infection. Causes of obstruction include calculi, strictures, edema or fibrosis of the

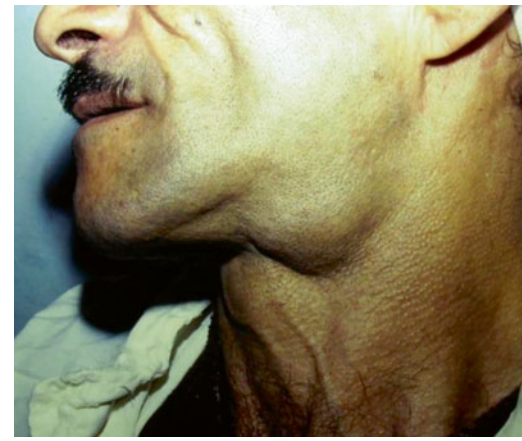

Fig. 3.29 A 56-year-old gentleman with left chronic submandibular sialadenitis. It could not be rolled over the lower edge of the mandible

papilla, pressure on the duct by adjacent masses, or duct invasion by a malignant neoplasm.

Chronic sialadenitis is usually considered a medical disease, with surgical intervention reserved for intractable symptoms of pain and swelling. In patients who present with pain and little demonstrable swelling, sialography may be diagnostic. It may show the evidence of ductal obstruction, the calculus, duct dilatation, sialectasia, or acinar atrophy.

Papillary Stenosis

Ulceration of the papilla of the submandibular duct may follow trauma from a denture. The obstruction and recurrent swelling will subside as the ulcer heals. Repeated trauma results in fibrosis which is only relieved by *papillotomy* with suture of the duct lining to the oral mucosa.

Sialolithiasis

Salivary calculi (sialolithiasis) relate to the formation and deposition of concretions within the ductal system of the gland. Approximately, *85 % of all salivary calculi occur in the submandibular gland* [178], with approximately 70 % of these demonstrable as radiopacities on routine plain radiography. The calculi vary in size and may be single or multiple. The formation of calculi is associated with chronic sialadenitis and, in particular, the recurrent nature of the problem. The exact mechanism of stone formation is unclear, but it appears to be related to the following conditions:

1. Salivary stagnation (stasis): the secretion of the submandibular gland is more viscid than that of the parotid gland, and Wharton's duct is independent (directed forward and upward).
2. Duct obstruction: the end of the duct opens in the floor of the mouth and is more liable to be obstructed by a stone, inflammation, and foreign bodies such as a small piece of a toothbrush or food particles.
3. Epithelial injury along the duct: this results in sialolith formation, which acts as a nidus for further stone formation.
4. Precipitation of calcium salts: the stones themselves are typically composed of calcium phosphate, calcium carbonate, and magnesium phosphate, in association with other salts and organic material such as glycoproteins, desquamated cellular residue, and mucopolysaccharides.

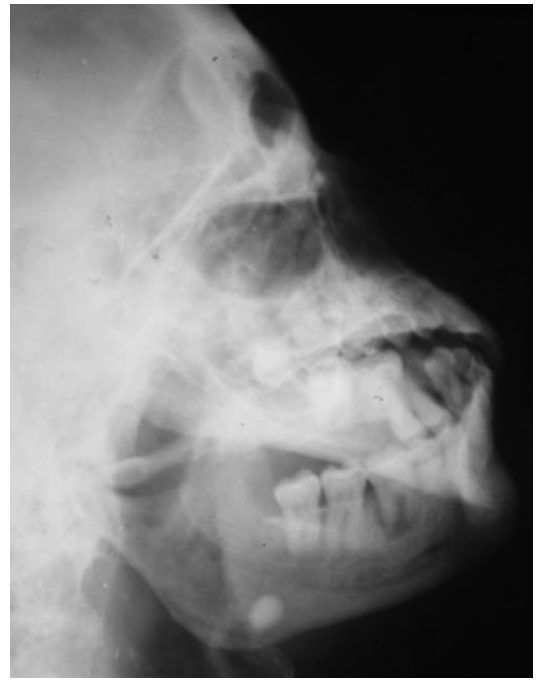

Fig. 3.30 Plain X-ray showing a radiopaque right submandibular calculus

Clinical Picture

The patient presents with a firm or hard submandibular *swelling*, which simulates a tumor and increases in size with meals. *Pain* is associated with meals and this helps to differentiate it from pain of dental origin. Intake of lemon juice (*lemon juice test*) causes aggravation of pain and increase in the size of the swelling.

Oral examination of the orifice of the duct reveals saliva pouring on the unaffected side, with little or no secretion seen ejecting from the swollen (affected) side. With *bimanual examination*, a stone may be felt within the duct or within the gland. The swelling itself may also be felt.

Investigations

Submandibular calculi are relatively easy to demonstrate by *plain radiography* (Fig. 3.30). *Sialography* may show a filling defect, if the stone is translucent (Fig. 3.31). In 2009, Bozzato

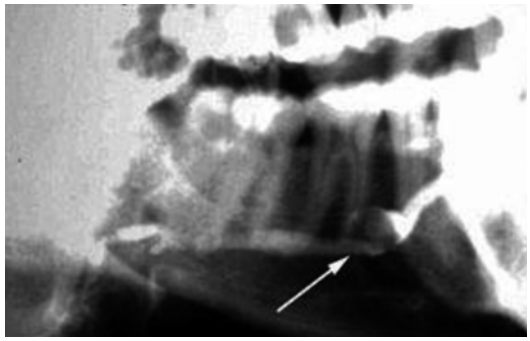

Fig. 3.31 Sialography showing a filling defect in the right submandibular gland indicative of a radiolucent calculus

et al. [179] reported that application of ascorbic acid as a contrast agent can aid in the *ultrasound* assessment of obstructive sialadenitis of the submandibular (and parotid) glands.

Treatment

In patients with *calculi* in proximity of the Wharton's duct opening, the duct can be cannulated and dilated, and the stone removed via a trans-oral approach. For ductal calculi in the floor of the mouth, a stitch is passed under the duct proximal to the stone to stop the stone slipping backward. An incision is made in the mucosa over the duct, which is then mobilized, and a stay suture is passed under the duct to bring it up into the top of the wound and to control it while the wall is incised to release the stone. Patients with deep intraparenchymal stones or multiple stones should have their glands excised on an elective basis. Ultrasonic lithotripsy is rarely effective.

3.6.3.3 Autoimmune Sialadenitis

Sjogren's Syndrome

Autoimmune diseases, in particular *Sjogren's syndrome,* can be associated with sialadenitis, affecting *all* major salivary glands, though preferentially affecting the parotid gland. Minor salivary glands are also affected. In these cases, the salivary and lacrimal glands are infiltrated with lymphocytes, smaller ducts are blocked, and the acini progressively destroyed. Intense infiltration of the gland with lymphocytes can result in diffuse enlargement or the formation of localized nodules, which must be distinguished from neoplasms. *Mucous* gland metaplasia of the duct epithelium leads to the formation of a gelatinous saliva in some patients. Strictures, duct dilatations, and ascending infection complicate the picture. Patients with Sjogren's syndrome are at greater risk than the rest of the population for developing reticulum cell sarcoma, either in the glands or in the related LNs [62].

The disease, which is associated with keratoconjunctivitis sicca, xerostomia, salivary gland enlargement, and lingual papillary atrophy, is confirmed through *biopsy* of the minor salivary glands of the lip. Numerous laboratory tests are also used to confirm the diagnosis, such as autoantibodies Sjogren's syndrome A (SS-A) and Sjogren's syndrome B (SS-B), rheumatoid factor, and antinuclear antibodies. Erythrocyte sedimentation rate (ESR) should also be conducted. Lack of lacrimal secretion can be shown by the *Schirmer test* and keratitis by r*ose bengal and fluorescein* staining.

Good hydration and prevention of complications should be undertaken. The dry eyes can be treated by diathermy obliteration of the lacrimal punctum and the instillation of artificial tears composed of methyl cellulose drops. Dental hygiene should be strictly maintained in order to prevent carries, and dental and rheumatology consults should be sought. Steroids and immunosuppressive agents generally alter the course of the disease but are rarely used in view of their side effects and the increased risk of ascending infection. Gland excision is rarely indicated [63].

Mikulicz's Disease/Syndrome

Mikulicz (*Johann von Mikulicz-Radecki, 1850–1905, a Polish surgeon*) described this disease in 1892 as a triad that includes (1) symmetrical enlargement of all the salivary glands, (2) narrowing of the palpebral fissures due to enlargement of the lacrimal glands, and (3) parchment-like dryness of the mouth.

Mikulicz's disease has been used to describe patients with a benign lymphoepithelial lesion characterized by bilateral lacrimal and salivary gland enlargement. Its meaning is somewhat

vague at present and should best be included as a variant of Sjogren's syndrome with its more specific histopathological changes of lymphoreticular cell proliferation, atrophy of the acinar parenchyma, and duct changes signifying chronic inflammation.

Mikulicz's syndrome, however, is used to describe enlargement of the salivary and lacrimal glands seen with some diseases such as leukemia, lymphoma, tuberculosis, syphilis, and sarcoidosis [176].

3.6.3.4 Sialadenosis

Sialadenosis refers to nonneoplastic noninflammatory swelling in association with acinar hypertrophy and ductal atrophy. *Etiologies* fall into five major categories:

1. Nutritional (e.g., vitamin deficiency, bulimia)
2. Endocrine (e.g., DM, hypothyroidism)
3. Metabolic (e.g., obesity, cirrhosis, malabsorption)
4. Inflammatory/autoimmune (e.g., Sjogren's disease, Heerfordt's syndrome)
5. Drug induced (e.g., thiourea)

Physical examination shows a non-tender swelling that is often bilateral and symmetric but can be unilateral and asymmetric. Treatment should be directed toward managing the underlying problem and achieving homeostasis. Gland excision is *not* indicated.

3.6.4 Tumors of the Submandibular Gland

Tumors of the submandibular gland are the second most frequent major salivary gland neoplasms after tumors in the parotid gland. They account for about 10 % of all salivary neoplasms [180–182], and approximately 50 % are malignant [181, 182].

3.6.4.1 Benign Tumors (BTs)

The most commonly encountered BT of the submandibular gland is the *pleomorphic adenoma* (approximately 50–65 %), the histological features and biological behavior of which are similar

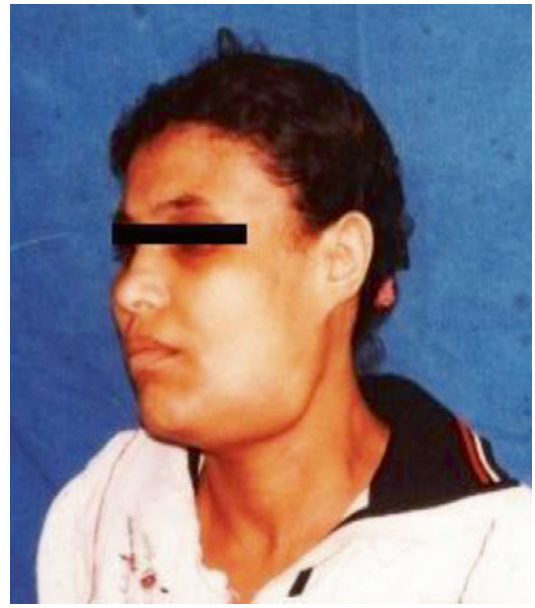

Fig. 3.32 A 27-year-old lady with a slowly growing left submandibular mass (proven histologically to be a pleomorphic adenoma)

to those of the parotid gland, but with an incidence of 1:10, respectively [64, 183, 184]. Typical presentation is that of a slowly growing painless mass (Fig. 3.32). Larger tumors have a multinodular appearance. The high recurrence rate associated is believed to be due to pseudopod formations at the periphery of the tumor and to inadequate excision (enucleation). Recurrence may occur months to years following inadequate excision, and malignant transformation (approximately 2–6 %) may also occur, particularly in long-standing tumors or in those that have recurred [184].

Other types of adenomas, such as the basal cell adenoma, are much less common, and *other BTs*, such as Warthin's tumor, oncocytomas, and myoepitheliomas, are very rarely encountered in submandibular (and sublingual) glands.

Hemangiomas affect mainly the parotid gland (90 % of cases), but occasionally, the submandibular gland is affected, as a part of massive facial lesions.

3.6.4.2 Malignant Tumors (MTs)

Malignant neoplasms of the submandibular (and sublingual glands) can be classified into three

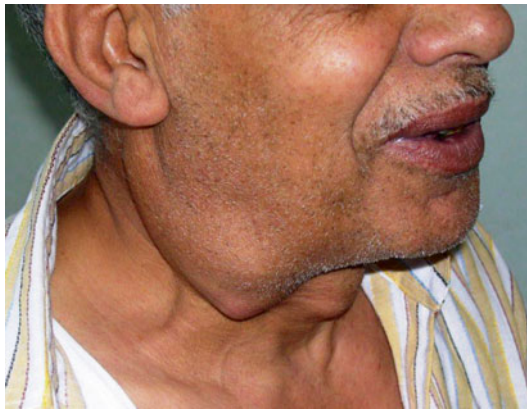

Fig. 3.33 A 62-year-old gentleman with a right submandibular mass of rapid growth, proven by histopathology to be an adenoid cystic carcinoma

major categories: (1) tumors of epithelial origin (MEC, ACC, acinic cell carcinoma, malignant mixed tumor, SCC, salivary duct carcinoma), (2) tumors of non-epithelial origin (sarcomas, lymphomas), and (3) secondary tumors. Among MTs, the most frequent is ACC, accounting for 36–63 % of cases [183–186], followed by MEC (17–22.2 %), SCC (17.3 %), and adenocarcinoma (15.4 %) [185].

Adenoid cystic carcinoma (ACC) usually develops over a short time as a submandibular mass (Fig. 3.33) with rapid growth and is frequently associated with pain and fixation to the mandible. Regional LN metastases may occur in approximately 30 % of patients. This tumor has a propensity to invade nerves, thus posing a risk of perineural spread through the mandibular or cervical branches of the facial nerve and through the lingual and hypoglossal nerves toward the skull base. The risk of distant metastases and the development of late recurrences are similar to those observed in the parotid gland [184].

Mucoepidermoid carcinomas (MEC), the next most common cancer, may be *low, intermediate, or high grade* in their histological appearance, with eventual outcome dependent upon this grading. Low-grade tumors are usually well circumscribed, resemble benign mixed tumors grossly, and recur after excision in approximately 15 % of patients. High-grade tumors, on the other hand, are aggressive and invade locally, causing fixation and extension to the nerve. On presentation, up to 50 % of patients with high-grade tumors have LN metastases [183, 184], and the risk of local failure can be as high as 40 % [184].

Squamous cell carcinoma (SCC) usually presents as a hard mass, often fixed, with a short history of 1 year or less. It is often asymptomatic but may be painful in 20 % of patients, and nodal metastases can occur in nearly 50 % of patients. It is important to ensure that this tumor is a primary tumor of the gland and not a metastatic lesion to the submandibular LNs from other SCC in the head and neck. Differentiating it from MEC must also be confirmed. Locoregional recurrence can occur in approximately 50 % of cases [184].

Adenocarcinoma arises infrequently in the submandibular gland. These are very aggressive tumors that invariably present with LN metastases, local extension to soft tissues, and invasion of the mandible, resulting in poor local control that adversely affects prognosis [184].

3.6.4.3 Clinical Presentation

Benign and malignant tumors of the submandibular gland usually present with a *painless* (72–87 %), firm, lobulated, solitary mass in the submandibular region [183, 186]. The presence of pain suggests malignancy, but sialadenitis must be ruled out first. The discharge of purulent saliva from the salivary duct is usually diagnostic of an inflammatory glandular process. Nevertheless, it must be borne in mind that a salivary gland tumor can coexist with obstructive sialopathy leading to sialadenitis.

Physical examination, including bimanual palpation, is important in order to evaluate the extension to adjacent structures. Sensory (lingual nerve) and motor (hypoglossal and marginal mandibular nerves) nerve deficits denote malignancy [186]. Occasionally, MTs may fungate by direct extension through the skin or in association with dermal lymphatic permeation.

3.6.4.4 Differential Diagnosis

A primary neoplasm of the submandibular gland should mainly be differentiated from *sialadenitis* and *metastatic* SCC to a LN. It should also be

differentiated from other causes of cervical LN enlargement such as atypical mycobacteria infection, cervicofacial actinomycosis, sarcoidosis, acquired or congenital cysts, benign follicular lymphadenopathy, and cat-scratch disease [128].

Episodic pain and mass are the hallmark of inflammatory disease (sialadenitis), although one-third of the lesions may be asymptomatic. Obstructive sialadenitis, due to stricture or calculus in the duct, is a common cause of enlargement of the submandibular gland. In these instances, pain and swelling are associated with eating, receding after several hours. Erythema may occur over the mass, and a stone may be palpated in the duct which can, occasionally, drain purulent saliva when the gland is compressed [187, 188]. A solitary SCC metastatic to a submandibular LN in the absence of an obvious primary lesion in the oral cavity (occult primary) is rather uncommon.

3.6.4.5 Diagnostic Imaging

The main objectives of imaging of major salivary gland lesions in general are:

1. To establish whether the mass is intrinsic or extrinsic.
2. To determine its relationship to the nerves.
3. To evaluate its full extent and possible invasion of surrounding structures. If there is any radiological evidence of malignancy, the study is extended to include the neck.

Plain radiographs, sialography, and nuclear scans add very little to the diagnostic information and are seldom indicated for evaluation of submandibular (and sublingual) gland tumors.

Ultrasonography (US) can differentiate between solid and cystic masses and between intra- and extra-glandular nodules. It can also provide important information regarding the contents of the mass, its size, and limits. Nevertheless, there are no definitive US criteria to differentiate between benign and malignant tumors.

Color Doppler sonography usually shows enhanced vascularization in MTs when compared with the normal parenchyma or with BTs. Low-grade MECs, particularly those <2 cm, however, usually have a homogeneous structure and present with smooth borders and may be erroneously considered as benign. High-grade MECs, in contrast, have irregular borders and typical heterogeneous echo pattern. It is noteworthy, however, that patterns of extra-glandular spread, such as perineural invasion and infiltration of the parapharyngeal space, mandible, and base of the skull, are *not* easily visible at US [189].

Computed tomography (CT) and magnetic resonance imaging (MRI) permit better visualization of masses within the salivary glands. Both are equally satisfactory in differentiating cystic from solid lesions and allow evaluation of the relationship with adjacent structures, including soft tissues and bones. However, CT scans are especially useful in the assessment of bone erosion, while MRI better evaluates soft tissue involvement and may detect tumor extension along cranial nerves.

3.6.4.6 Cytopathologic Diagnosis

Fine-needle aspiration cytology (FNAC) can accurately establish cytological diagnosis in over 90–95 % of patients in experienced hands [190]. Diagnosis of pleomorphic adenoma poses no difficulties in cytopathologic specimens. Aspirates are highly cellular containing both myxocartilaginous stroma and large sheets or small aggregates of epithelial cells. Determining the histopathological type of the primary tumor preoperatively can help in deciding the extent of surgical procedure (with or without neck dissection).

High-grade cancers such as adenocarcinomas and SCCs should be considered for neck dissection based on significant increased rates of occult LN metastases. On the other hand, sarcomas, ACC, and other histological types which are unlikely to involve LNs may not benefit from elective treatment of the neck [191].

3.6.4.7 Patterns of Spread

Malignant tumors of the submandibular gland may extend through the capsule to involve the adjacent mandible, mylohyoid muscle, tongue, as well as the lingual and hypoglossal nerves. Moderate to severe pain is usually associated with advanced tumors, while nerve deficits involving cranial nerves V, VII, and XII may be

found in 14 % of patients [187, 192]. Skin invasion and ulceration and extension to the oral cavity can occur in advanced cases.

3.6.4.8 Management

Benign Tumors

A subfascial dissection is usually performed to remove the submandibular gland without a cuff of surrounding normal tissue in cases of benign diseases such as small BTs and sialolithiasis or sialadenitis refractory to conservative management. This technique is rapid and has a low complication rate. Alternatively, Weber et al. [36] recommend level I neck dissection (submental [level Ia] and submandibular [level Ib] LNs) during the routine resection of submandibular gland tumors as this would provide adequate margins in the treatment of BTs and also serve to sample LNs adjacent to the gland in the treatment of MTs [193].

Malignant Tumors

Comprehensive management of MTs of the submandibular gland includes definitive treatment of the primary tumor and treatment (therapeutic or elective) of the neck; eventually, only neck observation is advised, as many neoplasms have a low propensity for lymphatic spread. Most of the clinical variables required to predict survival can often be obtained before definitive surgery. Based on findings of clinical evaluation, MRI, and FNAC, patients may be counseled as to surgical approach, need for neck dissection, and need for postoperative radiotherapy.

Factors Influencing Selection of Therapy

The *size of the primary tumor and histological grade* are the most important tumor factors affecting choice of initial therapy. Clinical (advanced-stage and submandibular site) and histological (higher cancer grade, presence of perineural invasion, presence of LN metastases) parameters are considered independent predictors of poorer clinical outcome in most series of major salivary gland MTs [183, 185, 186, 192–200]. Vander Poorten et al. [186] found that *age at diagnosis* ($p = .0006$), T stage ($p = .001$), and clinical skin invasion ($p = .005$) were the most significant predictors of poor survival among their patients. Interestingly, Hocwald et al. [200] reported that older patients tend to have a higher incidence of more aggressive tumors as compared to younger patients (79 % versus 56 %, respectively). They also observed that *men* tended to present with higher T stage tumors at diagnosis than did women, 53 % versus 26 % ($p = .02$). Bhattacharyya [185] identified patients with younger age, decreased tumor grade, and the addition of radiation therapy as factors associated with improved survival ($p < .001$, .005, and .015, respectively) in his series. *Factors predicting tumor recurrence* in most series include higher TNM stages, perineural growth, and LN metastases [183–186, 192–194, 200].

Resectable Tumors

Low-grade, low-stage MTs can be treated by excision of the submandibular gland with nodal dissection of level I. *High-grade, high-stage MTs*, however, require supraomohyoid neck dissection (SOND), in conjunction with the excision of the submandibular gland. For *advanced (loco regional) tumors*, more radical local resection and neck dissection are indicated [10, 22, 23, 36, 37]. It is worth mentioning that the morbidity secondary to sacrifice of hypoglossal, lingual, and marginal branch of the facial nerve is better tolerated than that after loss of the entire facial nerve. *Reconstruction* with regional, and sometimes microvascular free flaps, may be necessary. *Adjuvant postoperative radiotherapy* may be indicated, in selected cases, in an attempt at improving local and regional control. High-grade malignancies, recurrent tumors, gross or microscopic residual disease, tumor adjacent to the nerves, regional nodal metastases, and invasion of muscle, bone, skin, or nerve are all strong indications for postoperative radiotherapy [194–199].

Advanced Non-resectable Tumors

These are generally treated by radiotherapy with palliative intent. Treatment with neutron beam therapy is of particular value for adenoid cystic carcinomas.

Management of the Neck

Although the role of neck dissection in clinically proven metastases in salivary gland cancer is

Table 3.3 General guidelines for treatment of submandibular gland cancer [16]

	T1 and T2 (N0)	T1 and T2 (N0 and N1)	T3 and T4 (N0 and N+)
	Low grade	High grade	High grade
Tumor type	MEC (low grade) Acinar cell (low grade) Adenocarcinoma (low grade)	MEC (high grade) Acinar cell (high grade) Adenocarcinoma (high grade) Adenoid cystic Ex-pleomorphic adenoma Salivary duct carcinoma SCC	Any histological type
Treatment	Level I ND	Supraomohyoid ND (N0) Comprehensive ND (N+) PORT	Supraomohyoid ND (N0) Comprehensive ND (N+) PORT

MEC mucoepidermoid carcinoma, *SCC* squamous cell carcinoma, *ND* neck dissection, *PORT* postoperative radiotherapy

straightforward, routine elective treatment of the negative neck remains controversial. Some investigators recommend neck dissection only for patients with clinically evident LNs, whereas others also recommend elective neck dissection for tumors based on various prognostic factors [183–185, 193, 201].

The incidence of LN metastases in submandibular carcinomas at the time of initial presentation varies from 8 to 33 % [192–194, 199], which reduces the 5-year survival rates from 40 to 9 % [192, 194, 202–206].

Several authors have attempted to determine predictive factors for cervical metastases in salivary gland malignancy. Several studies have shown that risk of occult nodal metastases is higher in anaplastic, high-grade MEC, SCC, adenocarcinoma, and salivary duct carcinoma than in low-grade MEC, ACC, acinic cell carcinoma, and sarcoma [183, 184, 191, 193–196, 202–204]. An increased risk of occult metastases is also associated with advanced-stage primary cancer. Medina [207] summarized the indications reported in the literature for elective neck dissection in salivary gland cancers: high-grade tumors, T3–T4 tumors, tumors >3 cm, facial nerve (neural) invasion, age >54 years, extra-glandular extension, and perilymphatic invasion [183, 184, 193, 194, 199–207].

The treatment of *clinically positive node* metastases is surgical. The extent of neck dissection is determined by the grossly involved LNs, and an attempt should be made to preserve vital structures. The most common levels of neck involvement in submandibular (and sublingual) MTs are levels I–III [202, 204]. Since contralateral neck affection is rare, only the ipsilateral neck is treated.

Treatment of the *clinically negative neck* has included observation, elective neck dissection, and primary radiation. Currently, treatment of the N0 neck is only appropriate when the risk for occult metastases is high.

The general guidelines for treatment of submandibular gland cancer are shown in Table 3.3.

Chemotherapy

The role of chemotherapy in the treatment of salivary gland MTs has been confined to metastatic disease and locoregional disease not amenable to either salvage surgery or radiation therapy.

The most studied *single agent* is cisplatin. Licitra et al. [208] analyzed the results obtained from 25 patients treated for advanced carcinoma in a phase II trial (100 mg/m^2 of cisplatin every 3 weeks). They observed a response rate of 7 and 18 % rate in metastatic lesions and locoregional recurrence, respectively. The median response duration was 7 months and the median survival time was 14 months.

For *combination chemotherapy* with cisplatin, the most common agents used include 5-fluorouracil, cyclophosphamide, and doxorubicin. A regimen using all four drugs was tested in

17 patients and a 50 % response rate was observed. The median duration of response was 8 months and medial survival was 18 months [209].

Several *molecular targets* have been identified in salivary gland cancer such as C-kit proto-oncogene, EGFR, HER2 proto-oncogene, androgen receptors, p53 protein, and VEGF. These may ultimately provide useful information into diagnosis, biological behavior, and management of cancer of the salivary glands [210–217].

Take-Home Messages

- There are equal proportions of malignant and benign lesions in the submandibular gland.
- Nerves at risk during operations involving the submandibular gland are the marginal mandibular, lingual, and hypoglossal nerves.
- The smallest operation for benign tumors of submandibular gland is excision of the whole gland.
- Low-grade, low-stage MTs can be treated by excision of the submandibular gland with dissection of level I. High-grade, high-stage tumors, however, require supraomohyoid neck dissection, in conjunction with the excision of the submandibular gland.

3.6.5 Surgical Technique: Submandibular Sialoadenectomy

3.6.5.1 Steps of the Procedure

- The patient is placed on the operating table under general endotracheal anesthesia in a supine position with the neck turned to the opposite side.
- The skin incision is placed in an upper neck skin crease at least two fingerbreadths below the angle of the mandible to protect the mandibular branch of the facial nerve.
- The upper flap consisting of skin, subcutaneous fat, platysma muscle, deep cervical fascia, and the fascial capsule superficial to the gland is elevated up to the level of the lower border of the mandible in order to avoid injury of the nerve.
- The lower border of the gland is grasped and lifted up, the gland is separated from the muscular floor of the submandibular triangle, and the hypoglossal nerve is identified on the hyoglossus muscle. The anterior segment of the gland is released from the mylohyoid muscle. The facial artery is then identified and divided proximal to the gland between strong ligatures. This frees the gland posteriorly.
- The gland is retracted downward in order to divide its superior fascial attachments to the mandible and expose the facial artery and anterior facial vein just below the mandible. These vessels are divided as close to the gland as possible to avoid accidental damage of the mandibular branch of the facial nerve. Division of the facial vessels allows caudal retraction of the submandibular gland, providing full exposure of the underlying mylohyoid muscle.
- The mylohyoid muscle is retracted forward, thus exposing the deep part of the gland. With traction on the gland still maintained in a downward direction, the lingual nerve is dragged down from its position deep to the mandible and its attachment to the gland severed.
- Wharton's duct is isolated and divided as close as possible to the floor of the mouth. During this dissection, the hypoglossal nerve is seen in a deeper plane to Wharton's duct and should be carefully protected.
- After the removal of the surgical specimen, meticulous hemostasis is obtained followed by irrigation with saline solution. A single suction drain is inserted and the wound is closed in layers.

3.6.5.2 Postoperative Complications

The most common complication after submandibular gland excision is *injury to the marginal mandibular branch of the facial nerve* [218]. Temporary injury (temporary paresis) has been reported to range from 1 to 10 % of patients [219–221].

It is highly recommended that the incision should be placed at 3 cm below the angle of the mandible to consistently avoid injury to branches of the facial nerve. Injury to *the lingual nerve* is uncommon unless tumor or chronic inflammation presents difficulty in its separation from the gland. Rarer still is injury to the *hypoglossal nerve* in the course of resection of the contents of the submandibular triangle [220]. *Great auricular causalgia* and/or the development of *neuroma* is uncommon [222].

Injury to other important structures in the neck may also occur during submandibular sialoadenectomy such as the facial artery leading to severe hemorrhage and wall of the pharynx resulting in fistula formation. With careful dissection these complications are rarely encountered in experienced hands.

The *scar* that results from cervical incision may be aesthetically unsatisfactory in many patients, particularly those with a slender neck. Avoiding tension of the surgical wound and the use of intradermal sutures can help in preventing an unsightly scar.

3.7 Sublingual Glands

The paired sublingual salivary glands are the smallest of the three major salivary glands, weighing approximately 2 g each.

3.7.1 Surgical Anatomy

Sublingual salivary glands are almond shaped and lie immediately below the mucous membrane of the floor of the mouth just above the submandibular fossa. According to Batsakis, these are poorly encapsulated glands that do not represent unit organs but, rather, a *mosaic* composed of a large segment (major sublingual gland), which is drained by the sublingual or *Bartholin's* duct, and a group of 8–30 smaller glands (minor sublingual glands), which are drained by several openings (ducts of *Rivinus*) directly into the oral cavity or into the submandibular duct [223].

The sublingual glands are separated by the paired midline genioglossus and geniohyoid muscles. A crest of mucous membrane along the frenulum (*plica sublingualis*) represents the projection of the glands and openings of the sublingual ducts.

The blood supply to the sublingual gland comes from the sublingual and submental arteries, and the nerve supply from the chorda tympani and lingual nerves [1]. Lymphatic drainage goes into the submental and submandibular LNs.

3.7.2 Tumors of the Sublingual Glands

True sublingual gland tumors are rather unusual, and approximately, 75 % are *malignant*; MEC and ACC comprise 80 % of all carcinomas arising in this region [10]. *Benign tumors* of the sublingual gland are very rare, except for ranulas, which are benign cystic lesions.

Tumors of the sublingual gland, which are very rare, usually present as a painless mass under the lateral aspect of the ventral tongue. It may be associated with minimal discomfort, pain, numbness of the tongue, and difficulty with retention of a dental prosthesis. A high degree of suspicion must be employed for lesions in this region of the floor of the mouth. These salivary gland tumors can be differentiated from mucosal lesions of the floor of the mouth by their *submucosal* location. However, it is almost impossible to differentiate primary tumors of the sublingual glands from tumors of minor salivary origin in the floor of the mouth [9, 21].

3.7.2.1 Ranula

Its name derives from the Latin word *rana* (frog), due to the typical bluish appearance, similar to a frog's belly [224].

Pathogenesis There are two different concepts for the pathogenesis of ranula: (1) it is a *true cyst* (with an epithelial lining) resulting from due to ductal obstruction, and (2) it is a *pseudocyst* (without an epithelial lining) resulting from injury of the duct and extravasation of mucus

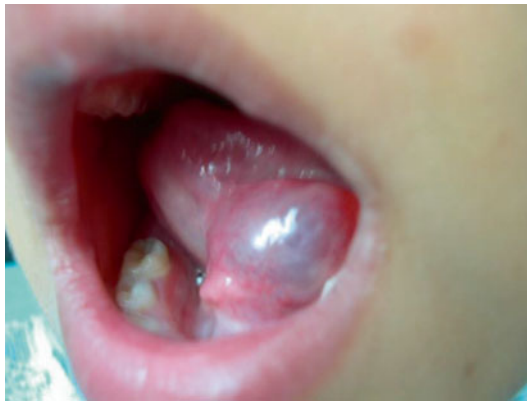

Fig. 3.34 Ranula. A cystic, translucent swelling with a bluish tinge in the floor of the mouth lateral to the midline

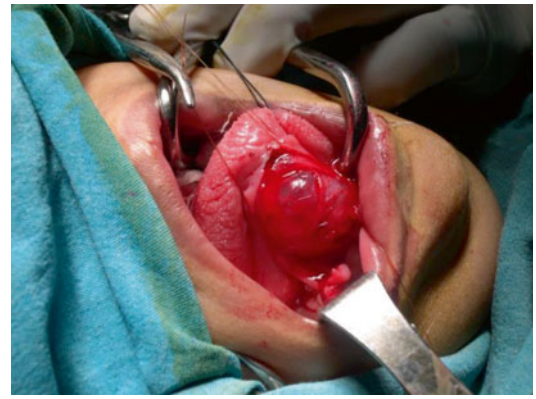

Fig. 3.35 Dissection of ranula

[225–227]. Recently, typical ranulas have been considered as an extravasation phenomenon of the sublingual gland [227, 228].

Types According to its extension, ranulas are sublingual, sublingual-submandibular, or submandibular [229]. The sublingual type is a simple ranula, while the other two extending into the neck are *plunging* ranulas (deep cervical ranulas).

Clinical Picture It usually affects children and young adults with no gender predilection. The clinical presentation is that of a slowly growing submucosal mass in the floor of the mouth, with a cystic appearance. Pathologically, there is a simple or multi-loculated cavity filled with amorphous or mucoid material [224]. The cyst varies in size between 1 and 5 cm in diameter. It is characteristically translucent and has a bluish tinge (Fig. 3.34). It is smooth and covered by tortuous veins, and the submandibular duct is displaced and stretched over it. The edge is difficult to feel and the cyst *cannot* be compressed or reduced.

Treatment Different approaches for treatment of ranulas have been proposed including simple incision, cyst extirpation, marsupialization, and excision of sublingual gland, which is most recommended [225–228]. Yoshimura et al. [230] compared three methods of ranula treatment in 27 patients and reported a recurrence rate of 25 % with excision of ranula only, 36 % with marsupialization, and 0 % with ranula and ipsilateral sublingual excision. Moreover, the comparative study in children by Crysdale et al. [231] showed a recurrence rate of 61 % with marsupialization, and 0 % with either excision of ranula only or with ranula and ipsilateral sublingual gland excision.

With the patient under general anesthesia, nasotracheal intubation and oropharyngeal packing (to prevent aspiration), excision of a ranula can be achieved through the oral cavity, which is opened with a self-retaining mouth retractor. An elliptical incision is then made over the curve of the cystic swelling and the mucosal flap over the cyst is carefully freed from the ranula, by both blunt and sharp dissection (Fig. 3.35).

The cystic swelling is then grasped with serrated forceps and freed from Wharton's duct by blunt dissection and from its connections with the underlying mylohyoid muscle. All small vessels in the field are controlled with bipolar coagulation forceps. After excision of the ranula together with the sublingual gland, the sound lingual nerve can be seen lying on the floor of the mouth next to Wharton's duct. After careful hemostasis, the wound is irrigated with saline solution and the mucosa is closed with 3–0 Vicryl sutures. Frequent oral irrigations with oral antiseptic solutions are recommended for optimal oral hygiene, and oral feeding is started with clear liquids and pureed foods.

3.7.2.2 Treatment of Sublingual Malignant Neoplasms

Since the sublingual gland lies directly beneath the mucosal surface of the anterior floor of the mouth, and close to the inner aspect of the mandible, treatment of a sublingual MT usually entails removal of the gland with a surrounding cuff of normal tissue (floor of the mouth and lateral aspect of the oral tongue). The development of a soft tissue cuff around an MT confined to the sublingual gland without extra-glandular extension can be achieved through excision of the mucosa (floor of the mouth and small segment of the tongue), the mylohyoid muscle, and the periosteum of the mandible.

Most salivary gland cancers arising in the floor of the mouth are done in concert with at least level I neck dissection, thus removing the submandibular gland. Treatment of a moderately advanced sublingual gland cancer includes ipsilateral neck dissection with resection of the sublingual gland and surrounding tissues (floor of the mouth and lateral aspect of the tongue), usually in association with a marginal resection of the mandible. A more advanced or recurrent cancer of the sublingual gland is likely to require resection of the floor of the mouth along with a partial glossectomy, mandibulectomy, supraomohyoid structures, and the lingual and hypoglossal nerves. The neck dissection is completed in the usual fashion except for level I, through which the specimen is attached to the primary tumor.

Removal of the sublingual gland is not without potential morbidity, most notably injury to the lingual nerve with subsequent numbness, injury to Wharton's duct with the possibility of obstructive sialadenitis, and ductal laceration causing salivary leakage [228].

3.8 Minor Salivary Glands

About 600–1,000 minor salivary glands, ranging in size from 1 to 5 mm, are found throughout the oral cavity, with the greatest density in the buccal and labial mucosa, the posterior hard palate, and tongue base. They can also be found along the tonsils, supraglottis, and paranasal sinuses. Any of these sites can be the source of glandular tumors.

3.8.1 Surgical Anatomy

Each gland has a single duct which secretes saliva directly into the oral cavity, which can be serous, mucous, or mixed. The majority of these glands are either mucinous or seromucinous, except for the serous *Ebner's glands* on the posterior aspect of the tongue [228]. Postganglionic parasympathetic innervation arises mainly from the *lingual nerve*. The palatine nerves, however, exit the sphenopalatine ganglion to innervate the superior palatal glands. The oral cavity region itself determines the blood supply and lymphatic drainage of the glands [224].

3.8.2 Tumors of Minor Salivary Glands

Tumors of the minor salivary glands account for 10–15 % of all salivary gland neoplasms [68]. The most common location is by far the palate, followed in decreasing order by the maxillary antrum, tongue, cheek, lips, and nasal cavity. Malignancy rates vary from 30 to 90 % [176, 204, 232].

3.8.2.1 Clinical Presentation

Tumors of the minor salivary glands rarely produce symptoms unless they have reached a relatively large size. The majority of patients are aged 60 years or older [222], with women slightly more affected than men [232]. Most present with a painless non-ulcerative, submucosal mass that is firm or hard, mobile or fixed. The mucosal layer is adherent to the mass and a small ulcer may be present. According to the location of the tumor, patients may also present clinically with nasal obstruction, Eustachian tube obstruction, hoarseness of voice, or dyspnea. Approximately one-quarter of patients present with local pain [222, 225], which warrants investigation by MRI to rule out nerve invasion [233]. At the time of presentation, more than 15 % of patients will have cervical LN metastases [142, 234].

3.8.2.2 Diagnosis

Physical examination and high suspicion of a submucosal swelling in the head and neck to

originate from minor salivary glands and to be more likely of malignant rather than benign origin are the most important clinical information that will help give an accurate diagnosis.

Imaging using CT and/or MRI will aid delineation of the tumor, accurate staging, and correct planning of surgical intervention. The use of FNAC may be helpful in correctly classifying the tumor as benign or malignant; however, the use of incisional or punch biopsy may reveal the correct histological type. Complete excision should be avoided as it is likely that the margins will be close or positive and that orientation of these incomplete margins will not be possible at the time of pathological analysis and will thus interfere with proper subsequent planning of surgical salvage. Searches for distant metastases are worthwhile but should not alter plans for surgical ablation for a symptomatic primary lesion. In many instances, distant metastases, particularly to the lungs, may remain indolent for many years.

3.8.2.3 Benign Tumors

Pleomorphic Adenoma It is the most frequent BT of minor salivary glands, most commonly occurring in the hard palate, followed by the upper lip. It has also been located in areas as diverse as the tongue [187, 220], nasal cavity and septum, larynx, and trachea. Young children may also present with pleomorphic adenoma [90, 91], the majority of which are located in the hard palate region. Some of these pleomorphic adenomas can become massive with malignant degeneration before presentation [223].

Other Benign Neoplasms Other BTs of minor salivary gland origin that have been reported in the oral cavity include basal cell adenoma [142].

3.8.2.4 Malignant Tumors

The most frequently encountered MTs of minor salivary glands are adenoid cystic carcinoma (32–69 %) [190, 235] and mucoepidermoid carcinoma (15–35 %), and the less frequently are acinar cell carcinoma, polymorphous adenocarcinoma, myoepithelial carcinoma, and carcinoma ex-pleomorphic adenoma [190].

Adenoid Cystic Carcinoma (ACC) It is a locally vicious tumor that spreads with perineural invasion with bone and soft tissue destruction. Margin failure at surgical resection is common, and LN metastases occur in approximately 15 % of patients and hematogenous spread, particularly to the lung and bone, in nearly 50 % [235]. These tumors can be graded according to Szanto et al. [236] as cribriform or tubular (grade I), <30 % solid (grade II), or >30 % solid (grade III).

Adenocarcinoma It arises from the mucous glands of the high nasal cavity, the nasopharynx, and the paranasal sinuses. Adenocarcinomas occur as papillary, sessile, and alveolar-mucous types, and most of them behave like the adenoid cystic variety, with a propensity for extensive local growth and rare regional metastases to cervical LNs [235]. Polymorphous low-grade adenocarcinoma (PLGA) needs to be differentiated from other types of adenocarcinoma because of differing biological behaviors, with generally better prognosis [224, 227, 237].

Mucoepidermoid Carcinoma (MEC) When present in the minor salivary glands, MECs tend to be intermediate or high grade, with an increased incidence of LN metastases as compared to other types of carcinomas, particularly when they occur in the oral cavity.

Carcinoma Ex-pleomorphic Adenoma (CEPA) It is much less common in the minor salivary glands than in the major salivary glands.

3.8.2.5 Treatment

The hallmark of treatment of resectable tumors of minor salivary gland origin, whether benign or malignant, is *wide surgical excision* in order to avoid recurrence. A multidisciplinary is essential. Patients requiring maxillectomy are fully evaluated preoperatively by the maxillofacial prosthodontist, and a preliminary prosthesis is fabricated so that it can be placed at the time of definitive surgery. Currently, neck dissection is only indicated when there are demonstrable metastases present (clinical or imaging) or when the neck is being surgically entered as an approach to the primary tumor.

Postoperative radiotherapy is frequently employed in the large primary tumors and those with close margins and has been shown to be effective in nearly all forms of these tumors, particularly adenoid cystic carcinoma [238, 239].

Primary radiotherapy is indicated for patients who refuse surgery or those with an inoperable/unresectable tumor [201]. The role of neutron radiotherapy is indicated, when available, for unresectable or inoperable locoregional cancer [240].

The role of chemotherapy remains controversial and should individualized, such as in a palliative situation for relief of symptoms when the cancer is unresectable or recurrent after treatment, for patients not amenable to radiotherapy, and those with distant metastatic cancer.

3.8.2.6 Prognosis

In general, treatment of all tumors of minor salivary glands has been disappointing, with cure rates of about 30 % of all patients at 10 years [235]. Tumor stage, histology, and grade are the most important predictors for survival [205]. These variables are able to influence treatment outcome, although stage seems to be more important than grading [234, 241].

In ACC, the prognostic factors associated with poor prognosis are perineural invasion, positive margins, and solid histological features. In MEC, reduced survival was associated with male gender, LN metastases, high-grade of malignancy, strong expression of proliferating cell nuclear factor (PCNA), and weak expression of c-erbB-2 gene (a gene with an important role in the development, differentiation, and mitogenic signaling in normal cells) [242].

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Swellings of the Jaw

4

Ahmad Eweida and Raymund Horch

4.1 Introduction

When discussing the swellings affecting the alveolar portion of the mandible and the alveolar process of the maxilla, both are usually included as one entity, namely, the "Jaws."

The mandible has many of the characteristics of a long bone particularly in relation to its vascular supply. The alveolar (superior) portion of the mandibular ramus is covered with mucoperiosteum and represents the lower jaw. The lower portion of the mandibular ramus has a large nerve running through it, the *inferior alveolar nerve* supplying the teeth, and emerges at the mental foramen as the mental nerve, to carry sensation from the lower lip and adjacent labial and buccal mucosa.

The maxilla in contrast to the mandible in no way resembles a long bone. It is a bony box, lined by respiratory type of epithelium, with four processes: frontal, zygomatic, palatal, and alveolar. The alveolar process is covered with mucoperiosteum and represents the upper jaw. The walls of the box are strengthened by bony reinforcements to transmit the occlusal stresses from the teeth to the base of the skull [1].

During early embryological development, the neural crest cells invade the developing branchial arches. The development of teeth primordial results from a series of inductive interactions between the migrating cells and the primitive oral epithelium [2].

4.2 Classification of Jaw Swellings

Swellings of the jaw can be classified according to their site of origin into four main categories as shown in Fig. 4.1, namely,

- Swellings arising from the mucoperiosteum (epulides)
- Swellings arising from tissues responsible for development of teeth (odontomas)
- Swellings arising from non-odontogenic cell remnants (developmental cysts)
- Swellings arising from the bone proper (bony swellings)

4.3 Epulides

Swellings arising from the mucoperiosteum (gums) are known as "epulides" (*any solid swelling situated in the gums*).

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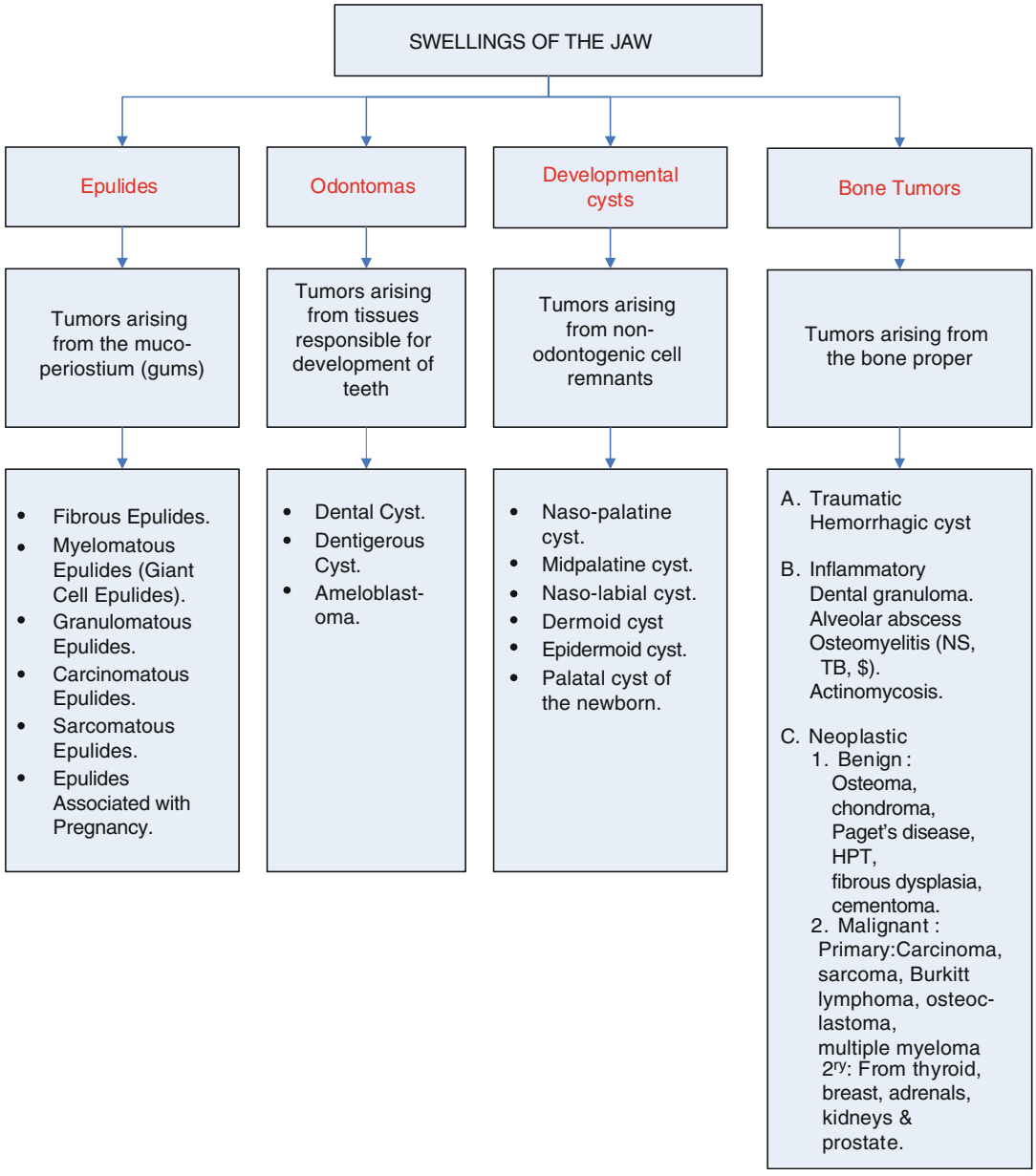

Fig. 4.1 Classification of swellings of the jaw according to origin

4.3.1 Fibrous Epulides

Fibrous epulides arise from the peridental membrane (mucoperiosteum) surrounding the teeth and present under the gums. It forms a tumor that simulates a "fibroma." It is the most common form and usually lies between the incisor teeth of the lower jaw. It usually affects middle-aged individuals with a female to male ratio of approximately 3:1.

The swelling is sessile at the beginning and then becomes pedunculated. It is whitish in color due to diminished vascularity, firm in consistency, and covered by intact mucosa. Treatment is by excision.

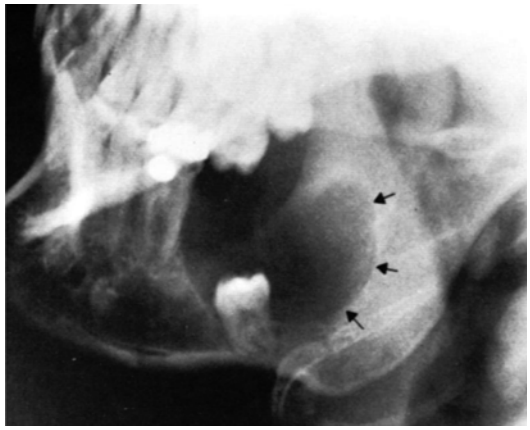

Fig. 4.2 Plain X-ray showing a *s*mooth, well-circumscribed lucent cavity (*black arrows*) containing the crown of an unerupted tooth, characteristic of dentigerous cyst

Other forms:

- Fibroangiomatous form: It bleeds easily on touch.
- Fibrosarcomatous form: It results from malignant transformation.
- Congenital epulides: It occurs since birth, varies from a few millimeters to 9 cm in diameter, and may interfere with feeding or respiration [3].

4.3.2 Myelomatous Epulides (Giant Cell Epulides)

Myelomatous epulides arise from the osteoblastic layer of the periosteum or from the alveolus itself. It contains osteoclasts and is considered an osteoclastoma of the alveolar margin. It is divided by septa into lobules and contains osteoclasts, giant cells, spindle cells, and fibroblasts. It usually affects patients between 30 and 40 years, but can occur at any age.

The swelling is most commonly situated peripherally, in the mandible or maxilla. It presents as a sessile, lobulated, bulky, red mass, fixed to the underlying tissues and covered with intact mucosa, which bleeds on touch owing to its high vascularity. Though painless, it is rapidly growing and liable to necrosis, ulceration, cyst formation, and malignant transformation. A plain X-ray will show eating up of the jaw under the tumor. Treatment is by excision.

4.3.3 Granulomatous Epulides

A granulomatous epulide is a mass of granulation tissue formed around a carious tooth or gingivitis. It presents as a soft, red, lobulated mass that bleeds easily on touch. It is not covered with mucosa. It is treated by removal of the cause of irritation, extraction of the affected tooth, and the use of mouthwash and antibiotics, in addition to scraping away of the granulation tissue. If persistent, painting with 3–5 % silver nitrate or surgical excision may be resorted to.

4.3.4 Carcinomatous Epulides

Carcinomatous epulide is now considered as an "alveolar carcinoma" arising from the mucous membrane covering the gum (squamous epithelium). It is a rapidly growing mass with necrosis and ulceration. Characteristically, it does not give metastases, but gradually eats up the underlying bone. The patient usually presents with a painful, infected, fungating, or ulcerating mass that may invade the bone and spread to cervical lymph nodes (LNs). A *biopsy* is a must for diagnosis. Treatment usually involves a combination of surgical and radiotherapy (RT) according to full assessment and staging.

4.3.5 Sarcomatous Epulides

A sarcomatous epulide is actually covered by mucous membrane of the gum, but may develop from fibrous tissue. Males, of the middle age, are more affected than females. The patient usually presents with a sessile mass, which may be fixed to the underlying jaw. It may be hard, firm, or soft (denotes degeneration or high-grade malignancy). Ulceration and bleeding occur later. A plain X-ray may show bone infiltration. Treatment is accomplished by a wide excision with a safety margin of the underlying bone or hemimandibulectomy.

4.3.6 Epulides Associated with Pregnancy

It results from increased estrogen level during pregnancy and bad oral hygiene. It usually occurs in relation to the posterior teeth, especially the upper jaw. The patient presents with hypertrophy of the gums and a tendency to bleed. It is usually prevented with good oral hygiene during pregnancy.

4.4 Odontomas

An odontoma is a swelling derived from cellular elements that take part in the development of teeth. It is well-agreed upon that some epithelial cell residues persist throughout life in the gubernacular canals and periodontal membranes. These cells remain as inactive single or cluster cells that could be triggered resulting in the development of well-recognized pathological entities. The origin of epithelial odontogenic neoplasms, hamartomas, or cysts is thought to be related to such cell rests. The evidence is, however, based mainly on morphology and co-localization rather than on solid molecular evidence [2].

4.4.1 Dental (Radicular or Subapical) and Dentigerous (Follicular) Cysts

Both dental and dentigerous cysts show a slowly growing painless swelling, hard in consistency (covered by bone), expanding the bone internally and externally resulting in an "eggshell crackling sensation." Table 4.1 summarizes the differences between both cysts.

Table 4.1 Differences between dental and dentigerous cysts

Point of difference	Dental (radicular) cyst	Dentigerous (follicular) cyst
Cause	Irritation of the epithelial debris (of Malassez) by a chronically infected tooth usually incisor or canine	Irritation of the same epithelial debris by "unerupted" tooth, usually premolar tooth
Site	Upper jaw > lower jaw	Lower jaw > upper jaw
Age	Middle age (30–40 years)	Younger age (7–25 years)
Pathology	Smaller in size	Larger in size
	Clear fluid inside rich in cholesterol	Viscid fluid inside + missed tooth
	Overlying tooth is present	Overlying tooth is absent
Plain X-ray	Clear cavity with evident outline + cholesterol crystals	No cholesterol crystals
	No tooth inside the cavity	Tooth inside the cavity (Fig. 4.2)
Treatment	Extraction of affected tooth and opening the cavity (via intraoral approach) and removal of the epithelial lining, then obliteration of the cavity with soft tissue or bone chips	De-roofing of the cyst and removal of the epithelial lining. If the tooth is upright, it is left to erupt, but if not, it is removed. The cavity is then obliterated

4.4.2 Ameloblastoma (Adamantinoma)

Ameloblastoma is an epithelial tumor that arises from ameloblasts (epithelial debris of Malassez), or it is a sort of basal cell carcinoma from the basal cells of the dental epithelium. It is reported to constitute about 1–3 % of tumors and cysts of the jaws and is known to be the most common tumor of the lower jaw in Egypt. Ameloblastoma affects the mandible more than the maxilla (5:1) particularly the angle of the mandible, but it can grow forward to the body of the mandible and/or upward to the ascending ramus.

Ameloblastoma occurs most commonly in adults (30–40 years), but may occur at a younger age. The patient presents with a chronic *painless* jaw swelling, which is characteristically well defined, lobulated, and expanding the jaw externally rather than internally. There may be ulceration of the mucous membrane and loosening of the overlying tooth or teeth. It is usually

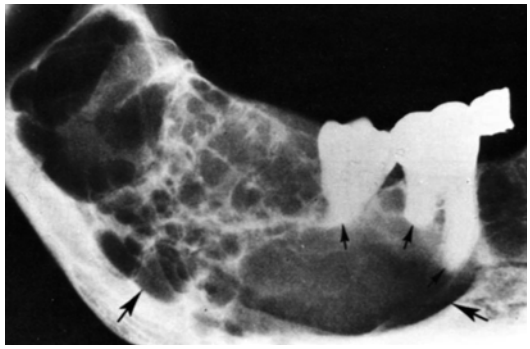

Fig. 4.3 Ameloblastoma. Note multi-locularity of the lesion (fine soap and bubble or honeycomb appearance), the well-defined margins (*large arrows*), and resorption of tooth root (*small arrows*)

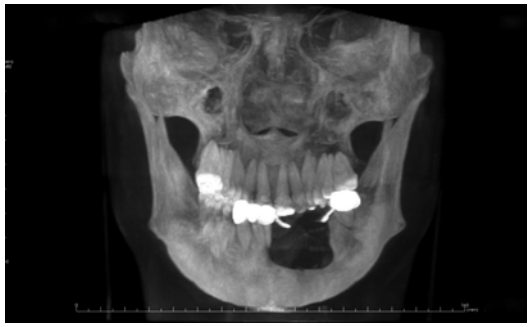

Fig. 4.4 A "3D" reconstructed CT image of the resultant defect after resection of a recurrent ameloblastoma requiring bone grafting

hard in consistency, but may have an "eggshell" crackling sensation due to degeneration.

Plain X-ray will show fine "soap and bubble" or "honeycomb" appearance (Fig. 4.3). Biopsy is essential for diagnosis. It should be differentiated from osteoclastoma (has fine and coarse soap and bubble appearance on plain radiography). Complications include ulceration, loosening of teeth, pathological fracture, and recurrence after removal.

Treatment varies from simple enucleation with curettage to wide local resection of the mandible (or maxilla) with reconstruction (Fig. 4.4). A radical approach should be adopted whenever possible as the conservative approach results in a significantly higher rate of recurrence than the radical approaches [4].

4.5 Bony Swellings

Bony swellings affecting the jaw are classified mainly into inflammatory and neoplastic swellings; the latter may be benign or malignant, either primary or metastatic (Table 4.2).

4.5.1 Inflammatory Lesions

4.5.1.1 Dental Granuloma

It may occur in the form of a giant cell granuloma, which represents a failure of an attempt at repair of a hematoma of the jaw. It affects females more than males, usually below the age of 20 years. A plain X-ray (occlusal view) will demonstrate an expansile radiolucency in the anterior portion of the mandible producing even, regular swelling of the buccal cortical plate (arrows) and intrusion of a canine tooth (C) (Fig. 4.5).

4.5.1.2 Alveolar (Dental) Abscess

It is an abscess that occurs in the socket of the tooth (alveolus). It can develop ant any age, with the first or second dentition. The patient presents with throbbing pain, painful swelling, and malaise, sweating, and anorexia. Physical examination reveals a hot, tender, reddish (hyperemic) swelling with an ill-defined edge. Large abscesses may fluctuate. The mass is clearly fixed to underlying bone. Upper cervical lymph nodes (LNs) are enlarged and tender.

4.5.1.3 Osteomyelitis

Osteomyelitis may be acute or chronic (specific due to tuberculosis, for example, or nonspecific from acute osteomyelitis, compound fracture of the jaw, blood-borne infection, or tumor infiltrating the jaw).

There may be history of tooth extraction. The patient presents with a painful, warm bony swelling with a nodular surface and a border that gradually merges into normal bone. Expansion may affect one side only or both. Physical examination reveals tenderness, redness, and hotness, with or without edema. Trismus may be present. Draining LNs are enlarged and painful. A sinus and/or abscess may be present. Delayed

Table 4.2 Classification of bony jaw swellings, according to pathology

Inflammatory	Neoplastic		
		Malignant tumors (MTs)	
	Benign tumors (BTs)	Primary MTs	Secondary MTs
Dental granuloma	Osteoma	Carcinoma: (adenocarcinoma, squamous cell carcinoma, lymphoepithelioma)	From cancer of: Thyroid Breast Suprarenal glands Kidneys Prostate
Alveolar Abscess	Chondroma	Sarcoma: (Osteogenic sarcoma, chondrosarcoma, fibrosarcoma, Ewing's sarcoma, etc.)	
Osteomyelitis (specific, nonspecific)	Paget's disease	Lymphoma (Burkitt's)	
Actinomycosis	Hyperparathyroidism	Osteoclastoma	
	Benign fibro-osseous lesions (fibrous dysplasia – cementoma)	Multiple myeloma	

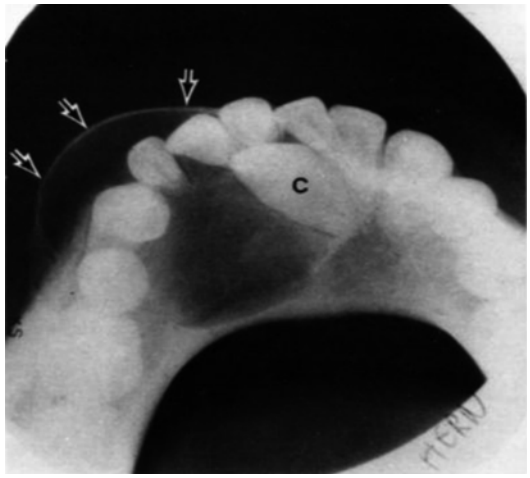

Fig. 4.5 Giant cell granuloma

sequestrum formation and delayed healing may occur due to inadequate rest (continuous motility of the jaw) and recurrent infection from the mouth. The lesion is usually difficult to heal. Treatment includes mouthwashes and appropriate antibiotics. If a sequestrum develops, sequestrectomy is performed via an incision along the lower border of the mandible. In case of abscess formation, incision and drainage is done.

4.5.1.4 Cervicofacial Actinomycosis

It usually affects adult males, most commonly at the angle of the jaw. The swelling is nodular, tender, warm, and fixed to the skin, with multiple sinuses discharging the diagnostic sulfur granules. Trismus is commonly present. It is sensitive to penicillin.

4.5.2 Neoplastic Lesions

4.5.2.1 Carcinoma of the Maxilla

Carcinoma of the maxilla arises from the "*maxillary antrum,*" which is *pyramidal* in shape. Its *base* is made by the lateral wall of the nose, *apex* by the zygomatic process of the maxilla, *floor* by the alveolar part of the maxilla, and *roof* by the floor of the orbit.

The pathological types include squamous cell carcinoma (SCC), adenocarcinoma, minor salivary gland tumor, and undifferentiated carcinoma. It spreads locally into all direction, by lymphatics to the upper deep cervical, retropharyngeal or submandibular LNs, and hematologically to the lungs, bone, brain.

The disease has a predilection for males with age range 38–89 years [5]. Diagnosis is usually made at a late stage where most of the patients have been long treated for sinusitis or blocked nose. The definitive presentation depends on the site and direction of growth of the tumor, as shown in Table 4.3.

It may present with pain in the region of the maxilla (referred to upper teeth) due to blockage and infection of the antrum and later due to

Table 4.3 Clinical presentation of carcinoma of the maxilla

Tumor location	Clinical presentation
Anterior and lateral wall	Swelling of the face and cheek
Medial wall	Nasal obstruction, anosmia, epiphora (infiltration of the nasolacrimal duct)
Posterior wall, nasopharynx	Dyspnea and change of voice
Roof	Proptosis and diplopia
Floor	Bulging of the hard palate

involvement of branches of the trigeminal nerve. The primary tumor may be occult and present with enlarged LNs in the neck.

Plain radiography will show a soft tissue shadow in the antrum and signs of bone destruction. CT scan will delineate the anatomy and bony involvement, and biopsy is essential for definitive diagnosis. The optimum management includes surgery, radiation, and systemic and topical chemotherapy in a variety of combinations and sequences. Survival from carcinoma of the maxilla is poor where the local disease extent and nodal disease at presentation are the only variables independently associated with cause-specific survival [5].

4.5.2.2 Sarcoma of the Maxilla

Contrary to carcinoma, sarcoma of the maxilla affects a younger age group and females more than males. It has a shorter history with more pain, causes a worse general condition, and has a worse prognosis. Pathologically, it may be a spindle cell, osteogenic, or fibrosarcoma.

The patient usually presents with a painful swelling in the face and loosening of teeth. There may be blocking of the nose with epistaxis, fetor oris, and increased salivation. The skin overlying the swelling is usually stretched and glistening and shows dilated veins.

Plain radiography will show clouding of the sinuses and bone destruction, which is better delineated by CT scan. Metastatic workup should be performed due to early spread. For treatment, a combined therapy is usually required (surgery, chemotherapy, and radiotherapy).

4.5.2.3 Burkitt's Lymphoma

Burkitt's lymphoma of the head and neck region usually involves the cervical LNs. Primary involvement of the nasal cavity and paranasal sinuses is uncommon. In paranasal Burkitt's lymphoma, the maxillary sinus is most commonly involved followed by the sphenoethmoidal sinuses [6].

Epstein-Barr (EB) virus is the most likely etiological factor. It occurs more commonly among children of the "Equatorial" regions of Africa between the ages of 2 and 14 years. The most common presentation (50 %) is that of a jaw swelling (osteolytic lesion of the maxilla or mandible). An abdominal tumor is the second most common presentation. Renal involvement is usually bilateral, and the nervous system may also be involved. In girls, involvement of the ovaries is characteristic. A plain X-ray or CT scan will show multiple osteolytic deposits with bone destruction. The tumor is sensitive to chemotherapy.

4.5.2.4 Osteoclastoma (Giant Cell Tumor)

It is a locally destructive tumor, which grows gradually with *no metastases*, and affects the mandible, but rarely the maxilla could be affected. It is similar to adamantinoma, with some differences highlighted in Table 4.4.

An osteoclastoma should be differentiated from ameloblastoma (refer to the table above) and other giant cell lesions, mainly:

- *Giant cell granuloma*:
  It represents a failure of an attempt at repair of a hematoma of the jaw. It affects females more than males, below the age of 20 years. Perforation of the cortex is very rare.
- Brown tumor of hyperparathyroidism (HPT):
  The jaw may be affected due to generalized bone affection (*von Recklinghausen's disease*). The *brown* coloration is due to hemorrhage inside the lesion.

Complete surgical resection is required for adequate treatment as incomplete resection leads to recurrence in about 70 % of cases [7].

Table 4.4 Differences between ameloblastoma and osteoclastoma

Criteria	Ameloblastoma	Osteoclastoma
Site of origin	Near the angle of the mandible	Near the symphysis menti
Growth direction	Upward and forward and may cross the symphysis menti	Backward in the body of mandible, but never crosses the S. menti
Age	Fourth and fifth decades	Adolescents or 20–40 years
Sex	Females > males (9:1)	Males > females
Shape of tumor	Lobulations (may be equal)	Variable lobulations (coarse and fine)
Jaw expansion	External > internal	Equal on both sides
Color	Pale or pink	Reddish or brownish
Plain X-ray	Fine soap bubbles	Coarse and fine soap bubbles
Special character	Radioresistant	Radiosensitive (postoperative RT)

4.6 Reconstruction of the Mandible

Reconstructive surgery has started as early as 1600 BC. Egyptian surgical papyri have been found describing methods for repairing broken noses and fractured mandibles and providing instruction in suturing to minimize scarring. Written evidence cites reconstructive treatment for facial injuries more than 4,000 years ago, and the physicians in ancient India were utilizing skin grafts for reconstructive work as early as 800 BC. However, reconstructive surgery, like most of other medical specialties, has rapidly progressed in the nineteenth and twentieth centuries. War was the driving force behind most of the developments in reconstructive surgery during the late 1800s and early 1900s. During the First World War, the physicians were confronted with extensive facial and head injuries. Shattered jaws, blown-off noses and lips, and gaping skull wounds caused by modern weapons required innovative restorative procedures. In the 1940s, many plastic surgeons served their countries during the Second World War. They expanded their reconstructive procedures to treat extensively wounded soldiers, sailors, and airmen [8].

Mandibular reconstruction entails restoring structure and/or function of the mandible following trauma, infection, tumors, or alveolar bone resorption following teeth loss. This chapter briefly discusses various modalities of mandibular reconstruction and focuses on the recent advances in reconstructive and regenerative therapies.

4.6.1 Reconstructive Stepladder

4.6.1.1 Alloplastic Devices

These artificial devices are designed and implanted to fit in a mandibular defect. The relatively easy procedure and the potential for aesthetic reconstruction without donor site morbidity have led many on the search for suitable alloplastic materials. Although these implants offered some restoration of continuity and bulk in the short term, the long-term results and, thus, the overall success have been disappointing. Currently, these devices are not favored and should be avoided especially when applied in previously irradiated areas of the head and the neck [9].

4.6.1.2 Corticocancellous Bone Grafts

These grafts are usually harvested from the anterior or posterior iliac crest. As these grafts are nonvascularized, they are only suitable for smaller defects (<4–6 cm) usually not subjected to radiotherapy (RT) and in patients medically too compromised to tolerate free flap surgeries [10]. Unfortunately, the rate of bony union and implant success with such nonvascularized bone grafts is less than that with vascularized bone flaps (free flaps). This was even demonstrated in comparative studies where the patients receiving vascularized bone flaps were older, had larger defects, and were treated primarily for malignant disease with an associated higher incidence of RT [11].

4.6.1.3 Pedicled Soft Tissue Flaps

This reconstructive option does not provide actual structural restoration of the bony mandible. A soft tissue pedicled flap, commonly the

pedicled pectoralis major myocutaneous flap, was widely used to cover titanium plates to prevent extrusion. Although this reconstructive option was essentially designed to provide a soft tissue pad for the reconstruction plates, the most common complication was still plate exposure [12]. Moreover, failure to deliver autogenous bone to reconstruct the mandible will eventually lead to reconstruction plate fatigue as the contralateral molar loading exerts a torsional force which is more likely to cause plate fracture [13]. As dental rehabilitation would not be possible, this option represents an alternative in patients who have lateral mandibular continuity defects with a poor prognosis, in whom dental rehabilitation is not desired or planned.

4.6.1.4 Free Vascularized Flaps

The use of free tissue transfer and microvascular reanastomosis for the reconstruction is a relatively recent practice. Prior to the past three decades, the majority of head and neck defects were closed with either local tissue or random skin flaps. Free flaps have revolutionized reconstruction. Even when these flaps are transferred from distant sites into areas of irradiation, compromised blood flow, and even salivary contamination, healing and support of functional loads are the usual results [14]. Together with their ability to support the osseointegrated implants for later dental rehabilitation, free bone flaps have now become the preferred method of mandibular reconstruction after oncologic surgical ablation.

Unfortunately, an ideal flap for all defects does not exist. Each patient and every defect must be evaluated separately to determine the best surgical approach. Nowadays, reconstruction is no more tailored to defects; it is rather tailored to the patient as a whole, and the patient himself is actively contributing to the decisions concerning various reconstructive modalities. Factors potentially influencing the long-term results and especially bone mass preservation in the reconstructed mandible include site of reconstruction (central, body, ramus), patient's age, adjuvant RT, delayed placement of osseointegrated dental implants, and the performance over time. Fibular osteocutaneous free flaps, scapular

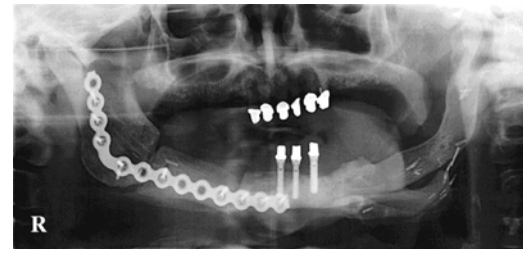

Fig. 4.6 Bilateral mandibular reconstruction; *Rt* side free scapula, *Lt* side free fibula

osteocutaneous free flaps (Fig. 4.6), iliac crest osteocutaneous free flaps, radial forearm osteocutaneous free flaps, and the latissimus-serratus-rib free flap are all available options for mandibular reconstruction [15–18].

For reconstructing defects after cancer extirpation, currently the vascularized free flaps are regarded as the "gold standard." The use of these flaps, however, presents several major inconveniences. Harvesting of autologous tissue may result in a significant donor site morbidity, the extent of which may vary, according to the donor site and possibly according to the intervention technique [19, 20]. The problems include bleeding, pain, infections, donor site fractures, and prolonged hospital stay [21, 22]. One of the most frequently used flaps for mandibular reconstruction is the free fibular flap that has been regarded as the classical "workhorse" for this purpose. However, even when a muscle-sparing technique is used to harvest the fibula flap, and the proximal 6 cm and distal 8 cm of fibula are left intact, some authors have reported significant sequelae at the donor site. It has been noted that complaints included ankle stiffness, mild ankle instability, and transient or permanent peroneal motor or sensory loss and significantly less range of motion in ankle flexion/extension compared with the unoperated contralateral side [23].

4.6.1.5 Tissue Engineering and Regenerative Medicine

This field of regenerative medicine promises new alternatives to surgical reconstruction through harnessing the regenerative capacity of the human body to repair itself. In the last few decades, the rapid expansion of knowledge about

the biological basis of wound healing and the role of cells, signals, and biological scaffolds have drawn the attention from "tissue reconstruction" to "tissue regeneration." New strategies started to emerge aiming at mimicking the normal healing process in regenerating lost or damaged tissues. The term "tissue engineering" was officially coined at a National Science Foundation workshop in 1988 to mean "the application of principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve tissue function" [24].

Tissue engineering and regenerative medicine depend on the presence of a biomaterial promoting cell growth and proliferation. In order to populate this biomaterial (scaffold) with new tissue, the body must effectively interact with this biomaterial. This necessitates the establishment of an early and reliable angiogenic response leading to the development of an adequate blood supply for the restoration of structure and function [25]. The three main components required for regeneration are the cells, scaffolds, and induction molecules (Fig. 4.7). When growing tissues in vitro (tissue engineering), all three components should exist; however, when referring to regenerative medicine, any of these can be provided to the body in an attempt to optimize its capacity for regenerating its own tissues. Adding cells or growth factors to the biomaterials can reinforce tissue regeneration [26], but the vascularization, and thus the integration, of these biomaterials is still considered the determining issue in the success of any critical size defect regeneration [27].

4.6.2 Vascularization: The Key for Regeneration

Adequate vascularization ensures not only successful tissue regeneration but also the active integration of this tissue in the human body. One of the most particular features of any normally functioning tissue is its ability to interact with the surrounding tissues to ensure homeostasis. Active incorporation within the vascular network of the organism would help this interaction to take place effectively. Adequate vascularization of any tissue, or tissue construct, is then a prerequisite for its sustainability and active integration.

4.6.2.1 Vascularization Concerns in the Mandible After Cancer Ablation

Vascular Pattern

The vascular supply of the craniofacial region is mainly of the cancellous bone type. In this type, the blood reaches its anatomical destinations more directly without significant branching. Most of the midfacial bones are covered with mucosa, which provide an additional source of direct periosteal blood supply. Together with a relatively large surface area to bone volume, these bones are less prone to vascular compromise. The blood supply of the mandible, however, is a mixture of that of the compact and cancellous bones and is therefore more susceptible to vascular compromise [28, 29].

Radiotherapy

It is true that the craniofacial region has its abundant and reliable blood supply; however, this will not always be the case after treatment with radiotherapy following cancer surgery [30]. Radiotherapy causes damage to normal epithelial, dermal, and endothelial cells. The resulting hypocellularity and hypoxic environment leads to scarring, endarteritis, and fibrosis that make secondary reconstruction of the surgical site a real challenge for the reconstructive surgeon [31].

Defect Size

Bone regeneration is principally a part of the fracture healing process. The majority of fractures heal well under standard conservative or surgical therapy. Extended bone defects following trauma or cancer resection, however, require more sophisticated treatment as spontaneous bone healing is unexpected. In large defects, failure to provide adequate scaffolding, efficient vascular invasion, and cellular recruitment

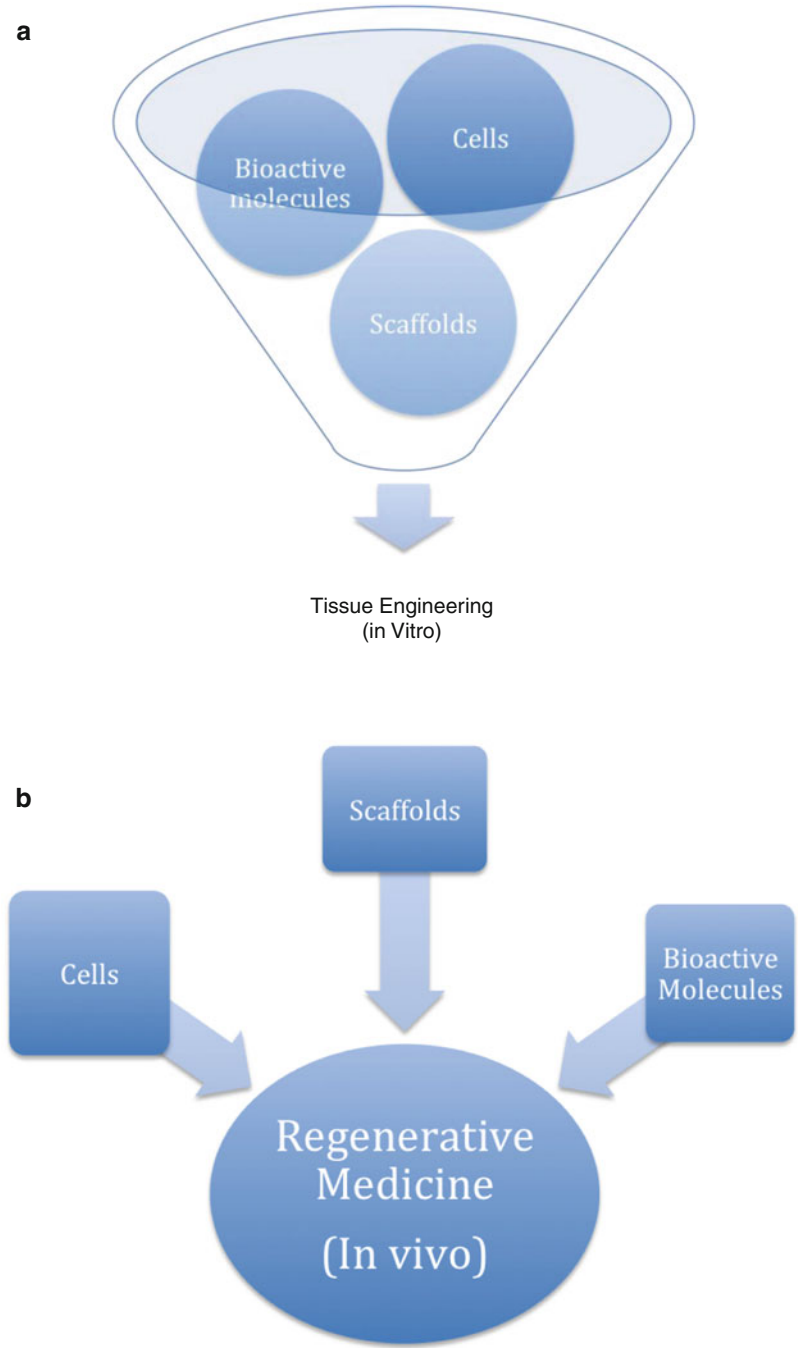

Fig. 4.7 Strategies for tissue engineering and regenerative medicine. (**a**) In vitro tissue engineering, (**b**) in vivo tissue regeneration

throughout the defect would lead to fibrosis instead of tissue regeneration. In regenerative medicine, and in a similar way, new tissue formation and bone regeneration at the central region of large constructs usually fails due to absence of adequate vascularization [32]. Although blood vessel ingrowth is often noted in implanted tissue constructs over time, the vascularization is too

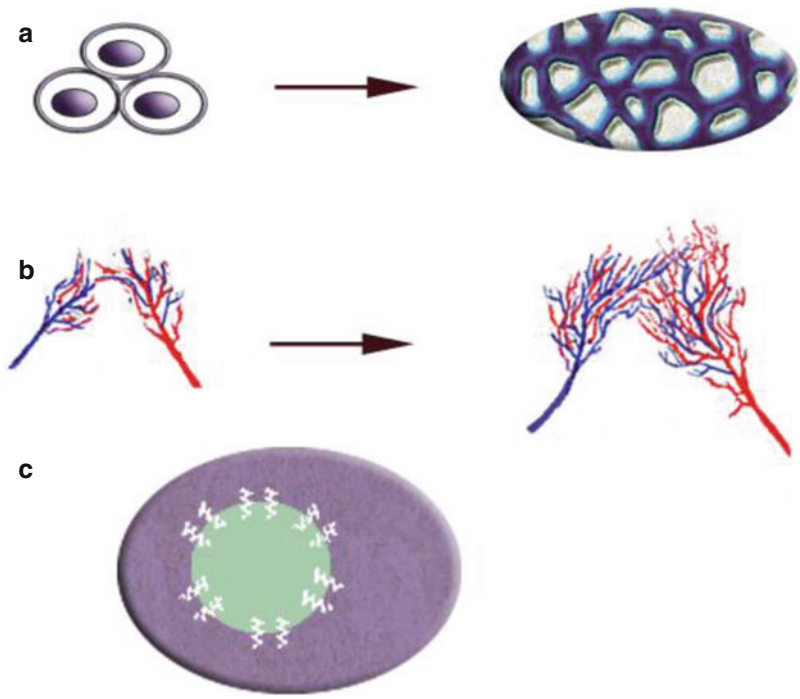

Fig. 4.8 Vascularization strategies; (**a**) vasculogenesis, (**b**) angiogenesis, (**c**) inosculation

slow or too limited to provide adequate nutrient and oxygen transport to the transplanted or the recruited cells [32].

The previous concerns have made most of the clinical trials for mandibular reconstruction using regenerative medicine modalities avoid reconstruction following cancer [33]. The trials were confined to reconstruction postinfection, trauma, benign tumors, or congenital anomalies [34–37].

4.6.2.2 Types of Vascularization

As postulated, vascular patterns, and vascularization are of crucial importance in relation to reconstructive surgery and are the main basis for the stepladder classification of the reconstructive options. Tissue engineering and regenerative medicine researchers have recognized this importance, and a lot of research groups have tried to augment the vascularity of scaffolds either through new capillary plexus formation from endothelial precursor cells (vasculogenesis) or through sprouting of microvessels from preexisting vasculature (angiogenesis) (Fig. 4.8).

Vasculogenesis

A network of newly developed microvessels may be engineered in vitro by seeding scaffolds with endothelial cells [38]. After implantation of those tissue constructs, the endothelial cells should develop interconnections to the blood vessels of the surrounding tissue, resulting in an adequate perfusion of the prefabricated microvascular network in a couple of days. The process is unfortunately not as easy as it sounds. The seeding of a scaffold with endothelial cells does not always guarantee the development of new blood vessels in vitro. Vasculogenesis depends not only on the seeded endothelial cells but also on the coordinated release of a variety of signaling factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) and involves other cell types, including smooth muscle cells and pericytes, which are normally found under in vivo conditions but not necessarily in vitro [39]. The attempt to mimic this cellular "environment" resulted in the emergence of what is called the co-culture techniques where the endothelial cells (EC) are being co-cultured with target tissue cells and fibroblasts then seeded as a mixture into the scaffolds [40].

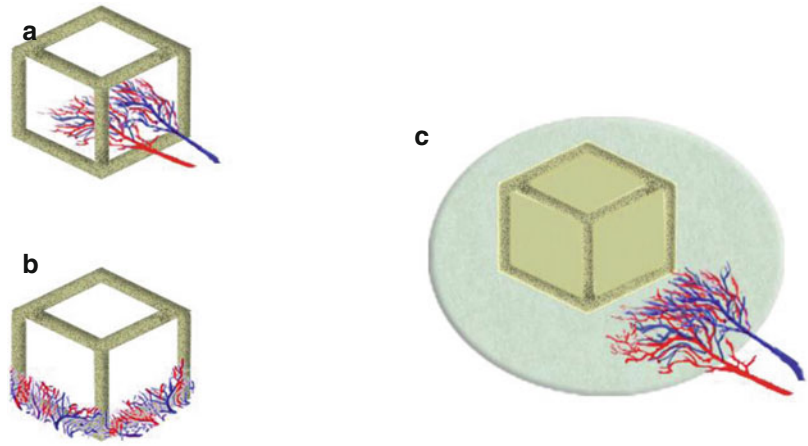

Fig. 4.9 Types of angiogenesis; (**a**) intrinsic (prefabrication), (**b**) extrinsic, (**c**) prelamination

The role of co-culturing could be related to higher levels of vascular growth factor release and/or to the direct cell-to-cell contact effect in inducing stable vascularization [41]. Yet, co-culture for promoting angiogenesis is technically difficult. Reaching a homogenous distribution of the seeded cells throughout a large 3D construct could represent a technical challenge. Another challenge would be the selection of the cells to be cocultivated. For example, cocultivation of EC together with fibroblasts, pericytes, or vascular smooth muscle cells (SMC) in fibrin gel did not lead to capillary networks, while younger or embryonic fibroblasts were able to support such endothelial organization in other gel systems [42].

Another major concern in the vasculogenesis process is the 3D configuration of the cultured cells. Establishing construct vasculogenesis should not only act on biological and cellular aspects of vasculogenesis but should also mimic the 3D hierarchal structure of a capillary network. Fabrication of scaffolds with channels mimicking the vascular networks led to the development of constructs with a preformed capillary "pattern." Creating such microcirculatory networks within the scaffolds has led to the evolution of highly sophisticated techniques of microvascular engineering, such as soft photolithographic techniques [43], and the development of computational simulation models of vascular assembly and remodeling [44].

Because so much effort is required to mimic a natural scaffold, recent approaches have shown that the naturally occurring scaffolds can be decellularized and processed so that they retain growth factors and structural elements that are important regulators of angiogenesis. For example, elastic fibers of an extracellular matrix scaffold were shown to act as "micro-guides" for endothelial cell and pericyte migration during capillary sprouting [45]. Ott et al. [46] have succeeded to create a whole-heart scaffold with intact 3D geometry and vasculature by decellularizing cadaveric hearts using detergents for coronary perfusion. Porcine jejunal segments were decellularized in a similar technique and seeded with porcine microvascular endothelial cells [47]. Naturally occurring scaffolds, however, have got their own disadvantages including rapid degradation, potential to harbor infection, and the possible immunologic response of the host to such implants.

Angiogenesis (Fig. 4.9)

The predominant physiologic mechanism of microvascular formation in the human body is that of sprouting angiogenesis. Angiogenesis starts from a preexisting vascular bed through migration, proliferation, and co-option of the existing endothelium [48]. Sprouting angiogenesis commences mainly with proteolytic degradation of the basement membrane around the endothelial cells (ECs) of a preexisting capillary or venule [49].

The majority of currently applied approaches rely on the so-called extrinsic mode of angiogenesis for the vascularization of tissue

constructs. In extrinsic angiogenesis, the neovascularization starts invading the construct from its periphery. Vascularization in this case does not depend on a definite vascular axis [50]. This method is suitable for vascularization of small constructs with a tissue thickness ranging from 2 to 3 mm [51]. The delay in blood vessel growth into larger scaffolds will end up by central necrosis due to the limited perfusion and oxygen supply to the deeply implanted tissues. This extrinsic type of vascularization requires also an optimal, well-vascularized, implantation site so that the construct can get its adequate blood supply. This is seldom available after cancer extirpation due to extensive tissue loss and eventual irradiation of the surgical field.

An intrinsic mode of angiogenesis, however, depends on a definite vascular axis, which can serve as a source of new blood vessels for prefabrication of tissues before transplantation (Fig. 4.9). Prefabrication is a technique of revascularization of a tissue graft by implanting an arteriovenous loop (AVL) or a vascular pedicle underneath or within a tissue graft, resulting in spontaneous angiogenic development from the loop or pedicle and subsequent revascularization of the tissue graft [52]. This mode of vascularization is also known as "intrinsic axial vascularization" and would be more suitable to regenerate tissues in harsh environments as after cancer ablation [33, 53, 54].

Inosculation

"Inosculation" refers to the development of direct connections between the already-existing capillaries of a tissue graft or construct and angiogenic recipient-site vasculature [55]. This occurs via an interaction between the implanted microvascular network and the microvasculature of the host site. It was previously suggested that the host vasculature plays the active role and the vessels within the tissue graft only provide a conduit for ingrowing wound bed (recipient) vessels, what was known as "internal inosculation." Other recent studies, however, provide evidence that the preformed microvascular network of the graft actively contributes to the process of revascularization leading to "external inosculation" [56]. This process may be observed when the angiogenic activity of the preformed microvascular network of the construct is high enough to induce angiogenesis well before it is initialized at the host site [57]. Whether the external or internal inosculation will predominate depends on many factors, such as the extent of host tissue hypoxia and the maturation stage of preformed blood vessels within the tissue construct as well as the tissue type and degree of the inflammatory reaction to the construct at the host site.

Successful engraftment of the construct to the host tissues does not only include the development of vascular connections between the host and the graft but also includes the remodeling of the construct vasculature after implantation. The microvascular network that is implanted may be completely different or absent after remodeling *in vivo* [49]. Vascular remodeling and even vascular regression are crucial for maturation and integration after construct implantation, yet premature vessel remodeling and regression would destroy the whole engraftment process [58].

The postulated vascularization strategies show that vasculogenesis requires a highly sophisticated technology that is still far from clinical practice. Recent trials to augment angiogenesis using microvascular techniques seem to be more feasible, and some studies have already shown good results at the preclinical and the clinical levels [50, 54, 59, 60]. Selecting a strategy for construct vascularization would depend on the size and cellular load of the construct, the vascular status of the recipient site, and the availability of nearby vascular axes. A small tissue construct (2–3 mm thick) would benefit from extrinsic angiogenesis. Intrinsic angiogenesis could be applied for larger constructs wherever a local vascular axis is available. Vasculogenesis could be applied in case of large cell-loaded constructs where immediate perfusion of the core tissue is required [61].

A major concern in the application of regenerative therapies after cancer, especially cell-based therapies, is whether these new techniques would increase the risk of tumor recurrence. Unfortunately, the factors that govern tissue regeneration and revascularization are also critical to cancer growth and metastasis [62].

4.6.3 Summary

The concept of reconstruction has dramatically changed during the last few decades from just "defect filling" to a more global concept concerned not only with structure but also with function. Reconstruction is no more tailored to defects; nowadays it is rather tailored to the patient as a whole where the patient himself is actively contributing to the decisions concerning various reconstructive modalities. A major advance in this context is the emergence of the regenerative medicine as an interdisciplinary field of medicine aiming at harnessing the human body to regenerate its own tissues. With the rapid progress in this emerging field, reducing or even abolishing the donor site morbidity will probably be the standard practice in mandibular reconstruction in the near future.

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Surgery of the Oral Cavity

5

Ahmad Eweida

5.1 Surgical Anatomy

The oral cavity extends from the lips anteriorly to the palatoglossal folds posteriorly. This includes the tongue, floor of the mouth, lips (posterior to the junction of the skin and vermilion border), hard palate, inner cheek mucosa including the vestibule of the mouth, and the gums. The floor of the mouth represents the area situated below the movable part of the tongue bounded by the dental arch and situated above the muscular diaphragm (mylohyoid muscle) that separates the oral cavity from the neck. Due to the anatomical and physiological proximity, the lesions of the oral cavity are usually discussed as one entity.

The tongue occupies most of the oral cavity and is richly innervated with five cranial nerves (V, VII, IX, X, XII) contributing to the complex innervation of this multifunctional organ. The embryologic origins of the tongue first appear at 4 weeks gestation. The body of the tongue forms from derivatives of the first branchial arch. This gives rise to two lateral lingual swellings and one median swelling (known as the tuberculum impar). The lateral lingual swellings slowly grow over the tuberculum impar and merge, forming the anterior two thirds of the tongue. Parts of the second, third, and fourth branchial arches give rise to the base of the tongue. Occipital somites give rise to myoblasts, which form the intrinsic tongue musculature [1].

The lymphatic drainage of the tongue is complex. Lymphatics from the tip of the tongue travel to the submental lymph nodes (LNs). Lymph from the medial anterior two thirds of the tongue drains into to the deep cervical lymph nodes (DCLNs), and lymph from the lateral anterior tongue goes to the submandibular LNs. The tongue-base lymphatics drain bilaterally into the deep cervical LNs.

Examination of the tongue is a main stay in the examination of the head and neck. Various signs would indicate various localized or systemic pathologies.

We will discuss briefly in this chapter the lesions with surgical interest related to the tongue and oral cavity.

5.2 Swellings of the Oral Cavity

According to the National Health and Nutrition Examination Survey, the point prevalence of tongue lesions is 15.5 % in US adults. Lesion prevalence is increased in those who wear dentures or use tobacco [2]. A recently appearing tongue mass

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Table 5.1 Most common varieties of oral cavity swellings

Localized swellings (masses)	Diffuse swellings (Macroglossia)
A. Cystic swellings	Vascular malformations
Retention mucous cyst (ranula)	Multiple neurofibromatosis
Sublingual dermoid cyst	Congenital causes:
Thyroglossal cyst (at foramen cecum)	1. Cretinism (muscle hypertrophy)
Hemangioma	2. Mongolism
Chronic abscess	Glycogen storage disease
Degenerated solid tumor (sarcoma)	Amyloidosis (amyloid infiltration)
Softened gumma or tuberculous (TB) nodule	Diffuse carcinoma
Hydatid cyst	Glossitis
B. Solid swellings	1. Acute glossitis
Stone in Wharton's duct	2. Chronic diffuse syphilitic glossitis
Neurofibroma	Allergy
Papilloma	
Lingual thyroid	
Carcinoma (usually an ulcer)	
Sarcoma	

or swelling is usually a clinically suspicious sign. A wide spectrum of causes could be responsible for either diffuse or localized tongue swellings (Table 5.1). These may include developmental, traumatic, inflammatory, or neoplastic causes. A tongue swelling could be also a reflection of a systemic disorder. Oral cavity swellings due to benign or malignant neoplasms will be discussed later in this chapter.

5.2.1 Ranula

A ranula is a large mucous retention cyst in the floor of the mouth (in Latin, ranula means a *small frog*) probably due to an unnoticed trauma of the duct system.

It usually occurs in children and young adults, affecting both genders equally. The main complaint is a swelling in the floor of the mouth that usually ruptures and refills. Physical examination reveals a small spherical cyst (only the top 1/2 is seen), about 1–5 cm in size, in the floor of the mouth, between the symphysis menti and the tongue, just to one side of the midline. Ranulae occasionally extend into the submandibular triangle of the neck (*plunging ranula or deep cervical ranula*). The cyst is characteristically translucent and has a bluish tinge. It is smooth and covered by tortuous veins, and the submandibular duct is displaced and stretched over it. The edge is difficult to feel and the cyst *cannot* be compressed or reduced.

Treatment options include *marsupialisation* (deroofing of the cyst and suturing the edges to the floor of the mouth) and *total or partial excision* of the sublingual gland through an intraoral approach [3].

5.2.2 Sublingual Dermoid Cyst

When the face and neck are formed by the fusion of the facial processes, a piece of skin may get trapped deep in the midline just behind the jaw and later forms a "sublingual dermoid cyst." Such cysts usually lie in the midline or may be slightly lateral. They may lie above or below the mylohyoid muscle (supra- or infrahyoid, respectively).

It usually occurs between 10 and 25 years, affecting both genders equally. The patient usually complains of a swelling under the tongue, which becomes painful and tender if it gets infected. Physical examination reveals a smooth, clearly defined, spherical swelling, about 2–5 cm in size, occupying the midline between the tongue and the inner surface of the chin. It may bulge into the submental triangle of the neck below the chin. The mucous membrane appears normal. It can be felt bimanually (with one finger in the mouth and the other beneath the chin). It is characteristically opaque and fluctuant.

Treatment is by surgical excision through the oral route rather than the cervical route because of the hidden scar.

5.2.3 Stone in Wharton's Duct

Stones and infection of the submandibular gland and duct are common. When such a stone migrates to the mouth of the submandibular duct (*Wharton's duct*), it forms a tender lump in the floor of the mouth. The lump bulges slightly into the mouth and, through the surrounding edema, feels hard. Occasionally, the surface of the stone can be seen through the open end of the duct. The submandibular gland is usually swollen and tender. The majority of stones (60 %) reside in the proximal duct or hilum of the submandibular gland.

Small mobile stones (<4 mm) could be retrieved (as per parotid) by baskets (via endoscopes and radiologically guided). The extracorporeal lithotripter is relatively inefficient in eliminating submandibular stones (30 % clearance). These stones are dealt with by an intraoral surgical technique either under local anesthetic or day-case general anesthesia. Based on a review of the treatment of 4600 salivary stones, submandibulectomy should be recognized as an uncommon event representing a minority of cases in the modern surgical practice (<3 %) [4].

5.2.4 Vascular Malformations

About 50 % of all vascular anomalies occur in the head and neck regions [5]. Although such lesions are usually of aesthetic concern, a lesion located in the tongue or closely related to the oropharyngeal airway may lead to more serious problems such as spontaneous bleeding or even hematemesis [6]. Though uncommon, progressive asymmetric growth of the tongue (macroglossia) can be also observed. In contrast to hemangiomas, malformations are not neoplasms and thus do not exhibit mitosis or increased endothelial cell turnover. Instead, vascular malformations are defined as structural abnormalities of the capillary, venous, lymphatic, and arterial system that grow in proportion to the child [7].

5.2.4.1 Classification

According to the classification of the International Society for the Study of Vascular Anomalies (ISSVA) approved in April 2014 [8], the vascular malformations were classified according to the *origin* mainly into four main categories:

1. *Simple* (capillary, venous, lymphatic, arteriovenous fistula, arteriovenous malformation)
2. *Combined* (lymphatic venous, capillary-lymphatic venous, etc.)
3. *Malformations of major named vessels*
4. *Associated with other anomalies*

Vascular malformations could be further classified according to the *flow pattern* into high- and low-flow malformations. The capillary, venous, and lymphatic variants belong to the low-flow pattern group and those with an arterial component belong to the high-flow one. Common vascular malformations in the tongue and oral cavity include venous malformations, arteriovenous fistulae, and lymphatic malformations.

5.2.4.2 Venous Malformations

Pathology

Congenital venous malformations consist of either localized or diffuse ectatic veins with abnormal collections of irregular venous channels. Although mostly in the skin, venous malformations are also commonly found in the cheek, tongue, lip, and mandible. They may be present in deep tissue, bone, muscle, or brain. Recently a loss-of-function mutation was discovered on the angiopoietin receptor gene TIE2/TEK in many solitary and multiple sporadic venous malformations [9]. In addition, upregulation of several factors including tissue growth factor beta (TGF-beta) and basic fibroblast growth factor (beta-FGF) has been also discovered in patients with venous malformations [10].

Clinical Presentation

A venous malformation is always present at birth but is not always evident. They may first become noticeable in childhood or even adulthood and they do not spontaneously involute. Small lesions are usually asymptomatic or the patients may complain only of disfigurement. Intravascular coagulation due to trauma or venous stasis may sometimes cause pain. For large lesions with significant thrombosis, distal embolization may

subsequently occur. When malformations are extensive, a blood coagulation profile should be performed. These patients are particularly at risk for a pulmonary embolus following surgery; they require anti-thromboembolic prophylactic treatment [11]. Trauma, infection, and hormone changes of puberty and pregnancy can be associated with growth of the lesions, probably because the progesterone receptors that have been discovered in these malformations [12, 13].

Superficial venous malformations have a bluish compressible mass with no palpable thrill or audible bruit. These lesions often enlarge in a dependent position or with Valsalva maneuver. Phleboliths are commonly seen on radiographs. Doppler echocardiography, MRI or MRA, and direct-puncture phlebography may be required to confirm the diagnosis and assess the extent of the lesion.

Treatment

Treatment depends on the location and extent of the venous malformation. When a lesion is symptomatic, localized, and accessible, *surgical excision* remains one of the most superior treatment options and may offer a cure for localized lesions. Excision of complex lesions remains difficult due to intraoperative bleeding. *Preoperative sclerotherapy* (or sometimes multiple sessions of sclerotherapy) can be used prior to excision (24–48 h) to decrease surgical risk. Complete cure is not to be expected in patients with extensive disease but combined modality therapy may offer a long-term control of the disease. Superficial lesions or the superficial component of deep lesions can be treated with the Nd:YAG *laser* [14].

5.2.4.3 Arteriovenous Fistulae

Pathology

Arteriovenous fistulae or malformations (AVMs) are congenital vascular lesions associated with a variable degree of arteriovenous shunting. They are clinically evident in childhood or during puberty. Rapid expansion has been also reported following pregnancy and trauma, including inadequate surgical intervention. A defect in vascular stabilization is thought to cause AVM, but it remains unclear whether these lesions are primarily congenital in origin. An acquired AV fistula can also occur due to direct trauma to vessels; however, this is uncommon in the oral cavity.

Clinical Presentation

The presentation of AVMs is commonly by a warm swelling with a palpable thrill and an audible bruit. Oral lesions can present early due to gingival involvement, disruption of deciduous teeth, and profuse periodontal bleeding. Traditional angiography or MRA to demonstrate their vascular anatomy is essential for confirming the diagnosis and developing a treatment plan. Moreover, CTA allows evaluation of local effects on surrounding tissues and bones and can define individual arterial feeders as well [15].

Treatment

Treatment of AVMs could be problematic especially with large and diffuse lesions due to complete replacement of normal tissues by the diseased vessels. Such lesions require reconstruction after excision. Recurrence is also common after embolization or even after surgical excision due to recruitment of new vessels [16]. When a lesion is small and asymptomatic, a period of *observation* is often the most convenient initial strategy. Large and diffuse lesions are usually symptomatic and a delayed treatment may lead to cardiac decompensation. *Intra-arterial embolization* combined with surgical excision currently offers the best chance for cure. Excision is preformed 24–48 h after embolization. This helps control blood loss and defines the surgical margins of the lesion. Complete *excision* is sometimes impossible because of the location and extent of the malformation. Long-term follow-up with a dedicated multidisciplinary team is thus crucial for AVM management.

5.2.4.4 Lymphatic Malformations

Pathology

Lymphatic malformations, previously known as "cystic hygroma" or "lymphangioma," are composed of dilated lymphatic vessels with inappropriate communication, lined by endothelial cells, and filled with lymphatic fluid. Their incidence is approximated to be 1 in 2000–4000 live births [17].

Lymphatic malformations are classically classified into macro-cystic, micro-cystic, or mixed according to the cyst size (2 cm^3) [7]. What usually affect the oral cavity are the micro-cystic or mixed variants. These small non-compressible vesicles can weep and at times cause pain or minor bleeding. Micro-cystic disease usually carries a worse prognosis and could be more aggressive, invasive, and difficult to control [18].

Clinical Presentation

Symptoms are usually related to the extent of the disease, which can be defined by MRI. The patient usually suffers from pain, dysphagia, and odynophagia.

Treatment

As spontaneous resolution is usually not anticipated, management of symptomatic disease is usually mandatory. Treatment is usually easier and carries a more favorable prognosis with the macro-cystic type. Treatment modalities include sclerotherapy [19], carbon dioxide laser [20], and surgical excision (with/without reconstruction). Multiple combined treatment modalities are sometimes necessary for the disease control.

5.3 Ulcers of the Oral Cavity

5.3.1 Etiological Classification

The most common varieties of oral cavity ulcers are summarized in Table 5.2.

5.3.2 Traumatic Ulcers

5.3.2.1 Dental Ulcers

Dental ulcers are caused by trauma from a broken tooth or ill-fitting dentures. The ulcer occurs mostly at the side of the tongue. It is painful, with sloping serrated edges, elongated shallow floor covered with granulation tissue, and soft or mildly indurated base. It heals in few days when the cause is removed; otherwise it should be biopsied, particularly if malignancy is suspected. Treatment is by extraction of the ragged tooth plus good oral hygiene. Antibiotics are used if superadded infection occurs.

5.3.2.2 Frenular (Pertussis) Ulcer

A frenular ulcer results from trauma of the frenulum of the tongue by the teeth during coughing in children with whooping cough, between 6 and 8 months of age (due to eruption of lower teeth). Treatment of the cause results in healing of the ulcer.

5.3.3 Inflammatory Ulcers

5.3.3.1 Herpetic Ulcers

Herpetic ulcers are caused by herpes simplex (HS) virus in patients with low resistance (e.g., following pneumonia). They appear in the tongue and angles of the mouth as multiple, small, painful ulcers, preceded by vesicles.

5.3.3.2 Tuberculous (TB) Ulcers

Tuberculous ulcers result from active pulmonary TB or infected milk (causing ulcers, or diffuse fibrosis – woody tongue). They usually appear at the tip and sides of the tongue as multiple, painful, shallow ulcers with undermined edges, yellowish floor, and soft base. Treatment is by antituberculous drugs and sanitorial management.

5.3.3.3 Syphilitic Ulcers

During the *first stage* of syphilis, a chancre may occur at the tip of the tongue together with enlarged submental and submandibular LNs. During the

Table 5.2 List of the most common varieties of oral cavity ulcers

Traumatic ulcers	Inflammatory ulcers	Dyspeptic ulcers	Malignant ulcers
Dental ulcers	Herpetic ulcers	Aphthous (metabolic or dyspeptic) ulcers	Epithelioma
Frenular ulcers	Tuberculous ulcers		Lymphoepithelioma
	Syphilitic ulcers		Adenocarcinoma
	Chronic superficial (nonspecific) glossitis		Basal cell carcinoma
			Malignant melanoma

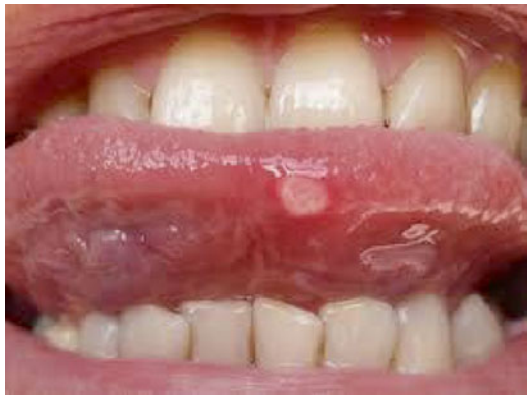

Fig. 5.1 Aphthous ulcer at the tip of the tongue

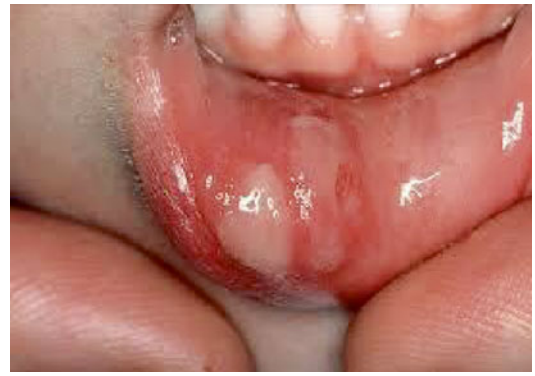

Fig. 5.2 Multiple aphthous ulcers at the inner side of the lower lip

second stage, mucous patches and snail track ulcers are present in the tongue (multiple and yellowish-white) associated with Hutchinson's warts or condylomata. Gummatous ulcer develops during the third stage of syphilis, at the midline of the dorsum of the tongue. It is painless, single, with clear-cut edges and washleather floor. Leukoplakia of diffuse fibrosis may also be present.

5.3.3.4 Chronic Superficial Glossitis

Chronic superficial glossitis may be associated with chronic repeated nonspecific ulcers, usually on the dorsum of the tongue. Ulcers are superficial, small, and painful. They are associated with fissures or vesicles and have a unilateral distribution. Untreated chronic superficial glossitis may lead to leukoplakia, erythroplakia, or overt squamous cell carcinoma (SCC). Treatment includes avoiding the predisposing factors, mouth gargles, close follow-up, and biopsy of any developing lesions.

5.3.4 Dyspeptic (Aphthous) Ulcers

Dyspeptic or aphthous ulcers represent the commonest type of ulcers of the oral cavity. They occur in patients with dyspepsia and are characterized by their short history and the painful erosions at the tip (Fig. 5.1) and sides of the tongue and inner sides of lips (Fig. 5.2) and cheeks (Fig. 5.3). Ulcers are small, multiple, with whitish floor, hyperemic margins, sloping edge, and soft base. The regional LNs are *not* enlarged.

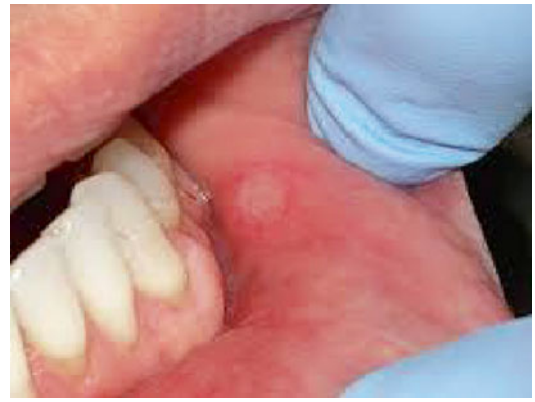

Fig. 5.3 Aphthous ulcer at the inner aspect of the left cheek

5.3.5 Malignant Ulcers

Malignant ulcers of the oral cavity are most commonly SCCs (*epitheliomas*) but may be *lymphoepithelioma* (in the posterior 1/3 of the tongue), salivary *adenocarcinoma* (from minor salivary glands), or, rarely, *basal cell carcinoma* (BCC) or *melanoma*. The epitheliomatous ulcer usually affects the tongue (Fig. 5.4) and lips (Fig. 5.5). It is characterized by a raised nodular everted edge, necrotic floor that bleeds easily on touch, and a hard indurated base. The commonest site is the anterior two thirds of the tongue. Regional LNs are usually enlarged and hard and either mobile or fixed according to stage of the disease. There may be also infiltration of deeper tissues including the bone in neglected cases.

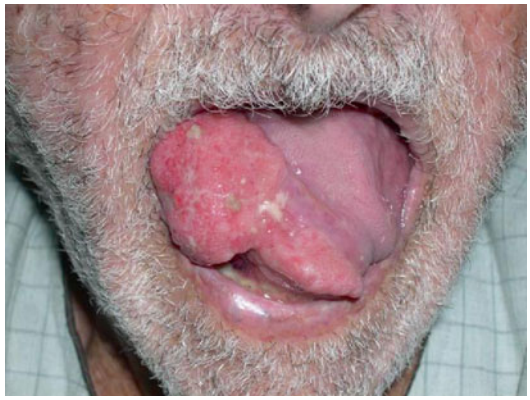

Fig. 5.4 A neglected epitheliomatous ulcer at the side of the anterior two thirds of the tongue in a 73-year-old gentleman. Note the large size and everted edge of the ulcer

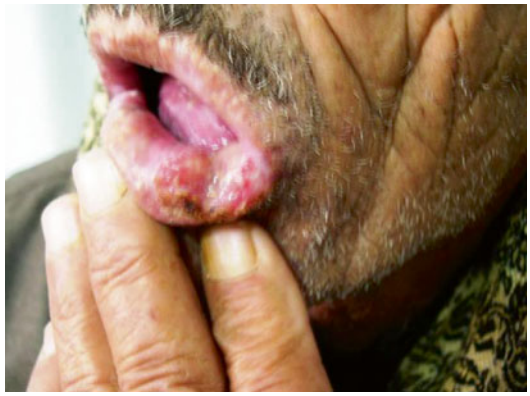

Fig. 5.5 A neglected epitheliomatous ulcer at the side of the lower lip (reaching the corner of the mouth) in a 62-year-old gentleman. Note the large size, everted edge, and necrotic floor of the ulcer

For details, see under "Neoplastic Lesions of the Oral Cavity." Differential diagnosis of tongue ulcers is summarized in Table 5.3.

5.4 Neoplastic Lesions of the Oral Cavity

5.4.1 Classification

Neoplastic lesions affecting the oral cavity are summarized according to their tissue of origin in Table 5.4.

5.4.2 Benign Tumors

5.4.2.1 Fibro-epithelial Polyp

A fibro-epithelial polyp presents as a firm swelling (fibrous tissue) on the inside of the cheek. It results from repeated biting or trauma.

5.4.2.2 Papilloma of the Oral Cavity

A papilloma of the oral cavity or tongue (Fig. 5.6) presents as a sessile or pedunculated, pale or pink, soft, and fleshy swelling. It should be removed with an adequate margin of tissue and biopsied for histological diagnosis.

5.4.2.3 Mixed Salivary Tumors of Minor Salivary Glands

A mixed tumor of the minor salivary glands usually presents as a submucous, rounded, firm,

Table 5.3 Differential diagnosis of ulcers of the tongue

	Malignant ulcer	Dyspeptic (aphthous)	Frenular (pertussis)	Dental (traumatic)	TB	Syphilitic
Site	Side of the tongue	Dorsal and undersurface	Undersurface and frenulum	Side of the anterior two thirds	Tip or back of the tongue	Midline of dorsum
Number	Single	Multiple	Single	Single	Single or multiple	Single
Pain	++	+++	+	++	+	–
Teeth	Sepsis	±	±	Ragged	±	
Edges	Everted	Sloping	Sloping	Sloping	Undermined	Punched out
Base	Indurated	Soft		Firm, granulation tissue	Soft	± Fibrotic
Floor	Tumor	Whitish			Yellowish	Washleather
Enlarged LNs	+	–	–	–	+	+

Table 5.4 Classification of the tongue and floor of mouth neoplasms according to origin

Origin	Benign tumors (BTs)	Malignant tumors (MTs)
A. Epithelial	*Papilloma*	Epithelioma (SSC)
		Lymphoepithelioma
		Adenocarcinoma
		Basal cell carcinoma (BCC)
B. Mesenchymal	Hemangioma	Hemangioendothelioma
	Neurofibroma	Fibrosarcoma
	Fibroma	Lymphoma
	Lipoma (very rare)	Rhabdomyosarcoma
C. Salivary gland origin	Mixed salivary gland tumor	Malignant salivary gland tumors
D. Thyroid origin	Lingual thyroid	Malignancy in remnants of thyroid tissue

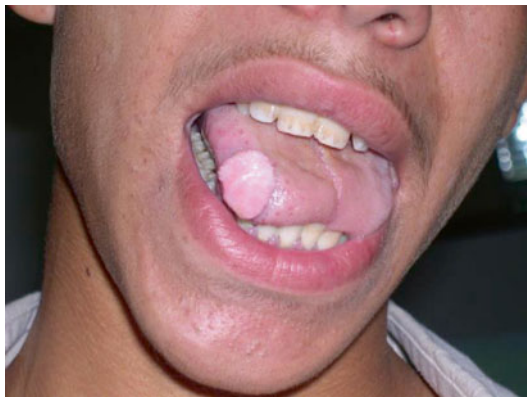

Fig. 5.6 Papilloma of the tongue in an 18-year-old young gentleman. Note the pale color and sessile nature of the lesion

mobile lobulated mass that increases in size with eating. It is treated by simple excision.

5.4.2.4 Lingual Thyroid

Lingual thyroid tissue presents as a mass at the dorsum of the tongue. It may cause respiratory obstruction and hemorrhage.

5.4.2.5 Hemangioma

Pathology

An infantile hemangioma is the most common tumor in infancy and occurs in approximately 10 % of the population. Risk factors include female gender, prematurity, low birth weight, and fair skin [21]. Unlike vascular malformations, hemangiomas are real tumors arising from the rapidly dividing endothelial cells. The two main types of hemangioma are "infantile" and "congenital" types. The rare "congenital" hemangioma is less understood and presents at birth. Infantile hemangiomas present shortly after birth most often as a well-demarcated, flat, and erythematous red patch. At this stage, hemangiomas may be confused with other red lesions of birth, but rapid proliferation and vertical growth will trigger the diagnosis.

Hemangiomas classically grow in three developmental phases: proliferation, quiescence, and involution. In most hemangiomas, 80 % of proliferation occurs by 3 months of life. Relative ischemia of the tumors due to rapid growth at this phase can lead to necrosis, ulceration, and eventual bleeding [22]. Historical reports suggest that involution of 50 %, 70 %, and 90 % of the hemangioma occurs by 5, 7, and 9 years of age, respectively [23].

Clinical Presentation

Head and neck hemangiomas frequently coincide with the distribution of the trigeminal nerve. Hemangioma of the oral cavity or the tongue is rather uncommon; however a beard-like facial distribution is usually associated with a subglottic hemangioma [24]. A child presenting with stridor and facial hemangioma should be considered to have subglottic disease until proven otherwise [12].

The diagnosis of a hemangioma depends mainly on the history and clinical examination. When in

doubt, a Doppler ultrasonography (US) and/or MRI will define the diagnosis. Watchful expectancy is usually considered in non-symptomatic lesions to differentiate from other vascular malformations and reach maximum involution.

Treatment

Treatment options for symptomatic hemangiomas include systemic propranolol administration, local corticosteroid injections, laser therapy, and surgical excision with various combination protocols.

5.4.2.6 Pyogenic Granuloma

The term is a *misnomer*, as the lesion has nothing to do with pyogenic infections. According to the recent ISSVA classification, the pyogenic granuloma belongs to *hemangiomas* as the endothelium shows evident hyperplasia [8]. It is seen commonly on the oral mucosa as smooth or lobulated exophytic hemorrhagic and compressible papule. The lesion may grow rapidly in size from few millimeters to centimeters. Due to its hyperplastic nature, it is usually friable and commonly ulcerates. The gingiva is the commonest site for occurrence of pyogenic granulomas with lateral borders of the tongue, buccal mucosa, and lips being the next common site. These lesions are usually asymptomatic, but problematic lesions could be treated conservatively through avoiding local irritating factors or through conservative surgical excision. Latest techniques like laser, cryosurgery, and electrodissection cause less bleeding and are well tolerated by patients with no adverse effects [25].

5.4.3 Malignant Tumors of the Oral Cavity

An estimated 263,900 new cases and 128,000 deaths from oral cavity cancer (including lip cancer) occurred in 2008 worldwide. Generally, the highest oral cavity cancer rates are found in Melanesia, South-Central Asia, and Central and Eastern Europe and the lowest in Africa, Central America, and Eastern Asia for both males and females [26].

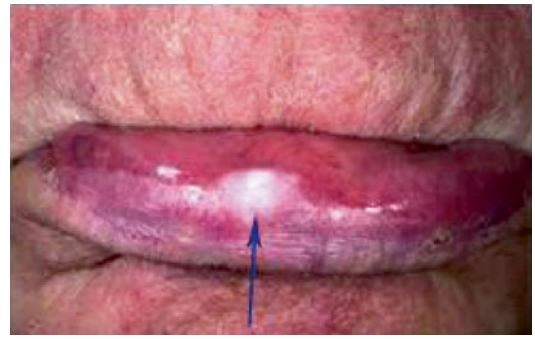

Fig. 5.7 Leukoplakia of the middle of the lower lip in a 67-year-old gentleman (*arrow*)

5.4.3.1 Predisposing Factors

1. Premalignant lesions [27]
   (a) The important premalignant disease of the tongue and oral cavity is *chronic superficial glossitis*, caused by the chronic irritation of syphilis, smoking, sharp tooth, spirits, spices, and sepsis (*6S*).
   (b) *Leukoplakia*: A homogenous thick predominantly white or grey patch, which cannot be wiped away (Fig. 5.7). It is not a definite histopathological diagnosis. It is only a clinical diagnostic term of exclusion where it cannot be characterized as any other definable lesion [28].
   (c) *Erythroplakia*: According to the original 1978 WHO definition, it is defined as "*any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterized clinically or pathologically as any other recognizable condition*." It could occur together with leukoplakia (erythroleukoplakia). It has the highest risk among the oral potentially malignant disorders (44.9 % of cases will turn malignant) [29].
   (d) *Lichen planus*: A chronic inflammatory lesion characterized by remission and recurrences, commonly presents bilaterally as reticular plaques. Asymptomatic patients do not require treatment but should be followed up regularly [30].
   (e) *Submucous fibrosis*.
   (f) *Benign tumors*, e.g., tongue papilloma.

2. Plummer-Vinson syndrome
3. Human papilloma virus (HPV) infection, which is usually related to oral sexual behavior [31, 32]
4. Smoking and other smokeless tobacco products
5. Alcohol consumption, where smoking and alcohol have synergistic effects [33]

5.4.3.2 Sites in the Tongue

Anterior Two Thirds (80 %)

Malignant tongue ulcers are most commonly distributed as follows: sides of the tongue (50 %), mid-dorsum (10 %), tip (10 %), and undersurface of the tongue (10 %).

Posterior Third (20 %)

Lesions at this site are usually linked to HPV infection with an increasing trend in the United States and some European countries due to change in the oral sexual behavior [34–36].

5.4.3.3 Pathology

Macroscopic Picture

- *Ulcer*: Everted edges, necrotic floor, and hard indurated base.
- *Nodule*: A nodule with an indurated base.
- *Cauliflower-like mass*: It has a bad prognosis.
- *Fissure*: A deep often infected fissure with surrounding induration.
- *Diffuse* (*woody*) *type*: This has the worst prognosis.

Microscopic Picture

1. *Primary tumor*
   - Squamous cell carcinoma (SCC): the main variant and occurs mainly in the anterior two thirds.
   - Lymphoepithelioma: mainly in the posterior third, intermingling of undifferentiated carcinoma cells with a prominent lymphoid stroma.
   - Adenocarcinoma: arising from the minor glands of the tongue.
   - Basal cell carcinoma (BCC).
   - Melanoma (very rare).
   - Hemangioendothelioma.
   - Rhabdomyosarcoma.
   - Lymphoma.
2. *Secondary tumor*: It is rare and the primary is usually a breast cancer.

Spread

1. *Direct spread*: to the gums, mandible, fauces, and glottis and, also, to the soft palate and pharynx if it lies in the posterior third of the tongue.
2. *Lymphatic spread*: occurs early within few weeks or months because of the rich blood and lymphatic supply of the region. Metastasis occurs mostly in order through the first station nodes (level I and II) and second station nodes including the level III, IV, and V where the central lesions are bilaterally drained [37].
3. *Blood spread*: quite rare (8–17 %) to lungs, liver, and bone where the probability of distant metastasis increases with respect to the stage of disease.

5.4.3.4 Clinical Presentation

Malignant ulcer usually occurs in individuals older than 50 or 60 years but may be as early as 20 or as late as 70 years. Males are more affected than females (2.2:1) [36]. A typical presentation would be:

1. Ulcer, fissure, nodule, mass, etc.
2. Pain: local or referred to the ear. The referred otalgia could be explained according to the convergence projection theory. The signals are falsely interpreted to be emerging either from the auriculotemporal nerve of the mandibular nerve (V3) (rather than the lingual nerve) or from the glossopharyngeal-tympanic branch (Jacobson's nerve) of the glossopharyngeal nerve (IX) rather than the lingual branch of the IX [38].
3. Increased salivation, which may be blood stained.
4. Fetor oris (foul oral odor) due to necrosis and infection.
5. Ankyloglossia: Limited movement with fixation (no protrusion or deviation).
6. Severe hemorrhage.
7. Dysarthria (diminished articulation) due to pain, salivation, and ankylosis.
8. Difficulty in chewing, swallowing, or speaking.

9. Lump in the neck: Cervical lymphadenopathy may be the first symptom especially in posterior lesions (*occult primary*).

Thorough clinical examination of the oral cavity for detection of the lesion and examination of the neck for LNs are mandatory. Other benign lesions should be ruled out and suspicious lesions should be biopsied.

5.4.3.5 Complications (Terminal Events)

Neglected cases of tongue cancer may be complicated with secondary infection, aspiration pneumonia, asphyxia (due to edema of the glottis, or compression of air passages by LNs), hemorrhage (from the primary tumor or LN due to erosion of a blood vessel such as the lingual artery), starvation and cancer cachexia, and, finally, spread (local, lymphatic, hematogenous).

5.4.3.6 Staging

Oral cavity cancer is classified according to the American Joint Committee on Cancer (AJCC) TNM Staging Classification for the Lip and Oral Cavity (7th ed., 2010) [39].

Primary Tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1: Tumor 2 cm or less in greatest dimension
T2: Tumor >2 cm but not >4 cm in greatest dimension
T3: Tumor >4 cm in greatest dimension
T4
- *T4a*: Moderately advanced local disease. Tumor invades adjacent structures (e.g., through the cortical bone [mandible or maxilla] into deep [extrinsic] muscle of the tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of the face).
- *T4b*: Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery. Note: Superficial erosion alone of the bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

Regional Lymph Nodes (N)

NX: Regional LNs cannot be assessed.
N0: No regional LN metastasis.
N1: Metastasis in a single ipsilateral LN, 3 cm or less in greatest dimension.
N2: Metastasis in a single ipsilateral LN, 3–6 cm in greatest dimension; in multiple ipsilateral LNs, none >6 cm; or, in bilateral or contralateral LNs, none >6 cm.
- *N2a*: Metastasis in single ipsilateral LN, >3 cm but not >6 cm in greatest dimension
- *N2b*: Metastasis in multiple ipsilateral LNs, none >6 cm in greatest dimension
- *N2c*: Metastasis in bilateral or contralateral LNs, none >6 cm in greatest dimension

N3: Metastasis in an LN >6 cm in greatest dimension.

Distant Metastasis (M)

M0: No distant metastasis
M1: Distant metastasis

5.4.3.7 Histological Grade (G)

GX: Grade cannot be assessed.
G1: Well differentiated.
G2: Moderately differentiated.
G3: Poorly differentiated.
G4: Undifferentiated.

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IV-A	T4a	N0	M0
	T4a	N1	M0
	T4a	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
IV-B	T4b	Any N	M0
	Any T	N3	M0
IV-C	Any T	Any N	M1

5.4.3.8 Investigations

1. General laboratory tests: Complete blood picture, serum urea and creatinine, coagulation profile, blood glucose level, etc.
2. Imaging:
   (a) Plain X-ray: Mandible, skull, and chest.
   (b) For the primary: MRI is superior to the CT in tumor staging and in defining the extrinsic and intrinsic tongue muscles.
   (c) For the neck nodes: CT scan would be sensitive in detecting involved LNs but neck US is more specific in diagnosing suspicious nodes, especially if combined with US-guided node fine-needle aspiration biopsy (FNAB).
3. Evaluation under anesthesia (EUA) is beneficial in defining the involvement of the tumor surroundings by fibrosis or tumefaction. This helps in planning for the extent of surgical excision and reconstruction.
4. Pharyngeo-laryngoscopy for SCC to exclude synchronous primary tumors where the incidence of synchronous second malignant tumors in the thorax is 4 % [40].
5. Biopsy (excisional or incisional).
6. Metastatic workup including a PET-CT scan in stage III and IV disease.

5.4.3.9 Treatment

A patient with oral cancer gets the best management plan through a multidisciplinary tumor board (including head and neck surgeon, reconstructive surgeon, radiologist, pathologist, radio-/chemotherapist, prosthodontist ± phonetician ± psychiatrist).

Surgical Treatment

It is the main stay treatment of operable cases aiming at local disease control and in some selected inoperable (but resectable) cases as a palliative modality to improve quality of life.

1. The primary tumor

   For T1–T4a (resectable) tumors, it entails en bloc wide local excision of the tumor with an adequate safety margin 1.5–2 cm of the palpable normal mucosa (preferably through an intraoperative frozen section) with reconstruction. The extent of resection depends on tumor stage (T) and varies from wedge resection up to subtotal glossectomy in advanced tongue cancer. Partial or segmental mandibular resection may be necessary to achieve adequate tumor-free margins. The primary tumor should be marked adequately for the surgical pathologist. Reconstruction varies accordingly from simple closure or split-thickness skin grafts up to free tissue transfer (workhorse is the free radial forearm fascio-cutaneous flap).
2. Neck nodes

   Due to the early metastatic behavior of the tumor, a prophylactic selective supra-omohyoid neck dissection (levels I–III) is recommended for clinically N0 necks. N-positive necks should be managed by ipsilateral or bilateral comprehensive neck dissection (either radical or modified radical according to the extent of invasion) [37].

Radiotherapy (RT)

1. As a definitive modality

   Curative treatment can be achieved for small tumors T1–2 with N0 neck by external beam irradiation applied to the primary tumor (total dose of 66–74 Gy in fractions along 7 weeks) and to the uninvolved neck (44–64 Gy in fractions). Palliative treatment is indicated in unresectable disease and patients unfit for surgery. It is usually combined with systemic chemotherapy.
2. An adjuvant therapy

   Following surgical resection to the primary site (a total dose of 60–66 Gy in fractions to be started within 6 weeks after surgical resection) and to the neck (60–66 Gy to the involved levels and 44–64 Gy to the uninvolved levels).

   Brachytherapy could be used instead of the external beam irradiation but should be resorted to in selected cases and in specialized centers [41, 42].

Chemotherapy

1. As a definitive modality: for inoperable patients, usually combined with RT
2. An adjuvant therapy: usually as a single agent in combination with RT in selected advanced tumors

Management of Recurrences
Recurrences should be reevaluated and treated with curative intent if feasible. Neck disease in an untreated neck should be addressed by formal neck dissection or modification depending on the clinical situation.

5.4.3.10 Follow-Up
All patients should have regular follow-up visits to assess possible tumor recurrence, nutrition, dental health, speech, and swallowing function.

5.4.3.11 Prognosis
For many head and neck cancer sites, survival of patients with stage I disease exceeds 80 %. For patients with locally advanced disease at the time of diagnosis (i.e., stages III and IV disease), survival drops below 40 % [43].

Prognosis of oral cancer, however, is multifactorial and does not only depend on the TNM staging system, which is a purely clinical staging system. Demographically, prognosis of oral SCC is poor with females, above 40 years of age, with comorbidities, with southeast Asian origin, with tobacco and alcohol consumption, and with non vegetarian diet.

Combination RT and surgical therapy provide a better prognosis. Patients with a tumor at the floor of the mouth, soft palate, and posterior tongue and when tumor diameter exceeds 2 cm, tumor thickness exceeds 5 mm, and total tumor volume is >6 cm^3 would have poor outcome. Histologically, patients with high-grade tumors with positive resection margins have bad prognosis. Regarding the neck nodes, development of nodal metastases reduces survival of a patient with a small primary tumor by about 50 %. The involvement of more than two cervical groups of LNs with extracapsular invasion would have poor survival rate. Some molecular markers could also adjunct the assessment of prognosis [44]. Some studies with multivariate analyses revealed that those who were single, widow/widower, or divorced/separated had a poorer prognosis than those who were married ($P = 0.008$). It showed also that those without religious belief tended to have higher probability of death than those who had religious belief ($P < 0.001$) [45].

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Surgery of the Face

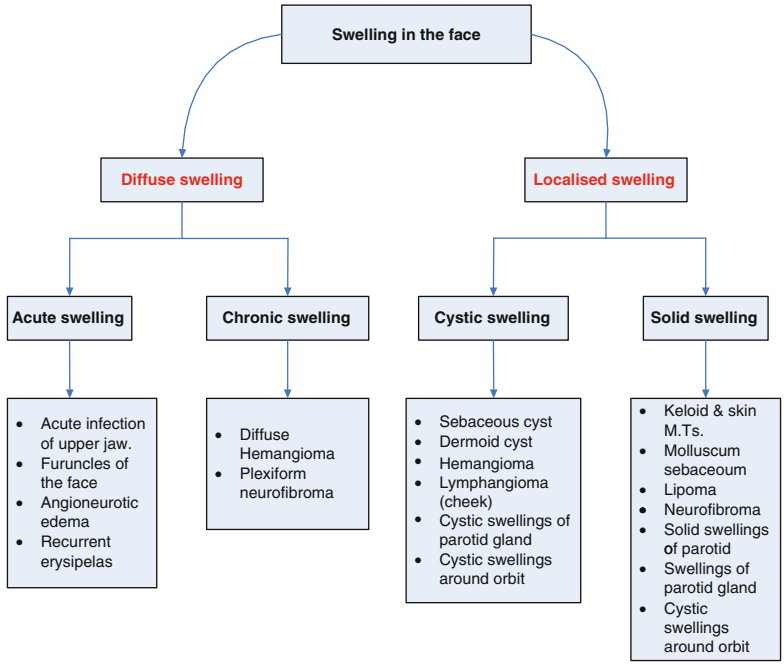
6

Mahmoud Sakr

6.1 Swellings of the Face

6.1.1 Classification

Swellings of the face could either be diffuse (acute or chronic) or localized (cystic or solid) as summarized in the diagram below.



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6.2 Diffuse Swellings

6.2.1 Acute Diffuse Swellings

The most common cause of acute diffuse facial swellings is *acute infection of the upper jaw*, which results from apical infection or after tooth extraction. Pain is marked, temperature is high, the swelling is diffuse, and edema may close the eyes. Other causes include *furunculosis* (multiple face furuncles), *angioneurotic edema* (Fig. 6.1), and *recurrent erysipelas.* The latter causes repeated attacks of swelling of the face mainly the upper lip. The rosy red color, absence of lymphadenopathy, raised margins with peripheral vesicles, and desquamation help in diagnosis.

6.2.2 Chronic Diffuse Swellings

Chronic diffuse facial swellings usually result from diffuse hemangioma (hemangiomatosis) or plexiform neurofibroma (neurofibromatosis).

6.2.2.1 Diffuse Hemangioma

There are two major categories of vascular anomalies: tumors and malformations [1]. Vascular tumors are endothelial neoplasms characterized by increased cellular proliferation. Hemangioma is the most common and is almost exclusive to infants. Vascular malformations, on the other hand, are the result of abnormal development of vascular elements during embryogenesis and fetal life. These may be single-vessel forms (capillary, arterial, lymphatic, or venous) or a combination. Vascular malformations do not generally demonstrate increased endothelial turnover. History and physical examination can distinguish between vascular tumors and vascular malformations with a diagnostic accuracy of over 90 % [2].

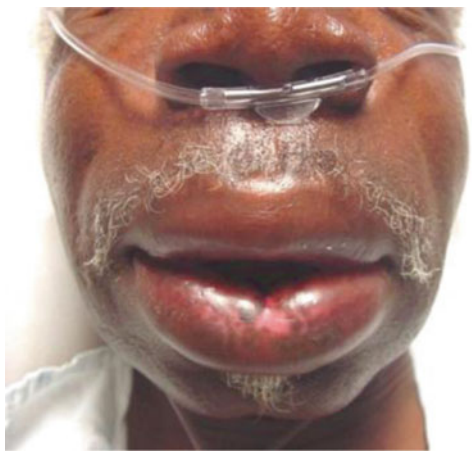

Fig. 6.1 Angioneurotic edema causing diffuse swelling in the face

6.2.2.2 Plexiform Neurofibromas (PNF)

Plexiform neurofibroma (PNF) is a rare type of generalized neurofibromatosis, which occurs due to overgrowth of neural tissue in the subcutaneous (SC) tissue [3, 4]. Such tumors are generally present at birth and often progress slowly during early childhood. The lesions can occur anywhere along a nerve and may appear on the face [4], orbit, and globe [5] and frequently involve the cranial and upper cervical nerves [6]. The condition results in functional disability and disfigurement by pulling down of important structures [7, 8]. Complications include bleeding from trauma, neurological deficits, and psychological disturbance [4], in addition to malignant transformation in 4–5 % of cases [8].

Diagnosis on clinical basis is not difficult; however, MRI evaluation of tumors involving the head and neck region can help in determining the local infiltration and precise anatomy.

Surgical management remains the mainstay of therapy, but it is limited in facial PNFs by the infiltrating nature of these tumors, inherent operative morbidity, postoperative functional disturbances [9, 10], and the high recurrence rate that may reach 20 % after complete resection and 45 % after incomplete resection [11]. Surgical interventions are thus commonly postponed to as long as possible [12] and should be undertaken only after giving due consideration to the possible psychological and social benefits. Periodic clinical examination and MRI evaluation are required for about 2 years for timely detection and repeat surgery to achieve further correction. No chemotherapeutic agent has yet been identified that reduces the size of these tumors [13].

6.3 Localized Swellings

6.3.1 Cystic Swellings

6.3.1.1 Sebaceous Cyst

It is very common in the face of young adults with acne vulgaris but may also occur in the elderly (Fig. 6.2). It is often multiple and is like a sebaceous anywhere else. Treatment is by surgical excision.

6.3.1.2 Dermoid Cyst

It occurs at the lines of fusion of the five parts constituting the face. The outer canthus is the most common site. Other sites are rare and include the inner canthus, at the fusion of the mandibular and maxillary processes, and in the midline of the chin. Treatment is also by surgical excision.

6.3.1.3 Hemangioma

Capillary, cavernous, or mixed hemangiomas may occur in the skin and SC tissue. Early onset, bluish coloration, and compressibility are characteristic. Propranolol is the treatment of choice for facial hemangiomas or those that affect function. Injectable or oral steroids and laser therapy remain viable treatment options as well [14].

6.3.1.4 Lymphangioma

Lymphangiomas are uncommon congenital malformations of the lymphatic system that are generally diagnosed during childhood and rarely seen in adults. It causes thickening of the tissues of the cheek, and clinically, it is translucent and does not empty on pressure. Management of this condition in the facial region is still challenging because they tend to infiltrate adjacent tissues, causing frequent recurrences. Radical surgery is the main line of treatment but should avoid the sacrifice of function or aesthetics of the patient [15].

6.3.1.5 Cystic Swellings of the Parotid Gland

Cystic parotid lesions are either *bilateral*, including Warthin's tumor, benign lymphoepithelial cysts, sialocele, and Sjogren's syndrome, or unilateral, including necrotic or infected lymph nodes (LNs) (for more details, refer to Chap. 3 "Surgery of the Salivary Glands").

6.3.1.6 Cystic Swellings Around the Orbit

(a) *External angular (sequestration) dermoid cyst:* The outer end of the eyebrow characteristically extends over the swelling which distinguishes it from a swelling of the lacrimal gland (Fig. 6.3). The skin is mobile over the swelling which is partly mobile on the underlying structures. There is evident indentation of bones beneath the swelling. It is no compressible, and its size does not increase on straining. Treatment is by excision.

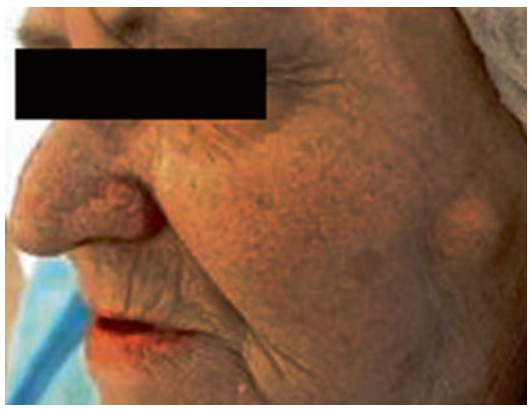

Fig. 6.2 A single sebaceous cyst in the left cheek of an 81-year-old lady

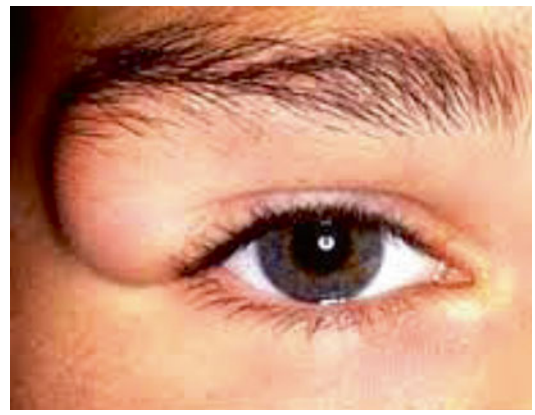

Fig. 6.3 A right supraorbital dermoid cyst at the outer canthus

(b) *Inner angular dermoid cyst:* It is less common than the external angular dermoid. It lies over the root of the nose, in a more or less central position.

(c) *Swellings of lacrimal glands:* The lacrimal gland may be the seat of a tumor (similar to salivary gland tumors) or Mickulicz disease. Its position is more medial to the site of the external angular dermoid.

(d) *Swellings of the lacrimal sac:*

Swellings of the lacrimal sac include *dacryocystitis* (inflammation of the lacrimal sac, which causes swelling below and medial to the inner canthus) and *mucocele of the lacrimal sac*, which results from blockage of the nasolacrimal duct and causes a cystic swelling between the root of the nose and the inner canthus, accompanied by lacrimation. There is usually a history of recurrent inflammation.

(e) *Mucocele of the frontal sinus:* It results from frontonasal duct blockage and lies just above and medial to the inner canthus. If it enlarges more, it displaces the globe.

6.3.2 Solid Swellings

6.3.2.1 Keloid (Greek *Crab's Claw*)

A keloid means hypertrophy and overgrowth of fibrous tissue extending beyond the original wound into normal tissues. It usually follows wounds, burns, vaccination marks, and tuberculous sinuses but may occur spontaneously. It occurs in certain sites more than others, such as the face, the neck, the ears, and over the sternum. It is also more common in darker races but less common in infants and old people. The incidence of keloid is known to increase in pregnant women and in patients with tuberculosis (TB) [16].

The lesion is elevated above the skin surface and is devoid of hair. It is unsightly, tender, and usually itchy, firm, and pinkish in color in its early states (Fig. 6.4), but later on, it becomes pale. It may give a clawlike processes and the margin is ill defined (Fig. 6.5). It should be differentiated from a *hypertrophic scar*, which results from excessive fibrous tissue formation, and is usually thick and reddish in color and may itch. However, unlike keloid, it is always confined to the scar, never gets worse after 6 months, and does not recur after excision [16].

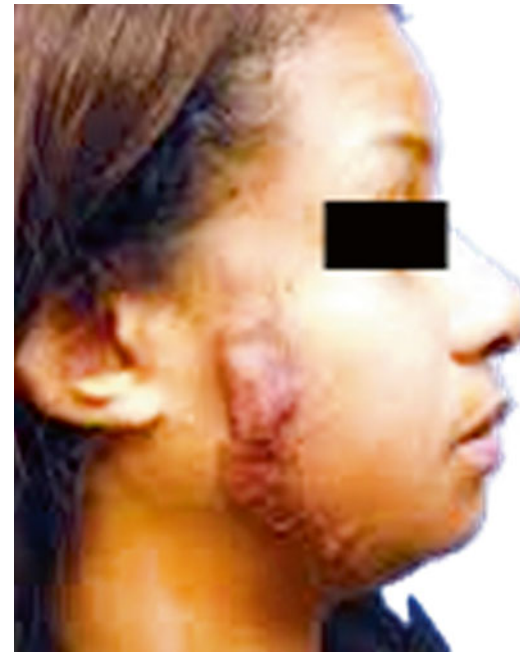

Fig. 6.4 Keloid of the right side of the cheek of a 30-year-old lady

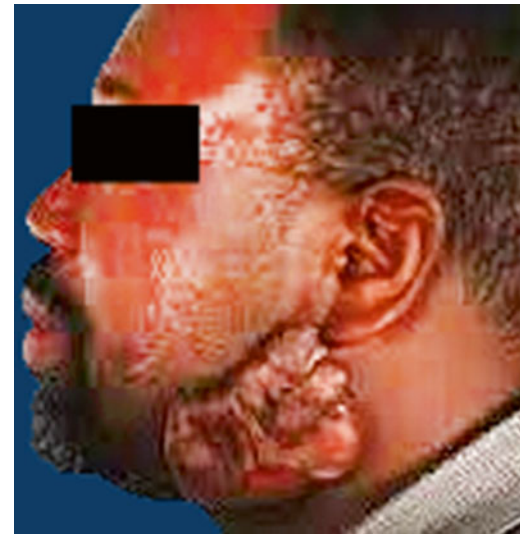

Fig. 6.5 Extensive keloid of the left side of the face extending down to the lateral side of the neck

Management of keloid is challenging as recurrence is very common particularly in chronic cases. The most effective treatment is superficial external beam *radiotherapy* (SRT), which can achieve cure rates of up to 90 %. In long-standing cases, *excision* and re-suturing whenever feasible, preceded, and followed by

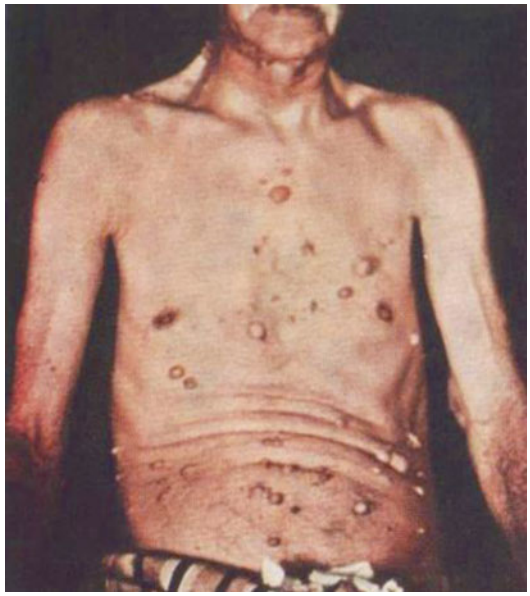

Fig. 6.6 Neurofibromatosis (Note multiple neurofibromata and café au lait pigmentation)

radiation may be required to achieve cure. Other therapeutic options include intralesional injection with a *corticosteroid* such as Kenalog, which aids in reduction of inflammation and pruritis, the use of *silicone* sheets, and shaving the keloid with resurfacing the area by a thin skin graft [17]. *Cryotherapy* or *cryosurgery* is easy to perform and has shown results with least chance of recurrence.

6.3.2.2 Lipoma

Lipoma of the face is a subcutaneous (SC) one and is similar to lipoma elsewhere. It is usually attached to the overlying skin by strands causing dimpling of the skin. It is freely mobile and soft, with lobulated surface and slippery edges.

6.3.2.3 Neurofibroma

Neurofibroma is rather common in the supraorbital region and the face. It may occur in the form of a firm nodule, fusiform in shape, along the course of a nerve, or it may present as a plexiform neuroma involving the skin and subcutaneous (SC) tissue. The skin may be redundant, overhanging, and pigmented causing severe disfigurement. Other neurofibromata and *cafe au lait* patches may be present (*Neurofibromatosis*) (Fig. 6.6).

6.3.2.4 Other Solid Swellings

Other solid swellings of the face are discussed in detail elsewhere in this book and include *malignant skin tumors, swellings of the parotid gland, swellings of the preauricular LNs, and swellings of the jaw.*

6.4 Ulcers of the Face

6.4.1 Classification

Ulcerative infective lesions		Ulcerating tumors
A. Nonspecific	*B. Specific*	
1. Chronic nonspecific ulcer	1. Tuberculosis (TB)	1. Molluscum sebaceum
2. Infected sebaceous cyst	2. Syphilis ($)	2. Basal cell carcinoma (BCC)
	3. Leishmaniasis	3. Squamous cell carcinoma (SCC)
	4. Leprosy	4. Malignant melanoma
	5. Actinomycosis	5. Metastatic mass ulceration
	6. Anthrax	6. Infiltrating deeply seated tumor that invades and ulcerates the skin

6.5 Ulcerating Infective Lesions

6.5.1 Nonspecific Ulcers

6.5.1.1 Chronic Nonspecific Ulcer

A chronic nonspecific ulcer could either be of the *exuberant type*, which presents with a wartlike, soft, and granulating lesion that bleeds easily, or the *flat type*, in which the ulcer is painful, with an irregular margin, a floor covered with granulation tissue (GT), a firm base, and purulent or serous discharge. Persistence of the cause maintains its chronicity.

6.5.1.2 Infected Sebaceous Cyst

An infected sebaceous cyst is easily diagnosed by its long history, irregular edge, and floor covered with purulent exudate, in addition to the painful

and firm base. In addition, hair follicle or punctum may be seen, and infected sebaceous-like material may come out on squeezing.

6.5.2 Specific Ulcers

6.5.2.1 Tuberculous (TB) Ulcers

Tuberculous ulcers are characteristically *painful*. The ulcer is common in the neck due to breakdown of LNs, in the maxillary region due to TB of underlying bone, and in the skin of the face due to lupus vulgaris. The outline of the ulcer is irregular and scarring may be present. The edge is undermined and bluish in color, with apple-jelly nodules (in lupus vulgaris) around it. The floor of the ulcer is pale and soft, covered with unhealthy granulation tissue, and the discharge is serous or watery.

6.5.2.2 Syphilitic ($) Ulcer

In *primary syphilis*, a chancre may occur in the face (lips, nose, or eyelids), surrounded by marked edema and associated with enlarged LNs. Swab examination will show the spirochetes and confirm diagnosis. In *tertiary syphilis*, a gummatous ulcer occurs in the frontal region. It is painless and has a serpiginous margin, punched-out edges, and a wash-leather floor. The skin around the ulcer shows pigmentation and scarring. It is fixed to the bone and plain radiography will show bone sclerosis. Other stigmata of syphilis are usually present and Wassermann-reaction (WR) is positive.

6.5.2.3 Leishmaniasis (Oriental Sore)

An oriental sore presents with a slowly progressive, painless, ulcer that may occur anywhere in the face (exposed to mosquito bites). It may be raised above the surface and have a cauliflower-like appearance. Diagnosis is reached by microscopic examination, which shows "*Leishmania donovani* bodies."

6.5.2.4 Actinomycosis

Actinomycosis, once thought to be a fungal infection, is currently known to be a bacterial one. It is characterized by multiple sinuses with sulfur-like granules (colonies of the organism) and diffuse dense fibrosis around the openings.

6.5.2.5 Anthrax

Anthrax affects mainly wool workers and horse workers. It presents as a localized, painful area of induration, with multiple sinuses, covered with yellow necrotic slough.

6.6 Ulcerating Tumors

6.6.1 Molluscum Sebaceum (Keratoacanthoma, KA)

Keratoacanthoma (KA) is a common low-grade skin tumor that is believed to originate from the neck of hair follicles [18]. It is commonly found on sun-exposed areas such as the face, forearms, and hands [19] and is unlikely to invade or metastasize. Many pathologists often label KA as "*well-differentiated SCC, KA variant*" [20], because about 6 % of KA manifests itself as SCC when left untreated [21], which mandates prompt and aggressive treatment [22].

The characteristic feature of KA is that it presents with a dome-shaped, symmetrical, ulcer with an umbilicated central hyperkeratotic core and surrounded by a smooth wall of inflamed skin (Fig. 6.7). Only when almost the entire lesion is submitted to histopathology can a true diagnosis of a KA be made. A shave biopsy is not recommended as it will often reveal only keratin fragments. This is especially important for facial and nasal KAs, as it allows the surgeon to treat the tumor with margin-controlled surgery and minimal tissue removal, like Mohs surgery. Recurrence after electrodesiccation and curettage is common.

6.6.2 Basal Cell Carcinoma (BCC)

Basal cell carcinoma (BCC) is a locally invasive carcinoma of the basal layer of the epidermis. It does not metastasize but still can kill by local infiltration. The deoxyribonucleic acid (DNA) of certain genes is often damaged in patients with

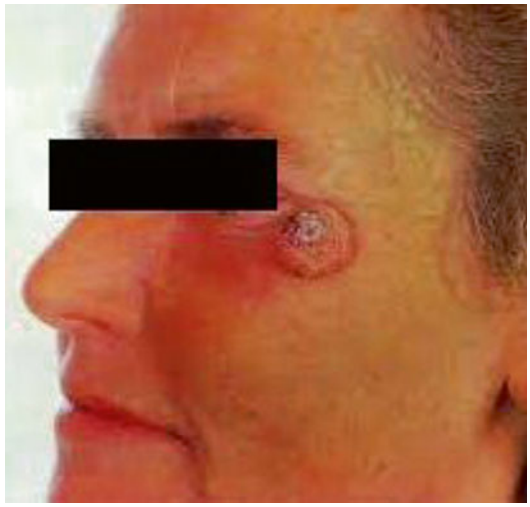

Fig. 6.7 Left facial keratoacanthoma (Note the central hyperkeratotic core)

BCC (mostly caused by exposure to light), which implicates that inheritance may be a factor.

6.6.2.1 Incidence

Approximately, 80 % of all skin cancers are BCCs. It usually occurs in elderly people (mostly >65 years – related to duration of exposure to UV light), affecting men more than women (2:1) probably due to increased recreational and occupational exposure to sun. It is more common in countries that have much bright sunlight and in fair-skinned people (e.g., Australia). Whites of Celtic ancestry have the highest risk for BCC. Incidence is low in dark-skinned individuals, Asians, and Hispanics.

6.6.2.2 Body (Anatomic) Distribution

Nearly, 70 % of BCCs occur on the head (most frequently on the face) [23, 24], 25 % on the trunk [25], and 5 % on other sites such as the penis [26], vulva [27, 28], or perianal skin. Very rarely, other organs are affected such as the prostate. On the face, the majority is found in the middle-third (bounded by a line joining the angle of the mouth to the ear lobule and a line from the outer canthus of the eye to the root of the helix), affecting mainly the lower eyelid, inner canthus, tip of the nose (Fig. 6.8), ala nasi, outer canthus, dorsum of the nose, glabella, and lastly the cheeks. Less commonly, BCC affects the lower

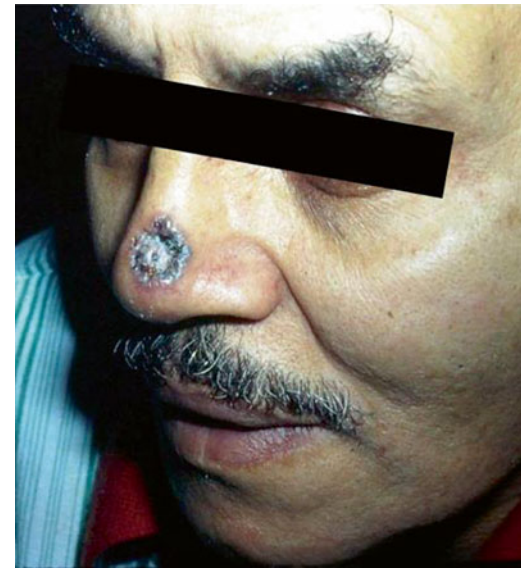

Fig. 6.8 BCC near the tip of the nose in a 42-year-old gentleman (Note the raised, rolled edge and dark pigmentation)

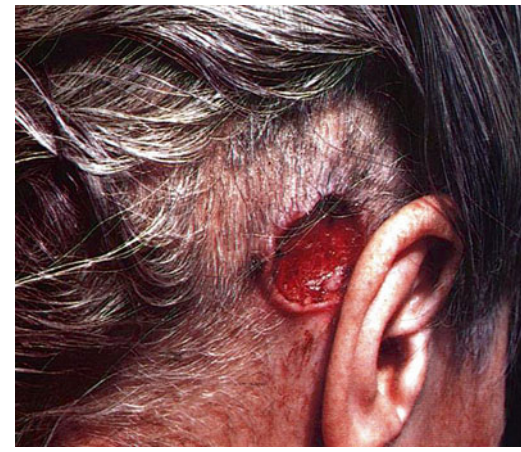

Fig. 6.9 Retroauricular BCC (uncommon site) in a 58-year-old lady (Note the inverted (rolled-in) edge of the ulcer and granulating floor)

and upper thirds; thus, the back of the ear (Fig. 6.9), upper eyelid, and lower lip are not commonly affected.

Recent data (2007) indicate that after adjusting for surface area, BCC occurrence is greater than four times more likely on embryonic fusion planes than on other regions of the midface, which supports the possibility of an embryologic role for BCC pathogenesis [29].

6.6.2.3 Etiology

The exact etiology of BCC is unknown, but environmental and genetic factors are believed to increase the risk.

Radiation exposure Sunlight, particularly chronic exposure, is the most frequent association with the development of BCC; risk correlates with the amount and nature of accumulated exposure, especially during childhood. A latency period of 20–50 years is typical between the time of ultraviolet (UV) damage and the clinical onset of BCC [30]. The skin can repair superficial damage, but the underlying cumulative damage remains, including DNA damage. The damage worsens with each successive sun exposure, causing a lifetime progression [31]. Wehner et al. (2012) in their systematic review and meta-analysis of 12 studies reported that indoor tanning was associated with a significantly increased risk of both BCC and SCC, particularly in those under the age of 25 years [32]. In another 2012 study, indoor tanning was strongly associated with early-onset BCC, particularly among women [33].

Gene mutations Recent studies (2007) showed a high incidence of *TP53* gene mutations in BCC, caused mainly by UV sunlight. However, genetic involvement has been demonstrated on chromosome 9 only in patients with familial basal cell nevus syndrome (Gorlin syndrome). Such mutation involves the *patched (PTCH)* gene, a tumor suppressor gene [34].

Immunosuppression Organ transplant patients must be instructed to limit sun exposure because immunosuppression and sun damage may cooperate to cause skin cancer. The incidence of skin cancer is tenfold higher in transplant patients than in the general population. A modest increase in risk of BCC has also been noted in patients with AIDS.

Xeroderma pigmentosum This is an autosomal recessive disease that results in the inability to repair UV-induced DNA damage. Characteristic features include pigmentary changes seen early in life, followed by the development of skin cancer (BCC, SCC, and malignant melanoma), corneal opacities, eventual blindness, and neurological deficits [35].

Other contributing factors These include exposure to or contact with arsenic [28, 36], tar, coal, paraffin [37], and certain types of industrial oil. Basal cell carcinoma can also be associated with albiminism, scars (e.g., burn complications) [38], previous trauma [39], vaccinations, tattoos, or previous non-melanotic skin cancer [40], as well as alcohol consumption [41].

6.6.2.4 Related Syndromes

Nevoid BCC Syndrome (Gorlin's Syndrome)

In addition to BCC, this autosomal dominant (AD) disorder can result in the early formation of multiple odontogenic keratocysts, palmoplantar pitting, intracranial calcification, and rib anomalies [42]. Other tumors can also occur such as medulloblastoma, meningioma, fetal rhabdomyoma, and ameloblastoma [41].

Bazex Syndrome

Features of Bazex syndrome include follicular atrophoderma (so-called ice pick marks, especially on dorsal hands), multiple basal cell carcinomas, and local anhidrosis (decreased or absent sweating) [31].

Rombo Syndrome

Rombo syndrome is an AD disorder characterized by BCC and atrophoderma vermiculatum, trichoepithelioma, hypotrichosis, milia, and peripheral vasodilatation with cyanosis [43].

6.6.2.5 Symptoms

Patients presenting with BCC often report a persistent *nodule or ulcer (often multiple)*, with a central scab that repeatedly falls off and then reforms, giving the patient a false impression that it is benign and not important. As tumors most commonly occur on the face, patients often complain of *disfigurement*. It may cause *itching*. If neglected and becomes deep, it may cause *pain* and *bleeding* and may become *infected*. Large

neglected rodent ulcer *destroying* one side of the face is nowadays, fortunately, rare. Patients often have a history of chronic sun exposure, including recreational sun exposure (e.g., sunbathing, outdoor sports, fishing, boating) and occupational sun exposure (e.g., farming, construction). Occasionally, patients have a history of exposure to ionizing radiation.

6.6.2.6 Physical Examination

Clinical presentation of BCC varies by type. Clinically, BCC could be categorized as being either superficial or penetrating. In the s*uperficial type,* there is a beaded, raised, or rolled-in edge (Fig. 6.10), a firm base, and a granulating floor with attempts of epithelization. The draining LNs are not enlarged. In the *penetrating type,* there is additional infiltration of deeper structures such as bone and cartilage.

Regarding the *color*, the raised part of the lesion (i.e., the edge of an ulcer or the center of a nodule) is smooth, glistening, and transparent. This gives the impression that there are pearly white nodules of tissue just below the epidermis. These nodules also give the ulcer its typical "rolled edge." The surface of the nodular type is covered by distinct blood vessels (telangiectases) which may give it a pink hue. The whole lesion may be colored (brown) by excess melanin, simulating a mole or melanoma (Fig. 6.11).

Basal cell carcinoma starts as a nodule that later ulcerates. The ulcer has a raised rolled-in edge but not everted. The center of the nodule can become large and look cystic (called cystic rodent ulcer). It is not cystic because it is solid and not fluctuant. The ulcer or nodule is usually small in *size* at presentation, but it can grow to a large size if neglected. The rolled *edges* are at first circular but later become irregular. An irregular raised edge around a flat white scar is sometimes called a "geographical or forest-fire BCC." The *base* consists of the tissue into which the tumor is eroding (fat, muscle, bone, eye, etc.), covered with granulation tissue. The base is usually not tender.

Most BCCs are superficial and confined to the skin. However, neglected cases may erode deep into the face destroying the skin and bone and exposing the nasal cavity, air sinuses, and even the eye and brain (rare). *Local LNs* should not be enlarged (unless infected or transformed into a SCC). Early lesions are freely mobile; later they invade deeply and become fixed. The lesion grows slowly (0.5 cm in 1–2 years), is not painful, and does not itch.

6.6.2.7 Complications

Spread is usually by direct infiltration of muscles, cartilage, and bone (locally malignant), leading to significant local destruction and considerable disfigurement [44, 45]. Orbital invasion can cause diplopia, proptosis, and ophthalmoplegia. Any limitation in ocular movements and/or diplopia should be tested. The BCC rarely causes regional or distant metastasis, with the exception of the metatypical and basosquamous types. To evaluate

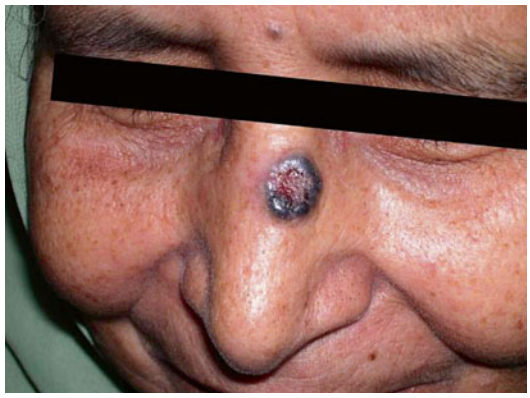

Fig. 6.10 Nasal BCC of a 60-year-old lady (Note the raised, beaded, inverted (rolled-in) edge of the ulcer)

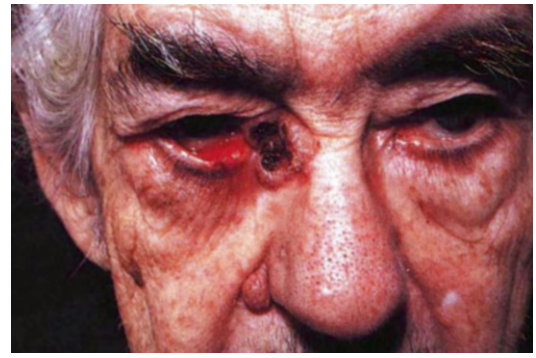

Fig. 6.11 BCC at the inner canthus of a 69-year-old gentleman (Note the dark-brown (blackish) coloration)

for LN metastasis, particular attention should be taken to examine the parotid, posterior auricular, suboccipital, and upper cervical groups of LNs.

Secondary infection will cause the local LNs to become enlarged and tender. *Hemorrhage* may easily occur if the lesion is traumatized and may be severe due to erosion of a blood vessel by the growing ulcer.

Epitheliomatous transformation (into a SCC) may occur and is evidenced by the rapid growth of the lesion, everted edges at least in a part of the ulcer, extension of induration beyond the base of the ulcer, loss of the pearly white margin, enlargement of local LN(s) which may become hard and fixed, evidence of distant metastases, and finally, the characteristic histopathological features of SCC on biopsy.

6.6.2.8 Clinic-pathological Types of BCC

Several different clinic-pathological types of BCC exist, each with distinct biologic behavior.

Nodular (Noduloulcerative) BCC

Nodular BCC is the most common type, representing more the 60 % of BCCs. It presents as a round, pearly, flesh-colored papule with telangiectases (Fig. 6.12). As it enlarges, it frequently *ulcerates* centrally, leaving a characteristic raised, pearly, beaded, border with telangiectases. Most lesions are seen on the face, although the trunk and extremities also are affected.

Variants of Nodular BCC

- *Cystic BCC.* It is an uncommon variant of nodular BCC that may be mistaken for inclusion cysts of the eyelid. Typically, a bluish-gray cyst-like lesion is observed. The cystic center of the tumor is filled with clear mucin that has a gelatin-like consistency. Often, the typical features of a nodular BCC are seen in addition to the cystic features.
- *Pigmented BCC.* It is another uncommon variant of nodular BCC with additional dark pigmentation from melanin deposition that imports a dark-brown or blue-black color. It may, therefore, be confused with malignant melanoma. However, it can be differentiated easily if a few basic rules are appreciated. Firstly, the pigment in a BCC is punctate, because it lies in islands of nevus cells, which have been left behind as the tumor infiltrates the skin; pigment in melanoma is more widespread and uniform. Secondly, the typical signs of a BCC (i.e., the rolled edge, telangiectases, and the central depression) can be observed (Fig. 6.13).
- *Keratotic BCC*. It is a variant of nodular BCC and is usually clinically indistinguishable from nodular BCC histologically.

Infiltrative BCC

With this variant of BCC, the tumor infiltrates deeper into the dermis in thin strands between collagen fibers, making the tumor margins less

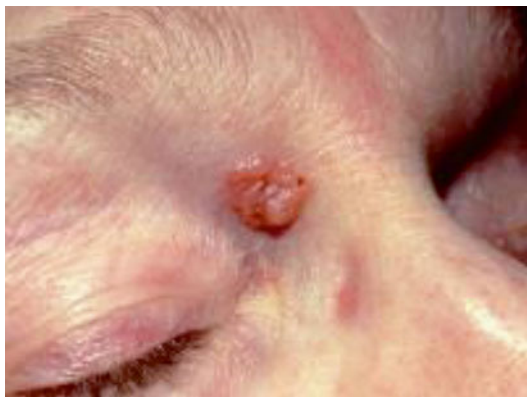

Fig. 6.12 Nodular BCC presenting as a waxy, translucent papule with central depression and a few small erosions

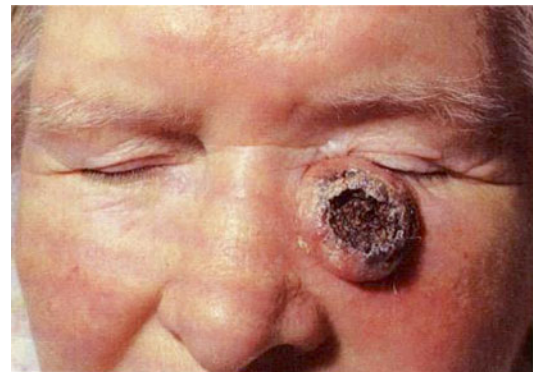

Fig. 6.13 Pigmented BCC simulating melanoma, in the face of a 64-year-old lady (Note the raised, beaded border)

clinically distinguishable. It may erode deeply into the underlying structures, known as "rodent ulcer" (*ulcus rodens*). Because of its growth pattern, electrodesiccation and curettage has a significantly higher recurrence rate as compared to nodular BCC. Mohs micrographic surgery is thus the treatment of choice.

Micronodular BCC

This type is rather rare and has the typical BCC distribution. It is firm in consistency, is not prone to ulceration, may appear yellow-white when stretched, and may have a well-defined border.

Morphea-Like (Fibrosing, or Sclerosing) BCC

Morphea-like BCC is an uncommon type of BCC accounting for nearly 10 % of lesions. The tumor cells induce a proliferation of fibroblasts within the dermis and an increased collagen deposition (sclerosis) that clinically resembles a scar. This tumor thus assumes an indurated, yellowish *plaque* with ill-defined borders over which the skin remains intact for a long period of time. The skin actually looks shiny and taut because of the intense fibroblastic response the tumor induces, giving its "scar-like" appearance (Fig. 6.14). It is more often initially overlooked than the nodular type. The margins of this form are difficult to identify because the tumor cells invade normal tissue well beyond the visible margin. It, therefore, requires a wider safety margin on excision than the typical BCC. Mohs micrographic surgery is the treatment of choice because recurrence is more likely with other treatment modalities.

Superficial BCC

Superficial BCCs are seen mostly on the upper trunk or shoulders (and *not* on the face). It grows slowly, has minimal tendency to invade surrounding tissues, and presents clinically as an erythematous, well-circumscribed patch or plaque, often with a whitish scale (Fig. 6.15). The tumor often appears multicentric, with areas of clinically normal skin between lesions. Numerous superficial BCCs may indicate arsenic exposure. Superficial BCC should be differentiated from psoriasis and eczema.

Gorlin Syndrome (Basal Cell Nevus Syndrome)

Gorlin syndrome (basal cell nevus syndrome) is an AD inherited condition, with the responsible gene located on 9q [46]. A feature of this syndrome is BCC. Multiple, often highly invasive, BCCs appear after puberty on the face, trunk, and extremities [47]. Other features (fortunately, uncommon) include mental retardation, congenital agenesis of the corpus callosum and medulloblastoma, odontogenic jaw cysts, bifid ribs and pectus excavatum, absent or undescended testes, mesenteric lymphatic cysts, palmar and plantar pits, ectopic calcification (particularly of the falx

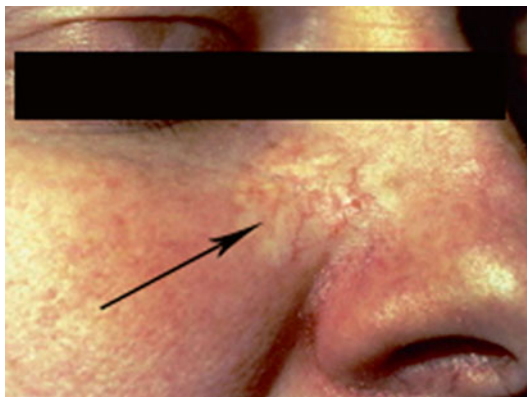

Fig. 6.14 A large, morphea-like (sclerosing) BCC on the right nasolabial fold (*arrow*)

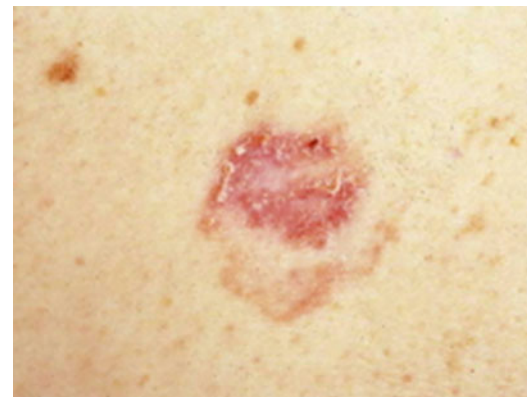

Fig. 6.15 Superficial BCC (on the trunk) showing erythema, scales, and a threadlike raised border

cerebri), as well as ocular and skeletal abnormalities such as hypertelorism, and shortening of the fourth and fifth metacarpals [48].

Other Types of BCC

Other types of basal cell carcinoma include the following:

1. *Polypoid (Pinkus tumor, fibroepithelioma*). According to several studies, this tumor, which was considered to be a premalignant skin condition, must be considered as a fenestrated variant of BCC [49–51]. It occurs mostly in the back and consists of thin, anastomosing strands of basaloid cells in a prominent stroma.
2. *Basosquamous.* This variant has the general configuration of a BCC, but contains also atypical squamous cells (squamatoid cells) and intermediate cells. It is more aggressive than typical BCC and has a metastatic potential.
3. *Geographical (forest-fire or field-fire variant).* This variant is characterized by an advancing edge and a healing center.
4. *Metatypical BCC.* This rare tumor is often aggressive, with an increased tendency for lymphatic and perineural spread. Histologically, nests and strands of cells mature into larger and paler cells, and peripheral palisading, if any, is less developed than in other types. Prominent stroma, prominent mitotic activity, and many apoptotic cells may be present.
5. *Infundibulocystic*. This rare type, which resembles the keratotic variant, is usually found on the face. Nests are arranged in an anastomosing pattern and lack stroma. Many small, infundibular cyst-like structures with keratinous material are present. Melanin is sometimes present as well.

6.6.2.9 Diagnosis

Skin Biopsy

A skin biopsy is often required to confirm the diagnosis and determine the histological subtype of BCC. Most often, a *shave biopsy* is all that is required. However, in case of a pigmented lesion, an *excisional* or *punch biopsy* may be indicated to ensure that the depth of the lesion can be determined if it proves to be a malignant melanoma. A punch biopsy should be avoided if curettage is planned for final treatment.

Histologically, tumor cells typically resemble the basal cell layer of the epidermis or analogous cells of hair follicles, sebaceous or sweat glands. It spreads microscopically beyond the visible lesion. Characteristic features include palisade arrangement of columnar cells at the periphery, central mass of polyhedral cells, stroma of fibrous tissue and chronic inflammatory cells. Cystic spaces may be seen. Mitotic figures are very rarely observed and are usually few. Basal cell carcinoma is divided histologically into two categories; *undifferentiated* and *differentiated*. In undifferentiated BCC, there is little or no differentiation, the carcinoma is referred to as solid BCC, and this form includes pigmented BCC, superficial BCC, sclerosing BCC, and infiltrative BCC. On the other hand, differentiated BCC often has slight differentiation toward hair (keratotic BCC), sebaceous glands (BCC with sebaceous differentiation), and tubular glands (adenoid BCC). Noduloulcerative (nodular) BCC is usually differentiated.

Imaging

Given that BCC rarely metastasizes, laboratory and imaging studies are not commonly indicated in patients presenting with localized disease. Imaging studies may be necessary when involvement of deeper structures, such as bone, is clinically suspected. In such cases, *CT scans* or *radiography* may be utilized.

The use of *ultrasonography* (US) is controversial, because of the inadequate accuracy (20 %) in delineating malignant from benign lesions. Furthermore, the claims of reliable tumor sizing and depth of invasion, though promising, are still passionately debated. As an adjunct tool, *laser Doppler* may assist ophthalmologists in distinguishing between benign and malignant adnexal skin lesions and in establishing the tumor margin. In histologically documented BCC of the eyelid, cutaneous perfusion was significantly greater [52].

6.6.2.10 Differential Diagnoses

The list of lesions from which BCC should be differentiated is rather long and includes actinic

keratosis, angiofibroma, Bowen disease, fibrous facial papule, malignant melanoma, keratoacanthoma (molluscum sebaceum), melanocytic nevi, psoriasis, sebaceous hyperplasia, and squamous cell carcinoma (SCC).

6.6.2.11 Staging

Since BCC rarely metastasizes, it is usually not staged, unless the cancer is very large and is suspected of metastasizing. Staging of BCC may be similar to that of SCC as follows:

Stage	Description
0	Cancer involves only the epidermis and has not spread to the dermis
I	Cancer is <2 cm and has not spread to LNs or other organs
II	Cancer is >2 cm but has not spread to LNs or other organs
III	Cancer has spread to tissues beneath the skin (e.g., muscle, bone, cartilage) and/or to regional LNs but not to other organs
IV	Cancer can be any size and has spread to other organs

High-Risk Tumors

High-risk BCCs include recurrent or incompletely excised BCC; tumors with indistinct borders; lesions in high-risk (the H, or mask) areas, mainly the embryonic fusion planes; tumors with rapid growth or large size (>2 cm); and aggressive histological variants or types including sclerosing and basosquamous BCCs, with perineural, peri-appendageal, or perivascular invasion. Moreover, BCCs that develop in sites with previous radiation therapy or in immunosuppressed patients are also considered to be high-risk tumors.

6.6.2.12 Treatment

Approach Considerations

According to the 2011 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, the goal of treatment of BCC and SCC is elimination of the tumor with maximal preservation of function and physical appearance. Management decisions should thus be individualized according to the patient's particular risk factors and preferences. In the majority of cases, the treatment of choice is surgery, which varies according to cancer size, depth, type, and location [44, 45], in addition to patient's age and general condition. Small and superficial BCC may respond to local therapy with chemotherapeutic and immune-modulating agents such as topical 5 % imiquimod and fluorouracil (5-FU) (most commonly used on smaller superficial nonfacial BCC on the trunk and extremities) [53].

For tumors that are more difficult to treat (i.e., infiltrative, sclerosing, micronodular, and recurrent BCCs) or those in which sparing normal tissue is important, Mohs micrographic surgery should be considered.

For metastatic BCC, the 2011 NCCN guideline recommends clinical trials of systemic chemotherapy, particularly platinum-based combination therapy, which has been observed to produce useful, even complete, responses in a few patients. Clinical trials of investigational biologic modifiers such as hedgehog pathway inhibitors are also recommended.

Surgical Modalities

In nearly all cases of BCC, surgery is the recommended treatment modality [44, 45]. Techniques used include electrodesiccation and curettage, curettage without desiccation, curettage with laser ablation, laser ablation without curettage, excisional surgery, Mohs micrographically controlled surgery, cryosurgery, and immunocryosurgery [54].

Electrodesiccation and Curettage (E&C) [55]

Under local anesthesia, a curette is used firmly in multiple directions to vigorously scrape the tumor away from adjacent normal skin, followed by electrodesiccation. The entire process may be repeated 1–2 more times. It is an operator dependent, relatively blind technique in which the specimen cannot be examined for margin control, which limits its success in high-risk areas, such as the face and ears. Furthermore, the aggressive subtypes of BCC, such as sclerosing, infiltrating, micronodular, and recurrent tumors, are usually

not friable, and therefore, E&C is unlikely to be successful. Healing by secondary intention often leads to atrophic, white scars that may not be satisfactory in aesthetically important areas. Finally, it is not suitable for patients with cardiac pacemakers. On the other hand, E&C is a simple and brief procedure (<5 min) and is effective in treating primary nodular and superficial BCC because these tumors tend to be friable and not embedded in fibrous stroma. The overall cure rate exceeds 90 % for low-risk BCCs. Small tumors (2–5 mm) have a 15 % recurrence rate (RR), whereas large tumors (>3 cm) have a 5-year RR of 50 %.

Curettage Without Dessication [54]

Under adequate local anesthesia, the tumor is scraped using a curette. This is often repeated two more times. It is a brief (<5 min) procedure, effective in treating primary nodular and superficial BCC, with cure rates as high as 95 %. Curettage alone is believed by some authors to have a better cosmetic outcome than that of E&C. However, it is neither widely accepted nor commonly performed, and it has the same disadvantages of E&C.

Curettage with Er:YAG Laser Ablation

After curettage, the newly formed ulcer is then ablated, along with a narrow (<1 mm) margin of adjacent epidermis using Er:YAG laser. This is often repeated two more times. This brief (<5 min) method is also effective in treating primary nodular and superficial BCC, with a 95 % cure rate, and is believed by some authors to have a better cosmetic outcome than does E&C, though with similar limitations and disadvantages.

Laser Ablation Without Curettage

A carbon dioxide laser is applied superficial BCC (most frequently) and nodular BCC. This procedure may be considered when a bleeding diathesis is present. It provides a bloodless field, minimal postoperative pain, and good cosmetic appearance without scar formation [56, 57]. With the recent devices, the reported RR went down from 50 to 3 % [58]. However, this procedure has been studied less than other methods, and a great variance in RR has been reported. Hypopigmentation may develop, which may not be apparent for 1 or more years.

Surgical Excision

This method can usually be performed in an ambulatory setting and provides the pathologist with a specimen to examine the tissue margins via routine paraffin processing or using frozen sections. Healing time is generally shorter with sutured closure than with granulation, and cosmesis compares favorably with that of curettage. The cure rate is also as high as 95 % [59].

Surgical excision is, however, operator dependent. The larger the safety margin, the higher the cure rate, although extensive tissue removal leaves a larger surgical defect and a poorer cosmetic result. In most cases, a 3–4-mm margin of normal, clinically uninvolved skin is excised [60]. Other reports recommend larger margins (at least 8 mm) for aggressive tumors.

Surgical excision is less effective in treating recurrent tumors and those without clearly defined clinical margins (e.g., infiltrating, micronodular, and sclerosing BCCs). If a positive margin occurs, additional surgery is needed. The 5-year RR for primary tumors >1.5 cm in diameter is approximately 12 %. Larger tumors (>3 cm) have a 5-year RR of 23 %. Reconstruction after surgical excision may be achieved by direct closure (in small lesions and areas with lax skin), full-thickness graft, or flaps.

Mohs Micrographically Controlled Surgery

Mohs micrographic surgery is *indicated* in tumors with poorly defined clinical borders, infiltrative or sclerotic variety, diameters >2 cm (or >1 cm in the face), and tumors arising in regions where maximum preservation of normal tissue and good cosmetic outcome are required such as the eyelids, nose, ears, and lips. Sometimes, massive, invasive BCC tumors may be treated with Mohs surgery to clear peripheral margins with deeper aspects that have been treated surgically by other methods [61].

A thin layer of tissue containing the tumor is removed until the last excised layer viewed microscopically (frozen section) is cancer-free. This technique can save the greatest amount of

healthy tissue and, according to several authors, is the criterion standard of care for BCC treatment, because it is associated with the highest cure rate (99 % for primary BCC, 90–95 % for recurrent BCC) [62, 63] and the lowest RR [64]. In an analysis, the 5-year RR for treated BCC after Mohs micrographic surgery was 1 %, compared with 7.5 % after cryosurgery, 7.7 % after E&C, 8.7 % after radiotherapy, and 10.1 % after surgical excision [65]. In another study, Malhotra et al. reported a 5-year RR of 0 % for primary tumors and of 7.8 % for recurring tumors [66]. The chief disadvantages of Mohs surgery, however, are its higher cost and time requirement compared with curettage, in addition to the risk of infection [67, 68].

Cryosurgery

Liquid nitrogen is applied to the clinically apparent tumor to destroy tumor tissue [69]. A temperature probe is inserted into the skin at a lateral margin. Treatment stops when the temperature at the lateral margins reaches −60 °C. A local anesthetic may be used, and the procedure may be repeated at the same session to ensure total destruction of malignant cells. The growth subsequently blisters or becomes crusted and falls off, usually within weeks. Temporary redness and swelling can occur, and in most cases, hypopigmentation may result. Cryosurgery is effective for the most common tumors, especially superficial BCC, and is useful for patients with bleeding disorders or intolerance to anesthesia. This method is used less commonly today and has a lower cure rate (85–90 %) than other surgical techniques, depending on the physician's expertise.

Contraindications for cryosurgery include patients with cold intolerance, cryoglobulinemia, cryofibrinogenemia, Raynaud disease (only for treatment of lesions on the hands and feet), platelet deficiency disorders, and sclerosing type of BCC.

Immuno-cryosurgery

This newer therapy combines the use of the topically applied imiquimod 5 % gel (for 5 weeks) with cryosurgery (by the end of the second week). It may be considered for small, clinically well-defined primary tumors with promising cure rates, although larger studies are needed to fully evaluate the efficacy of this treatment. Similar to cryosurgery, this procedure may be useful for debilitated patients who are not fit for other types of surgery [70]. Allergy to imiquimod or any of its ingredients is an additional contraindication to this modality.

Radiation Therapy (RT)

Total destruction of the tumor usually requires several treatments over a few weeks, or sometimes daily for 1 month. This method is ideal for tumors hard to manage surgically and for elderly patients or those with a poor general health condition. Cure rates reach 90–97 %% for primary tumors. In the past, RT was a common treatment modality but, is now used sparingly because of its long time and high cost. With the recent treatment modalities, RT has become a reasonable treatment choice for *recurrent* tumors. It may also be reserved for primary lesions requiring extensive oculoplastic surgery. Although RT limits damage to adjacent tissue and eliminates the need for skin grafting of large post-excisional defect, it can involve long-term cosmetic problems and radiation risks [71].

Photodynamic Therapy (PDT)

Photodynamic therapy is FDA approved for the treatment of superficial or nodular BCC, with cure rates ranging from 70 to 90 %. A light-sensitizing agent, topical 5-aminolevulinic acid (5-ALA), is applied to the lesion in the outpatient clinic. Subsequently, the medicated area is activated by a strong blue light, which selectively destroys BCCs with minimal damage to surrounding normal tissue. Patients may undergo one treatment, but often 2 treatments are performed 1 week apart for the treatment of superficial BCC [72]. Some redness, pain, and swelling may result. As a precaution, patients are advised to strictly avoid sunlight for at least 48 h because exposure may further activate the medication, causing severe sunburn.

Topical Medications

These creams, gels, or solutions are used to treat limited, superficial BCCs. Since there is no tissue

examined histologically, complete resection of the tumor cannot be emphasized.

Imiquimod is FDA approved only for superficial BCCs, with cure rates generally between 80 and 90 %. The imiquimod 5 % cream is rubbed gently into the tumor 5 times a week for up to 6 weeks or longer [73–78]. It works by stimulating the immune system and causing the body to produce interferon, a chemical that attacks cancer.

5-Fluorouracil (5-FU) is also FDA approved for superficial BCCs, with similar cure rates to imiquimod. The liquid or cream is gently rubbed into the tumor twice a day for 3–6 weeks. Side effects are variable, and some patients do not experience any discomfort, but redness, irritation, and inflammation usually occur.

Oral Medications

Erivedge™ (vismodegib) was approved by the FDA in 2012 for extraordinarily rare cases of metastatic BCC or locally advanced, life-threatening BCC. It works by blocking the "hedgehog" signaling pathway, which is a key step in the development of BCC. It is contraindicated in women who are or may become pregnant. Birth control must be used by couples if the woman is capable of becoming pregnant [79].

6.6.2.13 Prognosis

The prognosis for patients with BCC is excellent, with a 100 % survival rate for localized primary tumors. However, if BCC is allowed to progress significant morbidity and cosmetic disfigurement may result. Typically, basal cell tumors enlarge slowly and tend to be locally destructive. The incidence of metastatic BCC is less than 0.1 %. The most common sites of metastasis are the LNs, lungs [80], and bones [81]. Patients who are diagnosed with BCC have a 20 % chance of developing another tumor (not recurrence) within 1 year, a 35 % chance within 3 years and a 50 % chance within 5 years. Therefore, regular follow-up every 6–12 months is recommended [82].

The 5-year RR is about 5 %, depending on the histological subtype and type of treatment. Sclerotic, infiltrative, micronodular, and multifocal types are more likely than nodular types to recur. The RR is <1 % for primary BCCs treated with Mohs micrographic surgery. Most reports show that the distance to the closest resection margin is an important predictor of recurrence. Pieh and colleagues (1999) [83] reported a RR of 5.36 % after the first excision of the tumor, 14.7 % after the second operation, and 50 % after the third and fourth operations. The highest recurrence, about 60 %, was seen with lesions arising from the medial canthus.

6.6.3 Squamous Cell Carcinoma (SCC)

Squamous cell carcinoma (epithelioma, epidermoid carcinoma) is a carcinoma of the *prickle cell layer* of the epidermis that normally migrates outwards to the surface to form the superficial keratinous squamous layer. The tumor cells infiltrate the epidermis, dermis, and adjacent tissue. However, SCC occurs in diverse tissues, including the lips, mouth, esophagus, urinary bladder, prostate, lung, vagina, and cervix.

6.6.3.1 Incidence

The second-most common cancer of the skin after BCC is SCC, representing about 20 % of non-melanoma skin cancers. However, due to their more obvious nature and growth rates, SCCs represent 90 % of all head and neck cancers (mouth, nasal cavity, nasopharynx, throat, and associated structures). The incidence of SCC varies with age, gender, race, geography, and genetics. It increases with age, peaking around the age of 70 years, and occurs twice in men than in women. Caucasians are more likely to be affected, especially those with fair Celtic skin, if chronically exposed to UV radiation [1]. In certain geographic areas, prolonged exposure to direct, strong sunlight and arsenic may significantly increase the risk of SCC.

6.6.3.2 Etiology

Chronic sun exposure is the strongest environmental risk factor for developing SCC. Thus, it usually occurs in exposed areas such as the face, ears, neck, hands, or arms. Other risk factors

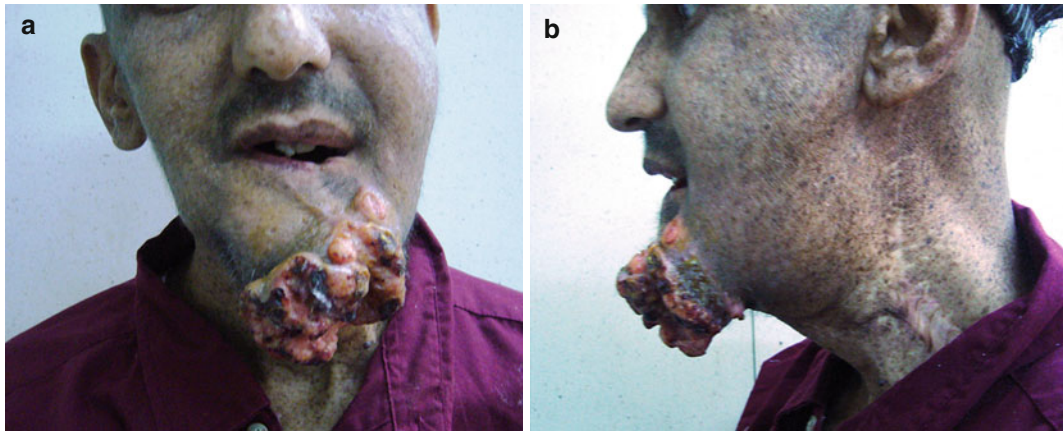

Fig. 6.16 (**a**) Huge recurrent SCC of the chin in a 61-year-old gentleman. (**b**) Lateral view of the same patient. Note the scars of previous operations

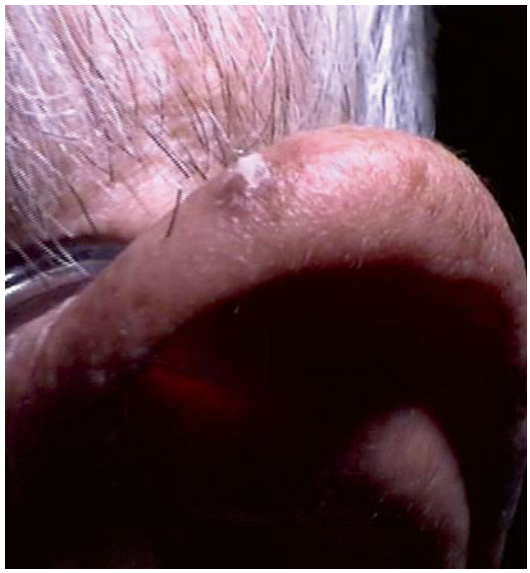

Fig. 6.17 Solar (actinic) keratosis of the ear pinna

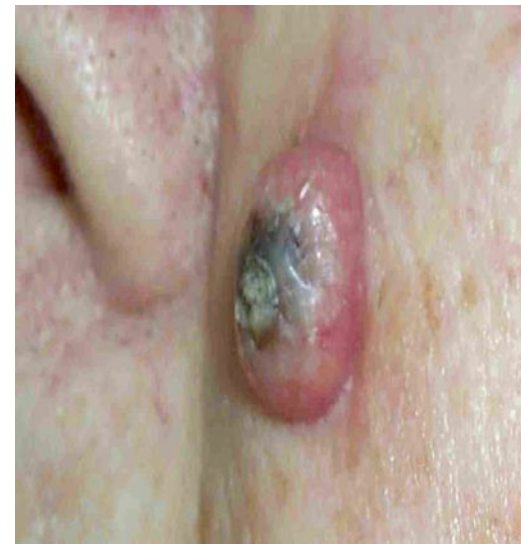

Fig. 6.18 Keratoacanthoma of the left cheek

include smoking, alcohol consumption, immunosuppression, and hematopoietic stem cell transplantation [84]. Approximately 25 % of mouth and 35 % of throat SCCs are associated with *Human papillomavirus* (HPV). A few rare congenital diseases predispose to SCC, such as xeroderma pigmentosum, characterized with a high RR (Fig. 6.16a, b).

Other SCC precursors include actinic (solar) keratosis (Fig. 6.17), keratoacanthoma (Fig. 6.18), and leukoplakia (Fig. 6.19).

6.6.3.3 Symptoms

The lesion caused by SCC is often *asymptomatic*. However, SCC usually begins as a small nodule, and as it enlarges, the center becomes necrotic and sloughs, turning the nodule into an ulcer. Thus, the patient may complain of bleeding and discharge from an ulcer or of a hard reddish plaque or a papule, often with an opalescent quality, with tiny blood vessels. The lesion may be multiple and may occur on chronic scars due to burns (Marjolin ulcer). It may become painful if

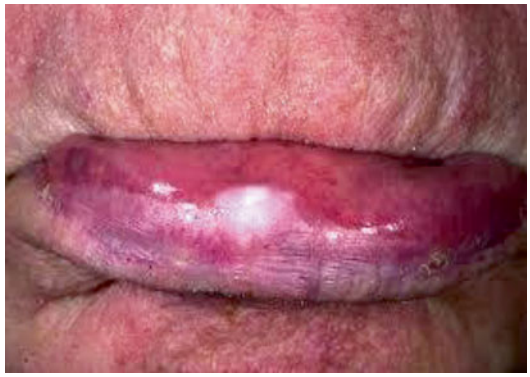

Fig. 6.19 Leukoplakia of the lower lip (Note the characteristic white discoloration of the lesion)

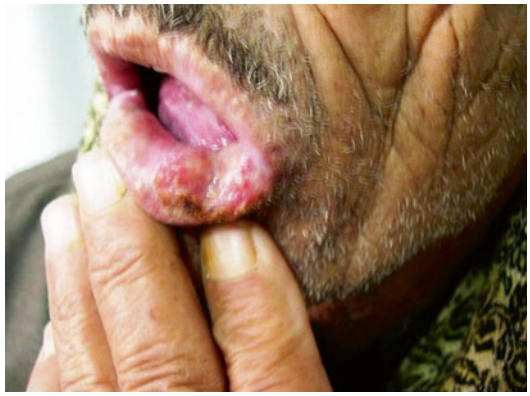

Fig. 6.20 SCC of the lower lip in a 59-year-old gentleman. Note the necrotic floor

it invades deep structures. The patient may also suffer from enlarged cervical LNs or systemic metastatic symptoms while being unaware of the primary lesion.

6.6.3.4 Physical Examination

Local examination usually reveals an ulcer that most commonly lies on the lower lip (Fig. 6.20), ears, and cheeks (Fig. 6.21). The edge of the ulcer is *everted* because excessive tissue growth raises it above and over the normal skin surface. This everted edge is usually dark red-brown in color because it is very vascular. The floor of the ulcer may be covered with old coagulated blood, serum, or *necrotic material*. If it becomes infected, the discharge becomes copious, bloody, purulent, and foul. The base

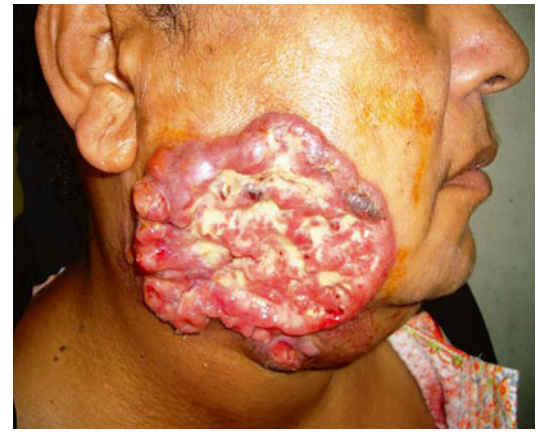

Fig. 6.21 A huge SCC occupying the right cheek of a 47-year-old lady. Note the everted edges and necrotic floor

of the ulcer is characteristically hard and indurated. Relations to surrounding structures depend on the extent of malignant infiltration, which causes the ulcer to become *fixed*. There may be evidence of chronic skin photodamage, such as multiple actinic keratosis. Local LNs are often enlarged and later become hard and fixed. The ulcer may be complicated by infection or bleeding, which may be massive and dangerous

Unlike BCC, epithelioma (SCC) has a substantial risk of metastasis, the risk of which is higher in SCCs arising in scars, on the lower lips or mucosa, and occurring in immunosuppressed patients. Generally, all types of distant metastases are uncommon. *General examination* may reveal lung collapse or pleural effusion caused by pulmonary metastases or hepatomegaly due to liver metastases.

6.6.3.5 Pathology

Microscopic picture of SCC shows tongues of malignant cells in all directions with clusters (positive for keratin). Cell nests are cut sections in the ramifications of the tumor appearing as rounded masses formed of cuboidal cells (peripheral), prickle cells (middle), and keratin (central) (Fig. 6.22). Malignant cells show pleomorphism and loss of polarity. The nucleus shows hyperchromatism, increased mitotic figures, and multiple neucleoli. *Bowen's disease*

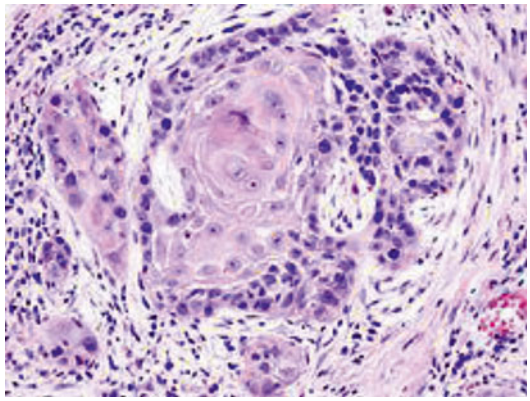

Fig. 6.22 Biopsy of a highly differentiated SCC (H&E stain)

is a sunlight-induced skin disease and is considered to be an early form of SCC.

Variants (Subtypes) of SCC

- *Adenoid (pseudoglandular) SCC*, characterized by a tubular microscopic pattern [85]
- *Basaloid SCC*, characterized by a predilection for the tongue base [85]
- *Clear-cell SCC* (clear-cell carcinoma of the skin), characterized by keratinocytes that appear clear as a result of hydropic swelling [85]
- *Signet-ring cell SCC* (signet-ring-cell SCC), characterized by concentric rings composed of keratin and large vacuoles (markedly dilated endoplasmic reticulum) that displace the cell nucleus toward the cell membrane (signet-ring appearance) [85]
- *Spindle-cell SCC*, characterized by spindle-shaped atypical cells [85, 86]

6.6.3.6 Diagnosis

Diagnosis of SCC is reached by *biopsy*. The pathological appearance of a SCC varies with the depth of the biopsy. For that reason, a biopsy including the subcutaneous (SC) tissue and basilar epithelium, to the surface is necessary for correct diagnosis. A "shave" biopsy might not provide enough information for a correct diagnosis and is considered the least ideal. An inadequate biopsy might be diagnosed as actinic keratosis with follicular involvement, while a deeper biopsy might reveal the true cancer. An *excision* biopsy is ideal, but not applicable in most cases. An *incisional* or *punch* biopsy is the alternative.

Imaging (plain X-ray or CT scan) of the related bone may be necessary for proper evaluation of the extent of the lesion. Investigations for detection of suspected metastases (lung, bone, liver, etc) should be done as indicated.

Differential diagnosis of SCC includes the following: BCC, keratoacanthoma, malignant melanoma, actinic keratosis, pyogenic granuloma, and infected seborrheic wart.

6.6.3.7 Marjolin Ulcer

It is a SCC that develops in a long-standing benign ulcer (usually venous) or scar (usually burn). The edge is *not* always raised and everted. Other features may be masked by the preexisting chronic ulceration or scarring. Unusual nodules or changes in a chronic ulcer or a scar should be suspicious. It is slightly less malignant and slower growing than spontaneous SCC due to excessive fibrosis but must be treated as vigorously.

6.6.3.8 Management

Treatment of the Primary Tumor

Surgical excision with a free margin of healthy tissue is the most frequent treatment modality. Reconstruction may be achieved by direct closure or a local flap. *Mohs surgery* is frequently utilized and considered the treatment of choice for SCC of the skin, mouth, throat, and neck [87]. Radiation therapy is often used afterward in high-risk cancer or patient types. Electrodesiccation and curettage (E&C) can be done on selected SCC of the skin. In areas where SCCs are known to be nonaggressive and where the patient is not immunosuppressed, E&C can be performed with good to adequate cure rate.

Radiotherapy may be used alone as a primary treatment option in advanced cases where surgery is not feasible and is an adjuvant therapy for those with metastatic or high-risk cutaneous SCC. Radiation therapy is undesirable in young people (below 40 years of age) because of the long-term risk of carcinogenesis. Heavily sun-damaged skin has poor radiation tolerance. The

use of *topical therapy*, such as imiquimod (Aldara) cream and PDT, is generally limited to premalignant and in situ lesions. At this time, *systemic chemotherapy* is used exclusively for patients with metastatic disease.

Treatment of Lymph Nodes

If LNs are *not palpable*, the patient may be followed-up; however, prophylactic LN block dissection may be resorted to if the tumor is deeply infiltrating, of high grade, or recurrent. The benefit of prophylactic block LN dissection with Marjolin's ulcers is not proven. If the nodes are *palpable and mobile*, block neck dissection is the treatment of choice, but if they were *palpable and fixed*, radiotherapy is the treatment option.

6.6.3.9 Prognosis

The long-term outcome of SCCs depends upon its subtype, available treatments, location, severity, and patient health-related variables such as associated illness and age. The long-term outcome is positive, as less than 4 % of SCCs are at risk of metastasis (and hence life-threatening) [88, 89]. Some particular variants of SCCs have a higher, though still positive, long-term outcome. Generally, SCCs of the head and neck have been found to have a greater risk of metastasis to the lymphatic system and hence possibly reducing treatment efficacy [90].

6.6.4 Malignant Melanoma (MM)

A melanoma is a malignant tumor (MT) that arises from *melanocytes*, dendritic cells that utilize tyrosine to produce *melanin*, a pigment that protects the body from damaging ultraviolet (UV) radiation. A cluster of melanocytes form *nevi* (moles) and melanoma results when these melanocytes undergo a malignant transformation [91, 92].

6.6.4.1 Embryology of Melanocytes

Melanocytes are derived from the *neural crest tissue*. Cells migrate during early gestation to the *skin, uveal tract, meninges, and ectodermal mucosa* (oral cavity, esophagus, vagina, and anal canal). Melanocytes are primarily located in the skin, residing in the basement layer of the epidermis and elaborate melanin under a variety of stimuli. The number of melanocytes per unit area of skin surface does not correlate with the propensity to develop melanoma. Melanocyte density in Caucasians and Blacks is about the same for any skin unit. Differences in skin pigmentation are determined by the *melanosome-pigment package* passed out of the melanocyte, by way of its dentritic process, and phagocytized by surrounding keratinocytes. These cells then migrate up to the dermis giving the phenotypic patterns and degrees of skin coloration observed in people.

6.6.4.2 Incidence

More than 90 % of all melanomas are cutaneous. It is the third common MT of the skin comprising about 3 % of all skin cancers. Melanoma is common in Caucasians and rare in Negroes. Its incidence varies worldwide, with the highest rates in Northern Europe, New Zealand, Australia, and North America [91].

The incidence of melanoma increases with age, and people in their 80s have the highest rate of occurrence [93]. Melanoma is rare in children and adolescents; only about 2 % of cases are diagnosed in patients younger than 20 years [91]. Generally, the median age of diagnosis is 53 years [92]. Men are affected slightly more than women, with a ratio of 1.3–1 [92, 94], and those who work out of doors, in excessive sunlight, are particularly susceptible.

Melanoma is usually *solitary*, often with multiple secondary nodules around the primary lesion. *Multiple* MM is very rare comprising nearly 1–4 % of all melanomas. In familial cases, the incidence of multiple lesions may be as high as 20 %.

6.6.4.3 Etiology and Risk Factors

The exact etiology of melanoma is still unknown for certain. However, the cause seems to be *multifactorial*; *sunlight* appears to provide the basic damage to the supporting stroma of the skin, which allows the development of melanoma in response to other carcinogenic factors. Approximately, 50–60 % of melanomas arise on top of benign

nevi. The triggering event for malignant transformation is not known. Nevi, which are liable for malignant transformation, include junctional nevi (increased junctional proliferative activity), congenital giant hairy nevus (bathing trunk nevus), and dysplastic nevus syndrome (familial atypical multiple mole melanoma). Nevi present in the soles, palms, *oral mucosa*, anal mucosa, external genitalia, and uveal tract are more liable to turn malignant.

Physical characteristics such as blue or green eyes, fair hair, pale complexion, high degree of freckling, and tendency to sunburn put one at greater risk for developing melanoma. The number of melanocytic nevi on the body and the presence of atypical melanocytic nevi increase the risk of melanoma [91].

Family history of melanoma is an important factor. The risk of melanoma increases 2.2-fold if there is one family member with melanoma and reaches 100 % if there are two or more family members with dysplastic nevi and/or melanoma [95]. Immunosuppression is also a risk factor for melanoma. Maternal-fetal transfer of melanoma is rare but should be noted, as melanoma is the cancer most likely to metastasize from the placenta to the fetus. External risk factors include geographic location and increased exposure to sunlight and UV radiation [91].

Several gene mutations that relate to the risk of melanoma have been identified. Cyclin-dependent kinase inhibitor 2A and melanocortin-1 receptor gene have been associated with an increased risk of hereditary melanoma [94]. *Dysplastic nevus syndrome* is a hereditary disease that increases the risk of melanoma 400–1000-fold [91]. A high prevalence of *BRAF* gene mutations appears to be an epidemiologic link between UV radiation and melanoma. Alterations in melanoma-specific pathways such as *NEDD9*, *MITF*, and *NRAS* also play a role in the development of melanoma [91].

6.6.4.4 Pathophysiology

The pathophysiology for the development of MM involves a series of morphologic stages that include melanocytic atypia, atypical hyperplasia, radial growth phase, primary melanoma in the vertical growth phase with or without in-transit metastases, regional LN metastatic melanoma, and distant metastatic melanoma [91]. However, not all steps must occur in order for melanoma to develop. The main goal of understanding the pathophysiology of the development of MM is to diagnose it early to prevent tumor invasion and metastasis.

6.6.4.5 Symptoms

The classic clinical presentation of melanoma varies by type. Early detection may be facilitated by using the ABCDE mnemonic to assess a mole: asymmetry, border irregularity, color variation or recent color change, diameter (increasing or >6 mm), and evolving lesion, including surface changes (shape, size, color, or elevation) and the development of new symptoms (bleeding, itching, ulceration). Several characteristics are used to help distinguish benign nevi from atypical nevi, including size, shape, color, location, and number. If any abnormality is suspected, a biopsy may be warranted [91]. This step is critical for evaluating a patient with multiple or atypical nevi, a history of excessive sun exposure, or melanoma [92].

6.6.4.6 Physical Examination

Local Examination

Approximately 90 % of MMs arise in junctional or compound mole, and 10 % arise de novo. The majority is found in the head and neck (and limbs). It may occur at mucocutaneous junctions in the mouth (and anus). The *color* of the lesion varies from pale pinkish-brown (Fig. 6.23) to black (Fig. 6.24). If it has a rich blood supply, it will develop a purple hue. The *shape* and *size* vary widely; MM can become a florid tumor, protruding from and overlapping the surrounding skin (Fig. 6.25). When small, the *surface* of the lesion is covered by smooth epithelium. When the epithelium dies from ischemic necrosis, the resulting ulcer is covered with a crust of blood and serum. Bleeding and infection may make the surface of the tumor wet, soft, and boggy. The primary tumor is usually firm in *consistency*, but satellite nodules feel hard. The malignant tissue is intimately fixed to the skin, and when *regional LNs*

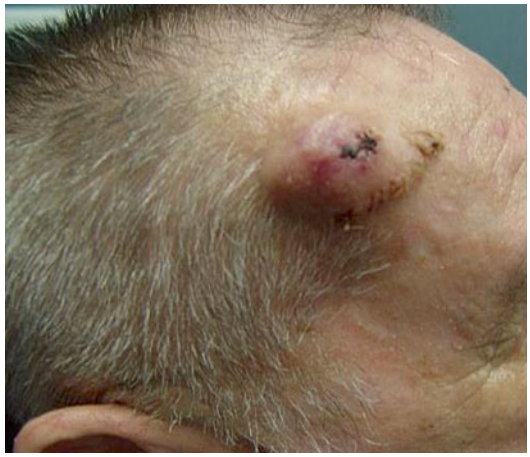

Fig. 6.23 Pinkish-brown MM of the forehead (Note the characteristic color of the tumor)

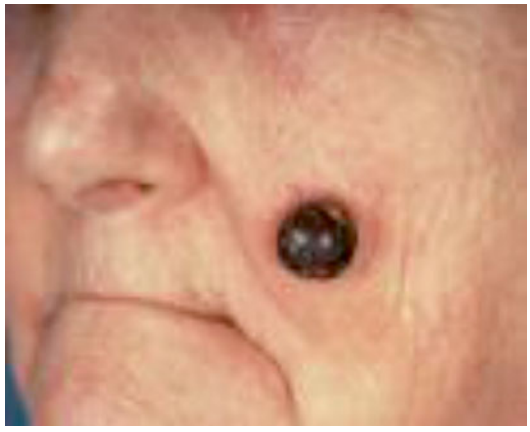

Fig. 6.24 Black MM of the left cheek in an old lady

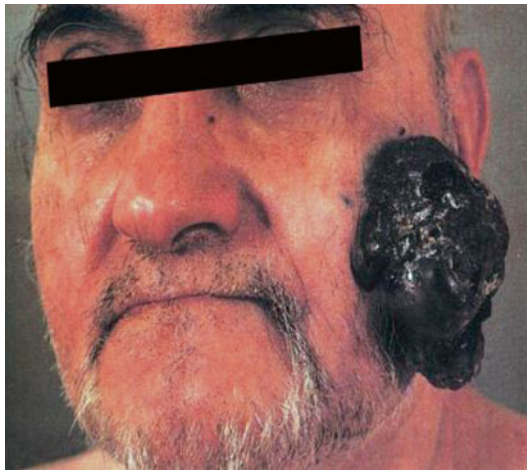

Fig. 6.25 Neglected MM (nodular) of the left cheek in an old gentleman

are involved, they become enlarged, hard, painless, mobile, or fixed. Examination of *surrounding tissues* may reveal a *halo or satellite nodules* around the primary lesion. If the tumor has been itchy, the surrounding skin may be excoriated.

General Examination

Malignant melanomas spread via lymphatics to the bloodstream and then to systemic organs such as the lungs, liver, and brain, resulting in pleural effusions, hepatomegaly, and jaundice, as well as neurological abnormalities, respectively. General physical examination is of extreme importance in such cases for proper staging, choosing the appropriate investigations, deciding the therapeutic plan, and estimating the prognosis.

6.6.4.7 Spread

1. *Direct spread:* To surrounding structures.
2. *Lymphatic spread:* By permeation to form satellites or embolization to form LN secondaries. Lymphatic spread can present as *enlarged LNs or in-transit metastases*. The latter result from melanoma cells being trapped between the primary tumor and regional LNs. This produces a region of cutaneous metastases located >3 cm from the primary site. Mechanical blockage of afferent lymph drainage by either metastatic disease or LN dissection is felt to be the cause of in-transit metastases. Once melanoma becomes metastatic, it has striking trophism for *small bowel mucosa* (causing gastrointestinal bleeding) and distant cutaneous sites.
3. *Blood spread:* Mainly to the lungs, liver, and brain. It may lead to "melanuria."

6.6.4.8 Classification (Clinic-pathological Types)

Melanoma is classified into four major types: *superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanoma, and nodular melanoma*. These types differ in appearance, site, and population affected. The superficial spreading, lentigo maligna, and acral lentiginous melanomas have a period of superficial (radial) growth and, if identified early, may be cured by surgical excision. However, nodular melanoma usually presents as a deeply invasive lesion, made up of exclusively a vertical growth phase. It has a

palpable nodular component, blue-black color in its early development, and is highly capable of early metastasis and is difficult to cure [91].

6.6.4.9 Staging of Melanoma

Staging of melanoma is of extreme importance for determining the prognosis of the disease and opt the most appropriate therapeutic plan.

The Clark Scale

This is a way of measuring how deeply the melanoma has grown into the skin and which levels of the skin are affected.

Level	Lesion (degree of invasion)	Comments
I	Melanocytes confined to the epidermis or dermal-epidermal junction. Also called "melanoma in situ"	Its main disadvantage is that different pathologists may interpret the levels of invasion variably
II	Melanocytes invade the papillary layer of the dermis	
III	Melanocytes reach the junction of the papillary and reticular layers	
IV	Melanocytes invade the reticular dermis	
V	Melanocytes invade the SC fat	

The Breslow Scale

For the Breslow scale (primary tumor thickness scale), a pathologist measures the thickness of the melanoma, at the deepest point of its vertical growth, with a micrometer. It measures in millimeters how far the melanoma cells have reached down through the skin from the surface.

Level	Lesion thickness	Comments
1	Thinner than 1 mm	It allows a more objective evaluation and easier comparison among pathologists. Thicker tumors have worse prognosis
2	1–2 mm	
3	2–4 mm	
4	Thicker than 4 mm	

The Day Scale (Modification of Breslow)

Day introduced a modification of Breslow scale that correlates also with survival.

Level	Lesion	Comments
Level 1	Thinner than 0.85 mm	The 8-year survival rates of levels 1, 2, 3, and 4 were 99 %, 93 %, 69 %, and 38 % respectively
Level 2	0.86–1.69 mm	
Level 3	1.7–3.6 mm	
Level 4	Thicker than 3.6 mm	

TNM and AJC (American Joint Committee) Staging System

This system combines the information from Clark and Breslow scales, as well as the status of the LNs and distant metastases to give a comprehensive staging of these patients (Fig. 6.26).

T	
T0	Typical melanocytic hyperplasia (Clark level 1); not a malignant lesion
T1	Invasion of papillary dermis (Clark level II), or 1 mm thickness or less (Breslow)
T2	Invasion of the papillary-reticular-dermal interface (Clark level III), or 1–2 mm (Breslow)
T3	Invasion of the reticular dermis (Clark level IV), or 2–4 mm thickness (Breslow)
T4	Invasion of SC tissue (Clark level V), or >4 mm (Breslow), or satellites within 2 cm of the primary tumor
N	
N0	No regional LN involvement
N1	Involvement of only one regional LN (mobile, not > 5 cm in diameter)
N2	Involvement of 2–3 regional LNs (fixed, or >5 cm in diameter)
N3	Involvement of 4 or more regional LNs
M	
M0	No known distant metastases.
M1	Involvement of the skin or SC tissue beyond the site of the primary LN drainage
MIa	Melanoma cells have spread to skin in other parts of the body or to LNs far away from where the melanoma started growing
MIb	Melanoma cells have spread to the lung
MIc	Melanoma cells have spread to other organs or cause high blood levels of a chemical made by the liver (lactate dehydrogenase)

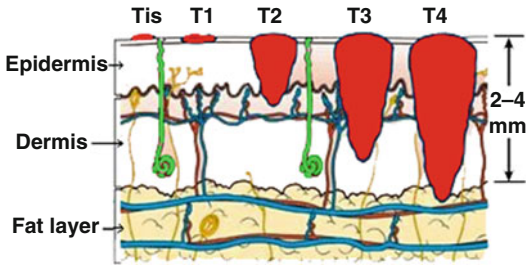

Fig. 6.26 The T part of the TNM staging system of melanoma (depth of the primary tumor)

The *T* part of the TNM system is further divided into two groups, *a* (not ulcerated) and *b* (ulcerated). Ulcerated melanomas have a higher risk of spreading than those which are not ulcerated.

The *N* part of the stage is further divided into groups *a* (micrometastasis in LNs), *b* (macrometastasis in LNs), and *c* (melanoma cells in small areas of the skin very close to the primary melanoma, i.e., satellite metastases, or in the skin lymph channels (in-transit metastases)).

Clinical Staging System (Number Stages of Melanoma)

Stage	Lesion
0	In situ melanoma. Melanoma cells are only in the epidermis
1A	The melanoma is <1 mm thick, not ulcerated, no LN or distant metastases
1B	The melanoma is <1 mm thick (ulcerated) or 1–2 mm (not ulcerated), no LN or distant metastases
2A	The melanoma is 1–2 mm thick (ulcerated) or 2–4 mm (not ulcerated), no LN or distant metastases
2B	The melanoma is 2–4 mm thick (ulcerated) or >4 mm (not ulcerated), no LN or distant metastases
2C	The melanoma is >4 mm thick (ulcerated), no LN or distant metastases
3A	The melanoma has spread into up to 3 LNs near the primary tumor, but the nodes are not enlarged and cells can only be seen under a microscope. No ulceration or distant metastases
3B	The melanoma is ulcerated and has spread to 1–3 LNs nearby, but the nodes are not enlarged and cells can only be seen under a microscope, *or* the melanoma is not ulcerated and it has spread to1–3 LNs nearby and the LNs are enlarged *or* The melanoma is not ulcerated and has spread to small areas of the skin or lymphatic channels, but nearby LNs do not contain melanoma cells
3C	There are melanoma cells in the LNs and small areas of melanoma cells in the skin or lymph channels close to the main melanoma, *or* the melanoma is ulcerated and has spread to 1–3 LNs nearby which are enlarged, *or* the melanoma may or may not be ulcerated and has spread to 4 or more nearby LNs, *or* the melanoma may or may not be ulcerated and has spread to LNs (amalgamated)
4	Distant metastases, most commonly to the lung, liver, or brain, or to distant LNs or areas of the skin

6.6.4.10 Investigations

Biopsy is necessary for diagnosis and microstaging. Lymphangiography is not sensitive. Labeled-monoclonal antibodies may be used for detection of deposits. Computed tomography scan and investigations are necessary for detection of suspected distant metastases.

6.6.4.11 Differential Diagnosis

Malignant melanoma has to be differentiated from other pigmented lesions: moles, pigmented BCC, pigmented papilloma, seborrheic keratosis, dermatofibroma, and pyogenic granuloma.

6.6.4.12 Prevention

The American Cancer Society (ACS) recommendations for prevention include limiting direct sun exposure between the hours of 10 am and 4 pm, when UV rays are the most intense; using sunglasses that protect the eyes and a broad-brimmed hat that shields the face; avoiding tanning beds and sunlamps; and using sunscreen and lip balm on sun-exposed areas [96–98].

The American Academy of Dermatology recommends using sunscreen with a sun protection

factor of 30 or more. One ounce (about a palmful) of sunscreen should be applied to the arms, legs, *neck, and face* every 2 h or sooner after sweating or swimming. Sunscreen should also be applied on cloudy days because UV rays are still present [91, 96–98].

6.6.4.13 Treatment

Management of MM depends on the stage of the disease. It involves establishment of diagnosis by excision biopsy of suspicious lesions (for microstaging) and (1) surgical treatment of the primary lesion (excision and reconstruction), (2) management of regional LNs, and (3) treatment of disseminated disease [91, 92].

Treatment of the Primary Lesion

Surgery is usually limited to patients with early-stage disease. Patients with stage III melanoma usually have lymph node involvement or in-transit metastasis. *In-transit metastasis* is when a tumor develops in the lymph vessel between the primary melanoma and the regional lymph node basin. In-transit metastases occur more than 2 cm from the original site and are more common in individuals with thick, ulcerated lesions. Surgery is also used to manage these distinct melanoma-associated lesions.

Local Excision

- *Low-risk lesions (T1, or lesions <1 mm "Breslow" and not extended beyond Clark level II):* An excisional biopsy with a safety margin of *1 cm* (deep fascia *not* included) will be curative in 98 % of cases [99].
- *Intermediate lesions (T2, or 1-2 mm thick, may extend to Clark level III):* An excisional biopsy with a safety margin of *2 cm* (deep fascia *not* included) is necessary.
- *Advanced lesions (T3 or T4, 4 mm thick or more, Clark level IV or V):* A safety margin of *2–5 cm* is indicated (some authors advocate removal of the deep fascia to ensure clearance at the base of the tumor; others believe that excision of the deep fascia is inadvisable as it may enhance spread). These lesions may have lymphatic involvement and are associated with a high recurrence rate.

Reconstruction

It is done immediately with *split skin graft (SSG) and* 2 years later by *flaps* (to be sure that there is no recurrence). Recently "free flaps" are used immediately after surgical extirpation such as TRAM flap.

Management of Regional LNs [100]

- *Therapeutic regional LN dissection (clinical stage II):* It is universally accepted when regional LNs are enlarged and firm (clinical stage II or occult tumor) to do radical neck dissection for a primary tumor in the head and neck.
- *Prophylactic (precautionary) lymphadenectomy (stage I):* Prophylactic lymphadenectomy remains a subject of debate. However, it is generally advised in the following situations in stage I disease: head and neck lesions >1 mm thick, recurrent lesions, and lesions of intermediate thickness in both sexes (1–4 mm thick).
- *For stage III disease or lesions >4 mm thick:* It is debatable whether block dissection should be done in these patients as the long-term survival is not altered by this treatment (i.e., no improvement in survival).

Treatment of Disseminated Disease

Although melanoma is curable if detected in its early localized form, metastatic melanoma continues to be a therapeutic challenge [92].

Palliative Surgery

Surgery for palliation in metastatic MM may be indicated for removal of painful or ulcerated SC metastases, relief of intestinal obstruction, resection of isolated pulmonary or cerebral metastases, and debulking prior to radiotherapy or systemic therapy.

Radiotherapy (RT)

Malignant melanoma is a highly *radioresistant* tumor. However, RT has a place in the treatment

of fixed, inoperable LNs, cerebral and bone metastases, and cutaneous recurrence not responsive to other forms of treatment.

Immunotherapy

Melanoma is one of the most immunogenic solid tumors, and immunotherapy appears to be a viable treatment option.

- *Interferon (IFN) alfa* is the only effective adjuvant therapy for patients who have undergone surgical resection for lesions >2 mm, with or without LN metastases [101]. However, the optimal IFN treatment modality has not been established yet. Some of the disadvantages of IFN therapy are high cost, unclear long-term benefit, and side effects [102, 103].
- *Interleukin-2 (IL-2)* does not have a direct effect on the tumor; rather, it works to regulate the immunologic activity. The high-dose regimen of recombinant IL-2 (aldesleukin) used to treat metastatic melanoma is 600,000 IU/kg/dose every 8 h, for a maximum of 14 doses in a 5-day period, given for two cycles, with a 10–14-day rest period between cycles [100]. Common side effects of IL-2 include hypotension, arrhythmias, severe infections, and shortness of breath; these effects are reversible. Because of the severe multiorgan toxicity associated with IL-2 therapy, treatment with higher doses is reserved for patients with good organ function who are being closely monitored.
- *Ipilimumab* (Yervoy) (FDA approved in 2011 to treat advanced or metastatic MM) [104]. It is a human immunoglobulin G1 monoclonal antibody that blocks cytotoxic T-lymphocyte–associated antigen 4, thereby increasing T-cell activation and proliferation, responsible for its antitumor action [100]. The usual dosage of ipilimumab in metastatic melanoma is 3 mg/kg IV every 3 weeks for four doses [105].

Chemotherapy

Patients with stage IV MM require cytotoxic, single- or double-agent, systemic therapy. Single-agent chemotherapy with dacarbazine, temozolomide, or fotemustine should be used in selected patients who are not candidates for treatment with high-dose IL-2. Poor response to chemotherapy or immunotherapy alone has led to the evolution of combination therapy. Biologic therapy has been combined to increase overall activity and, perhaps, response rates [91].

6.6.4.14 Prognosis of Melanoma

Although MM accounts for fewer than 5 % of skin cancer cases, it causes up to 75 % of skin cancer-related deaths [91, 93, 94]. The 5-year survival rates for melanoma increased from 82 % in 1975 to 92 % in 2004 [3]. Men older than 65 years of age have the highest mortality rate [91].

Stage of the disease, tumor thickness, level of tumor invasion, and ulceration are powerful predictors of prognosis and survival. Other predictors include serum lactate dehydrogenase (LDH) and regression of primary melanoma [91, 93, 94].

The following table summarizes the prognosticators of malignant melanoma:

Favorable	Unfavorable	Intermediate or no effect
Superficial spreading Malignant lentigo maligna Thin (<1 mm) Level I and II (Clark) Women before menopause Extremities Head	Nodular melanoma Acral lentiginous melanoma Thicker (>4 mm) Levels IV and V (Clark) Middle-aged persons BANS area (back, back of arm, neck, scalp)	Moderate thickness Level III Clark Women during pregnancy

6.7 Cavernous Sinus Thrombosis (CST)

6.7.1 Etiology

The condition most commonly results from contiguous spread of infection from a nasal furuncle (50 %), sphenoidal or ethmoidal sinuses (30 %), and dental infections (10 %). Less common primary sites of infection include the tonsils, soft palate, middle ear, or orbit (orbital cellulitis). Retrograde spread of infection to the cavernous sinus occurs via the superior and inferior ophthalmic veins [106].

The most common infectious microbe is *Staphylococcus aureus (*70 %), followed by *Streptococcus*. Gram-negative rods and anaerobes may also lead to CST and, rarely, *Aspergillus fumigatus* and mucormycosis.

6.7.2 Clinical Presentation

Cavernous sinus thrombosis (CST) is a serious and fatal condition. The clinical presentation can be varied. Both acute (fulminant) disease and subacute (indolent) presentations have been reported in the literature. Symptoms usually result from impaired venous drainage from the orbit and eye, while the most common signs of CST are related to anatomical structures affected within the cavernous sinus, mainly cranial nerves III–VI.

Classic presentations are sudden onset of unilateral periorbital edema, proptosis, ptosis, and chemosis (Fig. 6.27), in addition to headache, photophobia, and cranial nerve palsy (III–VI). Sixth nerve palsy is the most common. Periorbital sensory loss and impaired corneal reflex may occur. Papilledema, retinal hemorrhages, reduced visual acuity, and even blindness may occur from venous retinal congestion. Fever, tachycardia, toxemia, and headache with neck rigidity may be present. The pupil may be dilated and sluggishly reactive. Infection may spread to the contralateral sinus within 24–48 h of initial presentation.

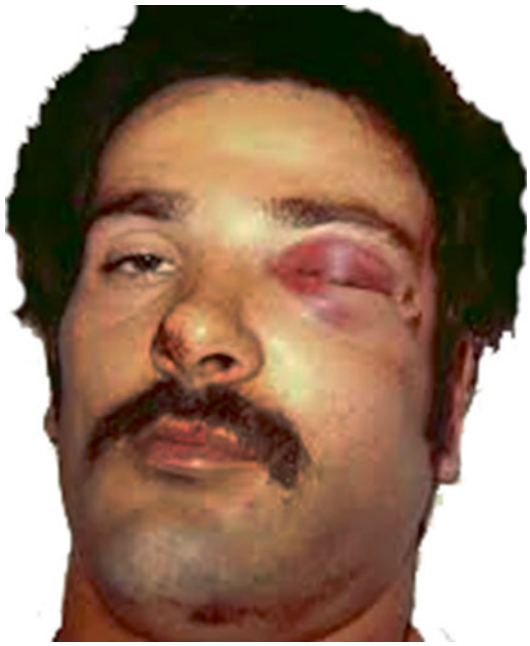

Fig. 6.27 Cavernous sinus thrombosis (Note edema and chemosis of the left eyelid)

6.7.3 Diagnosis

Proptosis, ptosis, chemosis, and cranial nerve palsy beginning in one eye and progressing to the other eye can establish the clinical diagnosis, which is confirmed by laboratory tests and imaging studies. *Laboratory tests* include complete blood count (CBC), blood cultures, and sinus cultures, which help identify the infectious primary source. *Lumbar puncture* is necessary to rule out meningitis.

Imaging studies include *sinus films*, which may show opacification, sclerosis, and air-fluid levels, typical findings that help in the diagnosis of sphenoid sinusitis. *Contrast-enhanced CT scan* may be normal in the early course of the disease but later may reveal underlying sinusitis, thickening of the superior ophthalmic vein, and irregular filling defects within the cavernous sinus. *Magnetic resonance imaging* (MRI) using flow parameters and an MR venogram are more sensitive than CT scan and are now considered the imaging studies of choice to diagnose CST. Findings may include deformity of the internal carotid artery within the cavernous sinus and an obvious signal hyperintensity within thrombosed vascular sinuses on all pulse sequences. *Cerebral angiography* is invasive and not very sensitive, and *orbital venography* is difficult to perform but is excellent in diagnosing CST.

Differential diagnosis of CST should include orbital cellulitis, internal carotid artery aneurysm, stroke, migraine headache, allergic blepharitis, thyroid exophthalmos, brain tumor, meningitis, and trauma.

6.7.4 Complications

Complications in treated patients include oculomotor weakness, blindness, pituitary insufficiency, and hemiparesis. However, complications

of untreated CST include extension of thrombus to other dural venous sinuses, carotid thrombosis with concomitant strokes, subdural empyema, brain abscess, or meningitis. Septic embolization may also occur to the lungs, resulting in acute respiratory distress syndrome (ARDS), pulmonary abscess, empyema, and pneumothorax.

6.7.5 Treatment

Recognizing the primary source of infection and treating it expeditiously are the best way to prevent CST.

6.7.5.1 Acute General Treatment

Appropriate therapy should take into account the primary source of infection as well as possible associated complications such as brain abscess, meningitis, or subdural empyema. *Broad-spectrum antibiotics* (BSABs) given intravenously (IV) are used until a definite pathogen is found. These include nafcillin 1.5 g IV q4h (vancomycin is a substitute in case of MRSA or resistant *Streptococcus pneumonia*) [107], cefotaxime 1.5–2 g IV q4h, and metronidazole 15 mg/kg load followed by 7.5 mg/kg IV q6h.

Anticoagulation with heparin is controversial [108]; Coutinho et al. [109] (2011) reported that anticoagulation treatment appeared safe and yielded significant reduction in the risk of mortality or dependency.

Steroid therapy is also controversial in many cases of CST [110–113]. However, it is absolutely indicated in cases of pituitary insufficiency. Corticosteroids may have a critical role in patients with Addisonian crisis secondary to ischemia or pituitary necrosis that complicates CST [114, 115].

6.7.5.2 Long-Term Treatment

If the primary source is sphenoidal sinusitis, surgical drainage with sphenoidotomy is indicated. All patients with CST are usually treated with prolonged courses (3–4 weeks) of IV antibiotics. In the presence of complications such as intracranial suppuration, 6–8 weeks may be warranted. All patients should be monitored for signs of complicated infection, continued sepsis, or septic emboli while antibiotic therapy is being administered.

6.7.6 Prognosis

The mortality rate of CST dropped from 70 to 100 % to approximately 20 % due to earlier diagnosis and treatment and the availability of antibiotics.

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Deep Neck Space Infections

7

Mahmoud Sakr

7.1 Introduction

Deep neck space infections (DNSIs) most commonly arise from a septic focus of the mandibular teeth, tonsils, parotid gland, deep cervical lymph nodes (LNs), middle ear, or sinuses. Before the widespread use of antibiotics, nearly 70 % of DNSIs were caused by spread from tonsillar and pharyngeal infections. Currently, tonsillitis remains the most common cause of DNSI in children, whereas odontogenic origin is the most common cause in adults [1–4]. These DNSIs often have a rapid onset and can progress to life-threatening complications. Clinicians must thus be aware of such infections and should not underestimate their significant risks of morbidity and mortality, particularly that they have become relatively uncommon in the postantibiotic era. Moreover, with the widespread use of antibiotics and/or profound immunosuppression, the classic local and/or constitutional manifestations of these infections may be absent [5].

Infections of the deep neck spaces present a challenging problem for several reasons: (1) the complex anatomy of the deep neck spaces renders localization of infection difficult; (2) the surgical access for infections of these deep locations makes the intervening neurovascular and soft tissue structures at risk of injury; (3) the possible involvement of the vital surrounding tissues (the bones, nerves, vessels, and other soft tissues) in the inflammatory process subjects the patient to more complicated sequelae such as neural dysfunction, vascular erosion, thrombosis, and osteomyelitis; and (4) the real and potential avenues of communication of the deep neck spaces with each other and with other regions, such as the mediastinum, allow infection to gain access to increasingly larger portions of the neck and other parts of the body.

Anatomically, within the deep neck are 11 spaces created by planes of greater and lesser resistance between the fascial layers. These include the submandibular space, parapharyngeal space, retropharyngeal space, peritonsillar space, danger space, prevertebral space, pretracheal space, carotid space, masticator space, temporal space, and the parotid space.

7.2 Ludwig's Angina

The term Ludwig's angina was originally described in 1836 by *Wilhelm Frederick von Ludwig* (a German physician and physiologist, 1790–1865). It describes inflammation and cellulitis of the submandibular space (primary site)

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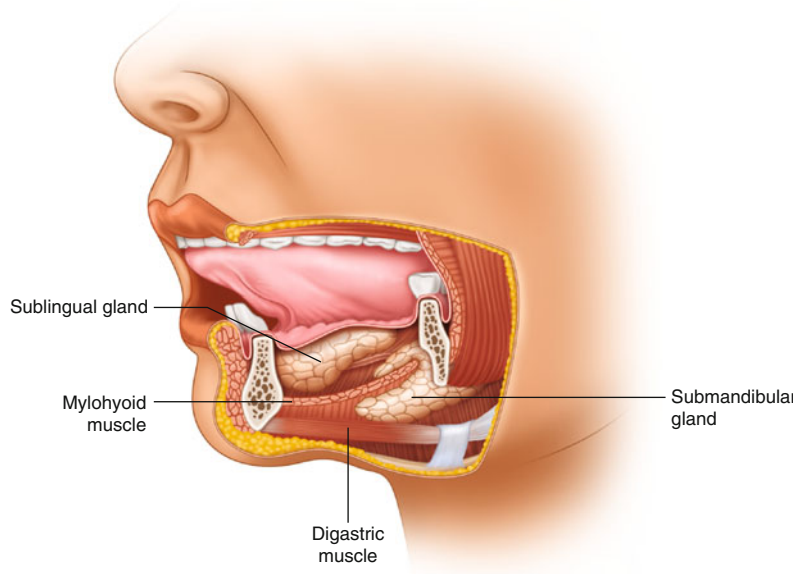

Fig. 7.1 Anatomy of the submandibular space. It has two subdivisions separated by the mylohyoid muscle: sublingual space inferiorly and submaxillary superiorly

that can result in life-threatening airway compromise and spread to other cervical spaces [6].

7.2.1 Surgical Anatomy

The submandibular space is bounded inferiorly by the superficial layer of the deep cervical fascia that extends from the hyoid to the mandible, laterally by the body of the mandible, and superiorly by mucosa of the floor of the mouth. It is divided by the mylohyoid muscles into two subdivisions: the sublingual space inferiorly and the submaxillary space superiorly. The sublingual space contains the sublingual gland, hypoglossal nerve, and Wharton's duct. It is in continuity with the submaxillary space through the posterior margin of the mylohyoid muscle, around which pus can readily tract (Fig. 7.1). Infection may also spread to the para- or retropharyngeal space.

7.2.2 Etiology

Infection in the submandibular space may be odontogenic in origin (90 %), usually from the second and third molars, or non-odontogenic (10 %) from mandibular fracture, tongue piercing, neoplasms, neck trauma, or sialadenitis. Infection usually starts in the submaxillary space and spreads to the sublingual space via the fascial planes rather than the lymphatics. The organisms most often isolated in patients with Ludwig's angina are *Streptococcus viridans* and *Staphylococcus aureus*. Anaerobes, including *Bacteroides*, are also frequently involved. Gram-negative organisms that have been isolated include *Neisseria*, *Escherichia coli*, *Pseudomonas*, *Haemophilus influenzae*, and *Klebsiella* species.

7.2.3 Clinical Manifestations

There is usually history of recent dental procedure and dental pain. As the submandibular space is expanded by cellulitis or abscess, the floor of the mouth becomes indurated (Fig. 7.2), and the tongue is forced upward and backward, causing airway obstruction. There is typically a bilateral submandibular edema, with marked tenderness and, occasionally, subcutaneous emphysema. The swelling of the anterior soft tissues of the neck above the hyoid bone sometimes leads to a characteristic appearance known as "bull's neck."

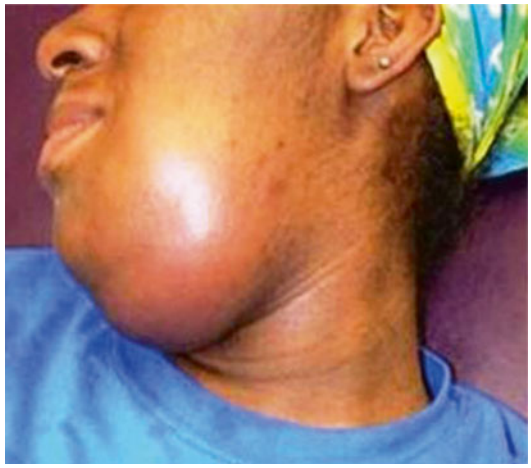

Fig. 7.2 Ludwig's angina (inflammation and cellulitis of the submandibular space)

Lymphadenopathy and fluctuance are not usually seen in patients with Ludwig's angina. Typically the patient presents also with drooling, trismus, neck pain, dysphagia, and dysphonia or, more specifically, a muffled tone at higher registers ("hot potato" voice) caused by edema of the vocal apparatus. Hoarseness, stridor, respiratory distress, decreased air movement, cyanosis, and a "sniffing" position (upright posture with the neck thrust forward and the chin elevated) are all signs of impending airway obstruction.

In addition to airway compromise, *complications* of Ludwig's angina may include cavernous sinus thrombosis and brain abscess. Other reported complications include carotid sheath infection and arterial rupture, suppurative thrombophlebitis of the internal jugular vein (IJV), osteomyelitis of the mandible, mediastinitis, pericardial and/or pleural effusion, empyema, subphrenic abscess, and aspiration pneumonia [7–11].

7.2.4 Diagnosis

Plain X-ray (PXR) of the neck and chest often shows the soft tissue shadow, the presence of gas, and the extent of airway narrowing. *Panoramic* radiographic views of the jaw may show a dental focus of infection. *Ultrasonography* (US) does not reveal anatomic details but has been used to identify fluid collections in the soft tissues, as has *gallium citrate Ga-67 scanning*. Moreover, US can help distinguish between phlegmon and abscess, give information about the surrounding vessels, and guide fine-needle aspiration (FNA) attempts.

Contrast CT scan is the gold standard in the evaluation of deep neck infections. It indicates the location, boundaries, and relation of infection to surrounding neurovascular structures. It also shows the presence of gas, fluid collection, and airway compromise. Chest CT may be helpful if extension into the mediastinum is suspected. Although *MRI scan* provides an excellent soft tissue resolution to help localize the region of involvement, it is not considered to be the initial modality of choice because of the increased time and expense [12].

Differential diagnoses of Ludwig's angina include angioneurotic edema, lingual carcinoma, sublingual hematoma (following anticoagulation), salivary gland abscess, lymphadenitis, cellulitis, and peritonsillar abscess (PTA).

7.2.5 Treatment

7.2.5.1 Medical Treatment

The *airway* is the first priority of treatment [13]. Airway management is accomplished by immediate orotracheal or fiberoptic nasotracheal intubation. If the patient is not intubated, a tracheostomy or cricothyroidotomy should be performed for airway control. Tracheostomy should be performed before any attempts at surgical drainage in these patients [14]. Intravenous (IV) broad-spectrum *antibiotics* should be started before culture results are obtained based on the local resistance patterns and most common etiologies. After completion of an IV course of antibiotics and the patient is clinically improving and has been afebrile for at least 48 h, oral antibiotics are given [15]. *Corticosteroids* have also been recently added to the therapeutic regimen to reduce edema [16].

7.2.5.2 Surgical Therapy

Surgical drainage is required in case of suppuration, which takes place in nearly 65 % of cases, and in patients with no improvement after 48–72 h of IV antibiotics. Separation of the superficial

lobes of the submandibular gland and division of the mylohyoid muscles are, usually, necessary to decompress the fascial spaces [17]. The most important *preoperative* considerations are stabilization of a secure airway, volume and metabolic resuscitation, and initiation of antibiotics. Needle aspiration under CT or US guidance may be used in patients with small easily reachable abscesses or in patients who are too unstable to undergo general anesthesia. It may also provide preliminary culture specimens before formal incision and drainage. *Postoperatively*, the patient should be closely monitored for signs of response to therapy, reaccumulation or impending complications, and for culture and sensitivity results for appropriate tailoring of the antibiotics. The patient's airway must also be monitored closely for any signs of obstruction.

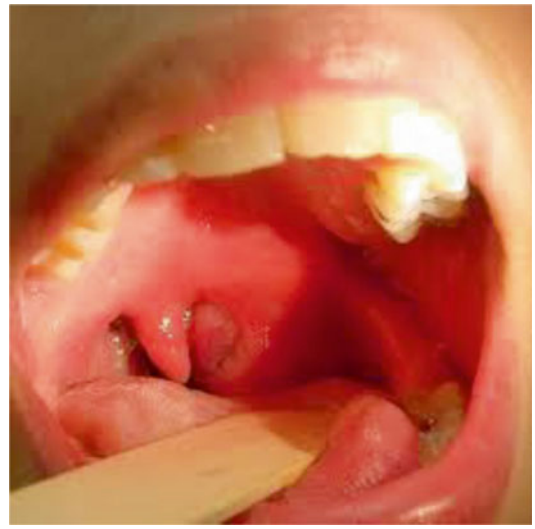

Fig. 7.3 Peritonsillar abscess in the left peritonsillar space

7.2.6 Prognosis

The prognosis in Ludwig's angina depends primarily on immediate protection of the airway and then on prompt antibiotic—and possibly surgical—treatment of the infection. Mortality in the pre-antibiotic era, the mortality rate of Ludwig's angina was 50 %, but with the advent of modern antimicrobial and surgical therapies, the mortality rate has been markedly reduced to less than 5 % [8–10].

7.3 Peritonsillar Abscess (PTA)

Peritonsillar abscess (PTA), also known as a *quinsy* or *quinsey*, occurs in the peritonsillar space, which is bounded by the tonsil medially and the superior constrictor laterally. The remaining borders are formed by the anterior and posterior tonsillar pillars. It is the most common DNSI that presents to the otorhinolaryngological emergency department and may spread to the parapharyngeal space if not managed promptly [18].

7.3.1 Etiology

Peritonsillar abscess usually arises as a complication of an untreated or inadequately treated acute tonsillitis, but may also occur de novo. The commonly involved aerobic pathogens include *Streptococcus*, *Staphylococcus,* and *Haemophilus*. Anaerobic pathogens including *Bacteroides* have also been incriminated [19–24].

Dental infection (such as periodontitis and gingivitis) may be a risk factor. Other risk factors include chronic tonsillitis, infectious mononucleosis (IMN), smoking, chronic lymphocytic leukemia (CLL), and stones or calcium deposits in the tonsils (tonsilloliths).

7.3.2 Clinical Presentation

Progressive unilateral sore throat and pain during swallowing are usually the earliest symptoms. As the abscess develops, persistent peritonsillar pain, pyrexia, malaise, headache, muffled voice, and distortion of vowels (hot potato voice) may appear. Neck pain associated with tender, enlarged LNs, otalgia, halitosis, dysphagia, and trismus are also common.

General physical signs include mild-to-moderate distress, fever, tachycardia, and dehydration. Locally, there is erythema and edema in the tonsillar area of the affected side (Fig. 7.3) with displacement of the uvula toward the unaffected side as well as enlargement and tenderness of the jugulodigastric LNs.

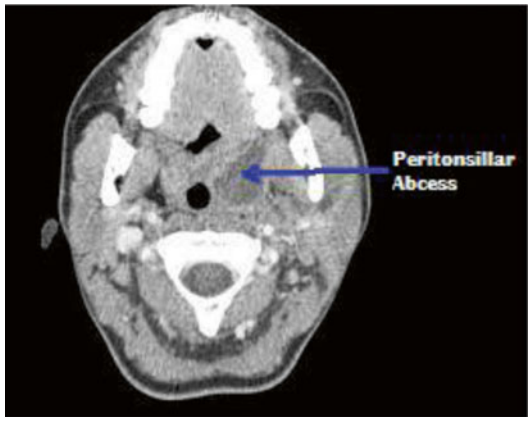

Fig. 7.4 CT scan showing peritonsillar abscess

Complications of PTA include septicemia, retropharyngeal abscess, and extension of the abscess in other deep neck spaces leading to airway compromise. The severity of complications depends on the timing of management, rapidity of illness progression, and characteristics of the affected fascial spaces.

7.3.3 Diagnosis

Peritonsillar abscess is usually diagnosed based on history taking and careful physical examination. Laboratory tests and imaging are not used often. Monospot test may be ordered to rule out infectious mononucleosis (IMN) which is associated with up to 20 % of PTAs. Pus from the abscess may be sent for culture and sensitivity to select the appropriate antibiotic. Ultrasound, both lateral and intraoral, even CT scan with contrast (Fig. 7.4) may be ordered to delineate the abscess and determine its extent.

Differential diagnoses of PTA include peritonsillar cellulitis, tonsillar abscess, dental infections, cervical adenitis, IMN, salivary gland infection, mastoid infection, foreign body aspiration, and neoplasms (lymphoma, leukemia).

7.3.4 Treatment

7.3.4.1 Medical Therapy

Patients with PTAs who are dehydrated require IV fluid administration until the inflammation resolves, and they are able to resume an adequate oral fluid intake. Antipyretics and analgesics are used to relieve fever and pain. Antibiotic therapy should begin after cultures of pus have been obtained. Infection is frequently penicillin resistant, so it is now common to treat with clindamycin [25] or metronidazole in combination with penicillin G benzathine [26]. Oral antibiotics may be prescribed once the patient is able to tolerate oral intake and should be continued for 7–10 days.

The use of steroids has been controversial. Ozbek et al. reported that the addition of a single dose of IV dexamethasone to parenteral antibiotics significantly lowered the length of hospital stay, throat pain, fever, and trismus as compared to only parenteral antibiotics [27].

7.3.4.2 Surgical Treatment

Needle aspiration can be carried out in children as young as 7 years, especially if conscious sedation is used. The fluid aspirated may be sent for culture, and in some cases, it may not need to be followed by an incision and drainage (I&D).

Intraoral I&D is performed after localizing the abscess, the opening is left open, and the patient is asked to gargle with saline solution. Successful aspiration or drainage leads to dramatic relief of the patient's symptoms.

Tonsillectomy with open I&D (*quinsy tonsillectomy*) has been a subject of controversy. Many studies have reported its safety, while others have shown that immediate or delayed tonsillectomy may not be necessary because of the high rate of success and low rates of recurrence and morbidity associated with intraoral drainage. However, when the abscess is located in an area that is difficult to access, a tonsillectomy may be the only means to drain it [28].

7.3.5 Prognosis

Most patients treated with antibiotics and adequate drainage of their abscess cavity recover within a few days. Patients presenting with recurrent abscess or chronic sore throat after proper I&D may require tonsillectomy.

Wang et al. reported that the risk of PTA recurrence increases with higher frequencies of previous tonsillitis in patients of all ages and in children managed with aspiration only [29].

7.4 Parapharyngeal Abscess

7.4.1 Surgical Anatomy

The parapharyngeal space (PPS) (Fig. 7.5) is shaped like an *inverted pyramid*, with the skull base superiorly, and the greater horns of the hyoid bone, the apex, inferiorly. The posterior border is formed by the prevertebral fascia and by the posterior aspect of the carotid sheath (posterolaterally), while the anterior boundary is the inter-pterygoid fascia and the pterygomandibular raphe. The PPS can be subdivided into anterior and posterior compartments by a line extending from the medial aspect of the medial pterygoid plate to the styloid process.

The anterior (pre-styloid) compartment contains the internal maxillary artery, inferior alveolar nerve, lingual nerve, and auriculotemporal nerve (ATN). Infections in this compartment often give significant trismus.

The posterior (post-styloid) compartment contains the carotid artery, internal jugular vein (IJV), last 4 cranial nerves, sympathetic chain, and lymphatics. This space provides a central connection for all other deep neck spaces. It connects posteromedially with the retropharyngeal space, inferiorly with the submandibular space, and laterally with the masticator space. It is directly involved by lateral extension of PTA, and the carotid sheath courses through this space into the chest.

7.4.2 Etiology

Infections in the PPS usually originate in the tonsils or pharynx. Spread is by direct continuity or by lymphatic drainage. Thus, a parapharyngeal abscess may be secondary to tonsillitis or bursting of a PTA. Other sources include dental

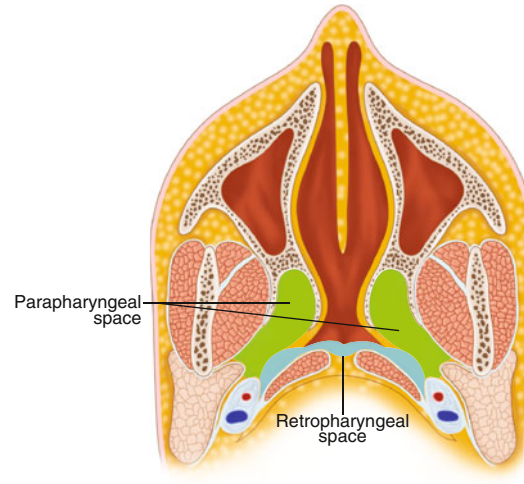

Fig. 7.5 Anatomy of the parapharyngeal space

infection (usually from the lower last molar tooth), periostitis, other deep head and neck spaces, and penetrating trauma of the neck [30]. A parapharyngeal abscess may be also iatrogenic, from injection of local anesthetic for tonsillectomy or mandibular nerve block.

7.4.3 Clinical Presentation

The first symptoms are identical to those of uncomplicated acute pharyngitis or tonsillitis (fever, sore throat, nasal voice, dysphonia, enlarged cervical LNs). Progression of the signs and symptoms is key as it pertains to inflammation and obstruction of the upper airways and/or GIT. There may be dysphagia, dyspnea, stridor, neck stiffness, trismus, and/or chest pain. General physical signs are those of septicemia and toxemia. Locally, there is tenderness and swelling below the angle of the mandible, indicating the presence of pus [31].

Infections of the PPS are important causes of morbidity and mortality because of the possible *complications*, which include acute edema of the larynx with respiratory compromise, thrombophlebitis of the IJV with septicemia (*Lemierre syndrome*), and spread of infection to the retropharyngeal space or mediastinum (along the

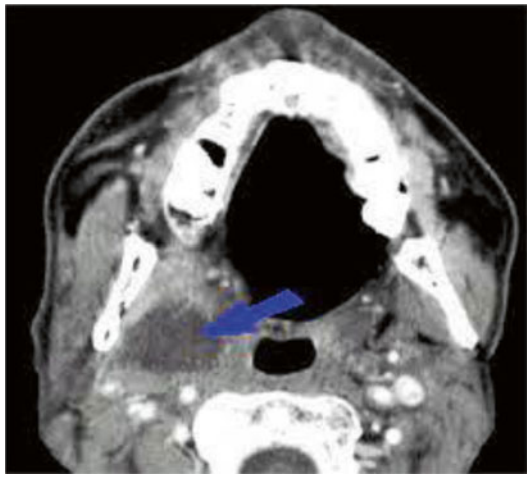

Fig. 7.6 Contrast-enhanced axial CT showing parapharyngeal abscess (*blue arrow*)

carotid space). Mycotic aneurysm with possible subsequent rupture of the internal carotid artery (ICA) and massive hemorrhage may also occur [32, 33].

7.4.4 Diagnosis

Diagnosis is primarily based on classical signs and symptoms and is confirmed by using CT scan with contrast (Fig. 7.6), which is considered the radiologic test of choice. It provides details of the size, location and relations of the abscess to large vessels, and other deep spaces of the neck. These details aid in determining the appropriate mode of management [34].

7.4.5 Treatment

Treatment may require airway control. Parenteral broad-spectrum antibiotics (e.g., ceftriaxone, clindamycin) and surgical drainage are generally required.

Posterior abscesses are drained externally through the submaxillary fossa, while anterior abscesses may often be drained via an intraoral incision. Several days of parenteral culture-determined antibiotics are necessary after drainage, followed by a 10–14-day course of oral antibiotics. Occasionally, small abscesses can be treated with IV antibiotics alone [32, 33].

Surgical drainage carries its own inherent risks and potential complications. Consequently, percutaneous aspiration under US or CT guidance has been suggested as an alternative to conventional surgical I&D.

Nutritional support needs special attention particularly in the presence of septicemia. Nasogastric (NG) feeding may be required.

7.5 Retropharyngeal Abscess (RPA)

7.5.1 Surgical Anatomy

The retropharyngeal space is sometimes considered a third medial compartment within the parapharyngeal space (PPS) because both communicate laterally (Fig. 7.5). This space lies posterior to the pharynx, bound by the buccopharyngeal fascia anteriorly, the prevertebral fascia posteriorly (Fig. 7.7), and the carotid sheaths laterally. It extends superiorly to the base of the skull and inferiorly to the mediastinum. It primarily contains retropharyngeal lymphatics.

Infection may enter this space directly from traumatic perforations of the posterior pharyngeal wall or esophagus, or indirectly, from the PPS. Infections of this space may drain into the prevertebral space and consequently into the chest resulting in mediastinitis and empyema. Abscess in this space may push forward, occluding the airway at the level of the pharynx.

Retropharyngeal LNs tend to regress by about age 5 years, making infection in this space much more common in children than adults.

7.5.2 Etiology

More than 60 % of RPAs in children are caused by upper respiratory tract infections, whereas

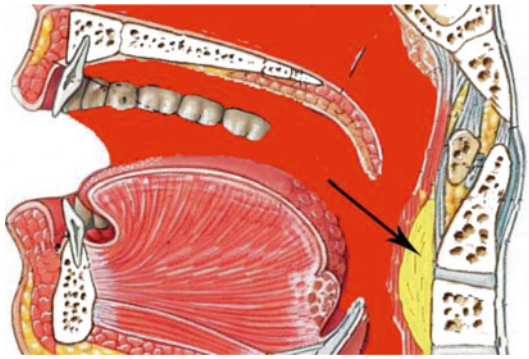

Fig. 7.7 Location of RPA (*arrow*) between the pharynx anteriorly and the prevertebral fascia posteriorly

most infections in adults are caused by pharyngeal trauma from endotracheal intubation, nasogastric tube insertion [35], endoscopy, foreign body ingestion, or removal. Other common sources of infection include the nose, adenoids, nasopharynx, and sinuses.

Patients who are immunocompromised or chronically ill are at increased risk for RPA. The most common organisms include aerobes (e.g., beta-hemolytic streptococci and *Staphylococcus aureus*) and anaerobes *(*e.g., *Bacteroides and Veillonella);* gram-negative organisms *(*e.g., *Haemophilus parainfluenzae* and *Bartonella henselae)* may also be observed. Often, mixed organisms are often cultured [36]. The incidence of RPA caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing [3].

7.5.3 Clinical Presentation

Retropharyngeal abscess is more common in males than in females, with a generally reported male preponderance of 53–56 % [3, 9, 37]. A study of children with RPA in the USA reported even 63 % of cases in males [10]. On the other hand, a study of cases in Nigeria reported a male-to-female ratio of 1:1 [38].

Initially, RPA was thought to be a disease limited to children with a mean age around 5 years [38–42], but now it is being encountered with increasing frequency in adults. *Symptoms* of RPA are different for adults and children. Symptoms in adults include

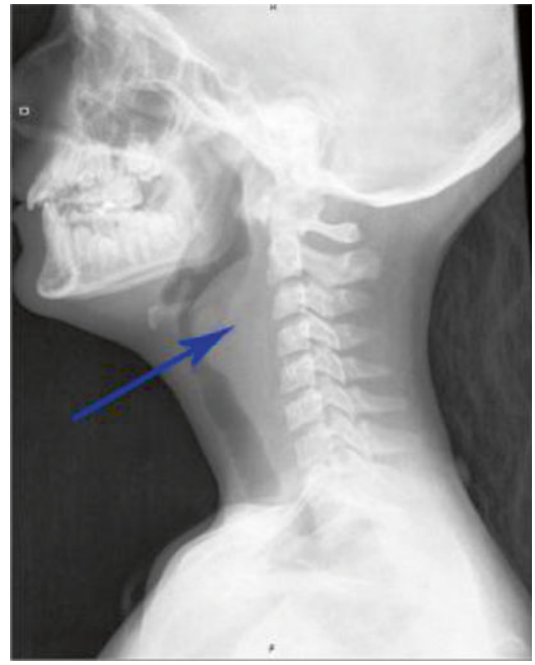

Fig. 7.8 Plain X-ray showing a retropharyngeal abscess. Note encroachment on the lumen of the pharynx (*blue arrow*)

sore throat, fever, dysphagia, odynophagia, neck pain, and dyspnea. Symptoms in children may include also neck stiffness, neck swelling, rhinorrhea, poor oral intake, and lethargy [41]. In addition to fever, *physical examination* usually reveals posterior pharyngeal edema or bulge [41], neck rigidity, stridor, torticollis, trismus, and cervical lymphadenopathy [41, 43]. Associated signs in children may also include tonsillitis, peritonsillitis, pharyngitis, and otitis media.

7.5.4 Diagnosis

A *plain X-ray* of the neck (lateral view) may show the retropharyngeal soft tissue mass with encroachment on the pharynx (Fig. 7.8). Diagnosis is confirmed by using *CT scan* with contrast (Fig. 7.9), which is considered the radiologic test of choice, as it provides details of the abscess and its anatomical relations to surrounding structures including large vessels and other deep neck spaces. If a spinal epidural abscess is

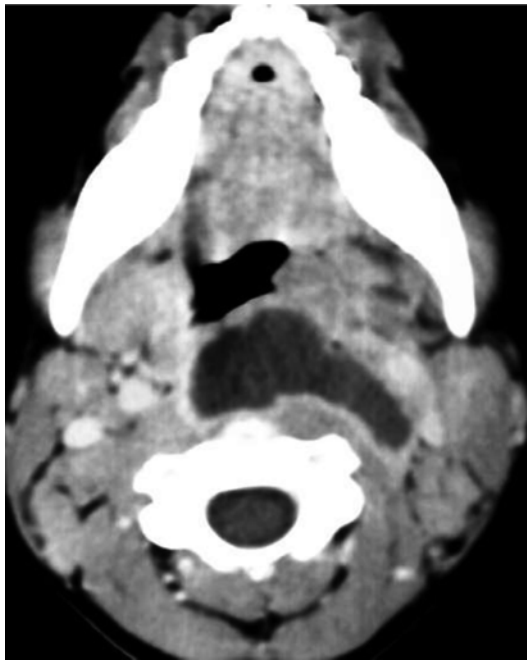

Fig. 7.9 CT scan (with contrast) showing CT findings more consistent with an abscess rather than a phlegmon. Note the larger size, the rim of contrast enhancement

suspected, immediate imaging of the spinal cord with gadolinium-enhanced *MRI* is needed. It is considered the procedure of choice as it delineates the extent of the abscess, which frequently extends over several levels.

Differential diagnoses of RPA include Brown-Sequard syndrome (lateral hemisection of the spinal cord), cauda equina syndrome, cavernous sinus thrombosis, encephalitis, epidural and subdural infections, epidural hematoma, meningitis, neoplasms of the brain or spinal cord, osteomyelitis, spinal cord injuries, and stroke (hemorrhagic or ischemia).

7.5.5 Treatment

Early recognition and aggressive management of RPA are essential because it still carries significant morbidity and mortality. Expeditious neurosurgical consultation should be initiated whenever a neurological pathology is suspected. Antibiotic treatment should be started as soon as possible in conjunction with surgical therapy [9]. Antibiotic therapy may occasionally be sufficient for children with small abscesses. However, most patients also require drainage through an incision in the posterior pharyngeal wall. Endotracheal intubation is done preoperatively and maintained for 24–48 h.

7.5.6 Prognosis

The relatively high mortality rate of RPA is due to its association with airway obstruction, mediastinitis, aspiration pneumonia, pericarditis, epidural abscess, jugular venous thrombosis, necrotizing fasciitis, septicemia, and carotid artery erosion [9, 44].

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Cervical: Lymphadenopathy

8

Mahmoud Sakr

8.1 Anatomical Considerations

The neck region contains around 300 lymph nodes (LNs) out of 800 LNs in the whole body. The detailed study of LNs by Rouviere in 1932 [1] and the later illustration of metastatic predilection of head and neck malignancies to certain LN regions by Lindberg et al. [2] paved the road to a clinically sound classification. The American Academy of Otolaryngology and Head and Neck Surgery (AAO-HNS) and the American Joint Committee on Cancer (AJCC) developed the currently widely accepted levels classification of the cervical LNs (Table 8.1, Figs. 8.1 and 8.2).

8.1.1 Delineation of the Levels of Cervical Lymph Nodes [3] (Fig. 8.1)

Level IA: Submental Region These LNs lie within the triangle bounded by the anterior belly of the digastric muscles (both sides) and the hyoid bone inferiorly.

Level IB: Submandibular Region These LNs lie within the triangle bounded by the anterior and posterior bellies of digastric muscle inferiorly and the body of the mandible superiorly. It should be noted that the submandibular gland should be included in the removed specimen if the LNs within this level are excised.

Level IIA and IIB: Upper Jugular Group Those are the LNs surrounding the upper third of the internal jugular vein (IJV). They extend from the skull base superiorly to the level of the inferior border of the hyoid bone inferiorly. Anteriorly, it is bounded by the lateral border of the sternohyoid muscle and the stylohyoid muscle. Posteriorly, it is bounded by the posterior border of the sternocleidomastoid (SCM) muscle. Level IIA LNs lie anterior to the vertical plane of the spinal accessory nerve, while IIB LNs lie posterior to this plane. Radiologically, level IB and level IIA LNs are separated by the vertical plane at the posterior aspect of the submandibular gland.

Level III: Middle Jugular Group This level extends from the inferior border of the hyoid bone superiorly to the inferior border of the cricoid cartilage inferiorly and is located around the middle third of the IJV. Again, the anterior boundary is represented by the lateral border of sternohyoid muscle, and the posterior boundary is the posterior border of the SCM. The jugulo-omohyoid LN belongs to this group.

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Table 8.1 Cervical LN level classification according to the AAO-HNS

Level	Area	Sublevels	Areas drained
I	Submental LNs Submandibular LNs	IA IB	Floor of mouth, anterior oral tongue, anterior mandibular alveolar ridge, and lower lip Oral cavity, anterior nasal cavity, midface soft tissue structures, submandibular gland
II	Upper internal jugular nodes; lying between the skull base and the hyoid bone	IIA, IIB	Oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, and parotid gland
III	Middle internal jugular nodes; lying between the hyoid bone and cricoid cartilage		Oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx
IV	Lower internal jugular nodes; extending between cricoid cartilage and the clavicle		The hypopharynx, cervical esophagus, and larynx
V	Posterior triangle (spinal accessory chain) LNs	VA VB	VA: nasopharynx and oropharynx VB: thyroid gland
VI	Pretracheal + prelaryngeal + paratracheal LNs		Thyroid gland, glottic and subglottic larynx, apex of piriform sinus, cervical esophagus
VII	Upper mediastinal LNs		

Level IV: Lower Jugular Group These LNs extend from the lower border of the cricoid cartilage to the clavicle, and they are located around the lower third of the IJV. Anteriorly, this group is bounded by the lateral border of sternohyoid muscle and posteriorly bounded by the posterior border of SCM. It should be noted that the "Virchow" LN belongs to this group.

Levels VA and VB: Posterior Triangle Group The upper limit of this group is the convergence of the trapezius and SCM muscles, while the lower boundary is formed by the clavicle. Anteriorly, it is bounded by the posterior border of SCM, and the posterior boundary is formed by the anterior border of the trapezius muscle. Level VA LNs and VB LNs are separated by an imaginary horizontal plane marking the lower border of the cricoid cartilage. Level VA LNs include the spinal accessory LNs, while VB includes LNs located around the transverse cervical vessels and the supraclavicular LNs.

Level VI: Central Compartment Group This level includes pretracheal, paratracheal, pre-cricoid (Delphian), and peri-thyroidal LNs (including LNs located along the recurrent laryngeal nerves [RLN]). This region extends from the hyoid bone superiorly to the suprasternal notch inferiorly. Laterally, it is bounded by the common carotid arteries (CCAs).

8.1.2 Neck Dissection

8.1.2.1 Historical Overview

The term neck dissection refers to the removal of the fibrofatty tissue of the neck with the intention of treating lymphatic metastasis in the neck region. This surgical procedure was first described by George Crile in 1906 although reports of similar procedures of en bloc resections go back to 1888 when Franciszek Jawdynski – a Polish surgeon – reported four cases. The work of Crile was further popularized by several surgeons including the famous American surgeon, Hayes Martin. However, the morbidity accompanying the radical approach of the original procedure stimulated the development of a more conservative approach. Based on anatomical understanding

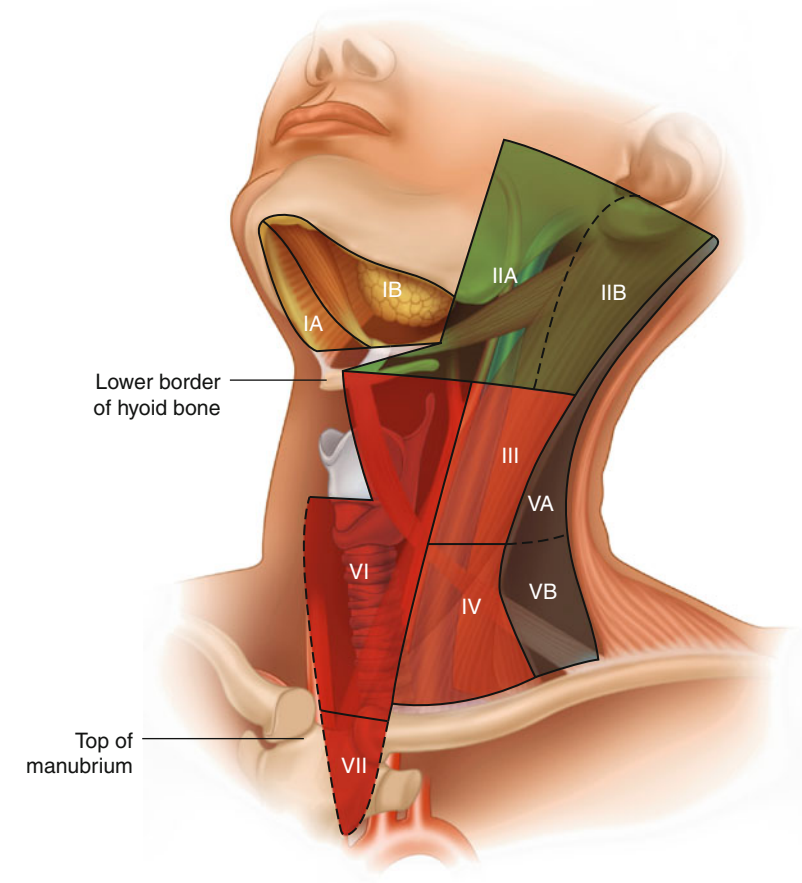

Fig. 8.1 Regional nomenclature of cervical nodes

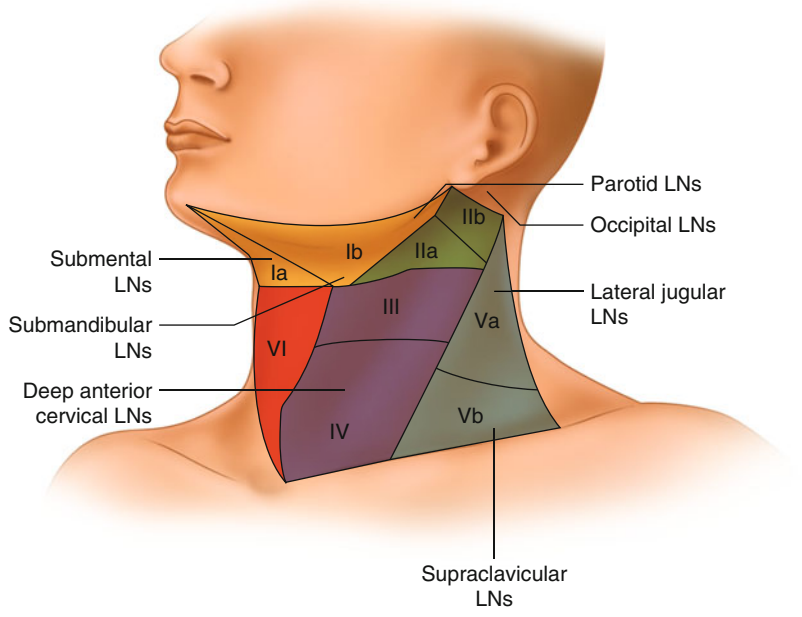

Fig. 8.2 Head and neck regions draining into each nodal level

of the lymphatic anatomy of the neck, Suarez introduced the principles of functional neck dissection in 1963. Later, Ettore Bocca published a description of an operative technique in the English literature aiming at the preservation of the non-lymphatic structures of the neck resulting in a better functional outcome and less morbidity, at the same time obtaining equivalent oncologic results [4, 5].

The ongoing experimentation and clinical studies resulted in a more precise understanding of the metastatic nodal patterns in head and neck malignancies [2, 6]. The resulting data allowed for a more conservative approach depending on the negligible risk of involvement of certain nodal regions in various oncologic scenarios ending in a wide range of surgical procedures. This variation called for an updated classification and nomenclature of operations involving surgical excision of the cervical lymphatics. In order to achieve this, AAO-HNS sponsored the work of the Committee of Head and Neck Surgery and Oncology to develop a unified classification of neck dissection operations. The first classification was established in 1991; this was later modified in 2002 and 2008 to become the currently accepted classification [7–11].

8.1.2.2 Classification of Neck Dissection (AAO-HNS and American Head and Neck Society) [3]

Radical Neck Dissection (RND)

This is the original standard operation of cervical lymphadenectomy to which all the other modifications have been applied. It entails removal of ipsilateral nodal groups extending from the lower border of the mandible superiorly to the clavicle inferiorly and from the lateral border of sternohyoid muscle, hyoid bone, and contralateral anterior belly of digastric muscle medially to the anterior border of trapezius muscle laterally. Thus, nodal groups of level I–V are removed, while the anterior compartment (central, level VI), suboccipital, peri-parotid (except for the infra-parotid LNs lying in the submandibular triangle), retropharyngeal, and buccinators LNs are not. It also includes the removal of spinal accessory nerve (SAN), IJV, and SCM.

Modified Radical Neck Dissection (MRND) (Figs. 8.3 and 8.4)

This entails the removal of the same nodal groups as described in RND while preserving one or more of the non-lymphatic structures (SAN, IJV, and SCM). According to the current terminology,

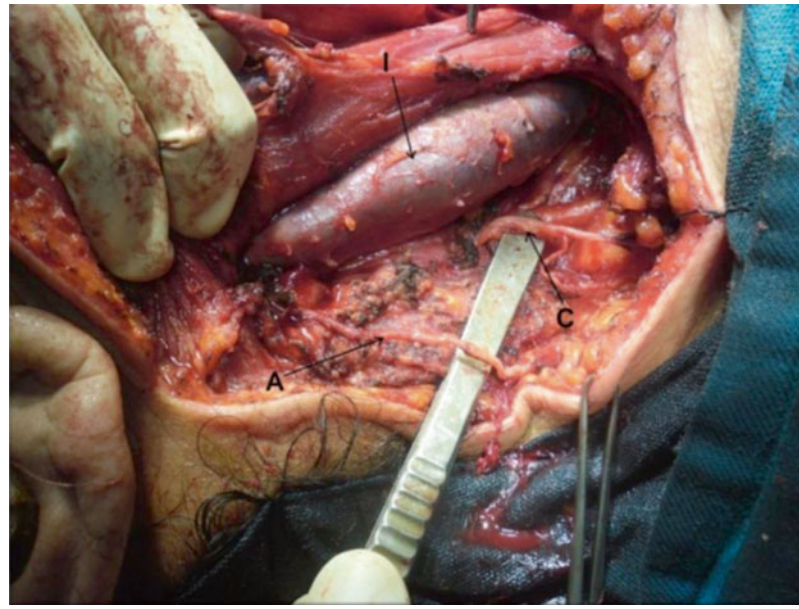

Fig. 8.3 Level V dissected, showing accessory nerve (*A*), branch from cervical plexus (*C*), and IJV (*I*)

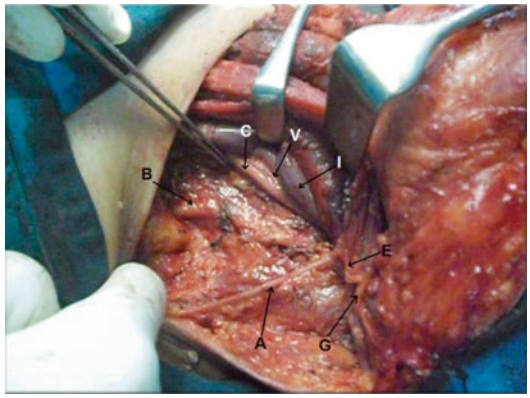

Fig. 8.4 Levels III, IV and V dissected, showing accessory nerve (*A*), great auricular nerve (*G*), Erb's point (*E*), IJV retracted (*I*), common carotid artery (*C*), vagus nerve (*V*), and trunks of brachial plexus (*B*)

the preserved non-lymphatic structure should be named in the operation title, e.g., modified RND with preservation of IJV and SAN.

Selective Neck Dissection (SND)

This refers to the cervical lymphadenectomy with preservation of one or more nodal groups included in the original RND. This approach is based on the predictable patterns of nodal metastasis according to the site of the primary malignancy. As a result, different variations of lymphadenectomy have been described including:

- Supraomohyoid neck dissection: removal of levels I–III.
- Lateral neck dissection: removal of levels II–IV.
- Posterolateral neck dissection: removal of levels II–V, suboccipital, postauricular, and the external jugular LNs.
- Anterior neck dissection: removal of level VI LNs.

To obtain a unified terminology as regards to the variations in the extent of excision, it is recommended to mention the levels and sublevels excised following the term SND, e.g., SND [level VI].

Extended Radical Neck Dissection (ERND)

This entails removal of additional LN groups (including retropharyngeal, superior mediastinal, paratracheal, or buccinator LNs) or non-lymphatic structures or both, which are not included in the standard RND operation. Examples of non-lymphatic structures that can be removed include the vagus nerve, hypoglossal nerve, carotid artery, paraspinal muscles, or the overlying skin. The additional removed structures should be mentioned in the operation title.

8.2 Cervical Lymphadenopathy: Pathology and Clinical Pattern

8.2.1 Definition

Lymphadenopathy (LA) is a pathological process of LNs manifested by abnormally increased size or altered consistency or number [12]. Cervical lymphadenopathy (CLA) refers to cervical nodal tissue measuring more than 1 cm in diameter [13]. However, palpable supraclavicular nodes of any size are considered abnormal [14]. It is not a disease by itself; rather, it is a sign of an underlying pathology that ranges from a trivial infection to a metastatic malignant neoplasm.

8.2.2 Classification

8.2.2.1 Etiological

Cervical lymphadenopathy may be classified according to its etiology into malignant, infectious, autoimmune, miscellaneous, and iatrogenic (due to medications). These broad categories can be easily remembered using the mnemonic MIAMI [14].

8.2.2.2 Pathological

In General, CLA may be due to lymphoid hyperplasia or infiltration [15].

1. Lymphoid hyperplasia is further subclassified, based on the anatomic and histopathology, into the following patterns: (1) follicular hyperplasia, (2) sinus hyperplasia, (3) paracortical hyperplasia, (4) necrotizing granulomatous lymphadenitis, (5) necrotizing

non-granulomatous lymphadenitis, and (6) acute lymphadenitis [12].

2. A lymph node may be infiltrated by malignant cells, in malignant lymphoma/leukemia, or by other cells, like lipid cells and glycogen-laden macrophages [15]. The former category includes a wide spectrum of lymphoid and hematopoietic neoplasms that are classified by the World Health organization (WHO) into (1) precursor B and T cell neoplasm, (2) mature B cell neoplasm, (3) mature T cell and NK cell neoplasm, (4) Hodgkin's lymphoma, (5) histocytic and dendritic neoplasm, and (6) post-transplantation lymphoproliferative disorders (LPDs) [16].
3. An additional pathological entity is spindle cell lesions of LN which include (1) bacillary angiomatosis, (2) Kaposi sarcoma, (3) palisaded myofibroblastoma, and (4) inflammatory pseudotumor of LN [17].

8.2.2.3 Clinical

- *Based on distribution*: CLA may be localized (only one area is involved), regional (two or more contagious areas are involved), or part of generalized (two or more noncontiguous areas are involved) [18].
- *Based on the duration*: CLA is further classified into acute (2 weeks duration), subacute (2–6 weeks duration), and chronic (does not resolve by 6 weeks).

8.2.3 Etiology

A wide range of causes can result in CLA (Table 8.2). A recent cross-sectional study has demonstrated that the most likely cause of CLA depends on the age group; reactive or nonspecific inflammation was the most common cause in those younger than 14 years; tuberculous

Table 8.2 Causes of CLA

I. Infectious	*II. Malignant*	*VI. Medications*
Viral	Hodgkin's lymphoma	Allopurinol
Infectious mononucleosis	Non-Hodgkin's lymphoma (NHL)	Atenolol
Infectious hepatitis	Acute lymphoblastic leukemia	Captopril
Herpes simplex	Chronic lymphoblastic leukemia	Carbamazepine
Rubella	Hairy cell leukemia	Cephalosporin
Measles	T cell lymphoma	Gold
Adenovirus	Multiple myeloma with amyloidosis	Hydralazine
HIV	Metastatic	Penicillin
Bacterial		Phenytoin
Streptococcus		Primidone
Staphylococcus		Pyrimethamine
Cat-scratch disease		Quinidine
Tularemia	*III. Immunological disease*	*VII. Miscellaneous*
Tuberculosis	Rheumatoid arthritis	Sarcoidosis
Syphilis	Systemic lupus erythematosus (SLE)	Histiocytosis X
leprosy	Sjogren's syndrome	Kikuchi's disease
Diphtheria	Drug hypersensitivity	Kawasaki's disease
Chlamydia	Silicone associated	Castleman's disease
Lymphogranuloma venereum	Serum diseases	Lymphomatoid granulomatosis
Trachoma	Graft versus host disease	
Rickettsial	*IV. Endocrine disease*	
Scrub typhus	Hyperthyroidism	
Rickettsial pox	Thyroiditis	
Fungal	Adrenal insufficiency	
Histoplasmosis	*V. Lipid storage disorders*	
Coccidiomycosis	Gaucher's disease	
Parasitic	Niemann-Pick's disease	
Toxoplasmosis		
Leishmaniasis		

Adapted from Sambandan et al. [13] and Upadhyay et al. [20]

lymphadenopathy was the predominant pathology in 14–59-year group, while cancer should be suspected if the patient is 60 years or older [19].

8.2.3.1 Infections

Cervical lymphadenopathy may occur when the draining nodes react to a nearby infection in the head and neck region including upper respiratory infection or when the infectious agent localizes in the node itself.

- *Acute bacterial infections* are most commonly caused by *Staphylococcus aureus* or *Streptococcus pyogenes* and should be suspected in patients with pustular or vesicular lesions of the face or scalp, history of earache or discharge, and history of sore throat or cough suggesting skin, ear, or upper respiratory infections, respectively. Infection with anaerobes like bacteroides may be suspected in patients with dental abscess or periodontal disease. *Pasteurella multocida* infection may follow animal bites, while *Yersinia pestis* infection may follow flea bites [21]. Clinically, adenopathy is often solitary unilateral and usually involving submandibular, upper deep cervical, submental, and occipital area in decreasing order of frequency. Enlarged LNs are tender and may be fluctuant, and the overlying skin is warm and erythematous [15]. The patient is feverish and usually has an evident source of infection.
- *Acute viral adenitis* typically follows an upper respiratory tract infection by rhinovirus, parainfluenza virus, influenza virus, respiratory syncytial virus, coronavirus, and adenovirus. Other less common etiologies are mumps, measles, rubella, varicella, and herpes simplex. Clinically, adenopathy is commonly multiple and bilateral. Lymph nodes are relatively small, typically not tender, and rarely suppurate, and the overlying skin is not warm nor erythematous. Patients usually have low-grade fever and commonly complaining of cough, rhinorrhea, conjunctivitis, or skin rash.
- *Infectious mononucleosis (IMN) is* particularly common in children and adolescents and is caused by Epstein-Barr virus which spreads primarily by saliva and replicates inside B lymphocytes and epithelial cells of the pharynx. Diagnosis is based on Hoagland's criteria: at least 50 % of lymphocytes and at least 10 % of atypical lymphocytes in the presence of fever, pharyngitis, and adenopathy. Cervical adenopathy usually involves the posterior group and may be associated with axillary adenopathy, inguinal adenopathy, or splenomegaly. Diagnosis should be confirmed serologically through the classic Paul-Bunnell test, which detect heterophil antibodies by agglutination of sheep red cells, or through the more sensitive detection of antibodies to viral capsid antigens [22].
- *Chronic infectious lymphadenopathy* is defined by failure to resolve or improve despite 2–6 weeks of appropriate therapy. Important causes of chronic infectious lymphadenopathy are detailed in the following sections.

Tuberculosis (TB)

Tuberculosis (TB) is an ancient multisystem disease that has been detected in Egyptian mummies dating to 5000 BC. It continues to be one of the most prevalent communicable diseases particularly among third-world countries. The developed countries witness a health challenge caused by TB because of increasing migration from developing countries and rising incidence of HIV in these countries [23]. The causative organism is *Mycobacterium tuberculosis*, though it can also be caused by other mycobacteria. Though TB can virtually involve any body organ, the lymphatic system is the most common site of extrapulmonary affection, within which cervical LNs are the most commonly involved [24]. The portal of entry usually determines the affected nodal group; involvement of jugulodigastric LNs usually denotes infection entering through tonsils or adenoids, while a pulmonary source is usually manifested by supraclavicular lymphadenopathy [25]. Histopathologically, tuberculous LNs demonstrate epithelioid, macrophages and giant cells, caseation necrosis, and scanty acid fast bacilli appearing as fragmented or beaded rods inside or outside cells [26].

In a study of 102 patients presenting with neck mass (Fig. 8.5) of tuberculous etiology, fever was present in 64 % of patients, weight loss in 42 %, and sweating in 18 % [24]. Locally, Jones and Campbell classified tuberculous lymphadenopathy into five distinct stages (Table 8.3) [27].

Syphilis

Syphilis is a sexually transmitted disease, caused by *Treponema pallidum*, which can invade mucous membranes not only of the genital region but also of the head and neck such as the lips, tongue, and tonsils. Clinically, chancre is usually present at primary site of infection; its absence, however, is reported in some cases in which diagnosis becomes more difficult. Enlarged LNs are multiple, firm, mobile, and not tender. Diagnosis is usually made serologically through rapid plasma reagin (RPR) test, *T. pallidum* hemagglutination assay (TPHA) test, and Venereal Disease Research Laboratory (VDRL) slide test [30, 31].

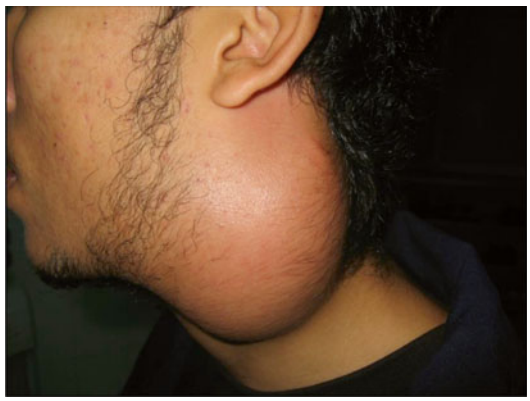

Fig. 8.5 Matted tuberculous cervical lymph nodes in a 23-year-old young gentleman

Cat-Scratch Disease

Cat-scratch disease is a zoonotic disease transmitted through cats, caused by *Bartonella henselae*. Diagnosis requires at least 2 of the following three criteria: (1) presence of typical clinical symptoms, (2) serological detection of antibodies against *B. henselae*, and (3) detection of Bartonella DNA in the extirpated lymph nodes. Clinical symptoms include fever, lymphadenopathy, asthenia, pharyngitis, laryngitis, and skin rash. Lymphadenopathy is the most common clinical manifestation with the cervical nodes being the most frequently involved [32].

Toxoplasmosis

Toxoplasmosis is a zoonotic disease transmitted through ingestion of undercooked meat containing oocytes of *Toxoplasma gondii* present in cat's feces. Cervical lymphadenopathy is present in 90 % of cases and may be associated with fever, sore throat, and myalgias. The nodal enlargement is usually solitary, discrete, mobile, and nontender [33].

Table 8.3 Stages of TB lymphadenopathy

Stage	Description	Pathogenesis	Clinical features
1	Discrete LNs	Nonspecific reactive hyperplasia;	Large, firm, and mobile LNs
2	Matted LNs	Periadenitis	Large and rubbery LNs, fixed to surrounding tissues
3	Cold abscess	Central softening and caseation deep to the deep fascia	Soft, smooth, nontender, fluctuant selling without involvement of the skin
4	Collar stud abscess	As a result of increased pressure caseous material perforates the deep fascia	Abscess is adherent to the overlying skin
5	Tuberculous sinus/ulcer	When the abscess bursts	Chronic nonhealing sinus or ulcer with thin, bluish, undermined edges and scanty watery discharge

Mohapatra et al. [28] and Thiagarajan et al. [29]

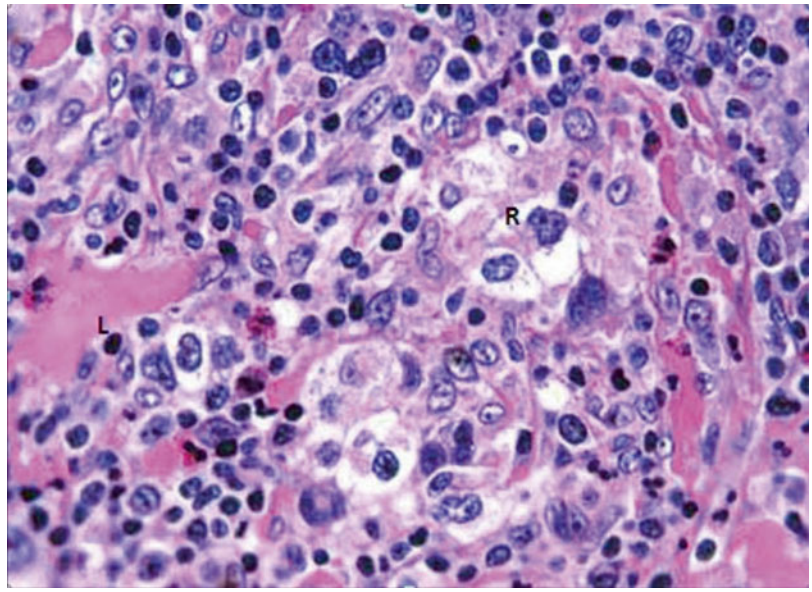

Fig. 8.6 H&E-stained section demonstrating classical pathology in Hodgkin's lymphoma (*L* lymphocyte, *R* Reed-Sternberg cells)

8.2.3.2 Malignancy

Although CLA is more commonly caused by a benign etiology, a sinister underlying malignant process is not uncommon, necessitating careful evaluation of such patients. Exclusion of malignancy is in fact the first and the single most important aim sought by the physician when evaluating CLA. The incidence of malignancy in patients with CLA seems to vary considerably with their demographics: age, gender, and race. The rate of malignant etiologies rises with *age*. A cross-sectional study by Biswas et al. [19] demonstrated that the rate of malignancy among patients with CLA was 12.1 %, 21.7 %, and 100 % in the age groups <14, 15–59, and ≥60 years, respectively. In their study, Shakya et al. [34] observed a malignancy rate as high as 50 % in patients with CLA in 51–60-year age group. Such high incidence of malignancy among the aforementioned age groups led to the belief that any neck mass in an adult should be suspected as malignant until proven otherwise [35]. *Gender* issue has also been studied with the uniform finding of higher frequency of malignancy among males [36]. Similarly, incidence of malignancy in patients with CLA differs among different *racial* groups. A malignancy rate as high as 50 % was observed among Iranians presenting with unknown neck masses [37], while it was 28.2 % and 4.8 % among Indians and Nepalese, respectively [19, 34].

Malignant cervical LNs may be caused by secondary metastasis from another primary or less commonly by lymphoma [19, 34]. However, in their audit of 140 patients with CLA, Magsi et al. [38] found that lymphoma was more common than metastasis. Among the latter group, Naeimi et al. [37] found that SCC was the most common pathology regardless of age with the larynx and hypopharynx being the most common sites of the primary tumor. Similar findings were reported by Biswas et al. [19] with adenocarcinoma coming second in frequency. Lymphoma, as a cause of malignant CLA, ranks the second in frequency with NHL being more common in some series [19], while others reported that Hodgkin's lymphoma was more common [37].

Histologically, the presence of Reed-Stenberg cells (large cells with abundant basophilic cytoplasm and multiple nuclei) in a background of inflammatory cells is characteristic of Hodgkin's disease (HD) (Fig. 8.6). The WHO classified HD into five subtypes according to the predominant cell types: (1) nodular sclerosis, (2) lymphocyte rich, (3) mixed cellularity, (4) lymphocyte depleted, and (5) nodular lymphocyte predominant [12]. In NHL, parafollicular or marginal

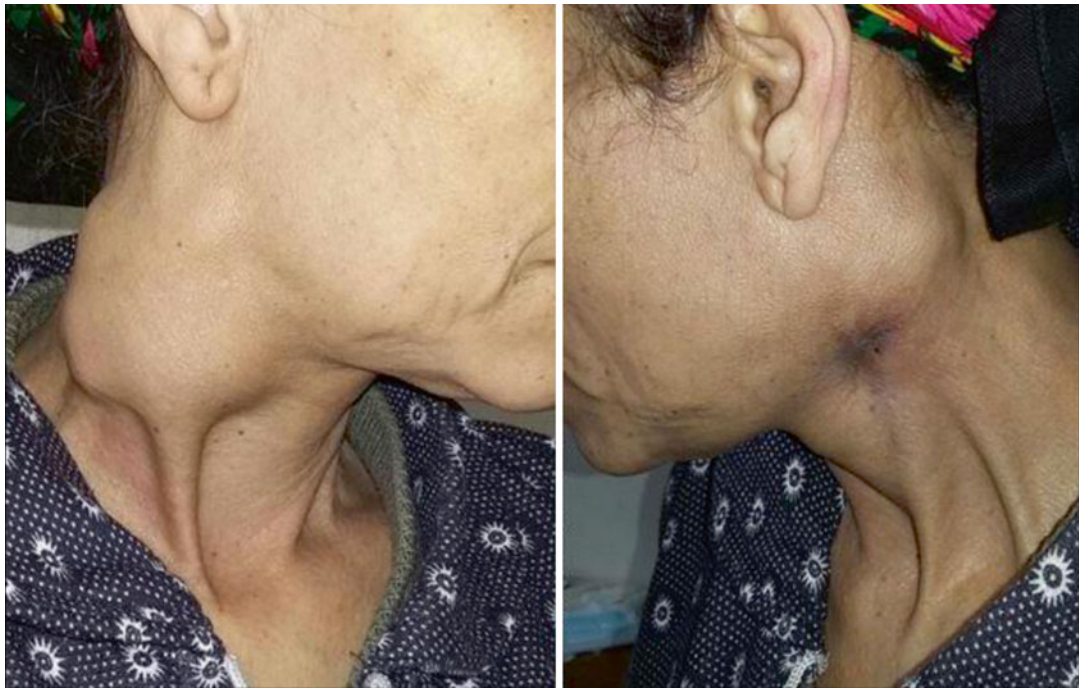

Fig. 8.7 Bilateral cervical lymphadenopathy, metastatic from unknown primary, in an old female patient

zone distribution of B cells occurs in nodal marginal zone b cell lymphoma, while complete, partial, sinus, or interfollicular involvement with variable cytology occurs in diffuse large B cell lymphoma, not otherwise specified [17].

Clinical features suggestive of malignant etiology of CLA include:

- *Generally:* NHL usually presents with generalized lymphadenopathy with or without hepatosplenomegaly, in contrast to Hodgkin's lymphoma in which the lymphadenopathy is initially localized and subsequently spreads orderly to contiguous nodal regions. Systemic manifestations like fever, weight loss, night sweats, and pruritus are called B symptoms and are suggestive of lymphoma: being less common in non-Hodgkin's type [18].
- *Regionally:* a pigmented skin lesion or mass that is mobile with deglutition may suggest metastatic deposits from nearby melanoma or papillary thyroid cancer [12].
- *Locally:* enlarged supraclavicular LN carries the highest risk of malignancy and should always be viewed with suspicion [39, 40]. Hard, fixed, painless lymph nodes are highly suggestive of metastatic deposits (Fig. 8.7), while rubbery or firm mobile nodes are more suggestive of lymphoma, though amalgamation (Fig. 8.8) and limitation of mobility may occur later [14].

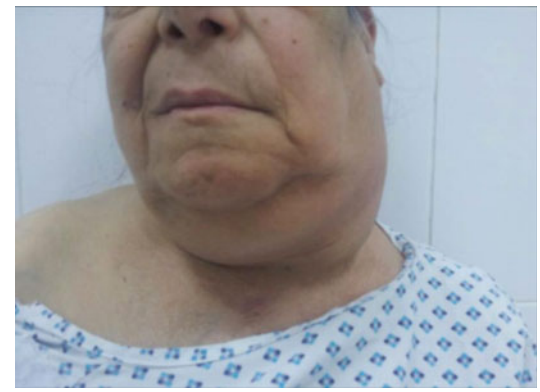

Fig. 8.8 Left-sided neck mass, turned out to be amalgamated LNs, in an old female with lymphoma

8.2.3.3 Autoimmune Disease

Lymphadenopathy is a detectable physical finding in up to 82 % and 69 % of rheumatoid arthritis

(RA) and systemic lupus erythematosus (SLE) cases, respectively, but it could also be seen in almost any autoimmune disorder. In these disorders, adenopathy of cervical nodes ranks second in frequency after axillary lymphadenopathy [41]. Histopathologically, inflamed nodes show reactive follicular hyperplasia, polyclonal plasma cell infiltration with occasional mitosis in the interfollicular area, moderate vascular proliferation, and no compression of reticulin fibers; this is to differentiate it from lymphoma in which interfollicular area shows many mitosis, scarce plasma cells, and compressed reticulin fibers [42].

When present, cervical lymphadenopathy is usually associated with axillary and/or inguinal lymphadenopathy. Lymph nodes are usually multiple, relatively small, soft, mobile, and not tender [43]. Diagnosis should be made on the ground of relevant clinical and laboratory criteria. Polyarthritis of small joints, lasting more than 6 weeks together with elevation of serum rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), and acute phase reactants (APR) is diagnostic for RA [44]. Presence of malar rash, discoid rash, nonerosive arthritis, photosensitivity, oral ulcers, and renal, neurologic, and hematologic disorders and elevated antinuclear antibodies and anti-DNA antibodies are diagnostic of SLE [45]. Dryness of the mouth and eyes is suggestive of Sjogren's syndrome [46].

8.2.3.4 Endocrine Disease

Sahlmann et al. [47] reported that cervical lymphadenopathy (levels II–IV, VI) occurred in more than 80 % of patients with autoimmune thyroiditis (AIT). Similarly, cervical lymphadenopathy was detected in 23 % of cases of Hashimoto's thyroiditis (HT) [48]. Graves' disease has also been reported to be associated with cervical lymphadenopathy [49, 50]. Pathology is reactive lymphoid hyperplasia. Therefore, AIT including HT should be included in differential diagnosis of patients with thyroid nodes and cervical LNs. Presence of cervical lymphadenopathy in a patient with clinical features of chronic adrenal insufficiency should alert the physician to the possibility of secondary adrenal involvement or to the very rare entity of primary adrenal lymphoma [51, 52].

8.2.3.5 Drug-Induced Lymphadenopathy

Certain medications can cause diffuse lymphadenopathy; of which phenytoin-induced lymphadenopathy is the most widely described in the literature. The reaction tends to occur few months after initiation of therapy and usually disappear within weeks after stopping drug administration. Pathophysiology is thought to be due to medication-induced immunologic disturbances, including reduced humoral and cellular immunity. Pathology usually reveals partial or complete effacement of the lymph node architecture by polymorphous infiltration of lymphocytes, plasma cells, and eosinophils [53, 54].

Phenytoin, in particular, has also been associated with a characteristic nodal pathology, termed pseudolymphoma. Differentiation from lymphoma is based on the absence of clonal proliferation of T cells. Clinically, cervical adenopathy tends to be bilateral and usually part of generalized lymphadenopathy. Condition is often associated with fever, rash, and eosinophilia. A high index of suspicion should always be kept since the condition can be easily confused with lymphoma. History of phenytoin exposure, improvement on phenytoin discontinuation, and pathological examination of a surgically excised lymph node are the clues to correct diagnosis [55].

8.2.3.6 Miscellaneous Causes of Cervical Lymphadenopathy

Kawasaki Disease (KD)

It is a type of systemic vasculitis of unknown etiology, also known as lymphocutaneous disease. It commonly occurs in children under 5 years of age. Cervical lymphadenopathy is present in approximately 42–65 % of KD patients [56]. Histopathologically, adenopathy is caused by sinus expansion and paracortical zone enlargement. Lymph nodes may also show ischemic changes in the form of necrotic foci, developing below the capsule and accompanied by fibrin thrombi in the surrounding small vessels [57]. Diagnosis should be clinically suspected in the presence of: (1) fever more than 5 days; (2) cervical lymphadenopathy, usually unilateral; (3) edema, erythema, and/or desquamation of the

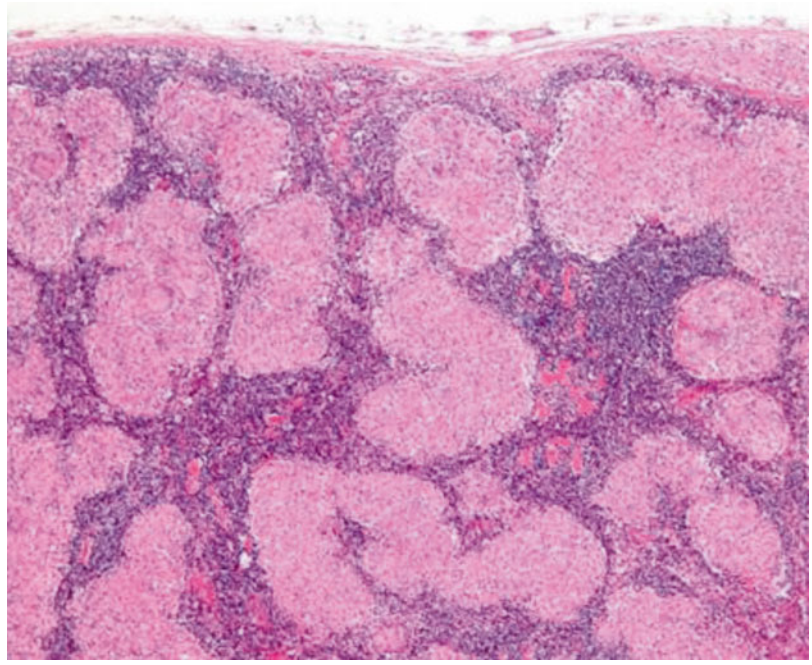

Fig. 8.9 H&E-stained section in an LN showing multiple sarcoid granulomas

palms and soles; (4) non-purulent bilateral conjunctivitis; and (5) strawberry tongue. A high index of suspicion should be kept when evaluating these children as the condition may be complicated by coronary artery abnormalities (aneurysm, thrombosis, infarctions) in 25 % of untreated children. Helpful laboratory data are elevated white cell count with neutrophilia and lymphopenia; elevated acute phase reactant, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR); and elevated liver enzyme, aspartate transaminase (AST) and alanine transaminase (ALT) [58].

Sarcoidosis

It is a multisystem chronic inflammatory condition of unknown etiology. Cervical lymphadenopathy is the most common head and neck manifestation of the condition, though it accounts only for 1.7 % of all head and neck lymphadenopathy. Histopathologically, it is characterized by the presence of noncaseating epithelioid cell granulomas (Fig. 8.9).

Diagnosis is usually established on the basis of compatible clinical and radiologic findings of hilar lymphadenopathy, pulmonary infiltration, and skin and ocular lesions. However, a diagnostic challenge arises when isolated cervical lymphadenopathy is the sole clinical feature. The latter condition usually necessitates exclusion of other granulomatous disease particularly tuberculosis, histopathological examination of surgically excised lymph node, and immunohistochemical detection of high expression of tumor necrosis factor-α (TNF-α) in epithelioid cells [59, 60].

Histiocytosis X

It is a rare disease predominantly affecting children. A controversy exists regarding its etiology: reactive versus neoplastic. Nodal involvement may be an isolated lesion or more commonly a part of systemic disease [61]. The pathological hallmark is presence of clonal proliferation of antigen-presenting dendritic cells called Langerhans cells (LCs) (Fig. 8.10): so-called Langerhans cells histiocytosis [59].

Clinically, the disease has a broad spectrum of severity. The mildest form is called eosinophilic granuloma and is characterized by solitary bone, skin, lung, or stomach lesions. The moderate form of the disease is called Hands-Schuller-Christian disease and is characterized by a triad of diabetes insipidus, exophthalmos, and lytic bone lesions. The most severe form is Letterer-Siwe disease and is a life-threatening multisystem disorder.

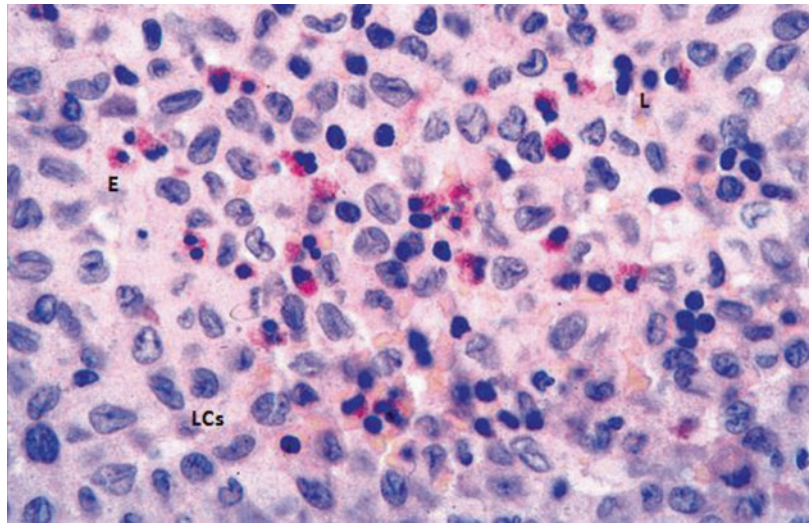

Fig. 8.10 H&E-stained section in a histiocytosis lymph node showing proliferation of Langerhans cell (*LCs*) and scattered eosinophils (*E*) and lymphocytes (*L*)

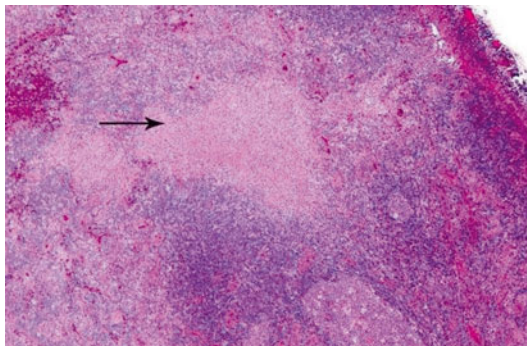

Fig. 8.11 H&E-stained section of an LN in Kikuchi-Fujimoto's disease showing area of necrosis (*arrow*)

Diagnosis can be made from fine-needle aspiration cytology which demonstrates many LCs through its characteristic nuclear features, namely, nuclear grooves and pseudoinclusions, as well as immunohistochemical detection of positivity for S-100, peanut agglutinin (PNA), MHC class II, CD1a, and langerin (CD207) [61].

Kikuchi-Fujimoto Disease (KFD)

It is a benign and self-limited disease, mainly affecting young Japanese women. Etiology is unknown; however, an infectious cause has been proposed. Histopathologically, the LN shows single or multiple areas of necrosis and histiocytic cellular infiltrate (Fig. 8.11), so-called histiocytic necrotizing lymphadenitis. Clinically, patients usually present with localized lymphadenopathy, fever, and leucopenia. The disease may be associated with autoimmune phenomena and may occur in the setting of SLE [62].

Castleman's Disease

It is a lymphoproliferative disorder (LPD) of unknown etiology. Histopathologically, LNs show follicular hyperplasia and marked capillary proliferation with endothelial hyperplasia. Two pathological types have been identified: hyaline vascular type and plasma cell type (Fig. 8.12) [63]. Clinically, there are two variants: unicentric and multicentric. In unicentric variant, the patient is often asymptomatic, and the disease is usually discovered accidentally on imaging which usually detects hilar or mediastinal lymphadenopathy. The multicentric type is a systemic disease, usually presenting with significant peripheral lymphadenopathy and hepatosplenomegaly as well as frequent fevers, night sweats, and fatigue [54]. Diagnosis is based on clinical suspicion, histological examination, and immunohistochemical detection of increased expression of vascular endothelial growth factor [64].

8.2.4 Neck Staging Under the "TNM Staging System" for Head and Neck Tumors

(*AJCC head and neck tumor staging by site* [3])

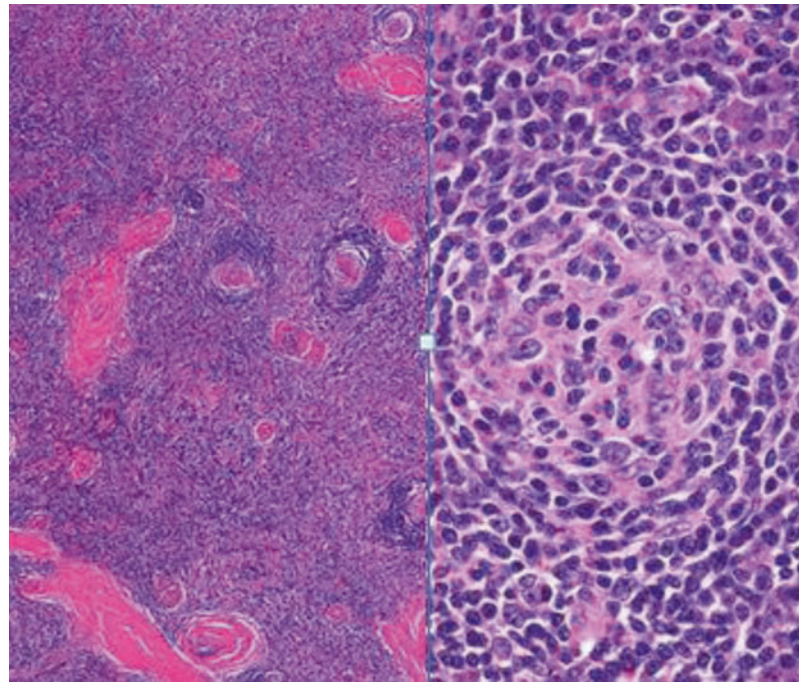

Fig. 8.12 H&E-stained section in lymph nodes with Castleman's disease (hyaline cell type on the left; plasma cell type on the right)

This staging system excludes the nasopharynx and thyroid.

8.2.4.1 Regional Lymph Nodes (N)

Nx: Regional LNs cannot be assessed
N0: No regional LNs metastasis
N1: Metastasis in a single ipsilateral LN, 3 cm or less in greatest dimension
N2: Metastasis in a single ipsilateral LN, >3 cm but not >6 cm in greatest dimension; in multiple ipsilateral LNs, none >6 cm in greatest dimension; or in bilateral or contralateral LNs, none >6 cm in greatest dimension
N2a: Metastasis in a single ipsilateral LN, >3 cm but not >6 cm in greatest dimension
N2b: Metastasis in multiple ipsilateral LNs, none >6 cm in greatest dimension
N2c: Metastasis in bilateral or contralateral LNs, none >6 cm in greatest dimension
N3: Metastasis in LNs more than 6 cm in greatest dimension

*Note: A designation of "U" or "L" may be used for any N stage to indicate metastasis above the lower border of the cricoid cartilage (U) or below the lower border of the cricoid cartilage (L). Similarly, clinical/radiological extracapsular spread (ECS) should be recorded as E− or E+.

8.2.4.2 Nasopharynx

Nx: Regional LNs cannot be assessed
N0: No regional LN metastasis
N1: Unilateral metastasis in cervical LN(s), 6 cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral retropharyngeal LNs, 6 cm or less in greatest dimension
N2: Bilateral metastasis in cervical LN(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
N3: Metastasis in LN >6 cm and/or to supraclavicular fossa
N3a: >6 cm in dimension
N3b: Extension to the supraclavicular fossa

*Note: Midline nodes are considered ipsilateral nodes.

8.2.4.3 Thyroid Gland

Regional LNs are the central compartment, lateral cervical, and upper mediastinal LNs.

Nx: Regional LNs cannot be assessed
N0: No regional LN metastasis
N1: Regional LN metastasis
N1a: Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian LNs)

N1b: Metastasis to unilateral, bilateral, or contralateral cervical (level I, II, III, IV, or V) or superior mediastinal LNs (level VII)

8.2.4.4 Mucosal Melanoma

Regional LNs are the central compartment, lateral cervical, and upper mediastinal LNs.

Nx: Regional LNs cannot be assessed
N0: No regional LN metastases
N1: Regional LN metastases present

8.2.4.5 Carcinoma of Unknown Primary (CUP)

Carcinoma of unknown primary site (CUP) represents around 5–10 % of all tumors; those are malignancies presenting with LN metastasis, while efforts for identification of the primary site of malignancy fail [65, 66].

A fair fraction of CUP presents with cervical nodal metastasis, SCC being the most common histological type, followed by adenocarcinoma, undifferentiated malignancy, and others including melanoma and lymphoma. Such affection is commonly unilateral with level II LNs being the most commonly affected group followed by level III. Generally speaking, upper and middle neck LN affections originate from the head and neck region, while isolated lower neck LN affections are usually associated with malignancies below the clavicles [67–69].

Nearly 25 % of malignancies in the pediatric population occur in the head and neck region, where the cervical nodes represent the most common site. Neuroblastoma and leukemia are the most common malignancies associated with cervical nodes during the first 6 years of life, followed by rhabdomyosarcoma and NHL. After 6 years, Hodgkin's lymphoma (HL) has the highest prevalence, followed by both NHL and rhabdomyosarcoma [70].

8.3 Diagnostic Approach

The diagnosis of the etiology of CLA should proceed in a step-by-step fashion, starting with careful history taking, examination, and investigative workup if necessary.

The value of patient history does vary widely. It can point directly to the cause and suggest the possible etiology or it can be nondiagnostic [71, 72].

The first target during the evaluation of CLA is to determine whether it is of the localized or generalized variety. Factors related to the size, consistency, and mobility of the LNs should also be considered as they may point clearly to a malignant nature.

When dealing with localized cervical lymphadenopathy, the draining sites of the affected levels should be thoroughly examined for sources of infection or possible malignant lesion. If the history and examination reveal a source of infection, then no further workup is required and treatment can be initiated. However, follow-up for adequate response is mandatory.

8.3.1 History Taking

The following factors should be considered during history taking:

Age: The probability of malignant nature is higher in older age populations. Data from one study performed in a referral center showed that 79 % of biopsies performed in young patients (<30 years) were of benign nature, while 60 % of biopsies from older patients (>50 years) showed malignant etiology [73].

Symptoms of infection: Fever, conjunctivitis, sore throat, dental pain, ulcers, or discharge. Night sweats and shivers can suggest tuberculosis (TB).

Localized symptoms of malignancy: Hoarseness of voice, dysphagia, stridor, ulcers, and pain should be sought, especially when a high index of suspicion is available.

Generalized symptoms of malignancy: Weight loss: an unexplained weight loss of more than 10 % during a period of 6 months should raise suspicion of lymphoma [74].

Symptoms of collagenic disease: Arthralgia, joint deformities, or myalgia.

Medical history: Allergies to certain drugs are common causes for lymphadenopathy (e.g., phenytoin).

Occupational and epidemiological exposures: History of a high-risk behavior, recent traveling to high-risk regions, or exposure to pets or specific occupational hazards can all suggest a specific underlying etiology, sometimes of a rare incidence.

Duration and response to previous medications: A short history of lymphadenopathy may favor acute infectious etiologies (viral, bacterial, etc.), while persistent nodal enlargement (more than 4 weeks) accompanies chronic infections, collagenic diseases, and malignancies. Also, response to previous medications (e.g., antimicrobials) may help validate the underlying pathology.

8.3.2 Physical Examination

The key features that should be sought are:

Distribution: It is crucial to determine whether the cervical lymphadenopathy is isolated (localized, enlargement of LNs in one region), regional (enlargement of LNs in 2 or more contiguous regions), or part of generalized lymphadenopathy (enlargement of LNs of 2 or more noncontiguous regions). Generalized lymphadenopathy accompanies systemic diseases specially if associated with splenomegaly. In the neck, supraclavicular LNs drain the gastrointestinal tract, genitourinary tract, and lungs. Enlarged supraclavicular LNs should raise a strong suspicion of malignancy as an underlying malignancy occurs in 54–85 % of cases [73, 75–77].

Size: The LNs of subcentimeter diameter are usually of no clinical significance, while LNs more than 2 cm in size of persistent nature mandate thorough diagnostic workup [72].

Mobility: Fixed LNs suggest metastatic causes, while freely movable nodes have a wide range of underlying etiologies including primary malignancies (e.g., lymphoma). Evaluation of supraclavicular LN mobility can be aided by performance of Valsalva maneuver.

Consistency: Hard LNs usually suggest a malignant nature. However, other forms of consistency can still accompany malignant nodes, and therefore consistency should not be relied upon for differentiation of the nodal nature. A tender LN can point out an underlying inflammatory process [78].

8.3.3 Investigations

If history and physical examination are diagnostic of infectious cause (bacterial), treatment should be initiated without further workup. If they are suggestive of viral causes, follow-up and/or specific serological tests can be done.

In case of low estimated risk of malignancy, patients with localized LNs and nondiagnostic initial workup can be followed up for 4 weeks. Empirical antimicrobials and steroids should be avoided for their lympholytic effect thus affecting the results of biopsy.

8.3.3.1 Imaging Modalities

Ultrasonography (US)

Ultrasonography (US) is the primary diagnostic technique that can be used when the clinical examination is not directly diagnostic of the nature of the LNs. The main target of ultrasonographic examination is to distinguish reactive, tuberculous, lymphomatous, and metastatic LN etiologies. This can be achieved by analysis of various nodal parameters.

Reactive LNs

Typical features include a low short-axis-to-long-axis ratio (S/L < 0.5) except for parotid and submandibular regions where they usually attain a more rounded contour (S/L = or > 0.5), together with the absence of suspicious criteria including irregular margins, peripheral halo, internal echoes, and tendency for fusion. Doppler US cannot distinguish inflammatory and neoplastic LNs on the basis of their flow patterns [61, 79].

Reactive LNs are usually found in the upper part of the neck (submandibular, parotid, and upper cervical) and the posterior triangle. Another important feature is the preservation of the echogenic hilum representing hilar

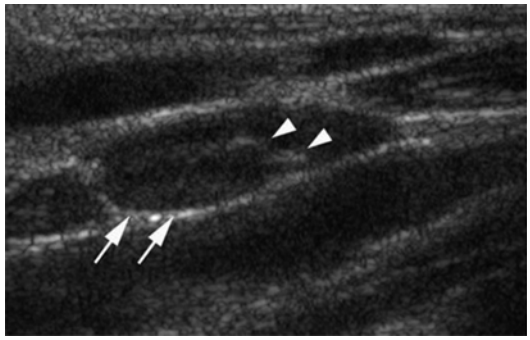

Fig. 8.13 Ultrasound showing reactive LN (*white arrows*) maintaining its echogenic hilum (*arrow heads*)

vascularity, which can be further confirmed by color Doppler [79]. Spectral Doppler US shows low vascular resistance in reactive LNs (resistive index, RI, and pulsatility index, PI) [80].

Regarding the size, 9 mm is the upper limit for the minimal axial diameter in both the submandibular and the subdigastric nodes, while 8 mm is the upper limit for the other cervical LNs (Fig. 8.13) [81].

Tuberculous LNs

Features include the presence of fusion tendency (nodal matting), hypoechoic core, posterior enhancement, multiple LNs, adjacent soft tissue edema (displays as a peripheral halo), and the presence of strong internal echoes denoting calcifications, caseation, and granuloma formation [61, 82, 83].

In a retrospective study, presence of strong echoes or a thin echogenic layer had a sensitivity and specificity of 100 % in distinguishing tubercular from malignant LNs [83]. Cystic necrosis is also common in tuberculous LNs resulting in displaced hilar vascularity on Doppler studies (Fig. 8.14) [79, 84].

Lymphomatous LNs

They usually attain a rounded contour, are hypoechoic with absent echogenic hilum, and may show intra-nodal reticulation [85]. On Doppler studies, they show mixed or peripheral vascularity with increased vascular resistance on spectral Doppler US. These features are similar in both Hodgkin's and NHL [79]. In one study, the main distinguishing feature of such LNs was

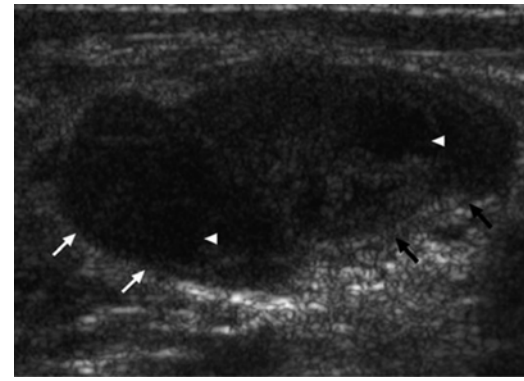

Fig. 8.14 Ultrasound showing tuberculous LN (*arrows*) with internal caseation (*arrow heads*)

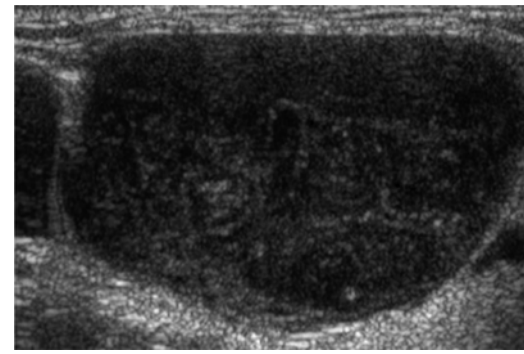

Fig. 8.15 Ultrasound showing LN with NHL

the homogenous pattern (no echogenic foci) [61]. However, another study demonstrated a heterogeneous micronodular pattern in most of the examined lymphomatous nodes (Fig. 8.15) [85].

Metastatic LNs

Metastatic malignant LNs usually display a rounded contour with hypoechoic nature with absence of an echogenic hilum. Echogenic foci may also be evident as a sign of coagulation necrosis. Evidence of intra-nodal cystic necrosis should suggest a metastatic nature, a pattern common in metastases from SCC [79]. Metastatic LNs from papillary thyroid carcinoma may display hyper-echogenicity, and punctate calcifications may also be present [80]. Extracapsular spread of the tumor should be suspected when the nodes acquire an ill-defined outline [79]. On color and power Doppler, metastatic LNs show mixed or peripheral vascularity [80].

Ultrasonography is being increasingly used as a great noninvasive modality to differentiate normal and abnormal nodes, where grayscale US has a sensitivity and specificity of 95 and 83 % in categorizing LNs into reactive and metastatic nodes [80]. However, distinguishing lymphomatous, metastatic, and tuberculous LNs can be a more complicated task due to overlapping parameters and relies on the common sonographic features in each category [61]. Doppler studies are essential in the setting of equivocal grayscale US results. One study demonstrated that power Doppler US helped in the correct identification of 17 % of patients with reactive LNs and 5 % of patients with metastatic malignant LNs [86].

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

The main application of CT for cervical nodal assessment is in the setting of evaluation of metastatic LNs in the head and neck region in different clinical scenarios:

I. Documented head and neck malignancy by biopsy or other imaging technique with no clinically palpable LNs, for confirmation of the N0 state as any evidence of nodal metastasis will alter both the staging and management of the tumor. It should be noted that cervical LNs metastasis represents the most important prognostic factor for squamous cell carcinoma (SCC) as it decreased the overall survival by 50 %; another 50 % worse prognosis would be expected on evidence of extracapsular extension [87–89]. At the same time, the level, number, and dimensions of the affected LNs have their clinical implications and are proved to correlate with distant metastases [87, 90].
II. Documented head and neck malignancy with palpable LNs on one side of the neck, for evaluation of the contralateral neck side. During evaluation, nodal necrosis should be considered the most important criterion for detection of metastatic LNs in the setting of head and neck cancer with specificity around 95 to 100 %; this appears as focal hypoattenuation of CT and T2 hyperintensity on MRI with peripheral nodal enhancement [91]. Detection of necrosis and cystic changes in LNs not qualifying to be considered metastatic on size basis is crucial during the evaluation process.

Size of the cervical LNs should not be a definitive criterion to exclude malignancy, as LNs less than 1 cm in the largest diameter can still contain malignant tissue and expanding the cutoff size to 1.5 cm in some centers can result in higher rates of false-negative findings.

For proper evaluation, the radiologist should be aware of both the simplified level classification of cervical LNs for easier communication with surgeons and pathologist and the drainage patterns of different head and neck malignancies, meticulous examination of the commonly affected levels is crucial before declaring the neck as N0. A finding of a less commonly affected level in the context of evaluating a certain malignancy should warrant reexamination of the more commonly affected nodes.

The ability of CT to detect micrometastases is restricted. Thus, tumors with high tendency for sending micrometastases are usually managed by neck dissection procedures even if no positive LNs are detected.

Extracapsular extension of tumor tissue has its significant impact in both the prognosis and probability of distant metastasis. However, this does not affect the staging of head and neck malignancies. It should be noted though that CT is not precise in detection of such extension.

III. For evaluation of carotid artery invasion by metastatic nodal tissue.

In many centers and in various clinical scenarios, carotid artery invasion by tumor tissue renders the tumor irresectable (although different surgical techniques may be pursued). Thus, detection of such invasion has a great influence on the planned management. Unfortunately, CT is not precise in detection of direct carotid artery invasion. The reliance on the contact surface alone between tumor tissue and carotid artery can

be hugely misleading as a single focal contact can be accompanied by evident intraoperative invasion. Studies show no superiority in CT for detection of carotid artery invasion compared to Doppler studies.

IV. For postoperative follow-up for evidence of recurrent primary and nodal disease.

The CT is a valuable tool in postoperative survey of recurrence at the primary site or at the nodal levels, where radiotherapy and postoperative fibrosis result in difficult LN palpation.

V. In case of metastatic LN proven by biopsy without a clinically proven source of primary (CUP) for the detection of the primary site of malignancy.

Computed tomography of the head and neck, chest, and abdomen can help localize the site of clinically non-evident malignancy. Careful examination of aerodigestive mucosa is mandatory as a finding of focal thickening may save the patient from more aggressive and invasive diagnostic approaches.

It should be noted that a finding of cystic LN in young patients can point out occult metastasis of thyroid origin; this finding can be mistaken with developmental cystic lesions of the neck in this age group.

Other Imaging Modalities

Other imaging modalities such as *FDG-PET scan* has a high sensitivity for detection of affected LNs. Also, it has a great role in the diagnostic approach for carcinoma of unknown primary (CUP). It has been shown to allow the detection of primary malignancy in 25 % of these cases (PET-CT). However, it can give false-negative results in cases of metastasis from papillary or medullary thyroid cancers.

Another modality is the *MRI diffusion*, which is being widely tested for better precision in detection of affected LNs.

8.3.3.2 Biopsy

Biopsy is required for generalized lymphadenopathy when the initial workup is nondiagnostic and for persistent CLA with a high estimated risk of malignancy.

Excisional Biopsy

Excisional biopsy is required to diagnose and grade lymphoma into Hodgkin's and non-Hodgkin's varieties. It should be taken from the most abnormal or the largest LN site. However, inguinal LN biopsy should be avoided for its low diagnostic yield. In the setting of high estimated risk of malignancy, an unrevealing biopsy should be considered nondiagnostic rather than negative biopsy, and further workup is required. If results of biopsy show atypical lymphoid hyperplasia, this again should be considered nondiagnostic and further workup including another biopsy should be considered. Tissue biopsy of LNs remains a standard requirement whenever a reactive nature of LNs due to a bacterial or viral cause cannot be confirmed by imaging or serological tests.

Core Needle Biopsy

An US-guided core needle biopsy using automated needles allows for a larger yield of tissue sample and obtaining a specimen with preserved histological architecture allowing for more precise diagnosis and allows for the use of various histological and immunohistochemical techniques. Also, a biopsy obtained by core needle technique may suffice for typing of lymphoma without further need of excisional biopsy.

In a study evaluating 247 patients with cervicofacial lymphadenopathy, US-guided core needle biopsy was shown to have a specificity of 100 %, sensitivity of 98.1 %, and accuracy of 98.7 % in differentiating benign from malignant LNs. In the same study, 80 % of cases of lymphoma could proceed to treatment without the need of excisional biopsy [92].

Traditionally, disadvantages include the probable injury to neural or vascular elements (this can be improved by using imaging guided biopsy) and tumor cell spillage (needle-track metastasis). However, Southam et al. [93] found no cases of track metastasis during a period of 7 years follow-up after applying cutting needle biopsies in head and neck lesions in a large series.

It would be wise to utilize core needle biopsy when results of FNAC are equivocal and a high index of suspicion is present, especially when

excisional biopsy carries a higher risk for the patient considering his general medical condition or impossible due to fixation of the nodal tissue to surrounding structures. Also, core needle biopsy can be a time-saving replacement for typing of lymphoma if a sufficient yield can be obtained instead of excisional biopsy, as this usually requires hospitalization and general anesthesia. Still, an equivocal result with considerable suspicion requires repeating the core needle biopsy or open excisional biopsy.

8.4 Technique of Modified Radical Neck Dissection (MRND) [94, 95]

Different neck incisions are described for MRND. Classically, the Kocher transverse collar incision can be extended laterally providing adequate exposure in most cases. This incision is known as *half apron incision*, which carries favorable cosmetic results (Figs. 8.16 and 8.17). The bilateral extension of Kocher incision is called "*apron incision*." Good exposure can also be achieved by a vertical extension toward the angle of the jaw. However, cosmetic results are less favorable. A horizontal incision in the upper part of the neck in parallel to the initial incision results in better cosmesis.

Dissection then proceeds in the sub-platysmal plane and anterior to the external jugular vein (EJV) for proper elevation of the upper flap (Fig. 8.18).

Care should be taken during the advancement of the cranial flap, as vigorous retraction may result in injury of the marginal mandibular branch (MMB) of the facial nerve as it runs in a level just below the mandible. Such injury will result in dribbling from the angle of the mouth and deviation of this angle toward the sound (healthy) side.

The SCM muscle can usually be preserved and retracted medially or laterally. Fascia over the SCM is then incised longitudinally over its length and gently dissected. The great auricular nerve (GAN) and EJV should be preserved whenever possible and retracted in a posterior direction (Fig. 8.19).

The anterior section of the superficial fascia is then dissected from the SCM muscle. It is thus

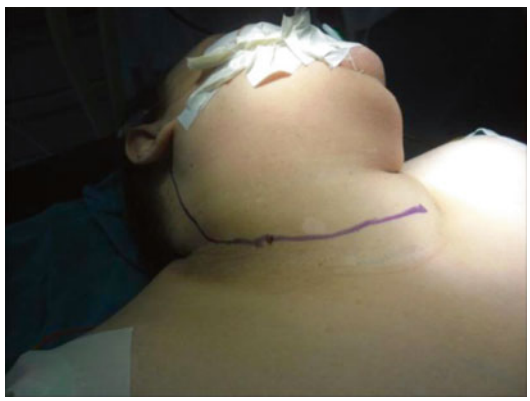

Fig. 8.16 The marked site of skin incision (half apron incision)

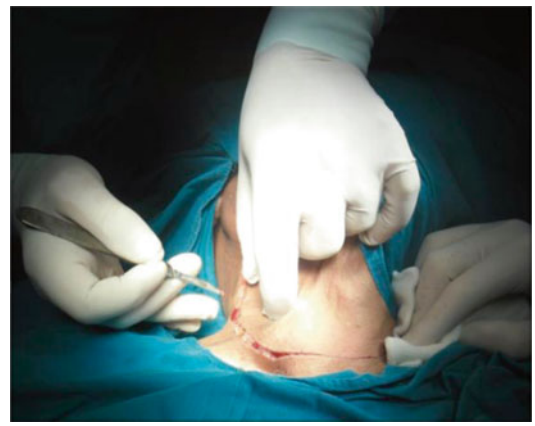

Fig. 8.17 Skin incision (half apron incision)

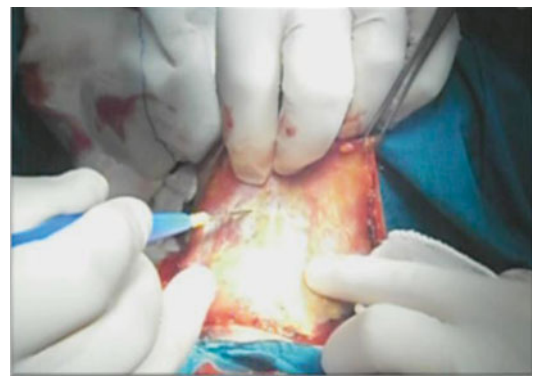

Fig. 8.18 Upper flap elevation

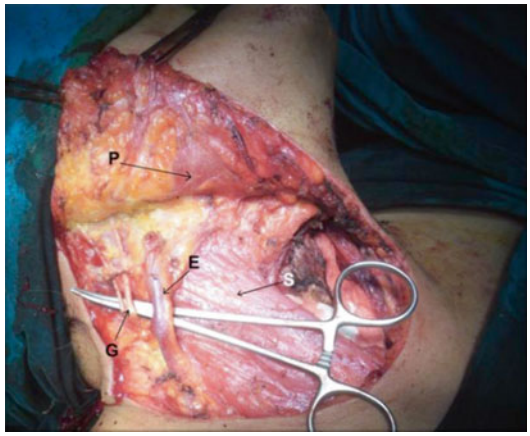

Fig. 8.19 Upper flap elevated, showing SCM muscle (*S*), platysma (*P*), external jugular vein (*E*), and great auricular nerve (*G*)

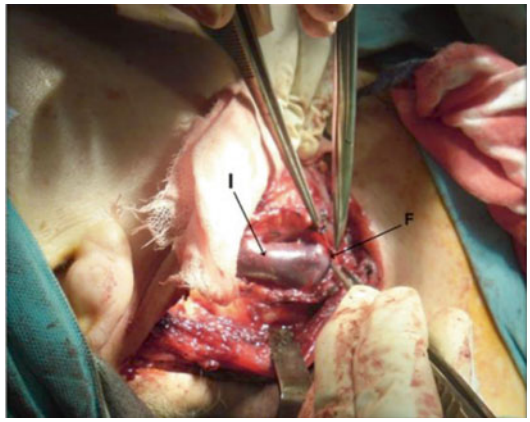

Fig. 8.20 Level III dissection, showing IJV (*I*) and fascia over it (*F*)

left in continuity with the fascia covering the IJV and its related chain of LNs. Dissection then follows either medially at the junction of the lower part of the IJV and the clavicle or laterally at the junction of the anterior border of the trapezius muscle and the clavicle.

On the left side, the thoracic duct should be identified just above the junction of the innominate vein, IJV, and subclavian veins. Distention of the duct can be achieved by gentle compression over the surrounding areolar tissue making its identification easier (Fig. 8.20). If injured, the thoracic duct should be ligated and divided or else a chyle fistula may result.

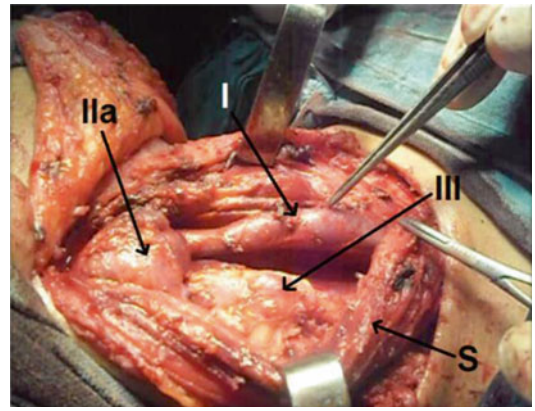

Fig. 8.21 Level III anatomical cervical level of the LNs dissected, showing IJV (*I*) and SCM muscle retracted (*S*)

The IJV is dissected free from its surrounding LN-bearing tissue, which contains the beginning of the MRND. Special attention must be drawn to the lower jugular nodes, which are located behind the vein. The vein should be retracted either medially or laterally to obtain a good view of this area (Fig. 8.21). This retraction should be done gently to avoid tearing the vein, which might cause air embolism.

One should then proceed with careful dissection to expose the carotid artery, sympathetic chain, and vagus nerve. The LN-containing fatty tissue is mobilized laterally and superiorly along the clavicle, creating the inferior border of the lateral compartment dissection specimen. At this stage of the operation, care should be taken to avoid injury of the pleura. The phrenic nerve is identified as it runs obliquely on the scalenus anterior muscle. The brachial plexus is identified between the scalenus anterior and medius muscles (Figs. 8.22 and 8.23).

The anterior border of the trapezius muscle is dissected, and the spinal accessory nerve (SAN) is identified approximately 1 cm anteriorly from the margin of the muscle. The trapezius muscle represents the lateral border of the lateral neck compartment. The SAN runs parallel to the trapezius muscle over the levator muscle of the scapula. The nerve itself is rarely invaded by tumor but is often surrounded by LNs. It should be carefully dissected from the adjacent tissues upward to the cranial part of the SCM muscle (Figs. 8.24 and 8.25).

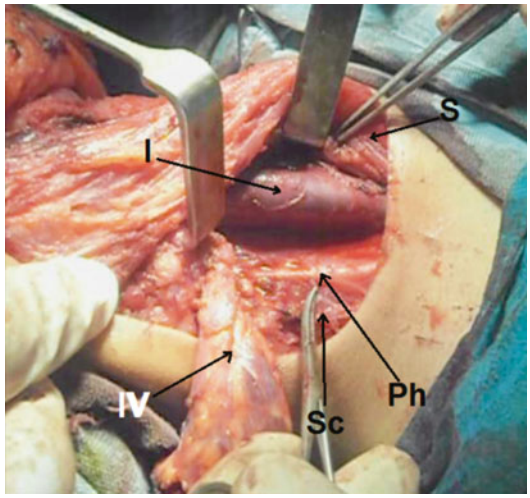

Fig. 8.22 Level IV dissection at right side, showing IJV (*I*), SCM muscle retracted (*S*), phrenic nerve (*Ph*), and scalenus anterior (*Sc*)

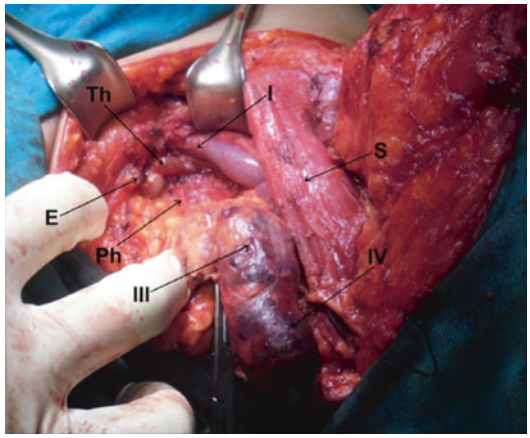

Fig. 8.23 Levels III and IV dissection at left side, showing IJV (*I*), SCM muscle retracted (*S*), phrenic nerve (*Ph*), thoracic duct (*Th*), and scalenus anterior (*Sc*)

A plexus of branches from the cervical sensory nerves (lesser occipital, greater auricular, supraclavicular, and transverse cervical nerves) is located caudal and parallel to the SAN and the phrenic nerve, and these nerves should be preserved when possible (Fig. 8.26). The GAN turns toward the SCM muscle near this point (Fig. 8.27). In this area, too, care must be taken to preserve the branch of the occipital artery, which vascularizes partly the SCM muscle.

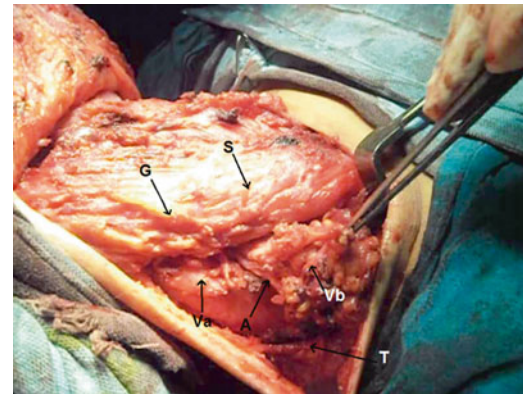

Fig. 8.24 Level V dissection, showing level Va, level Vb, accessory nerve (*A*), trapezius muscle (*T*), great auricular nerve (*G*), and SCM muscle (*S*)

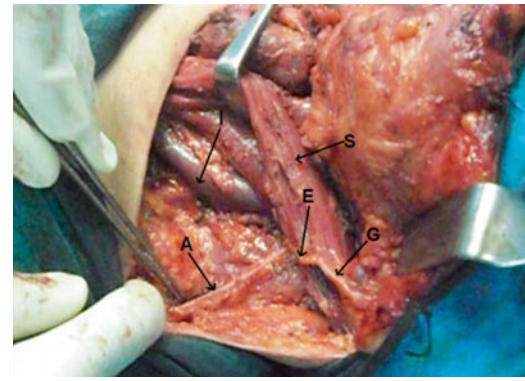

Fig. 8.25 Level V dissected, showing accessory nerve (*A*), great auricular nerve (*G*), Erb's point (*E*), SCM muscle retracted (*S*), and IJV (*I*)

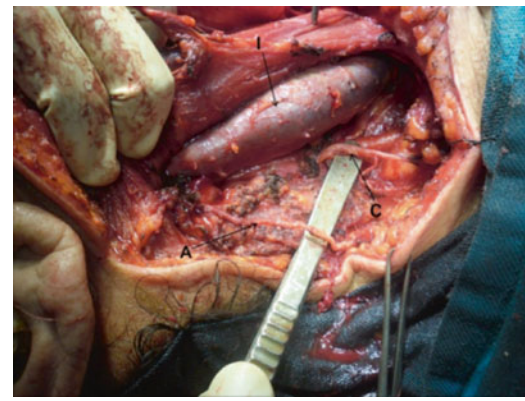

Fig. 8.26 Level V dissected, showing accessory nerve (*A*), branch from cervical plexus (*C*), and IJV (*I*)

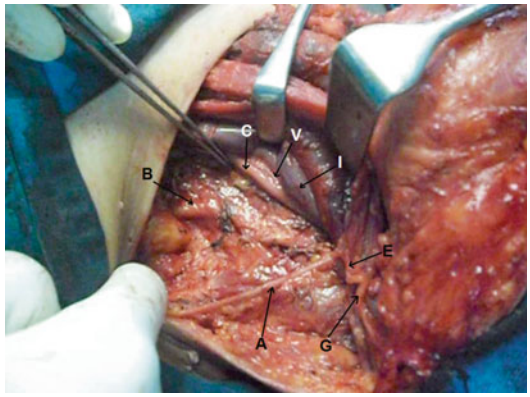

Fig. 8.27 Levels III, IV and V dissected, showing accessory nerve (*A*), great auricular nerve (*G*), Erb's point (*E*), IJV retracted (*I*), common carotid artery (*C*), vagus nerve (*V*), and trunks of brachial plexus (*B*)

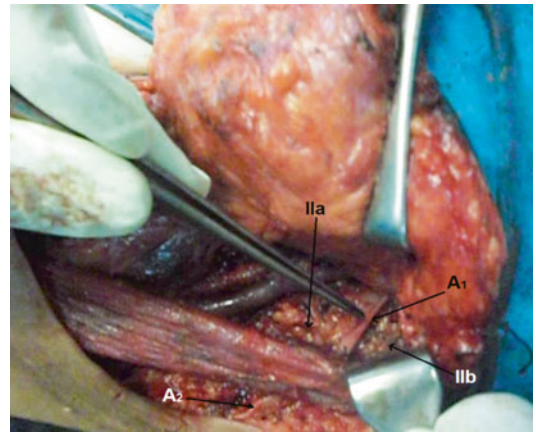

Fig. 8.29 Level II dissected, showing level IIb, level IIa, accessory nerve at level II (A_1), and accessory nerve at level V (A_2)

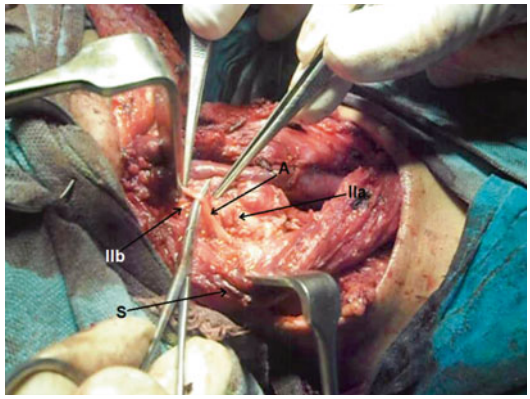

Fig. 8.28 Level II dissection, showing level IIb, level IIa, accessory nerve (*A*), and SCM muscle retracted (*S*)

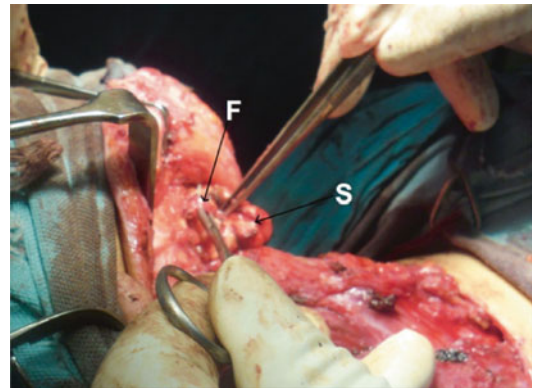

Fig. 8.30 Level I dissection, showing submandibular gland (*S*), and facial artery (*F*)

The occipital artery represents the upper posterior limit of the dissection of the lateral compartment. The dissection continues to the prevertebral fascia. The tissue behind and above the SAN is mobilized from the nerve itself and is dissected upward from the levator muscle of the scapula and splenius muscle of the head (Fig. 8.28).

The inferior, lateral, and upper posterior parts of the dissection are completed, and the specimen is passed underneath the SCM muscle, which is now retracted laterally. The anterior part of the specimen is freed from the carotid sheath and jugular vein, and the dissection continues superiorly along the jugular vein, mobilizing the mid- and upper jugular LNs (Fig. 8.29).

The hypoglossal nerve, which runs behind the facial vein, is identified. Sometimes the facial vein has to be ligated and transected to obtain an adequate exposure to the hypoglossal nerve while removing the upper jugular LNs. The submandibular gland and surrounding nodes are removed en bloc as a level I dissection (Fig. 8.30). The procedure is begun by incising the fascia below the gland, dissecting it up, and identifying the anterior belly of the digastric muscle, clearing the submental fat, and elevating the fascia and LNs from the lateral surface of mylohyoid muscle.

The lateral superior fascia and vessels are divided earlier when the marginal nerve was identified. Care must be taken to include the

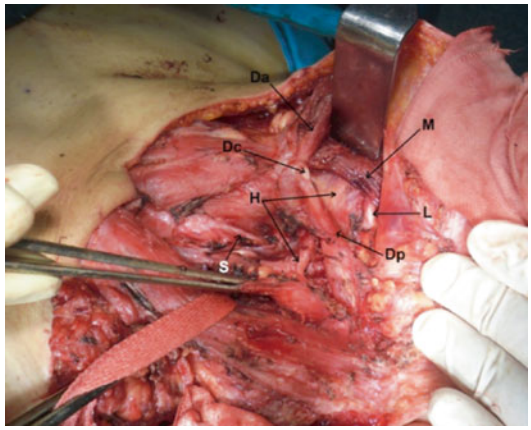

Fig. 8.31 Level I dissected, showing anterior belly (*Da*), central tendon (*Dc*), posterior belly (*Dp*) of digastric muscle, mylohyoid muscle (*M*), lingual nerve (*L*), hypoglossal nerve (*H*), and superior thyroid artery (*S*)

submental fat pad in the specimen, which is performed by grasping the fat pad just medial to its attachment to the anterior belly of the digastric muscle and dissecting the midline tissue in the submental triangle in an inferior direction.

The mylohyoid muscle is then retracted anteriorly, exposing the lingual nerve. The attachments of the gland to the lingual nerve at the submaxillay ganglion are divided and ligated, and the submandibular duct is divided and ligated (Fig. 8.31).

The gland is retracted inferiorly with the attached pre-vascular nodes on its lateral surface. Leaving the fascia attached to the submandibular gland inferiorly will allow the contents of level I to remain a part of the ND specimen. The specimen can now be removed. Careful hemostasis is performed, and suction drains are often used. The platysma muscle is approximated and the skin is closed (Figs. 8.32, 8.33, 8.34, 8.35, and 8.36).

In the classical radical neck dissection (RND), excision of SCM muscle, SAN, and IJV is performed (Figs. 8.37 and 8.38).

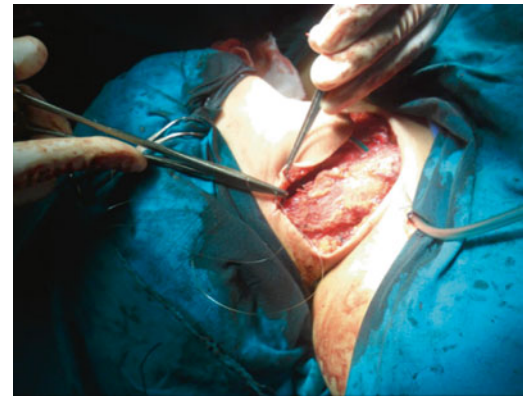

Fig. 8.32 Closure of platysma with drain inserted

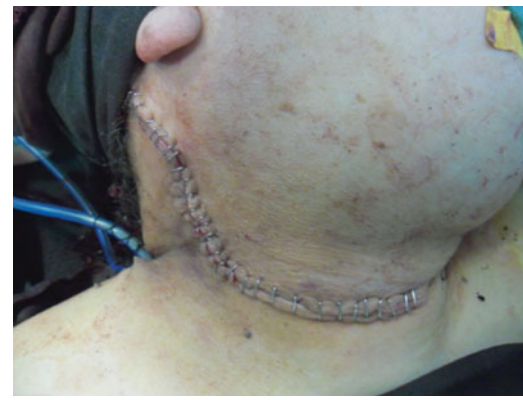

Fig. 8.33 Skin closure with two drains inserted

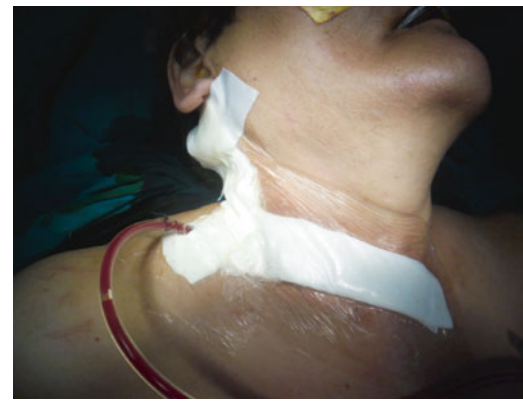

Fig. 8.34 Dressing put on the wound

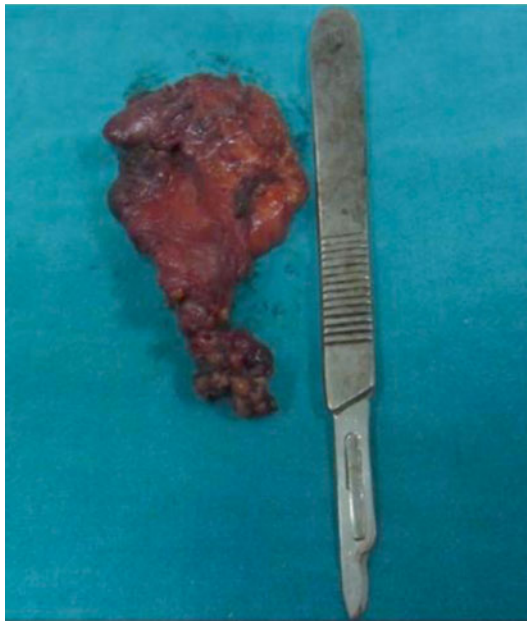

Fig. 8.35 Level I dissection specimen

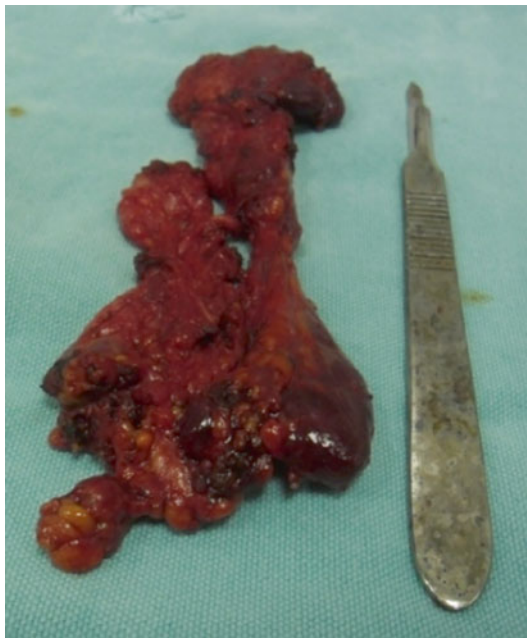

Fig. 8.36 MRND specimen

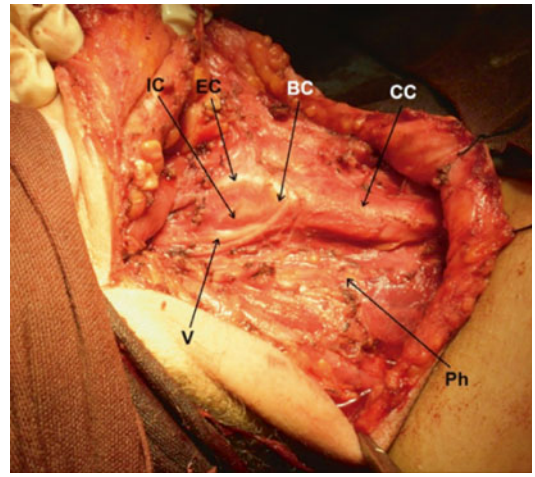

Fig. 8.37 Right neck side after RND, showing common carotid artery (*CC*), carotid bifurcation (*BC*), external carotid artery (*EC*), internal carotid artery (*IC*), vagus nerve (*V*), and phrenic nerve (*Ph*)

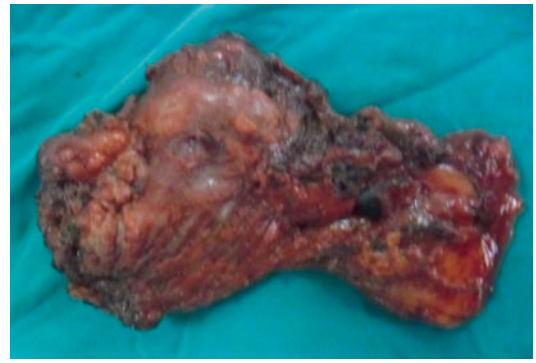

Fig. 8.38 RND specimen

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Swellings of the Neck

9

Tarek Koraitim

9.1 Surgical Anatomy

9.1.1 Triangles of the Neck

9.1.1.1 Anterior Triangle

The anterior triangle of the neck is bounded by the anterior border of the sternomastoid muscle, the lower edge of the mandible, and the midline. In clinical practice the structures deep to the sternocleidomastoid (SCM) muscle are considered to be inside the anterior triangle. The anterior triangle consists of four triangles, namely, digastric (submandibular) triangle, carotid triangle, muscular triangle, and submental triangle. The midline of the neck extends from the "symphysis menti" above to the "suprasternal notch" below (Fig. 9.1).

9.1.1.2 Posterior Triangle

The posterior triangle of the neck is bounded by the posterior border of the sternomastoid muscle, the anterior edge of the trapezius muscle, and the clavicle. The posterior triangle consists of two triangles, occipital triangle and subclavian (supraclavicular) triangle (Fig. 9.1) [1, 2].

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9.2 Introduction

Neck swellings represent a very important entity in the surgical practice. Sticking to the definition, a neck swelling should include any mass that presents in the neck whatever its origin is. However, for the sake of classification, neck swellings described in this chapter will not include masses arising from the thyroid gland, parathyroid glands, salivary glands, pharynx, larynx, or lymph nodes, as these entities are detailed in separate chapters. Accordingly, diseases of such organs will be mentioned in this chapter only by name, so that differential diagnosis is complete.

Swellings of the neck are generally categorized into two groups: midline and lateral neck swellings. Midline neck swellings include those few swellings which clinically present in the neck midline from the submental triangle just below the chin above to the suprasternal notch below. Swellings which do not respect this anatomical imaginary midline are termed lateral neck swellings, whether presenting in the anterior or posterior triangles.

Midline and lateral neck swellings may be further classified in different ways. They may be classified as solid versus cystic, congenital versus acquired, or according to the anatomic subregion of presentation. It should be noted that half of all neck masses seen in a general hospital are of thyroid origin [2].

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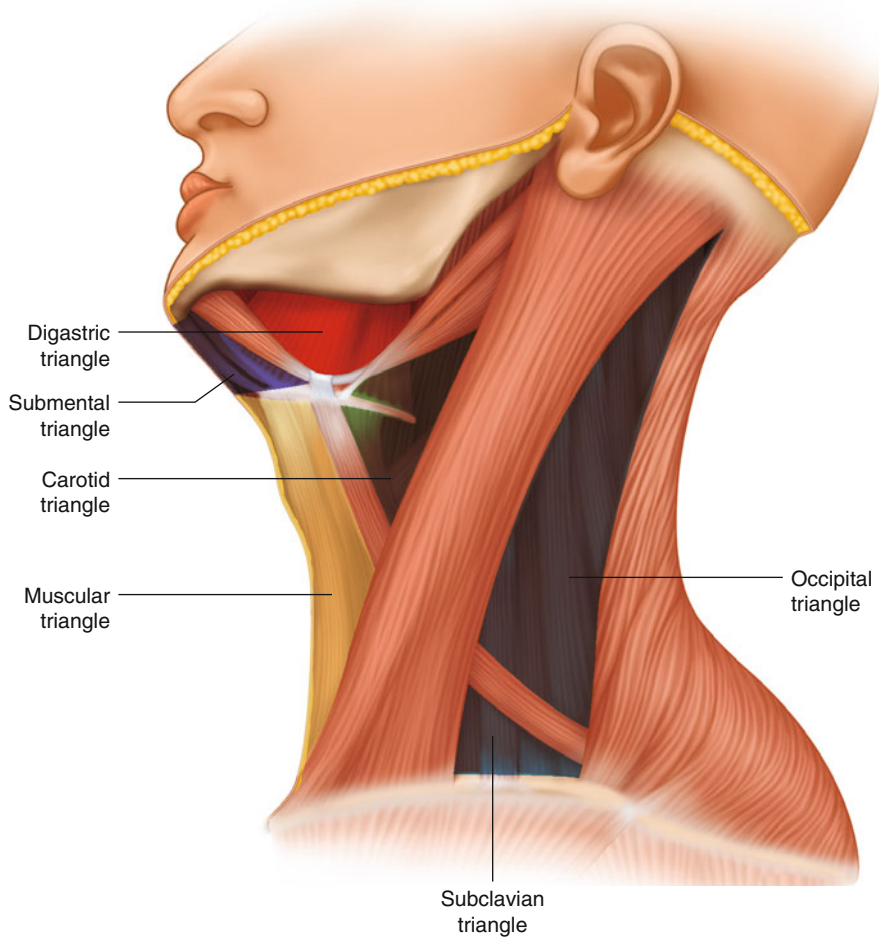

Fig. 9.1 Triangles of the neck: *anterior triangle* (submental, digastric, carotid, and muscular triangles) and *posterior triangle* (occipital and subclavian triangles)

9.2.1 Diagnosis of a Neck Mass

A complete history with full head and neck examination, including flexible laryngoscopy, is crucial to reach a proper diagnosis. This is also dependent on the location of the mass and the patient's age. In children, most neck masses are inflammatory or congenital. However, in the adult population, a neck mass >2 cm in diameter has a >80 % probability of being malignant.

Fine-needle aspiration, preferably with the assistance of ultrasound (US) or CT guidance, can provide a valuable tool for early treatment planning that provides less oncologic disruption to a tissue mass than an open biopsy. The use of CT scanning and/or MRI imaging is dictated by the patient's presentation.

If no definite diagnosis can be concluded after this workup, an open biopsy may be the last resort for reaching a proper diagnosis and plot a therapeutic plan. Special caution should be taken while handling the biopsied material to avoid tissue destruction and the need for rebiopsy. Putting the skin incision for such a biopsy should take into consideration the possibility of performing a future neck dissection, composite resection, and/or a major reconstruction [3].

9.3 Midline Neck Swellings

Midline neck swellings are summarized, according to their anatomical site, in Table 9.1.

9.3.1 Neck Dermoid Cysts

Neck dermoid cyst may present anywhere along the midline. It may present as a sublingual mass above or below the mylohyoid muscle and may bulge into the submental triangle. It is either epidermoid, true dermoid, or teratoid, which is the rarest variety. It usually presents between 10 and 25 years of age, affecting both sexes equally. The patient complains of a swelling, which becomes painful and tender if infected. On examination, the swelling is smooth, spherical, opaque, fluctuant, and clearly defined.

It is treated by surgical excision. If it is sublingual in position, the mucous membrane appears normal and the cyst can be felt bidigitally. Surgical excision is preferable through the oral route because of the hidden scar (Fig. 9.2) [2, 4].

Table 9.1 Classification of midline neck swellings

Anatomical region	Causes
A. Submental region	1. Submental lymph nodes (LNs) 2. Sublingual dermoid cyst 3. Hourglass ranula 4. Abscess related to the mandible (central incisors)
B. Hyoid bone region	1. Thyroglossal cyst 2. Median ectopic thyroid tissue 3. Subhyoid bursitis 4. Tumor of the hyoid bone
C. Laryngeal region	1. Prelaryngeal (Delphian) LNs 2. Laryngeal tumors 3. Bursa in front of Adam's apple 4. Chondritis of thyroid cartilage
D. Tracheal region	1. Pretracheal LNs 2. Nodule in the isthmus of the thyroid gland
E. Suprasternal space (space of Burn)	1. Enlarged LNs 2. Lipoma 3. Teratoma 4. Thymoma 5. Aneurysm of the aorta or innominate artery 6. High aortic arch

9.3.2 Abscess in Relation to the Mandible

Infection may occur in relation to carious central incisors leading to a "subperiosteal abscess." A sinus may be present. Plain X-ray appearance is diagnostic.

9.3.3 Subhyoid Bursitis

This rare condition usually affects old patients. It forms a translucent sausage-shaped swelling parallel to the lower border of the hyoid bone. The swelling is mobile with protrusion of the tongue.

9.3.4 Median Ectopic Thyroid Tissue

It is usually mistaken for a thyroglossal cyst as it usually presents in the upper two-thirds of the neck; however, it is solid and not cystic. It may be the only thyroid tissue present in the body. This

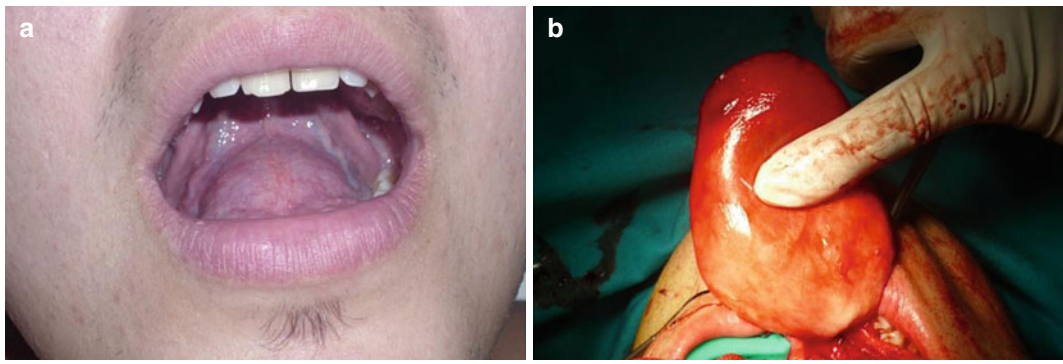

Fig. 9.2 (**a**) Sublingual dermoid cyst presenting as an intraoral swelling. (**b**) The cyst being excised through an intraoral route

can be determined preoperatively by scanning and so it may be left in place or excised [5, 6].

9.3.5 Tuberculous Thyroid Chondritis

The thyroid cartilage is thickened and tender and a rectangular abscess may complicate the condition. Tuberculous laryngitis and open pulmonary tuberculosis (TB) may coexist.

9.3.6 Cyst/Nodule of the Thyroid Gland Isthmus

This lesion is mobile with deglutition. Other parts of the thyroid gland may be affected as well. Absence of a track between it and the hyoid bone as well as being not mobile with tongue protrusion differentiates it from thyroglossal tract cyst.

9.3.7 Thyroglossal Cyst

9.3.7.1 Embryology and Pathogenesis

The thyroid gland buds off the foregut diverticulum at the base of the tongue in the region of the future foramen cecum at 3 weeks of embryonic life. As the fetal neck develops, the thyroid tissue becomes more anterior and caudal until it rests in its normal position. The "descent" of the thyroid is intimately connected with the development of the hyoid bone.

Residual thyroglossal duct system left behind in the migration may persist and subsequently present in the midline of the neck as a thyroglossal duct cyst. Rarely, midline ectopic thyroid tissue masquerades as a thyroglossal duct cyst and may represent the patient's only thyroid tissue [2, 4, 7].

9.3.7.2 Sites

A thyroglossal cyst may present in the substance of the tongue (lingual thyroglossal cyst), in the suprahyoid region (as a mass in the floor of the mouth or submental triangle), or in the infrahyoid region, which is the commonest site, as the duct obliterates from above downward. This latter type might present in front of the thyroid cartilage, cricoid cartilage, or even at the suprasternal notch. Occasionally it presents as an intrathyroidal mass. The commonest site of all is the peri-hyoid bone cyst [1, 4, 8].

9.3.7.3 Incidence

Remnants of thyroglossal duct are estimated to persist in 7 % of the population. Cystic remnants are the commonest congenital anomaly of the neck. The lesion is most commonly appreciated in the 2- to 4-year-old child when the baby fat disappears. Some authors state that the incidence is higher in females and some deny any sex predilection [1, 2]. Ninety percent of the cases occur in the midline and 10 % are lateral, of which 95 % are left and 5 % are right. It is three times more common than the branchial cysts [2, 8].

9.3.7.4 Pathology

The cyst lined by cubical or stratified squamous epithelium. It contains mucoid fluid or cheesy yellowish material rich in cholesterol. Sometimes, the wall may contain "ectopic thyroid tissue" [4].

9.3.7.5 Clinical Picture

The cyst is painless and presents for a long time. Pain, tenderness, and an increase in size occur only if the cyst becomes infected, usually after upper respiratory tract infection. On examination, the cyst is 0.5–5 cm large, well defined, rounded, and with a smooth surface. It moves vertically up with protrusion of the tongue (characteristic sign) or swallowing. The lower jaw is held still with the mouth opened. The clinician holds the cyst between the finger and thumb and feels it tugged upward when the tongue protrudes. It is a difficult sign to elicit so one should not expect much movement. This sign is due to the cyst being abnormally attached to the hyoid bone by a fibrous tissue remnant and the hyoid bone being normally attached to the tongue through the hyoglossus muscle (Figs. 9.3 and 9.4). Although diagnostic, its absence does not exclude the diagnosis. This sign is absent from most of the cysts which are below the thyroid cartilage (which are indeed rare). Such a fibrous tissue track allows the cyst to be moved sideways but not up and down. Some cysts may form on both sides of the hyoid bone, i.e., dumbbell-shaped lesion. It fluctuates easily; however, few are not, being so tense. Many are opaque due to

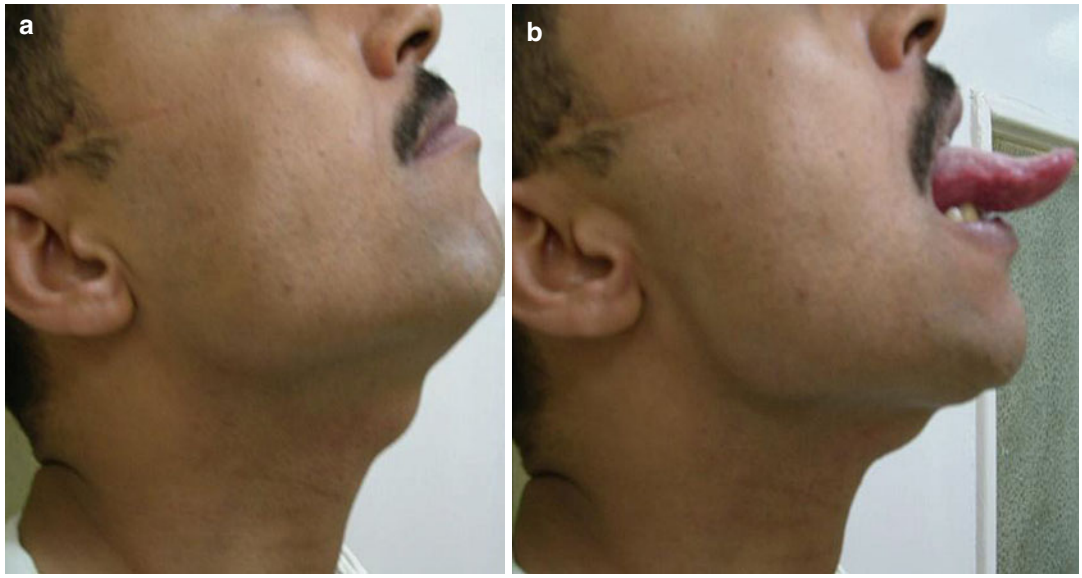

Fig. 9.3 (**a**) Thyroglossal cyst with the tongue in place. (**b**) With the tongue protruded. Note the upward movement of the cyst

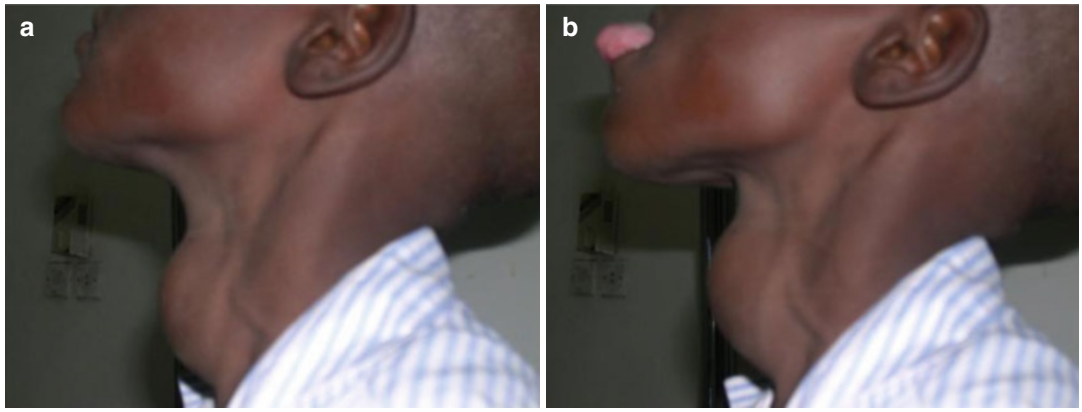

Fig. 9.4 (**a**) Thyroglossal cyst with the tongue in place. (**b**) With the tongue protruded. Note the upward movement of the cyst. The cyst is large enough to mimic a goiter

desquamated epithelial cells or debris of previous infection, few are illuminant, and many are too small to illuminate [1, 3, 8–10].

9.3.7.6 Complications

Complications include *infection*, which is inevitable, as the lymphatic tissues in its wall communicate with the neck LNs. *Ectopic thyroid tissue* present in the cyst might lead to goiter manifestations. However, the most serious complication is the development of *carcinoma*. Thyroglossal carcinoma has no sex predominance, with a peak incidence in the fourth decade in females and in the sixth decade in males. Such tumors are very rare and are most commonly papillary thyroid carcinoma (PTC), followed (equally) by mixed papillary-follicular and squamous cell carcinoma. Adenocarcinoma was reported. Pure follicular and anaplastic carcinomas are extremely rare. Medullary cancer has never been reported. Their pathogenesis is debatable, and some presume they are metastasis from occult PTC; however, most authors suggest they are de novo neoplasms. Thyroglossal cyst carcinoma should be suspected whenever the cyst grows rapidly, when the US demonstrates a

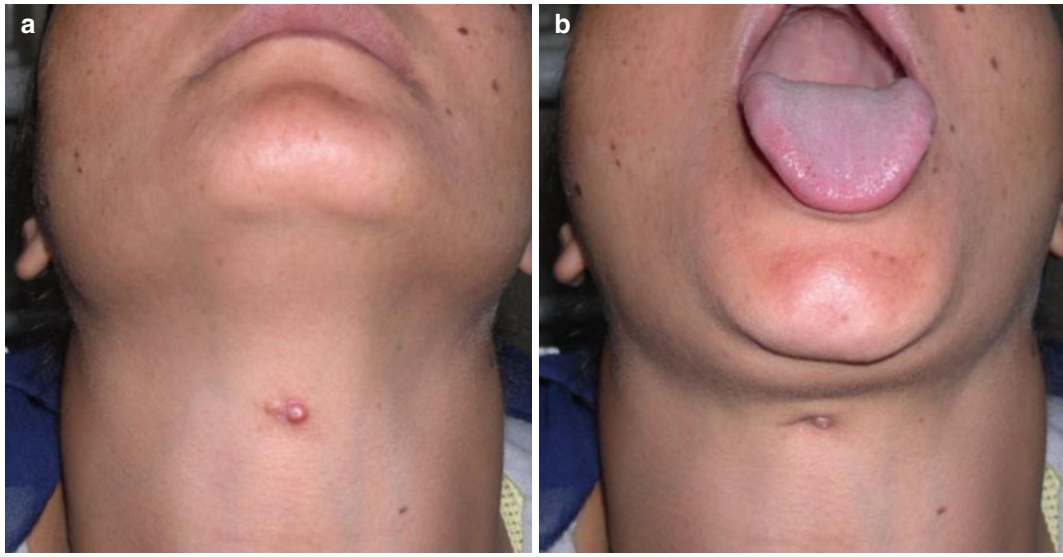

Fig. 9.5 (**a**) Thyroglossal fistula with the tongue in place, (**b**) Upward movement of the fistulous opening with protrusion of the tongue

complex anechoic pattern or in the presence of calcifications. Still, they are treated by Sistrunk operation with low recurrence rates. This may be followed by thyroxin suppression therapy and regular measurements of thyroglobulin, which becomes undetectable if successful removal of the carcinoma was achieved, as long as TSH is adequately suppressed by thyroxin [2, 8].

9.3.7.7 Differential Diagnosis

A thyroglossal cyst should be differentiated from swellings in the midline of the neck, namely, dermoid cyst, sebaceous cyst, lipoma, enlarged LN, hypertrophied thyroid pyramidal lobe, and choristoma.

9.3.7.8 Treatment (Sistrunk Operation, 1928)

Prior to excision, an imaging study is performed to identify functioning thyroid gland in the lower neck. This ensures that the cyst does not contain the only functioning thyroid tissue in the patient, if any. A transverse incision is made over the cyst. Removal of the cyst, tract, central portion of the hyoid bone, as well as a core of tissues up to the foramen cecum is done. Incomplete excision leads to recurrence, and a recurrent lesion is more liable to recur again. Factors predictive of recurrence included more than two infections prior to surgery, age below 2 years, and inadequate initial operation. Failure to remove the central part of the hyoid bone results in recurrence in three out of four patients [4, 7, 9, 10, 11].

9.3.7.9 Thyroglossal Fistula

This is an acquired fistula related to the thyroglossal duct. It represents about 15 % of the cases. It is never congenital. The opening is small, midline, and with a crescentic skinfold above it. It moves up with swallowing and with protrusion of the tongue (Fig. 9.5).

There is intermittent discharge from the fistula which is often a seat of recurrent attacks of inflammation. The track may be felt as a thick fibrous cord extending up to the hyoid bone. It is surgically treated by excision through Sistrunk operation, but the incision is elliptical around the sinus, instead of being transverse [1, 7].

9.4 Lateral Neck Swellings

Lateral neck swellings are summarized, according to their consistency and anatomical location, in Table 9.2.

Table 9.2 Classification of lateral neck swellings

Anterior triangle	Posterior triangle
Solid swellings	*Solid swellings*
1. Lymph node enlargement 2. Thyroid gland nodule 3. Submandibular gland swellings 4. Parotid swellings (lower pole of the gland) 5. Swellings of the angle of the jaw 6. Paragangliomas (glomus tumors) 7. Schwannoma 8. Ganglioneuroma 9. Sternocleidomastoid (SCM) tumor 10. Lipoma	1. Lymph node enlargement 2. Lipoma 3. Cervical rib
Cystic swellings	*Cystic swellings*
1. Pyogenic abscess 2. Cold abscess 3. Thyroid cyst 4. Branchial cyst 5. Plunging ranula 6. Laryngocele 7. Carotid artery aneurysm 8. Arteriovenous fistula	1. Pyogenic abscess 2. Cold abscess 3. Retropharyngeal abscess 4. Cystic hygroma 5. Pharyngeal pouch 6. Subclavian aneurysm 7. Pneumatocele

9.4.1 Solid Swellings of the Anterior Triangle

9.4.1.1 Lymphadenopathy

Enlargement of cervical LNs is the most common cervical swelling, whether presenting in a single fashion or a multiple fashion. Cervical LNs are enlarged in children mainly due to inflammatory causes and in adults mainly due to neoplastic causes. In adults, LNs tend to be more firm and less tender than those usually found in the neck of children due to recurrent upper respiratory tract infections. Cervical LN enlargement may represent a local disease in the neck (Fig. 9.6), be a part of generalized disease as lymphoma, or reflect a metastatic disease from below the clavicles as in the case of Virchow's LNs.

Sonographic features of LNs help much in the diagnosis of their nature. Being rounded, of irregular contour, lost echogenic hilum, lost central and scattered peripheral vascularity, and internal necrosis are all in favor of malignancy. Elastography index and type of calcification if any are other parameters that might be included in the sonography report. The advantages of computed tomography in the imaging cervical LNs are the detection of extracapsular invasion as well as accurate assessment of their relation to carotid sheath vessels. Level VII LNs are definitely assessed by CT much more accurately than by US. Fine-needle aspiration cytology (FNAC) is a very important tool in completing the assessment of the patients presenting with cervical LNs [12].

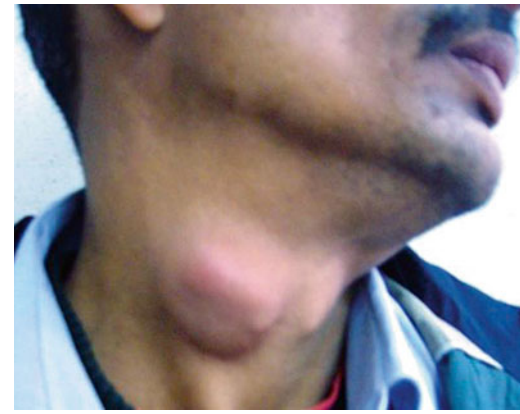

Fig. 9.6 A 35-year-old gentleman with enlarged and matted cervical LNs

9.4.1.2 Thyroid Swelling

A thyroid swelling is characteristically mobile with deglutition, and lies in the lower part of the front of the neck, deep to the SCM and strap muscles.

9.4.1.3 Swelling of the Lower Pole of Parotid Gland

Swellings arising from the lower pole of the parotid gland may be present in the lateral side of the neck, below the angle of the mandible (Fig. 9.7). This situation may give rise to diagnostic difficulty and should be included in differential diagnosis of a mass in the lateral side of the neck. A CT scan of the neck is helpful in identification of the parotid origin of the swelling.

9.4.1.4 Paragangliomas (Glomus Tumors: Chemodectomas)

Paragangliomas are tumors that are derived from neuroendocrine tissues in the paraganglia of

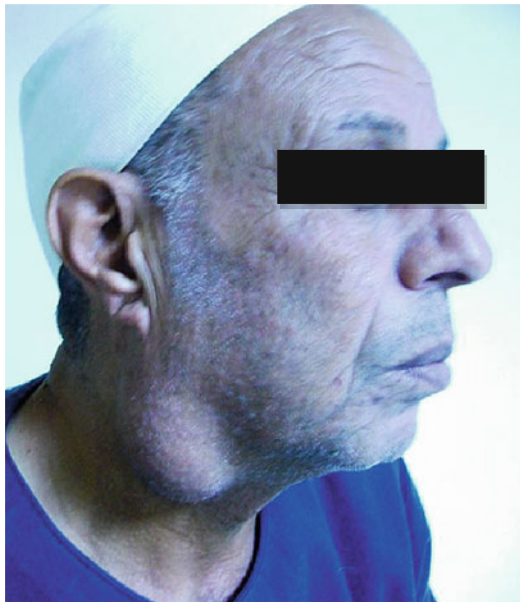

Fig. 9.7 Right parotid swelling (adenolymphoma) in a 64-year-old gentleman

nerves and are known to occur in the cervical, thoracic, and abdominal paravertebral spaces. They may also occur in the adrenal medulla where they are known as pheochromocytomas. Tumors that are thought to be derived from parasympathetic system are nonsecretor and nonfunctional tumors, whereas those which are thought to be derived from the sympathetic system are generally secretor and functional ones [13].

At imaging, four sites of origin may be distinguished and include carotid body tumor, glomus vagale, glomus jugulare, and their fourth partner, glomus tympanicum. Glomus vagale and glomus jugulare tend to displace the internal carotid artery (ICA) anteriorly. Glomus vagale tumors have smaller intracranial extensions and better developed capsules than glomus jugulare tumors.

Carotid body tumors show a greater tendency to splay the internal and external carotid arteries. What is the carotid body? It is a nest of chemoreceptor cells of neuroectodermal origin (3–6 mm) located on the posteromedial side of the carotid bifurcation (the carotid bulb). It responds to increased CO_2, decreased O_2, and acidity, i.e., hypoxia, resulting into increased blood pressure, heart rate, and depth and rate of respiration. It is usually benign but can become quite large and locally malignant, with regional metastases occurring in 20 % of cases and distant metastases rarely. All the three are tumors of the post-styloid parapharyngeal space [2, 3]. According to Shamblin's classification, carotid body tumors are classified into three types depending on the degree of difficulty of resection. Type I describes tumors that are localized and easily resected, type II describes those which are adherent to or partially surrounding vessels, and type III describes those which intimately surround or encase the vessels and nerves [13].

Carotid Body Tumor

Carotid body tumors have a high incidence at high altitudes, such as in Peru, Colorado, and Mexico City. Chronic hypoxia leads to carotid body hyperplasia. Average presentation is in the fifth decade. No sex predominance is reported. Ten percent of the patients have a positive family history, where the disease is inherited as an autosomal dominant (AD) disease. The tumor presents on both sides in 30 % of the cases and has an association with adrenal pheochromocytoma. It usually runs a long history because it is a slowly growing tumor [2, 14].

Pathology

The carotid body tumor has a much more prominent surface vasculature than the glomus vagale and can be deeply embedded in the vessel wall, making resection extremely painstaking. Cells are histologically similar to normal carotid body. Cells are large, uniform epithelioid cells surrounded by a vascular stroma. It is hormonally inactive with rare proven metastases.

Symptoms

The tumor presents as a painless slowly growing lump over 5–7 years. Rarely, this is associated with attacks of transient cerebral ischemia manifested by giddiness, fainting, or transient paralysis or paresis, due to compression of the carotid artery by the tumor.

Clinical Examination

On examination the tumor is found in the upper part of the anterior triangle of the neck, in level

with the hyoid bone, deep to the cervical fascia, and beneath the anterior edge of the sternomastoid muscle. Its size is variable from 2 to 10 cm. As it becomes larger, it extends upward. The overlying skin is normal. Hutchinson termed it the "potato tumor," oval and hard. It has a smooth surface but sometimes is bosselated, with an indistinct edge. It is not tender and exhibits a normal temperature. It has a firm and rubbery consistency, is dull to percussion, and does not fluctuate. It is fixed to the carotid vessels, where it shows transmitted pulsations. It might sometimes show expansile pulsations from a soft very vascular tumor, and such tumors are also compressible and hence refill in steps synchronous with carotid pulse. However, sometimes it is not pulsating at all. A bruit may be present and the mass may decrease in size with carotid compression. The common carotid artery (CCA) can be felt below it, and the external carotid artery (ECA) may pass over its superficial surface (palpable pulsations). About 30 % of the cases present with a pharyngeal mass pushing the tonsil medially and anteriorly. Thus, biopsy of a pharyngeal swelling must never be taken from within the mouth. It can be moved horizontally with ease but has very little vertical mobility. Local LNs are not enlarged. Nerve involvement is rare [1–3, 13].

Investigations

Whenever a carotid body tumor is suspected, biopsy is contraindicated, but careful FNAC with a very narrow-gauge needle has been described. *Carotid angiography* will demonstrate a tumor circulation, cross-circulation if present, and determine tumor extent. Magnetic resonance imaging (MRI) is also useful to determine tumor extent. Some paragangliomas are demonstrated by metaiodobenzylguanidine (^{125}I-MIBG) scintigraphy [15, 16].

Treatment

Metastases are exceptionally rare and the disease is rarely fatal. Thus, the mere presence of a carotid body tumor does not justify an attempt at removal. Provided that the patient has good general health, the indications for removal of a carotid body tumor are age <50 years; small- or medium-sized tumors; those extending into the palate or pharynx interfering with swallowing, speaking, or breathing; and tumors with an aggressive growth pattern. Although these tumors were originally thought to be radioresistant, cures have recently been reported. Radiotherapy using ^{131}I-MIBG can be of value in patients who refuse surgery, in high-risk cases, or in metastatic disease [2, 7, 14–16].

Excision of a Carotid Body Tumor

An incision is made from the mastoid process to the clavicle down the anterior border of the SCM muscle. Dissection is adopted to expose the carotid sheath where the common carotid artery, internal jugular vein, and vagus nerve are identified. The common carotid artery is freed on all sides, preserving the vagus nerve carefully. A tape is placed loosely around the common carotid artery to allow easy and rapid occlusion of the carotid artery if the internal carotid artery is damaged later in the operation. Dissection proceeds from below upward along the adventitia, mobilizing the vagus nerve. On approaching the tumor, one will encounter large numbers of thin-walled veins, more brown than red in color. These veins bleed very easily and are a source of difficulty in this procedure. This difficulty can be overcome by dissection with two non-toothed dissecting forceps with fine points. The tissue is grasped close to the adventitia of the artery with these forceps and pulled apart. Surprisingly, this produces much less bleeding than attempts at sharp dissection, which are slow, tedious, and attended by steady bleeding. However, sometimes traditional ligation of such vessels freeing the tumor in a piecemeal fashion is sometimes necessary. The use of vascular clips may be time preserving. It should always be possible to preserve the vagus nerve but the hypoglossal nerve is often stretched and may need to be divided [2, 13, 14].

Glomus Vagale

Vagal paragangliomas arise from nests of paraganglionic tissue within the perineurium of the vagus nerve at its ganglion nodosum, i.e., just below the skull base. In large tumors

there may be a small intracranial extension through the foramen jugulare. Intravagal tumors, however, are not restricted to this site and may be found at various sites along the nerve and down to the level of the carotid artery bifurcation.

In 50 % of the patients, there is more than 3-year history. It most commonly presents as a slowly growing and painless mass. It is associated with pulsating tinnitus, deafness, syncope, and/or vertigo. Pharyngeal pain is a late sign indicating irritation of the pharyngeal plexus, often preceding the onset of cranial nerve palsies. The mass is high in the anterolateral aspect of the neck, often noted near the origin of the SCM muscle with medial displacement of peritonsillar structures.

The diagnosis is confirmed by arteriography which tends to overestimate size owing to a surrounding pharyngeal plexus of veins. Surgery is indicated for vagal paragangliomas because of their tendency to spread into the cranial cavity. The approach used is that described for parapharyngeal tumors (transoral with mandibulotomy with transcervical approach or trans-parotid with transcervical one). The numerous thin-walled veins should be dealt with in the same way as for carotid body tumors. The most dangerous part of the dissection is superiorly where the internal carotid artery loops over the tumor and then immediately enters the skull. Injury is frequent at this site and therefore the help of a vascular surgeon is advisable [2, 4, 13, 14].

Glomus Jugulare

The glomus jugulare arises from the nonchromaffin paraganglionic cells around the jugular ganglion in the jugular bulb. There is usually a similar disease bulk above and below the skull base, in contrast to the glomus vagale. Advanced lesions erode the skull base and extend laterally to the middle ear cleft [2, 4, 13, 14].

Glomus Tympanicum

Glomus tympanicum arises in the middle ear and presents with pulsatile tinnitus and hearing loss [2, 4, 13, 14].

9.4.1.5 Schwannoma

It is a benign tumor of the neurolemma (nerve sheath of Schwann). It may arise from the vagus nerve, sympathetic chain, glossopharyngeal nerve, or any of the nerves in the neck. It presents as a painless lump in the neck. There may be pressure effects, as on the recurrent laryngeal nerve (RLN) causing hoarseness of voice or on the esophagus causing dysphagia. It is a deeply seated mass, at about the middle of the neck, and characterized by being smooth, encapsulated, and firm. It moves from side to side but not up and down. It is treated by surgical excision [17–19].

9.4.1.6 Ganglioneuroma

This is a slow-growing benign neurogenic tumor of the sympathetic ganglia. It is most commonly seen in the posterior mediastinum, retroperitoneum, pelvic and sacral sympathetic ganglia, and very rarely in the heart, middle ear, orbit, and spermatic cord (Fig. 9.8) [14, 17].

9.4.1.7 Sternocleidomastoid (SCM) Tumor

It is a swelling that usually manifests after the third or fourth week of life, affecting the middle third of the SCM muscle. The mother usually gives a history of "breech" presentation or difficult labor. It is defined as "ischemic contracture of a segment of the sternomastoid muscle." This is due to an "arterial insult" of the sternomastoid artery which is a branch of the superior thyroid artery supplying mainly the middle third of the muscle. It is a lesion very similar to Volkmann's ischemic contracture. It is not a "hematoma" of the SCM muscle anymore!

Pathology

It is formed of immature fibroblasts and degenerating muscle fibers. At 6 months of age, this tumor will disappear spontaneously, but in some cases, contracture of the sternomastoid muscle occurs at the site of the tumor resulting in "congenital torticollis."

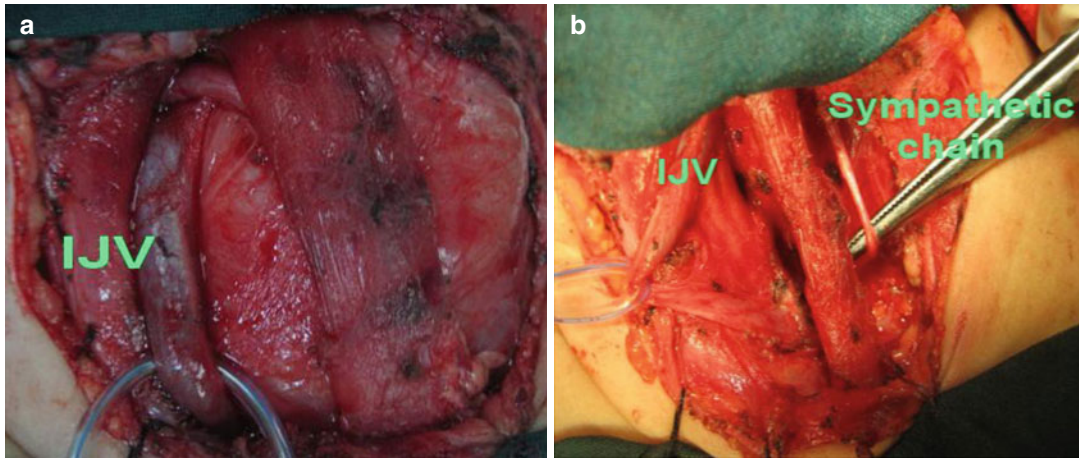

Fig. 9.8 (**a**) Internal jugular vein (IJV), SCM muscle, and ganglioneuroma all dissected from one another. (**b**) IJV and SCM muscle apparent after excision of the mass with the sympathetic chain from which the mass arose, preserved

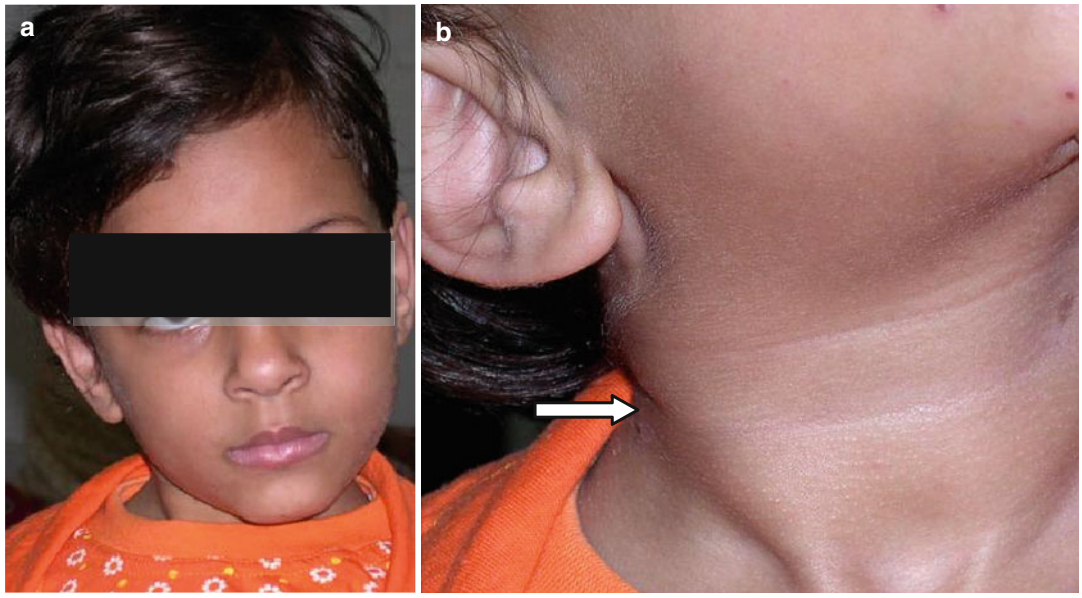

Fig. 9.9 (**a**) Neck torticollis due to right SCM tumor. (**b**) Fusiform mass of the middle third of the right SCM muscle (*arrow*)

Clinical Picture

It is a smooth swelling in the middle third of sternomastoid muscle, usually 1–2 cm, being fusiform, with its long axis along the line of the sternomastoid muscle. The anterior and posterior edges of the lump are distinct, but the superior and inferior edges, where the lump becomes continuous with normal muscle, are indistinct. At first, the lump is firm, solid, easy to feel, and may be tender (in the first few weeks of life). Gradually it becomes harder and begins to shrink and may become impalpable (Fig. 9.9).

Because each SCM muscle rotates the head to the contralateral side and tilts the head to the ipsilateral side, so in the presence of a SCM tumor, shortening

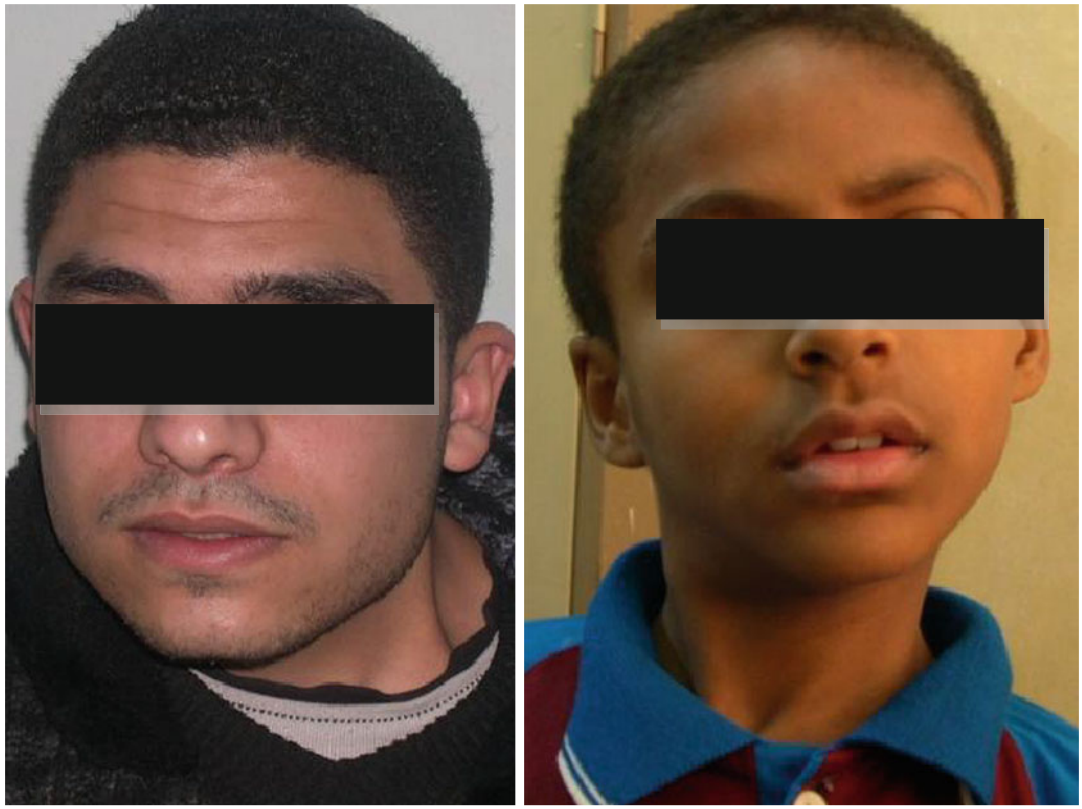

Fig. 9.10 (**a**) Neck torticollis due to left SCM tumor. (**b**) Neck torticollis due to right SCM tumor

of the left muscle, for example, turns the head toward the right but tilts the head to the left. Both these deformities may be present and the resulting disease is called congenital torticollis (Fig. 9.10).

Forced movement to correct the deformity may cause pain and may be resisted by the child. Untreated, it may cause face asymmetry, unilateral amblyopia, and cervical vertebral deformities. Torticollis can be a means of correcting a squint. Move the head into a vertical and central position and watch the eyes. If the torticollis is secondary to a squint and not a SCM tumor, the squint will appear as the head is straightened [1, 4, 20].

Treatment

The condition is treated by tenotomy where the sternomastoid muscle is cut at the sternal end, followed by the use of a collar for few weeks and subsequent physiotherapy. If tenotomy is not sufficient, a Z-myoplasty may be needed.

9.4.2 Cystic Swellings of the Anterior Triangle

9.4.2.1 Pyogenic Abscess

A pyogenic abscess is painful and tender. The overlying skin is red and hot. There may be signs of toxemia. It is treated with incision and drainage, usually under general anesthesia.

9.4.2.2 Cold Abscess (TB Abscess)

It is the commonest cystic swelling in the lateral side of the neck. It is common in the upper part but may occur in any group of LNs. It is characterized by multiplicity. The mass is fixed to the surrounding structures such as muscle or skin. Symptoms of TB toxemia or other TB lesions may be present. Aspiration reveals caseous material. Nondependent valvular aspiration should be performed to avoid sinus formation. Plain X-ray may show calcification.

9.4.2.3 Branchial Cyst

Embryology and Pathogenesis

Paired branchial arches originally appear as mesodermal condensations in the walls of the primitive pharynx in the fourth gestational week. Between the six branchial arches lie five branchial grooves or clefts externally and five pharyngeal pouches internally. The fifth arch fails to develop due to early degeneration of its blood supply. The branchial clefts are lined by ectoderm, the pouches by endoderm, and in between there is a thin layer of mesoderm between each pouch and groove. The mesoderm of each arch differentiates then into cartilage and muscle (Table 9.3) [1, 4].

During the seventh week of gestation, the second branchial arch grows more caudally to fuse with the fourth branchial arch, thus covering the third and fourth. Fusion of the ectodermal lining of the sinus occurs, and now the sinus is a buried space lined by squamous epithelium. It then disappears completely. Persistence of the cervical sinus results in a branchial cyst, while failure of the operculum between the second and fourth arches to fuse gives rise to a branchial sinus or fistula. Accordingly, the branchial cyst will be existing deep to the structures originating from the second arch, i.e., hyoid bone, external carotid artery, and facial nerve, and superficial to the structures originating from the third arch, i.e., stylohyoid and stylopharyngeus muscles, internal carotid artery, internal jugular vein, and glossopharyngeal and hypoglossal nerves.

A fistula is seen most commonly with the second branchial cleft and extends from the anterior border of the SCM muscle inferiorly, inward through the bifurcation of the carotid artery, and enters the posterolateral pharynx just below the tonsillar fossa. The third branchial cleft remnant courses posterior to the common carotid artery, ending in the pyriform sinus region. Surgical excision is preferred to establish the definitive diagnosis of a branchial cleft cyst and to avoid nontreatment of a masquerading head and neck regional metastasis [1, 4].

Incidence

Branchial anomalies represent about 17 % of all pediatric cervical masses [2]. Although congenital, it appears late in life, 15–25 years or later. The disease may be affecting females more than males.

Pathology

The cyst is lined by cubical or stratified squamous epithelium, covered by a fibrous tissue capsule

Table 9.3 Neck branchial apparatus and its derivatives

Arch	Derivative	Muscles of	Nerve	Artery
First arch	Maxilla Malleus and its anterior ligament Incus Sphenomandibular ligament Mandible	Mastication	Trigeminal (V)	Maxillary
Second arch	Stapes Styloid process Stylohyoid ligament Lesser cornu and upper body of hyoid bone	Facial expression	Facial (VII)	Stapedial
Third arch	Rest of hyoid bone		Glossopharyngeal (IX)	Part of ICA
Fourth arch	Laryngeal cartilages	Pharynx Larynx	Superior laryngeal nerve of vagus (X)	Definitive aorta on the left side Subclavian artery on the right side
Sixth arch			Inferior laryngeal nerve of vagus (X)	Definitive pulmonary trunk

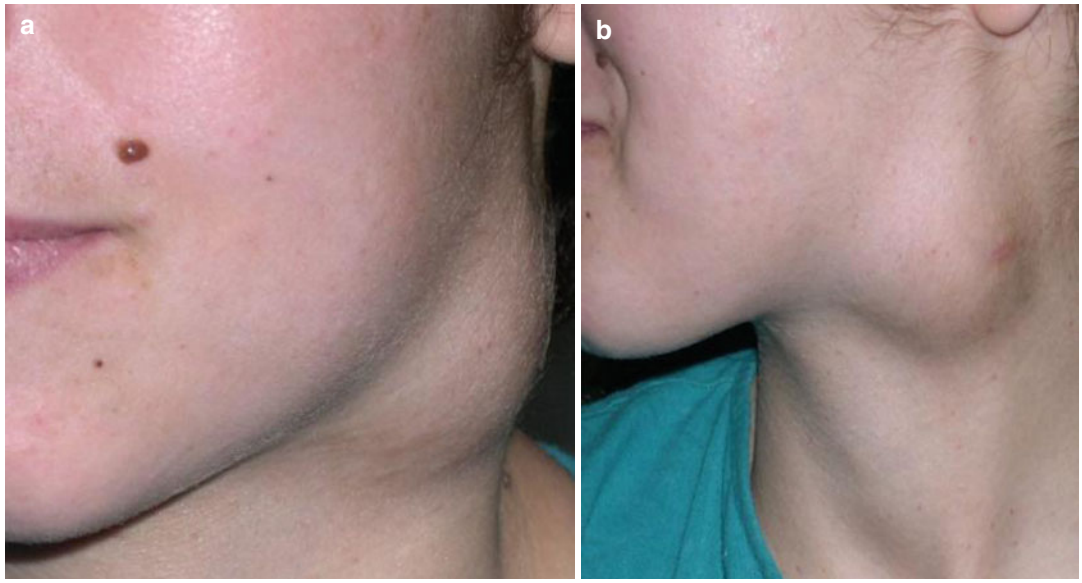

Fig. 9.11 Left second branchial arch cyst. (**a**) Anterior view. (**b**) Lateral view

containing lymphoid tissue which might lead to repeated attacks of inflammation due to its communication with other lymph channels in the neck. The fluid in the cyst is rich in cholesterol and is made of mucoid material simulating tuberculous pus.

Clinical Picture of the Second Branchial Arch Cyst

It lies deep to the upper third of the anterior border of the sternomastoid muscle, below the angle of the mandible, partially under cover of the muscle and partially projecting into the carotid triangle. It is usually unilateral. On examination, most branchial cysts are 5–10 cm wide, rounded or oval, with its long axis running forward and downward (Fig. 9.11).

The cyst has a smooth surface and may feel hard if tense or soft if lax. The overlying skin is mobile. It is mobile from side to side but may be tethered to surrounding structures. It cannot be reduced or compressed. It is trans-opaque because it contains desquamated epithelial cells that make the contents thick. Sometimes, aspiration reveals fluid which is golden yellow, rich in fat globules, and cholesterol crystals (seen under the microscope) secreted by the sebaceous glands in the epithelial lining. Such cysts may transilluminate. Rarely, branchial cleft anomalies occur in association with biliary atresia and congenital cardiac anomalies, an association that is referred to as *Goldenhar's complex* [1–4, 20, 21].

Differential Diagnosis

Should be done from other lateral cysts of the neck, particularly cold abscess, rhabdomyosarcoma, and cystic metastasis from squamous cell carcinoma (SCC) of the tonsil or tongue base to a cervical LN

Complications

Complications of a branchial cyst include abscess formation and rupture with the formation of an acquired branchial fistula. However, the most serious complication, yet very rare, is the branchogenic carcinoma, which is a SCC.

Treatment

Through a transverse incision in the neck running across one of the creases, if possible, the cyst is excised by careful dissection to preserve the important nearby structures, as the track passes through the carotid fork, and here it is superficial to the glossopharyngeal and hypoglossal nerves.

The cyst should be removed intact (Fig. 9.12), otherwise, the part left causes a

branchial fistula. If it is infected, incision and drainage of the abscess under an antibiotic cover should be done. The result will be either reformation of the cyst later on or the formation of an acquired fistula which should be excised completely [2, 21].

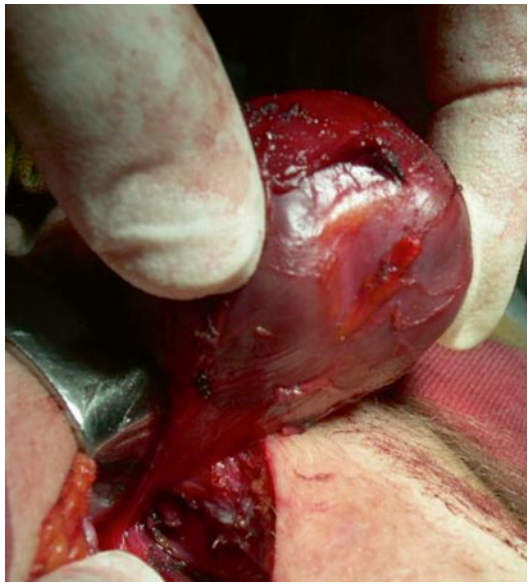

Fig. 9.12 Branchial cyst delivered through a transverse neck incision and completely removed

Branchial Fistula

Congenital Type

It presents earlier in life than the cyst (at 3–6 months). The opening is at the junction of the middle and lower third of the SCM muscle. It may be bilateral in 30 % of the patients.

A track (lined by squamous epithelium) extends from the opening upward between the ICA and ECA to the supratonsillar fossa in the oropharynx. The opening is crescent in shape, discharges mucoid material which may be pyogenic if infected.

Treatment (stepladder operation)

A series of two or sometimes three small transverse incisions in a "stepladder" fashion is preferred to a long oblique incision in the neck, which is cosmetically undesirable. A ureteric catheter or a fine lacrimal duct probe could be inserted inside the track to facilitate dissection. Injection of a small amount of methylene blue dye into the tract also may be useful. However, in most of the cases, the track is well defined and no guide of whatever kind is ever needed. Care should be taken to avoid injury of the carotid fork and glossopharyngeal and hypoglossal nerves (Fig. 9.13).

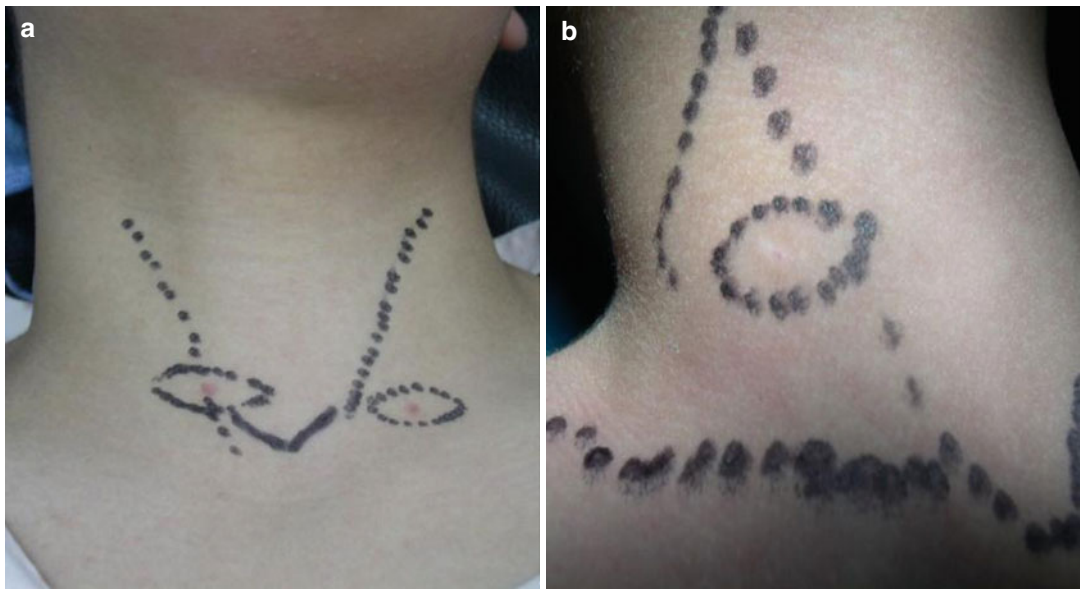

Fig. 9.13 (**a**) Bilateral congenital second branchial fistulae. (**b**) Closer view for the skin opening of the right branchial fistula. Dotted lines denote muscular borders as well as the clavicle

Acquired Type

The acquired type is less common than the congenital, and the opening is high in the neck. It results from rupture or incision of an infected branchial cyst or incomplete removal of a branchial cyst. It is treated by complete excision along its whole length, to avoid recurrence.

First Branchial Arch Anomaly (FBAA)

First branchial arch anomalies (FBAA) form about 1–8 % of branchial anomalies and are commoner in females (69 %). Type I FBAA anomalies are cysts or sinuses opening medial, inferior, or possibly posterior to conchal cartilage and pinna. Tracts, when present, run parallel to the external auditory meatus. Type II anomalies are regarded as duplication of membranous and cartilaginous parts of external auditory canal. They consist of a fistula running from floor of ear canal to neck with opening of the sinus being localized above the hyoid bone anterior to the SCM muscle. Type II FBAA is more common than type I. In either case, the course of the tract is quite variable [22, 23].

Third/Fourth Branchial Arch Anomaly

This is a rare but serious condition. The patient is usually a young child, presenting with repeated lower neck abscesses or, more commonly, a skin opening at the site of a recurrent one. The sinus tract usually passes through the ipsilateral thyroid lobe then curves medially to open in the pharynx near the piriform fossa. Neck CT scan may show air foci in the ipsilateral thyroid lobe, which is almost pathognomonic. Treatment is excision of the skin opening by an elliptical skin incision, with the sinus track to the thyroid lobe, an ipsilateral hemithyroidectomy, and then following the track to the pharynx [20, 24].

9.4.2.4 Laryngocele

It is a unilateral (occasionally bilateral), narrow-necked, air-containing diverticulum resulting from herniation of the mucous membrane of the larynx through the thyrohyoid membrane where it is pierced by the superior laryngeal vessels. Symptoms include cervical swelling that appears or enlarges on straining and may be associated with dyspnea. It occurs more in professional trumpet players, singers, and glassblowers. The swelling is tense resonant, translucent, and compressible [4].

9.4.2.5 Carotid Artery Aneurysm

The swelling may show expansile pulsation and a bruit. It is mobile across, not along, the axis of the related artery. Proximal and distal compression on the affected artery causes decrease and increase in the size of the aneurysm, respectively [13].

9.4.3 Solid Swellings of the Posterior Triangle

Solid swellings of the posterior triangle include *lymphadenopathy*, which is the commonest solid swelling of the neck, and *lipoma*, which is similar to lipoma elsewhere. A *cervical rib* may also present with a solid swelling in the posterior triangle of the neck.

9.4.3.1 Cervical Rib Syndrome

Scalene Syndrome: Superior Thoracic Aperture Syndrome

Although a cervical rib can cause serious neurological and vascular symptoms in the upper arm, clinical examination of the neck usually reveals no abnormalities. The abnormal rib is usually detected with an X-ray. It usually occurs during adolescence and middle age, affecting women as twice as men.

Varieties of Cervical Rib

1. A complete rib: It may contain a false joint in its length and articulates anteriorly with the manubrium sterni or first rib.
2. The free end of the rib expands into a large bony mass.
3. A rib ending into a tapering point connected by a fibrous band to the scalene tubercle of the first rib.
4. A fibrous band only. It does not appear on plain X-ray.

Pathology

The subclavian artery and the trunks of the brachial plexus pass in front of the first rib and behind the clavicle between the scalenus anterior and scalenus medius. Compression may occur by the cervical rib (it forms the new floor instead of the first rib), which may be unilateral or bilateral, complete or incomplete, bony, cartilaginous, or fibrous. Compression may also occur due to enlargement of the transverse process of the seventh cervical vertebra. The main pathology is poststenotic dilatation of the blood vessels and angulation and fibrosis of the nerves.

Symptoms

Only 5 % of patients have symptoms, which may include a *swelling or fullness* at the root of the neck (clinical diagnosis is difficult), *neurological symptoms* (common) in the form of pain in the C8–T1 dermatomes, wasting and weakness of the small muscles in the hand, as well as *vascular symptoms* (uncommon) such as Raynaud's phenomenon, trophic changes, even rest pain, and gangrene, particularly of the tip of the index finger. It may cause poststenotic dilatation (subclavian artery aneurysm) leading to the formation of a mural thrombus, which may result in showers of emboli to the extremities.

Local Examination

A bony swelling, which is hard and fixed, may be felt at the base of the neck. It is usually unilateral, more on the right side, but may be bilateral (Fig. 9.14). Compression of the subclavian artery may be shown by *Addison's deep-breathing test* in which rotation of the head toward the affected side and taking a deep breath and holding it results in reduction of radial pulse volume. A positive Addison's sign is nonspecific for the presence of a cervical rib, as many individuals without a cervical rib will have a positive test.

Investigations

Plain X-ray of the neck will show the abnormal cervical rib(s) (Fig. 9.14). A "CT" scan will delineate the anatomical relationships of the cervical rib (Fig. 9.15).

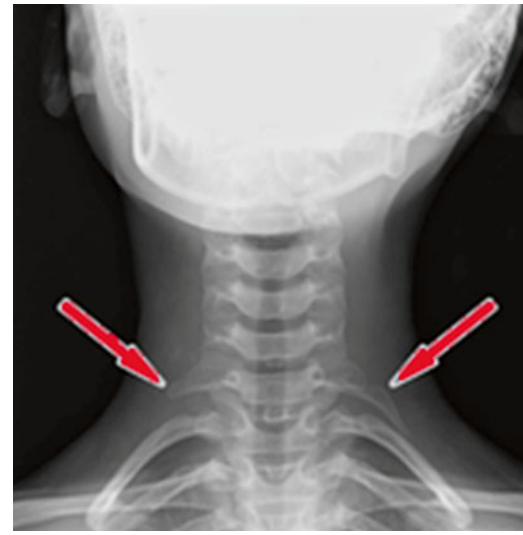

Fig. 9.14 Plain X-ray showing bilateral cervical ribs (*arrows*)

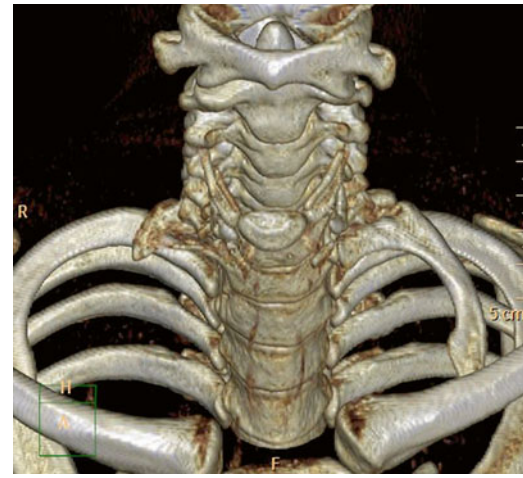

Fig. 9.15 3D computed tomography (CT) scan showing left cervical rib

Differential Diagnosis

A cervical rib should be differentiated from other causes of a *solid swelling* in the lateral side of the neck, as well as from other causes of pain and paresthesia of the shoulder, arms, and hands. The latter includes the following:

- *Cervical causes*: Cervical disk protrusion, cervical arthritis, and cervical cord tumors.
- *Shoulder-hand syndrome*: The primary lesion is subdeltoid bursitis or coronary occlusion. It

causes atrophy and then sympathetic overactivity (cold, sweaty, painful hands), and later on joints become fibrosed and stiff.
- *Vascular causes*: Angina, Raynaud's disease, thromboangiitis obliterans, migratory thrombophlebitis, and diffuse vasculitis.

Nervous causes: Herpes zoster, peripheral neuritis, and syringomyelia.

Treatment

Asymptomatic cases require no treatment. Patients with *mild symptoms* will only require physiotherapy (muscle strengthening and postural exercises) but may also need to change their profession. Patients with *severe symptoms*, on the other hand, will require scalenotomy (division of the muscle) or excision (to avoid recurrence) in addition to removal of the cause (cervical rib or cartilage).

9.4.4 Cystic Swellings of the Posterior Triangle

9.4.4.1 Cystic Hygroma

Etiology

The lymph system arises from two jugular sacs, two posterior sciatic sacs, and a single retroperitoneal sac. Endothelial out-buddings from these extend centrifugally to form the peripheral lymphatic system. The formation of cystic hygroma is attributed to those endothelial fibrillar membranes which sprout from the wall of these sacs, penetrate the surrounding tissue, canalize it, and produce more sacs or cysts [2, 4]. It is defined as sequestration of some lymphatics and loss of communication with the main trunk. It might present in the posterior triangle at the base of the neck, in the upper part of the neck below the angle of the mandible, in the axilla, in the groin, in the mediastinum, or in the retroperitoneal space.

Pathology

Cystic hygroma affects 1 in 12,000 births. It is multilocular, occasionally unilocular cysts occur. Superficial cysts are large and deep ones are small. It grows slowly, usually superficially, but may grow in any plane of the neck. They are lined by endothelium and contain lymph. Adjacent connective tissue may show extensive lymphocytic infiltration.

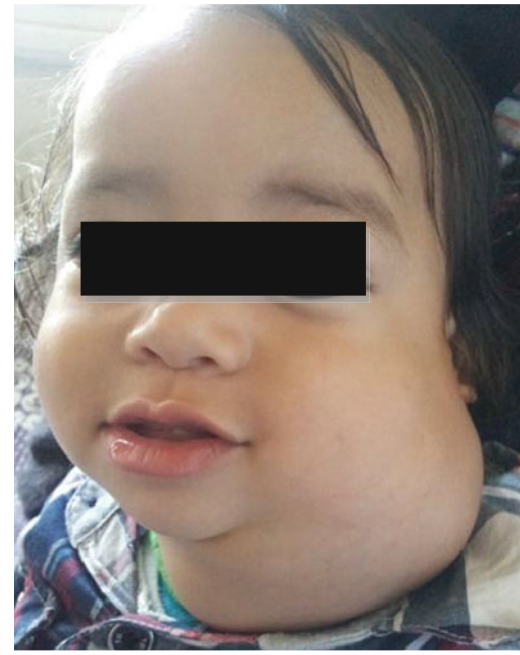

Fig. 9.16 Large cystic hygroma occupying the left side of the neck

Clinical Picture

The majority present at birth or in early years of life, but occasionally they stay empty until trauma or infection in adult life causes them to fill up and become visible. It varies in size from few centimeters across to huge lumps filling the whole side of the neck (Fig. 9.16). Occasionally, as a result of infection, the swelling becomes inflamed and increases rapidly in size. It is painless, nontender, and slowly growing. The superficial cysts feel lobulated, while deep cysts feel smooth.

The swelling is soft cystic and is partially compressible but cannot be reduced. It is dull to percussion and fluctuates easily. Large cysts will conduct a fluid thrill.

The swelling is characteristically brilliantly translucent, because it is close to the skin and contains clear fluid. It develops in the subcutaneous tissues; thus, they are superficial to the neck

muscles and close to the skin but are rarely fixed to it. A particularly troublesome variant of cystic hygroma is that which involves the tongue, floor of the mouth, and structures deep in the neck. It is essential to perform a thorough examination of the oropharynx as a cyst in the posterior triangle may deeply extend beneath the SCM muscle into the retropharyngeal space. The local LNs should not be enlarged [1–4, 7].

Diagnosis

The diagnosis of cystic hygroma by prenatal US before 30 weeks of gestation has detected a "hidden mortality" as well as a high incidence of associated anomalies, including abnormal karyotypes and hydrops fetalis. Occasionally, very large lesions can cause obstruction of the fetal airway. Such obstruction can result in the development of polyhydramnios by impairing the ability of the fetus to swallow amniotic fluid. In these circumstances, the airway is usually markedly distorted, which can result in immediate airway obstruction unless the airway is secured at the time of delivery. Orotracheal intubation or urgent emergency tracheostomy while the infant remains attached to the placenta, the ex utero intrapartum technique (EXIT) procedure, may be necessary to secure the airway.

Complications

It may obstruct labor, if huge in size. It may cause local pressure symptoms or mediastinal syndrome due to compression. Infection by *Streptococcus* or *Staphylococcus* may ensue. In the neck, this can cause rapid enlargement, which may result in airway compromise. It occasionally contains nests of vascular tissue. These poorly supported vessels may bleed and produce rapid enlargement and discoloration of the hygroma.

Treatment

Surgical Treatment

Surgery is the treatment of choice. Excision is to diminish pressure manifestations and liability to inflammation and to improve the cosmetic appearance. Radical ablative surgery is not indicated for this lesion. Conservative excision and unroofing of remaining cysts is advised, with repeated partial excision of residual hygroma if necessary, preserving all adjacent crucial structures. Postoperative wound drainage is important and is best accomplished by closed-suction technique. Fluid may accumulate beneath the surgically created flaps in the area from which the hygroma was excised, requiring multiple needle aspirations.

Sclerosing Therapy

It is difficult to inject all the cysts as it is a multilocular swelling. Complications of injection sclerotherapy include cellulitis and affection of blood vessels and nerves. Injection of sclerosing agents (OK-432 or bleomycin) with favorable results has been reported. OK-432 is composed of a lyophilized mixture of group A *Streptococcus pyogenes* and has been used in neonates without systemic toxicity. The use of these agents has not been widely adopted [2].

Other Less Popular Methods

Aspiration usually fails and carries the risk of introducing infection. It may be used temporarily to alleviate pressure manifestations. *Conservative* treatment aims at spontaneous obliteration with mild repeated attacks of inflammation resulting into fibrosis and obliteration. *Deep X-ray* causes fibrosis and results in partial regression of the swelling.

9.4.4.2 Pharyngeal Pouch (Zenker's Diverticulum)

Pathogenesis

It represents a *pulsion* diverticulum due to uncoordinated swallowing where the lower sphincter-like fibers of the inferior constrictor muscle do not relax, resulting in herniation of the pharyngeal mucosa through the weak part at the junction between the upper and lower parts of the inferior constrictor, the thyropharyngeus and cricopharyngeus muscles, respectively (Killian's dehiscence) (Fig. 9.17). The disease affects middle and old age, being more common in men [2, 4].

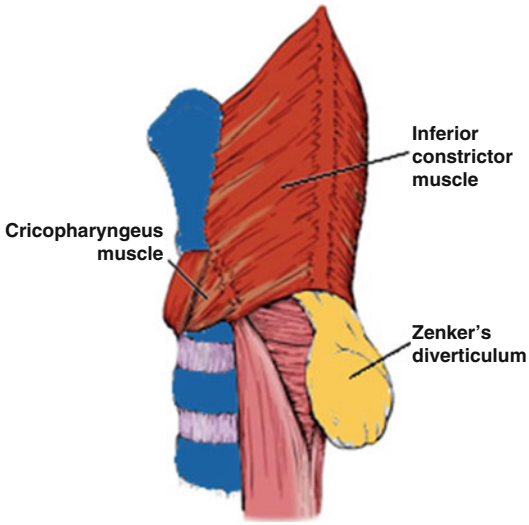

Fig. 9.17 Anatomical site of Zenker's diverticulum

Clinical Presentation

Usually, there is a long history of halitosis and recurrent sore throats, followed by the main complaint of regurgitation of food with no acid or bile taste in it. Choking and bouts of cough are also manifestations of this regurgitation and if aspiration of food particles occurs during night, a lung abscess may develop. As the pouch increases in size, it hangs down beside the esophagus causing dysphagia and/or a neck swelling. Dysphagia may be severe enough and long standing to induce malnourishment and weight loss.

The mass presents behind the SCM muscle at the junction of the upper and middle thirds, usually to the left. It increases in size after eating and straining and disappears on pressure with a gurgle. It can be compressed and sometimes emptied but not completely reduced. Its shape is indistinct because only part of its surface is palpable. The surface is smooth with soft consistency and sometimes indentable. It is dull to percussion and does not fluctuate or transilluminate. Cervical LNs should not be enlarged. Barium swallow is diagnostic.

Complications

The most dangerous complication that may ensue is the development of a carcinoma in the pouch. Its incidence is rare, about 0.5 % of cases, with a male to female ratio of 5:1. It usually affects long-standing diverticula of more than 7 years duration. The patient as well as the clinician should be alerted whenever there is increased dysphagia, weight loss, or blood in the regurgitated food. It is usually an invasive squamous cell carcinoma, but few cases of carcinoma in situ (CIS) were reported. Thus, most of the cases require total pharyngolaryngetomy as for a post-cricoid carcinoma.

Treatment

Treatment options include endoscopic and open procedures. Endoscopic route is preferable because of the mean age of the patients and the high incidence of comorbidities. Endoscopic procedures include endoscopic diathermy application (Dohlman's procedure, 1960), endoscopic laser treatment (Bradwell et al., 1997), and endoscopic staple-assisted esophago-diverticulostomy (Koay and Bates, 1996). Open procedures include diverticulectomy, diverticulopexy, and cricopharyngeal myotomy [2].

9.4.4.3 Pneumatocele

Pulmonary pneumatoceles are thin-walled, air-filled cysts that develop within the lung parenchyma, usually in patients with emphysema and as a sequelae to acute pneumonia, commonly caused *by Staphylococcus aureus*. It appears at the root of the neck, increases with straining and cough, and decreases with compression.

Pathophysiology

The exact mechanism of pneumatocele formation remains controversial. An endobronchial ball-valve mechanism leading to distal dilatation of the bronchi and alveoli was proposed by Conway (1951) [25] and Carrey (1953) [26]. However, in 1972, Boisset [27] concluded that pneumatoceles are caused by bronchial inflammation that ruptures the bronchiolar walls and causes the formation of "air corridors" through which air dissects down to the pleura and forms pneumatoceles, a form of subpleural emphysema.

Traumatic pneumatocele has a different pathophysiology from the infectious type [28]. Initially,

the lung is compressed by the external traumatic force, followed by rapid decompression from increased negative intrathoracic pressure. A "bursting lesion" of the lung occurs, leading to pneumatocele formation.

Epidemiology

Incidence of postinfectious pneumatocele formation ranges from 2 to 8 % of all cases of pneumonia in children [29]. However, it can be as high as 85 % in staphylococcal pneumonias. Pneumatoceles are therefore found more frequently in infants and young children. One study reported that 70 % of pneumatoceles occurred in children younger than 3 years [30].

Etiology

Infectious etiologies associated with pneumatocele formation include *Staphylococcus aureus* (most common), *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, group A *Streptococci*, *Serratia marcescens*, *Klebsiella pneumoniae*, adenovirus, *Pseudomonas aeruginosa*, and *Mycobacterium tuberculosis*. *Noninfectious etiologies* include hydrocarbon ingestion, trauma, and positive pressure ventilation (PPV) especially among premature infants with respiratory distress syndrome [31–34].

Pneumatocele formation is associated with hyperimmunoglobulin E (IgE) syndrome (*Buckley-Job syndrome*) due to higher incidence of *Staphylococcus pneumoniae* resulting from immunodeficiency [35, 36].

Clinical Picture

Children present with typical features of pneumonia, including cough, fever, and respiratory distress. No clinical findings differentiate pneumonia with or without pneumatocele formation.

Physical examination may reveal variable degrees of respiratory distress, with tachypnea, retractions, grunting, and nasal flaring. High fever (40–41 °C) is almost always present. Lung examination findings depend on the stage of the pneumonia. Auscultation of the chest reveals focal or bilateral decreased breath sounds. Inspiratory crackles are frequently heard. As the pneumonia resolves and the pneumatocele persists, the lung examination can be normal or shows only focal decreases in breath sounds, depending on the size of the pneumatocele.

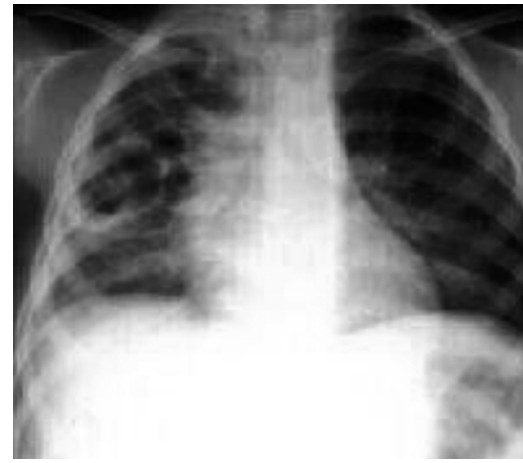

Fig. 9.18 Pneumonia with multiple pneumatoceles

Complications

A *tension pneumatocele* can develop if air trapping continues, most frequently with PPV. Expansion of the pneumatocele can cause hemodynamic instability and severe airway obstruction. If untreated, this can result in respiratory failure and death.

Rupture of a pneumatocele into the pleural space can lead to *pneumothorax*, which can cause lung collapse or bronchopleural fistula.

Secondary infection of a pneumatocele may occur, requiring drainage, which may be diagnostic and therapeutic. If drained, the fluid should be cultured for bacteria and fungus.

Investigations

Laboratory Studies

Blood culture can guide antibiotic therapy. *Sputum analysis* is a good noninvasive method to discover potential pathogens. If effusion is present, *culturing pleural fluid* from thoracentesis can also identify the causative organism.

Imaging Studies

Initial *chest X-ray* may reveal pneumonia, pneumatocele (Fig. 9.18), parapneumonic effusion, or

empyema. Radiographic evidence of a pneumatocele most often occurs on day 5–7 of hospitalization. Rarely, it may be visible on the initial chest radiograph. Chest radiograph findings are shown in the images below. Usually, *chest CT* scan with contrast is not necessary to diagnose a pneumatocele but occasionally helps to differentiate it from a lung abscess. Rarely, *CT-guided needle aspiration* of the pneumatocele can relieve compression from a large and/or tension pneumatocele.

Procedures

Percutaneous catheter drainage should only be considered in the presence of a significant tension pneumatocele, or a secondarily infected pneumatocele, to improve the patient's cardiovascular status [37].

Differential Diagnoses

A pneumatocele should be differentiated from a cystic or compressible mass in the lateral side of the neck. A lung pneumatocele should be differentiated also from a bronchogenic cyst, cystic adenomatoid malformation, hyperimmunoglobulinemia E (JOB) syndrome, pneumococcal infections, pneumonia, pulmonary sequestration, *Staphylococcus aureus* infection, and tuberculosis.

Treatment

Treatment of the underlying pneumonia with antibiotics is the first-line therapy. Close observation in the early stages of the infection and periodic follow-up care until resolution of the pneumatocele is usually adequate treatment.

In most circumstances, pneumatoceles are asymptomatic and do not require surgical intervention [38]. *Percutaneous catheter drainage* of a pneumatocele that involves >50 % of hemithorax with severe atelectasis, tension pneumatocele, bronchopleural fistula, or an infected pneumatocele is rarely required. Recently, *video-assisted thoracoscopy* has been used successfully to treat enlarging multicystic pneumatoceles [39].

Prognosis

In general, a noncomplicated pneumatocele carries an excellent prognosis. The natural course is slow but complete resolution with no further clinical sequelae. Rare complications, including tension pneumatocele, can lead to death from respiratory or cardiovascular collapse due to progressive enlargement of the pneumatocele. However, this is rare and, if detected promptly, can be properly treated.

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Tumors of the Pharynx

10

Mahmoud Sakr

10.1 Tumors of the Nasopharynx

The nasopharynx is the most superior part of the pharynx. It is a vault-shaped dome that acts as a conduit between the nasal cavity and the oropharynx for respiration (Fig. 10.1). It is bounded from all sides by rigid bony structures with little soft tissue overlying, except part of its floor, which is composed of the soft palate.

10.1.1 Benign Tumors (Nasopharyngeal Fibroma/ Angiofibroma)

Nasopharyngeal fibroma or angiofibroma is a benign tumor, which is highly destructive causing pressure necrosis of the bone. It is composed of immature fibroblasts and blood vessels and is covered by intact mucous membrane unless traumatized.

It commonly affects young males. Usually the boy presents with progressive nasal obstruction, recurrent epistaxis, and nasal discharge. If left untreated, it may expand into the orbit and cause blindness. Physical examination reveals a firm mass in the nasopharynx (Fig. 10.2).

Transpalatal excision is the treatment of choice.

10.1.2 Malignant Tumors

The nasopharynx is called the "blind spot" (Fig. 10.2). Diagnosis is usually delayed for 8–18 months. It is a common site for occult primary tumors. Approximately 80–85 % of cancers are squamous cell carcinoma (SCC), and the remainder is primarily lymphoma, adenocarcinoma, and melanoma [1]. There are two varieties of SCC,

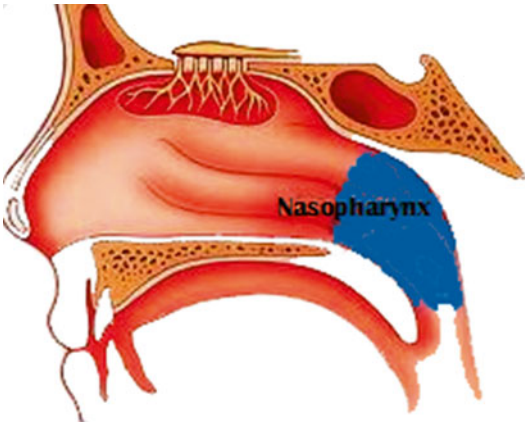

Fig. 10.1 Anatomy of the nasopharynx. The uppermost part of the pharynx

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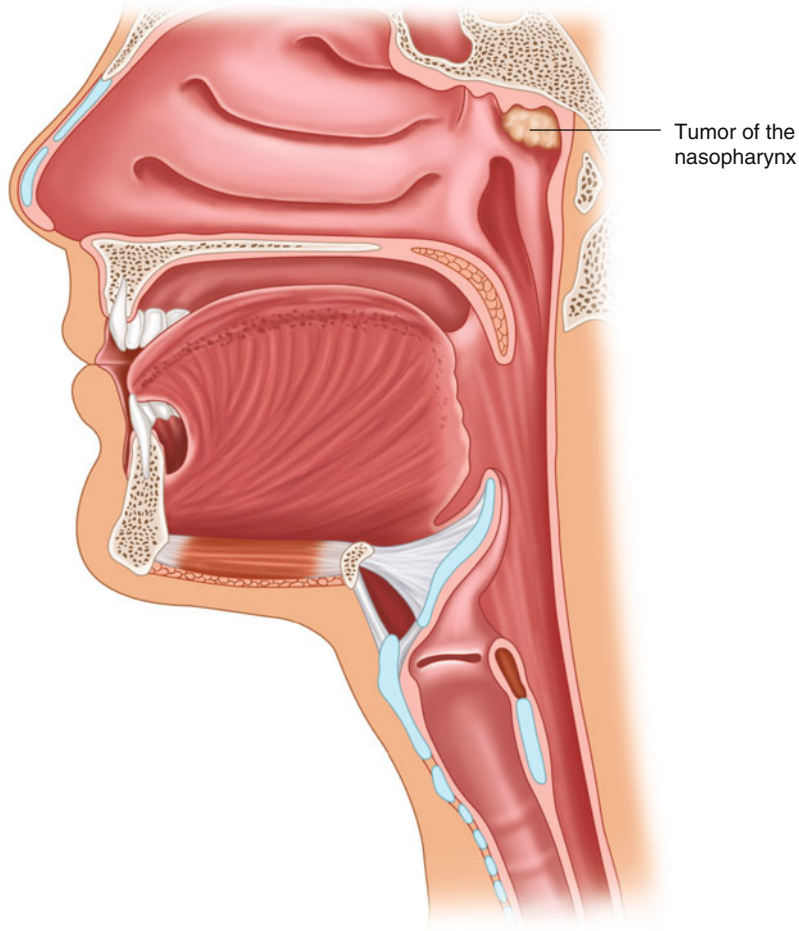

Fig. 10.2 Location of nasopharyngeal tumor

keratinizing and nonkeratinizing of which lymphoepithelioma is an important form characterized by islands of lymphocytes scattered through the epithelioid tumor.

In the WHO classification, three histopathological types of nasopharyngeal carcinomas (NPC) are recognized [2]:

Type I: SCC with varying degrees of differentiation
Type II: Nonkeratinizing carcinoma
Type III: Undifferentiated carcinoma (often known as lymphoepithelioma) (Fig. 10.3).

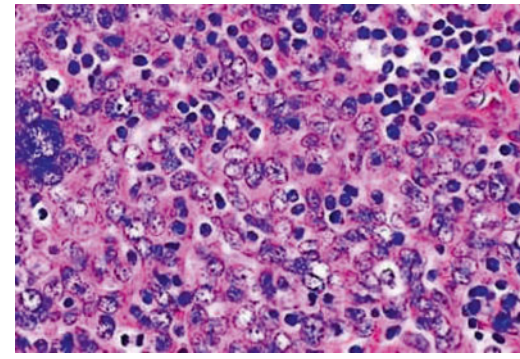

Fig. 10.3 Undifferentiated nasopharyngeal carcinoma (lymphoepithelioma), HE 600×450

Nasopharyngeal cancer is more common among the Chinese, and those patients have a high titer of Epstein-Barr virus antibodies in their serum [3]. In the early course of the disease, the only symptom may be a sense of needing to clear the throat. Later, unilateral nasal obstruction, epistaxis,

and/or discharge, cervical adenopathy and cranial nerve palsy may be noted. Unilateral conductive impairment of hearing, with or without tinnitus, is also a common presenting symptom due to obstruction of the Eustachian tube by the primary tumor. The obstruction may lead to serious otitis media. The rich lymphatic network within the parapharyngeal space results in contralateral metastases and affection of retropharyngeal LNs near the jugular foramen as well as possible involvement of the last four cranial nerves [4].

The primary tumor extent should be evaluated by both CT scan and MRI. The MRI is more sensitive than CT for detection of the primary tumor, its direct soft tissue extent, regional nodal metastasis, and perineural extension; however, CT is a better tool for defining bone erosion. Positron emission tomography (PET) scanning in NPC may be useful in detecting both local failures after treatment and distant metastases; however, its definitive role remains to be defined.

Histological confirmation of the diagnosis is essential. The diagnostic sensitivity of biopsy under local anesthesia has been found to be comparable to that obtained by examination under general anesthesia. The biopsy is facilitated by direct visualization of the nasopharynx with a fiber-optic nasopharyngoscope. Patients with advanced stage NPC have been reported to have higher plasma EBV-DNA levels than those with early-stage disease [5]. Further studies demonstrated that EBV-DNA may be a valuable tool for monitoring of NPC patient response during radiotherapy and chemotherapy [6], as well as early detection of tumor recurrence [7].

The treatment of choice for NPC is radiotherapy (RT), except for small early lesions and tumors that recur after RT. With advances in technology, the modern RT for NPC should be that of three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) with inverse planning. Such techniques yield superior local control when compared to standard 2D methods [8]. The use of adjuvant chemotherapy cannot be recommended as a standard therapeutic approach in patients with locoregionally advanced disease [9–12].

In absence of significant skull-base erosion and intracranial extension or cranial nerve palsy, surgical resection of recurrent or persistent local tumor is the mainstay salvage treatment [13, 14]. There are several approaches to the nasopharyngectomy, namely, transcervical, transoral and transpalatal, posterolateral, trans-maxillary (maxillary swing) [14], and midface deglove [15]. There is no "ideal" surgical approach that suits all cases of local relapses and therefore it should be tailored to the individual patients depending on the disease extent. Cervical LN metastases are usually found in 70 % of patients when first diagnosed, and radical neck dissection (RND) is the treatment of choice in such cases.

The median survival for patients with distant metastases is around 9 months. Wide ranges of chemotherapeutic agents have been used in the treatment of patients with locally recurrent and metastatic NPC. New active agents include paclitaxel and gemcitabine. Cisplatin-containing regimens yielded with encouraging response rates of 50–90 % [16].

10.2 Tumors of the Oropharynx

The oropharynx is the middle part of the throat which includes the base of the tongue, the tonsils, the soft palate, and the walls of the pharynx. Oropharyngeal cancer (OPC) is rather uncommon. It can occur at any age, but is more likely to affect people over the age of 50 years, and is more common in men than in women. Oropharyngeal cancer can be divided into two types, the one related to human papillomavirus (HPV) infection (HPV-positive cancer) [17–20] and HPV-negative cancer, which is usually linked to alcohol or tobacco use [21]. There are several differences between HPV-positive and HPV-negative tumors in many aspects including histological appearance, differentiation, risk factors, and prognosis [22].

There are different histopathological types of OPC, but the most common is the squamous cell carcinoma (SCC) (Fig. 10.4). Other rare types include salivary gland cancer, lymphoma, small-cell cancer, and sarcoma.

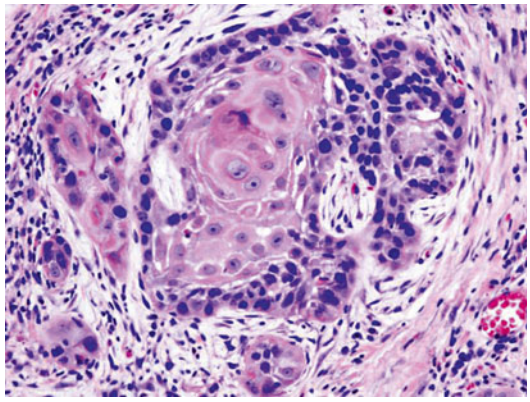

Fig. 10.4 Squamous cell carcinoma (SCC) of the oropharynx, HE 600×450

The factors that can increase the risk of developing OPC include smoking and chewing tobacco, heavy alcohol use, poor nutrition, HPV and EBV infections, Plummer-Vinson syndrome, asbestos exposure, and P53 mutation [23].

The most common symptoms of OPC include a persistent sore throat, dysphagia, unexplained weight loss, voice changes, earache, a lump in the back of the throat or mouth (Fig. 10.5), a lump in the neck, retrosternal dull pain, and cough.

The primary tumor extent should be evaluated by both CT scan and MRI. Histological confirmation of the diagnosis is essential.

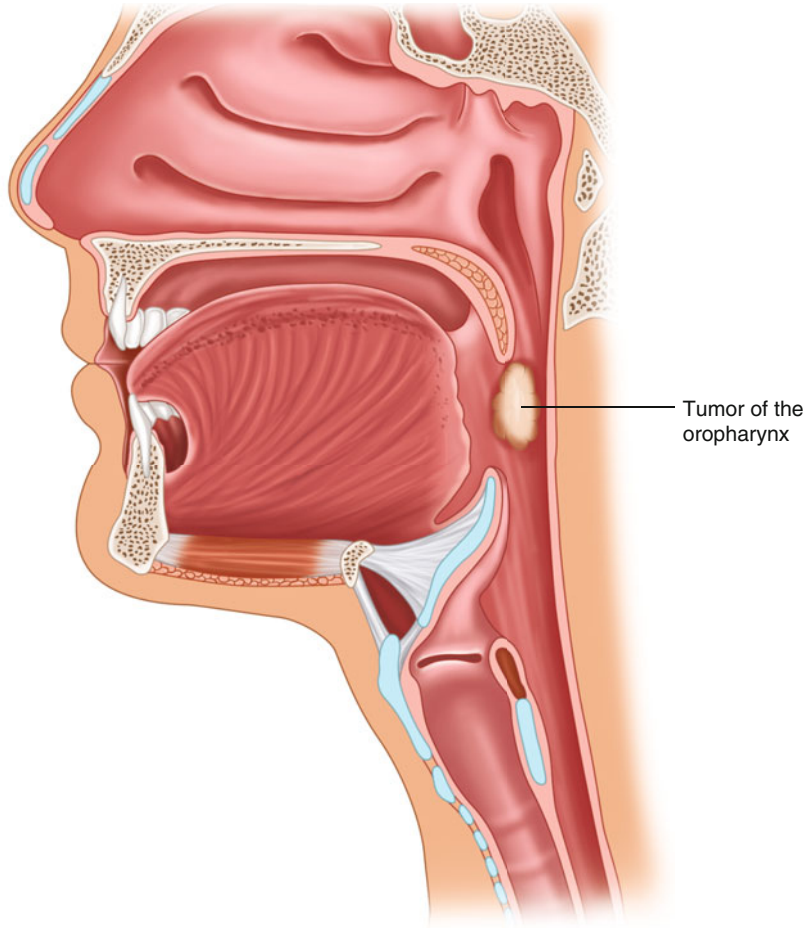

Fig. 10.5 Location of nasopharyngeal tumor

Treatment of OPC depends on the stage and grade of the tumor as well as the general condition of the patient. The usual treatments include surgery, radiotherapy (RT), chemotherapy, and targeted therapies.

In *early* OPC, both surgery and RT are equally effective. The latter is used if surgery is likely to seriously affect the patient's speech and swallowing. Larger tumors are often treated with a combination of different treatments. Currently, intensity-modulated radiotherapy (IMRT) is used to precisely shape the RT beams to the area of cancer, thereby improving its efficacy and reducing its side effects [24]. Radiotherapy can be used as radical RT for cure or as adjuvant therapy after surgery to reduce the risk of recurrence. For *locally advanced* OPCs, RT may be given together with chemotherapy (chemoradiation) [25]. It can also be given to cervical LNs.

Surgical resection may also be used, although RT with or without chemotherapy is more commonly used. Surgery can also be used to relieve symptoms or to treat recurrence after RT. Cervical LNs are treated by neck dissection.

Chemotherapy may be given, before RT or surgery (neoadjuvant chemotherapy), at the same time as RT (chemoradiation), after RT or surgery (adjuvant chemotherapy) and for metastatic disease. Chemoradiation may be used instead of surgery in locally advanced disease. This can avoid the effects on speech and swallowing that surgery may cause. The side effects, particularly a sore skin and mouth, are worse when chemotherapy and RT are given together.

Targeted therapies for OPC include "cetuximab" infusion (the most commonly used) which interferes with attachment of epidermal growth factor (EGF) on their receptors in cancer cells, thereby stopping growth of the tumor and may also make it more sensitive to the effects of RT [26].

Several studies have found better prognosis for HPV-positive tumors and reported similar findings in patients treated with either primary surgical or nonsurgical therapies [27–30]. A meta-analysis confirmed that HPV-positive OPC cancer patients had a 28 % lower risk of death than their negative counterparts [31]. The HPV status was also associated with a better response to induction chemotherapy in two recent studies [32, 33].

10.3 Tumors of the Hypopharynx

The hypopharynx is the region between the oropharynx above and the esophageal inlet below. Hypopharyngeal cancers (HPCs) are often named for their location, including pyriform sinus, lateral pharyngeal wall, posterior pharyngeal wall, or post-cricoid pharynx. The pyriform sinus is involved in 65–85 % of cases, the posterior pharyngeal wall in 10–20 %, and the post-cricoid area in 5–15 % [34].

There is a male preponderance with a male-to-female ratio of about 3:1. The incidence of HPC rises in people above the age of 40 years [35]. Patients diagnosed with HPC are typically men aged 55–70 years with a history of tobacco use and/or alcohol ingestion. Asbestos may pose an independent risk for the development of HPC [36]. The role of human papillomavirus (HPV) in HPC is unclear, although it may play more of a role in cancers of the oropharynx and oral cavity. Nutritional (Plummer-Vinson syndrome, iron and vitamin C deficiencies) and metabolic deficiencies are implicated in rare instances.

Symptoms of HPC include dysphagia, chronic sore throat, and FB sensation in the throat or referred *otalgia*. A metastatic cervical LN is often the presenting symptom in approximately 50 % of cases. Other symptoms, which usually develop later, include weight loss, hemoptysis, laryngeal stridor, and hoarseness of voice due to direct extension of the tumor into the arytenoid cartilage or to the recurrent laryngeal nerve (RLN). Halitosis (fetid breath) may occur due to bacterial overgrowth in a fungating necrotic tumor. Nearly 70 % of patients with HPC have stage III disease at the time of presentation.

More than 95 % of HPCs are SCCs, less than 60 % are keratinizing, 33 % are nonkeratinizing, and all are usually poorly differentiated. Variants

include basaloid SCC, superficial spreading cancer, sebaceous cancer, adenosquamous cancer, signet ring, and verrucous types. Uncommon histological types include adenocarcinoma, lymphoma, and sarcoma.

Flexible fiber-optic endoscopic examination is important for localization and staging of the primary tumor. Typically, HPC is advanced at presentation, and an obvious abnormality is usually present in either the pharynx (Fig. 10.6) or the neck. Typical findings of HPC include mucosal ulceration, pooling of saliva in the pyriform fossa, edema of the arytenoids, or fixation of the cricoarytenoid joint and/or true vocal cords. During the flexible laryngoscopy, the assessment of vocal cord is important for staging.

In general, 30 % of patients have local disease at the time of diagnosis, 60 % have local regional disease, and 10 % present with distant metastases. Tumors of the medial wall of the pyriform sinus usually spread to the aryepiglottic folds and may invade into the larynx by involving the paraglottic space, while tumors of the lateral wall and apex commonly invade the thyroid cartilage. Metastasis to the regional LNs is common and should be assessed for size, location, and mobility. Differentials include cat scratch disease, Hodgkin disease, NHL, pharyngitis, and extramedullary plasmacytoma.

Imaging studies should *not* be considered as a replacement for a flexible fiber-optic examination. *Chest X-ray* films are important to check for

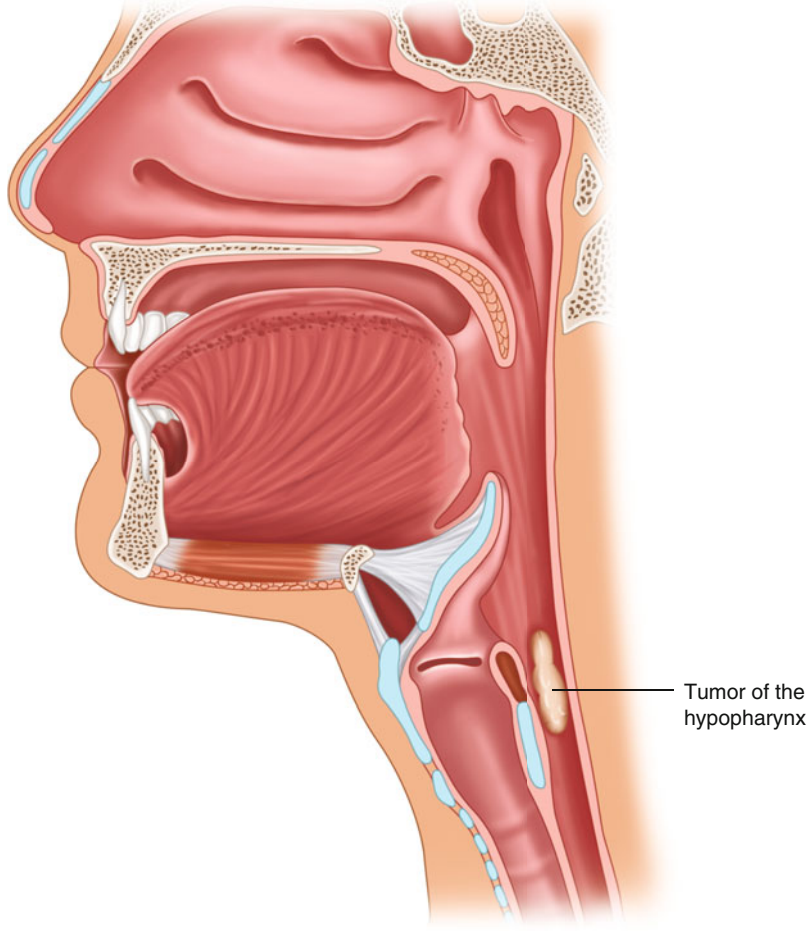

Fig. 10.6 Location of hypopharyngeal tumor

lung metastases, synchronous lung cancer, and comorbid heart or lung disease. *Barium swallow* is not usually used unless the lesion is too large to introduce a scope. Its findings can help determine the inferior border of the lesion and involvement of the esophageal inlet. In order to visualize the primary tumor and identify regional LNs prior to definitive treatment, contrast-enhanced *CT scan and MRI* are used; MRI (with gadolinium) is better than CT for delineating soft tissue extension, while CT scan (with bone windows) is superior in detecting bone invasion. If HPC is aggressive (T4, N2-N3, or poorly differentiated), chest CT scan or *positron emission tomography* (PET) scan is considered for the most sensitive detection of metastases. Integrated PET/CT is helpful in locating and localizing the occult primary tumor and regional disease, as well as in differentiating between malignant disease and posttreatment changes.

Examination under anesthesia (EUA) is critical for defining the anatomic extent of disease and for obtaining a *biopsy*, which is necessary to establish the diagnosis. Biopsies of all suspicious lesions are usually taken during a triple endoscopy (*panendoscopy*). Bronchoscopy and esophagoscopy are performed to rule out synchronous cancers. Multiple pharyngeal tumors can be found in nearly 15 % of cases, while synchronous lung or esophageal tumors can be found in approximately 5–10 %.

The goal of management of HPC is to achieve the highest locoregional control with the least functional injury, preserving respiratory function, deglutination, and phonation. Several new treatment options have been introduced recently. These include modern conservative surgical approaches that include robotic assistance and laser dissection, and new RT techniques such as IMRT for increased conformal irradiation, and the use of biologic agents such as the monoclonal antibody cetuximab (Erbitux), which specifically binds and prevents the activation of the epidermal growth factor receptor (EGFR) [37].

No single therapeutic regimen offers a superior advantageregardingsurvival.Laryngopharyngectomy and neck dissection with postoperative adjuvant RT have been the most frequently used surgical therapies for HPC. Radiotherapy alone can be considered in patients with early tumors and no cervical nodal involvement. Combined chemotherapy and RT directed at the primary tumor are the most common nonsurgical approaches for advanced tumors [38].

In general, early HPC is not common. Small lesions, particularly of the lateral or posterior wall, may be amenable to partial pharyngectomy or partial laryngopharyngectomy (PLP) [39]. In such cases, RT may be the treatment of choice, offering better functional outcome and the ability to address occult cervical nodal disease [40].

Various primary surgical options are used to manage HPC attempting at yielding favorable local control and functional outcomes in properly selected patients. For T1/T2 tumors, the choices of appropriate therapy include both primary RT and conservation surgical approaches. Conservation surgery may be precluded in favor of RT in patients with poor pulmonary function or poor overall general condition that prevents them from tolerating minor aspiration in the early postoperative period. Similarly, tumor involvement of certain anatomic subsites such as the pyriform apex or post-cricoid region may also favor RT over conservation surgery. Most T4 lesions and many extensive T3 tumors with poor residual laryngeal function warrant more radical primary surgical therapies. The absence of functional outcome data that compare conservation surgery with nonsurgical approaches complicates the treatment decision.

Conservation procedures include (1) *partial lateral pharyngectomy*, which provides excellent swallowing outcomes in tumors confined to the lateral pyriform sinus wall. In a recent series of 30 cases, the 3-year local control rate using this approach was 88.5 % [39, 41]; (2) *supraglottic hemi-pharyngolaryngectomy*, which is essentially an extension of the traditional supraglottic laryngectomy to include the pyriform sinus mucosa on one side [42]. It provides high local control rates for small tumors of the upper pyriform sinus [43]; however, the wide application of this procedure has been limited by concerns over high recurrence rates for more extensive pyriform lesions; (3) *supra-cricoid hemi-laryngopharyngectomy*, which can be used to safely encompass more extensive T2 pyriform

lesions [44]. Postoperatively, there is a gradual recovery of swallowing ability such that more than 90 % of patients no longer depended on gastrostomy tube at 1 year after the operation [45]; (4) *posterior partial pharyngectomy*, which is useful for limited midline posterior pharyngeal wall tumors; and (5) transoral CO_2 laser resection, which involves specialized transoral endoscopes with an operating microscope coupled to a CO_2 laser. It can be used to excise all HPCs that are candidates for open conservation surgery, in addition to the added theoretical advantage of not violating other normal anatomic structures of the anterior neck, thus yielding better functional outcomes. An 87 % local control rate has been reported using transoral laser procedures in a series of 129 pyriform sinus cancers [46].

Radical surgical procedures that do not spare the larynx are typically reserved for T4a tumors and for some smaller tumors in which laryngeal function after primary chemoradiotherapy is expected to be poor. Restoration of good swallowing function can be achieved with primary closure in some tumors that required total laryngectomy and limited partial pharyngectomy; however, pedicled or free tissue transfer is often required to achieve pharyngeal closure. Tumors that require total laryngopharyngectomy also need a free tissue transfer for successful restoration of swallowing function.

Reconstruction is often accomplished using pectoralis major pedicled myocutaneous flaps for smaller partial pharyngectomy defects and either a free tissue transfer of jejunum or various tubed fasciocutaneous free flaps (e.g., radial forearm or anterolateral thigh) for larger defects. Gastric pull-up techniques may be required to reconstruct excisions that produce long esophagectomy defects. In 2011, the first completely synthetic trachea was produced and transplanted. It was made of nanocomposite material that allowed the stem cells taken from the patient's bone marrow and lining cells from the nose to be seeded with the patient's tissue.

Some surgeons consider prevertebral musculature or C-spine involvement, massive mediastinal nodal enlargement, and carotid artery involvement to be contraindications to surgery. These cases usually represent advanced and aggressive disease.

Hypopharyngeal tumors metastasize to the neck early, most likely with pyriform fossa tumors and least likely with post-cricoid ones. Because of the high incidence of clinically positive nodes with HPC, treating both neck nodes at the time of management of the primary lesion is prudent.

Patients with early lesions and negative nodes have a 5-year survival rate higher than 70 % [47]. Most cases, however, are advanced at the time of presentation, and the overall survival rate rarely exceeds 25 % in any series. General local control rates have been reported to be around 80 % [48]. Distant metastases occur in approximately 25 % of patients. The lungs, liver, and bones are the main organs affected. The principal cause of death is local tumor recurrence. Distant metastases, second primary cancers, and comorbid diseases are secondary causes.

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Surgery of the Thyroid Glands

11

Mahmoud Sakr

11.1 Embryology

In the fetus, at 3–4 weeks of gestation, the thyroid gland appears as an epithelial proliferation in the floor of the pharynx at the base of the tongue between the tuberculum impar and the copula linguae, at a point later indicated by the foramen cecum. The thyroid then descends in front of the pharyngeal gut as a bilobed diverticulum through the thyroglossal duct. Over the next few weeks, it migrates to the base of the neck. During migration, the thyroid remains connected to the tongue by a narrow canal, the thyroglossal duct.

Thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) start being secreted from fetal hypothalamus and pituitary gland, respectively, at 18–20 weeks of gestation, and fetal production of thyroxin (T4) reaches a clinically significant level at 18–20 weeks. Fetal triiodothyronine (T3) remains low (<15 ng/dL) until 30 weeks of gestation and increases to 50 ng/dL at term. Fetal self-sufficiency of thyroid hormones protects the fetus against abnormalities such as brain development anomalies caused by maternal hypothyroidism [1].

The portion of the thyroid containing the parafollicular C cells, those responsible for the production of calcitonin, are derived from the fourth pharyngeal pouch endoderm (at 5th to 6th weeks stage). This is first seen as the ultimobranchial body, which joins the primordial thyroid gland during its decent to its final location in the anterior neck. The final coalescing occurs when the fetus is approximately 9 weeks old and the ultimobranchial C cells (parafollicular cells) reside within the basement membranes of follicles and form approximately 10 % of the adult thyroid. Calcitonin is secreted by the parafollicular cells that are distinct from follicular cells of the thyroid being derived from neural crest rather than the endoderm. This explains why medullary carcinomas are associated with pheochromocytomas and other tumors with a common cell origin.

11.2 Surgical Anatomy

The thyroid gland is a brownish-red and highly vascular endocrine gland located anteriorly in the lower neck, extending from the level of the fifth cervical vertebra (C5) down to the first thoracic (T1). The normal gland weighs between 20 and 35 g in adults and consists of two elongated lateral lobes with superior and inferior poles connected by a median isthmus overlying the second to fourth tracheal rings. The superior poles extend

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toward the oblique line of the thyroid cartilage, lying deep to the sternothyroid muscle and superficial to the cricothyroid muscle [2].

A conical *pyramidal lobe* often ascends from the isthmus or the adjacent part of either lobe (more often the left) toward the thyroid cartilage, to which it may be attached by a fibrous or fibromuscular band, the levator of the thyroid gland. Remnants of the thyroglossal duct may persist as accessory nodules or cysts of thyroid tissue between the isthmus and the foramen cecum of the tongue base. Usually, two pairs of parathyroid glands lie in proximity to the thyroid gland.

11.2.1 Fascia and Ligaments

The thyroid gland is enveloped by a fibrous *capsule* condensed from the pretracheal fascia. The *anterior suspensory ligament* extends from the superomedial aspect of each thyroid lobe to the cricoid and thyroid cartilage. The posteromedial aspect of the gland is attached to the side of the cricoid cartilage, first and second tracheal rings, by the *posterior suspensory ligament* (*Berry's ligament*). This firm attachment of the gland to the laryngoskeleton is responsible for movement of the thyroid gland and related structures during swallowing. On its way to the larynx, the recurrent laryngeal nerve (RLN) usually passes deep to Berry's ligament or between the main ligament and its lateral leaf. Deep to the ligament, but lateral to the nerve, is the posteromedial portion of the thyroid lobe, which may be overlooked during thyroidectomy [3]. Modern surgical resection of the thyroid gland involves a "capsular dissection." Maintenance of the capsule helps reduce the damage to the plexus of veins that lie on its surface and its highly vascular parenchyma. Additionally, it reduces chance of injury to the adjacent neurovascular structures.

11.2.2 Relation with Strap Muscles

The lateral surface of the thyroid is covered by the sternothyroid muscle, and its attachment to the oblique line of the thyroid cartilage prevents the superior pole from extending superiorly under the thyrohyoid muscle. More anteriorly are the sternohyoid and superior belly of the omohyoid muscle, overlapping inferiorly by the anterior border of the sternocleidomastoid (SCM) muscle. The sternohyoid and sternothyroid muscles are joined in the midline by an avascular fascia that must be incised to retract the strap muscles laterally in order to access the thyroid gland during thyroidectomy. Transection of strap muscles, if necessary for better exposure, should be done high in the neck because the motor nerve supply from the *ansa cervicalis* enters these muscles inferiorly.

11.2.3 Arterial Supply

The arterial supply to the thyroid gland comes from the superior and inferior thyroid arteries and, occasionally, the thyroidea ima. These arteries have abundant collateral anastomoses with each other, both ipsilaterally and contralaterally.

11.2.3.1 Superior Thyroid Artery (STA)

The superior thyroid artery (STA) arises as the first branch of the external carotid artery (ECA) and passes in a caudal direction to join the superior pole of the thyroid. It has close relations to the external branch of the superior laryngeal nerve (SLN), which lies deep to the artery before turning medially to supply the cricothyroid muscle. High ligation of the STA during thyroidectomy places this nerve at risk of inadvertent injury, which would produce dysphonia by altering pitch regulation. The STA divides into anterior and posterior branches. From the posterior branch, a small parathyroid artery passes to the superior parathyroid gland [4].

11.2.3.2 Inferior Thyroid Artery (ITA)

The inferior thyroid artery (ITA) arises from thyrocervical trunk, a branch of the subclavian artery, and passes in the tracheaesophageal groove (TEG) into the posterolateral aspect of each lobe. Most of its branches penetrate the posterior aspect of the lateral lobe. It has a variable

branching pattern and a variable relationship with the recurrent laryngeal nerve (RLN), most commonly passing in front of the nerve.

The RLN can be found after it emerges from the superior thoracic outlet, in a triangle bounded laterally by the common carotid artery (CCA), medially by the trachea, and superiorly by the thyroid gland [5]. Another hint to the location of the RLN is the Zuckerkandl tubercle, an extension of the thyroid, close to Berry's ligament. On rare occasions, the nerve may pass directly from the vagus to the larynx, close to the superior thyroid vessels [6].

11.2.3.3 Thyroidea Ima Artery

The "thyroidea ima" is a single artery that arises from the brachiocephalic artery or the arch of the aorta. It enters the thyroid gland at the inferior border of the isthmus and is present in less than 10 % of patients.

11.2.4 Venous Drainage

The veins of the thyroid gland form a plexus of vessels lying in the substance and on the surface of the gland. This plexus is drained by three pairs of veins. The *superior and middle thyroid veins* drain into the internal jugular vein (IJV), while the *inferior thyroid veins* follow different paths on each side. The right passes anterior to the innominate artery to the right brachiocephalic vein or anterior to the trachea to the left brachiocephalic vein. On the left side, drainage is to the left brachiocephalic vein. Occasionally, both inferior veins form a common trunk called the *thyroid ima vein*, which empties into the left brachiocephalic vein.

11.2.5 Lymphatics of the Thyroid Gland

Lymphatic drainage of the thyroid gland is extensive and flows multi-directionally, with intraglandular and subcapsular lymphatic drainage IJV. Immediate lymphatic drainage flows to the periglandular nodes, to the prelaryngeal (Delphian), pretracheal and paratracheal nodes along the RLN, and then to mediastinal lymph nodes (LNs). Regional metastases of the thyroid carcinoma can also be found laterally, higher in the neck along the IJV. This can be explained by tumor invasion of the pretracheal and paratracheal nodes causing an obstruction of normal lymph flow.

11.2.6 Innervation of the Thyroid Gland

Principal innervation of the thyroid gland is derived from the autonomic nervous system. Parasympathetic fibers come from the vagus nerves, and sympathetic fibers are distributed from the superior, middle, and inferior ganglia of the sympathetic trunk. These small nerves enter the gland along with the blood vessels. Autonomic nervous regulation of the glandular secretion is not clearly understood, but most of the effect is postulated to be on blood vessels, hence the perfusion rates of the glands [7].

11.2.6.1 Nerves Related to the Thyroid Gland

The relationship of the thyroid gland to the RLN and to the external branch of the superior laryngeal nerve (SLN) is of major surgical significance because damage to these nerves leads to disability in phonation or to difficulty breathing. Both nerves are branches of the vagus nerve.

1. Recurrent laryngeal nerve (RLN)

   The *right* RLN arises from the vagus nerve, loops posteriorly around the subclavian artery, and ascends behind the right lobe of the thyroid. It enters the larynx behind the cricothyroid muscle and the inferior cornu of the thyroid cartilage and innervates all the intrinsic laryngeal muscles except the cricothyroid. The *left* RLN comes from the left vagus, loops posteriorly around the arch of the aorta, and ascends in the tracheoesophageal groove posterior to the left lobe of the thyroid, where it enters the larynx and innervates the musculature in a similar fashion as the right nerve.

   Several factors make the RLN vulnerable to injury, especially in the hands of inexperienced

surgeons. The nerve is not always in the TEG where it is expected to be. It can often be posterior or anterior to this position or may even be surrounded by thyroid parenchyma. Thus, the nerve is vulnerable to injury if it is not visualized and traced up to the larynx during thyroidectomy. The variable relationship of the RLN to the ITA is another factor (Fig. 11.1). The nerve

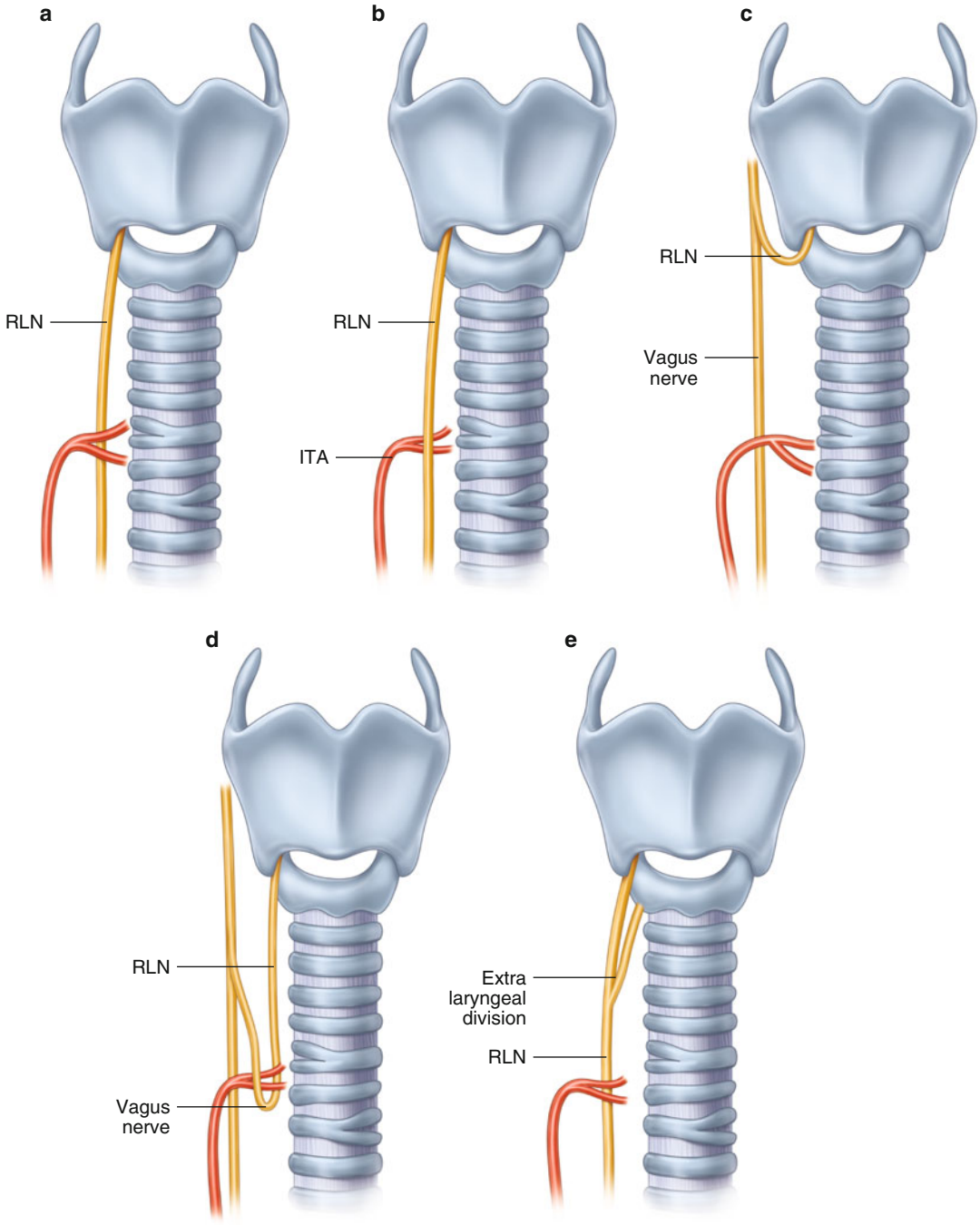

Fig. 11.1 Anatomical relations between the recurrent laryngeal nerve (*RLN*) and inferior thyroid artery (*ITA*) The RLN may pass posterior (**a**), anterior (**b**), or superior (**c**), to the ITA. The RLN may also make a loop around the ITA (**d**), or pass posterior to the artery and give off an extralaryngeal division (**e**)

often passes anterior, posterior, or through the branches of the ITA. Medial traction of the lobe often lifts the nerve anteriorly, thereby making it more vulnerable. Likewise, ligation of this artery, practiced by many surgeons, may be dangerous if the nerve is not identified first. Moreover, in the presence of large nodules, the RLN may not be in their "regular" anatomic location but may be found even anterior to the thyroid gland. Finally, there may be a *non-RLN*, which occurs more on the right side (0.6 %) than on the left side (0.04 %) and is associated with vascular anomalies. Once more, there is no substitute for identification of the nerve in a gentle and careful manner.

2. External branch of the superior laryngeal nerve (SLN)

   The external branch of the superior laryngeal nerve (SLN) innervates the cricothyroid muscle. It is important to the pitch of voice as the cricothyroid muscle is tensor of the vocal cords. In most cases, this nerve lies close to the vascular pedicle of the superior pole of the thyroid lobes descending on the fascia of the inferior pharyngeal constrictor. In some patients, the external branch of the SLN lies on the anterior surface of the thyroid lobe, making the possibility of damage during thyroidectomy even greater. In only 15 % of patients is the SLN sufficiently distant from the superior pole vessels to be protected from manipulation by the surgeon. Unfortunately, many surgeons do not even attempt to identify this nerve before ligation of the upper pole vessels of the thyroid [8].

11.2.7 The Parathyroid Glands

The parathyroid glands are small glands that secrete parathyroid hormone (PTH), the major hormone that controls serum calcium homeostasis. Usually four glands are present (in about 80 % of cases), two on each side, but 3–6 glands have been reported. Because of their small size, their delicate blood supply, and their usual anatomic position adjacent to the thyroid gland, these glands are at risk of being accidently removed, traumatized, or devascularized during thyroidectomy.

The *superior* parathyroid glands arise embryologically from the *fourth* pharyngeal pouch. They descend only slightly during embryologic development, and their position in adult life remains quite constant. This gland is usually found adjacent to the posterior surface of the middle part of the thyroid lobe, often just anterior to the RLN as it enters the larynx. The *inferior* parathyroid glands arise from the *third* pharyngeal pouch, along with the thymus; hence, they often descend with the thymus. Because they travel so far in embryologic life, they have a wide range of distribution in adults, from just beneath the mandible to the anterior mediastinum. Usually, however, these glands are found on the lateral or posterior surface of the lower part of the thyroid gland or within several centimeters of the lower thyroid pole within the thymic tongue [9].

The parathyroid glands can be recognized by their tan appearance, their small vascular pedicle, and the fact that they bleed freely when biopsy is performed, as opposed to fatty tissue with their darkening color of hematoma formation when they are traumatized. With experience, one becomes much more capable of recognizing the parathyroid glands and of differentiating them from either LNs or adipose tissue. Frozen section examination during surgery can be helpful in their identification [10].

11.3 Histology

The thyroid gland is formed of connective tissue stroma and parenchyma of endocrine cells. The connective tissue (true) *capsule* of the thyroid gives off multiple fibrous *septa* (*trabeculae*) passing into the gland, carrying blood vessels, nerves, and lymphatics, to form *lobules*. The gland is further divided into 20–40 much smaller functional subunits called *follicles* which store a *colloid* substance which functions as a hormone store. The colloid is maintained by a single layer of follicular epithelial cells sitting on a basal lamina. These follicles are surrounded by fenestrated capillaries, lymphatics, and so-called parafollicular or C cells.

Microscopically, each lobe or lobule is supplied by an intralobular artery and vein. It is made of

two types of secretory cells: *follicular cells* that secrete T3 and T4 and, in smaller number, the *parafollicular or clear cell (C cells)*, which secrete thyrocalcitonin. The follicles are separated from each other by a highly vascular connective tissue, and each follicle is lined with a single layer of flattened to low columnar epithelium depending on their degree of activity. The basement membrane can only be seen with the electron microscope.

Oncocytes (Hürthle cells, oxyphilic cells, Ashkenazy cells) are large follicular cells with abundant deep eosinophilic granular cytoplasm and numerous mitochondria. They are commonly seen in long-standing Graves' disease, autoimmune thyroiditis, radiation-induced thyroiditis, follicular-derived neoplasms, and some adenomatoid goiters [11–13].

Solid cell nests (SCN) are thought to represent remnants of the ultimobranchial body, which in turn is derived from the branchial cleft pouch complex 4–5. They are not an uncommon finding in the posterolateral or posteromedial portion of the lateral lobes of the thyroid gland. They can be found in up to 28 % of glands. Histologically, epithelial cells in nests and cords are seen, and small glandular lumina containing a mucinous secretion are often present [14–16].

11.4 Physiology

The function of the thyroid gland is to synthesize, store, and secrete thyroxin (T4) and triiodothyronine (T3). Monoiodotyrosine (MIT) and diiodotyrosine (DIT) are also found in thyroid venous blood.

Inorganic iodide (I^-) is *absorbed* from gastrointestinal tract (GIT) and actively *trapped* by the acinar cells of the thyroid gland via a transport mechanism that is frequently called the "I^- trapping mechanism" or "I^- pump." A transporter named *pendrin* is located on the luminal surface of the follicular cell and is responsible for allowing passage of I^- into the follicle. In the acinar cells, I^- is *oxidized* to iodine (I_2) and *bound* to the 3-position of tyrosine molecules with the aid of the enzyme thyroid peroxidase (TPO) to form MIT and then to the 5-position to form DIT. Two DIT molecules then undergo an oxidative *condensation* with the release of an alanine residue and the formation of T4. Condensation of MIT with DIT results in T3 formation. These reactions occur while the tyrosine molecules are attached to thyroglobulin. The peptide bonds between the iodinated residues and the thyroglobulin are broken by proteases in lysosomes, and so T4, T3, DIT, and MIT are *liberated* into the cytoplasm. The iodinated tyrosines are de-iodinated by a microsomal iodotyrosine dehalogenase. Then, T3 and T4 are *released* into the circulation [17].

Most circulating T3 are derived from peripheral conversion of T4, which is really a prohormone and is significantly less potent than the more metabolically active hormone T3. In the blood, the majority of circulating T3 and T4 are bound to the plasma proteins, mainly thyroxine-binding globulin (TBG) and prealbumin. It is only the "free" unbound forms of hormones that are metabolically active, and T3 is quick acting within few hours, while T4 acts more slowly from 4 to 14 days.

Production of T3 and T4 is regulated by the *hypothalamic-pituitary-thyroid axis* which is a multiloop feedback circuit. The production of T3 and T4 from the thyroid is stimulated directly by the thyroid-stimulating hormone (TSH), produced by the anterior pituitary. Levels of T3 and T4 are also increased indirectly by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus in response to low levels of T3/T4 and acts on the pituitary to increase TSH production. Conversely, TRH and TSH production are suppressed by high levels of T3 and T4. Additionally, TRH production is also suppressed by high levels of TSH. In this way, the circulating levels of active thyroid hormones are self-regulating in disease-free individuals [18].

The thyroid also contains parafollicular C cells, which produce the hormone calcitonin, which reduces levels of serum calcium, counteracting the actions of PTH. This is achieved by inhibiting osteoclast activity in bone, inhibiting renal resorption of calcium, and inhibiting absorption of calcium in the intestines. Blood levels of PTH are far more clinically relevant to calcium homeostasis than calcitonin, and no exogenous replacement for calcitonin is required following thyroidectomy.

11.5 Investigating the Enlarged Thyroid

11.5.1 Serological Investigations

11.5.1.1 Thyroid Function Tests

The serum level of *TSH* should be routinely measured, while *T3 and T4* levels are required if TSH level was abnormal (Table 11.1). When hypothyroidism is confirmed, *thyroid peroxidase* (TPO) antibodies should be requested to check for autoimmune thyroid disease such as Hashimoto's thyroiditis. *Serum thyroglobulin* (Tg) level does not help in the initial management of thyroid nodule and is *not* recommended. Serum Tg levels may be elevated in patients with cancer but are not diagnostic, since similar increases are seen in benign thyroid disorders. However, serum Tg is a useful test in the follow-up of patients who have undergone thyroid resection for differentiated thyroid cancer. A level >10 ng/ml is a reliable indicator of locally recurrent or metastatic disease and predicts the need for ablative dose of ^{131}I [19, 20].

Basal plasma *calcitonin* levels may be useful if MTC is suspected (family history of MTC or paraneoplastic syndromes, such as Cushing's syndrome (ACTH) or carcinoid syndrome with watery diarrhea and vasomotor flushing). In addition, pheochromocytoma is associated with MTC in MEN type II, and patients present with sympathetic nervous system hyperactivity [21].

Table 11.1 Serological tests in thyroid disease

TSH	Additional testing	Diagnosis
Normal	Not needed	Euthyroid
Decreased	Free T4 ↑ Free T4 normal Free T4 ↓	Hyperthyroid T3 thyrotoxicosis Nonthyroid dis. or drugs
Increased	Free T4 ↑ Free T4 normal Free T4 ↓	Thyroid resistance or pituitary tumor Subclinical hypothyroid Hypothyroid

11.5.2 Imaging

11.5.2.1 Ultrasonography (US)

Ultrasonography (US) is the imaging study of choice for thyroid nodules. It can identify nodules too small to be palpated, the presence of multiple nodules and central or lateral neck lymphadenopathy and provides accurate measurements of nodule diameter allowing serial scans and better assessment of *growth*. Additionally, it allows characterization of nodules by sonographic features that suggest malignancy. *Comet tail sign* and *coarse calcification* suggest very low risk of malignancy. Hypoechoicity and absent halo with indistinct margin are associated with moderate risk of malignancy. The presence of microcalcification is highly suggestive of malignancy, especially papillary thyroid carcinoma (PTC) [22] (Fig. 11.2).

Color flow patterns are categorized as (a) type 1, no blood flow; (b) type 2, perinodular flow; and (c) type 3, intranodular blood flow (perinodular vessels may or may not be present). Although nonspecific, thyroid cancers may have internal hypervascularity, whereas benign nodules may have peripheral vascularization. However, type 3 vascularization can be found in both benign and malignant nodules [23]. Completely avascular nodules are more likely to be benign.

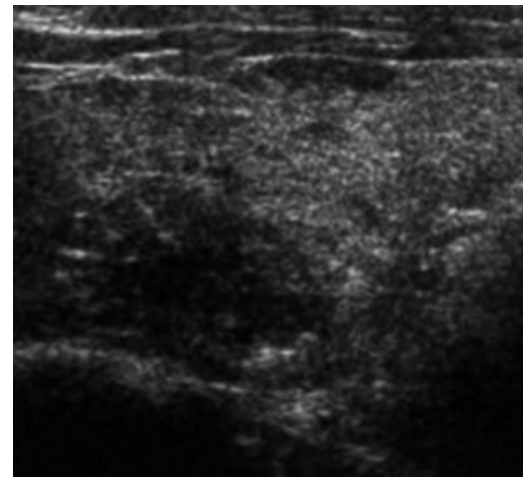

Fig. 11.2 Ultrasonography showing hypoechoic, ill-defined margin and microcalcifications. Biopsy proved to be a papillary thyroid carcinoma (PTC)

There is certainly some subjectivity to sonographic features, and characteristics vary depending on the histology such that US alone cannot reliably distinguish malignant from benign lesions. Although they do not obviate the need for biopsy, these features are extremely useful in selecting the site within a nodule for fine-needle aspiration biopsy (FNAB) in order to improve diagnostic yield or to select appropriate nodules to aspirate within an MNG [24, 25].

11.5.2.2 Magnetic Resonance Imaging (MRI) and Computed Tomography (CT)

Magnetic resonance imaging (MRI) is superior to scintigraphy in evaluating substernal (retrosternal) goiters. Magnetic resonance imaging is noninvasive and easily tolerated but is relatively expensive. Unlike contrast media used with CT, contrast media used in MRI do not influence thyroid function. Computed tomography gives structural information about the gland and its relationship to adjacent structures. Both CT and MRI are relatively expensive and have a limited ability in distinguishing between benign and malignant lesions. However, they are necessary in some cases to determine the staging and extent of the disease and in planning surgery. Indications of CT and/or MRI include the presence of a fixed thyroid mass, hemoptysis indicating pulmonary metastasis, cervical LNs, or when limits of the goiter cannot be determined clinically (retrosternal). They can also show involvement of the larynx, pharynx, trachea, esophagus, or major blood vessels [26].

It is important to avoid iodine contrast media in CT scan to ensure subsequent radioiodine treatment uptake by the remaining thyroid tissue is not compromised. This difficulty may be overcome by requesting for gadolinium-enhanced MRI scan.

11.5.2.3 Thyroid Scintigraphy

The use of radionuclide agents has been helpful in delineating the presence, size, and function of thyroid nodules. Two radioactive iodine (RAI) isotopes have been employed in clinical use. Scanning with ^{123}I has the advantages of low-dose radiation (30 mrad) and a short half-life (12–14 h). This compares favorably with the use of ^{131}I with a higher dose (500 mrad) and a longer half-life (8–10 days). Scanning with ^{123}I is usually used for patients with a suspected lingual thyroid or substernal goiter, whereas ^{131}I is used in patients with well-differentiated thyroid carcinoma (WDTC) to screen for distant metastasis. Thyroid cancers should have little uptake of the radionuclide; however, this deficient area on scanning could be masked by overlying normally functioning tissue. Malignancy has been shown to occur in 15–20 % of "cold" nodules and, additionally, in 5–9 % of nodules with uptake that is "warm" or "hot," mandating continued aggressive approach to clinically suspicious nodules even if they are not "cold" [27].

Technetium pertechnetate 99 m (^{99m}Tc) is also used for the evaluation of thyroid nodules. This substance is trapped by the thyroid but not organified and has a short half-life and a low radiation dose. Screening with ^{99m}Tc also shows uptake in salivary glands and major vascular structures and, therefore, requires a higher sophistication of interpretation [20].

11.5.3 Biopsy

11.5.3.1 Fine-Needle Aspiration Cytology (FNAC): Freehand or US Guided

Fine-needle aspiration cytology is the most important step (cornerstone) in the management of thyroid nodules. Freehand or palpation-guided FNAC has a sensitivity of 65–98 % and a specificity of 72–100 % [28]. The US-guided FNAC improves the accuracy of FNAC. The acellular or nondiagnostic (Thy 1) aspirate is reduced from 14 to 8 % with US guidance [28]; sensitivity increases from 92 to 98 % and specificity from 69 to 71 % [29]. Moreover, it can also be used to help localize impalpable nodules and lesions <1 cm or when initial freehand FNAC was nondiagnostic.

Indications and Aims of FNAC

The *indications* for FNA are all thyroid nodules with a maximal diameter >1 cm and smaller nodules with suspicious findings on US. A lower limit for the maximal diameter does not exist. There are technical difficulties in the sampling procedure in tiny lesions (<0.5 cm), even under US guidance [30]. The *aims* of the FNAB include the following [30]:

- To confirm the benign diagnosis of a nodule justifying the clinicians for a conservative approach avoiding an unnecessary surgery
- To confirm the clinical diagnosis of a diffuse goiter like Hashimoto's thyroiditis or subacute de Quervain thyroiditis
- To recognize an aggressive thyroid tumor and to recognize or at least to suspect a clinically relevant low-grade tumor among all nodular enlargements of thyroid
- To classify or to suspect some tumor types demanding a special therapeutic approach such as MTC, lymphoma, anaplastic carcinoma, or metastatic carcinoma from a primary site other than the thyroid
- To clarify eventual postoperative enlargements in the thyroid region, differentiating mainly between residual and recurrent disease versus granulomas or LN enlargements
- To explore various neck enlargements outside the thyroid gland, mainly cystic lesions of the neck, and differentiate between ectopic thyroid cysts, thyroglossal cyst, branchial cyst, and cystic degenerated LN metastases of PTC
- To confirm the presence of LN metastases

Limitations of FNAC

The main limitation of the diagnostic approach of the thyroid nodules with FNA is the inadequate and indeterminate smears. Fine-needle aspiration cytology is not successful in (1) the detection of a microscopic focus of PTC, (2) differentiation of follicular adenoma from follicular carcinoma, (3) determination of the extent of the thyroid tumor, (4) exclusion of LN metastases, and (5) the safe recognition of a parathyroidal lesion [31].

Table 11.2 Diagnostic FNA categories and recommended actions (BTA guidelines) [32]

Category	Description	Recommended action
Thy 1	Nondiagnostic, insufficient sample Cyst containing colloid or histiocytes only, in absence of epithelial cells	To repeat FNAC (US guidance may help) If the cyst is aspirated to dryness with no residual swelling, clinical/US follow-up alone may be sufficient
Thy 2	Benign, nonneoplastic Cyst containing benign epithelial cells	Repeat FNAC in 3–6 months. Two nonneoplastic results 3–6 months apart should exclude neoplasia
Thy 3	Follicular or Hürthle cell lesion/suspected folic or Hürthle tumor	MDT discussion – diagnostic lobectomy
Thy 4	Suspicious of malignancy	MDT discussion – total thyroidectomy
Thy 5	Diagnostic of malignancy	MDT discussion – total thyroidectomy

MDT multidisciplinary team

Cytology Results of FNAC

Cytology results can be placed in five diagnostic categories (Thy 1–Thy 5) as indicated by the *British Thyroid Association (BTA) Guidelines* [32]. This will help with subsequent management as summarized in Table 11.2. The probability of a benign thyroid nodule being accurately diagnosed as benign from a single FNAC is 90 %. However, the accuracy of diagnosis increases significantly to 98 % if two separate aspirates were performed on separate occasions [22]. As such, having two aspirates reduces the false-negative rate to only 1.2 % [22].

The recently issued *Bethesda System for Reporting Thyroid Cytopathology* (BSRTC) [33], based on an NCI-sponsored conference (2007), is currently considered to be the most suitable for communicating findings from thyroid smears (Table 11.3).

The Nondiagnostic Smears

All smears lacking specific cellular elements, well preserved and prepared, and sufficient for a

Table 11.3 The Bethesda System for Reporting Thyroid Cytopathology: Recommended Diagnostic Categories [33]

Category	Description
I	*Nondiagnostic or unsatisfactory*: Cyst fluid only – virtually acellular specimen, others (obscuring blood, clotting artifact, etc.)
II	*Benign*: Consistent with a benign follicular nodule (adenomatoid nodule, colloid nodule, etc.) – consistent with Hashimoto's thyroiditis – consistent with granulomatous (subacute) thyroiditis
III	*Atypia* of undetermined significance or follicular lesion of undetermined significance
IV	*Follicular neoplasm* or *suspicious* for a follicular neoplasm
V	*Suspicious for malignancy*
VI	*Malignant*

diagnosis should be characterized as nondiagnostic. The clinician should manage the patient on the basis of all other's finding, asking for a re-biopsy, in an interval estimated according to the clinical needs [34].

Accuracy of FNA in Exploring Cervical LNs in the Presence of a Thyroid Carcinoma

A positive finding of a metastasis is principally a safe diagnosis, whereas a negative smear does not exclude the presence of a metastasis since it might be missed by sampling. Cervical LN metastases frequently undergo extensive cystic degeneration, resulting in acellular smears. Cystic foci in LNs remain highly suspicious, even by negative FNA results. The measurement of thyroglobulin (Tg) in the cystic fluid would be a helpful option to confirm a suspicion if the amount of cancer cells are not sufficient for the diagnosis [30].

Core Biopsy (With or Without US Guidance)

A core biopsy, preferably under US guidance, should be considered after two aspiration procedures showing nondiagnostic specimen (Thy 1) or when a thyroid lymphoma was suspected. Thyroid lymphoma typically presents with a rapidly increasing neck swelling in an elderly woman or on a background of autoimmune thyroiditis.

11.5.4 Flexible Laryngoscopy

Indirect laryngoscopy is important to assess vocal cord movements. Patients with difficulty breathing (increased respiratory rate or diminished oxygen saturation) or stridor should be referred as an "emergency."

11.6 Multinodular Goiter (MNG)

11.6.1 Introduction

Goiter (enlarged thyroid gland) is derived from the Latin word "tumidum gutter," which means "swollen throat." *Thyroid enlargement* may be diffuse or nodular (multinodular or a solitary nodule); *hormonal status* may be euthyroid, hypothyroid, or hyperthyroid; and *histologically*, the enlarged thyroid may be benign or malignant.

Multinodular goiter (MNG), defined as an "enlarged thyroid gland with multiple nodules," is a quite common condition with a marked female preponderance. It affects about 13 % of the world population, ranging from 5 % in the Americas to 32 % in the Eastern Mediterranean area [35]. The cause of MNG is probably multifactorial. Iodine (I_2) deficiency, naturally occurring goitrogens, thyroid growth factors (GFs), and heredity have been postulated as possible contributors to goiter development [36]. Thyroid nodules may lead to a variety of clinical sequelae including compressive symptoms, hoarseness, dysphagia, and, importantly, cancer [37, 38], the incidence of which approaches that of patients with a solitary thyroid nodule (STN) [39].

11.6.2 Pathogenesis

The pathogenesis of MNG (Table 11.4) mainly describes two concepts, namely, the I_2 deficiency

Table 11.4 Pathogenetic mechanisms of goiter

Iodine deficiency
Autonomy
Immunological thyropathy
Thyroiditis
Cyst formation, hematoma, trauma
Tumors
Neoplastic production of TSH or TSH analog
Acromegaly
Hormonal resistance
Enzyme deficiency
Involvement of thyroid gland in extrathyroidal/ systemic diseases
Goitrogenic substances

goiters (*endemic* goiters) and the non-I_2 deficiency goiters (*sporadic* goiters) [40].

In I_2 deficiency, less thyroid hormones are produced. A feedback mechanism involving the hypothalamus and pituitary gland leads to increased thyroid-stimulating hormone (TSH) production and consequently to proliferation of thyroid follicles [30], resulting in hypertrophy and hyperplasia of the thyroid gland in a diffuse and homogenous manner [41]. In contrast, in nodular goiter, nodules are surrounded by normal and connective tissue suggesting that they result from heterogeneity of growth [40]. Autonomous growth may occur in toxic as well as in euthyroid nodular goiter depending on whether the gland produces excessive amounts of hormones or not [42].

Other possible factors leading to thyroid proliferation and development of nodules, even in the absence of I_2 deficiency, are the epidermal GF and the insulin-like GF [43]. Iodine deficiency alone cannot explain neither the nodularity nor heterogeneity of most goiters. Iodine-independent mechanisms have been attributed to the evolution of thyrotoxicosis and to the poor response of nodular goiters to TSH suppressive therapy, in contrast to diffuse I_2 deficiency goiters, which respond well to I_2 or T4 (Eltroxin) treatment [40, 44].

For prophylaxis of endemic goiter in I_2-deficient areas, a supplementation with 150 μg I_2/day is recommended for adults and is increased in pregnancy to 200 μg I_2/day. This dose should be adjusted for children to 50 μg for the first year of life, 90 μg for ages 1–6 years, and 120 μg for ages 7–12 years [45, 46].

11.6.3 Clinical Assessment

11.6.3.1 Patient's History

The patient's history may be without complaint or may, apart from an awareness of the goiter size, include a globus sensation, dysphagia, dyspnea, choking, or stridor. The rate of growth over time as well as symptoms of hypo- or hyperthyroidism must be evaluated. Symptoms of hyperthyroidism include increased appetite, weight loss, heat intolerance, nervousness, irritability, agitation, palpitation, diarrhea, muscular weakness (myopathy), as well as oligo-/dysmenorrhea. On the other hand, the main symptoms of hypothyroidism are weight gain (myxedema), depression, concentration weakness, cold intolerance, fatigue, constipation, and oligo-/amenorrhea [45].

11.6.3.2 Physical Examination

Palpation of the thyroid gland is performed from the back of the patient, asking them to swallow. Typically, it moves up with deglutition. The size of the gland is evaluated, nodules are palpated (Fig. 11.3), and signs of local compression are assessed. Retrosternal goiter (RSG) may not be visible on clinical examination and may be unrecognized for many years. It may cause superior vena caval obstruction. Additionally, cervical lymph nodes (LNs) should be examined for enlargement, which may indicate malignancy.

Signs of hyperthyroidism may include tachycardia, tachyarrhythmias (extrasystoles, atrial fibrillation or flutter), hyperreflexia, fine tremors, warm and moist hands, soft and fine hair, as well as hair loss. *Thyrotoxic crisis/coma* is a severe condition of untreated exacerbated hyperthyroidism that may occur in Graves' disease, autonomous adenoma, or multinodular toxic goiter. It presents with tachycardia, tachyarrhythmia, hyperthermia, diarrhea, vomiting, dehydration, muscular weakness, excitation (grade 1), disorientation, hallucination, somnolence (grade 2), and coma (grade 3).

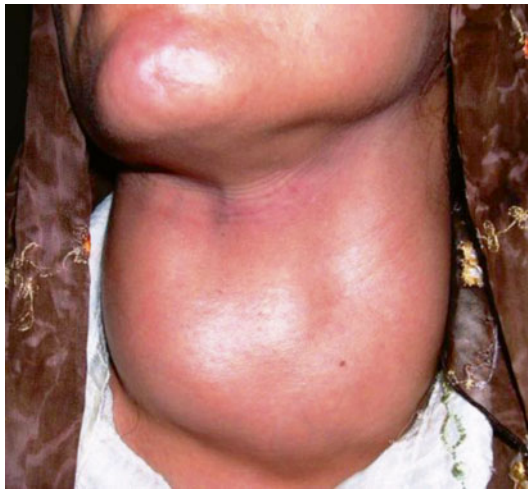

Fig. 11.3 A 28-year-old lady with an enlarged thyroid gland. Note the nodular appearance

Signs of hypothyroidism include bradycardia; hypotension; cardiac insufficiency; slow tendon reflexes; dry, pale, cold, rough, and doughy skin (myxedema); rough hair; and a hoarse voice. *Myxedema coma* is a severe condition that frequently occurs after chronic untreated hypothyroidisms with acute exacerbation due to infection, operation, severe general disease, cold, or sedative. It presents with somnolence, severe hypothermia, hypotension, bradycardia, hypoventilation, hyponatremia, hypoglycemia, and possible pericardial and pleural effusion.

11.6.4 Complications of MNG

Neglected or untreated MNGs may present with complications, which include:

Toxicity Secondary thyrotoxicosis may develop in 10–20 % of cases, usually above the age of 30 years. Toxic nodular goiter is treated by surgery after patient preparation.

Malignant Transformation Development of papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC) is the most important complication, which usually occurs in long-standing cases. Clinical criteria of malignant transformation are listed in Table 11.5.

Table 11.5 Clinical criteria of malignant transformation of an MNG

Glandular criteria	Extra-glandular criteria
Rapid recent growth	Compression symptoms become more evident
Fixation of the swelling – restricted mobility with deglutition	Vocal cord paralysis due to infiltration of the recurrent laryngeal nerve (RLN)
Consistency becomes harder	Horner's syndrome due to infiltration of the cervical sympathetic trunk
Edges become ill defined	Cervical lymph node (LN) enlargement
Onset of pain	Unequal carotid pulsations

Compression Manifestations The pressure manifestations may result from the rapidly enlarging thyroid, retrosternal extension, malignancy, or hemorrhage. The sequelae will depend on the structures compressed (or infiltrated):

- *Trachea*: Dyspnea results from displacement of the trachea to one side by an enlarging unilateral goiter; compression from both sides, in bilateral goiters (scabbard trachea); or tracheomalacia (softening of trachea) in long-standing cases.
- *Esophagus*: Dysphagia, however, usually results from infiltration rather than compression and should alert the physician to the possibility of cancer.
- *Neck veins*: The patient presents with mediastinal syndrome and congested face.
- *RLN:* Hoarseness of voice mostly occurs due to malignant infiltration than just pressure on the nerve.

Calcification In long-standing cases, calcification may occur either in the capsule or in the septa. Plain radiography is diagnostic. It results in a "hard" nodule and may be mistaken clinically for malignancy.

Cyst Formation Development of cysts/pseudocysts in MNGs results from rupture of neighboring acini, hemorrhage, infection, or degeneration of nodules.

Hemorrhage Bleeding may occur suddenly, precipitated by straining, causing sudden increase in the size of the gland, pain in the neck, and sudden compression of the trachea with impending suffocation augmented by reflex spasm of pretracheal muscles. Urgent treatment is necessary to relief compression immediately by aspiration of the cyst, division of the pretracheal fascia, and incision and evacuation of the hematoma. Urgent thyroidectomy is performed to remove the hemorrhagic nodule.

Infection Multinodular goiters rarely get infected, but infection has been reported to occur in an MNG more commonly than in a normal gland.

11.6.5 Investigations

11.6.5.1 Laboratory Findings

The most important parameter is the basal TSH serum level. It is normal in the euthyroid state. If not, fT4 and fT3 should be performed. If an autoimmune process is suspected, thyroid autoantibodies should be tested such as the antithyroperoxidase (TPO) and anti-TSH receptor antibodies. It must be noted that they may also be positive in healthy individuals or in patients with goiter or autonomy [43].

11.6.5.2 Imaging Findings

Ultrasonography (US)

All patients scheduled for thyroid (or parathyroid) surgery should undergo a preoperative ultrasound (US). It is the most precise tool for evaluating the thyroid and nodule *size* [43]. The normal volume of the thyroid is 7–20 ml, and nodules larger than 2 mm in diameter may be identified [47]. Besides the size, US provides valuable information regarding *echogenicity* (the normal thyroid is isoechogenic or slightly hyperechogenic), nodular *composition* as it allows differentiation between solid nodules and simple or complex cysts, presence of *calcifications* (micro, i.e., 1 mm or less, or macro), as well as *shape and margins*. Moreover, US may differentiate extrathyroidal structures from the thyroid gland and may give information on regional lymphadenopathy [48]. Color flow Doppler US gives further information on vascular flow and velocity, and US examination is combined with an FNA cytological sample in cases of suspected malignancy.

Scintigraphy

Scintigraphy has become rare due to the progress in US techniques. It should be performed only if it has an impact on the therapeutic plan, for instance, in a young patient with an STN, possibly a carcinoma, or in case of hyperthyroidism [43]. According to scintigraphy, thyroid nodules may be "hot" in the presence of autonomously functioning thyroid tissue (rarely malignant) or "cold" in which case the incidence of malignancy is 10–20 % [49].

Radiography and Tomography

Plain chest X-rays may show a substernal goiter (Fig. 11.4), and CT scan and MRI are indicated for large tumors extending to adjacent structures such as the mediastinum or the retropharyngeal region [49].

11.6.5.3 Fine-Needle Aspiration (FNA)

For the evaluation of the potential malignancy of a nodule, US-guided FNAC may give further information. Indications are suspected malignancy with the following findings: young patient, previous radiation exposure of the neck, rapid growth, cold in scintigraphy, and US findings of hypoechogenicity, loss of halo, size >1 cm diameter, ill-defined margin, and the presence of microcalcifications [45].

11.6.5.4 Airway Assessment

Signs of significant airway obstruction are stridor, labored breathing, intercostal retractions, and agitation in case of RSG vena caval obstruction [50]. *Indirect laryngoscopy* may be helpful and should be a routine examination [51], particularly in repeat surgery for recurrent goiter or if there is evidence of recurrent laryngeal nerve (RLN) dysfunction. A *chest X-ray* is evaluated for tracheal deviation and compression [52]. Other examinations, such as *CT and MRI*, are not routinely performed, but may give additional information

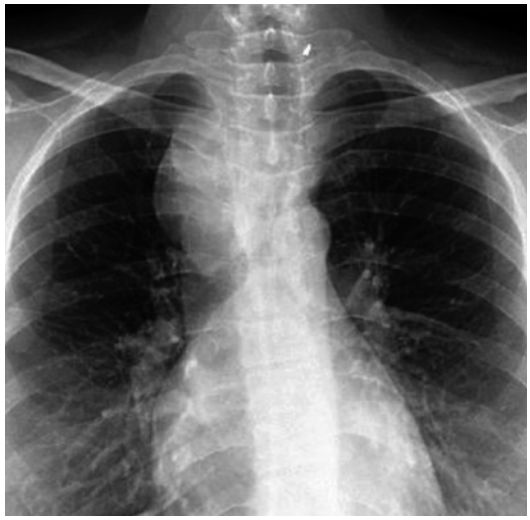

Fig. 11.4 Plain X-ray of the chest showing a mediastinal soft tissue shadow; retrosternal goiter

especially in cases of RSG [52]. *Respiratory function tests* are debatable [53]. In patients with evidence of a compromised airway, the airway is assessed using *fiberoptic laryngoscopy* after application of topical anesthesia and oxygen [50].

11.6.6 Management of MNG

11.6.6.1 Nonoperative Treatment

Conservative treatment of MNG with *L-thyroxin* may be effective or at least partially in reducing the volume of relatively small, benign, solitary, solid thyroid nodules [54–58]. Low TSH suppression is effective in reducing nodule volume [31]. However, some authors reported a volume reduction without treatment, probably due to spontaneous regression [55, 59].

Alternatively, radioactive iodine (*RAI*) therapy may be used in elderly patients or those with contraindications for surgery [60]. The lifetime risk of cancer due to RAI is negligible in patients over 65 years old.

In Graves' disease, surgery, RAI therapy, and treatment with antithyroid drugs (ATDs) are all options, whereas autonomy is a classical indication for radiotherapy except in solitary autonomous nodules where surgery is equally effective. Thyroid neoplasms are an indication for surgery as are I_2-induced hyperthyroidism and intractable hyperthyroidism not responsive to conservative management [43].

Table 11.6 Indications of surgery and annual TSH monitoring for patients with MNG (Thy 2)

Indications of surgery	Indications of annual TSH monitoring
Compression syndrome	The goiter is small or modest in size
Cosmetic reasons	The patient is euthyroid with normal TSH
Follicular or Hürthle cell lesion (Thy 3)	Clinically asymptomatic without signs of compression
Concern about malignancy (Thy 4)	FNAC of all suspicious nodules is benign
Persistent troublesome toxic nodules	

11.6.6.2 Surgical Treatment

Indications and Extent of Surgery

Indications for surgery of the thyroid gland vary depending on the pathology: in euthyroid MNG the main indications are goiter size, compression symptoms, and suspected malignancy. Various surgical options exist, ranging from hemithyroidectomy (lobectomy) to total thyroidectomy (if the thyroid gland contains nodules throughout).

Because of a reportedly high frequency of complications in some series, controversy exists about the routine use of total thyroidectomy (TT) for the management of "benign" MNG [61–63]. However, it is noteworthy that, when performed by experienced hands, TT, compared with subtotal resection, does not increase morbidity in benign pathologies [64–69]. In cases of retrosternal goiter (RSG), TT is preferred owing to the malignant potential and in order to reduce recurrence rate (RR) [70].

It is important to emphasize that proper training and surgical experience are significantly associated with low complication rates in thyroid surgery [71, 72].

Multinodular Goiter (Benign/Thy 2)

Patients with MNG, diagnosed with FNA as being benign (Thy 2), could receive either definitive surgery or annual monitoring with TSH levels (Table 11.6).

Thyroid Nodules Associated with Hypo-/Hyperthyroidism

These nodules are very *unlikely* to be cancer. They are more likely to be *benign* toxic nodule or Hashimoto's thyroiditis. The frequency of malignancy in cold nodules is 10–20 % and only 4 % in hot nodules [73, 74]. These nodules should still be aspirated and if confirmed to be benign (Thy 2) after two aspirates 3–6 months apart, with no other suspicious features, can be safely managed by an endocrinologist and referred back for reevaluation if there was any change in the swelling.

Dominant Nodule in MNG

Patients with hyper- or hypothyroidism associated with MNG with no other suspicious features in history and clinical examination have a low risk of thyroid cancer [32]. They are referred to an *endocrinologist*. When a *dominant nodule* is noted to be growing and become suspicious, it should be aspirated and treated accordingly depending on cytology results. Low-risk patients who are euthyroid with MNG of long duration and slow growth have a very *low r*isk of thyroid cancer [32]. Patients can be *observed* at intermediate or long intervals.

Thyroid Cystic Swelling

It should be clearly stated that in order to help the pathologist in interpreting FNAC, the cyst should be *aspirated to dryness under US guidance* and any *residual mass* should be noted and subjected to FNAC immediately as a separate specimen [32]. For a thyroid cyst that is shown to be benign on FNAC and does not recur at follow-up, clinical observation alone may be sufficient. *A recurrent thyroid cyst* should be *re-aspirated* during follow-up and the sample sent for cytology. Patients with *high risk factors* in history and clinical examination can be considered for diagnostic *lobectomy*. Some surgeons would consider diagnostic lobectomy for a cyst that has recurred for three times or more. *Surgery* can also be considered at patient's request.

Results of Surgical Treatment of MNG

The rate of secondary hemorrhage is approximately 1 %, whereas the rate of persistent RLN paresis and of hypoparathyroidism has dropped to <1 % in the last two decades [75, 76]. Adequate surgery is part of the prophylaxis of recurrence [77]. In a case-control study, young age and multiple nodules at initial surgery have been identified as independent risk factors for recurrence [63]. Despite suppressive thyroxin treatment postoperatively, 14 % of patients develop recurrence after subtotal thyroidectomy after a median follow-up of 14.5 years [78]. Without suppression the RR reaches up to 41 % [79, 80]. Since TT can be performed with a minimal complication rate, this option is increasingly being accepted and recommended for the treatment of MNG [66, 81].

Prophylaxis of Recurrence

In addition to adequate surgery, postoperative suppression therapy with L-thyroxin is important for prophylaxis of recurrence [77] provided that the proper dose is given. In I_2 deficiency goiter with no substitution, 25 % of patients will have a recurrence. The aim should be a TSH in the lower normal range (0.3–1 mU/l), in contrast with malignancies where the TSH should be suppressed to <0.1 mU/l. Strong TSH suppression, however, increases the risk of cardiac complications and accelerates osteoporosis [82, 83].

Treatment of Recurrent Goiter

Surgery for recurrent goiter has a higher complication rate than in the primary setting [38, 70]. Temporary RLN palsy was found in 5 % and permanent in 3 %, both significantly higher than at primary operation [84]. The indication is therefore restricted to third-degree goiters or suspicion of malignancy. Preoperatively, indirect laryngoscopy for documentation of the RLN function is essential. Intraoperative nerve monitoring may be helpful in the identification of the nerve, which may be altered in position [45]. If preoperative unilateral RLN paresis is present, if possible, only ipsilateral hemithyroidectomy should be considered [77].

11.7 Retrosternal Goiter (RSG)

11.7.1 Introduction

Extension of the goiter beyond the confines of the neck into the thoracic cavity with more than 50 % of the mass inferior to the thoracic inlet is called

retrosternal goiter (RSG) or intrathoracic goiter. Most of these goiters are slow growing and often do not cause symptoms until the mass reaches a critical size and causes compression symptoms. Although the majority of these lesions are benign in nature [85–88], approximately 6–16 % may be malignant, and a few cases may exhibit thyrotoxicosis.

11.7.2 Incidence

It has been reported that the incidence of RSG among patients undergoing thyroid surgery ranges from 5 to 19 % [86–91] and that RSG accounts for about 5–11 % of all mediastinal masses [86].

11.7.3 Anatomical Classification

Retrosternal goiters are located in the superior mediastinum, either anteriorly or posteriorly. They are classified as either primary (Fig. 11.5) or secondary (Fig. 11.6) goiters. *Primary goiters* account for <1 % of all RSGs. They originate from ectopic embryonal thyrocytes that have descended into the chest with the arch of the aorta. *Secondary goiters* are cervical goiters that have migrated to the intrathoracic location favored by the negative mediastinal pressure and fixation of the soft tissues. The main differences between the primary and secondary RSGs goiter are shown in Table 11.7.

Secondary RSGs in the anterior mediastinum usually originate from the lower pole of the thyroid gland and descend along the anterolateral aspect of the trachea and anterior to the RLN and carotid vessels. Occasionally, a goiter originating from the posterolateral aspect of the thyroid may descend into the posterior mediastinum pushing the esophagus to the opposite side and causing forward displacement of the trachea and tilting of the larynx. In this case, the RLN, inferior thyroid artery, and the carotid vessel lie anterior to the

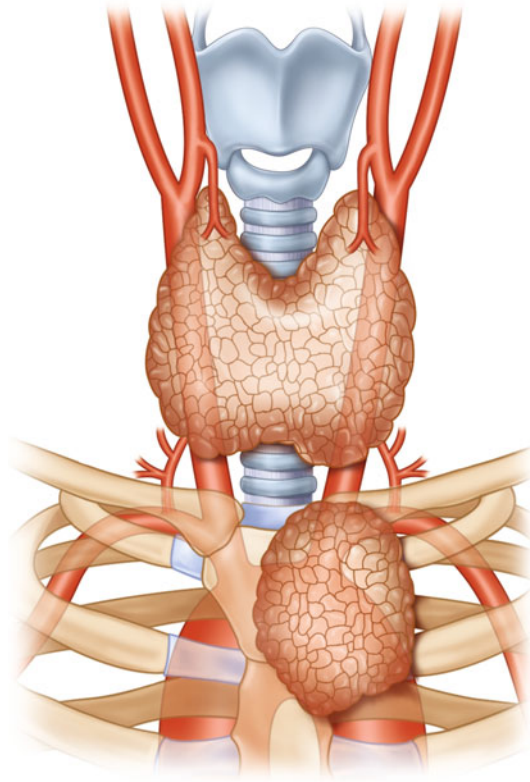

Fig. 11.5 Primary retrosternal goiter: intrathoracic goiter originating in the chest

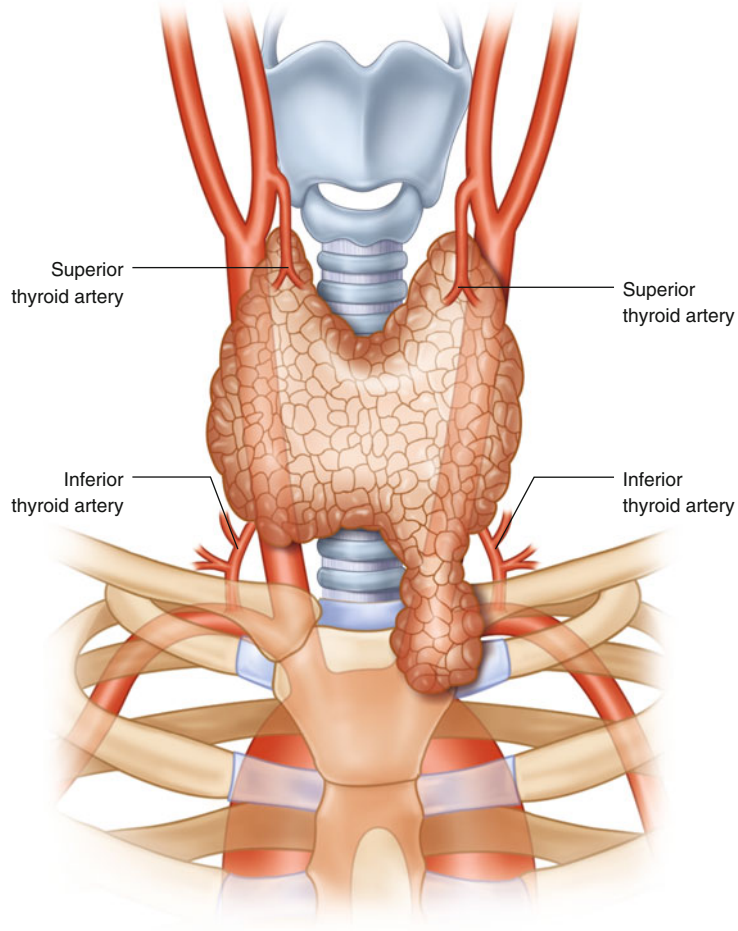

Fig. 11.6 Secondary retrosternal goiter: originating from the left thyroid lobe

goiter. DeAndrade [91] reported that 9.4 % (128/1300) of RSGs occurred in the posterior mediastinum.

Table 11.7 Differences between primary and secondary RSGs

Differences	Primary RSG	Secondary RSG
Origin	From ectopic thyroid tissue in the chest	Extension of cervical thyroid into the chest
Blood supply	Intrathoracic aorta	Inferior thyroid artery
Connection with cervical thyroid gland	None	Usually contiguous with the cervical gland or connected by a fibrous band
Cervical mass	None	Yes in 80–90 % of patients

11.7.4 Clinical Manifestations

11.7.4.1 Symptoms

Patients with RSG are usually in their fifth or decade of life, with a female to male ratio of 3:1. Approximately, 20–35 % of patients are asymptomatic. A neck lump is present in 40–50 % of patients. Other symptoms are the result of compression of intrathoracic structures. Compression of the airway occurs in about 50 % of patients and may present with dyspnea, stridor, or a choking sensation [89, 90] and may require urgent intubation or a semi-urgent operation in 22 % as reported by Newman and Shaha [85]. In some patients, dyspnea is experienced only when the head is turned toward one side or by lying down flat.

Table 11.8 Clinical symptoms and signs of patients with RSG

Symptoms	Signs
Asymptomatic Neck lump Compression *Airway*: dyspnea, stridor, raspy cough, wheezing, chocking *Esophageal*: dysphagia *Nerve*: hoarseness of voice, Horner's syndrome *Vascular*: SVC syndrome, TIA, cerebral edema, GI bleeding	Cervical mass Dilated veins of the neck Tracheal deviation Flushing of skin Pemberton's sign Horner's syndrome

SVC superior vena cava, *TIA* transient ischemic attack, *GI* gastrointestinal

Dysphagia is present in about 30–40 %, being more common with RSGs located in the posterior mediastinum. Hoarseness of voice is reported in 13 % of patients [86]. Unusual symptoms result from vascular compression causing downhill upper gastrointestinal bleeding from esophageal varices, effort axillary vein thrombosis, transient ischemic attacks (TIA), and cerebral edema.

11.7.4.2 Physical Examination

A palpable lump in the neck, with impalpable lower border and dull sternal percussion, may be demonstrated in about 80–90 % of patients [86]. Other signs include dilated neck veins and tracheal deviation. Raising the arms or hyperextension of the neck may cause dilatation of cervical veins and flushing of the face or even respiratory difficulty/stridor (Pemberton's sign). Common signs and symptoms of RSG are listed in Table 11.8.

11.7.5 Diagnosis

11.7.5.1 Plain Chest X-Ray (CXR)

Plain CXR is the most cost-effective method for diagnosis of RSG. Findings include deviation and/or compression of the trachea (Fig. 11.7), soft tissue density or a mass, and occasionally calcifications (Fig. 11.8) and reflection of the mediastinal pleura below the trachea.

11.7.5.2 CT Scan and MRI

Both CT scan (Fig. 11.9) and MRI can provide more precise information about the relationship between the various intrathoracic organs and the goiter This information helps the surgeon to plan the operative approach.

11.7.5.3 Scintigraphy

A radionuclide thyroid scan may be useful in differentiating goiter from other mediastinal masses. Nevertheless, a solitary, large cyst may appear as a "cold" nodule on thyroid scan and thus provide a false-negative result.

11.7.5.4 US and FNA

Ultrasonography is generally *not* necessary but can be helpful in selected patients, and FNAC is *not* recommended as it is not easily accessible and may cause bleeding or pneumothorax.

11.7.6 Differential Diagnosis

A mediastinal mass in the anterosuperior compartment should be differentiated from a dermoid cyst, aneurysm, lymphoma, teratoma, pleural cyst, and secondary carcinoma. Differential diagnosis of masses in the posterior mediastinum should also include tumors of neurogenic origin.

11.7.7 Treatment

11.7.7.1 Pharmacotherapy

A patient with elevation of TSH or defects in thyroxin synthesis is a candidate for suppressive therapy. However, RSGs, especially those that have cystic change and hemorrhage, do not respond to thyroxin therapy. Overall, only about 20–30 % of patients respond to such treatment after 1 year, and cessation of therapy is often followed by recurrence. Presence of cardiac disease and osteoporosis in elderly patients poses

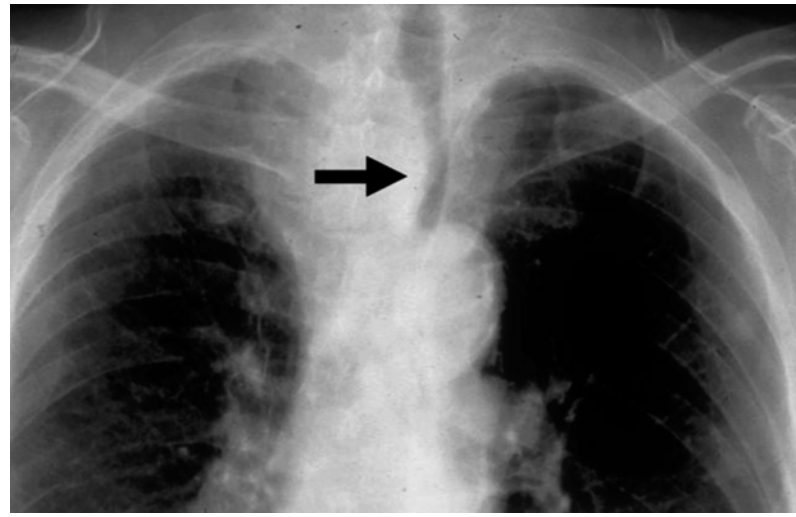

Fig. 11.7 Chest X-ray showing left tracheal deviation (*arrow*) by a retrosternal goiter (RSG)

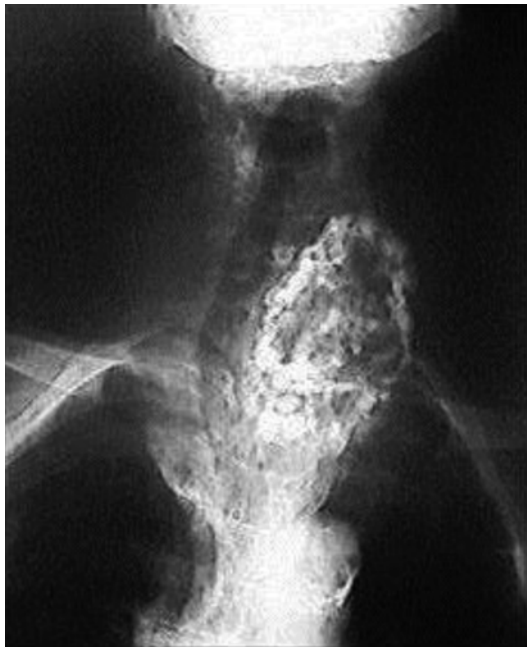

Fig. 11.8 Plain X-ray showing calcification in a retrosternal goiter with right tracheal deviation

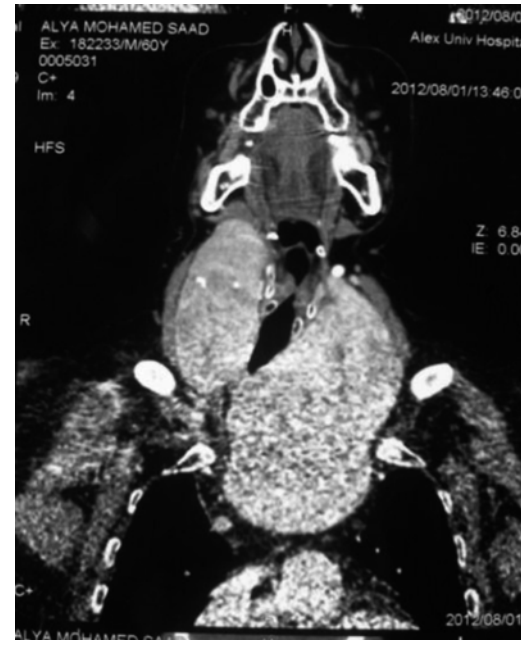

Fig. 11.9 Computed tomography (CT) scan showing secondary retrosternal goiter (RSG) extending from the left thyroid lobe into the mediastinum

an additional hazard to suppressive thyroxin therapy. Failure of suppressive therapy is probably based on autonomicity. Once stimulated for a long time, autonomous growth occurs, and the hyperplasia is no longer a fully reversible process.

11.7.7.2 Radioactive Iodine (RAI) Therapy

The use of radioactive iodine (RAI) for the treatment of nontoxic goiter was first reported by Keiderling in 1964, but it was not until 1994 that its use in RSGs was evaluated by Huysmans et al. [92].

In their prospective study of 19 patients with large compressive goiters, 11 had intrathoracic extensions for >2 cm. They reported a 40 % reduction in the volume of the goiter using MRI and a 10 % decrease in tracheal narrowing and deviation in 75 % of their patients. However, one-third of their patients did not have any improvement in dyspnea.

Radiotherapy is not without risk of complications, which may include radiation-induced thyroiditis, stridor from a transient increase in volume, neck pain, occasional hyperthyroidism, sore throat, mild dysphagia, and dryness of mouth.

11.7.7.3 Surgical Therapy

Surgical treatment is the most effective therapy for RSG, and the presence of RSG is itself an indication for operation [87]. It is currently believed that TT is the procedure of choice, particularly that about 95 % of cases can be performed via a cervical incision. Ligation of the ITA branches close to the thyroid capsule, preservation of the blood supply to the parathyroid gland, and minimal dissection of the RLN are the hallmarks of a safe operation.

Approach to RSG

Most RSGs can be resected through the standard cervical Kocher's incision [70, 93, 94]. The head is reclined and the patient positioned in anti-Trendelenburg of about 15–20° to reduce the venous pressure. In order to gain good access, the incision should be placed 1–2 cm higher than usual [93]. The skin/platysma flap is elevated, the cervical fascia is separated at the midline, and the muscles are held aside or incised laterally in the case of a very large goiter.

First, the upper pole is mobilized under ligation of the superior thyroid vessels with preservation of the external branch of the ELN. This is important in the subsequent upward movement of the thyroid gland from the retrosternal to a cervical position. The RLN and superior parathyroid glands are routinely identified [95] particularly that the inferior parathyroids may be more difficult to locate in RSG.

The next step is the delivery of the thyroid gland by blunt dissection with the finger inferiorly, completed by sharp dissection under vision. The inferior vascular structures are then ligated as near as possible to the gland, selectively ligating the branches of the ITA at the level of the thyroid capsule [70]. The inferior thyroid artery (ITA) should not be ligated at the main stem [45, 77]. If the thyroid lobe cannot be brought to the neck, more room is provided by removing the opposite thyroid lobe in its cervical position.

Table 11.9 Indication for sternotomy for RSG

Goiter size significantly larger than the thoracic inlet
Primary intrathoracic goiter with intrathoracic blood supply
Goiters in the posterior mediastinum displacing or compressing the aortic arch
Goiters associated with SVC syndrome
Recurrent RSG
Malignant RSG with LN metastasis

In cases of very large intrathoracic goiters, invasive tumors, dense adhesions in recurrent cases, uncontrollable hemorrhage, or truly ectopic intrathoracic gland with its major blood supply from intrathoracic vessels, a *mediastinal* approach using *sternotomy* is required [70, 93]. Indications for sternotomy are listed in Table 11.9. As an alternative to complete sternotomy, a partial upper sternal split (*manubriotomy*) is possible in most cases [94]. Division of the manubrium to below the manubriosternal junction is performed. The innominate vein and the pleura freed from the back of the manubrium. The manubrium and the upper sternum are divided in the middle and gently spread with a right-angled retractor. Sternotomy is closed using sternal wires. If complete sternotomy is performed, the skin incision is extended to just above the xiphoid process, and the pericardial and diaphragmatic attachments are freed from the back of the sternum before its division. For resection of a crossed RSG with extension from a left-sided gland to the right mediastinum, right anterolateral *thoracotomy* can be helpful [93].

Complications of RSG Surgery

As with cervical goiter, the main complications of RSG surgery are hemorrhage, RLN injury, and hypoparathyroidism. An intrathoracic goiter was

found to be an independent risk factor for postoperative complications [68]. In a prospective study of 2,235 thyroid resections, 312 were performed for RSG [96] in which the complication rate was significantly elevated, including hemorrhage, wound infections, transient hypocalcemia, and transient RLN paresis.

In addition, *mediastinal* injuries may occur during RSG surgery. If mediastinal hemorrhage occurs, immediate surgical revision via a complete sternotomy is indicated for adequate control. *Pneumothorax* after pleural injury is treated with insertion of a chest tube. More rare complications are *infections* (mostly due to an infected hematoma), *injury* of the pharynx and trachea, or sympathetic chain with resultant Horner's syndrome. Sternal infection may manifest late and is treated with a surgical debridement.

11.8 Solitary Thyroid Nodule (STN)

The most important distinction in the workup of a solitary thyroid nodule (STN) is whether or not it represents a malignant lesion. Thus, the primary goal is to distinguish those nodules that require surgical excision from those that can be safely observed.

11.8.1 Pathological Classification

Many thyroid diseases can present clinically as an STN such as colloid cysts, adenomas, Graves' disease, thyroiditis, infections, and malignancies (Table 11.10).

Table 11.10 Pathology of thyroid nodule

Benign
Adenomatous nodules or colloid nodules
Follicular adenoma
Hürthle cell adenoma
Thyroid cysts
Inflammatory lesions (thyroiditis)
Developmental abnormalities (cystic hygroma, dermoid, teratoma)
Malignant
Papillary carcinoma
Follicular carcinoma
Hürthle cell carcinoma
Mixed papillary/follicular carcinoma
Medullary carcinoma
Anaplastic carcinoma
Lymphoma
Metastatic disease

Table 11.11 Important clinical factors in the diagnosis of thyroid cancer

History taking	Physical examination
Family history Gender Age <20 or >60 years History of head and neck irradiation Rapidity of growth Associated symptoms (pain, dysphagia, dysphonia, dyspnea) Growth on thyroid hormone suppression	Solitary *versus* multiple nodules A hard nodule Fixation to adjacent structures Diameter 4 cm or more Cervical lymphadenopathy

11.8.2 Clinical Considerations

11.8.2.1 History Taking

Several aspects of the history and physical examination can increase the suspicion of malignancy (Table 11.11). Any nodule developing prior to puberty should be viewed with suspicion. It has been reported that more than 50 % of all thyroid nodules in children are malignant [97]. The incidence of malignancy is also higher in nodules that develop after the age of 65 years. Benign nodules are more common than malignant nodules in both males and females; however, the proportion of malignant nodules in males is twice that of females.

One of the most important aspects of the past medical history is whether the patient has received. If a patient with an STN has a history of head or neck irradiation in childhood, the prevalence of cancer is 30–50 % [85]. Other factors to consider in the past medical history include symptoms of pheochromocytoma or

hyperparathyroidism (HPT), long-standing constipation and/or diarrhea, hypertension, and/or episodes of nervousness. These should alert the clinician to the possibility of medullary thyroid carcinoma (MTC) in association with a familial MEN syndrome.

The time course for development of an STN is important to note. A nodule that has been stable in size for years is almost always benign. Thyroid malignancies usually develop over weeks or months. Entrapment of the RLN, invasion of thyroid capsule, or spread into adjacent tissues can lead to local pain in the neck or radiating to the jaw and ear. Dysphagia, dysphonia, dyspnea, hoarseness, and hemoptysis may all reflect esophageal or tracheal involvement by a thyroid cancer. Nodules associated with hyperthyroidism are usually benign functioning adenomas, whereas a nodule in a patient with hypothyroidism is often caused by autoimmune thyroiditis.

11.8.2.2 Physical Examination

Although it is almost impossible to distinguish a benign nodule from a malignant nodule by palpation, a thorough physical examination should be performed. A relatively *rapidly growing, hard* nodule is associated with a higher risk of malignancy. Hard nodules may be due to calcifications in benign adenomas, however.

A nodule *fixed* to surrounding tissues such as the trachea or strap muscles is most likely malignant. However, fixation of the thyroid can also occur with severe chronic thyroiditis. *Vocal cord paralysis* strongly suggests an invasive cancer, but again, benign conditions such as Hashimoto's thyroiditis or MNG can rarely affect vocal cord function. The most significant physical findings suggestive of malignancy are the unilateral, firm, mobile, non-tender, discrete LNs resulting from metastatic thyroid cancer, most commonly papillary thyroid carcinoma (PTC) (Table 11.11).

11.8.3 Laboratory Tests

Thyroid function tests may also be useful in the evaluation of an STN, since a suppressed TSH level is suggestive of benign pathology, as it is uncommon for thyroid cancer to cause thyrotoxicosis or thyroiditis [98]. Abnormalities in the thyroid gland function are most often associated with a benign nodule. Malignant thyroid nodules generally have normal thyroid function tests.

11.8.4 Imaging Studies

11.8.4.1 Ultrasonography (US)

Thyroid US has been used preoperatively to evaluate thyroid nodules (Table 11.12); however, *alone*, the sensitivity, specificity, and positive predictive value for US are quite low.

The use of US-guided FNA can improve the diagnostic accuracy and should be considered whenever confronted with a patient whose thyroid nodule is difficult to palpate on physical examination or in whom the initial FNAB was nondiagnostic [5].

Still however, interpretation of the aspirate for definitive diagnosis may still not be possible. In

Table 11.12 Ultrasound features of thyroid nodule suggestive of malignancy

Highly suggestive
Extracapsular extension
Suspicious cervical LNs
Taller than wider nodule
Microcalcification
Irregular ill-defined margins
Markedly hypoechoic
Moderately suggestive
Elastography
Texture (>50 % solid)
Increased intranodular vascularity
Absence of halo
Minimally suggestive
Hypoechoic
Macrocalcification
Isoechoic, hyperechoic
Complex nodules
Peripheral calcification (eggshell)
Spongiform nodules

cases of follicular neoplasia, FNA may not be able to distinguish malignant from benign disease, since the diagnosis of follicular carcinoma is histological, specifically by identification of capsular or vascular invasion. This scenario is similar when dealing with Hürthle cell neoplasms [99, 100]. In such cases, pathology reports may be suspicious for malignancy, of which nearly 20 % will actually be malignant Hürthle or follicular neoplasms.

11.8.4.2 Scintiscan

Radioisotopes of iodine or technetium are based on the assumption that malignant thyroid tissue neither traps nor incorporates iodine and therefore should appear nonfunctioning or "cold" on uptake scan. Normally functioning nodules are "warm," and hyperfunctioning nodules appear as "hot" on the scan. The incidence of malignancy is higher in cold nodules as compared with warm or hot nodules. Thyroid scans have generally been replaced as a first-line test by FNAB [101].

11.8.5 Fine-Needle Aspiration Biopsy (FNAB)

Fine-needle aspiration biopsy (FNAB) has become the diagnostic procedure of choice for STNs. It is a simple outpatient procedure, and complications such as hematoma or infections are rare. It has been shown repeatedly to be a better predictor of malignancy than other preoperative tests and has substantially decreased the number of patients requiring surgery for benign disease [102]. The cytodiagnostic categories of Bethesda Classification [33] with the corresponding estimated risk of malignancy are listed in Table 11.13.

Table 11.13 Bethesda Classification of FNAB findings of a thyroid nodule [33]

Category	Description	Risk of malignancy (%)
I	Nondiagnostic	1–4
II	Benign	0–3
III	Atypia of undetermined significance/follicular lesion of undetermined significance	5–15
IV	Follicular neoplasm/ suspicious for follicular neoplasm	15–30
V	Suspicious of malignancy	60–75
VI	Malignant	97–99

11.8.6 Management

The management of an STN depends on several factors as shown below and demonstrated in the suggested management algorithm (Fig. 11.10).

11.8.6.1 Clinically Non-palpable Incidental Nodule <1 cm (Incidentaloma)

Either non-palpable nodules <1 cm are noted during surgery or imaging performed for another purpose should be observed. These nodules have a *very low risk* of cancer [32] in patients with *low risk* (as per history taking, clinical examination, and US findings). In addition, there is no evidence to show that treatment of sub-centimeter micro-carcinomas improves outcome [74, 103]. The exception to the above is an *incidentaloma* identified by *FDG-PET scan.* These carry a 50 % chance of malignancy and should be managed as STN or "incidentaloma" >1 cm [74].

11.8.6.2 Benign Nodule

If FNAC indicates a benign nodule, there are three options for treatment: surgery (hemithyroidectomy), observation, and hormone suppression. Surgery may be considered if the nodule is causing symptoms, or is esthetically unpleasant to the patient, and also in those patients who are at increased risk for thyroid cancer despite a benign FNA.

If the patient does not require surgery, the nodule may either be observed or suppressed with L-thyroxin. This should either reduce the size of the nodule or prevent its further growth; otherwise, malignancy should be suspected and

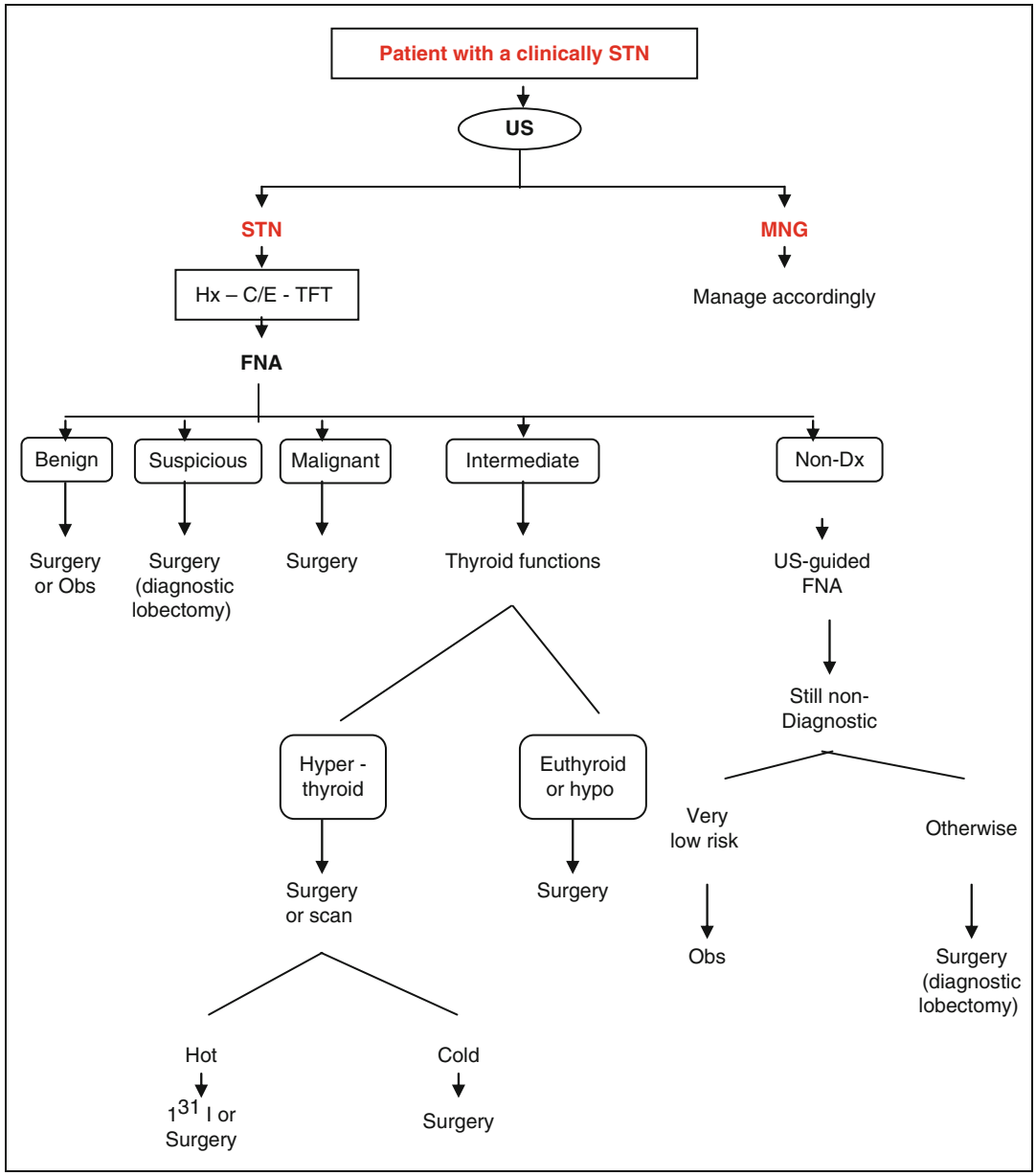

Fig. 11.10 Algorithm for the management of an STN. *Hx* history, *Dx* diagnostic, *C/E* clinical examination, *TFT* thyroid function tests, *Obs* observation, *US* ultrasound, *FNA* fine-needle aspiration

surgery considered. Several studies have failed to demonstrate the efficacy of thyroxin therapy for solitary nodules [104]. There has also been some concern that the use of thyroxin, especially in postmenopausal women, may lead to osteoporosis [105].

11.8.6.3 Indeterminate Lesion

When FNAC demonstrates follicular or Hürthle cell neoplasm, *surgery* is indicated to reach a definite diagnosis. If the nodule is hyperfunctioning, a thyroid scintiscan may be appropriate. A "hot" nodule may be observed, treated with

^{131}I or surgically excised. If the plan is to treat a hyperfunctioning nodule with surgery, the thyroid scan may be omitted.

11.8.6.4 Suspicious Nodule

Suspicious STNs should be treated with surgical resection to avoid missing a thyroid cancer. The principal surgical approach to solitary, undetermined nodule is ipsilateral lobectomy (hemithyroidectomy).

11.8.6.5 Malignant Nodule

Treatment of Differentiated Thyroid Cancer

Principles and Strategies

Differentiated carcinoma of the thyroid includes both papillary and follicular variants. The primary treatment for these cancers is *resection*, albeit with controversy about its extent. Three primary surgical strategies exist for the management of differentiated thyroid cancer, namely, total thyroidectomy (TT), near-total thyroidectomy, and hemithyroidectomy (lobectomy with isthmusectomy). Whereas TT involves removal of the entire thyroid gland and its capsule, near-total thyroidectomy preserves the posterior capsule of the thyroid contralateral to the tumor. Both procedures are considered as completely ablative approaches. However, they expose the patient to the risk of bilateral dissection and necessitate lifelong thyroid hormone supplementation. Alternatively, hemithyroidectomy allows preservation of normal thyroid tissue, thereby obviating the need for lifelong supplementation and eliminating the risk for hypoparathyroidism and bilateral vocal cord paralysis. Subtotal thyroidectomy (preservation of several grams of thyroid tissue) is *not* a recommended treatment option for patients with differentiated thyroid cancer due to the higher complication rates encountered when subsequent surgery is indicated [106].

Treatment: Papillary Thyroid Cancer (PTC)

Total Thyroidectomy In patients with high-risk lesions or extrathyroidal extension, it is generally accepted that TT is the appropriate treatment as it results in excision of cancer that was occult on the preoperative assessment and permits a more sensitive postoperative follow-up surveillance for recurrent disease. After a TT (or near-total thyroidectomy), postoperative RAI can be used to identify and ablate any residual thyroid cancer, and serum thyroglobulin is a more accurate marker of recurrent or persistent PTC following TT when compared with more conservative thyroid resections. It is thus conceivable that TT is a safe and effective primary treatment for patients with PTC, particularly with the low complication rate (<2 %) reported by experienced surgeons [107, 108]. Pacini et al. [109] reported that approximately 44 % of 182 patients studied harbored histologically confirmed PTC at completion thyroidectomy and suggested TT in order to eradicate all neoplastic tissue in patients with PTC. The authors also recommended completion thyroidectomy for patients with a history of PTC that were initially treated with hemithyroidectomy. Moreover, Hay et al. [110] found that patients who underwent lobectomy for PTC had a higher RR (14 %) and nodal metastases (19 %) as compared to TT%, though with a similar survival rate and distant metastases. Finally, elimination of all PTC via TT may prevent progression to anaplastic thyroid cancer from residual tissue left behind during thyroid hemithyroidectomy.

Hemithyroidectomy The use of hemithyroidectomy for the treatment of PTC is supported by some authors as it avoids the risk of some potential complications of bilateral procedures such as RLN and parathyroid injuries and also provides similar survival benefit to TT [111–113]. In patients with excellent prognosis (tumor size <1 cm, confined to the thyroid without evidence of any metastatic disease, in an otherwise healthy female below 45 years of age), hemithyroidectomy may be used.

Lymph Node Dissection Careful stratification of patients with PTC into those who require lymph node (LN) dissection and those who do not is

important for minimizing surgical morbidity. *Gross nodal disease* occurs in 20–30 % of adult patients with PTC [114]. Nodal metastases confirmed by preoperative US or CT or by intraoperative exploration should be treated with node dissection [106], specifically removal of ipsilateral central neck LNs (level 6) and lateral compartment nodes (levels 2–5). On the other hand, microscopic regional LN metastases occur in approximately 80 % of patients with PTC [110] and may often be ablated by adjuvant RAI therapy, but better be removed at the initial operation as they may be the site of persistent disease [115–117]. Removal of central neck LNs has been reported in retrospective studies to be associated with an improvement in survival rate and regional RR [118–120]. The current American Thyroid Association (ATA) Guidelines advise that staging/prophylactic level 6 LN dissection for all patients undergoing thyroidectomy for well-differentiated thyroid carcinoma should be considered [121]. Prophylactic lateral neck node dissection is not recommended because it is not associated with improved overall survival of patients and involves violation of additional planes by a more extensive operation.

Treatment: Follicular Thyroid Cancer (FTC)

Surgical resection remains the primary method of therapy for follicular thyroid cancer (FTC). If the tumor is confined to the thyroid (T1–2 N0 M0), TT and hemithyroidectomy with extirpation of central LNs are both adequate. For larger tumors (T3–T4), TT along with postoperative RAI therapy is indicated. Morbidity is minimal in the hands of experienced surgeons. Since FTC spreads primarily via hematogenous routes, cervical LN metastases are not as common as with PTC (35 % versus 67 %, respectively). Still however, therapeutic modified neck dissection is appropriate for patients with clinically apparent disease. Postoperative RAI scans and ablation are also essential to help detect any residual disease and eliminate it.

11.8.6.6 Treatment of Oncocytic (Hürthle Cell) Thyroid Cancer

Treatment strategies of oncocytic (oxyphilic or Hürthle cell) carcinoma, a variant of FTC, are similar to those of FTC because of similarities in the natural history and prognosis. However, it is important to distinguish the two entities. Radioactive iodine uptake in oncocytic carcinoma is much less than that of FTC; hence, postoperative diagnosis and ablation of residual disease with RAI are more difficult [122].

11.8.6.7 Treatment of Medullary Thyroid Carcinoma (MTC)

Prior to surgery, patients with MTC should have baseline calcitonin levels and assessment of catecholamine secretion to rule out a pheochromocytoma. Medullary carcinoma must be treated with a TT since it may be unknown if the patient is part of a familial syndrome and therefore would be expected to have multicentric disease. A central LN dissection is indicated for occult cancers detected after family screening, whereas palpable lesions require an ipsilateral modified radical neck dissection.

11.8.6.8 Treatment of Anaplastic Carcinoma

Though rare, anaplastic carcinomas are very aggressive neoplasms with a very poor prognosis. Two-thirds of patients die within 1 year of diagnosis. In the rare case that all gross disease can be excised, resection may be appropriate. Chemotherapy and radiotherapy may be used for palliative treatment.

11.8.6.9 Nondiagnostic Biopsies

The results of FNAB, even with US guidance, may be repeatedly nondiagnostic. This particularly occurs with cystic nodules. The rate of malignancy in these nodules is extremely low, and *observation* may be appropriate. However, diagnostic lobectomy should be performed after a repeat nondiagnostic FNAB. The routine use of frozen section is excessively costly, and false-positive results could lead to unnecessary thyroidectomies. The decision to do a more extensive resection should be based on the patient's history or characteristics of the nodule [123].

11.9 Thyrotoxicosis

11.9.1 Introduction

Thyrotoxicosis refers to a syndrome characterized by signs and symptoms of sympathetic overactivity and hypermetabolism due to excessive amounts of thyroid hormone. *Hyperthyroidism* is defined as excess synthesis or secretion of thyroid hormone by the thyroid gland. Some patients with thyrotoxicosis, such as those with subacute thyroiditis or excess thyroxin intake, do not have hyperthyroidism (Table 11.14).

11.9.2 Clinical Manifestations

The clinical manifestations of thyrotoxicosis are diverse and result from increased thyroid hormone levels that sensitize nerve cells to catecholamines and cause the symptoms of increased sympathetic nervous system activity. Older patients usually have fewer and more subtle symptoms (*apathetic hyperthyroidism*). They also more frequently present with cardiovascular manifestations such as atrial fibrillation, angina, or congestive heart failure (CHF).

11.9.2.1 Symptoms

Patients complain of a neck swelling of variable size in addition to symptoms of toxicity, which include nervousness, anxiety, irritability, weight loss despite increased appetite, palpitations, heat intolerance, excessive sweating, insomnia or sleep disturbances, fatigue, weakness, hair loss, brittle nails, dyspnea on effort, increased frequency of bowel movements, reduced libido, impaired fertility, and menstrual disturbances.

Table 11.14 Causes of thyrotoxicosis

Associated with hyperthyroidism	Not associated with hyperthyroidism
Graves' disease Toxic multinodular goiter Solitary toxic adenoma Iodine-induced Hashimoto's thyroiditis Thyrotropin-producing pituitary tumor Thyroid hormone resistance syndromes	Subacute thyroiditis Radiation thyroiditis Excess thyroid hormone ingestion (iatrogenic, thyrotoxicosis factitia) Struma ovarii Functioning metastatic thyroid cancer

11.9.2.2 Local Examination

The thyroid gland becomes diffusely enlarged with a smooth surface and fleshy consistency. In moderate and severe cases, pulsations due to increased vascularity could be seen (inspection), a thrill may be felt (palpation), and a bruit may be heard (auscultation). The skin overlying may show dilated veins.

11.9.2.3 General Examination

Findings of general examination depend on the severity of the condition and age of the patient. They are summarized in Table 11.15.

11.9.3 Diagnosis

The TSH level is low in all patients with thyrotoxicosis except in rare cases of TSH-secreting pituitary tumors or pituitary resistance to thyroid hormone. When TSH level is low, T3 and T4 levels should be obtained. In patients with a suppressed TSH and a normal FT4 level, T3 levels are important to make a diagnosis of T3 toxicosis. Measurement of thyroid-stimulating immunoglobulins and antithyroid antibodies is useful for diagnosing Graves' disease or thyroiditis in selected patients. A thyroid scintiscan can differentiate a hypofunctioning nodule in a patient with Graves' disease from a solitary toxic nodule.

11.9.4 Differential Diagnosis

Thyrotoxicosis should be considered in children with a growth spurt, behavioral problems, or myopathy and in elderly patients with tachycardia or arrhythmias, unexplained diarrhea, and loss of weight. It should be differentiated from anxiety neurosis; organic diseases, which cause heart diseases, anemia, or gastrointestinal

Table 11.15 General examination findings in thyrotoxicosis

Systems/organs	Manifestations
Body metabolism	Increased metabolism leads to excessive sweating, loss of weight in spite of good appetite, and intolerance to hot weather
Nails	The junction of the nail with its bed becomes straight or concave (thyroid acropachy) and onycholysis
Digestive system	Diarrhea, nausea and vomiting (thyrotoxic crisis), abdominal distention, increased glucose intolerance, and glycosuria (polyphagia and polydipsia)
Respiratory system	Dyspnea on effort
Nervous system	Increased irritability, nervousness, easy excitability, fine tremors, choreiform movement of the hands and arms, and frank psychosis (in severe cases)
Cardiovascular system	Attacks of palpitation on exertion or on rest, tachycardia, cardiac arrhythmias superimposed on a sinus tachycardia (as the disease progresses) in the form of multiple extrasystoles, paroxysmal atrial tachycardia, paroxysmal atrial fibrillation, persistent atrial flutter not responsive to digoxin, and congestive heart failure (CHF)
Musculoskeletal system	Myopathy (weakness), osteoporosis (vertebral collapse or fractures), and pretibial myxedema (localized, bilateral leathery thickening of the skin of the fronts of the legs)
Eye manifestations	
	Lid retraction (Dalrymple's sign): Spasm of the involuntary part of the levator palpebrae superioris muscle (Muller's muscles) causes widening of the palpebral fissure, so a band of white sclera appears between the margin of the upper eyelid and the cornea (*no proptosis*)
	Lid lag (Von Graefe's sign): Lack of harmony between movement of the upper eyelid and the eyeball. The eyelid lags behind the eyeball as the patient looks down following the examiner's finger
	Stellwag's sign: Staring look due to infrequent blinking, a mild degree of lid retraction, or exophthalmos
	Joffroy's sign: No wrinkling of the forehead on looking upward due to weakness of the frontalis muscle
	Moebius sign: Lack of convergence on looking at a near object for a long time due to easy fatigability of skeletal muscles of the eye
	Gifford's sign: Difficulty in passive eversion of the eye
	Rosenbach's sign: Involuntary spasm of the eyelids when closed
	Backer's sign: Abnormal pulsation of the retinal vessels
	Thyrotoxic exophthalmos: Abnormal protrusion of the eye ball, usually bilateral but may be unilateral
	Malignant exophthalmos: Edema and pigmentation of eyelids, diplopia and squint from ophthalmoplegia, edema and chemosis of conjunctiva, and corneal, which may end in panophthalmitis and blindness

diseases; myasthenia gravis or other muscular disorders; menopausal syndrome; pheochromocytoma; and other causes of exophthalmos and primary ophthalmopathy.

11.10 Graves' Disease

Graves' disease (*Basedow's or Parry's disease*) is an autoimmune disorder with a genetic predisposition that typically affects young individuals between 20 and 40 years of age, with a female to male ratio that varies from 4:1 to 10:1. It is the most common cause of spontaneously occurring thyrotoxicosis, accounting for 60–90 % of all cases, and frequently occurs in association with other autoimmune diseases.

11.10.1 Pathogenesis

Reduced activation of suppressor T lymphocytes by specific antigen that occurs due to an inherited abnormality in antigen presentation

encoded for by histocompatibility genes has been postulated to be the main defect behind the development of thyrotoxicosis [124]. The autoimmune dysfunction may be precipitated by environmental factors such as stress, infection, or trauma. The defect in suppressor T-cell function allows for thyroid-directed B lymphocytes, which are normally suppressed, to produce thyroid antibodies directed against the TSH receptor which stimulates the follicular cells in a manner similar to TSH. Graves' disease is also characterized by thyroid autoantibodies to other antigens including thyroglobulin and thyroid peroxidase (TPO).

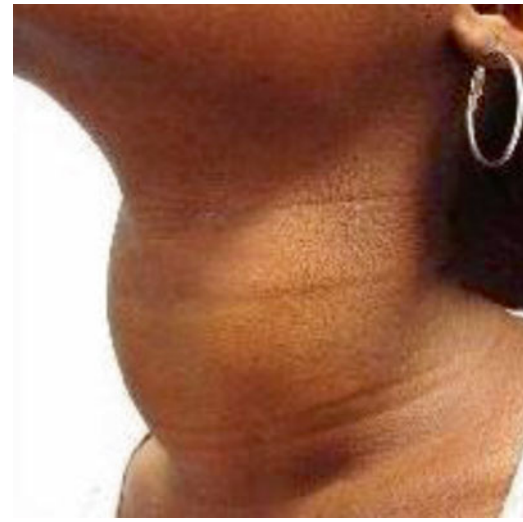

Fig. 11.11 Diffuse goiter with no nodules (smooth)

11.10.2 Pathology

Macroscopically, the gland is smooth and diffusely enlarged, reddish brown, and friable. The cut surface shows a varying picture depending on the colloid content, vascularity, and the amount of fibrous stroma. *Microscopically*, the gland shows marked vascularity, epithelial proliferation of the cells lining the follicles, and lymphocytic infiltration of the stroma.

11.10.3 Clinical Presentation

Patients with Graves' disease typically have a diffuse symmetric goiter (Fig. 11.11) often with an audible bruit in addition to the variable presence of ophthalmopathy, dermopathy, and acropachy.

The extrathyroidal manifestations of Graves' disease result from tissue deposition of glycosaminoglycans in response to the immune reaction against tissue antigens shared with the thyroid gland or antigens that cross-react with the TSH receptor.

Ophthalmopathy occurs more in patients with higher levels of thyroid receptor antibodies [125]. Eyelid retraction, lid lag, and stare look may occur with thyrotoxicosis regardless of its cause; however, periorbital edema, chemosis, exophthalmos (Fig. 11.12a–b), diplopia, and decreased visual acuity are more specific for Graves' disease and occur as a result of edema, glycosaminoglycan deposition, leukocyte infiltration, and fibrosis of the orbit and extraocular muscles.

Dermopathy, in the form of pretibial myxedema, occurs in 0.5–4 % of patients. It consists of violaceous, plaque-like thickening or induration of the skin of the lower legs and feet and may be associated with pain and pruritus. *Acropachy* is rare (<1 %) and is manifested by thickening or clubbing of the fingers or toes, nail changes, and periosteal new bone formation.

11.10.4 Diagnosis

The diagnosis of Graves' disease is usually established by the presence of hyperthyroidism, diffuse symmetric goiter, low TSH levels, and increased thyroidal RAI uptake (typically diffuse and symmetric). Measurement of thyroid receptor antibodies is not routinely necessary. Documentation of high titers of thyroid-stimulating immunoglobulins during pregnancy in women with a history of Graves' disease may be important in predicting the risk of fetal and neonatal thyrotoxicosis [124]. Scintigraphy is used selectively to help differentiate thyrotoxicosis caused by Graves' disease from toxic MNG, a solitary toxic thyroid nodule, or Graves' disease with a concomitant dominant thyroid nodule.

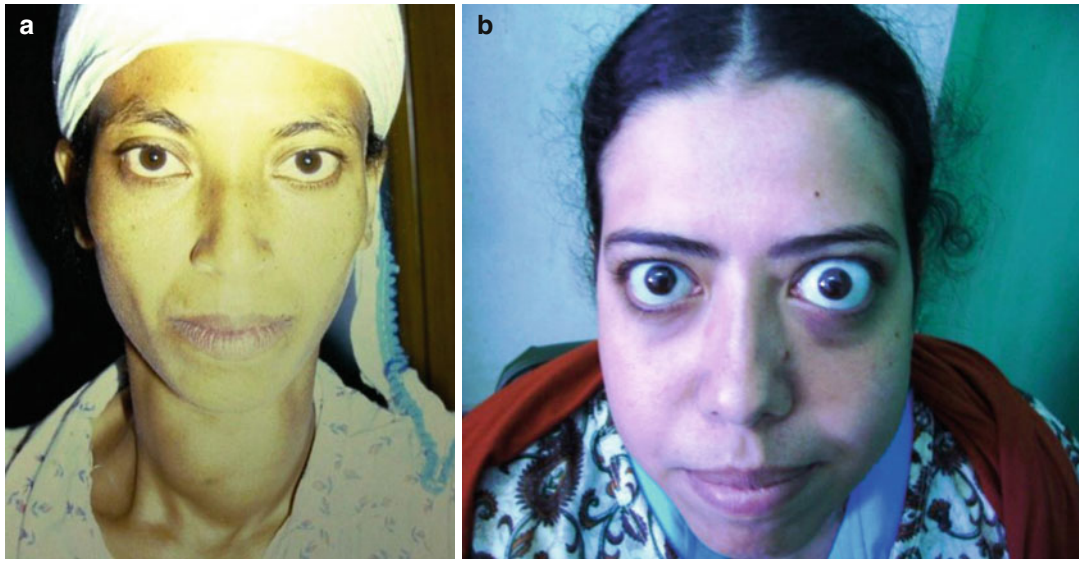

Fig. 11.12 (**a**) A 33-year-old patient with exophthalmos. (**b**) A 24-year-old lady with severe exophthalmos. Note white sclera all around

11.10.5 Management

11.10.5.1 Radioactive Iodine (RAI)

In the United States, the majority of patients with Graves' disease are treated with RAI, which emits beta particles that locally destroy the follicular cells of the thyroid gland. Nordyke and Gilbert reported that 90 % of their patients treated with a 10 mCi of RAI were cured. A higher dose may be required in patients with large thyroid glands (>50 g). However, they emphasized that delayed hypothyroidism develops in most patients with Graves' disease treated with RAI regardless of the dose of ^{131}I used. Accordingly, definitive treatment of hyperthyroidism is the most important consideration [126].

Symptomatic improvement usually occurs 6–8 weeks after receiving RAI treatment, and complications are rare. Serum TSH levels are monitored in all patients, and thyroid replacement with L-thyroxin is begun when TSH levels are elevated. A pregnancy test should be obtained prior to RAI administration in all women of the child-bearing age as it is contraindicated during pregnancy (and lactation).

11.10.5.2 Antithyroid Drugs (ATDs)

The thioamide drugs propylthiouracil (PTU) and methimazole are used for the treatment of Graves' disease in children, pregnant or breastfeeding women, elderly patients with mild to moderate symptoms without a goiter, and in preparation of patients for RAI or surgery. Both drugs decrease thyroid hormone synthesis by a dose-dependent inhibition of the thyroid peroxidase enzyme. In addition, PTU blocks the peripheral conversion of T4–T3. When compared to methimazole, PTU has a greater protein binding which results in less passage across the placenta and the mammary epithelium, and that is why it is preferable in women who are pregnant or breastfeeding. The half-life of PTU is 2 h and is given 2–3 times/day, whereas methimazole has a half-life of 6 h and is given 1–2 times/day.

A high thioamide dose is given initially (PTU 100–200 mg or methimazole 10–30 mg). Once the free T4 and T3 levels have normalized, the thioamide dose is tapered to the lowest dose that will maintain a euthyroid state. Patients are kept on a maintenance dose usually for 1–2 years.

Remissions are variable and most often last for <6 months. Hedley et al. reported that 40–80 % of patients develop recurrent thyrotoxicosis after discontinuation of ATDs [127].

Minor side effects of thioamides may be dose related or agent related and include skin rash, pruritus, urticaria, nausea, vomiting, myalgias or arthralgias, fever, and transient leukopenia. In such cases, drug dosage is reduced or the other thioamide drug substituted, though cross-sensitivity may occur. Major side effects are idiopathic and include agranulocytosis, hepatitis, aplastic anemia, and vasculitis.

11.10.5.3 Surgical Treatment

Surgery for treatment of Graves' disease results in immediate symptomatic improvement and is indicated in pregnant patients intolerant to ATDs, large goiters with compressive symptoms, concomitant solitary cold nodule, patients who fail to respond to multiple doses of RAI, and those who prefer surgery.

The standard operation had been a bilateral subtotal thyroidectomy in an attempt at maintaining a euthyroid state postoperatively and reducing the risk of RLN injury and hypoparathyroidism while minimizing the risk of recurrent hyperthyroidism. However, it has been reported that 10–15 % of patients suffer from recurrent hyperthyroidism after bilateral subtotal thyroidectomy and the majority of patients become hypothyroid within 10 years. Consequently, total thyroidectomy (TT) has become the procedure of choice provided it is performed by experienced hands. In addition, TT has also been recommended for patients with severe or progressive ophthalmopathy and high TSH receptor antibody titers [125]. Total removal of the thyroid gland is advocated to decrease TSH receptor antibodies and other antibodies directed against the extraocular muscles, orbit, and optic nerve [125].

Prior to elective surgery, patients are rendered biochemically euthyroid using ATDs. A β-adrenergic-blocking agent (propranolol) is also used for symptomatic treatment and maintaining the resting heart rate between 60 and 80 beats/min. Preparing the patient for surgery is important in order to eliminate the risk of perioperative thyroid storm.

11.11 Toxic Multinodular Goiter (Plummer's Disease)

Toxic MNG accounts for 5–15 % of cases of thyrotoxicosis. It more commonly affects women and typically occurs in elderly patients with a long-standing MNG. It is thought to occur due to progressive generation of autonomously functioning thyroid follicles overtime that have a greater capacity to synthesize T4 and T3, eventually resulting in toxic MNG.

11.11.1 Diagnosis

Thyrotoxicosis is generally mild in comparison to Graves' disease, and infiltrative ophthalmopathy does not occur; however, patients often have large goiters with compressive symptoms, and cardiovascular manifestations occur more commonly because the patients are older. Laboratory evaluation reveals a low serum TSH level with or without elevated serum FT4 and/or T3 levels. Routine scintiscanning is not necessary.

11.11.2 Treatment

The goal in treatment is to eradicate all autonomously functioning thyroid follicles by surgical resection or ^{131}I therapy. Because of the marked thyroid enlargement and frequent associated compressive symptoms, *surgical resection*, in the form of total thyroidectomy, is the usual treatment. A subtotal thyroidectomy is performed only when it can be accomplished without leaving abnormal thyroid tissue behind. Patients are also pretreated with ATD preoperatively to normalize their free T4 or T3 levels before proceeding with thyroidectomy.

Radioiodine may also be used for treatment. However, toxic MNGs can be resistant to RAI therapy, which is also usually *not* effective in alleviating compressive symptoms related to thyroid enlargement. Treatment with ^{131}I is usually reserved for elderly patients with multiple concurrent medical problems that place them at high risk for surgery. Treatment with ATDs should be considered prior to RAI administration especially in patients with underlying heart disease. It must be discontinued 3–5 days prior to treatment to optimize RAI uptake and then resumed 1 week after treatment.

11.11.2.1 Solitary Toxic Nodule

A solitary toxic nodule is a discrete, autonomous, hyperfunctioning nodule that occurs in an otherwise normal thyroid gland and causes hyperthyroidism. It accounts for nearly 3–10 % of all cases of spontaneous thyrotoxicosis. The term *hyperfunctioning* nodule means that it takes up greater radioiodine than the normal adjacent thyroid tissue. Only 25 % of all hyperfunctioning nodules are toxic nodules. The term *autonomous* means it functions independently of the hypothalamic-pituitary-thyroid feedback mechanism and secretes thyroid hormone despite suppressed TSH levels.

11.11.3 Diagnosis

The clinical thyrotoxic manifestations of a solitary toxic nodule are generally milder than in patients with Graves' disease. It usually occurs more commonly in women and in patients <50 years of age. Physical examination reveals a single, discrete nodule in the thyroid gland.

The initial diagnostic test is serum TSH, free T4, and free T3 levels. Hyperfunctioning nodules preferentially secrete T3, and so serum T3 levels are more likely to be elevated in patients with an autonomous nodule. A thyroid scan using ^{131}I confirms the presence of a hyperfunctioning nodule. The pathology of a toxic solitary nodule is almost uniformly either a follicular adenoma or an adenomatous nodule. Carcinoma occurs in only about 1 % of cases [128].

11.11.4 Treatment

Patients with a hyperfunctioning thyroid nodule who are *asymptomatic* can be *observed*. Treatment is recommended in the presence of *subclinical hyperthyroidism* for patients who are at high risk of cardiac side effects, for postmenopausal women with decreased bone mineral density, and those who have a hyperfunctioning nodule >3 cm in diameter.

Both ^{131}I and surgery (hemithyroidectomy) have been reported to be effective in the treatment of solitary *toxic* nodules. *Surgical treatment* has the advantages of immediate symptomatic relief, avoidance of radiation exposure to the normal thyroid tissue, and the low risk of complications. Both postoperative hypothyroidism and recurrence of hyperthyroidism are uncommon. *Radioiodine treatment* usually requires higher doses of ^{131}I than are normally used for treatment of Graves' disease. It has the disadvantages of delay in symptomatic relief; exposure of normal thyroid tissue to radiation, which may result in hypothyroidism in up to 35 % of patients; and concerns related to persistence of the nodule [129].

Other less attractive therapeutic options include *ATDs* and percutaneous *ethanol injection*. The ATDs are not curative and must be given lifelong because to avoid recurrence of hyperthyroidism. Their use is limited to preparing patients for surgical or RAI treatment, but may also be considered in elderly patients with medical problems that preclude surgery or RAI therapy. Ultrasound-guided ethanol injection is effective in reversing hyperthyroidism, but it requires multiple painful injections and can be complicated by transient RLN paresis.

11.12 Thyroiditis

Thyrotoxicosis secondary to thyroiditis is uncommon. It is typically transient and self-limited. It may occur as a result of chronic lymphocytic or Hashimoto's thyroiditis (*hashtoxicosis*), silent (painless) thyroiditis, subacute (de Quervain's) thyroiditis, and RAI-induced thyroiditis. In

contrast to hashtoxicosis in which RAI uptake is increased, silent, subacute, and RAI-induced thyroiditis are all characterized by the inability to trap iodine, follicular cell destruction, and release of preformed thyroid hormone resulting in thyrotoxicosis with a low RAI uptake.

11.12.1 Hashimoto's Thyroiditis

Thyrotoxicosis in patients with Hashimoto's thyroiditis typically occurs in the early course of the disease and is transient in nature. It is thought to be the result of lymphocyte production of stimulatory anti-TSH receptor antibodies, which are present in 10–25 % of all patients with chronic lymphocytic thyroiditis. Those patients have marked elevation of antithyroglobulin and antithyroid peroxidase (antimicrosomal) antibody titers and focal or diffuse lymphocytic infiltration of the thyroid gland. Most patients are women between the ages of 30 and 50 years. They may have a firm goiter and rarely ophthalmopathy. As the disease progresses, thyrotoxicosis resolves and hypothyroidism develops. If symptoms of thyrotoxicosis become problematic, a beta-adrenergic blocking agent or ATD may be used. Patients are followed up clinically, and their serum TSH levels are monitored for the inevitable development of hypothyroidism, which will require hormone replacement therapy.

11.12.2 Silent (Painless) Thyroiditis

Silent thyroiditis is the major cause of thyrotoxicosis in patients with low RAI uptake. It is an autoimmune disorder which accounts for <5 % of all cases of thyrotoxicosis. It is a form of lymphocytic thyroiditis characterized by single or recurrent episodes of acute inflammation of the thyroid gland resulting in release of stored thyroid hormone. Patients are usually women between the age of 30 and 40 years. Symptoms of thyrotoxicosis are usually acute, mild, and self- limited and may be followed by transient hypothyroidism. Clinically, patients may have a firm, non-tender goiter. Antithyroid peroxidase and antithyroglobulin antibodies may be elevated, and serum thyroglobulin level is markedly elevated. In general, the condition requires no therapy, unless symptoms become problematic. In such cases, a beta-adrenergic antagonist and anti-inflammatory therapy with prednisone can be used. Because increased thyroid hormone synthesis is not the cause of thyrotoxicosis, ATDs are not effective. Surgical or RAI treatment may be beneficial in the rare patient with recurrent disabling episodes of silent thyroiditis with thyrotoxicosis.

11.12.3 Subacute Thyroiditis (de Quervain's, Granulomatous, or Giant Cell Thyroiditis)

Subacute thyroiditis is a subacute, self-limited inflammatory condition of the thyroid gland, characterized by neck pain, fever, myalgias, malaise, mild to moderate thyroid enlargement, exquisite neck tenderness, and symptoms of thyrotoxicosis, which occur during the initial phase of inflammation. *Etiology* is multifactorial. A viral infection may trigger an abnormal cell-mediated immune response directed at the thyroid follicular cells causing follicular cell destruction and release of preformed thyroid hormone. A genetic predisposition may also be involved as suggested by the association of the HLA BW35 haplotype with subacute thyroiditis in certain patients [130]. *Diagnosis* is supported by the presence of a markedly elevated erythrocyte sedimentation rate (ESR), an increased serum thyroglobulin level, and a suppressed RAI uptake. *Treatment* is primarily supportive using nonsteroidal anti-inflammatory agents, or prednisone. Thyrotoxicosis usually requires no treatment and resolves within 3–6 weeks. If symptoms become problematic, a beta-adrenergic blocking agent, but not ATDs, may be given. If follicular cell destruction is extensive, hypothyroidism may develop during the recovery phase. Nevertheless, nearly 95 % of patients become euthyroid within 6 months of onset.

11.13 Iodine-Induced Thyrotoxicosis

Iodine-induced thyrotoxicosis usually occurs in elderly patients with a preexisting MNG who are given a large iodine (I_2) load (e.g., oral expectorants, intravenous contrast material, etc.). It is the only cause of hyperthyroidism with a low RAI uptake and accounts for <1 % of all causes of thyrotoxicosis. *Pathogenesis* is not fully understood. In normal individuals, large doses of iodine lead to an inhibition of I_2 transport and a rapid decrease in thyroid hormone synthesis and release (Wolff-Chaikoff effect). It may also occur as a result of supplying excess I_2 to areas of autonomous function in the thyroid gland (Jod-Basedow effect) or due to increase in the I_2 set point of the thyroid gland which leads to increased thyroid hormone synthesis. Diagnosis is suspected by a history of a recent exogenous I_2 load in a patient with a goiter and is supported by a serum iodide concentration >1.5 mg/dl and a 24-h urinary iodide excretion >1000 mg. *Treatment* most often consists of discontinuation of the iodide source, although this may be problematic in patients with refractory arrhythmias on amiodarone [131]. Thioamide drugs may also be used either alone or in combination with a beta-adrenergic antagonist and/or potassium perchlorate, which competitively inhibits I_2 uptake by the thyroid gland. Radioiodine therapy is *not* an option because the high I_2 load suppresses RAI uptake by the thyroid gland. Total thyroidectomy may be indicated in patients with amiodarone-induced thyrotoxicosis that is refractory to medical therapy or as an initial therapy for patients who present with resurgence of life-threatening cardiac arrhythmias [131].

11.14 Thyroiditis

11.14.1 Introduction

Thyroiditis represents about 20 % of all thyroid diseases [132] and is caused by several factors, most commonly autoimmune diseases (Table 11.16). Thyroid autoantibodies are mainly directed against thyroid peroxidase (TPO) or thyroglobulin (Tg) and have an association with defined HLA haplotypes implying a genetic predisposition [133]. Iodine therapy, viral infections, pregnancy, menopause, stress [134], and immune-modulating drugs such as interferon-α have also been linked to autoimmune thyroiditis. Except for Graves' disease, most cases of autoimmune thyroiditis present initially with hyperthyroidism that returns to euthyroidism or falls to permanent hypothyroidism (subclinical or overt).

Table 11.16 Etiology of thyroiditis

Autoimmune thyroiditis	Nonimmune thyroiditis
Chronic lymphocytic thyroiditis (Hashimoto's)	Acute infectious thyroiditis
Fibrotic variant of Hashimoto's thyroiditis	Radiation-induced thyroiditis
Atrophic thyroiditis (primary myxedema)	Palpation/trauma-induced thyroiditis
Variants of autoimmune thyroiditis	Sarcoidosis
Postpartum thyroiditis	Vasculitis-associated thyroiditis
Silent or painless thyroiditis	Postoperative necrotizing thyroiditis
Subacute de Quervain's thyroiditis	Drug-induced thyroiditis
Fibrotic Riedel's thyroiditis	Carcinoma-associated thyroiditis

Clinically, thyroiditis is divided into acute, subacute, and chronic forms [135], and patients may present either with severe thyroid pain (e.g., acute suppurative thyroiditis, subacute de Quervain's thyroiditis, radiation thyroiditis, traumatic thyroiditis) or without evident inflammation but with goiter or thyroid dysfunction (e.g., silent thyroiditis, Hashimoto's or Riedel's thyroiditis).

11.15 Autoimmune Thyroiditis

11.15.1 Hashimoto's Thyroiditis (Chronic Lymphocytic Thyroiditis, Struma Lymphomatosa)

Hashimoto's thyroiditis is the most frequent autoimmune thyroiditis and the most common cause of hypothyroidism [132]. Women are 10–20 times

more affected than men, with a peak incidence in the fifth decade of life. A genetic association with the haplotypes HLADR3, HLADR4, and HLADR5 has been reported. Many other autoimmune diseases are associated with Hashimoto's thyroiditis such as Graves' disease, juvenile diabetes, Addison's disease, pernicious anemia, rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematosus (SLE).

Hashimoto's thyroiditis is caused by a breakdown in self-tolerance to thyroid autoantigens. This is exemplified by the presence of circulating autoantibodies against Tg and thyroid TPO in the vast majority of cases. The inciting events have not been elucidated, but possibilities include abnormalities of regulatory T cells or exposure of normally sequestered thyroid antigen. Induction of thyroid autoimmunity is accompanied by a progressive depletion of thyroid epithelial cells by apoptosis and replacement of thyroid parenchyma by mononuclear cell infiltration and fibrosis. Multiple immunological mechanisms may contribute to thyroid cell death, including CD8+ cytotoxic T-cell-mediated cell death, cytokine-mediated cell death, and, less likely, binding of antithyroid antibodies followed by antibody-dependent cell-mediated toxicity.

Patients with Hashimoto's thyroiditis mostly present with a painless homogeneous goiter and manifestations of hypothyroidism. Low levels of thyroid hormones with high TSH and circulating thyroid autoantibodies against TPO (in 70–90 % of cases) and Tg (in 40–70 % of cases) confirm the diagnosis [132]. Occasionally, the patient presents initially with hyperthyroidism (*hashtoxicosis*) associated with the presence of anti-TSH receptor antibodies. The FNAC may frequently show Hürthle cells, and it may be difficult to distinguish Hashimoto's thyroiditis at times from a follicular neoplasm, PTC, or low-grade MALT lymphoma. Immunohistochemistry studies may help to reach the diagnosis.

Being an autoimmune disease, the clinical course of Hashimoto's thyroiditis is one of relapsing episodes, with up to 25 % of the patients showing a spontaneous recovery. The binding of autoantibodies to the thyrocytes accounts for complement and T-lymphocyte-mediated lysis of the thyrocytes and non-regulated release of T3 and T4, resulting in the transient hyperthyroidism occasionally noted. Later on, destruction of the thyroid parenchyma may lead to permanent hypothyroidism. Replacement thyroid hormone therapy is indicated when overt hypothyroidism is identified, and most patients will require lifelong therapy.

Fibrotic Hashimoto's Thyroiditis A fibrotic variant of Hashimoto's thyroiditis accounts for up to 10 % of cases, mainly in elderly patients with a preexisting goiter. It is characterized by a rapid increase of goiter size, which may lead to the suspicion of malignancy, Riedel's fibrosing thyroiditis. However, the extensive fibrotic changes and metaplasia noted on biopsies are always limited to the gland.

Atrophic Hashimoto's (Autoimmune) Thyroiditis (*Primary or Idiopathic Myxedema*) The atrophic autoimmune thyroiditis is the cause of primary myxedema and should not be confused with end-stage fibrotic Hashimoto's thyroiditis. Most of the patients do not show signs or symptoms of hypothyroidism until the fourth to sixth decade of life, and women are five times more affected than men [136].

11.15.2 Focal Lymphocytic Thyroiditis (Focal Autoimmune Thyroiditis, Chronic Nonspecific Thyroiditis)

This low-grade autoimmune thyroiditis is characterized by focal lymphocytic infiltrates of <5 % of the thyroid gland and is found coincidentally in 50 % of women's and 25 % of men's autopsies, without clinical relevance.

11.15.3 Postpartum Thyroiditis

A postpartum thyroiditis occurs in 2–16 % of women within 1 year after delivery (or abortion) [137, 138]. The disease represents an exacerbation of a preceding (undiagnosed) autoimmune

thyroiditis and is classically linked to the haplotypes HLADR3, HLADR4, and HLADR5. Most patients (85 %) develop autoantibodies against TPO and Tg, which may disappear with time. Women with a known autoimmune thyroiditis prior to pregnancy and an elevated titer of autoantibodies against Tg during pregnancy nearly always suffer from a postpartum exacerbation of their autoimmune thyroiditis. Clinically, patients may show a transient hyperthyroidism state, which rapidly converts to hypothyroidism, and then to euthyroidism within 12 months. Treatment consists of thyroid hormone replacement when required.

11.15.4 Subacute de Quervain's Thyroiditis (Granulomatous, Pseudotuberculous, or Giant Cell Thyroiditis)

Subacute de Quervain's thyroiditis is a self-limiting disease accounting for 0.5–3 % of all thyroid diseases and lasts for up to 2 months [139]. A post-viral cytokine-mediated inflammation of the thyroid is suspected because of the seasonal frequency and association with upper respiratory tract infection. In 50 % of patients, antibodies against mumps, measles, influenza, adenovirus, coxsackievirus, or echovirus are found. Furthermore, a genetic predisposition exists with the haplotype HLA-Bw35.

Women are 3–6 times more affected than men, with a peak incidence between the second and fifth decades of life. Symptoms include pain in the neck that irradiates to the jaw, ear, face, and down to the chest, fever, lassitude, and weakness. Physical examination reveals an exquisitely tender and enlarged gland. The erythrocyte sedimentation rate (ESR) is markedly elevated. Initially, there is transient hyperthyroidism from destruction of the thyroid follicles by the local inflammation process. Later on, hypothyroidism emerges due to inability to cope with the body's demand for thyroid hormones, and finally, as healing occurs, euthyroidism is restored. However, permanent hypothyroidism requiring replacement therapy may occur in 15 % of patients, and recurrence may be noted, at a low rate of 4 % [140].

Subacute should be differentiated from acute suppurative thyroiditis. In de Quervain's thyroiditis, the gland sonographically reveals irregular hypoperfused areas instead of hyperperfused tissue seen with acute suppurative thyroiditis. On FNA, the differential diagnosis further includes palpation thyroiditis, in addition to other granulomatous diseases such as sarcoidosis, tuberculosis (TB), and rheumatoid diseases.

Treatment is supportive with nonsteroidal anti-inflammatory drugs (NSAIDs) and β-blockers in severe cases with hyperthyroidism. Corticosteroids are useful when the NSAID medication is not successful, and symptoms usually improve within 2–3 days after the initiation of treatment. However, it may take about 4 weeks for the disappearance of the thyroid mass.

11.15.5 Painless Thyroiditis (Subacute Lymphocytic Thyroiditis)

Patients with painless thyroiditis present with a diffuse but mild enlargement of the thyroid gland. Thyroid function tests reveal a transient hyperthyroidism, followed by hypothyroidism. Autoantibodies against TPO and Tg are found as well as an association with HLADR3 and HLADR5 haplotypes. Histological examination reveals lymphocytic infiltration with destruction of follicles (in contrast to Hashimoto's thyroiditis) and absence of giant cell granulomas (in contrast to subacute thyroiditis). Women are more often affected than men with a peak of incidence in middle life and in the postpartum period. It is a self-limited disease and rarely necessitates thyroid replacement therapy.

11.15.6 Riedel's Fibrosing Thyroiditis

Riedel's thyroiditis is a rare chronic thyroiditis in which the thyroid gland is replaced by fibrous tissue. The underlying etiologic mechanisms are unclear, though an autoimmune relation is suspected, due to elevated titers of thyroid autoantibodies. It is generally considered as a part of a multifocal fibro-inflammatory process also

involving other tissues such as the mediastinum, liver, lung, retroperitoneum, and orbit.

Women in middle to advanced ages are more affected than men. The clinical picture often resembles malignancy due to the hard consistency of the gland. Patients usually complain of a rapid indolent enlargement of the thyroid that becomes very hard and may suffer from neck discomfort, dysphagia, hoarseness of voice, and hypoparathyroidism (due to involvement of the RLN and parathyroid glands). Approximately, 30–40 % of patients develop overt hypothyroidism. Physical examination, laboratory analysis, cytology, and imaging features are not useful for differentiating between Riedel's thyroiditis and neoplastic diseases or the fibrotic variant of Hashimoto's thyroiditis [141].

Histological examination is necessary to establish the final diagnosis, and so surgical biopsy is mandatory. The differential diagnosis further includes anaplastic carcinoma and sarcoma of the thyroid. In contrast to the fibrotic variant of Hashimoto's thyroiditis where fibrosis is strictly limited to the gland, Riedel's thyroiditis displays a dense fibrotic replacement of thyroid parenchyma that penetrates the capsule and extends into contiguous neck structures. Once the diagnosis is confirmed, treatment is supportive with thyroid hormone replacement, when required.

11.16 Non-autoimmune Thyroiditis

Nonimmune thyroiditis consists of a heterogeneous and rare group of thyroid inflammatory diseases. Some of them are infectious while others are clearly iatrogenic, such as drug-induced thyroiditis and postoperative necrotizing thyroiditis.

11.16.1 Acute Infectious Thyroiditis (Acute Suppurative Thyroiditis)

Infectious thyroiditis is a rare disease of the thyroid caused by bacterial or fungal infection, though mycobacterial, parasitic, and viral forms of thyroiditis have also been described, particularly in immunosuppressed hosts. The thyroid gland appears to be relatively resistant to infection. The protective mechanisms include a rich vascular supply, extended lymphatic drainage, a fibrous capsule, fascial planes that anatomically separate the thyroid from other cervical structures, and the high iodine content of the gland, which may have bactericidal effect. Infection of the gland occurs, either through hematogenous spread from a primary focus or by direct extension from adjacent neck structures, especially in children [142]. Other less common sources of infection include neck trauma or lymphatic spread, or rarely, surgical site infections [143]. The most common predisposing factor for suppurative thyroiditis is immunosuppression associated with HIV, TB, old age, or debilitating diseases. Other predisposing factors include preexisting thyroid diseases, such as MNG, autoimmune thyroiditis, and cancer [143–165].

Patients usually present with fever and a painful, mostly unilateral, enlargement of the thyroid and local inflammatory signs. The thyroid function tests are usually normal, but a slight hyper- or hypothyroidism may occur. Laboratory tests show leukocytosis and elevated ESR. Neck US shows patchy hyperperfused areas in the thyroid with liquid content (pus) when an abscess is present. An FNAC and cultures can identify the pathogen identification and guide the antimicrobial treatment. Immunosuppressed patients tend to present with more chronic thyroid infections, bilateral disease, and less prominent signs and symptoms. Diagnosis may be reached with a high index of suspicion and aspiration biopsy.

The differential diagnoses include de Quervain's thyroiditis, hemorrhage into a thyroid nodule, infected thyroglossal or branchial cyst, infected cystic hygroma, and cervical lymphadenitis. In addition to FNA, US helps to establish the diagnosis, which may further be refined by CT scan.

When an abscess is identified, surgical drainage is essential. Occasionally, complete resection of an affected gland is required. In patients with recurrent acute thyroiditis, an undetected fistula must be postulated. Complete removal of the infected fistula is therefore required to prevent recurrence. Injection of 0.5 % methylene blue solution through a Nelaton's catheter into the fis-

tula usually enables the complete resection of the tract. When the origin of the fistula is difficult to identify, transection of the inferior pharyngeal constrictor muscle makes intervention easier.

11.16.2 Drug-Induced Thyroiditis

Certain drugs have been reported to cause thyroiditis, such as chronic I_2 therapy, long-term lithium therapy, and anticonvulsants (e.g., phenytoin, carbamazepine) [132]. Moreover, patients with chronic hepatitis or cancer treated with interferon-α will develop a painless thyroiditis in about 1–5 % of cases [146]. Elevated antithyroid antibodies are noted in a higher percentage in these patients, and permanent hypothyroidism or Graves' disease may appear. Thus, TSH should be measured prior to initiation of interferon-α therapy and periodically during treatment [147].

Interleukin-2 (IL-2) is also used for immunemodulation and in malignant melanoma, renal cell carcinoma, and leukemia, alone or in combination with chemotherapy. A painless thyroiditis has been reported in about 2 % of the patients treated with IL-2. Finally, the antiarrhythmic drug amiodarone contains 35 % I_2 and may cause a thyrotoxic crisis or, conversely, cause hypothyroidism. Amiodarone decreases the conversion of T4 to the biologically active T3. It is worth mentioning that if the decision is taken to stop amiodarone therapy, the drug is not eliminated for months due to its very long half-life [148].

11.16.3 Postoperative Necrotizing Thyroiditis

Postoperative necrotizing thyroiditis is a rare surgical complication owing to the very rich vascular supply of the thyroid [149, 150]. It is related to a trauma of the gland by vigorous manipulation at surgery or through repeated FNA [151]. Such manipulation could induce an acute thyroiditis, which in turn may lead to thyrotoxicosis or to a necrotizing thyroiditis. No predictive marker or factor has been identified. Histologically, the specimen typically shows postoperative granulomas, as found in other organs (bladder, prostate) following surgery.

11.16.4 Radiation Thyroiditis

Radiation thyroiditis occurs in a dose-related fashion after RAI or external beam radiation therapy (EBRT), which causes follicle destruction resulting in a transient hyperthyroidism, followed eventually by hypothyroidism. Neck pain and tenderness usually develop 5–10 days following treatment. Symptoms are mild and subside spontaneously in a week.

11.16.5 Other Causes of Nonimmune Thyroiditis

Other causes of thyroiditis are related to a local process, such as an *acute hemorrhage* into a thyroid cyst or nodule. *Palpation thyroiditis* refers to a mild, self-limited thyroiditis occurring after physical examination, surgery, or trauma to the thyroid. It is not associated with any thyroid disease. Finally, thyroiditis may be caused by systemic diseases, such as a *vasculitis-associated thyroiditis* (phenytoin therapy), *sarcoidosis*, [152], *metastatic cancer*, or a *globus hystericus*.

11.16.6 Indications of Surgery in Thyroiditis

Surgical interventions are exceptionally indicated for the management of a thyroiditis, accounting for <1 % of all thyroid procedures [153]. Fortunately, patients with *autoimmune thyroiditis* are effectively managed with thyroid hormone replacement therapy, and surgical treatment is the exception. Technical difficulties are encountered by the surgeon as the glands are firm, rigid, and highly vascular and the surrounding tissues are inflamed with lymphadenopathy, rendering the parathyroids and RLNs at risk. In the rare instance where a large *Hashimoto's goiter* may develop and become symptomatic, total thyroidectomy

(TT) is an option [135, 153, 154]. Moreover, as thyroiditis patients bear a higher risk of developing thyroid carcinoma, a cold nodule suspicious on FNA may indicate a thyroid lobectomy. Similarly, the rapid growth of a chronic lymphocytic thyroid gland is suggestive of non-Hodgkin lymphoma (NHL). While TT may surgically cure a stage I lymphoma (confined to the thyroid), most thyroid lymphomas involve regional LNs and distant sites and require multimodal systemic therapy. Open biopsy or thyroid lobectomy is sufficient in these cases to establish the definitive diagnosis.

A *subacute de Quervain's thyroiditis* exceptionally deserves thyroidectomy. This indication is given when intractable neck pain is present in spite of a consequent analgesic and L-thyroxin replacement therapy over a period of 6 months [153]. The *fibrotic variant of Hashimoto's thyroiditis* is characterized by a rapid enlargement of a preexisting goiter which causes suspicion of a thyroid cancer and consequently surgery. *Riedel's fibrosing thyroiditis* often requires an open biopsy to confirm the diagnosis and rule out an anaplastic carcinoma or isthmectomy and/or lobectomy to decompress the trachea and esophagus. However, thyroidectomy can be highly demanding because of the dense fibrotic reaction extending beyond the thyroid, which puts the surrounding structures at risk of injury. *Amiodarone-induced thyrotoxicosis* in the setting of a rare patient with otherwise intractable arrhythmia is an indication for thyroidectomy. Finally, the *acute suppurative thyroiditis* is a classic indication for surgical drainage followed by antibiotic therapy and rarely for lobectomy when the suppurative process is necrotizing.

11.17 Malignant Thyroid Disease: Introduction

Thyroid cancer is the most common endocrine malignancy, but only represents 1 % of all newly diagnosed malignancies [32]. The wide spectrum of aggressiveness of thyroid cancer is extraordinary, ranging from differentiated malignancies in which most patients live out close to their normal lifespan to anaplastic varieties that are almost universally lethal. It is crucial to ensure that patients presenting with thyroid nodules are not over- or undertreated.

11.17.1 Classification

11.17.1.1 World Health Organization (WHO) Classification

A classification of thyroid tumors, as suggested by WHO, is shown in Table 11.17 [155].

11.17.1.2 Pathological Classification

Most thyroid tumors arise from the follicular cells, and most are well differentiated. Poorly

Table 11.17 WHO classification of thyroid neoplasms

I. Primary tumors
1. Epithelial tumors:
(a) Tumors of follicular cells:
Benign (follicular adenoma)
Conventional
Variants
Malignant (carcinoma)
*Differentiated:
Follicular carcinoma.
Papillary carcinoma:
Conventional
Variants
*Poorly differentiated:
Insular
Others
*Undifferentiated (anaplastic)
(b) Tumors of C (and related neuroendocrine) cells:
Medullary carcinoma
Others
(c) Tumors of follicular and C cells
2. Sarcoma
3. Lymphoma (and related hematopoietic neoplasms)
4. Miscellaneous neoplasms
II. Secondary tumors
III. Tumorlike lesions
1. Tumors with oncocytic (Hürthle cell) features:
Oncocytic adenoma (Hürthle cell adenoma)
Oncocytic carcinoma (Hürthle cell carcinoma)
Papillary oncocytic (Hürthle cell tumors)
2. Tumors with clear cell features
3. Tumors with squamous features
4. Tumors with mucinous features

Table 11.18 Pathological classification of thyroid neoplasms

I. Well-differentiated (low-grade malignancy)	1. Usual papillary thyroid carcinoma (PTC)
	2. Micro-carcinoma (<1 cm)
	3. Follicular variant of PTC
	4. Usual follicular thyroid carcinoma (FTC)
	5. Hürthle cell carcinoma
II. Intermediate differentiation	1. Medullary thyroid carcinoma (MTC)
	2. Diffuse sclerosing variant of PTC
	3. Columnar cell variant of PTC
	4. Insular carcinoma
	5. Tall cell variant of papillary carcinoma
III. Poorly differentiated (high-grade malignancy)	Anaplastic (undifferentiated) carcinoma

differentiated and undifferentiated types are rare (Table 11.18). Well-differentiated carcinomas include papillary and follicular carcinomas.

11.17.2 Screening

At present there is no screening program to detect thyroid cancer for the general population. Screening is possible for familial MTCs associated with specific oncogene mutations. The genetic basis of papillary, follicular, and anaplastic thyroid cancer has been investigated, and the roles and potential prognostic value of several genes, e.g., *RET, TRK, ras, BRAF,* and *p53*, have been identified. Testing for these genes is *not* routinely available in clinical practice [156].

While screening generally is not possible, a family history for thyroid cancer should be taken in each case, and if there is a strong familial incidence of thyroid cancer or association with other cancers, genetic advice should be considered in appropriate cases from the regional genetics service.

11.17.3 Risk Factors for Thyroid Carcinoma

11.17.3.1 History Taking

It is important to focus on gender; age; duration of the swelling and, more importantly, its rate of growth; history of neck irradiation; and family history of thyroid cancer. Other associated symptoms such as difficulty swallowing or breathing would suggest compressive effect. A hoarse voice is a strong indication of RLN palsy and malignancy [73]. Other associated diseases should also be noted. These are summarized in Table 11.19 [103].

Male gender carries 2–3 times the risk of thyroid cancer as compared to women [74, 157]. At an age below 20 years, the risk of malignancy is doubled, while above 70 years, the risk of malignancy is quadrupled [74, 157].

There is a 40 % absolute risk of malignancy for a thyroid nodule in a patient with previous exposure to irradiation, particularly during childhood. Low dose carries a 100 times increased risk of malignancy (lifetime risk), while high dose carries a 300 times increased risk (lifetime risk). The latency period is 10–15 years, and cancer mostly occurs 20–30 years after radiation exposure [73, 158]. History of rapid growth in a few weeks [73, 158, 159] and the presence of hoarseness of voice or vocal cord palsy indicate a higher risk of malignancy [159].

11.17.3.2 Clinical Examination

The larger tumor size, especially when >4 cm, and the presence of obstructive symptoms indicate higher risk of malignancy [157, 159]. Firm/hard consistency or fixed swelling indicates high risk, while a soft, mobile, or cystic swelling indicates a low risk of malignancy [159]. Presence of cervical lymphadenopathy indicates high risk of malignancy [159] (Table 11.19).

Flexible laryngoscopy is important to assess vocal cord movements. The so-called "classic" red flag physical finding is true vocal cord paralysis. However, this finding by itself can be of limited help in assessing malignant potential as the three main causes of unilateral vocal cord paralysis can be

Table 11.19 Risk factors for thyroid cancer [103]

Risk factors	
History taking	Physical examination
Male gender Age <20 or >70 years Low-iodine diet (endemic goiter) Radiation exposure (during childhood) Family history of thyroid cancer Hashimoto's thyroiditis (risk of lymphoma) Family or personal history of thyroid adenoma Multiple endocrine neoplasia (MEN II a, b) Gardner syndrome Familial adenomatous polyposis Cowden disease Nonpolyposis colon cancer syndrome (NPCC)	True vocal cord fixation Very firm or hard nodules Fixation to skin, surrounding musculature, and extracapsular spread Associated cervical lymph nodes (LNs) Recent rapid growth Large nodules (>4 cm) Persistent diarrhea (MTC)

broadly categorized as iatrogenic, malignant, and idiopathic. Reviews of unilateral cord paralysis quote figures for malignancy ranging from 7 to 25 % with the vast majority due to lung cancer. If lung cancer is excluded, all other malignancies, including thyroid cancer, represent well under 10 % of unilateral vocal cord paralysis. In contrast, idiopathic causes account for 30–40 % of vocal cord paralysis cases.

11.18 Well-Differentiated Thyroid Cancer

Differentiated thyroid carcinoma (DTC) refers to both papillary and follicular carcinomas, which arise from the thyroid follicular cell. Among many unique features of DTC, two require special mention. First, *age* is the most important prognostic factor. It is interesting to note that the mortality in patients with thyroid cancer in the younger age group is extremely low, while that in the elderly patient is quite high. There is no other human cancer that parallels this biological behavior. This is the only cancer where age is included in the staging system. There is no stage III and IV cancer in patients below the age of 45 years [160–162]. Second, the presence of *nodal metastasis* has almost no prognostic implication. This clinical behavior is not seen in any other malignancy. In the majority of cancers, the presence of nodal metastasis decreases the survival by almost 50 %, while in well-differentiated thyroid cancer (WDTC), there is no apparent effect on outcome [163].

The mortality of DTC remains low; most deaths are directly related to the high-risk group, generally elderly patients with poorly differentiated histology or locally aggressive tumors. There is considerable debate and controversy about the management of the disease [164]. There are vigorous proponents of routine total thyroidectomy (TT), whereas other authors recommend less than TT, depending on the prognostic factors and risk groups [165].

11.18.1 Staging (Tables 11.20a, 11.20b, and 11.20c)

11.18.2 Management of DTC

11.18.2.1 Surgical Treatment

Fine-needle aspiration cytology (FNAC) should be used in the planning of surgery. Patients with a PTC >1 cm or with high-risk FTC should undergo near-TT or TT, while those with PTC ≤1 cm or low-risk FTC may be treated with thyroid lobectomy alone. Serum thyroglobulin (Tg) should be checked in all postoperative patients with DTC, but not sooner than 6 weeks after surgery. Patients will normally start on L-thyroxin 100 μg daily after the operation. This should be stopped 2 weeks before ^{131}I ablation or therapy.

Most patients with a tumor >1 cm, who have undergone a near-TT/TT, should have ^{131}I ablation. Pregnancy and breastfeeding should always be excluded before administering ^{131}I. Breastfeeding should be stopped 4 weeks and preferably 8 weeks before ^{131}I ablation or treatment and should not be resumed. A post-ablation scan (3–10 days after ^{131}I ablation) should be performed.

Table 11.20a TNM Classification according to tumor, nodes, and metastases [166, 167]

Primary tumor (pT)	
pT1	Intrathyroidal tumor, ≤1 cm in greatest dimension
pT2	Intrathyroidal tumor, >1–4 cm in greatest dimension
PT3	Intrathyroidal tumor, >4 cm in greatest dimension
pT4	Tumor of any size, extending beyond thyroid capsule
pTX	Primary tumor cannot be assessed
Regional LNs (cervical or upper mediastinal)	
N0	No nodes involved
N1 N1a N1b	Regional nodes involved Ipsilateral cervical nodes Bilateral, midline, or contralateral cervical nodes or mediastinal nodes
NX	Nodes cannot be assessed
Distant metastases	
M0	No distant metastases
M1	Distant metastases
MX	Distant metastases cannot be assessed

Undifferentiated or anaplastic carcinomas: All are Stage IV

Table 11.20b Papillary or follicular carcinoma staging

Stage	Under 45 years	45 years and older
Stage I	Any T, any N, M0	pT1, N0, M0
Stage II	Any T, any N, M1	pT2, N0, M0 pT3, N0, M0
Stage III		pT4, N0, M0 Any pT, N1, M0
Stage IV		Any pT, any N, M1

Table 11.20c 10-year mortality rate (MR) for DCT (papillary or follicular) [166]

Stage	10-year cancer-specific mortality (%)
I	1.7
II	15.8
III	30
IV	6

Patients treated with ^{131}I will require L-thyroxin therapy in a dose sufficient to suppress the serum TSH to <0.1 mIU/L. L-thyroxin can be started 3 days after ^{131}I in a dose sufficient to suppress TSH to <0.1 mIU/L. In low-risk patients, TSH <0.5 mIU/L is acceptable.

Reassessment with a whole-body scan (WBS) after stopping L-thyroxin for 4 weeks and stimulated serum Tg is indicated no earlier than 6 months after ^{131}I ablation. If abnormal uptake of the tracer is detectable, a ^{131}I treatment dose should be given and a posttreatment scan (3–10 days after ^{131}I treatment) performed. The patient should then restart L-thyroxin.

11.18.2.2 Radioactive Iodine (RAI) Ablation and Treatment for DTC

Following a TT or near-TT, some radioiodine uptake is usually demonstrable in the thyroid bed. ^{131}I-induced destruction of this residual thyroid tissue is known as *radioiodine remnant ablation. Radioiodine therapy* refers to *administration of ^{131}I with the intention to treat recurrent or metastatic disease.* The principles and procedures are similar for the administration of ^{131}I for ablation or treatment.

Preparation for ^{131}I Ablation or Therapy

Patients should adopt a low I_2 diet for 2 weeks prior to ^{131}I, and other sources of excess I_2 should be eliminated (e.g., recent CT with contrast) [168]. *If ^{131}I can be administered within 3–4 weeks of thyroidectomy, no thyroid hormone replacement is required in the interim period.* This would usually allow TSH to rise to >30 mIU/L at the time of ablation. For most centers, however, the interval between thyroidectomy and ^{131}I ablation will be longer. In such cases, patients should start T3 20 mg tds after surgery; this should be stopped 2 weeks before planned ablation to allow serum TSH to increase to >30 mIU/L.

If there is doubt about completeness of surgery, a pre-ablation scan can be performed to assess remnant size [169]. Demonstration of large thyroid remnants should lead to consideration of further surgery before ^{131}I ablation.

Pregnancy must be excluded before ^{131}I ablation. Breastfeeding must be discontinued for 4 weeks, preferably 8 weeks before ^{131}I ablation or treatment, and should not be resumed. Pretreatment sperm banking should be considered in male patients likely to have >2 high-dose ^{131}I therapies [170]. Adequate hydration at the

time of treatment and for several days afterward, regular emptying of the urinary bladder, and avoidance of constipation help to prevent a reduction in sperm count.

Postoperative ^{131}I Ablation

Patients >45 years with tumors >1.5 cm should receive ^{131}I ablation to reduce local and distant recurrence and cancer mortality [171, 172]. The benefit of ^{131}I ablation for low-risk patients may however be questionable. Other factors such as invasion, metastases, completeness of excision, and associated disease should be considered. Benefits of ^{131}I ablation include:

1. Eradication of all thyroid cells including residual postoperative microscopic disease and thus possible reduction of risk of local and distant tumor recurrence
2. Reassurance to patients imparted by the knowledge that serum Tg is undetectable and iodine scan negative, implying that all thyroid tissue has been destroyed
3. Possible prolonged survival [173]
4. Increased sensitivity of monitoring by serum Tg measurements and possibly earlier detection of recurrent or metastatic disease [174]

Indications of Remnant Ablation with ^{131}I

No Indication for (Low Risk of Recurrence or Cancer-Specific Mortality) [175, 176]. Patients should satisfy all the following criteria for ^{131}I ablation to be omitted: complete surgery, favorable histology, tumor unifocal, ≤1 cm, N0, M0, or minimally invasive FTCs, without vascular invasion, <2 cm [177], and no extension beyond the thyroid capsule.

Definite Indications The presence of any of the following is a definite indication for *^{131}I ablation:* distant metastases, incomplete tumor resection, or complete tumor resection but high risk of recurrence or mortality (tumor extension beyond the thyroid capsule, or >10 involved LNs and >3 LNs with extracapsular spread) [178].

Probable Indications Any one of the following categories is a "probable" indication for ^{131}I ablation: less than TT, status of LNs not assessed at surgery, tumor size >1 cm and <4 cm, tumors <1 cm with unfavorable histology (tall cell, columnar cell, or diffuse sclerosing papillary cancers, widely invasive or poorly differentiated follicular cancers), and multifocal tumors <1 cm [178].

Short-Term and Long-Term Side Effects of ^{131}I Ablation Treatment

The main side effect is transient hypothyroidism, unless rh TSH is used [179–183]. The *possible early effects* include abnormality of taste and sialadenitis (can be minimized by good hydration), nausea (can be minimized by antiemetics), neck discomfort and swelling within a few days of RAI (rare, simple analgesics should be tried initially, but a short course of steroids may be necessary), radiation cystitis, radiation gastritis, bleeding into secondary deposits, and edema in cerebral secondary deposits (extremely rare) [178].

The *possible late effects* include dry mouth, abnormal taste, sialadenitis, lacrimal gland dysfunction, lifetime risk of leukemia and secondary cancers (0.5 %) [184], radiation fibrosis [185], increased risk of miscarriage (may persist for 1 year after ^{131}I therapy) [186], and infertility in men [170].

11.18.2.3 External Beam Radiotherapy (EBRT) for the Treatment of DTC

External beam radiotherapy (EBRT) is only occasionally used in the treatment of DTC. *Postoperative adjuvant EBRT* may be indicated to reduce local recurrence in patients at high risk due to residual disease where further surgery is not appropriate [158, 187]. *High-dose EBRT as part of primary treatment* is indicated for unresectable tumors that do not concentrate RAI and unresectable bulky tumors in addition to RAI treatment.

11.18.3 Follow-Up of WDTC

Follow-up should be lifelong because (1) the disease has a long natural history, (2) late

recurrences are not rare and can be treated successfully, (3) regular follow-up is also necessary for monitoring of treatment (TSH suppression, the consequences of supraphysiological L-thyroxin replacement, treatment of hypocalcemia, (4) *lifelong suppress*ion of serum TSH level below normal (<0.1 mIU/L) is one of the main components of treatment in high-risk cases, and (5) patients should be monitored for late side effects of ^{131}I treatment.

Surveillance for recurrence is based on (1) annual clinical examination, (2) annual measurement of serum Tg and TSH, and (3) diagnostic imaging and FNAC when indicated.

11.18.3.1 Voice Dysfunction

Voice dysfunction may result if there is ELN and/or RLN injury. It must be investigated if symptoms persist beyond 2 weeks after surgery. The patient should be referred to a specialist for direct and/or indirect laryngoscopy [188].

11.18.3.2 Management of Hypocalcemia

Serum calcium (Ca) should be checked on the day after surgery and daily until the hypocalcemia improves [189]. A decline in serum Ca in the first 24 h after surgery indicates the need for Ca supplementation [190]. If hypocalcemia develops, Ca supplement should be started at an initial dose of 500-mg elemental calcium three times daily. The dose is adjusted as indicated by the response. Occasionally IV Ca gluconate may be required. Mild asymptomatic hypocalcemia usually does not require treatment, although monitoring is indicated. If hypocalcemia does not improve or worsens, alfacalcidol should be added.

Hypoparathyroidism is often transient, and a predictor of this is increase in serum PTH at the time of occurrence of hypocalcemia [191]. Thus, most patients on calcitriol/alfacalcidol/Ca supplements can have this treatment withdrawn. Supplements should be slowly and gradually reduced and serum Ca monitored every few months until withdrawn and eucalcemia restored. Calcitriol/alfacalcidol/calcium supplement withdrawal should take place during *euthyroidism.*

If hypoparathyroidism is permanent, the lowest dose of supplements should be given to maintain the serum Ca at the lower end of the normal range, while avoiding hypercalciuria. In stable cases annual measurement of serum Ca is recommended. Close monitoring of serum Ca is needed to prevent hypercalcemia. After TT, 30 % of patients will need Ca supplement ± alfacalcidol. By 3 months, <10 % of patients will still need Ca [191].

11.18.3.3 Long-Term Suppression of Serum Thyrotropin

L-thyroxin should be used in preference to T3 for long-term suppression. The dose should suppress the TSH to <0.1 mIU/L [192] and should be adjusted by 25 μg (every 6 weeks) until serum TSH is <0.1 mIU/L). To achieve this, most patients may require 175–200 μg daily.

11.18.3.4 Measurement of Serum in Long-Term Follow-Up

Thyroglobulin (Tg) is secreted by both normal and cancerous thyroid cells. In patients who have not had a TT and ^{131}I ablation, the interpretation of serum Tg measurements is limited by the inability to differentiate between *tumor* and *thyroid remnants* [193]. Detectable serum Tg is highly suggestive of thyroid remnant, residual, or recurrent tumor. A serum Tg rising with time while on suppressive thyroxin treatment highly suggests tumor recurrence or progression.

TSH-Stimulated Serum Tg Measurement The diagnostic sensitivity of serum Tg measurements increases by elevated TSH concentration [194]. Tumor recurrence or progression can be diagnosed earlier by detecting increased Tg after TSH stimulation than by measuring Tg on suppressive thyroxin therapy; Tg should be measured when serum TSH is >30 mIU/L.

11.18.3.5 Role of US and Whole-Body ^{131}I Scan (WBS) in Routine Follow-Up

After TT and postoperative ^{131}I ablation, diagnostic WBSs have relatively low sensitivity in detecting residual or recurrent disease compared with measurement of serum Tg [195]. Ultrasound is sensitive for the detection of residual disease in

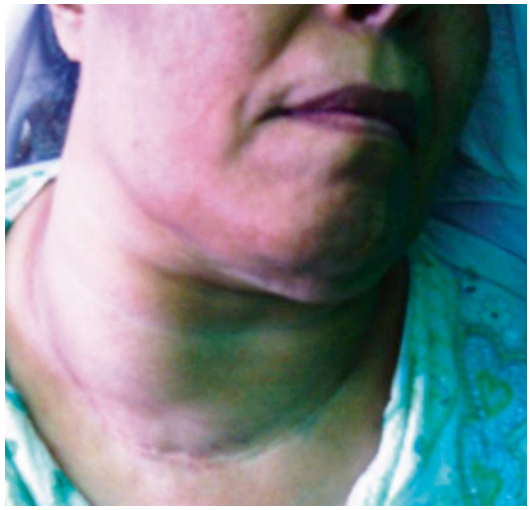

Fig. 11.13 A 47-year-old lady with recurrent thyroid cancer. Note the swelling on the right side and the scar of previous surgery

the thyroid bed and metastatic disease in LNs. It may also have a particular role when serum Tg measurements are unreliable because of the presence of assay interference.

11.18.4 Recurrent/Persistent DTC

Early detection of recurrent disease (Fig. 11.13) can lead to cure or long-term survival, particularly if disease is operable or takes up RAI [173, 178]. Distant metastases develop in 5–23 % of patients with DTC, mainly in the lungs and bones.

11.18.4.1 Recurrence in the Thyroid Bed or Cervical LNs

Surgical re-exploration is the preferred method of treatment, usually followed by ^{131}I therapy [195]. Recurrent neck disease uncontrolled by surgery and ^{131}I treatment is best treated by high-dose palliative *EBRT*. As patients are likely to survive for a significant period, radical EBRT (doses 50–66 Gy) is often necessary with a daily fractionation.

11.18.4.2 Metastases in the Lungs and Other Soft Tissue Areas

These sites are usually not amenable to surgery and should be treated with ^{131}I therapy [185]. If the tumor takes up radioiodine, long-term survival is possible in such cases [196]. There is no maximum limit to the cumulative ^{131}I dose that can be given to patients with persistent disease. A normal CBC must be confirmed prior to each ^{131}I treatment, and impairment of renal function demands a lower dose [197].

11.18.4.3 Cerebral Metastases

EBRT has a palliative role in the treatment of cerebral metastases along with surgery if appropriate.

11.18.4.4 Bone Metastases

Extensive bony metastases are generally not curable by ^{131}I treatment alone. For solitary or limited number of bony metastases that are not cured by ^{131}I therapy, EBRT with or without resection and/or embolization should be considered in selected cases. The EBRT also has a very important role in the treatment of spinal cord compression for vertebral metastases [198].

11.18.4.5 Other Metastatic Sites

Metastasectomy or radiofrequency ablation may be helpful in cases with a limited number of metastases.

11.18.4.6 Palliative Care

Palliative care is not necessary in most patients with DTC because they are cured. High-dose palliative EBRT may be appropriate in good performance status patients with anticipated survival of >6 months. It also has a role in palliation of symptoms from fungating LNs, bleeding tumor, stridor, SVC obstruction, and dysphagia [199]. Stridor can also be alleviated by palliative surgery. *Palliative chemotherapy* may have a role in end-stage disease uncontrolled by surgery, ^{131}I therapy, or EBRT.

11.19 Papillary Thyroid Cancer (PTC)

Papillary thyroid carcinoma (PTC), which is a differentiated type of thyroid cancer derived from follicular epithelial cells, is the most common histological type, constituting 80 % of all

thyroid carcinomas [195]. Women are more affected than men in a ratio of 2:1–4:1. It has become the sixth most common cancer in women. It can present in any age group, the mean age at the time of initial diagnosis being approximately 40 years. Papillary carcinoma accounts for more than 90 % of thyroid malignancies in children [200].

11.19.1 Risk Factors

Both genetic and environmental factors may increase the risk of developing PTC. About 3 % of cases of PTC are *familial* [201]. Some familial syndromes known to be associated with PTC include *familial adenomatous polyposis* (FAP) and its variant, *Gardner syndrome* (both caused by a mutation in the APC gene), *Cowden syndrome* (also known as multiple hamartoma syndrome, caused by a mutation in the PTEN gene), and *Carney complex* (caused by a mutation in the PRKAR1A gene) [202, 203]. A *family history* of PTC in two first-degree relatives increases the risk of PTC three- to ninefold, and these families are likely part of a familial non-medullary thyroid cancer (FNMTC) kindred, whose specific genetic defect has not yet been determined [204].

The strongest evidence linking thyroid cancer to an *environmental* cause exists for exposure to *ionizing radiation*. In 5–10 % of the cases, there is a history of irradiation exposure to the neck, and the nonneoplastic gland may show nuclear aberrations as a result. These data are derived from studies of children who were exposed to the nuclear fallout from Chernobyl, adult survivors of the atomic bombings of Hiroshima and Nagasaki, and patients who received head and neck radiotherapy (RT) in childhood for the treatment of a variety of benign conditions [205].

Other factors that have been investigated to determine their impact on the risk of developing thyroid cancer include *hormonal factors*, *iodine intake*, and the presence of *Hashimoto's thyroiditis*. Even though the majority of patients with PTC are women, no convincing hormonal associations have been elucidated [206]. Studies examining the influence of I_2 intake on the risk of thyroid cancer have shown conflicting results, and at the present time, I_2 intake is generally not considered to affect a patient's risk of developing thyroid cancer [207]. The influence of Hashimoto's thyroiditis on thyroid cancer risk is controversial, but large studies have shown an increased prevalence of Hashimoto's thyroiditis in patients with PTC [208, 209]. Whether the frequency of PTC is increased in Graves' disease remains a controversial subject [210].

11.19.2 Gross Features

The size of the primary tumor ranges from microscopic to huge. A very high proportion of thyroid cancers measuring <1 cm in diameter are PTCs. Grossly, most cases are solid, whitish, firm, and clearly invasive; fewer than 10 % are surrounded by a complete capsule. Marked cystic changes are seen in 10 % of cases. Papillary formations may be evident to the naked eye [211].

11.19.3 Microscopic Features

Classical or not otherwise specified (NOS) PTC is characterized by the formation of papillae and a set of distinctive nuclear features (Fig. 11.14a, b) [212–215]. These *papillae* are nearly always associated with the formation of follicles, the ratio between the two components varying greatly from case to case. The follicles tend to be irregularly shaped, often tubular and branching. Tumors with a combination of papillary and follicular structures have the biological behavior of PTC and should therefore be classified as such instead of as mixed carcinomas [212–215].

Diagnosis of PTC depends on characteristic *nuclear features* rather than a papillary architecture, which may be minor or absent. These nuclear features consist of (1) ground-glass nuclei [216], (2) nuclear pseudo-inclusions (cytoplasmic invaginations that appear as sharply

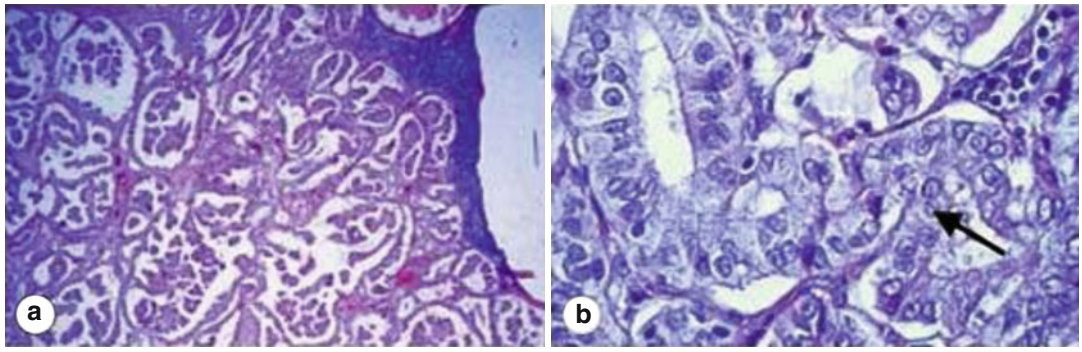

Fig. 11.14 (**a**) PTC metastatic to an LN: typical appearance of PTC with complex and branching papillae. (**b**) Higher magnification showing optical clear, overlapping, and grooved (*arrow*) nuclei

outlined acidophilic formations) [217], and (3) nuclear grooves (infoldings of a redundant nuclear membrane) [202, 213].

Mitosis is very scanty or absent [218]. Over half of the cases show extensive *fibrosis*. *Psammoma bodies* are seen in approximately half of the cases. Their presence strongly suggests the diagnosis of PTC, as their occurrence in other thyroid lesions is exceptional [219]. These laminated basophilic structures stain for mucin, calcium, and iron and appear to arise from necrosis of individual tumor cells, which occasionally may be seen at their very center [220, 221]. *Lymphocytic infiltration* of the stroma is seen in 25 % of cases, and it is not clear whether it represents a reaction to the tumor or the expression of preexisting thyroiditis [222].

Multiple *microscopic foci* of tumor are found in about 20 % of cases [223, 224]. Controversy still exists as to whether this represents multicentricity or intrathyroidal lymphatic permeation. *Blood vessel invasion* is found in only 5 % of cases. The mode of spread of PTC is most commonly via lymphatics within the thyroid leading to "multifocal" disease and to cervical LN metastases [212, 224]. About 50 % of PTCs have nodal metastases at initial diagnosis [225].

11.19.3.1 Histological Variants of PTC

There are several histological variants of PTC, some of which are associated with a more guarded prognosis than others (Table 11.21) [211].

Table 11.21 Variants of PTC and their prognosis [53]

Good	Variable	Guarded
Micro-carcinoma	Oxyphilic cell	Diffuse sclerosing
Encapsulated	Follicular	Tall/columnar cell
Macrofollicular	Solid sclerosing	Diffuse follicular
	Solid/trabecular	
	With nodular fasciitis-like stroma	

Papillary Micro-carcinoma

The term refers to PTC measuring <1 cm in diameter and replaces the older designation of occult PTC [212]. It may be incidentally found in autopsy (4–35 % of cases) [226–228] or in surgical specimens. Prognosis is excellent despite occasional regional LN metastases.

Encapsulated Variant

The tumor is totally surrounded by a fibrous capsule, which may be intact or focally infiltrated by the tumor. These tumors have an exceptionally good prognosis, and, although some lesions have shown LN involvement, distant metastases or death due to the tumor is practically nonexistent [229].

Follicular Variant

Follicular variant of PTC has the characteristic nuclear features of PTC and an almost totally

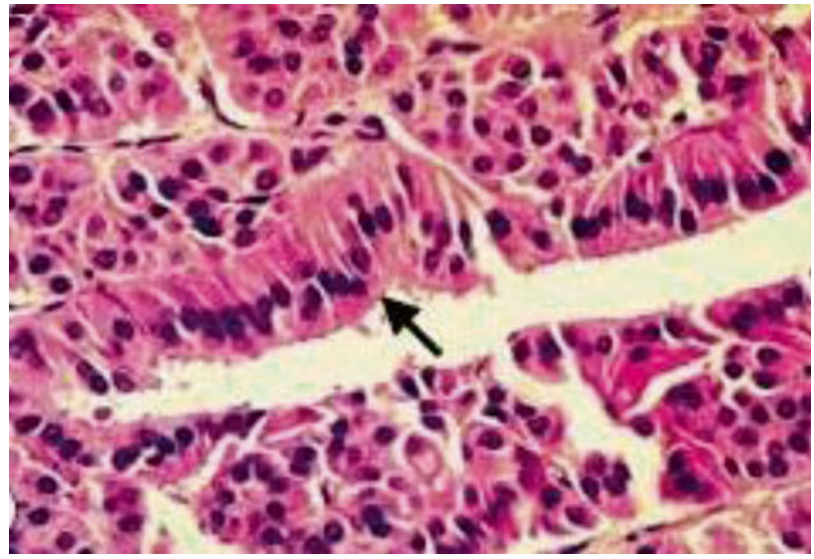

Fig. 11.15 Tall cell variant papillary carcinoma, lined by tall cells (*arrow*)

follicular architecture [230]. Follicular variant of PTC can be either encapsulated or poorly circumscribed and infiltrative. The encapsulated follicular variant has a generally favorable prognosis, while the other two types need to be treated more aggressively. The biological behavior of this variant is analogous to that of conventional PTC. However, when considered in conjunction with their higher propensity for angioinvasion and lower incidence of LN metastases [156], it has become evident that at least a subset of the encapsulated follicular variant display biological features that are more comparable to minimally invasive follicular carcinoma than conventional papillary carcinoma [231, 232].

Tall Cell and Columnar Cell Variants

The main histological feature of the tall cell variant of PTC is the presence of "tall" cells (the height being twice the width), with an intense eosinophilic cytoplasm, lining well-developed papillae (Fig. 11.15). In the columnar cell variant, there is a marked nuclear stratification and the cytoplasm is clear, sometimes with subnuclear vacuolization [212, 224]. Both the tall cell and columnar cell variants are said to be more aggressive than classical PTC [233, 234]. However, recent studies suggest that the clinical behavior of these rare variants depends on tumor size, extrathyroidal invasion, and distant metastases [235, 236].

Tall cell variant papillary carcinomas harbor BRAF mutations in most cases (50–100 %) and often have RET/PTC translocations as well. The occurrence of these two aberrations together may synergistically enhance MAPK signaling, contributing to the aggressive behavior of this variant [237].

Diffuse Sclerosing Variant

The diffuse sclerosing variant is an unusual form of PTC first described by Vickery et al. [56], who noticed that it more frequently affects children and is associated with a poor prognosis. This tumor is characterized by diffuse involvement of one or two lobes and clinically may be misdiagnosed as Hashimoto's thyroiditis [212]. Its hallmark, microscopically, is the presence of widespread intrathyroid lymphatic permeation by numerous neoplastic micro-papillae. Lymph node metastases are present in almost all cases [238, 239]. The diffuse sclerosing variant carcinomas lack BRAF mutations, but RET/PTC translocations are found in approximately half the cases.

Other Variants of PTC

Variants such as solid variant, spindle cell variant, clear cell (Fig. 11.16) and oxyphilic (Hürthle) cell variant, papillary carcinoma with lipomatous

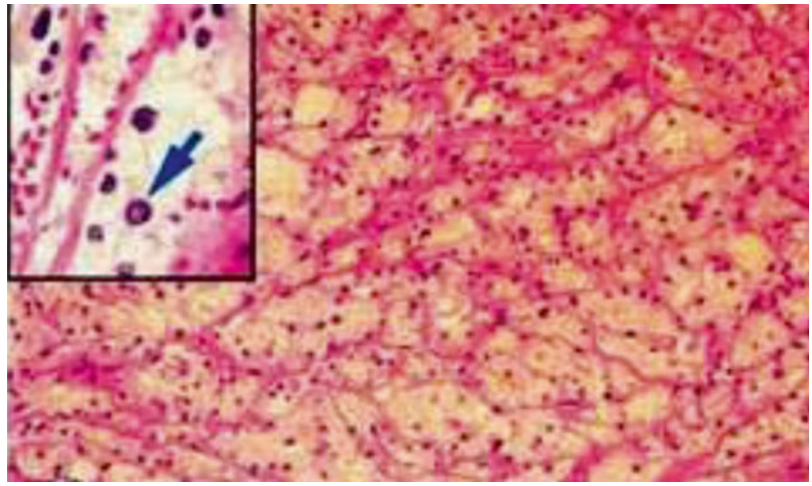

Fig. 11.16 Papillary carcinoma with clear cell changes: typical intranuclear inclusion (*inset*)

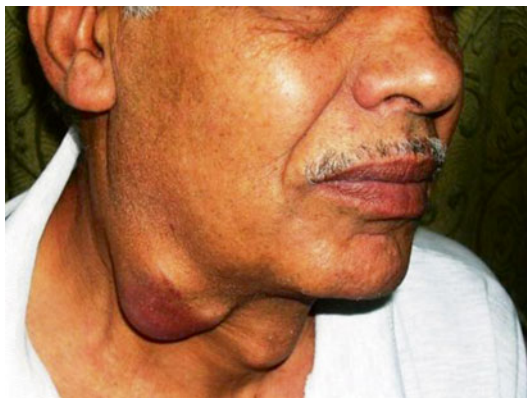

Fig. 11.17 A 58-year-old gentleman with right cervical lymphadenopathy and a non-palpable thyroid gland. Occult papillary thyroid carcinoma

stroma, Warthin-like tumor or with nodular fasciitis-like stroma, and cribriform PTC have been reported, but they are too few in number for an adequate assessment of their prognostic implication [240, 241]. The term solid and/or trabecular variant is used when a NOS papillary carcinoma has a solid and/or trabecular pattern throughout the tumor [212].

11.19.4 Clinical Aspects

The most likely thyroid tumor type to manifest cervical nodal metastasis is PTCs [242]. Patients with PTC are usually asymptomatic and present with an STN or with a gland that contains multiple nodules. Some patients present with a palpable cervical LN (occult PTC) (Fig. 11.17). Occasionally, a patient presents with symptoms worrisome for an aggressive or invasive thyroid cancer such as hoarseness, dysphagia, or hemoptysis [243]. Distant metastases are uncommon, occurring in fewer than 4 % of patients at the time of initial diagnosis [244].

In clinical terms, the behavior of *follicular variant* of PTC (FVPTC) is generally regarded as being similar to the pure PTC. Some reports have suggested differences in the frequency of LN involvement, distant metastases, and prognosis [245]. Another variant is the papillary thyroid *micro-carcinoma* (PTMC). It is accepted that these tumors are common and rarely behave as cancers (with metastasis and invasion) [115, 245–249]. A subset of patients with PTMC, however, presents with palpable neck node metastasis, which then leads to the diagnosis of PTCs that were initially not apparent [250].

11.19.5 Lymphatic Spread

The thyroid gland has an extensive network of draining lymphatics, both intra- and extra-glandular [251, 252]. The extra-glandular lymphatic network is complex. It comprises four main groups of collection channels: (1) the i*nfero-medial* route draining to the pre- and paratracheal

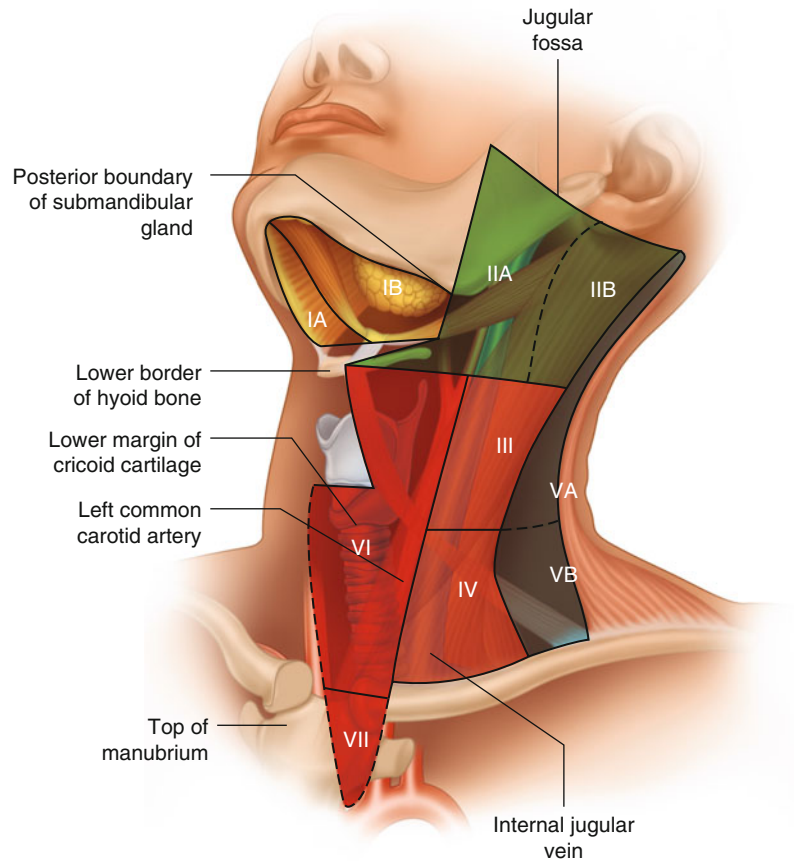

Fig. 11.18 Regional nomenclature of cervical lymph nodes (levels I–VII)

LNs (main route for metastases); (2) the *supero-medial* route, which terminates in the Delphian LNs situated at the level of cricothyroid membrane; (3) the *superolateral* route extending up to the superior LNs of the internal jugular chain; and (4) the *inferolateral* route draining the LNs of the supraclavicular and jugulo-subclavian chains. The thyroid lymphatic network is hence rich in anastomoses between the numerous lymphatic channels. This explains the multiple patterns of LN metastases from PTC.

Almost all patients suffering from PTC have clinically evident disease in the neck when they are first seen. In large studies, the disease was localized to the thyroid gland in 67 % of cases, thyroid and LNs in 13 %, and LNs alone in 20 % [253–260]. In another series, 35 % of patients with PTC presented with locoregional LN metastases [261]. Some series have reported the incidence of cervical metastasis in children with PTC to be as high as 90 % [262]. Cervical metastases from PTC were reported to occur in predictable patterns with disease commonly presenting at levels II through V, with level III being the most commonly affected area and level I being the least [263–266]. Level VI represents the central compartment and is mentioned in many other series as the first station of nodal spread from PTC. Classification of the levels of neck nodes [267, 268] is demonstrated in Fig. 11.18.

Despite the recognized sequence of lymphatic dissemination, discontinuous lymphatic spread, or skip metastasis, is not uncommon in node-positive PTC. The significance of this finding is unknown. The frequency of skip metastasis varies between 11.1 and 37.5 % in node-positive PTC [269–271]. Consequently, clearing the central LN compartment

should be considered when lateral or mediastinal LN compartments are involved [272].

The prognostic significance of cervical LN metastases is still controversial. Some authors find it to be a significant predictor of recurrence and survival [273–277] and that a neck dissection improves prognosis [278–280], while other believe otherwise and reported that LN involvement in PTC has not been shown to have a negative impact on cure rates or survival [281–284]. A matched pair analysis from Memorial Sloan Kettering Cancer Center, New York, suggested that the presence of neck node metastases had a significant impact on recurrence in patients older than 45 years only [163]. In spite of this debate in the literature concerning the clinical significance of this lymphatic spread, it becomes more worrisome when the disease has extended to contralateral or bilateral neck nodes or to mediastinal LNs [273]. The spread of metastatic tumor beyond the LN capsule is an especially worrisome finding, as is extension of the primary tumor to tissues outside of the thyroid gland [285].

11.19.6 Distant Metastases

Blood-borne metastases are less frequent in PTC than with other thyroid carcinomas. The most common site is the lung [211, 286]. Pulmonary metastases can have a miliary micronodular pattern that may be detectable only by ^{131}I scintiscan, or they can be rounded and macronodular [287]. Usually, lung metastases are detected by chest X-ray (Fig. 11.19) or CT scan (Fig. 11.20).

One large-scale review of 13 series comprising 1,231 patients estimated that 5 % of PTCs have extended beyond the neck at diagnosis [288].

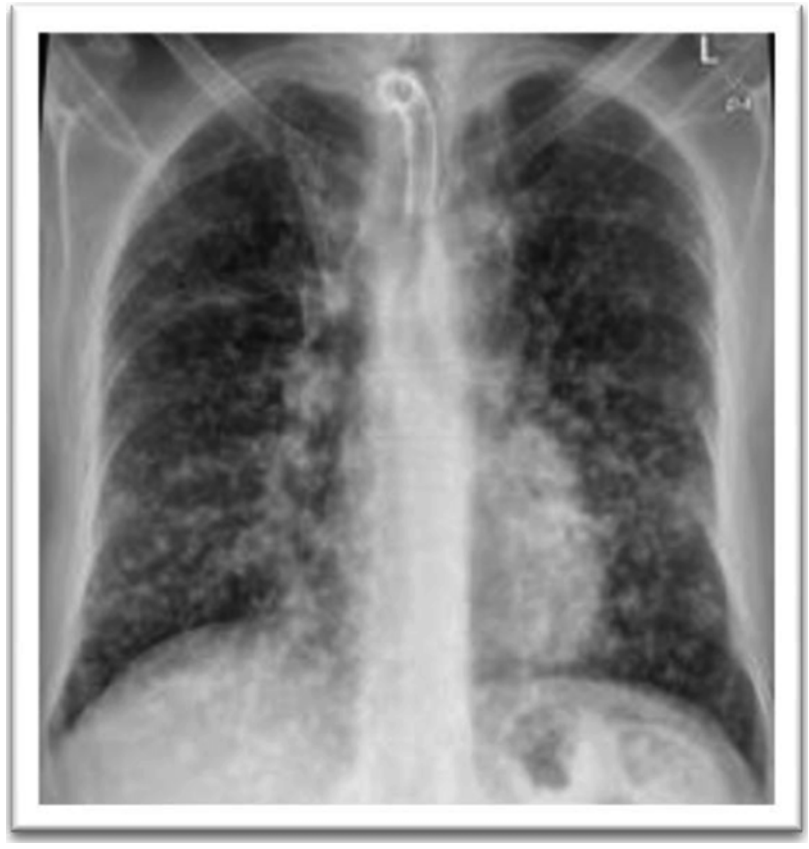

Fig. 11.19 X-ray chest showing PTC with miliary lung metastases

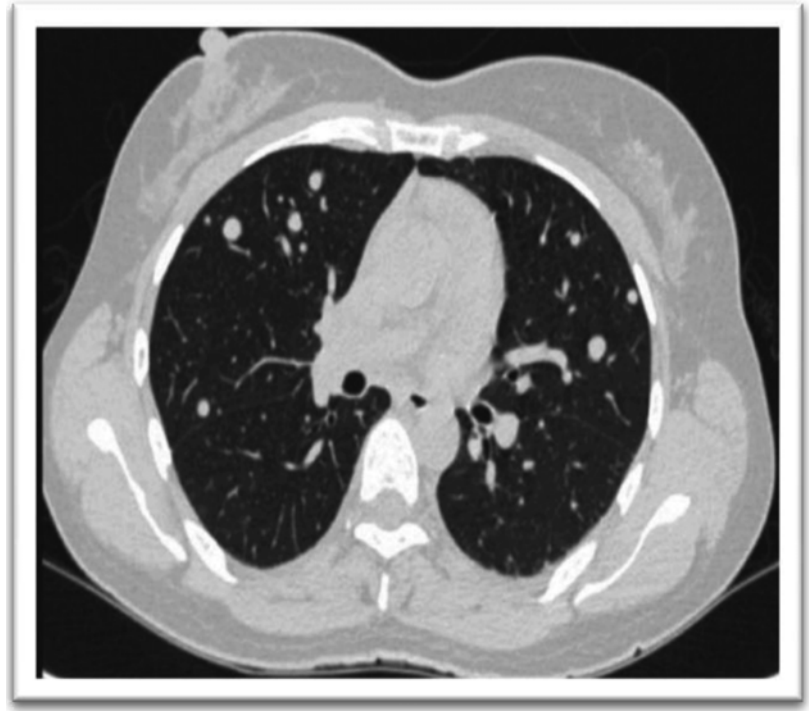

Fig. 11.20 CT chest showing lung metastases caused by papillary thyroid carcinoma (PTC)

This distant spread of tumor was most common within the lung (49 %), followed by the bone (25 %), lung and bone (15 %), and CNS or other tissues (10 %). However, it is estimated that the incidence of overall distant metastases in PTC is up to 10 % [289]. Overall, close to 50 % of these patients die of their disease within 5 years [288].

In contrast to squamous carcinoma of the head and neck, and indeed most other solid tumors, distant dissemination is not a death sentence. About half of those receiving RAI for pulmonary deposits alone will survive for 10 or 15 years. The prognosis is, however, much worse for those with osseous disease and in patients whose tumors fail to concentrate iodine [290].

11.19.7 Evaluation of the Neck in PTC (Primary Tumor and LNs)

11.19.7.1 Physical Examination

Evaluating neck metastases based on physical examination findings has been the classic method. During the clinical evaluation, careful palpation of the neck is a must, with specific attention to location, size, consistency, and mobility of each node. Direct attention to nodes that appear fixed to underlying neurovascular structures or visceral organs or that demonstrate skin infiltration should be paid [291, 292]. Unfortunately, clinical palpation of the neck demonstrates a large variation of findings among various examiners. Although inexpensive to perform and repeat, palpation findings are generally accepted as inaccurate [292, 293].

11.19.7.2 Ultrasound (US)

Ultrasonography (US) provides valuable information regarding *echogenicity* (Fig. 11.21), nodular *composition* (solid nodules *versus* simple or complex cysts) (Fig. 11.22), presence of *calcifications* (micro, i.e., 1 mm or less, or macro) (Fig. 11.23), as well as *shape and margins*. Moreover, US may differentiate extrathyroidal structures from the thyroid gland and may give information on regional lymphadenopathy (Fig. 11.24) [48]. Color flow Doppler US gives further information on vascular flow and velocity. Normal cervical

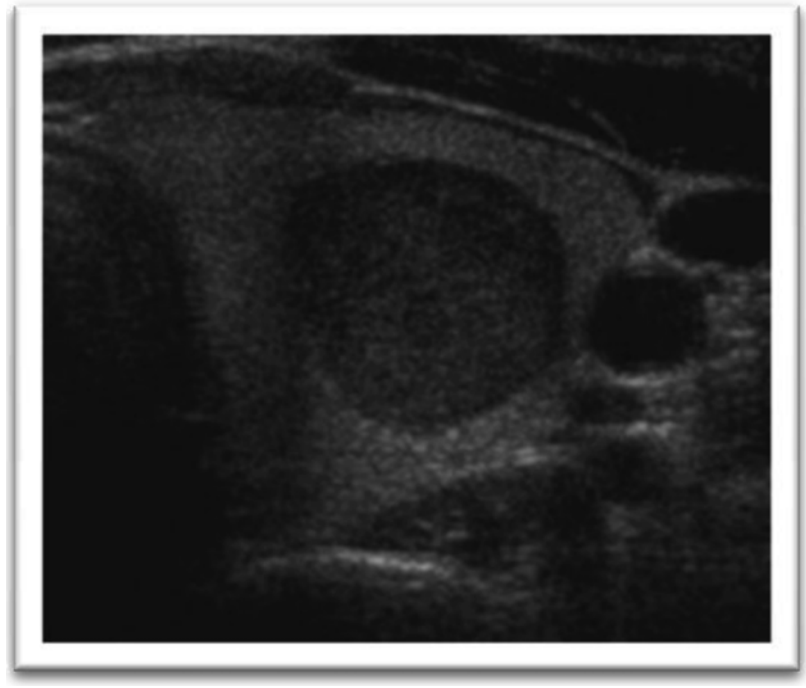

Fig. 11.21 US neck showing hypoechoic nodule in left thyroid lobe (proved to be PTC)

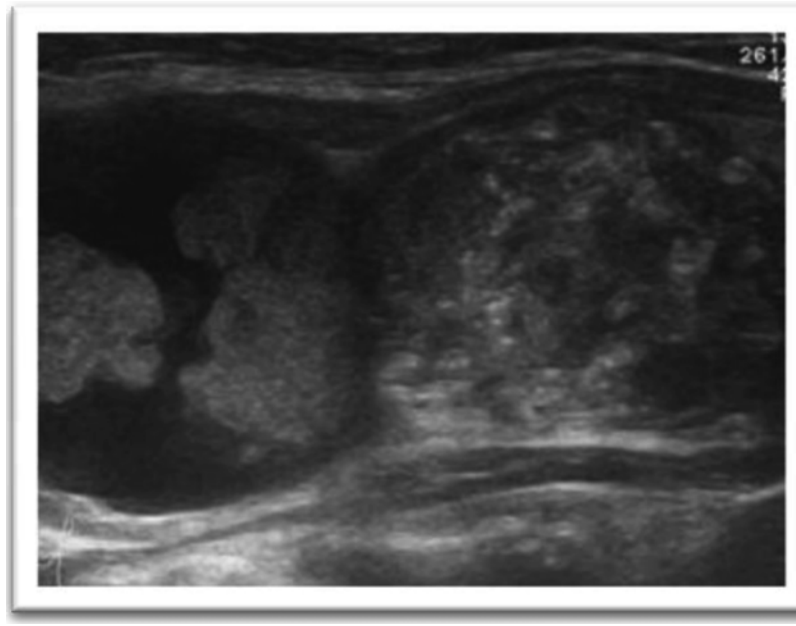

Fig. 11.22 US neck showing heterogeneous solid and partly cystic thyroid mass (extensive PTC)

LNs appear sonographically as somewhat flattened hypoechoic structures with varying amounts of hilar fat [294]. They may show hilar vascularity but are usually hypovascular [295]. Malignant infiltration alters the US features of the LNs, resulting in enlarged nodes that are usually rounded and show peripheral or mixed vascularity [296]. Using these features, US has been shown to have an accuracy of 89–94 % in differentiating malignant from benign cervical LNs [297, 298].

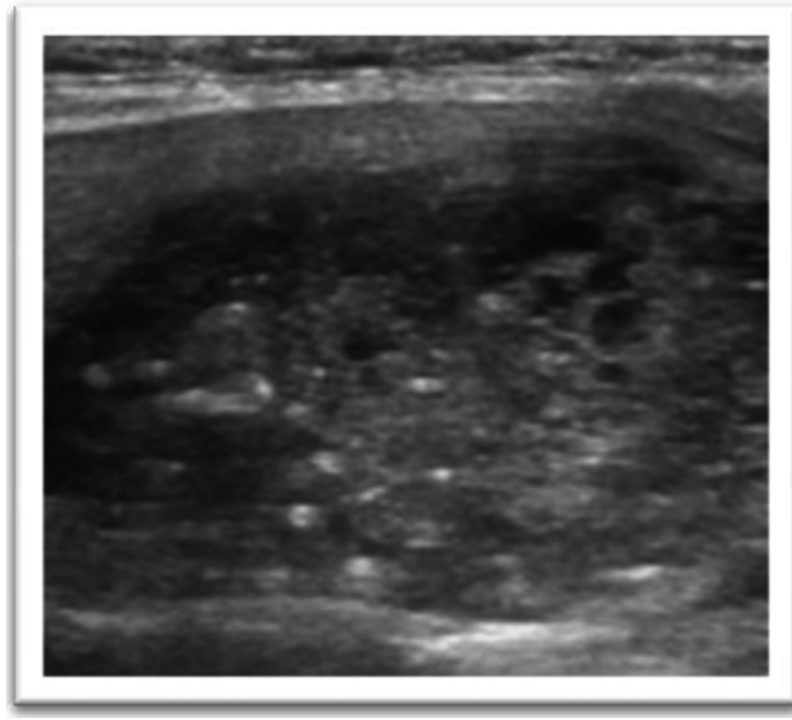

Fig. 11.23 US neck showing PTC with a hypoechoic mass and punctate calcifications

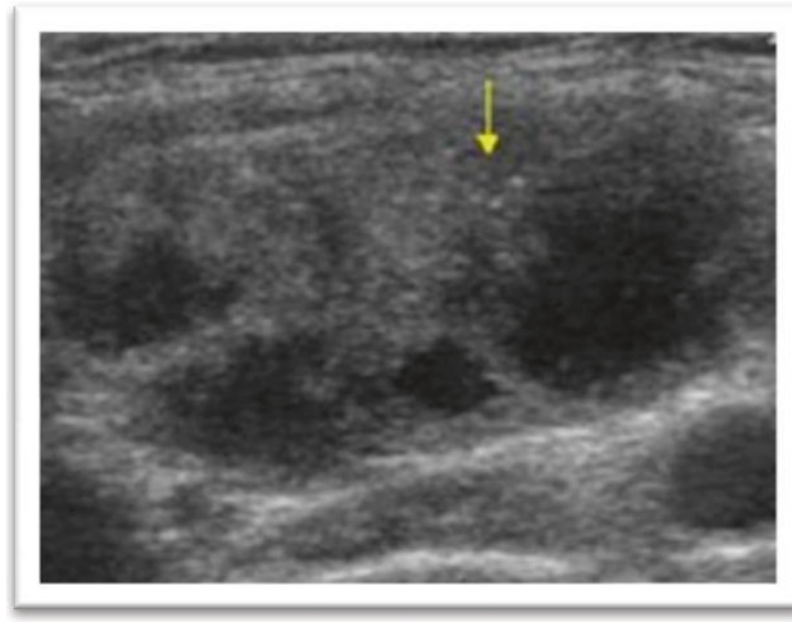

Fig. 11.24 US neck showing PTC with LN metastasis with punctate calcifications (*arrow*)

11.19.7.3 Cross-Sectional Imaging (CT and MRI)

Cross-sectional imaging such as CT scan and MRI are noninvasive, have high patient acceptance, and require a short examination time. Both CT scan and MRI are indicated for large tumors extending to adjacent structures such as the mediastinum, retropharyngeal region, or paravertebral muscles (Fig. 11.25). They can also provide valuable information on cervical lymph

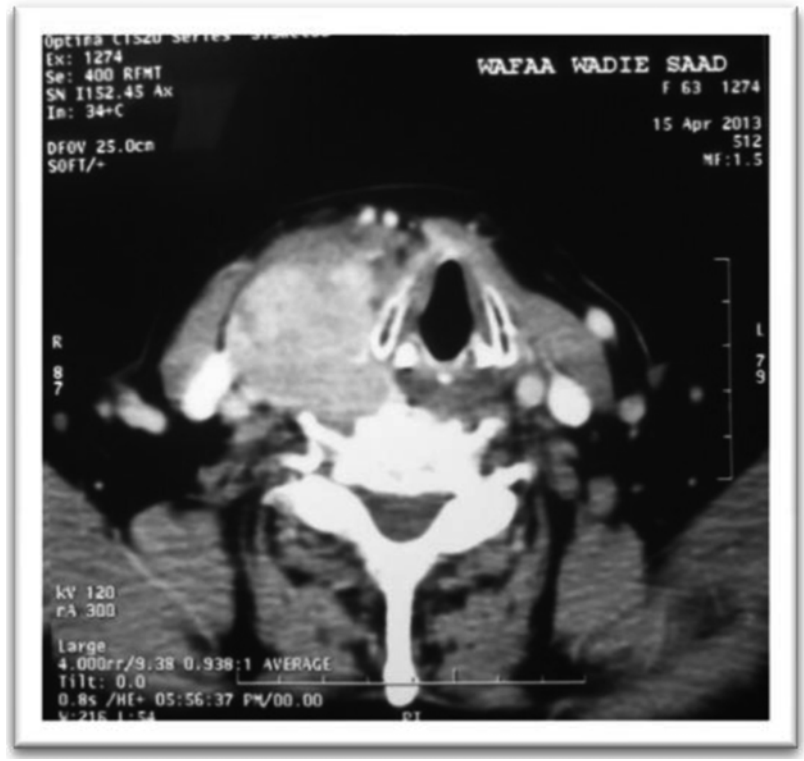

Fig. 11.25 CT neck showing right-sided thyroid neoplastic lesion with query invasion of paravertebral muscles

nodes and their characteristics and level (Figs. 11.26, 11.27, 11.28, and 11.29).

On cross-sectional imaging, a normal LN usually measures <1 cm in size, has a smooth and well-defined border and a central fatty hilum, has an oval shape, and shows uniform, homogenous density or signal intensity. The primary yardstick for nodal staging by CT and MRI is LN size, with the additional ability to assess for nodal morphology and signal intensity changes [299–304].

11.19.7.4 Cytology

The fine-needle aspiration (FNA) has been used extensively for the diagnosis of primary and secondary malignant disorders involving LNs, though the same does not hold true for nonneoplastic disorders. In malignant conditions of LNs, FNA enjoys a high sensitivity and specificity, the average being 95 % [305–309]. With the recent advances in US and CT scan technologies, focal lesions can be aspirated using these procedures [309–311].

Fine-needle aspiration virtually has eliminated the need for open biopsy of metastatic cervical lymphadenopathy and the sequela of violating tissue planes prior to undertaking the definite treatment of the tumor [309, 310]. Fine-needle aspiration is also quite helpful in differentiating metastatic squamous cell adenopathy from metastatic thyroid malignancy and even from enlarged LNs secondary to lymphoproliferative and reactive adenopathy [311].

The high sensitivity of FNA for PTC is strongly correlated with tumor size. Tumors smaller than 0.5 cm and tumors larger than 3 cm may be more difficult to successfully aspirate on FNA, and the follicular variant may be more difficult to recognize as papillary [312].

11.19.8 Surgery for DTC

11.19.8.1 Elective Surgical Treatment

Management of the Primary Tumor (Thyroid Surgery)

The terms *subtotal lobectomy* and *subtotal thyroidectomy* are imprecise and should be avoided.

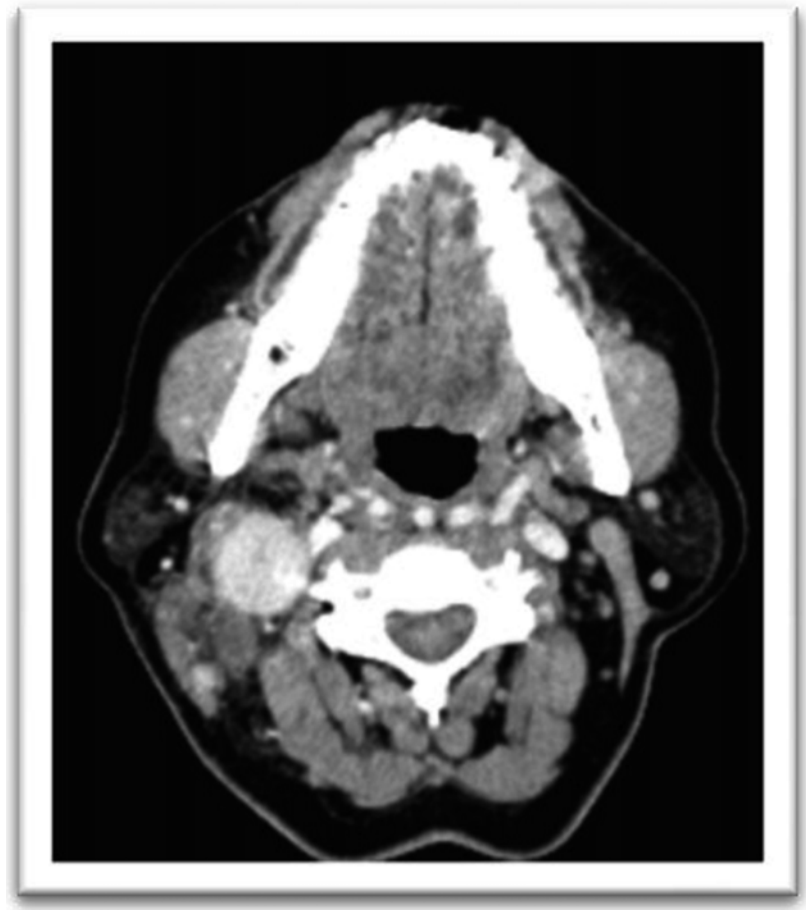

Fig. 11.26 CT neck showing enlarged right upper deep cervical LN (level II)

They are inappropriate for the treatment of thyroid cancer. The following terms should be used (Table 11.22).

The *RLNs* should be identified and preserved in virtually all instances. Permanent damage to an RLN should occur in <5 % of thyroid cancer. Nerve injury rates are higher after reoperative surgery [242]. Infiltration by cancer contributes to RLN palsy rates [313]. Attempts should also be made to preserve the *ELN* by ligation of the STA at the capsule of the gland. Injury rates may be higher than for RLN damage [314].

The *parathyroid glands* should whenever possible be identified and preserved. If their vascular supply is compromised, the gland/glands should be excised and reimplanted into the muscle [315, 316]. LN dissection (level VI) results in increased risk of postoperative hypoparathyroidism [317].

Management of the Nodal Spread

The levels of LNs in the thyroid surgery are listed below (Table 11.23). Types of neck dissections are summarized in Table 11.24.

Differences exist regarding the procedure of choice for addressing the neck in PTC, from (1) a prophylactic ND in a clinically negative neck [280, 318, 319] to (2) expectant management with resection limited to palpable LN metastases, i.e., selective removal or berry picking [280, 281, 320, 321], based on the view that nodal disease is clinically insignificant and unlikely to influence survival [322], or (3) a formal comprehensive dissection of all lateral LNs (MRND) [323–325] in a clinically positive neck, based on the consensus of the high frequency of occult nodal disease with reduced recurrence-free survival.

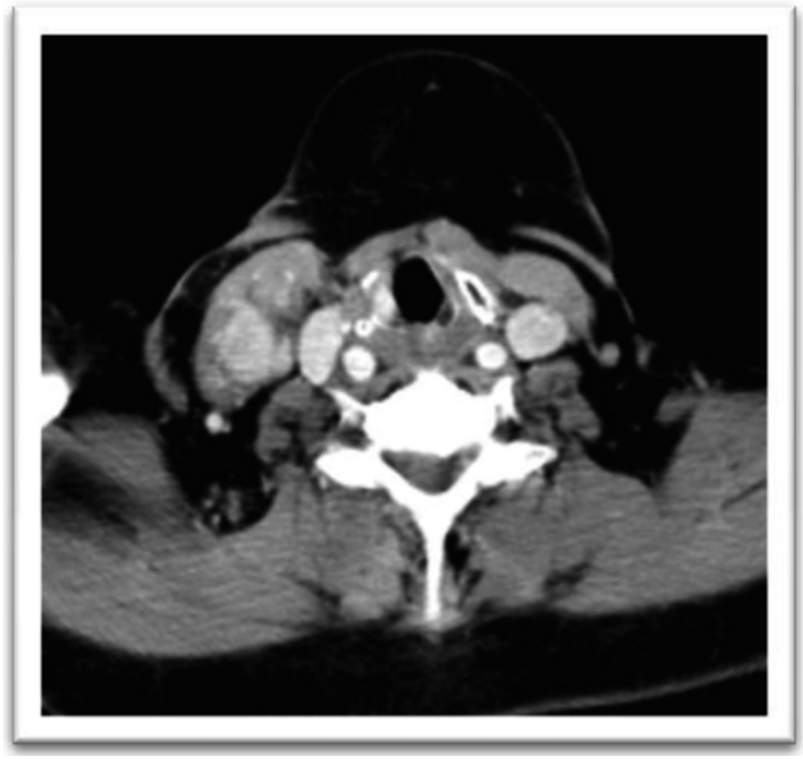

Fig. 11.27 CT neck showing enlarged left middle deep cervical LN (level III)

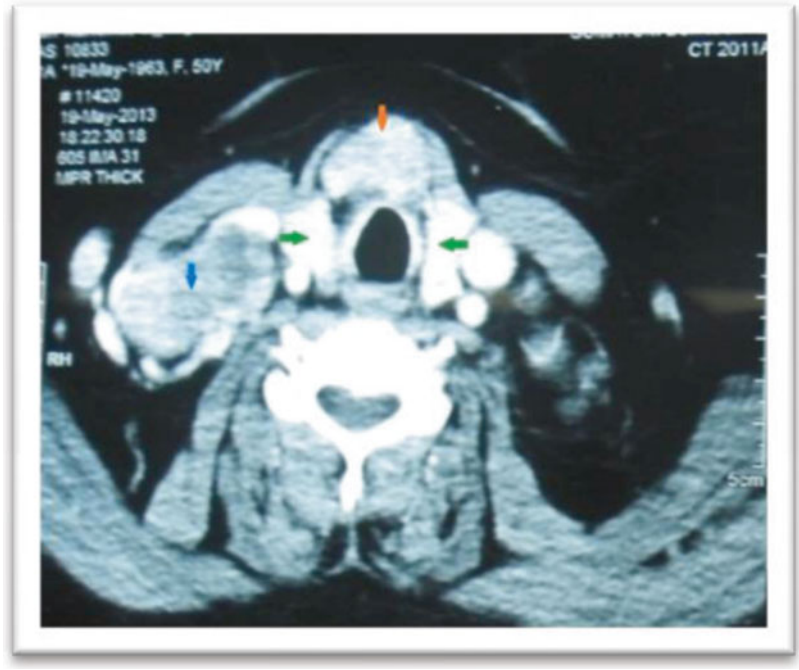

Fig. 11.28 CT neck showing enlarged right middle deep cervical LN (level III) (*blue arrow*), prelaryngeal (Delphian) LN (level VI) (*orange arrow*), and goiter (*green arrow*)

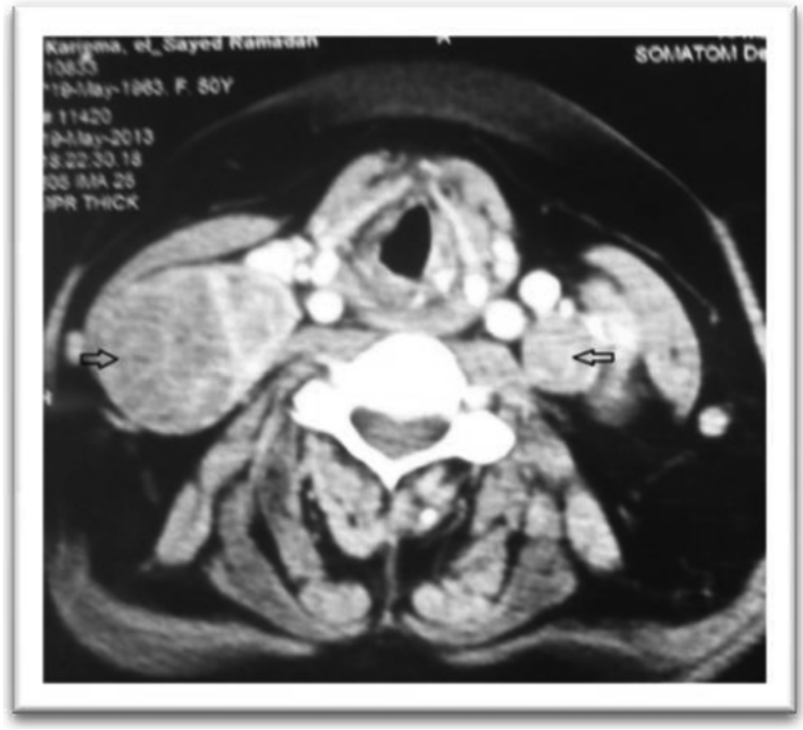

Fig. 11.29 CT neck showing bilateral enlarged middle deep cervical LN (level III) (*arrows*)

Table 11.22 Terms used in thyroid surgery

Lobectomy	Complete removal of one thyroid lobe including the isthmus
Near-total lobectomy	Total lobectomy leaving behind only the smallest amount of thyroid tissue (significantly <1 g) to protect the RLNs
Near-total thyroidectomy	Complete removal of one thyroid lobe (lobectomy) with a near-total lobectomy on the contralateral side *or* a bilateral near-total procedure
Total thyroidectomy (TT)	Removal of both thyroid lobes, isthmus, and pyramidal lobe

Table 11.23 Levels of lymph nodes in thyroid surgery

Lateral compartment of neck	
Level I	Submental (Ia) and submandibular nodes (Ib)
Level II	Deep cervical chain skull base to hyoid. Divided spinal accessory nerve to IIa (medial) and IIb (lateral)
Level III	Deep cervical chain level of hyoid to level of cricoid
Level IV	Deep chain from cricoid to suprasternal notch
Level V	Posterior triangle nodes, divided by *omohyoid muscle* into Va (above) and Vb (below)
Central compartment of the neck	
Level VI	Pretracheal and paratracheal nodes from hyoid to sternal notch and to the carotid arteries laterally
Mediastinal nodes	
Level VII	Superior mediastinal nodes superior aspect to brachiocephalic vein
Compartment 4	
LNs between the brachiocephalic vein and tracheal bifurcation within the anteroposterior mediastinum	

Surgical Decision for Treatment of PTC

Patients with a node-negative cancer of <1 cm (pT1) can be adequately treated by *lobectomy* [173, 174]. For tumors >1 cm, multifocal disease, extrathyroidal spread, familial disease, clinically involved nodes, and children with history of previous neck irradiation, *TT* is indicated [275].

If the diagnosis of thyroid cancer is made after thyroid lobectomy and completion (contralateral), lobectomy is required; it should be offered *within 8 weeks* of histological diagnosis of cancer.

In patients with no clinical LNs but who are high risk (male, >45 years, tumors >4 cm, extracapsular or extrathyroidal disease), TT and central node dissection should be done [242].

Table 11.24 Types of neck dissection (ND)

Type of neck dissection	Description
Selective neck dissection	Cervical lymphadenectomy of less than levels I–V. The spinal accessory nerve (SAN), internal jugular vein (IJV), and sternocleidomastoid muscle (SCM) are preserved
Radical neck dissection (RND)	A classical RND removes all the lymphatic tissue in levels I–V plus SAN, SCM, and IJV
Modified RND (MRND)	Removal of LNs I–V + preservation of one or more non-lymphatic structures as follows:
	1. MRND type I: preservation of the SAN
	2. MRND type II: preservation of the SAN and IJV
	3. MRND type III (functional): preservation of the SAN, IJV, and SCM
Extended neck dissection	Removal of one or more additional LN groups, e.g., parapharyngeal, and superior mediastinal nodes and/or non-lymphatic structures

Palpable disease in level VI nodes discovered at surgery is treated by a level VI node dissection. When suspicious/clinically involved nodes are apparent preoperatively or are encountered at surgery in the lateral neck, and confirmed by needle biopsy or frozen section, then a selective neck dissection (levels IIa–Vb) is recommended, preserving the SAN, SCM, and IJV [326].

Surgery for Papillary (or Follicular) Micro-carcinoma

Patients with DTCs <1 cm have an extremely low risk of death from thyroid cancer (0.1 %) [202] and hence can be treated adequately by *thyroid lobectomy* provided that the tumor does not extend beyond the thyroid capsule and there is no evidence of metastases, vascular invasion, multifocality, or contralateral disease. Otherwise, completion thyroidectomy and radioiodine are necessary [290]. Future treatment involves TSH suppression with thyroxin and measurement of the serum Tg [290].

11.19.8.2 Emergency Surgery

It is rare for emergency surgery to be needed in PTC. However, acute presentation of a patient with thyroid cancer and severe airway compromise requires urgent/immediate surgery.

11.19.8.3 Surgery for Locally Advanced Disease

When preoperative vocal cord (VC) examination shows no sign of RLN palsy, every attempt should be made to dissect the tumor from the nerve/nerves. In patients with unilateral nerve involvement and extensive extrathyroidal disease, the nerve may have to be sacrificed to achieve a curative procedure. It may not be possible to remove the entire tumor without damaging both RLNs. A small residue of tumor may be left behind to protect the nerve/nerves and be subsequently dealt with by ^{131}I ablation and L-thyroxin with or without EBRT [313].

In individual patients with locally advanced disease involving the upper aerodigestive tract and/or one or both RLNs, curative excisional surgery of the tracheal wall and/or esophagus should be considered. When radical curative surgery is not possible or agreed to by the patient, treatment with radical radiotherapy ^{131}I should be considered.

11.19.9 Prognostic Indicators

In general, survival for patients with PTC is believed to be relatively good, especially when compared with that of patients with other thyroid and nonthyroid malignancies. However, not all patients with PTC fare well, and one of the major challenges is to identify patients with poor prognosis to offer more aggressive and efficacious treatment [246]. Factors playing role in prognosis and survival include the following:

1. *Age:* Nearly all the deaths from PTCs occur when the tumor manifests itself after the age of 40 years.
2. *Gender*: Women are said to have a better prognosis than men, although in some series the difference was not significant.
3. *Extrathyroidal extension*: This feature adversely affects the prognosis in a very significant manner and has have been incorporated into the staging system of thyroid carcinoma, which, as in most other sites, has proved to be a powerful prognostic predictor.

4. *Microscopic variant*: Among the different variants of PTC, the diffuse sclerosing, tall/columnar cell, and diffuse follicular variants have the worst prognosis (Table 11.20a).
5. *History of previous irradiation*: Contrary to previous statements, the prognosis of tumors in which this antecedent is present does not seem to differ significantly from the others.
6. *Tumor size:* A rough inverse correlation is present between tumor size and prognosis.
7. *Capsule and margins:* Tumors that are encapsulated and/or have pushing margins have a better outcome than the others.
8. *Multicentricity:* Patients in whom this is a prominent feature have a greater incidence of metastasis and a lesser chance of disease-free survival.
9. *Distant metastases:* Prognosis is adversely affected by metastases to the lungs and is more influenced by metastases to other sites, such as the skeletal system.
10. *Poorly differentiated, squamous, or anaplastic foci:* These features have a markedly detrimental effect on prognosis. Fortunately, they are present in fewer than 5 % of the cases.
11. *Grading:* This parameter bears a definite relationship with prognosis that has been underestimated. However, it needs to be clearly defined in terms of criteria (necrosis, mitotic activity, etc.) and properly standardized for it to reach its full potential.
12. *Circulating tumor cells:* Presence of circulating tumor cells (as determined with an RT-PCR assay for thyroglobulin (Tg) mRNA) seems to be associated with a higher likelihood of metastatic disease, but may not play a practical role in clinical management.

11.19.9.1 Prognostic Scales/Scores

AGES Scale This is a postoperative prognostic scale originated in Mayo Clinic. It is an acronym standing for *A*ge, pathological tumor *G*rade, *E*xtent of disease, and *S*ize of tumor. Two groups are identified with this system: *low-risk patients* (young, with WDTC, no metastases, and small primary lesion) and *high-risk patients* (older, with poorly differentiated tumors, local invasion, distant metastases, and large primary lesions) [327].

MACIS Scale This more sophisticated postoperative scale is a modification of the AGES system. Factors assessed are distant *M*etastases, *A*ge at presentation (<40 or >40 years), *C*ompleteness of original surgical resection, extrathyroidal *I*nvasion, and *S*ize of original lesion (in cm) [327].

AMES Score Cady and Rossi described a prognostic scoring system, originating in Lahey Clinic, based on *A*ge, *M*etastases, *E*xtent, and *S*ize of tumor. Stage for stage, risk of death is mostly related to age and gender [328–330]. Age limits were defined as older than 40 years in men and older than 50 years in women. Patients <45 years of age without distant metastases usually are considered to be at low risk [327]. Distant metastasis at the time of diagnosis was the greatest predictor of survival [331]. Extent of tumor indicated extracapsular tumor invasion, and size limits were greater than 5 cm.

The most significant single prognostic indicator overall is *distant metastases*, especially to the bone. Local invasion of the primary tumor through the thyroid capsule into the adjacent structures increases the mortality tenfold over matched patients with intrathyroidal tumors [332].

From these different systems, patients as well as differentiated thyroid tumors are finally stratified into low-risk and high-risk patients and tumors as shown in Table 11.25 [290].

Table 11.25 Stratification of patients and differentiated thyroid tumors

Risk	Description
Low-risk patients	Females under the age of 45 years
High-risk patients	All males and females over 45 years (patients under 16 years should be regarded as high risk and are usually best treated aggressively)
Low-risk tumors	PTC <1 cm in size and minimally invasive FTC <1 cm in size
High-risk tumors	PTC and FTC >1 cm in size, any tumor associated with significant multifocality, local or distant spread

11.20 Follicular Thyroid Cancer (FTC)

Follicular thyroid carcinomas (FTCs) account for 5–15 % of primary thyroid cancers, but are more frequent in areas with dietary iodine deficiency, where they constitute 25–40 % of thyroid cancers.

11.20.1 Gross Features

Follicular carcinomas appear as single nodules that may be well circumscribed or widely infiltrative. Sharply demarcated lesions may be exceedingly difficult to distinguish from follicular adenomas by gross examination. Larger lesions may penetrate the capsule and infiltrate well beyond the thyroid capsule into the adjacent beck structures. They are gray to tan pink on cut section and may be somewhat translucent due to the presence of large, colloid-filled follicles. Degenerative changes such as center fibrosis and foci of calcification are sometimes present.

11.20.2 Microscopic Appearance

Microscopically, most FTCs composed of fairly uniform cells forming small follicles containing colloid (Fig. 11.30). In other cases, follicular differentiation may be less apparent, and there may be nests or sheets of cells without colloid. Occasional tumors are dominated by cells with abundant granular, eosinophilic cytoplasm (Hürthle cell or oncocytic variant of FTC). Whatever the pattern, the nuclei lack the features typical of PTC, and psammoma bodies are not present.

While nuclear features (optically clear nuclei, nuclear grooves) are helpful in distinguishing papillary from follicular neoplasms, there are no reliable cytological difference between follicular adenomas and minimally invasive follicular carcinomas. Making this distinction requires extensive histological sampling of tumor-capsule-thyroid interface to exclude capsular and/or vascular invasion. However, it is worth mention that there still exists a controversy among pathologists regarding the minimum criteria for diagnosing follicular carcinoma, whether it is invasion of capsule, invasion through capsule, and invasion into veins in or beyond the capsule [333]. The criterion for vascular invasion applies solely and strictly to veins in or beyond the capsule; the presence of tumor plugs within intratumoral blood vessels has little prognostic significance, whereas the definition of capsular invasion is controversial [333, 334]. Some authors require penetration of the capsule to diagnose a follicular tumor as carcinoma, while

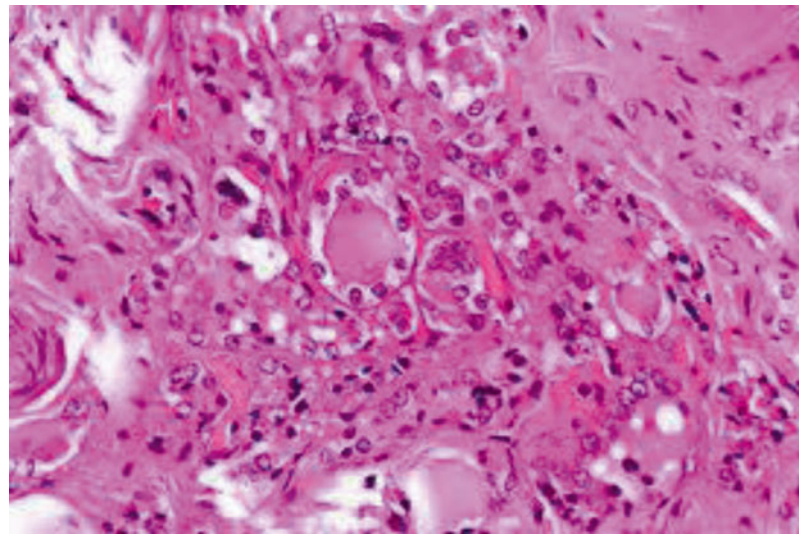

Fig. 11.30 FTC consisting of fairly uniform cells forming small follicles containing colloid

others need tumor invasion through the capsule into the surrounding normal thyroid [334, 335].

Distant metastases have been reported in follicular carcinoma diagnosed only on the basis of capsular and not vascular invasion; however, in some cases, metastases were already present at initial diagnosis [336]. Unlike in papillary cancers, *lymphatic spread* is uncommon in follicular cancers.

In contrast to minimally invasive follicular carcinoma, the diagnosis of carcinoma is obvious in widely invasive follicular carcinomas, which infiltrate the thyroid parenchyma and extrathyroidal soft tissue. Histologically, these cancers tend to have a greater proportion of solid or trabecular growth pattern, less evidence of follicular differentiation, and increased mitotic activity. Up to 80 % of patients with widely invasive follicular cancer can develop metastases with a fatality rate of 50 %.

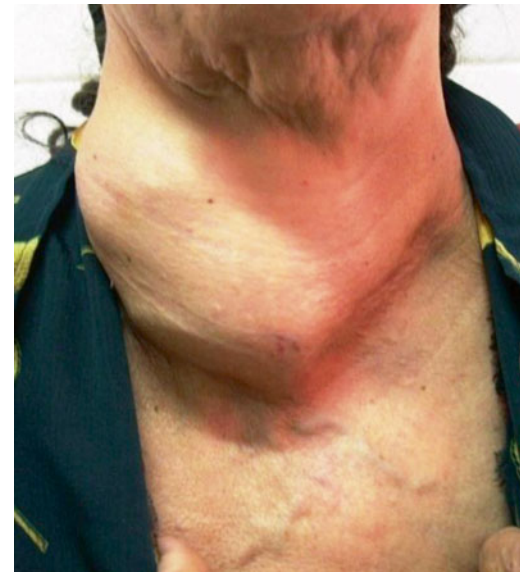

Fig. 11.31 A 41-year-old lady with a large, hard, irregular thyroid mass that proved by histology to be a follicular carcinoma. Note the dilated veins over the sternum

11.20.3 Clinical Aspects

Follicular thyroid carcinomas (FTCs) are more common in women (3:1) and occur more in older patients than do papillary carcinomas, with the peak incidence between 40 and 60 years of age [337]. Symptoms suggesting carcinoma include hoarseness of voice from a vocal cord paresis, rapid growth of a thyroid nodule, dysphagia, hemoptysis, or pain in the neck. Uncommon presentations include cervical lymphadenopathy; symptomatic bone pain from metastatic disease to the spine, pelvis, or ribs; asymptomatic lung metastases found radiographically; and focal neurologic abnormalities from distant spread to the brain.

Physical examination may reveal a hard, irregular, solitary, fixed thyroid mass causing local compressive symptoms with or without associated cervical lymphadenopathy (Fig. 11.31). Direct laryngoscopy should be performed to identify the existence of a vocal cord paresis or, rarely, tracheal invasion when present. A thyroid mass with an associated ipsilateral vocal cord paresis contains carcinoma until proven otherwise.

Multicentricity and LN involvement are less frequent (10–20 %) in FTC than in PTC [338], and metastases to the lungs and bones result from a tendency of these tumors to spread by hematogenous pathways instead of lymphatic channels.

11.20.4 Surgical Decision for the Treatment of Follicular Carcinoma

Fine-needle aspiration cytology (FNAC) cannot at present distinguish follicular adenoma or benign hyperplastic nodules from carcinoma [339]. Thy 3 cytology usually mandates *lobectomy* as the least surgical procedure.

Frozen section is unhelpful when the FNAC diagnosis is that of a follicular lesion (Thy 3).

If definitive histology reveals a *follicular adenoma* (Fig. 11.32) or a *hyperplastic nodule*, no further R/ is required.

A follicular carcinoma <1 cm with minimal capsular invasion should be treated by *lobectomy* [340].

Patients with follicular cancer showing evidence of vascular invasion should be treated with total thyroidectomy (*TT*).

Patients with follicular carcinoma >4 cm should be treated with *near-total TT or TT*.

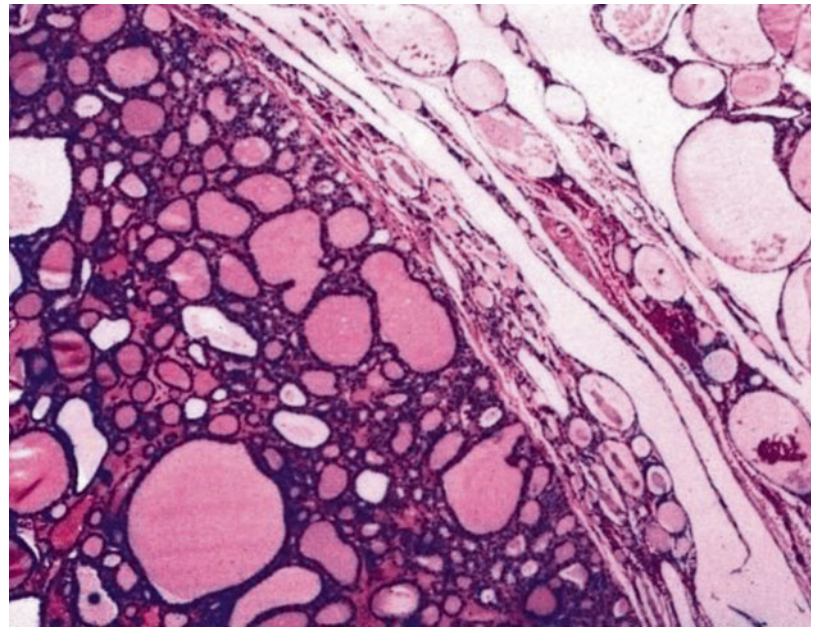

Fig. 11.32 Follicular adenoma with regular cells and no capsular or vascular invasion

Low-risk patients (women, patients <45 years with tumors <2 cm) may be treated by lobectomy alone and L-thyroxin [341].

Clear recommendations for otherwise low-risk patients with tumors 2–4 cm showing minimal capsular invasion only cannot be made [325].

Palpable/suspicious cervical LNs are dealt with in a similar manner to PCT.

If the diagnosis of thyroid cancer has been made after thyroid lobectomy and completion (contralateral), thyroid lobectomy is required; the latter should be offered *within 8 w*eeks of histological diagnosis of cancer.

11.20.5 Prognostic Factors

The outcome of patients with FTC of the thyroid is generally worse than that of PTC and is directly related to the stage of disease at the time of diagnosis. Patients are divided into four clinical stages based on the extent of disease at presentation:

Stage I	Intrathyroidal disease
Stage II	With cervical LN metastases
Stage III	With extrathyroidal extension
Stage IV	With distant metastases

The overall 5-year survival rate of FTC is approximately 91%. Independent prognostic factors that influence survival in follicular carcinoma include (1) age >45 years, (2) extrathyroidal extension (capsular invasion and angioinvasion), (3) distant metastases, (4) lymph node involvement, (5) tumor size >4 cm, and (6) an aneuploid DNA pattern [342].

11.21 Hürthle Cell (Oncocytic) Tumors

11.21.1 Introduction

Hürthle cell neoplasms are an uncommon group of thyroid epithelial tumors that generate much controversy and have additional names in the literature such as *Ashkenazy cell* or *Langhans tumors*. There is ongoing disagreement regarding the cell of origin of these neoplasms: follicular versus parafollicular. Furthermore, some surgeons consider all Hürthle cell neoplasms to be potentially malignant and therefore warrant aggressive surgical therapy [343], while others believe that certain histopathological features can predict the biological behavior of Hürthle cell

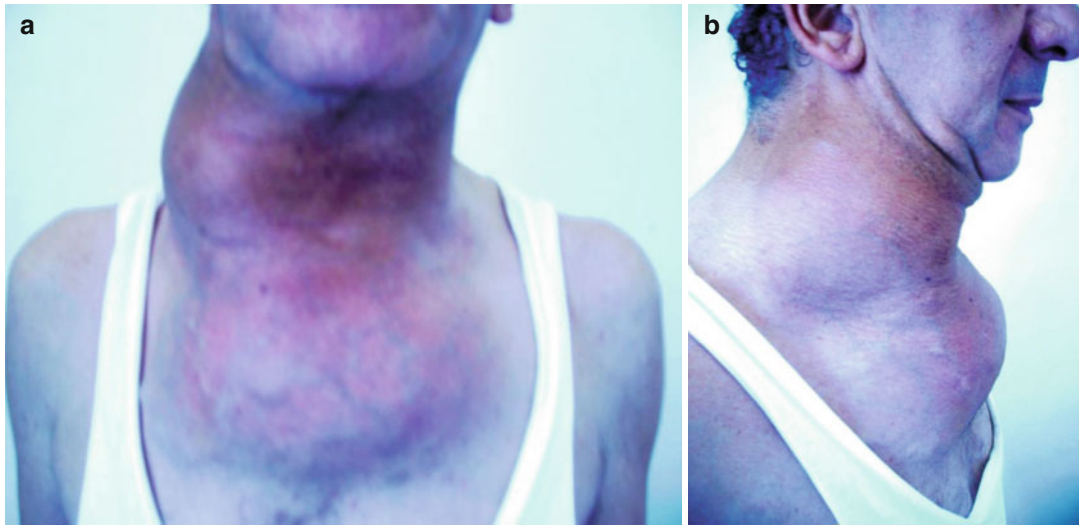

Fig. 11.33 A 53-year-old gentleman with a huge thyroid gland, more on the right side, and retrosternal extension. Biopsy proved to be a Hürthle cell carcinoma (**a**). Lateral view of the same patient. Note the huge size and dilated veins (**b**)

neoplasms and consequently can identify patients for whom a more conservative treatment is appropriate [344].

There is an increased incidence of malignancy with increasing age, prior exposure to radiation, and concomitant papillary or follicular cancer at a site different from the index nodule [343, 345]. Once a Hürthle cell neoplasm is proven to be malignant, surgery is the only effective therapy.

11.21.2 Clinical Presentation

Hürthle cell neoplasms comprise 4.5–10 % of all thyroid neoplasms [122, 343–345], of which 10–35 % are Hürthle cell carcinomas [122, 344]. At the time of diagnosis of Hürthle cell carcinoma, approximately 75 % are confined to the thyroid gland, 15 % have distant metastases, and 10 % have lymph node (LN) metastases [343, 345].

The clinical presentation of Hürthle cell neoplasms is similar to that of follicular neoplasms, appearing mostly as a solitary, nonfunctioning nodule. The presence of symptoms should raise the suspicion of carcinoma, which may be aggressive in nature, grow rapidly, and cause compressive manifestations (Fig. 11.33). However, about 30 % of patients with Hürthle cell neoplasms will have an additional benign thyroid disease such as Graves' disease, MNG, or Hashimoto's thyroiditis and, accordingly, may present with symptoms of hyperthyroidism.

Hürthle cell neoplasms generally present later in life than papillary and follicular tumors, most commonly appearing in the sixth decade of life, and are more common in females, though malignant lesions are more common in men [343].

11.21.2.1 Histopathological Features

Hürthle cell neoplasms of the thyroid gland are characterized by large polygonal cells, distinct cell borders, voluminous granular cytoplasm because of huge number of mitochondria filling the cell, large nucleus, and prominent nucleolus (Fig. 11.34) [346]. However, these features can also be found in nodular goiter, foci of nonspecific chronic thyroiditis, long-standing hyperthyroidism, and Hashimoto's thyroiditis [11].

Thus, the mere presence of Hürthle cells does not necessarily signify a neoplastic process. The presence of a capsule surrounding Hürthle cells, on the other hand, is the defining characteristic of Hürthle cell neoplasms, which contain at least a 75 % Hürthle cell component.

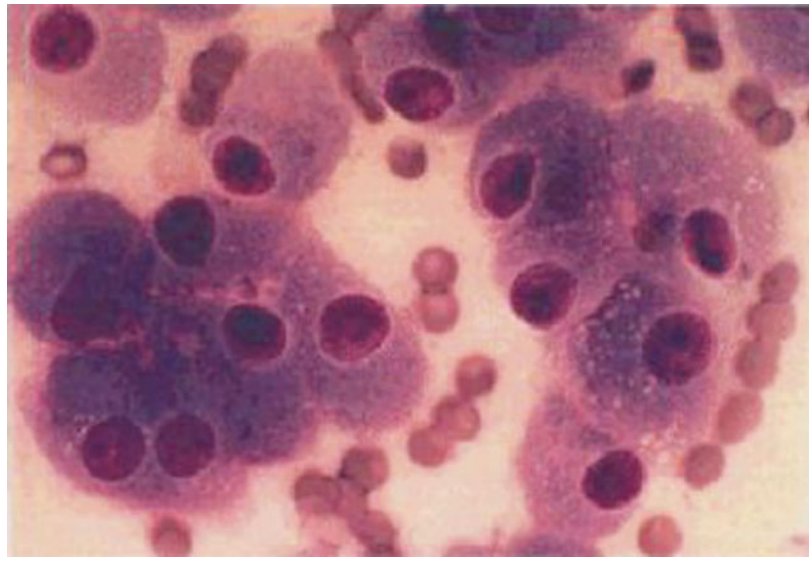

Fig. 11.34 Hürthle cells arranged in loosely cohesive clusters and single cells. The cells are polyhedral and have abundant granular cytoplasm with well-defined cell borders. Nuclei are enlarged and have a central prominent macronucleolus

Hürthle cell tumors are generally believed to be a variant of follicular neoplasms [345]. However, other authors believe that they represent a distinct entity, citing the unique oncogenic expression and the relative inability of Hürthle cells to absorb radioiodine [344].

11.21.3 Diagnosis

Fine-needle aspiration can accurately differentiate Hürthle cell neoplasms from nonneoplastic disorders, but the differentiation of a benign from a malignant process is much more difficult. The diagnosis of Hürthle cell carcinoma is based on the presence of capsular or vascular invasion, extrathyroidal extension, or distant disease, features which are not reliably determined by cytology and are more reliably determined by *permanent sections* rather than by *frozen section*. The measurement of nuclear DNA content and ploidy patterns have also been disappointing in the differentiation of Hürthle cell adenomas and carcinomas [343]. As a result of these difficulties, *surgical therapy* is most often required to secure a correct diagnosis.

11.21.4 Management

Because of the difficulty in differentiating benign from malignant Hürthle cell neoplasms and the potential malignant behavior of benign lesions, many surgeons advocate treatment with total thyroidectomy (TT) for all Hürthle cell neoplasms [343, 345]. However, others support a more conservative approach, recommending TT only for histologically documented malignant disease [1], particularly that most patients with Hürthle cell carcinoma do not respond to ^{131}I ablation therapy.

McLeod and Thompson [343] recommended that, following FNA, all patients with a Hürthle cell neoplasm should undergo ipsilateral lobectomy with frozen section analysis. If the results show Hürthle cell nodules in association with a benign thyroid disorder, such as Graves' disease or Hashimoto's thyroiditis or if there are no signs of invasion, the operation is terminated. On the other hand, if frozen section analysis reveals a malignant process, TT should be performed.

If upon interpreting the permanent sections of a thyroid lobectomy, the diagnosis changes from a Hürthle cell adenoma to carcinoma, completion thyroidectomy (contralateral thyroid lobe) is performed within a few days of the initial procedure.

11.21.5 Prognosis

Hürthle cell carcinomas are generally more aggressive than follicular and papillary carcinomas with a 10- year survival of 65 %. The extent

of disease and hence surgery greatly influence outcome. An aneuploid DNA pattern has also been shown to independently correlate with decreased patient survival [122, 343, 347]. Unlike follicular carcinomas, lesion size, patient age, and histological grade do not seem to significantly influence prognosis

11.22 Anaplastic Thyroid Carcinoma (ATC)

Anaplastic thyroid carcinomas (ATCs) are undifferentiated tumors of the thyroid follicular epithelium, accounting for approximately 5 % of thyroid tumors. They are aggressive, with a mortality rate approaching 100 %. Approximately, 25 % of patients with ATCs have a past history of a WDTC, and another 25 % harbors a concurrent WDTC in the resected specimen [348]. This leads to the belief that early management of DTC is essential to decrease the overall incidence of ATC.

11.22.1 Clinical Aspects

Patients with anaplastic carcinoma are older than those with other types, with a mean age of 65 years. There is a higher incidence in women, probably due to overall higher incidence of thyroid disease in females.

Anaplastic carcinoma usually presents as a rapidly enlarging bulky neck mass (Fig. 11.35). The history is generally of short duration, extending between 3 and 4 months. In most cases, the disease has already spread beyond the thyroid capsule into adjacent neck structures (Fig. 11.36) or has metastasized to the lungs at the time of presentation. Symptoms related to compression and invasion, such as hoarseness, dysphagia, cervical pain, and dyspnea, are common. Metastases to distant sites generally involve the lungs (75 %), adrenal glands (33 %), and brain (15 %).

Physical examination usually reveals a firm/hard mass in the thyroid region that appears to be fixed and cannot be separated from the trachea. Vocal cord paralysis, due to direct extension to the recurrent laryngeal nerve (RLN), is a common finding, and LN enlargement is also quite frequent

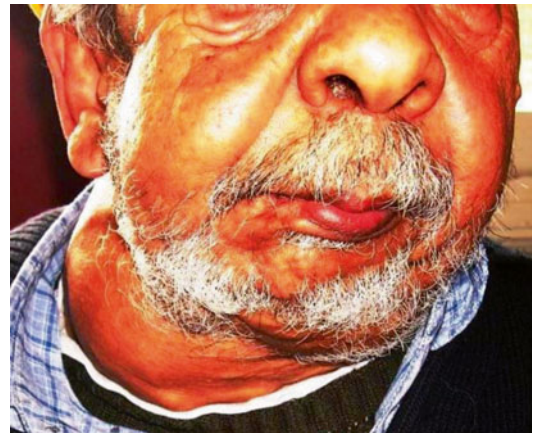

Fig. 11.35 A 62-year-old gentleman with a large, hard, irregular, and fixed thyroid swelling, involving mainly the right lobe and causing compression manifestations. It proved by histology to be anaplastic carcinoma

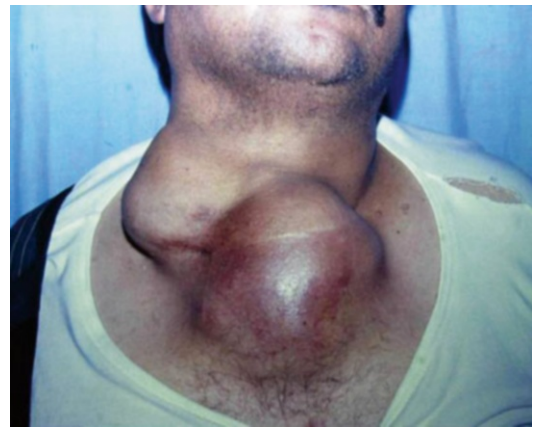

Fig. 11.36 A 47-year-old gentleman with a huge recurrent thyroid carcinoma with acute inflammation on top. First operation was performed for PTC. Biopsy of the recurrence proved to be anaplastic carcinoma

(about 80 %). In most cases death occurs in 6–12 months because of advanced local disease, distant metastases, airway problems, or cachexia.

11.22.2 Diagnosis

The presence of giant and spindle cells on FNA should trigger the diagnosis. Confirmation may be obtained by core or open biopsy, although open biopsy is best avoided to avoid tumor fungation. It is important to rule out poorly differentiated

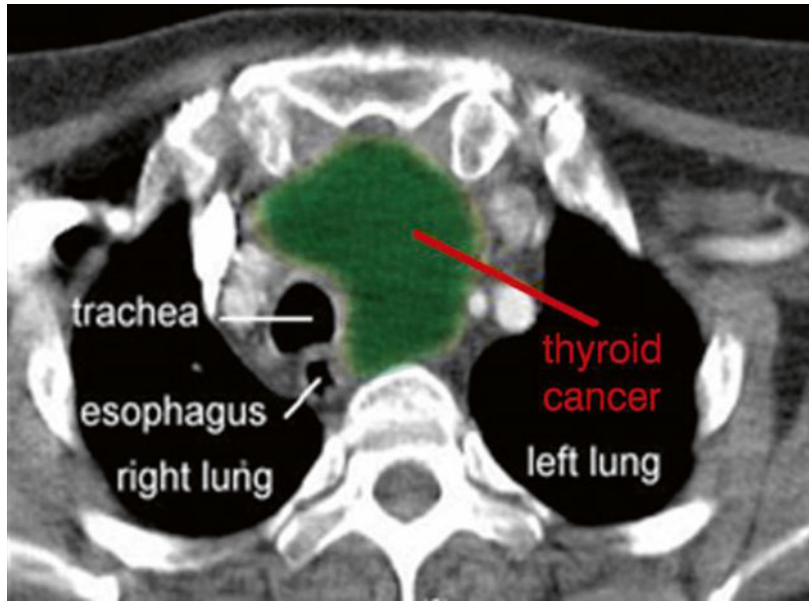

Fig. 11.37 CT scan showing a large thyroid gland involving the trachea and esophagus (anaplastic carcinoma)

thyroid cancer or lymphoma. This may require, in select cases, appropriate immunohistochemistry.

The CT scan is very helpful in evaluating the extent of the disease in the central compartment, lymph node metastasis, and the position of the trachea (Fig. 11.37). Chest X-ray is routinely performed to rule out gross metastasis.

11.22.3 Gross Appearance

Grossly, ATC appears as a large, necrotic, and hemorrhagic mass that is typically widely invasive, often replacing most of the thyroid gland parenchyma with infiltration of the surrounding soft tissue and adjacent structures of the neck. The cut surface of the tumor can be brownish or whitish in color, and in both cases, discrete yellowish areas of necrosis are usually evident.

11.22.4 Microscopic Appearance

Microscopically, these neoplasms are composed of highly anaplastic cells, with variable morphology, including (1) large spindle cells with a sarcomatous appearance (Fig. 11.38); (2) pleomorphic giant cells, including occasional osteoclast-like multinucleated giant cells (Fig. 11.39); (3) squamous cells resembling squamous carcinoma, occurring in solid (Fig. 11.40) or nest (Fig. 11.41) architecture [349]; and (4) mixed spindle and giant cells. Foci of papillary or follicular differentiation may be present in some tumors, suggesting an origin from a WDTC (Fig. 11.42). Metastatic anaplastic carcinoma may be also present in cervical LNs (Fig. 11.43). Immunohistochemistry reveals that the neoplastic cells express epithelial markers like cytokeratin, but are usually negative for markers of thyroid differentiation, like Tg. Carcinoembryonic antigen (CEA) may be localized in certain areas of the tumor [350, 351].

Most of the anaplastic thyroid cancers show a high index of P53 mutation [352], which may play an important role in the progression of DTC to ATC [353]. The expression of *ras* mutation in WDTC reflects an early event of oncogene activation, while the high expression of P53 in ATC suggests a late event.

11.22.5 Treatment

Since the average life expectancy of patients with anaplastic carcinoma is 6–12 months, the role of initial aggressive surgery is always questioned. Kim and Leeper showed promising results in the mid-1980s with the use of adriamycin-based

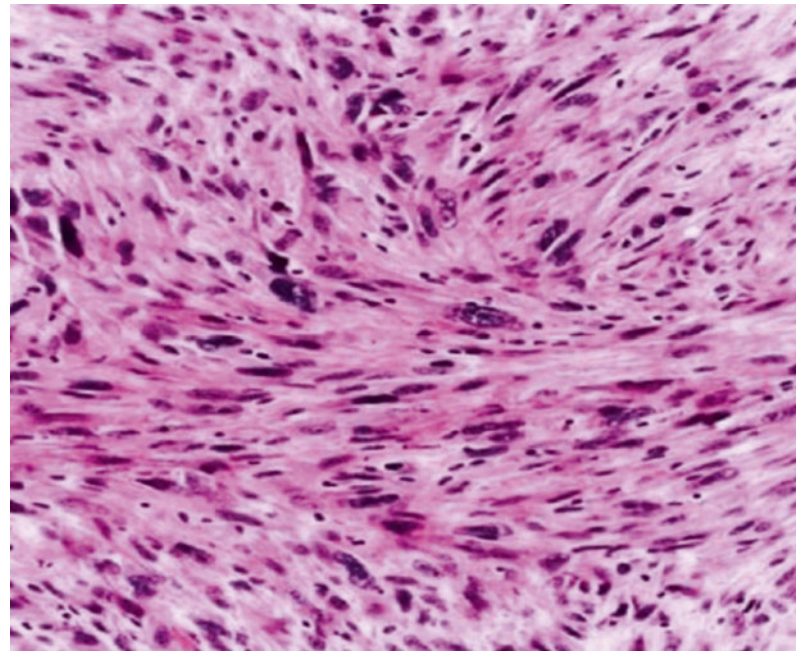

Fig. 11.38 Sarcomatoid ATCs. Spindle cells are pleomorphic and show a storiform pattern of growth

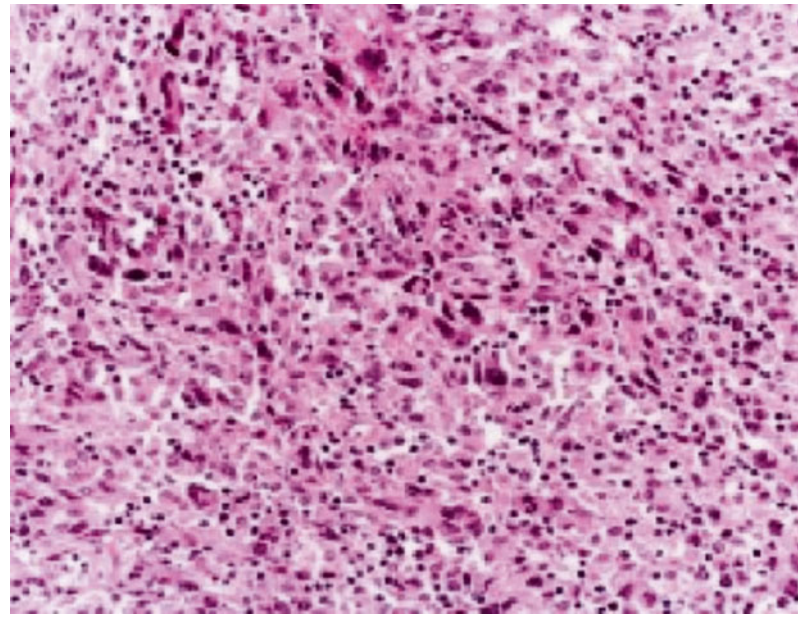

Fig. 11.39 Neoplastic giant cells, characterized by pleomorphism and bizarre multiple hyperchromatic nuclei

chemotherapy and external beam radiation therapy (EBRT) [354]. Unfortunately, in spite of the aggressive treatment approach of chemotherapy, radiation therapy in various forms, and salvage surgery, the overall outcome has essentially remained unchanged.

Venkatesh et al., from MD Anderson, reported a large study of 121 patients with anaplastic thyroid cancer [355]. About 25 % of their patients had areas of WDTC. The mean survival for the entire group was 7.2 months. Their experience showed that younger patients lived longer and patients who presented at an earlier stage responded better than a patient with metastases at the time of presentation. They recommended multimodality treatment and further evaluation.

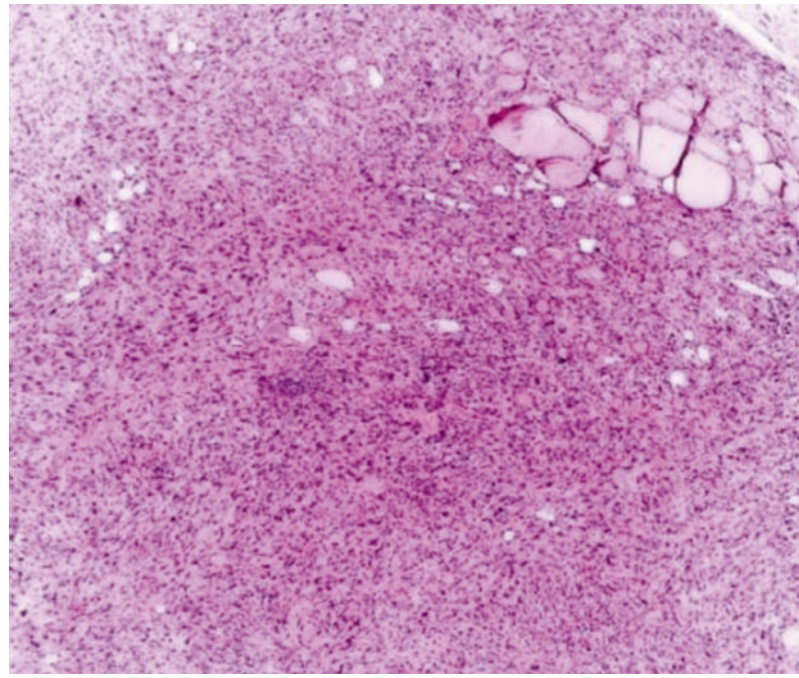

Fig. 11.40 Epithelioid-squamoid category, neoplastic cells showing a solid architecture

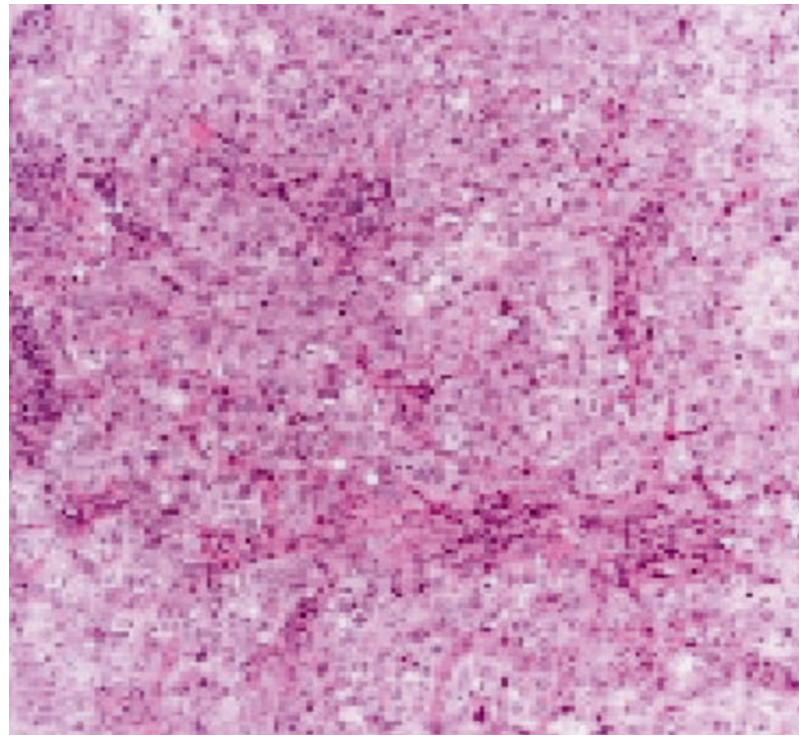

Fig. 11.41 Epithelioid-squamoid category, neoplastic cells showing a nested architecture

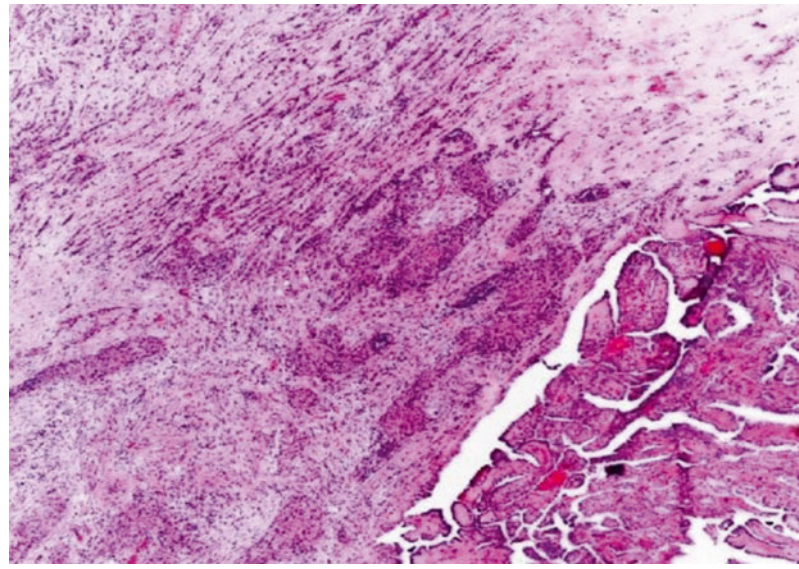

Fig. 11.42 Residual foci of PTC seen in the lower right corner. The main bulk of the tumor is composed of strands of squamous atypical cells and spindle neoplastic elements

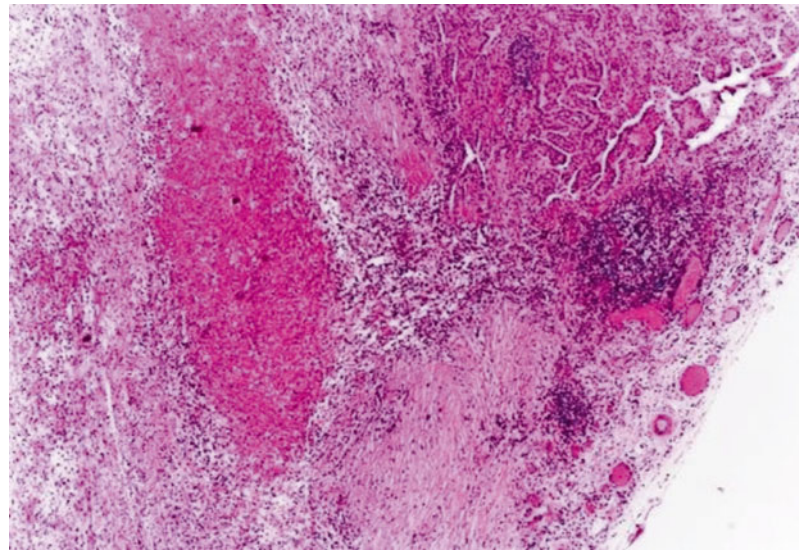

Fig. 11.43 LN metastasis of WDTC with anaplastic areas. Residual foci of PTC are present in the right upper corner, but the metastatic deposits are made mainly of spindle cells and necrotic areas

11.23 Medullary Thyroid Carcinoma (MTC)

Medullary thyroid carcinomas (MTCs) are neuroendocrine neoplasms derived from the parafollicular cells or C cells of the thyroid and account for approximately 5 % of thyroid neoplasms [356]. Medullary carcinomas, similar to normal C cells, secrete calcitonin, the measurement of which plays an important role in the diagnosis and postoperative follow-up. In some instances, the tumor cells elaborate other polypeptide hormones, such as serotonin, adrenocorticotrophic hormone (ACTH), and vasoactive intestinal peptide (VIP), which are responsible for the paraneoplastic syndrome as a presentation of familial MTC (e.g., diarrhea due to VIP or Cushing syndrome due to ACTH).

About 70 % of tumors arise sporadically. The remainder occurs in the setting of multiple endo-

Table 11.26 Features of medullary thyroid carcinoma (MTC) [357]

Clinical setting	Features of MTC	Inheritance pattern	Associated abnormalities	Genetic defect
Sporadic MTC	Unifocal	None	None	Somatic RET mutations in >20 % of tumors
MEN-2A	Multifocal, bilateral	AD	Pheochromocytomas, HPT	Germline missense mutations in extracellular cysteine codons of RET
MEN-2B	Multifocal, bilateral	AD	Pheochromocytomas, mucosal neuromas, megacolon, skeletal abnormalities	Germline missense mutation in tyrosine kinase domain of RET
FMTC	Multifocal, bilateral	AD	None	Germline missense mutations in extracellular or intracellular cysteine codons of RET

crine neoplasia (MEN) syndrome 2A or 2B or as familial tumors without an associated MEN syndrome (familial MTC [FMTC], inherited as autosomal dominant) (Table 11.26). This necessitates an integrated management approach to both the patients and their families. Activating point mutation in the RET proto-oncogene plays an important role in the development of both familial and sporadic MTCs.

When MTC arises as part of a familial syndrome, treatment of the other endocrine tumors is required. Distant metastatic spread may occur to the liver, lungs, and bone. Patients may survive for many years even with a significant tumor burden. However, MTC causes death by either local complications, such as invasion of vital structures in the neck and upper mediastinum, or by complications of distant metastases [358].

11.23.1 Clinical Presentation

Both forms of MTC (sporadic and familial) are lesions of adulthood, with a peak incidence in the 40s and 50s. Cases associated with MEN types 2A or 2B occur in younger patients. Patients with MTC present a neck lump, metastasis, dysphagia, and hoarseness. The tumor frequently spreads to regional lymphatics, including paratracheal, jugular chain, and upper mediastinal LNs. Systemic effects may occur due to coincident secretion of calcitonin and other peptides (frequent loose stools, vasomotor flushing, and less commonly Cushing syndrome). In all cases, a comprehensive family history must be taken to include first- and second-degree relatives to search for features of MTC or other endocrinopathies (MEN2).

11.23.2 Gross Features

Sporadic lesions are usually solitary. In contrast, bilaterality and multicentricity are common in familial cases. Larger lesions often contain areas of necrosis and hemorrhage and may extend through the capsule of the thyroid. The tumor tissue is firm, pale gray, and infiltrative.

11.23.3 Microscopic Picture

Microscopically, MTC is composed of polygonal to spindle-shaped cells, which may form nests, trabeculae, and even follicles [359]. Small, more anaplastic cells are present in some tumors and may be the predominant cell type. Acellular amyloid deposits derived from calcitonin polypeptides are present in the stroma in many cases (Fig. 11.44), although it is not necessary for the diagnosis. About 25 % of medullary carcinomas do not contain amyloid [360], and calcifications are usually noted in areas of amyloid deposition. Calcitonin is readily demonstrable within the cytoplasm of the tumor cells.

Electron microscopy reveals variable numbers of membrane-bound electron-dense granules

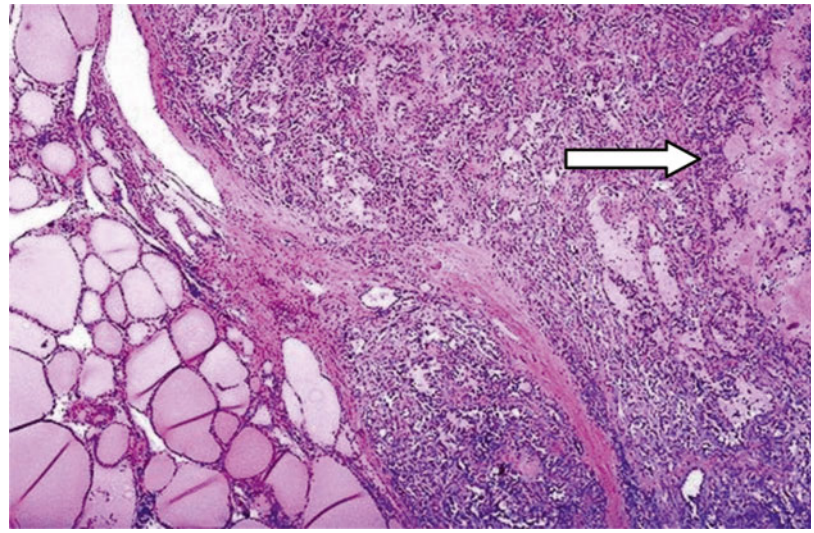

Fig. 11.44 MTC (*at the center and to the right*), which is much more cellular than the adjacent normal thyroid follicles (*at the left*). Note the pink hyaline material with the appearance of amyloid (*arrow*)

within the cytoplasm of neoplastic cells. One of the features of FMTC is the presence of multicentric C-cell hyperplasia in the surrounding thyroid parenchyma, a feature which is usually absent in sporadic lesions. Thus, the presence of multiple prominent clusters of C-cell hyperplasia throughout the gland should raise the specter of inherited predisposition, even if a family history is not present.

11.23.4 Investigations

11.23.4.1 Preoperative Investigations Should Include

1. A baseline value for calcitonin [361].
2. A 24-h urine sample assayed for catecholamines and metanephrines to rule out pheochromocytoma and a serum calcium (Ca) to exclude hyperparathyroidism (HPT). *These tests should be performed in all MTC patients prior to neck surgery even in the absence of a positive family history or symptoms*.
3. *RET* mutation analysis to establish the possible genetic basis for the disease.
4. A stimulation test with Ca/pentagastrin may be indicated to confirm a diagnosis of MTC preoperatively in relatives of patients with familial MTC, to exclude the rare causes of false-positive basal calcitonin elevation, or when calcitonin levels are only mildly elevated [361].
5. Routine preoperative staging of MTC with US and CT/MRI (chest, thorax, abdomen) is *not* essential *prior* to first-time intervention as it does *not* alter the need for neck surgery. These investigations, however, may provide the surgeon with information to guide the extent of surgery in the central neck compartment and superior mediastinum.

11.23.5 Treatment

11.23.5.1 Surgical Treatment

Surgical treatment of MTC is influenced by several factors: (1) ineffectiveness of RAI because MTC cells do not take up iodine, (2) multicentricity of MTC in 90 % of patients with the hereditary forms of the disease and in 20 % of patients with the sporadic form, (3) nodal spread in about 50 % of MTC patients (with the exception of children whose MTC is discovered as part of a genetic or biochemical screening program), and (4) the availability of assessment of the adequacy of surgical extirpation by measuring postoperative stimulated calcitonin levels.

The aims of first-time surgical treatment of MTC are to obtain locoregional control (the neck

and superior mediastinum) and, in some patients, a biochemical as well as clinical cure. Therefore, as an appropriate treatment, it is widely accepted that all patients with established MTC should undergo *total thyroidectomy (TT) and central LN dissection* (level VI).

Patients with pT2–4 tumors, or palpable LNs in the central or lateral compartment, should in addition undergo *bilateral selective neck dissection* of levels IIa–Vb. In the absence of direct invasion, the SCM/IJV/SAN should be conserved. Routine dissection of levels I, IIb, and Va is *not* required unless there are palpable/suspicious nodes at these sites. When there is strong suspicion or evidence of level VII, the patient should be considered for further surgery, which will require a sternotomy [362].

Patients with distant metastases at presentation often have prolonged survival. Even in the presence of disseminated disease, surgery (TT and central compartment node dissection) should be considered to prevent subsequent compromise of the trachea, esophagus, and RLNs.

Prophylactic surgery should be offered to *disease-free* carriers of germline *RET* mutations, identified by genetic screening programs [363]. Ideally, these patients would be expected to have C-cell hyperplasia (CCH) rather than MTC, but, in many cases, by the time of presentation, the transition from CCH to MTC will have occurred. It is important to distinguish the need for therapeutic surgery from prophylactic surgery. This will depend upon *genotype, age, and basal calcitonin*.

Children with MEN-2B should undergo *prophylactic thyroidectomy* within the first year of life. Children with MEN-2A should undergo prophylactic thyroidectomy before the age of 5 years [21, 53]. In children with MEN-2A under 10 years, it may be unnecessary to perform LN dissection. In older children and those with MEN-2B, central lymphadenectomy should probably be performed at the time of thyroidectomy. Gene carriers from kindred with FMTC should undergo prophylactic thyroid surgery after the age of 10 years; LN dissection is not indicated before the age of 20 years.

Investigation of Persistent or Increasing Hypercalcitoninemia

Postoperative samples should be measured no earlier than 10 days after thyroidectomy [361]. *Plasma calcitonin levels are most informative 6 months after surgery* [361]. There is good evidence that meticulous initial surgery reduces the risk of postoperative hypercalcitoninemia, but high calcitonin levels after surgery are a common finding. This will depend upon the preoperative basal calcitonin, stage of the tumor at presentation, and adequacy of initial surgery.

True local recurrence is unusual after adequate initial surgery. When initial surgery was incomplete, reoperation on the neck (lymphadenectomy of the central and/or lateral compartments) with curative intent should be considered. Mediastinal lymphadenectomy may be necessary when there is a strong suspicion of or proven nodal disease at this site.

It is important to distinguish locoregional, persistent/recurrent disease from distant micro- or macrometastases as the cause of hypercalcitoninemia. Noninvasive imaging (chest and abdominal CT or MRI and cervical and/or abdominal US, bone scan) should be performed, but may not be helpful because of the morphological pattern of metastatic MTC in the lung and liver (miliary disease). Laparoscopy or selective arteriography may identify occult hepatic metastases. Other less invasive options to detect metastatic MTC in patients with rising calcitonin and negative whole-body CT or MRI include pentavalent ^{99m}Tc-dimercaptosuccinic acid (DMSA), ^{131}I-MIBG, ^{111}In-octreotide, and 18FDG-PET scans.

Reoperative surgery in the neck and mediastinum should be considered in persistent or recurrent MTC, even when there are known distant metastases, to prevent the complications of large-volume disease affecting the airway, esophagus, or laryngeal nerves. Reoperation, at present, appears to offer the most consistent improvement in calcitonin levels, compared to other treatments [364].

11.23.5.2 Radiotherapy and Chemotherapy

Routine adjuvant external beam radiotherapy (EBRT) has *not* been shown to improve survival,

but may improve the relapse-free rate if there is gross residual disease or extensive nodal disease [365]. *Chemotherapy* is generally ineffective, but may be tried for progressive and symptomatic disseminated disease. *Radiolabeled somatostatin analogue and/or* ^{131}*I-MIBG treatment* may be useful in some cases, but has not been evaluated in clinical trials. *Alpha-interferon* may also have a role; however, the evidence base is scanty at present.

11.23.6 Follow-Up

Lifelong follow-up is recommended. Response to primary surgery can be assessed clinically and by the measurement of serum calcitonin and tumor markers, usually 6 months after surgery [361]. Elevated but stable calcitonin postoperatively may be treated conservatively, provided treatable disease has been excluded radiologically. Progressively rising levels should trigger imaging for further staging. In the absence of recurrent symptoms, appropriate follow-up intervals are 6–12 months.

11.23.7 Molecular Genetics: Genetic Investigation of a Patient with MTC

About 25 % of MTCs are hereditary, as part of MEN2/FMTC syndrome. Lack of family does not exclude heritable disease. The disease may not be apparent in relatives because of *skipped* generations, or an isolated case may be the start of a new family. Inherited MTC without other endocrinopathies also occurs. It is inherited in similar ways but tends to be more indolent than other forms of MTC [366]. Because of the rarity of MTC and the complexity of genetic investigation and management, cases should be managed by a specialist clinical service in close liaison with a regional genetics center.

11.23.7.1 Clinical History

A clinical history suggestive of MEN-2 syndrome would include (1) symptoms/history of pheochromocytoma and parathyroid disease; (2) features of MEN-2B such as facies, constipation/diarrhea, mucosal neuromas, medullated corneal nerve fibers, marfanoid habitus, colonic ganglioneuromatosis, and Hirschsprung's disease (may be associated with MEN-2); and (3) family history including all first- and second-degree relatives, with attention to features suggestive of MEN-2 (thyroid, adrenal, and parathyroid disease).

11.23.7.2 Genetic Testing

Before Testing

The patient should be referred to the clinical genetics service. Because of the possibility of heritable disease, every case of MTC should be offered genetic testing unless there are good reasons for not undertaking this. Testing should always begin with the affected individual, if available. If the affected individual is not available, the decision and strategy for testing should be discussed with the clinical genetics service. Before blood is taken, a clear explanation must be given of the nature of the test, the possible outcomes, and the implications of a positive or negative result for the individual and the family.

11.23.7.3 Testing

Ideally 10-ml EDTA anticoagulated blood should be taken from the affected individual. The sample, clinical details, and family history should be sent to the appropriate genetics laboratory. Patients with no special clinical features should be tested first for *RET* mutations in exons 10 and 11; if these are negative, they should be tested for exons 13–16. Failure to screen exons 13–16 constitutes an incomplete test. Patients with clinical features of MEN-2B should be tested first for mutations in codons 918 and 922 (exon 16), 883 (exon 15), as well as codons 804 and 806 (exon 14). Patients with clinical features of Hirschsprung's disease should be tested first for mutations in codons 609, 611, 618, and 620 (exon 10).

Mutation Testing of Tumor If no blood sample is available from the affected individual, DNA may be obtained from either frozen or

paraffin-embedded tumor. The *RET* mutations may be either germline or somatic in origin. A somatic MEN-2B-type (codon 918) mutation is commonly present in sporadic tumors, but may also be present in tumors from MEN-2A cases. This finding cannot therefore be used to exclude heritable disease.

11.23.7.4 Action Based on Results

If a Mutation Is Found

Permission must be obtained from the patient to disclose this result to anyone else, including the general practitioner (GP) and family.

A plan should be made for the treatment of the individual and for the further investigation of the family. *Regarding the individual,* mutation implies MEN-2 and thus (depending on the site of the mutation) a future risk of other MEN-2 components such as further thyroid tumors and adrenal and parathyroid disease. *Regarding the family,* those at risk should be offered testing for the specific *RET* mutation. Contacting and investigating the family require expertise and coordination and should normally be undertaken by a specialist clinical genetics department, in liaison with the relevant clinical teams.

If No Mutation Is Found

It is essential to check with the genetics laboratory that a complete mutation screen has been carried out, to include exons 10, 11, and 13–16 of the *RET* gene. If not, completion should be asked for. If there is strong presumptive evidence from the individual or family history of inherited disease, then (1) further research-based search for novel mutations is considered and discussed with the clinical genetics department and (2) biochemical screening of family members at risk using stimulated (IV Ca/pentagastrin) calcitonin testing from age 5 years should be considered.

If there is no clinical evidence to suggest inherited disease, the need for stimulated calcitonin screening of family members at risk is unclear. There are a few MEN-2 families (mostly with FMTC only) in which *RET* mutations have not so far been identified. Thus, a failure to find a *RET* mutation in an isolated case of MTC cannot completely exclude the possibility of heritable disease. The extent of the remaining risk is very small (around 1 % or less), depending on the clinical features of the patient. Young age at onset of the MTC (<35 years) and the presence of CCH in the thyroid are suggestive but not conclusive of inherited disease, nor does the absence of these features exclude it. The correct action in this situation may differ from family to family.

11.23.8 Multiple Endocrine Neoplasia-2B (MEN-2B)

11.23.8.1 Recognition

- Any new patient with MTC, especially a child or young adult, should be carefully assessed for clinical features suggestive of MEN-2B [367].
- The clinical features of MEN-2B may be hard to recognize, and the syndrome is sometimes diagnosed in error.
- More than 98 % of MEN-2B patients reported to date have mutations in either *RET* codon 918 (95 %) or 883 (3 %). Unless the clinical evidence is strong, preferably with radiological and/or biopsy support, the absence of these mutations excludes MEN-2B with high probability. Where there is doubt, the patient should be referred for a specialist opinion [367].

11.23.8.2 The Child of an MEN-2B Patient

Because MEN-2B can present with clinically significant MTC in the neonatal period, and is often metastatic by the time the patient is 5 or 6 years old, treatment of the newborn child of a known MEN-2B carrier should be planned in advance with specialist advice.

Because MTC occurs early in MEN-2B and is particularly aggressive, thyroid surgery in an affected child should be done as early as possible, preferably before the age of 12 months.

Prenatal testing is possible. Couples who ask about prenatal testing for MEN-2 should be referred to a genetics clinic.

11.24 Other Rare Thyroid Malignancies

11.24.1 Poorly Differentiated Thyroid Carcinoma (PDTC) (Insular Carcinoma)

Poorly differentiated thyroid carcinomas (PDTCs) are a heterogeneous group of malignant thyroid tumors including carcinomas that originate from follicular epithelium (often with evidence of coexistent papillary or follicular carcinoma). However, Sakamoto et al. proposed that the term PDTC should be applied to the tumors that are solid or trabecular and have loss of follicular and/or papillary architecture [368].

11.24.1.1 Diagnosis

The diagnosis of PDTC cannot be made with certainty by FNA cytology and is primarily made by histological examination. The common pathological feature of poorly differentiated carcinomas are solid/ trabecular/insular growth, large size, frequent extrathyroidal extension, extensive vascular invasion, presence of necrosis, and increased mitotic activity (Fig. 11.45). They may be associated with well-differentiated components, of either follicular or papillary type, and, less frequently, with anaplastic carcinomas [369].

Rarely, PDTC can be seen as encapsulated tumors; in this small subset, the survival is better than expected for poorly differentiated thyroid cancer. A distinct molecular pathway has been reported in poorly differentiated carcinomas, which almost exclusively involves RAS gene alteration [348].

11.24.2 Biological Behavior

The aggressive nature of this tumor is evident by the presence of mitotic figures, foci of necrosis, and frequent lymphovascular invasion. Metastases to regional LNs, lung, and bones are common with a high mortality rate as compared with conventional PTC and FTC. The biological behavior of PDTC is described as "intermediate" between WDTC and anaplastic thyroid carcinoma (ATC) in terms of prognosis [370].

11.24.3 Treatment

Aggressive treatment, not typically necessary for routine WDTC and not effective for ATC, may

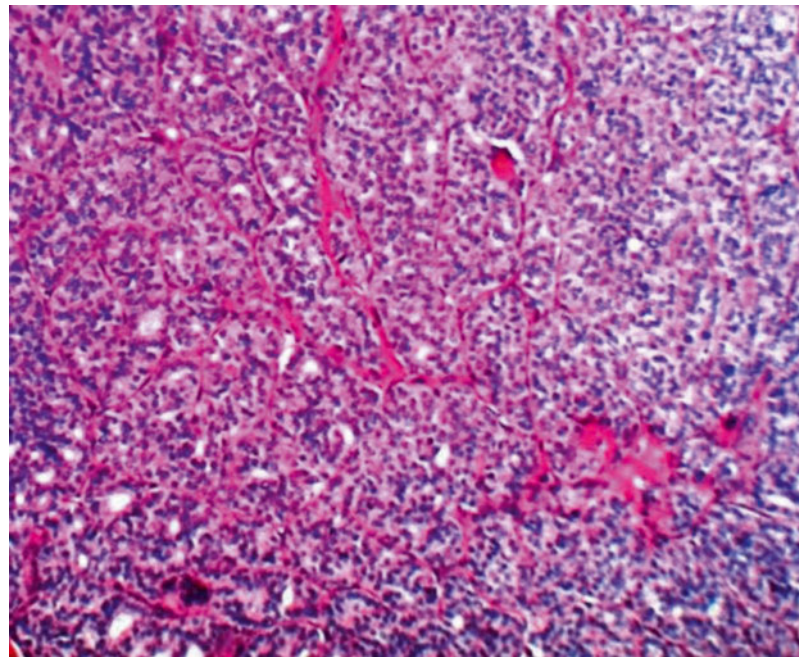

Fig. 11.45 Insular carcinoma of the thyroid gland (PDTC) with increased mitotic activity

uniquely result in substantial benefit in PDTCs. Given the lack of morbidity and potential for benefit, ^{131}I therapy should be considered in all patients postoperatively. It is also recommended that EBRT should be considered in all patients with PDTC with T3 tumors without distant metastasis, all patients with T4 tumors, and all patients with regional LN involvement.

11.25 Thyroid Lymphoma

Thyroid lymphomas comprise <5 % of thyroid malignancies and 2 % of all lymphomas [371–373]. The majority are non-Hodgkin's lymphomas (NHL) of B-cell origin [372, 374, 375]. *Primary lymphoma* of the thyroid occurs, in most cases, on a background of Hashimoto's thyroiditis, which is the only known risk factor [376, 377], and can increase the risk of developing thyroid lymphoma by up to 60 times [378]. *Secondary involvement* of the thyroid by lymphoma can occur in 20 % of patients dying from generalized lymphoma [379].

11.25.1 Clinical Presentation

The peak incidence of thyroid lymphoma is in the sixth decade [380]. It occurs more than twice as frequently in women [374, 375]. The most common presentation is a rapidly growing thyroid mass that causes symptoms by compression and/or infiltration of surrounding neck organs (Fig. 11.46). The most common symptoms are dyspnea, dysphagia, choking, and pain [374]. The classic symptoms of NHL (fever, night sweats, weight loss) are present in only 10 % of patients. Because of the association with Hashimoto's thyroiditis, a history of hypothyroidism is not uncommon (15 %) [380]. Hyperthyroidism is rare.

Physical examination usually reveals a hard, smooth, rubbery mass, which can be either bilateral or unilateral [375]. The thyroid gland may be slightly tender and is often fixed to adjacent structures. Up to 50 % will have palpable cervical LNs [381]. It is important to distinguish between ATC and thyroid lymphoma. Anaplastic thyroid carcinoma is rapidly progressive with a poor prognosis and a 2-year survival approaching 0 % compared to 80 % for thyroid lymphoma [382].

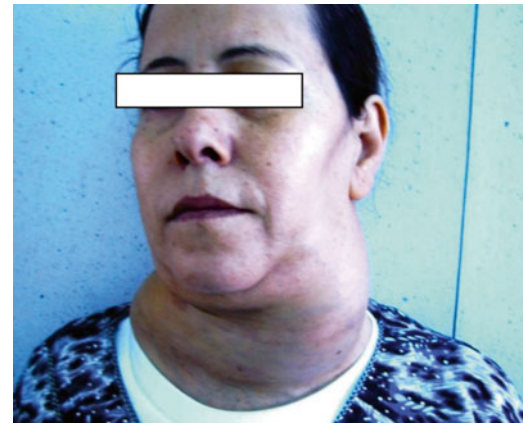

Fig. 11.46 A 52-year-old lady with a large thyroid gland, rapidly growing over 2 months and extending more on the left side. Biopsy proved to be a lymphoma

11.25.2 Diagnosis

Advances in *FNA* technology and immunocytochemical studies have now made FNA diagnosis of lymphoma possible in most patients (Fig. 11.47) [380]. *Incision biopsy* is *not* essential for the diagnosis of thyroid lymphoma [383].

Ultrasound for lymphoma usually shows an asymmetric pseudocystic pattern that is frequently misinterpreted as benign simple cysts [380]. The local extent of the tumor (invasion of the trachea or esophagus or retrosternal extension) can be evaluated using either *MRI* or *CT scan*. Lymphomas appear homogeneous on CT with little to no calcifications or necrosis, while ATC tends to be more heterogeneous with prominent calcifications and necrosis [382]. *Nuclear imaging* plays no role in the diagnosis of thyroid lymphoma.

11.25.3 Treatment

11.25.3.1 Radiation Therapy/Chemotherapy

Thyroid lymphomas are very sensitive to both radiation and chemotherapy. For localized disease,

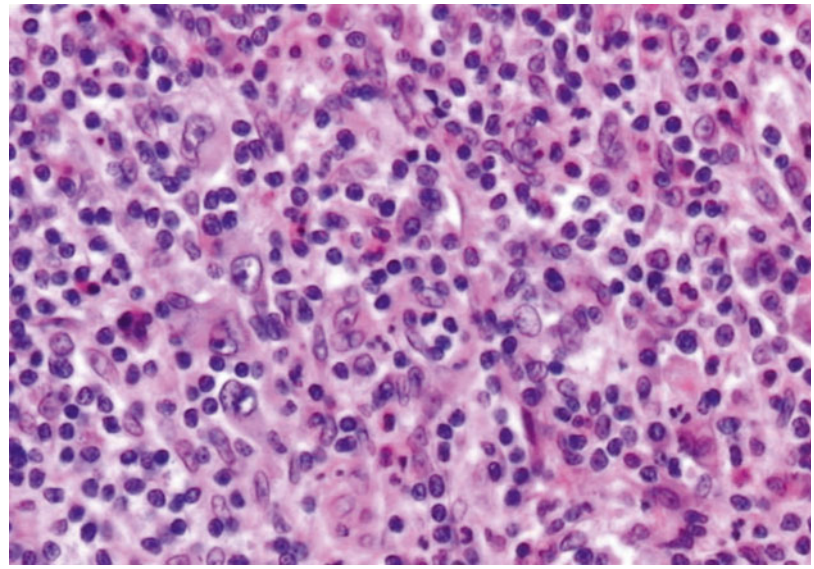

Fig. 11.47 Non-Hodgkin lymphoma (NHL) of the thyroid gland. Note the abundant large abnormal lymphocytes

radiotherapy (RT) of the neck and upper mediastinum is the primary therapy. The local response rate is dramatic and reaches up to 75 % [371, 384]. However, approximately 30 % of patients develop distant relapses [371], indicating the need for adjuvant chemotherapy even in patients who appear to have localized disease. *Chemotherapy* can thus be used as an adjunct to RT in localized disease or as the primary therapy in advanced lymphomas. The standard chemotherapy consists of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) [375, 385]. Several different regimens have been used, but no single combination has been proven to be superior. *Combining RT with chemotherapy* (combine modality) has been reported by several authors to result in a better response rate and disease-free survival than either alone [371, 386, 387].

11.25.3.2 Surgical Role

Recently, FNA combined with modern immunephenotypic analysis has eliminated the need for surgical intervention for the diagnosis of lymphoma [388]. Moreover, several studies have shown no advantage to surgical resection in comparison to RT or combined modality therapy [389, 390]. Therefore, it is generally accepted that thyroidectomy is *not* indicated for the treatment of thyroid lymphoma [391] even when the complication rate was no higher than that for benign disease [392].

Some surgeons still, however, advocate surgical decompression in the highly symptomatic patient [393, 394]. Surgical intervention is also occasionally needed on an urgent basis for decompression of the airway or tracheostomy, which may be ultimately required in up to 25 % of patients with thyroid lymphoma during the course of their treatment.

11.25.4 Prognosis

Prognosis is generally excellent. The initial remission rate reaches up to 85 %; however, half have been shown to suffer from a relapse within 10 years [387]. Combined treatment with RT and chemotherapy without extensive surgery has been reported by several authors to have equal or superior 5-year survival rates (SR) while avoiding the inherent risks of thyroid surgery [390]. Most deaths due to disease occur within the first 3 years of diagnosis [374].

Patients with stage IE disease tend to have a better prognosis with a 5-year survival rate of 80 %, as compared to 50 % in those with stage IIE disease [387]. Bulky tumors, extrathyroidal extension, and the presence of LN metastasis are

associated with a worse prognosis [386, 395]. Age is also a significant prognostic factor, as in other thyroid cancers. Patients less than 65 years have a substantially better prognosis with an overall 5-year SR of 81 % as compared to only 37 % in those older than 65 years [385].

Histological subtype can also help to define prognosis. The most common histological subtype is diffuse large B-cell lymphoma (50 % of patients), which is associated with a high incidence of disseminated disease and subsequent poor prognosis [377, 386]. The MALT lymphomas, which are usually associated with Hashimoto's thyroiditis, tend to be localized and have an excellent prognosis [377] with a 5-year SR 90 % [396].

The grade of the tumor affects the therapeutic plan and hence prognosis. For *low-grade* lesions, local therapy with surgery or RT may be adequate. For *intermediate-grade* tumors, even if the disease appears to be localized, the treatment should consist of combined RT and chemotherapy. For *high-grade* tumors, the mainstay of therapy is chemotherapy with or without radiation as a local control adjuvant.

11.26 Metastatic Lesions to the Thyroid

Tumors metastasize to the thyroid via (1) direct extension from tumors in adjacent structures, (2) by retrograde lymphatic spread, or (3) hematogenously. Hematogenous metastases to the thyroid vary according to the tumor type. The most common primary tumors are carcinomas of the kidney (renal cell carcinoma), lung, colon, and melanoma [397].

11.26.1 Clinical Presentation and Diagnosis

Metastatic lesions account for 1–7 % of all thyroid malignancies identified during the workup of a thyroid nodule [398, 399], occurring most commonly during the sixth or seventh decade of life [397]. The majority of patients present with an asymptomatic thyroid nodule and occasionally with dysphagia, stridor, or hoarseness.

Diagnosis can be made by FNA in the majority of cases [400, 401], but is limited in its ability to distinguish between a primary thyroid cancer and a metastatic lesion, particularly between an anaplastic thyroid cancer and a high-grade metastatic lesion [398, 401, 402]. However, it is difficult to distinguish by FNA. Despite the potential limitations, FNA should be the diagnostic procedure of choice for any patient with a new thyroid nodule and a history of malignancy.

11.26.2 Treatment

Surgical intervention may be indicated in order to determine the diagnosis. The role of surgery in the treatment of a known metastatic lesion is less clear. In a widely metastatic disease, surgical resection plays no role in the management. In such cases, the treatment of choice is systemic therapy for the primary tumor. Occasionally, patients may present with isolated thyroid metastasis and surgery may assist in local disease control and provide some disease-free survival advantage.

11.26.3 Prognosis

When a thyroid metastasis is part of a widely metastatic disease, the prognosis is poor with a survival of <2 years [402]. When the thyroid is the only identified site of metastatic disease, prognosis is better. In a series of ten patients with isolated disease, Chen et al. reported a 100 % local control at 5 years with a 60 % 5-year survival [403]. The second factor affecting prognosis is the source of primary tumor. Breast and lung cancer tend to have the worst prognosis, with a mean survival of only 3 months [397]. The best prognosis exists for renal cell carcinoma [403, 404]. The third factor that alters prognosis is the disease-free interval. The best outcomes have been reported in patients with indolent tumors who present with long disease-free intervals [404]. Additional factors affecting outcomes are the ability to perform a complete surgical

resection and the effectiveness of adjuvant therapy for the tumor type.

11.27 Molecular Basis for Thyroid Carcinogenesis

11.27.1 Introduction

According to their origin, thyroid malignancy can originate from either follicular or parafollicular cells (C cells). Both differentiated and anaplastic thyroid carcinomas arise from the follicular cells, while medullary carcinoma arises from parafollicular cells. Differentiated thyroid carcinoma (DTC) is further classified into papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Medullary thyroid carcinoma (MTC) can be further classified into familial and sporadic patterns. Sporadic MTCs account for 70 % of the cases and are characterized by unifocal involvement. On the other hand, familial MTCs (30 % of cases) are typically multifocal. Familial MTCs usually present as a part of MEN-2A (together with pheochromocytoma and parathyroid hyperplasia) or MEN-2B syndromes (together with pheochromocytoma and mucosal neuromas and/or GIT ganglioneuromas), but can still present as pure familial MTC (FMTC) [405, 406].

Thus, familial thyroid carcinomas can be either familial MTC (FMTC), for which the underlying genetic pattern is well established, or familial non-medullary thyroid carcinoma (FNMTC), for which the genetic background is bit by bit revealed and currently emerging. Although considered as rare forms (5–15 % of NMTC patients), familial papillary and follicular carcinomas can be broadly classified into two groups: a group with extrathyroidal familial pathologies with higher incidence of FNMTC as in the case of familial adenomatous polyposis (FAP), PTEN hamartoma tumor syndrome, Carney complex type 1, and Werner's syndrome. The other group is characterized by the predominance of the thyroid malignancy as in pure familial PTC (FPTC), FPTC with multinodular goiter, and FPTC associated with renal cell carcinoma [405].

11.27.2 Genetic Background for FMTC

A germline point mutation in the RET gene on chromosome 10q11.2 is responsible for the hereditary MTC. The RET proto-oncogene has 21 exons distributed over 60 kb. Analysis of the nucleotide sequence revealed that it encodes a receptor tyrosine kinase with four cadherin-related repeats and a cysteine-rich region in the extracellular domain. About 85 % of all mutations responsible for FMTC are well known. In the majority of MEN-IIA and FMTC patients, mutations are clustered in six cysteine residues (codons 609, 611, 618, and 620 in exon 10 and codons 630 and 634 in exon 11) in the RET cysteine-rich extracellular domain (Fig. 11.1). These mutations have been detected in about 95 % of MEN-IIA syndrome and 85 % of FMTC families. Somatic RET point mutations have been identified in about 50 % of patients with sporadic MTC [405, 407].

11.27.3 Genetic Background for FNMTC

A recent review [408] on the genetics of familial non-medullary thyroid cancer performed through review of references from the English literature confirmed six potential regions for harboring an FNMTC gene: MNG1 (14q32), TCO (19p13.2), FPTC/PRN (1q21), NMTC1 (2q21), FTEN (8p23.1–p22), and the telomere-telomerase complex. Important genes reported to have been excluded are RET, TRK, MET, APC, PTEN, and TSHR. The familial cancer syndromes associated with NMTC are summarized in Table 11.27, and those with predominance of NMTC are shown in Table 11.28.

11.27.4 Evolving Molecular Understanding of Sporadic Cases of Thyroid Carcinoma

Thyroid follicular cell growth requires the effect of TSH through cAMP pathway and growth factors

Table 11.27 Familial cancer syndromes associated with NMTC [1]

Syndrome	Inheritance	Gene mutation	Location	Incidence of thyroid cancer	Type of thyroid cancer
FAP	AD	APC tumor	5q21	2–12 %	PTC, cribriform, or classical variant
Cowden syndrome	AD	PTEN tumor suppressor gene	10q23.2	>10 %	FTC, occasional PTC
Carney complex	AD	PRKAR1-x	2p16 17q22–24	4 and 60 %	FTC and PTC
Werner's syndrome	AR	WRN gene	8p11–p12	10 %	FTC, PTC, ATC

FAP familial adenomatous polyposis, *AD* autosomal dominant, *AR* autosomal recessive, *PTEN* phophatase and tensin, *PTC* papillary thyroid cancer, *FTC* follicular thyroid cancer, *ANT* anaplastic thyroid carcinoma

Table 11.28 Familial syndromes with predominance of NMTC [1]

Tumor type	Type of study	Inheritance	Chromosomal loci	Candidate genes
PTC associated with PRN	Kindreds with PTC and PRN	Unknown	1q21	Unknown
Familial MNG with PTC	Kindreds with PTC and MNG	AD	14q	Unknown
FPTC	Kindreds with PTC	Unknown	2q21	Unknown
Familial TCO and without oxyphilia	Kindreds with TCO	AD	19p13.2	Unknown/TCO/TIMM44

PRN familial renal cell neoplasia, *MNG* multinodular goiter, *FPTC* familial papillary thyroid carcinoma, *TCO* familial carcinoma with oxyphilia

(e.g., IGF-1) through MAP kinase (MAPK) and phosphatidyl-inositol-3 kinase (PI3K) pathways [409]. In radiation-induced PTC, expression of RET/PTC was reported to be the main mutation. RET/PTC is a chimeric gene formed by chromosomal recombination, and the product retains the tyrosine kinase domain of RET. Normally, RET is not expressed or expressed in low quantities in follicular cells. Recombination occurs with heterologous gene, in the form of either RET/PTC-1 or RET/PTC-2. These mutations are present in 66–87 % of the radiation-induced PTC. However, it is not exclusive to this type as it is found in around 40 % of sporadic pediatric PTC and 15–20 % of sporadic adult PTC [410, 411].

Other effectors of the MAPK pathway are also implicated in the thyroid carcinogenesis including BRAF, the predominant isoform of the serine-threonine kinase (RAF) in thyroid cells [411]. Recent studies reported mutations of BRAF as the most common mutation in PTC (36–69 %). This mutation was also reported to be associated with more aggressive behaviors of PTC, as it is detected in tall cell PTC and anaplastic carcinoma resulting from dedifferentiation of PTC [411]. Interestingly, studies show no overlap between the aforementioned mutations (RET/PTC, BRAF, or RAS mutations). Collectively, these mutations are found in around 70 % of PTC cases [411, 412].

11.27.5 When to Suspect a Familial Pattern

Figure 11.48 shows the algorithm of when to suspect a familial pattern of non-medullary thyroid carcinoma (NMTC) [1].

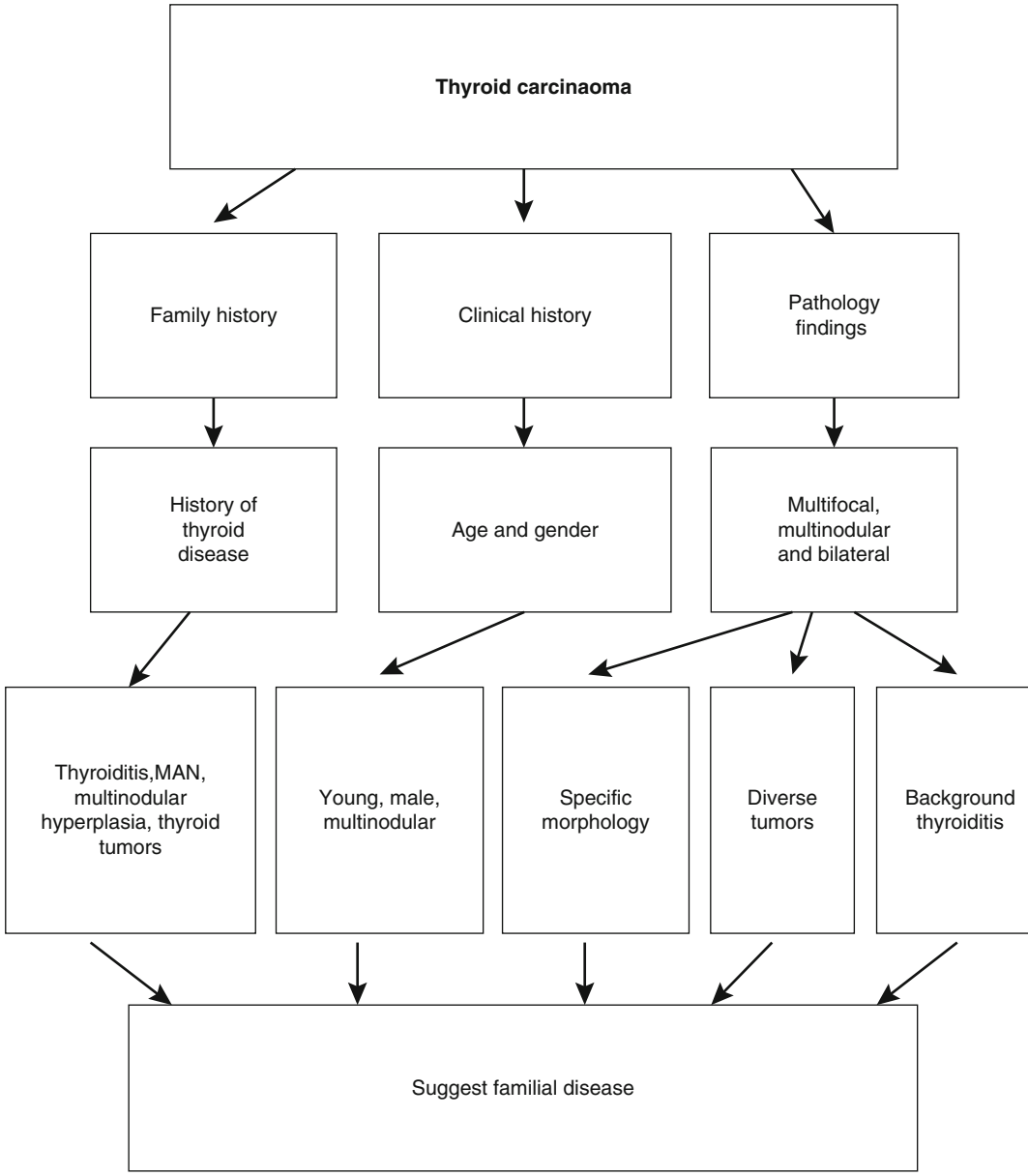

Fig. 11.48 Algorithm: when to suspect a familial pattern of non-medullary thyroid carcinoma

11.28 Thyroidectomy

Thyroidectomy is one of the most commonly performed operations in general surgery [413]. It is considered a safe procedure with low morbidity and very low mortality that approaches zero.

11.28.1 Indications

Absolute indications of thyroidectomy include (1) compression of the trachea and (2) malignancy or suspicion of malignancy. *Relative indications* include (1) nodular toxic goiter; (2) failure of antithyroid drugs (ATD) in the treatment of

thyrotoxicosis due to resistance, relapses, or reactions; (3) thyrotoxicosis in the young under 45 years of age; (4) social and economic factors when the patient is unable or unwilling to undergo long-term supervision with medical treatment; and (5) intrathoracic goiter [414].

11.28.2 Total Thyroidectomy (TT) for Benign Disorders

The use of total thyroidectomy (TT) remains controversial for small differentiated thyroid carcinomas, but even more controversial is its use to treat benign diseases [415, 416]. Most surgeons avoid the procedure owing to the possible complications such as permanent RLN palsy and permanent hypoparathyroidism; subtotal thyroidectomy has thus been the preferred operation for benign thyroid diseases. Currently, however, an increasing number of TTs are performed in specialist endocrine surgery units, and the indications include MNG and Graves' disease. This policy proved to eliminate all abnormal tissues in the neck including micro-carcinomas and lower recurrence rates [65, 417–420]. In addition, TT eliminates the source of the Graves' disease autoantibodies and alleviates any associated endocrine ophthalmopathy in 80–85 % of patients. After TT, hormone replacement with L-thyroxin is relatively easy and can be achieved by monitoring the thyroid hormone serum levels. As a result, TT is currently regarded as the surgical procedure of choice to treat Graves' disease and MNG [421], particularly that the reported risk of postoperative complications of the RLN and PTGs in specialized units is equivalent for total, subtotal, and hemithyroidectomy [421–424].

11.29 Conventional (Open) Thyroidectomy

Conventional thyroidectomy has many advantages. There is no need to divide any muscle, except the platysma. This operation has enjoyed a high success rate with a concomitantly negligible operative mortality and morbidity rate. Most of the procedures can be carried out through cervical incisions of 4–6 cm in length, in less than 90 min, with an excellent cosmetic result.

11.29.1 Surgical Technique

Thyroid operations should be performed in a blood-free field so that vital structures can be identified. Operating telescopes (magnification: 2.5× or 3.5×) are also recommended because they make it easier to identify the normal parathyroid glands (PTGs) and the RLN. If bleeding occurs, pressure should be applied. The vessels should be clamped only if they are precisely identified and the RLN has been identified [68].

As a rule, dissection should always be done first on the side where the suspected tumor is; if there is a problem with the dissection on this side, a less than total thyroidectomy can be performed on the contralateral side to prevent complications. There is, however, one exception to this rule: if the tumor is very extensive, the surgeon will sometimes find it easier to do the dissection on the easier side first to facilitate orientation with respect to the trachea and the esophagus [68, 425].

11.29.1.1 Skin Incision

A Kocher transverse incision paralleling the normal skin lines of the neck is made 1 cm caudal to the cricoid cartilage (Fig. 11.49). This locates it precisely over the isthmus. As a rule, the incision should be about 4–6 cm long, extending from the anterior border of one sternocleidomastoid (SCM) muscle to that of the other and passing through the platysma [426]. The length of the incision should be modified as necessary for good exposure. Patients with short, thick necks, low-lying thyroid glands, or large thyroid tumors require longer incisions than those with long, thin necks and small tumors.

A sterile marking pen should be used to mark the midline of the neck, the level at which the incision should be made (i.e., 1 cm below the cricoid), and the lateral margins of the incision (which should be at equal distances from the midline so that the incision will be symmetrical) [427].

The upper flap is dissected first by placing three Alice forceps on the dermis and retracting anteriorly

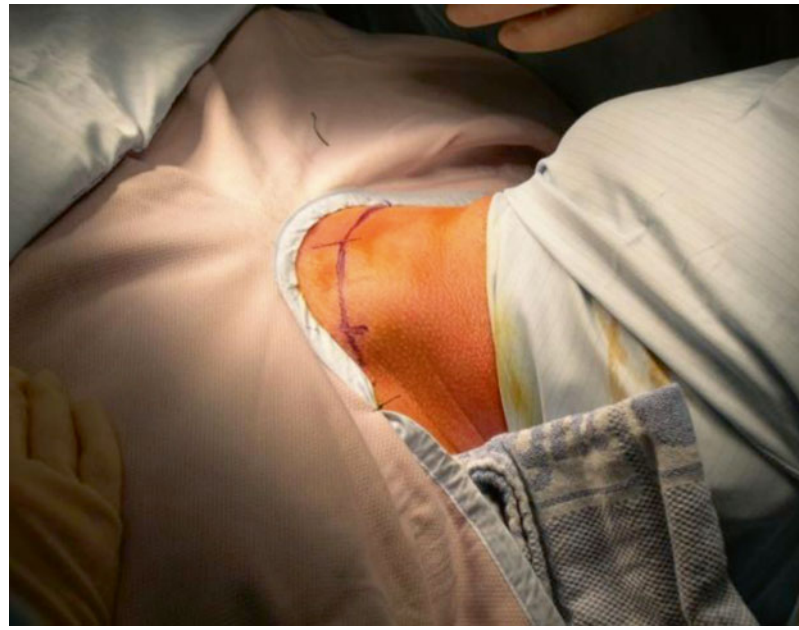

Fig. 11.49 Thyroidectomy incision in the skin crease, 1 cm below the cricoid cartilage

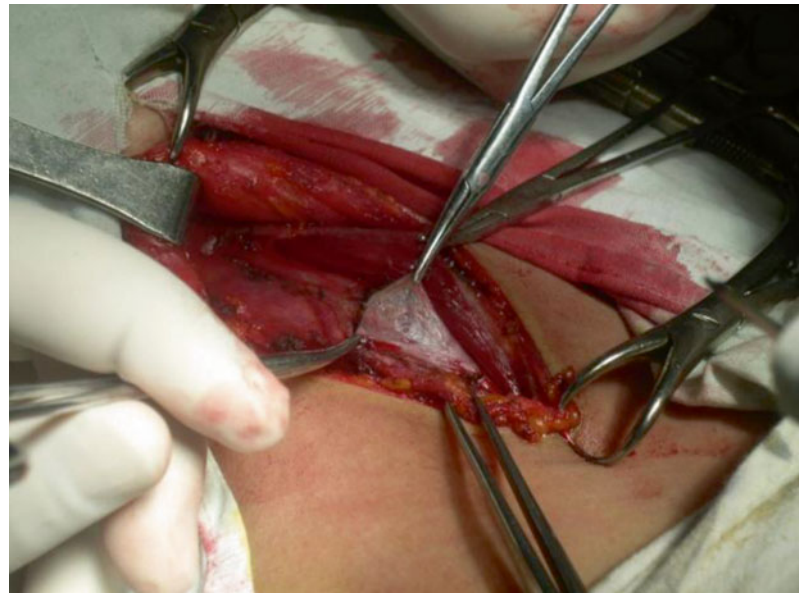

Fig. 11.50 Midline incision and separation of the strap muscles

and superiorly. This blood-free plane is deep to the platysma and superficial to the anterior jugular veins. Cephalic dissection can be done quickly with the electrocautery or a scalpel, and lateral dissection can be done bluntly. The same principles are applied to dissection of the lower flap. In thin patients, the surgeon must be careful not to dissect through the skin from within, especially at the level of the thyroid cartilage [426, 428].

11.29.1.2 Dissection of Strap Muscles

The thyroid gland is exposed via a midline incision through the superficial layer of deep cervical fascia between the strap muscles. Because the strap muscles are farthest apart just above the suprasternal notch, the incision is begun at the notch and extended to the thyroid cartilage [428, 429] (Fig. 11.50). The sternothyroid muscle is then dissected free from the thyroid

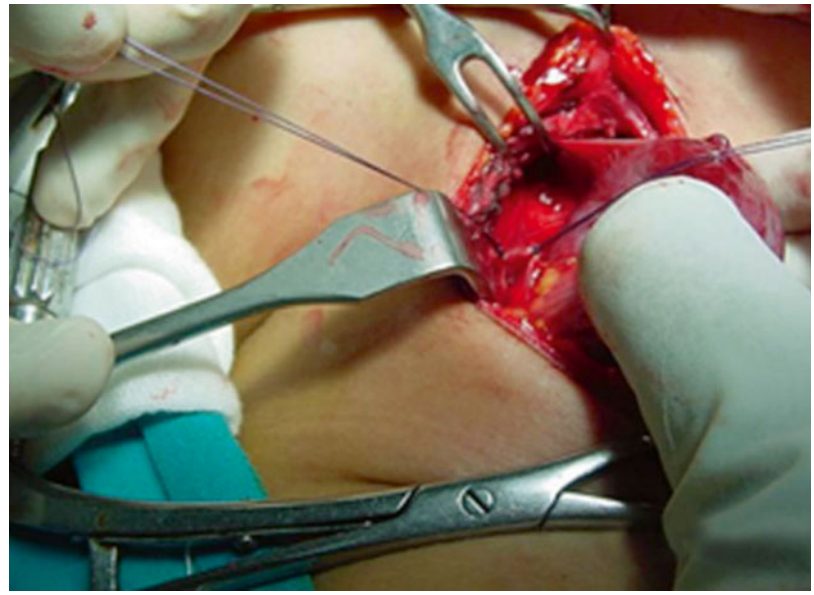

Fig. 11.51 Division of the middle thyroid vein to free the thyroid gland laterally

and the pre-thyroidal fascia by blunt or sharp dissection until the middle thyroid vein or veins are encountered laterally [61, 430].

The thyroid is retracted anteriorly and medially and the carotid sheath laterally; this retraction places tension on the middle thyroid veins and helps expose the area posterolateral to the thyroid where the PTGs and the RLNs are situated. The middle thyroid veins are divided to give better exposure behind the superior portion of the thyroid lobe [431, 432] (Fig. 11.51).

As a rule, it is not necessary to divide the strap muscles; however, if they are adherent to the underlying thyroid tumor, the portion of the muscle that is adhering to the tumor should be sacrificed and allowed to remain attached to the thyroid [433]. The middle thyroid veins should be cleaned of adjacent tissues to prevent any injury to the RLN when these veins are ligated and divided. It is always safest to mobilize tissues parallel to the RLN [434].

11.29.1.3 Mobilization of Thyroid Gland and Identification of Upper PTGs

Dissection is performed superiorly, laterally, and posteriorly with a small peanut sponge on a clamp. The superior thyroid artery (STA) and veins are identified by retracting the thyroid inferiorly and medially. They are individually identified and divided low on the thyroid gland to prevent injury of the EBSLN (Fig. 11.52). The tissues lateral to the upper lobe of the thyroid and medial to the carotid sheath can be mobilized caudally to the cricothyroid muscle (Fig. 11.53); the RLN enters the cricothyroid muscle at the level of the cricoid cartilage, first passing through Berry's ligament [435, 436]. The upper PTG is often identified at the level of the cricoid cartilage [437].

To prevent injury to the external branch of the EBSLN, the vessels are divided and ligated on the thyroid surface, the thyroid is retracted laterally and caudally, and dissection is carried out on the medial edge of the thyroid gland and lateral to the cricothyroid muscle. As alternatives to sutures, devices such as the Harmonic Scalpel (Ethicon Endo-Surgery, Inc.) and the LigaSure Precise (Valleylab) may be used to control vessels [438, 439].

It is essential to avoid injury of the EBSLN, which is the motor branch of the SLN and is responsible for tensing the vocal cords. In about 80 % of patients, the EBSLN runs on the surface of the cricothyroid muscle; in about 10 %, it runs with the superior pole vessels; and in the remaining 10 %, it runs within the cricothyroid muscle. Injury to the EBSLN occurs in as many as 10 % of patients undergoing thyroidectomy [440]. The

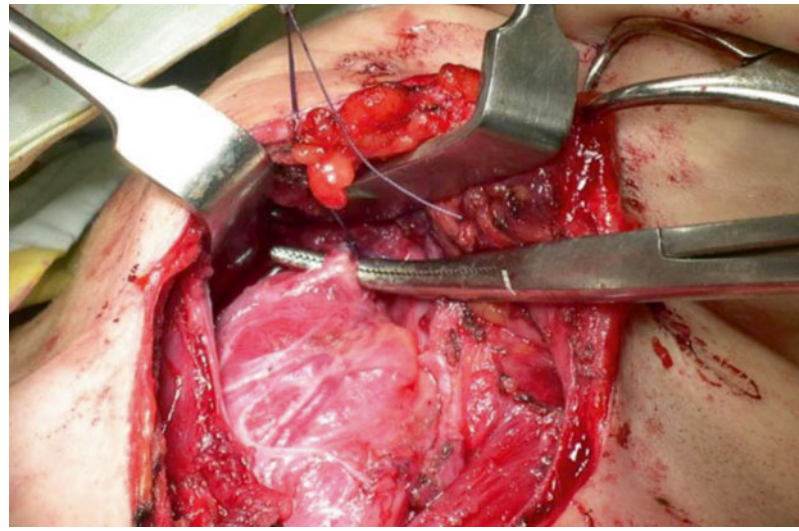

Fig. 11.52 The STA is individually identified and divided low on the thyroid gland to prevent injury of the EBSLN

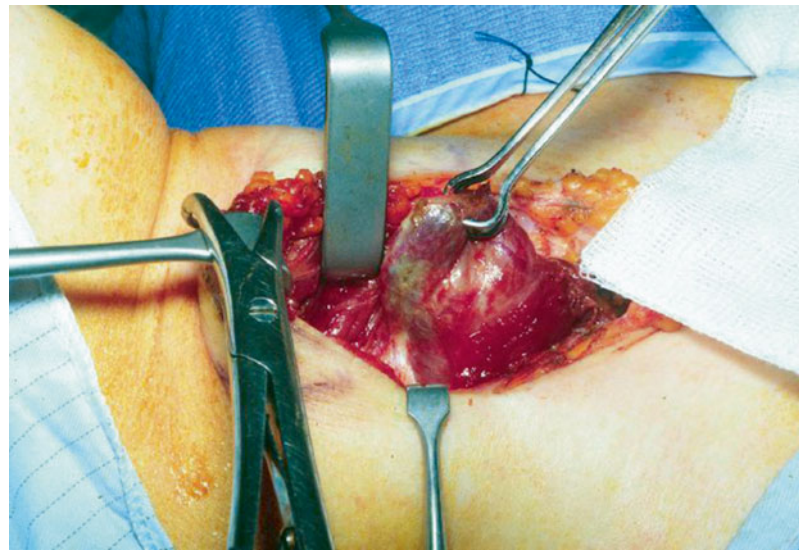

Fig. 11.53 Mobilizing the upper part of the thyroid lobe caudally to the cricothyroid muscle

best ways of preventing such injury are (1) providing gentle traction on the thyroid gland in a caudal and lateral direction and (2) ligating the superior pole vessels directly on the capsule of the upper pole individually and low on the thyroid gland rather than to cross-clamp the entire superior pole pedicle [437, 440].

11.29.1.4 Identification of RLNs and Lower PTGs

When the thyroid lobe is further mobilized, the lower PTG is usually seen anterior to the RLN, usually inferior to where the ITA crosses the RLN [441]. The carotid sheath is retracted laterally, and the thyroid gland is retracted anteriorly and medially to facilitate the identification of the RLN [442] (Fig. 11.54). The nerve is situated more medially on the left (running in the tracheoesophageal groove) and more obliquely on the right. Dissection should proceed cephalic along the lateral edge of the thyroid.

With the thyroid retracted anteriorly, these short peritracheal vessels running through the suspensory ligament of Berry are successively clamped with curved mosquito clamps on the tracheal surface from posterior to anterior and

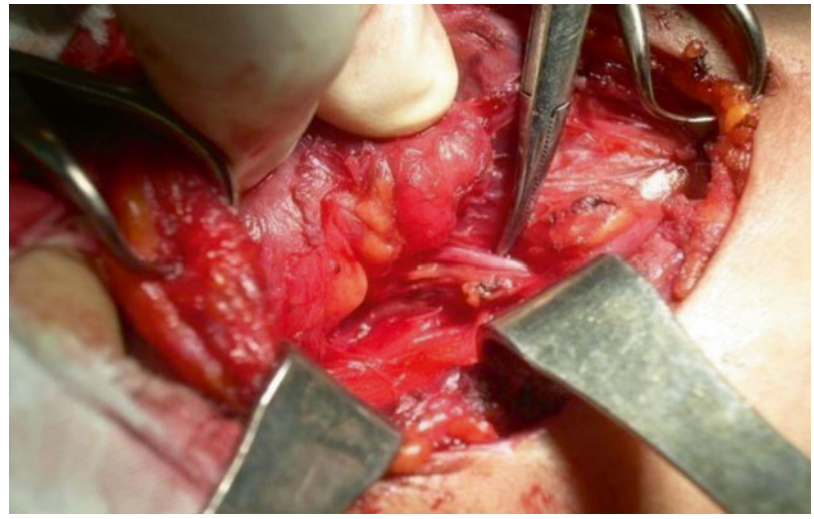

Fig. 11.54 Identification and dissection of the RLN

sharply divided. The minute arterial branches must be ligated or suture ligated; they may be the source of a severe, rapidly developing bleeding with compression. When a short bleeding stump retracts beneath the RLN, bleeding must be controlled with fine stick tie ligatures, with the nerve being carefully protected [443]. In some patients (about 15 %), the peduncle of Zuckerkandl, a small protuberance of thyroid tissue on the right, tends to obscure the RLN at the level of Berry's ligament [444]. Fatty and lymphatic tissues immediately adjacent to the thyroid gland are swept from it with a peanut sponge on a clamp, and small vessels are ligated. No tissue should be transected until one is sure that it is not the RLN [445].

The upper PTGs are usually situated on each side of the thyroid gland at the level where the RLN enters the cricothyroid muscle [441]. Because the RLN enters the cricothyroid muscle at the level of the cricoid cartilage, the area cephalic to the cricoid cartilage is relatively safe [445].

11.29.1.5 Mobilization of Pyramidal Lobe

The pyramidal lobe is found in about 80 % of patients. It extends in a cephalic direction, often through the notch in the thyroid cartilage to the hyoid bone. One or more lymph nodes (LNs) are frequently found just cephalic to the isthmus of the thyroid gland over the cricothyroid membrane (Delphian LNs) [429]. The pyramidal lobe is mobilized by retracting it caudally and by dissecting immediately adjacent to it in a cephalic direction. Small vessels are coagulated or ligated (Fig. 11.55).

11.29.1.6 Thyroid Resection

Once the PTGs have been carefully swept or dissected from the thyroid gland and the RLN has been identified, the thyroid lobe can be quickly resected (Fig. 11.56). For TT, the same operation is done again on the other side [444, 446].

11.29.1.7 Drainage

The fear of a hematoma enlarging and obstructing the airway prompts many surgeons to use drains routinely after any type of thyroid surgery [447, 448]. However, drains may be blocked by blood clots, add the patient's discomfort, deteriorate the cosmetic result, and increase hospital stay [449]. The routine need for use of drains in thyroid surgery has been debated.

11.29.1.8 Closure

The sternothyroid muscles are approximated, and a small opening is left in the midline at the suprasternal notch to allow any clotted blood to exit. The sternohyoid muscles are approximated in a similar fashion, as is the platysma. The skin is then closed with a subcuticular stitch. A sterile dressing is applied [450].

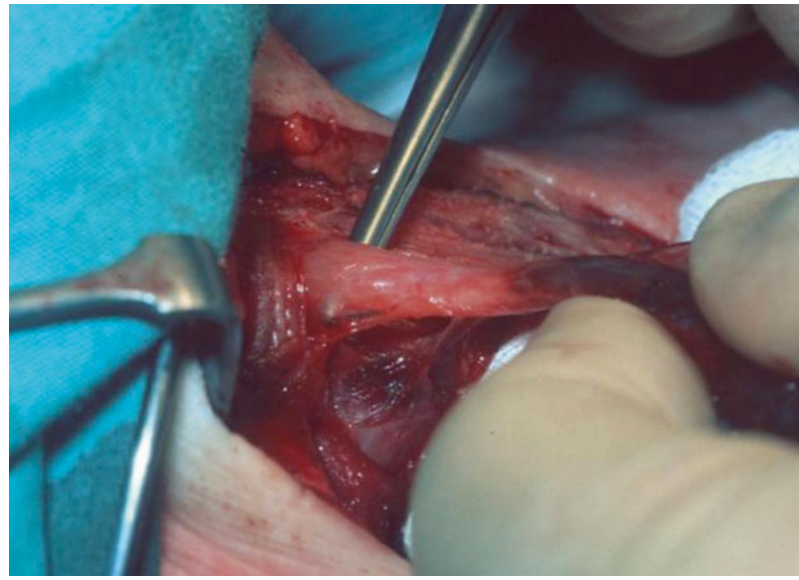

Fig. 11.55 Mobilization of the pyramidal lobe

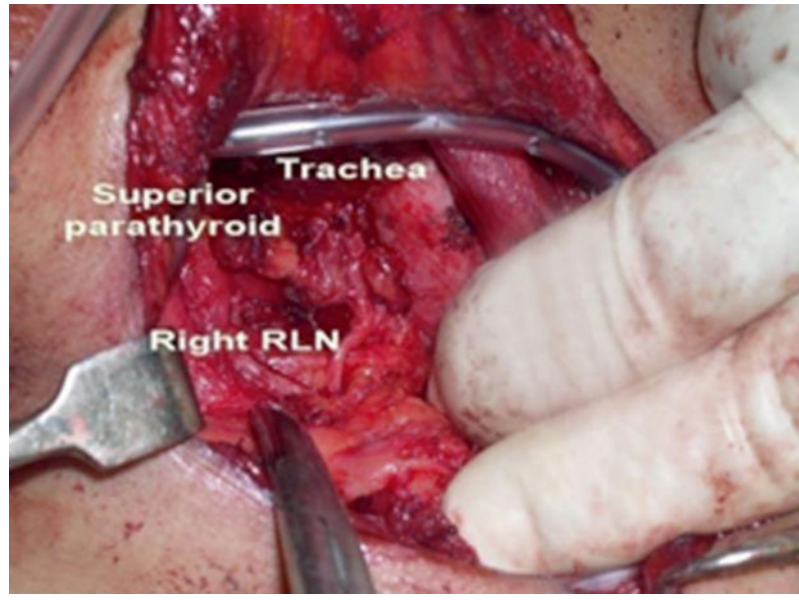

Fig. 11.56 Resection of the thyroid lobe with the parathyroid gland preserved and the RLN identified and dissected throughout its course

11.29.2 Postoperative Care

The duration of a thyroid operation is 1–3 h, depending on the size and invasiveness of the tumor, its vascularity, and the location of the PTGs. Postoperatively, the patient is kept in a low Fowler's position with the head and shoulders elevated 10–20° v 6–12 h to maintain negative pressure in the veins. The patient typically resumes eating within 3–4 h, and an antiemetic is ordered as needed [107].

11.30 Flapless Conventional Thyroidectomy

The flapless conventional thyroidectomy (FCT) is considered to be a safe and technically feasible surgical modality, which is therefore an effective alternative to a traditional conventional thyroidectomy. A flapless conventional thyroidectomy could also be listed among other variables when defining surgical invasiveness, since

it is associated with reductions in blood loss, the surgical cost, postoperative pain, and postoperative analgesic requirement. The amount of analgesics used within the first 24 h after surgery was significantly less in patients receiving a flapless thyroidectomy than those receiving the conventional thyroidectomy. Similarly, patients receiving flapless thyroidectomy experienced less postoperative pain like that in other MITS.

The potential advantages of a flapless conventional thyroidectomy over a conventional thyroidectomy include less tissue trauma, less blood loss, less postoperative pain, and less postoperative analgesic requirement. In addition, the flapless surgery procedure does not require any specialized instruments or additional charges [451].

11.31 Minimal Invasive Thyroid Surgery (MITS)

11.31.1 Introduction

After nearly a 100 years of performing a thyroidectomy essentially the way it was described by Theodore Kocher [452] in the nineteenth century, the past decades have seen dramatic changes in modern surgical technique [453, 454]. Much of this change has been technologically driven, with the introduction of high-resolution endoscopy [455, 456].

Minimally invasive surgery is defined as the ability of the surgeon to perform traditional surgical procedure in novel ways to minimize the trauma of surgical exposure. Many criteria are used to define and discriminate among minimally invasive techniques (length of incision, pain, duration of operation, general or local anesthesia, cost, cosmetic results, and cure of the disease). When used in the context of the thyroid (and parathyroid) procedures, the term "minimally invasive" is currently not specific enough and overlaps with the conventional open procedure. It was proposed that this term may be used only to describe thyroid procedures that are routinely associated with an incision shorter than 3.0 cm (and 2.5 cm for parathyroidectomy) [457–460]. In recent years, endoscopic surgery has emerged as an option for thyroid and parathyroid abnormalities. Surgeons in Japan and Italy have provided leadership in this field. It appears to be driven by patient demand for either a smaller scar on the neck or no scar at all [461].

The concept of MITS is attractive because patients are concerned not only about the result of treating their thyroid disease but also outcomes such as better cosmesis, reduced hospital stay, and decreased pain [462–464].

Many different techniques have been developed for MITS over a short period; these can be broadly classified into pure/or completely closed endoscopic techniques, video-assisted techniques, and minimally invasive open surgery. Ikeda et al. [465] classified minimally invasive thyroid procedures as follows: (1) minimally invasive/mini-incision, (2) minimally invasive video-assisted thyroidectomy (MIVAT), and (3) completely closed endoscopic (supraclavicular approach, axillary approach, anterior chest approach, and breast approach). However, other authors believed that the extra-cervical endoscopic approaches, while they have the advantage of avoiding a cervical incision, require extensive dissection that exceeds that of conventional surgery and in this regard cannot be considered minimally invasive [456, 466–469].

The concept of surgical invasiveness cannot be limited to the length or to the site of the skin incision. It must be extended to all structures dissected during the procedure. Therefore, minimally invasive thyroidectomy should properly be defined as "operations through a short, less than 3 cm, and discrete incision that permits direct access to the thyroid, resulting in a focused dissection" [461].

11.31.2 Advantages and Disadvantages of MITS

Judicious patient selection is the most important cornerstone for the success of any MITS technique for both benign and malignant thyroid swellings. As technology continues to develop and impact on surgical techniques, it is likely that these minimally invasive approaches will become

more widely used and easier to perform. As of now, MITS appears to be a useful addition to conventional thyroid surgery. Long-term follow-up and comparative trials are needed to validate these interesting techniques. There is a need to look into the expanding indications as well as the completeness of MITS procedures [463].

The application of MITS has expanded in the last decade and is being considered as an alternative to the conventional. Major advantages of MITS techniques include reduced tissue trauma, shorter hospital stay, better cosmetic results, minimal postoperative pain, reduced cost of healthcare, and, above all, patient comfort. Video-assisted endoscopic techniques in addition offer a magnified, illuminated view of the operating field. The main disadvantages of MITS procedures are the longer duration of surgery, steep learning curve, and increased cost of surgery due to the equipment usage. The reported important complications are similar to those seen after conventional thyroid surgery [470–478].

Endoscopic surgery does not provide better results in terms of hospital stay and postoperative pain when compared with the conventional open or mini-thyroidectomy procedures [479]. In thyroid surgery, pure endoscopic techniques are more time-consuming than conventional techniques. They take from 90 min for a thyroid lobectomy by cervical access up to 280 min for a total thyroidectomy by a chest wall approach. Whether minimally invasive procedures are actually less costly than conventional procedures is difficult to quantify [480, 481].

11.31.3 Direct Access MITS (Mini-incision)

In MITS performed by a *minimized cervical incision*, the access to the thyroid gland is direct. However, the volume of the nodule (<30–35 mm at largest diameter) and, even more importantly, the volume of the thyroid lobe (less than 20–30 ml) limit their indications. With advanced energy devices [482, 483] and the evolution of robust laryngeal nerve monitoring [484, 485], a faster and probably safer thyroidectomy could be accomplished through a smaller incision. This has been widely recognized and is increasingly embraced [486–488].

Thyroid operations that minimize the incision but keep it in the neck may be considered minimally invasive. These operations have some advantages over conventional cervicotomy in terms of postoperative pain and cosmetic results [460, 461, 489–493].

11.31.4 Minimally Invasive Video-Assisted Thyroidectomy (MIVAT)

Minimally invasive video-assisted thyroidectomy (MIVAT) was first introduced by Miccoli in 1999 and was rapidly adopted [494, 495]. The MIVAT procedure involves a gasless minimally invasive access (through a 15- to 20-mm midline incision) to the thyroid gland characterized by external retraction, magnified endoscopic vision, and dissection by means of needlescopic and ultrasonic devices. This technique proved to be feasible, as safe as traditional surgery, and viable for the treatment of small thyroid nodules [496]. Since 1999, the MIVAT approach has been widely used for both benign and malignant thyroid lesions in both adult and pediatric patients [497–499].

Later, it was used also to approach "low-risk" PTCs after demonstrating its ability to achieve thyroidectomy completeness for these patients [500]. Finally, the attempt to perform endoscopic central node compartment clearance via the same minimal access was accomplished, and the entire procedure proved to be viable and oncologically correct for dealing with a prophylactic total thyroidectomy in RET gene mutation carrier patient [501]. Patients with PTC who underwent MIVAT had a good outcome during a 5-year follow-up period. The outcome was similar to that for patients treated with conventional thyroidectomy and the same degree of exposure to postsurgical RAI treatment [502]. A study done by Ruggieri et al. [503] suggested that small nodules are one of the best indications for MIVAT.

The MIVAT has shown to be as safe as the existing gold standard operation. Furthermore,

the primary outcome measure of pain and secondary outcome measure of cosmesis both showed statistically significant better results for MIVAT compared to conventional thyroidectomy. This was achieved at the expense of operative time, which was significantly longer for MIVAT [504].

Based on their experience on MIVAT and central neck dissection (CND) via an average of 2-cm central neck incision, Bo Wu and Zheng Ding developed a procedure called video-assisted selective lateral neck dissection (VASLND) for PTC with suspicious node metastasis at level III, IV, or IIa through an extended 4–6-cm cervical incision [268, 505, 506].

11.31.5 Pure Endoscopic Techniques of Thyroidectomy

Pure endoscopic techniques using a *cervical access* are technically challenging due to the limited room for dissection. They are time-consuming, but with increasing experience and advances in surgical instrument design, shorter operating times are anticipated. Fear of insufflation-related complications, such as hypercapnia, extensive emphysema, and gas embolisms, is not sustained if appropriate precautions are taken, i.e., low flow one L/min and insufflation pressure <10 mmHg [461].

Considering the extent of the dissection required in some of the endoscopic techniques, one can wonder if the term minimally invasive is appropriate. This is particularly true for techniques using a non-cervical approach or combined cervical and *non-cervical approaches*. They consist of access to the thyroid field through an axillary, anterior chest, or mammary approach or combined approaches such as axillary and mammary approach or axillary and postauricular approach. These techniques are most developed in Asia, as in these countries, extra-cervical scars balance favorably with cervical scars [465, 474, 491, 507–510].

These operations allow the resection of large thyroid tumors, up to 60 mm in size, and enlarged glands, up to 60 ml in volume. These extra-cervical approaches have the main advantage of leaving no scar in the neck but cannot reasonably be described as minimally invasive, as they require more dissection than conventional open surgery. In addition, some of these procedures may require division of neck muscles. Whether transection of the omohyoid muscle or strap muscles, sometimes required in extra-cervical approaches, affects functionality is not clear. Postoperatively, it may cause an uncomfortable catching sensation on swallowing by adherence of skin or platysma to the sternohyoid muscle. Following extra-cervical techniques, patients suffer from moderate to severe pain, gradually subsiding within a week. Postoperative paresthesias or numbness generally subside within 6 months. A risk of subcutaneous hemorrhage without any evidence for increasing infection rates is present as a result of the extensive dissection [465, 474, 491, 507–510].

Ikeda and colleagues [465] developed novel techniques for endoscopic thyroidectomy that involved the use of *anterior chest approach* and the *axillary approach* with CO_2 insufflation. They compared these two types of endoscopic procedures with conventional open surgery. All patients in the axillary group were satisfied with the cosmetic results, whereas those in the anterior chest wall or open cervical group complained about the cosmetic appearance. Nakano and coworkers [511] modified the anterior chest wall technique. They did not use gas insufflation. Two Kirschner wires were attached to a winching device and inserted horizontally beneath the skin to lift the neck skin. A specially made retractor was passed through the tunnel on the chest wall into the neck.

Park and coauthors [512] reported a series of 100 patients who underwent endoscopic thyroidectomy via a *breast approach*. Incisions were made in both upper circumareolar areas. Subcutaneous tunnels were dissected up to the neck through which endoscopes were placed. CO_2 insufflation was used. The remaining dissection was carried out under visual endoscopic guidance. The incisions on the breast yielded a satisfactory cosmetic result with minimal scarring. Shimizu and colleagues (2003) [508] described an *axillary, bilateral breast approach*.

This led to acceptable scars on the breasts, and the axillary approach eliminated the scar from the parasternal port, as occurs with the pure breast approach.

In 2008, a *trans-oral access* for endoscopic thyroid resection has been proposed. The concept of thyroid surgery, via a natural orifice and without any skin incision, may be appealing to most patients, but the invasiveness and the potential complications of such access must be carefully evaluated by prior experimental studies [513].

11.32 Complications of Thyroidectomy

The morbidity associated with thyroid surgery is very low, but remains a matter of concern since thyroid disease often occurs in younger patients who have long life expectancy. Most complications can be avoided by an experienced endocrine surgeon.

General complications associated with thyroidectomy include cardiac and pulmonary problems; gastrointestinal dysfunction such as nausea, vomiting, and ileus; and renal and urinary tract problems. *Local complications* common to all operations include postoperative bleeding, infection, and keloid formation, while those specific to thyroidectomy include injury to the RLN, EBSLN, hypoparathyroidism, and airway obstruction. Other local complications such as injury to the esophagus, trachea, thoracic duct, IJV, carotid artery, and spinal accessory nerve are extremely rare [514–519].

11.32.1 Bleeding

The thyroid gland is extremely vascular, and bleeding can occur anywhere in the operative field. Special care must be taken with the superior thyroid vessels as these can retract and become difficult to control. Postoperative bleeding can be life-threatening by compromising the airway. Any postoperative respiratory distress can be thought of as attributable to a neck hematoma until proved otherwise. Most bleeding occurs within 4 h of operation, and virtually all occur within 24 h. Several studies have reported the successful use of bipolar vessel sealing systems [520–522] or the harmonic scalpel [523, 524] in shortening the length of thyroid surgery and reducing blood loss, while retaining a good hemostasis.

Drains do not prevent hemorrhage and are unlikely to prevent airway compromise since they are usually blocked by clot formation. If respiratory distress occurs, the wound should be opened immediately to release and drain the hematoma. If respiratory distress is not relieved, a tracheostomy should be performed. An alternative approach is to insert an endotracheal tube to secure the airway and then return the patient to the operating theater to gain hemostasis. Seromas also occur after thyroidectomy, and most of them are small and do not pose any respiratory problem. They resolve spontaneously, though some must be aspirated [525–527].

11.32.2 Respiratory Distress

Respiratory distress does not only occur due to respiratory compression and/or laryngeal edema by bleeding and hematoma formation. It can also occur with tracheal collapse from chondromalacia or kinking of a soft tortuous trachea. These problems are quite rare and usually occur with long-standing large MNGs. Tracheostomy is the standard treatment in such cases, although prolonged endotracheal intubation and external splinting of the trachea by custom-made rings or Marlex mesh have been tried [528].

11.32.3 Recurrent Laryngeal Nerve (RLN) Injury

Patients with a *single RLN injury* may remain asymptomatic, but are more likely to have temporary or permanent hoarseness. Injury of the RLN associated with thyroidectomy has progressively decreased but still occurs in 0.1–5 % of patients. If the nerve is inadvertently transected, it should be reanastomosed immediately, if recognized

intraoperatively, to avoid permanent hoarseness (>1 year). In such cases, a number of measures can help lessen hoarseness. These include speech therapy, Teflon injection into the vocal cord, and nerve anastomoses. *Bilateral RLN injury* will cause respiratory distress and stridor since both vocal cords will assume a midline position. Patients will require reintubation or tracheostomy to secure an airway. A vocal cord lateralization procedure can be performed if the injury has been present for over a year [529].

11.32.4 External Branch of the Superior Laryngeal Nerve (EBSLN) Injury

Damage to the EBSLN occurs in 0.3–2 % of patients undergoing thyroidectomy. The nerve may be injured when taking down the superior pole of the thyroid lobe. The patient will complain of voice weakness and a subtle loss of voice pitch. In case of *bilateral injury,* patients can experience swallowing disorders and be susceptible to aspiration [530].

11.32.5 Other Nerve Injuries

Rarely the *cervical sympathetic trunk* may be injured during thyroidectomy, resulting in Horner's syndrome. This is a rare complication, but can occur with very large glands, with invasive tumors, or with recurrent goiters due to obliteration of normal tissue planes by scar tissue. Injury to the *spinal accessory nerve* (SAN) can occur with neck dissections when combined with thyroidectomy but should not occur with thyroidectomy alone [530].

11.32.6 Hypoparathyroidism

Transient asymptomatic hypocalcemia occurs in most patients undergoing thyroidectomy, but this complication has decreased dramatically with the increased understanding of the anatomy and physiology of the parathyroid glands (PTGs). *Permanent hypoparathyroidism* has been reported in <1–2 % of patients. It occurs if all the PTGs are removed, injured, or rendered ischemic during thyroidectomy. Symptoms of acute postoperative hypocalcemia usually develop 1–7 days postoperatively. If untreated, carpal pedal spasm, tetany, and life-threatening cardiac arrhythmias may occur [315].

For symptomatic patients, intravenous (IV) calcium gluconate must be administered. Asymptomatic patients with mild hypocalcemia should be treated with oral calcium supplements. If the total serum calcium is <8 mg/dl, vitamin D replacement therapy should be initiated with one alpha-hydroxy cholecalciferol. It is important to also measure serum phosphorous in these patients. If the serum phosphorous is low, the cause of hypocalcemia may be the "bone hunger" syndrome, but if the serum phosphorous is high, the cause of hypocalcemia is hypoparathyroidism. If hypocalcemia and hyperphosphatemia remain after a year, permanent hyperparathyroidism is present and the patient will require long-term therapy with oral calcium and vitamin D.

Permanent hypoparathyroidism can be prevented by giving special attention to identifying the parathyroid glands and preserving their blood supply during thyroidectomy by individually ligating the branches of the inferior thyroid artery (ITA). If a gland cannot be left *in situ* with an intact vascular pedicle, it should be removed and autotransplanted (after being confirmed by frozen section) into the ipsilateral SCM muscle or brachioradialis of the non-dominating hand.

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Surgery of Parathyroid Glands

12

Tom R. Kurzawinski

12.1 Introduction

Parathyroid glands were the last major organ to be discovered (1850), perhaps a testimony to their small size, varied location and puzzling physiology. Their role in calcium metabolism and parathyroid hormone (PTH) excess and deficiency was defined in the first half of the twentieth century. Recent recognition of PTH structure, cloning of receptors and discovery of genes responsible for familial syndromes complemented our current understanding of their role in health and disease.

Hyperparathyroidism (HPT) was initially thought to be rare and always presenting with advanced renal and skeletal pathology. Nowadays, it is considered a common endocrine disorder, four times more common in women than men, with rising incidence of 25–30 new cases per 100,000 per year and prevalence of 1–7 in 1000. It is the third commonest endocrine condition after thyroid disease and diabetes (prevalence 1 in 13 and 1 in 17, respectively) and frequently diagnosed in asymptomatic patients.

A series of successful parathyroidectomies performed from 1925 onwards established surgery as the foremost treatment of HPT, the position it still holds today. The number of patients with HPT referred for surgery is increasing at the time when global healthcare funding is under severe pressure. Parathyroid surgeons must adopt a pragmatic approach when choosing diagnostic tests (not to over investigate), selecting right operations (simpler, better), aiming for excellent outcomes (to meet high expectations of our patients) and achieving all of these in the most cost-effective way (government priority).

12.2 Anatomy

Normal parathyroid glands are bean-shaped structures measuring 2×4×6 mm, orange brown in colour, with an average weight of 30 mg each. The majority of patients (90 %) have 4 parathyroids, but it is possible to have more (5 %) or less (5 %) than 4 glands. Parathyroid glands develop in tandem with thyroid from pharyngeal pouches, two inferior glands arising from the 3rd and two superior from 4th pharyngeal pouches. Embryologic development explains their varied locations in the neck and mediastinum. Superior glands are most frequently found within 1 cm of RLN crossing inferior thyroid artery. Inferior glands are more variable but most are found at inferior pole of thyroid. Ectopic glands could be found behind the oesophagus, in the mediastinum, thyrothymic ligament and carotid sheath. Parathyroids are frequently enmeshed within

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fibrous thyroid capsule but a location deep within the thyroid parenchyma is rare (0.1 %). Inferior thyroid artery supplies the majority of them (80 %). Parathyroids are composed mainly of chief cells secreting PTH and oxyphil cells supporting them metabolically [1].

12.3 Physiology

Parathyroid glands regulate calcium homeostasis by modulating bone metabolism and absorption of calcium in the kidney and intestine. Changes in calcium concentration are sensed by a calcium-sensing receptor (CaSR) on chief cells and lead to rapid alterations in parathyroid hormone synthesis and secretion. Human PTH is a linear polypeptide synthesised by chief cells as a part of a large molecule and trimmed intracellularly to an active hormone containing 84 amino acids. In response to hypocalcaemia PTH is released from secretory granules and acts directly on the bone (osteoclasts) and kidney (distal nephron), increasing calcium reabsorption. It also regulates formation of D3 (proximal tubules) and by this action increases calcium absorption from the intestine. Circulating PTH is metabolised in the liver and kidneys and its biological half-life is 5 min [2].

12.4 Pathology

Hyperparathyroidism is an abnormal state of calcium homeostasis where one or more parathyroid glands secrete inappropriately large amount of PTH. Classification of HPT into primary, secondary and tertiary reflects different mechanisms by which an excess of parathyroid hormone develops. *Primary HPT (PHPT)* is the commonest of the three and indicates that abnormal changes occurred first within the parathyroid gland itself. Pathological changes causing enlargement and increased inappropriate secretion of PTH include formation of adenoma (single 80 %, double 4 %), hyperplasia (15 %) and rarely cancer (1 %). Distinction between hyperplasia and adenoma is difficult and is based on finding a rim on normal parathyroid tissue at the periphery of the adenoma. *Secondary HPT* is caused by prolonged hypocalcaemia due to chronic renal disease, low vitamin D (rickets) or malabsorption. Low calcium stimulates parathyroid glands leading to compensatory hypertrophy and increased output of PTH. Despite high PTH levels calcium remains low and in early stages secondary HPT can be reversed (e.g. renal transplant).

Long-lasting secondary HPT can lead to development of parathyroid nodules autonomously secreting PTH resulting in rising calcium level, a condition known as *tertiary HPT.*

HPT could be *sporadic* or *familial*. Familial HPT accounts for 1–2 % of cases of HPT in adults but 24–46 % in children. Familial HPT is caused by inherited or de novo mutations of genes responsible for multiple endocrine neoplasia type 1 and 2a (MEN1 and MEN2a), hyperparathyroidism jaw tumour syndrome (HPT-JT), familial isolated HPT (FIHPT) and neonatal severe HPT (NSHPT) (Table 12.1).

12.5 Clinical Presentation

A range of clinical symptoms caused by prolonged oversecretion of PTH and hypercalcaemia vary from inconspicuous (fatigue) to painful (renal colic) and dangerous (hypercalcaemic crisis). Hypercalciuria can lead to kidney stones, nephrocalcinosis, renal impairment and nephrogenic diabetes insipidus. Prolonged reabsorption of calcium from the bones causes osteopenia, osteoporosis and in severe cases bone deformity known as osteitis fibrosa cystica. Weakened bones can cause bone pain and increase risks of fractures of long bones and collapse of vertebrae. Persistently elevated calcium levels can cause abdominal pain, frequently nonspecific but sometimes associated with peptic ulcer or pancreatitis. Other presentations include neuropsychiatric disorders, muscle weakness and pain, depression and fatigue. Very high, untreated calcium levels can cause hypercalcaemic crisis and present as thirst, nausea and vomiting and lead to dehydration, confusion, coma, ventricular arrhythmias and death [3–5].

Table 12.1 Familial causes of primary hyperparathyroidism (PHPT)

Condition	Inheritance and mutation	Organs affected
MEN 1	Autosomal dominant MEN1 gene on chromosome 11	Parathyroid (90 %), neuroendocrine tumours (NET) of the pancreas and gastrointestinal tract (60 %), pituitary adenomas (30 %), NET of thymus and bronchus, adrenal hyperplasia and adenomas, lipomas, leiomyomas and skin disorders such as angiofibromas and collagenomas
MEN 2A	Autosomal dominant MEN2A gene on chromosome 10	Parathyroid (20–30 %), medullary thyroid carcinoma and adrenal phaeochromocytomas
JTHPT	Autosomal dominant HRPT2 gene on chromosome 1	Mainly HPT and fibro-osseous lesions of mandible and maxilla. Risk of parathyroid carcinoma in 10–15 %. Associated with renal lesions – renal cell carcinoma, Wilms' tumour, hamartomas and cysts
FIHPT	Different mutations: MEN1, CaSR, HRPT2	Parathyroid gland
FHH/NSHPT	Autosomal dominant CaSR gene	

In the past, most patients presented with severe complications, but introduction of automated multichannel analysers in the 1970s dramatically increased the number of patients diagnosed with high calcium. Nowadays diagnosis of PHPT is made earlier. Approximately, 80–85 % of patients are diagnosed with biochemical abnormalities before they develop any symptoms.

12.6 Investigations

Biochemical tests: The diagnosis of PHPT is established by measuring serum calcium and PTH, which shows hypercalcaemia and inappropriately high PTH levels. Routine biochemical assessment of patients with PHPT should include renal function tests and vitamin D3 levels. In asymptomatic patients presenting with a mild hypercalcaemia, marginally elevated PTH and hypocalciuria, the diagnosis of FHH should be excluded by measuring the calcium-to-creatinine ratio (low in FHH). Genetic testing for mutations of the CaSR could be used in ambiguous cases. This is important, as FHH is a benign disease with no end organ damage and does not need treatment. Bone density scan and ultrasound of the kidneys should be considered.

Genetic mutations causing HPT are rare in adults but frequent in children. Positive genetic test is helpful in establishing diagnosis of familial HPT, planning treatment and initiating biochemical and genetic screening of other members of the family. In patients with positive family history, testing for mutations should start with the menin gene [6] followed by parafibromin (HRPT2) gene [7–9] if the gland is an atypical adenoma or carcinoma. RET mutation analysis is recommended for patients with features consistent with MEN2a [10]. Alternative to sequential genetic screening described above is to perform an analysis of all genetic mutations associated with hyperparathyroidism at once. Currently available panel of genetic tests include MEN1 and MEN2, CaSR, CDC73, CDKN 1A, CDKN 1B, CDKN 2B and CDKN 2C and is cheaper than performing these tests separately.

Imaging of abnormal parathyroid glands is a critical part of the preoperative workup especially in patients with sporadic PHPT. Its role is to identify the position of enlarged gland in the neck or mediastinum and differentiate between single and multiple gland diseases. Identification of a single enlarged gland by using two different

imaging techniques (concordant findings) enables the surgeon to plan a minimally invasive approach. Imaging is less helpful in familial and renal HPT when neck exploration and removal of multiple glands are usually required. In these situations embarking on surgery without localization studies is acceptable [11].

Ultrasound (US) scanning of the neck is usually performed using a high-frequency (12–15 MHz) transducer, which enables the detection of enlarged parathyroid glands, description of their size and position in relation to thyroid and other anatomical structures. Adenomas typically appear as homogenously echoic nodules on gray scale (Fig. 12.1) and are highly vascular on colour Doppler imaging.

Limitations of US include difficulty in identifying adenomas, which are either deep-seated (retrosternal/mediastinal) or related to air-filled structures such as the trachea and oesophagus. In addition, US is an operator-dependent investigation, and therefore outcomes will tend to relate to the level of experience of the centre and individual radiologist.

Nuclear imaging is usually performed with ([^{99m}Tc] methoxyisobutylnitrile (MIBI)), which avidly localises in mitochondria present in large numbers in the oxyphil cells of parathyroid tissue. Parathyroid adenomas and to a lesser degree hyperplastic glands demonstrate higher tracer uptake in the early stage and delayed washout in the late image as compared to the surrounding thyroid tissue. The use of SPECT, which produces 3D images from two cameras, has been shown to improve its sensitivity [12] (Fig. 12.2). Nuclear imaging is better than ultrasound at detecting ectopic adenomas. However, in the presence of thyroid nodules, differentiation of the abnormal parathyroid and thyroid tissue can be difficult. A systematic review of 54 studies identified the sensitivity of ultrasound to be 78 % in detecting solitary adenomas, 35 % in hyperplasia and 16 % in double adenomas. The sensitivity of MIBI was 88 % in detecting solitary adenomas, 44 % in detecting hyperplastic glands and 30 % in detecting double adenomas [13].

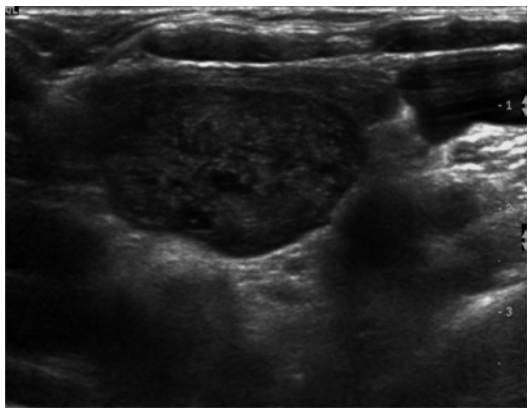


Fig. 12.1 Ultrasound image clearly demonstrating an enlarged parathyroid gland

Computed tomography (CT), *magnetic resonance imaging (MRI)* and *venous sampling* are rarely required in modern practice and should be reserved for cases where standard investigations are negative or in recurrent HPT requiring reoperation. Axial, thin cuts and contrast-enhanced CT images from the base of the skull through the mediastinum can help to identify abnormal parathyroids in the neck not seen on other scans and ectopic glands in the mediastinum. MRI is limited by similar appearances of cervical lymph nodes and parathyroid adenomas and venous sampling is an invasive test, which is now almost completely obsolete [14].

12.7 Treatment

12.7.1 When to Operate and What Benefits to Expect

Causal links between hyperparathyroidism and its harmful effects are well established in large populations, but asserting whether there is such a link in each individual case could be difficult. There is general consensus that symptomatic patients presenting with end organ damage such as renal stones, severe osteoporosis or pancreatitis should be offered surgery, both on account of seriousness of presentation and consequences of not treating it. The decision to operate is more complex when faced with uncertainty whether subtler symptoms such as fatigue or depression

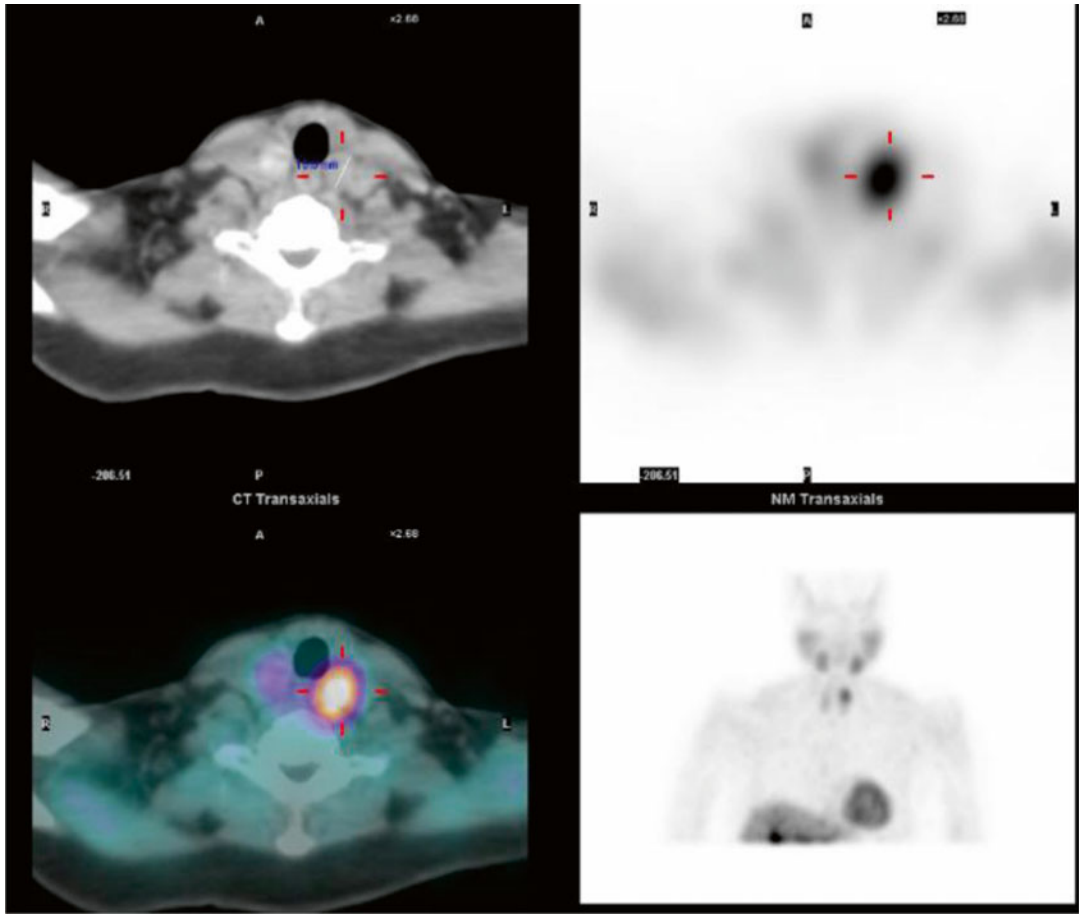


Fig. 12.2 CT/MIBI image of enlarged parathyroid in left upper position

are caused by PHPT or in 80 % of patients who declare no symptoms at all.

When deciding whether to operate, the surgeon should take into account existing *Guidelines*, evidence from *Observational Studies* and *Randomized Controlled Trials* (RCTs). Regularly updated *NIH Guidelines* advise surgery in asymptomatic patients younger than 50 years, when calcium level is >0.25 mmol/l above upper limits of normal, creatinine clearance GFR reduced to <60 ml/min or bone mineral density *T* score ≤ -2.5 at any site. Evidence from *Observational Studies* suggests that even subtle abnormalities of calcium and PTH levels are associated with adverse health outcomes. Between 1/4 and 1/3 of patients with asymptomatic PHPT left untreated for 10–15 years develop progressive disease with worsening hypercalcaemia, hypercalciuria and reduced bone density. Patients younger than 50 years have increased risk of disease progression. Patients who had parathyroidectomy had significant improvement in BMD at hip and lumbar spine but not forearm. Patients with untreated PHPT have increased mortality predominantly from CVD, but in patients who had surgery, there was a decline in mortality. Another study of patients with PHPT showed increased standardised morbidity and mortality for coronary and cerebrovascular diseases and cancer such as colon, kidney and breast. Dyslipidaemia and diabetes are more prevalent in patients with PHPT.

Evidence from RCTs informs us that surgery reduces formation of renal stones, improves BDM and reduces fractures. Although

parathyroidectomy improves dyslipidaemia, no overall improvement in cardiovascular events or decreased mortality has been observed. Impact of surgery on quality of life and neuropsychological outcomes is uncertain, as results of studies are contradictory.

12.7.2 Surgery

The aims of surgery in patients with PHPT are immediate and permanent cure of abnormally high levels of calcium and PTH, alleviation of the symptoms and prevention or reversal of end organ damage. The choice of operating technique, which includes *bilateral neck exploration (BNE)* or *minimally invasive parathyroidectomy (MIP)*, depends on the underlying parathyroid pathology and imaging results indicating the number and location of glands to be removed. In patients who need removal of 1–3 abnormal glands, normalisation of calcium and PTH levels without postoperative supplementation is the goal. When all four glands are abnormal and have to be removed, the goal is normocalcaemia maintained either by calcium and vitamin D3 supplementation or autotransplantation of parathyroid tissue.

12.7.2.1 Bilateral Neck Exploration (BNE)

Bilateral neck exploration (BNE) with visualisation of all four parathyroid glands, irrespective of the underlying parathyroid pathology, has been the gold standard surgical treatment for many past decades [15]. It is an effective and safe procedure, able to cure 95 % of patients with sporadic and 80–90 % of patients with familial PHPT. Typically, BNE is performed through a collar incision with exposure and dissection of all the parathyroid glands prior to deciding which glands should be removed. It allows not only direct visualisation of four glands but also enables exploration of sites of potential ectopic glands. Decisions regarding which glands are abnormal and need removing are based on prior knowledge of preoperative imaging and the size of the glands observed during surgery. BNE remains the operation of choice in three distinct scenarios: first, in familial PHPT when multiple glands are expected to be abnormal; second, when all imaging is negative; and third, when MIP fails to identify the enlarged gland and thereby conversion to BNE is necessary. Complication rate after parathyroidectomy is not well quantified but expected to be below 4 % with bleeding and infection accounting for 1 % and transient or permanent laryngeal nerve injury for 2–3 %.

In patients with familial HPT, extent of parathyroidectomy depends on underlying pathology. In *MEN1,* four-gland parathyroidectomy is often recommended as subtotal (less than four glands) parathyroidectomy is associated with high rates of recurrence requiring further surgery. Sometimes the decision is taken to remove 3 or 3½ parathyroids achieving immediate cure and accepting high risk of recurrence. In *MEN2a,* where frequently single gland is involved, removal of 1–3 glands can be curative without the risk of permanent hypocalcaemia. As the risk of PHPT in MEN2a is relatively low (10 %), parathyroids removed incidentally during prophylactic thyroidectomy should be reimplanted into the muscle. *HPT-JT* syndrome has a 15 % risk of parathyroid carcinoma, and surgical options include the removal of the single abnormal gland with subsequent annual surveillance of calcium and parathyroid hormone levels [15] or prophylactic total parathyroidectomy to prevent future malignancy or recurrent HPT. *FIHPT* is a complex disease associated with mutations in different genes including CaSR, MEN1 and HRPT2. The current recommendation is to remove 1–4 abnormal glands using intraoperative PTH and consider autotransplantation. In neonates with *NSHPT*, four-gland parathyroidectomy is essential to achieve cure, and in our experience removal of less than four glands results in persistently high levels of calcium and PTH.

Parathyroid autotransplantation is frequently considered when multiple parathyroid glands are removed. First described in 1926, it is a common and established practice when normal parathyroids are incidentally removed during thyroidectomy. Autotransplanting abnormal parathyroid tissue is controversial and presents a dilemma. It is potentially desirable, since there is no direct

hormonal replacement therapy available for the parathyroid hormone, and the medical management of postoperative hypoparathyroidism requires vitamin D and calcium supplementation. However, transplanted abnormal parathyroid tissue could cause recurrence requiring more surgery. If autotransplantation is pursued, it can be carried out either during the primary procedure or after cold storage (cryopreservation in −135 °C) usually within 24 months. The excised gland is divided to multiple small pieces and placed in the sternocleidomastoid or forearm muscles. Alternative procedure involves intramuscular injections of parathyroid glands. Good graft function has been reported in 86–100 % of adult patients [16].

12.7.2.2 Minimally Invasive Parathyroidectomy (MIP)

Minimally invasive parathyroidectomy (MIP) was introduced two decades ago and represents a significant development in surgical management of PHPT. Growing acceptance of MIP as a procedure of choice is due to realisation that solitary adenomas are responsible for majority of cases of sporadic HPT [17]. Improved accuracy of preoperative imaging allows precise localization of the adenoma and enables its targeted removal, without the need for dissection of remaining parathyroid glands. Majority of patients could be now selected for MIP and benefit from the surgery performed through smaller incisions, better scars, less pain and reduced hospital stay. There are two distinctive techniques employed to perform MIP. First is a *mini-incision parathyroidectomy,* which usually involves a 1 inch or smaller lateral incision overlying the affected parathyroid gland [18]. Dissection is carried out between the sternomastoid and strap muscles towards the lateral border of the thyroid, which is retracted medially and upwards with retractors. Blunt dissection allows direct visualisation of enlarged parathyroid and important landmarks such as the carotid, inferior thyroid artery and recurrent laryngeal nerve. If enlarged gland is not found in the position indicated by preoperative localization, dissection could be carried towards upper or lower pole through the same incision. If the abnormal gland is on the opposite side, incision is extended horizontally across midline and BNE is performed. The advantage of this technique is its simplicity, speed and no need for special equipment [19, 20]. Second is *endoscopic*, also known as *video-assisted parathyroidectomy.* The endoscope is introduced either in the midline, laterally between the carotid sheath and the strap muscles or via a trans-axillary approach. Space is created either by insufflation of carbon dioxide or gasless retraction and instruments are introduced through the same or separate incisions. The disadvantage of this approach is requirement for videoscopic equipment and increase in operating time [21]. *Robotic parathyroidectomy* using trans-axillary approach keeps the scar away from neck, but its cost is unnecessarily high and it is unlikely to become commonly used. MIP, irrespective of technique employed, can cure as many as 98 % of patients with sporadic PHPT, with a success rate that is similar to BNE.

12.7.2.3 Intraoperative Techniques Aiding the Localization and Confirmation of Cure

Failure of the surgery to cure HPT (5–10 %) is predominantly due to either multigland disease (hyperplasia, double adenomas) unrecognised by preoperative localisation studies or the inability to find parathyroid glands in unusual locations (ectopic glands). Various operative adjuncts are commonly used to overcome these problems and improve cure rate.

Frozen section of resected specimens is the oldest and most widely used technique to confirm that removed tissue is a parathyroid gland. It has 99 % accuracy in differentiating parathyroid from non-parathyroid tissue. It is not reliable in distinguishing an adenoma from hyperplasia. The limitation of the frozen section is its inability to determine whether the remaining parathyroid glands function normally, therefore not being able to confirm cure.

Methylene blue injected intravenously approximately an hour before surgery has been widely used to aid intraoperative localisation of parathyroid glands. The evidence from retrospective

studies suggests that though operative times are reduced, use of methylene blue did not demonstrate significant improvement in cure rate or recurrence. Methylene blue can cause anaphylaxis and the serotonin syndrome in patients taking selective serotonin reuptake inhibitors. Because of its neurotoxicity manifesting as toxic metabolic encephalopathy, it should be used with caution.

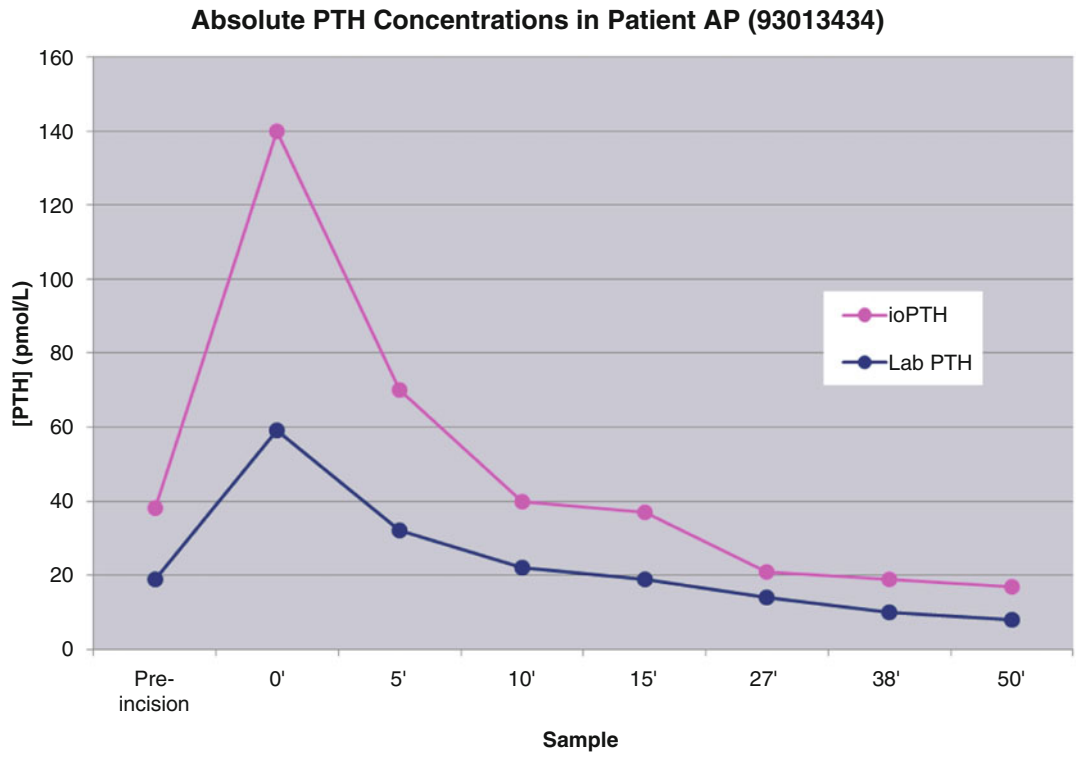
Fluorescence-guided parathyroidectomy is used to locate and differentiate the normal and enlarged parathyroid glands. Patients take oral aminolevulinic acid (ALA) 4–5 h prior to surgery. The operating field is illuminated with violet-blue light (405 nm wavelength), to which the parathyroid glands selectively demonstrate red fluorescence. Initial case series reported good ability to identify the parathyroid glands, but potential side effects include skin sensitivity to normal light (patients remain in hospital for 24–28 h post procedure in dim-lit rooms to avoid this), transient elevation in liver enzymes, nausea and vomiting.

Radio-guided parathyroidectomy (RGP) involves the injection of MIBI preoperatively and the use of a portable γ-probe to localise the abnormal parathyroid in vivo and determine ex vivo radioactivity count after the excision. Parathyroid adenomas' radioactivity count is 59 %, while thyroid and hyperplastic glands count is 16 % above background activity. Using a cut-off of 20 % with a positive MIBI scan preoperatively, excision of abnormal parathyroid could be confirmed. In patients where the excised glands do not meet the count criteria of >20 % of the background count, further exploration of the contralateral side is performed through the same incision. The reported success rates for RGP are high at 93–97 %. RGP can be also successfully performed regardless whether preoperative MIBI scans are positive or negative. The disadvantage of this technique is cost, logistics and exposure to radiation.

Intraoperative parathyroid hormone (IOPTH) monitoring is possible because, in patients with normal renal function, PTH has a biological half-life of less than 5 min. Therefore, removal of the abnormal, hypersecreting parathyroid gland results in rapid reduction in the PTH levels. Blood sampling is done before, at 5 and 10 min after excision of the abnormal parathyroid and biochemical cure is confirmed by 50 % reduction of PTH compared to the highest pre-excision level (Fig. 12.3). Measurements are done in the operating theatre next to the patient and take 12 min. Monitoring of IOPTH is the simplest and most effective technique of confirming cure and success of operation. It helps to overcome the inaccuracies of preoperative localisation studies when multigland disease has been missed. Persistently high PTH level indicates that not all abnormal glands were removed and further exploration is necessary [22, 23]. Monitoring of IOPTH is most helpful in patients with discordant imaging, patients who had single preoperative localisation study (e.g. only US in pregnant women) and in reoperations for recurrent HPT. Monitoring of IOPTH changed operative management in only 2 % of cases with concordant but in 74 % of cases with discordant imaging. The IOPTH assays in the removed specimen can be also used to differentiate between parathyroid and non-parathyroid tissue; however, frozen section may be superior for this purpose. Its disadvantage is high cost.

12.7.3 Special Situations

PHPT in children differs from PHPT in adults in that it is 100 times less frequent, equally common in boys and girls, more frequently familial and almost always symptomatic at presentation. Neonates are exclusively affected by CaSR mutations causing neonatal severe HPT. Older children have higher proportion of familial to sporadic disease and routine genetic testing is recommended. Despite these differences, biochemical and genetic testing as well as preoperative localisation studies have the same accuracy and value in both children and adults. Sporadic PHPT in children, similarly to adults, is caused in great majority of cases by single parathyroid adenoma and can be cured by MIP. Children with familial PHPT should undergo BNE and removal of multiple abnormal parathyroid glands [24].



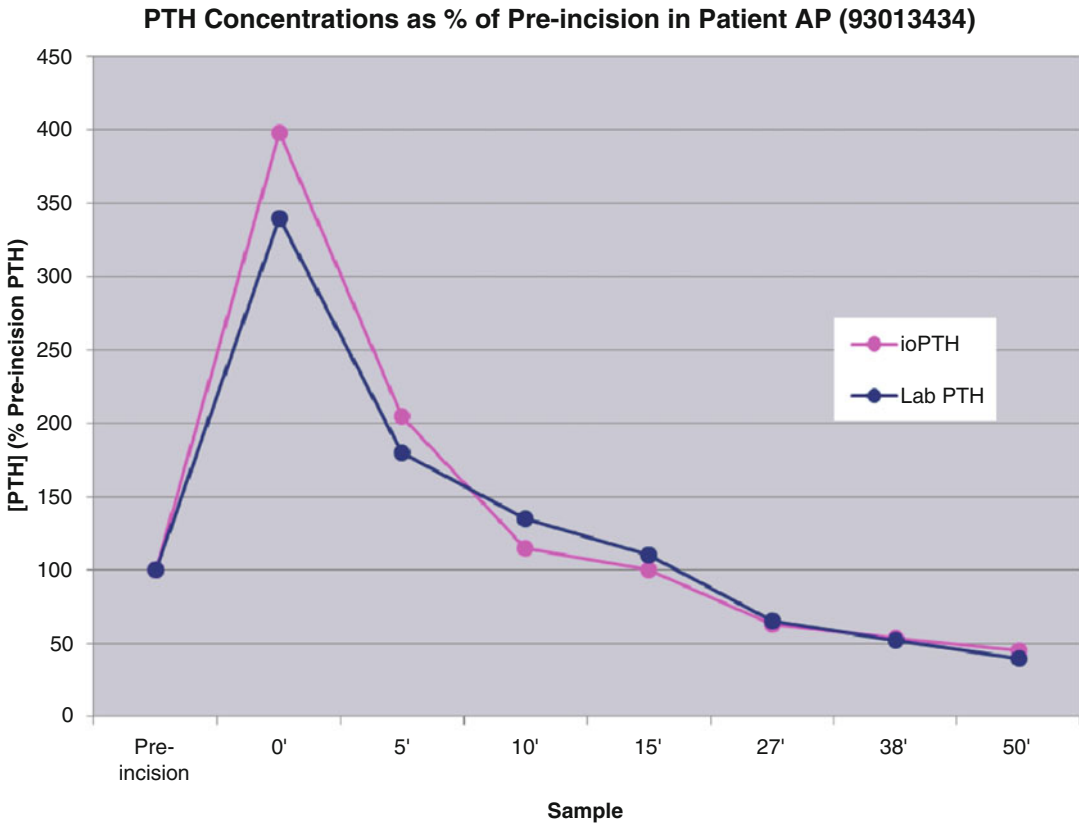


Fig. 12.3 Comparison of IOPTH concentration changes during surgery measured by main laboratory platform and equipment based in theatre

PHPT in pregnancy is a risk to the mother and baby and is frequently diagnosed late. It presents as dehydration, hyperemesis and pre-eclampsia and is associated with 3.5-fold increase in spontaneous abortion and stillbirth. Foetal effects are intrauterine growth retardation, low birth weight, hypocalcaemia and tetany in neonate. Medications to lower calcium could be used, but parathyroidectomy in the second trimester is safe and the best treatment [25].

Renal hyperthyroidism could be treated with calcimimetics but parathyroidectomy is indicated in 20% of patients poorly controlled, not responding or having severe side effects to cinacalcet. Total parathyroidectomy cures renal HPT but long-term hypoparathyroidism can cause adynamic bone disease detrimental to skeletal health. 3½ gland parathyroidectomy and total parathyroidectomy with autotransplantation have 90–100 % cure rate at 24 months, but in long-term recurrence rate ranges from 0 to 80 %. The number of glands to be removed depends on patient age, stage of disease and eligibility for renal transplantation and should be always discussed with the nephrology team.

PHPT in elderly affects 2 % of elderly population and about ¼ of parathyroidectomies for PHPT are performed in patients older than 70 years. Parathyroidectomy in the elderly is safe and should be considered as it offers significant improvement in symptoms and cardiovascular and skeletal health [26].

*Intrathoracic parathyroid*s can be found in 10 % of patients with PHPT. Glands located above aortic arch can be almost always removed through cervical approach. Adenomas situated deeper might require open approach (thoracotomy or partial/full sternotomy) or their minimally invasive alternatives (video-assisted thoracoscopy or mediastinoscopy). Angiographic or chemical ablation can also be used [27].

Parathyroid cancer is found in 1 % of patients with PHPT and could present as a hard palpable mass. It should be also suspected in patients with normal examination but very high levels of calcium and PTH. Infiltrating tumours should be resected with adjacent thyroid and involved soft tissue. If the diagnosis is made postoperatively on histology, second operation and hemi-thyroidectomy should be considered. Local recurrence develops in about 10 % of patients and 5- and 10-year survival is 86 and 49 %, respectively. Distant metastases and associated hypercalcaemia should be treated with a combination of ablation procedures and systemic therapy to control calcium (cinacalcet) and chemotherapy [28].

Redo parathyroidectomy is necessary in 5–10 % of patients with recurrent or persistent PHPT. The commonest causes of failure are wrong diagnosis, suboptimal imaging, ectopic glands, familial disease and an inexperienced surgeon. If reoperation is necessary, it is essential that diagnosis of PHPT is confirmed and imaging, operating notes and histology of previous surgery are reviewed. Additional imaging and relevant genetic tests should be carefully planned. Majority of redo operations are neck explorations sometimes combined with sternotomy, but MIP or thoracoscopy should be considered. Reoperations have increased risks of postoperative complications but success rate is high at 90–95 % [29, 30].

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Surgery of the Suprarenal Gland

13

Tarek Ezzat and Ioannis Christakis

13.1 Surgical Anatomy

The first anatomical report of the adrenal glands comes from Eustachius in 1563. The anatomical division in two zones, an outer cortex and an inner medulla, came in 1805 by Cuvier [1]. Other prominent scientists that have contributed to the understanding of the role and function of the adrenal glands are Thomas Addison who described the features of adrenal insufficiency, Harvey Cushing who in 1932 reported 11 patients with the characteristic features of the syndrome that today bears his name, and Conn who in 1955 described the syndrome resulting from excessive secretion of this mineralocorticoid [2].

The two different zones of the adrenal gland are in essence two distinct endocrine organs. The cortex originates from the mesoderm around the fifth week of gestation near the gonads, while the medulla is ectodermal in origin and arises from the neural crest [2]. As a result, ectopic adrenocortical tissue can be found in the ovaries, spermatic cord, and testes, while neural crest cells that have migrated to the para-aortic and paravertebral areas may contain extra-adrenal medullary tissue. The largest of the latter is located to the left of the aortic bifurcation near the inferior mesenteric artery origin and is designated as the organ of Zuckerkandl. Adrenal medullary tissue can also be found occasionally in the neck, urinary bladder, and para-aortic regions.

The adrenal glands are paired, retroperitoneal organs and are located anteromedially to the kidneys, near the superior poles at the level of the eleventh ribs. The adult adrenal gland weighs 4–8, measures 4 × 3 × 1 cm, and is larger in women than in men. The volume of the larger portion, the cortex, is 8–20 times that of the medulla [3]. The two glands have a different shape; the left is crescentic or semilunar, is more flattened, and may extend on the medial surface of the kidney almost to the hilum, while the right gland is more triangular or pyramidal and lies higher on the kidney [3]. The renal fascia of Gerota covers each adrenal gland together with the associated kidney, while the adrenal gland is also covered by a layer of fat.

Each adrenal gland due to its shape has only an anterior and posterior surface. Their anatomical relationship to other structures is summarized in Table 13.1 [3]:

13.1.1 Vascular Supply

The adrenal and the thyroid and parathyroid glands are the viscera with the greatest blood

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Table 13.1 Anatomical relations of the right and left adrenal glands

Surface	Right adrenal gland	Left adrenal gland
Anterior surface	Superior: "bare area" of the liver Inferior: peritoneum and first part of the duodenum (occasionally) Medial: inferior vena cava (IVC) Lateral: "bare area" of the right lobe of the liver	Superior: peritoneum and the stomach Inferior: body of the pancreas
Posterior surface	Superior: diaphragm Inferior: anteromedial aspect of the right kidney	Medial: left crus of the diaphragm Lateral: medial aspect of the left kidney

supply per gram of tissue. The arterial supply of the adrenal glands comes from three main sources:

- The superior adrenal arteries, arising from the inferior phrenic arteries. One artery may be larger than the others, or all may be of similar size.
- The middle adrenal artery arises from the aorta just proximal to the origin of the renal artery. It can be single, multiple, or absent.
- One or more inferior adrenal arteries arise from the renal artery, an accessory renal artery, or a superior polar artery.

A total of 50–60 arteries penetrate the capsule over the entire surface as all of the abovementioned arteries branch freely before entering the adrenal gland [4]. The pattern of the arterial supply has been shown to vary between each individual [5–7]. In the majority of cases (61 % of individuals), the supply by the middle or inferior adrenal arteries may be lacking, while the superior adrenals are absent in only about 2 % of cases. In a small subset of the population (5 % of individuals), the arterial supply is derived entirely from one source, a singular vessel supplying the superior, middle, and inferior branches.

The adrenal venous drainage is much simpler with a single vein emerging at the hilum and draining the entire adrenal gland. The left vein passes downward over the anterior surface of the gland and is joined by the left inferior phrenic vein before entering the left renal vein. The right vein is typically very short and opens into the posterior side of the inferior vena cava. The right adrenal vein does not usually have any tributaries other than from the adrenal gland. Accessory veins occur in 5–10 % of patients; on the right, these vessels may drain into the right hepatic vein or the right renal vein; on the left, accessory veins may drain directly into the left renal vein [2].

13.1.2 Lymphatic Drainage

The lymphatics of the adrenal gland drain into the renal hilar nodes, lateral aortic nodes, and nodes of the posterior mediastinum above the diaphragm by way of the diaphragmatic orifices for the splanchnic nerves. Rouvière stated that lymphatics from the upper pole of the right adrenal gland may enter the liver [8]. The majority of capsular lymphatic vessels pass directly to the thoracic duct without the intervention of lymph nodes [9].

13.1.3 Innervation

The adrenal cortex appears to have only vasomotor innervation. Most of the fibers reaching the gland from the splanchnic nerves, the lumbar sympathetic chain, the celiac ganglion, and the celiac plexus enter the medulla. These fibers are preganglionic and end on the medullary chromaffin cells [10]. This arrangement is not as anomalous as it might appear; chromaffin cells arise from the same embryonic source as do the postganglionic neurons elsewhere. Most of these preganglionic fibers in humans are nonmyelinated [11].

13.2 Applied Physiology

The adrenal cortex appears yellow because of its high lipid content and accounts for approximately 80–90 % of the gland's volume, while the adrenal

medulla constitutes up to 10–20 % of the gland's volume and is reddish-brown in color [2].

The adrenal cortex is composed of three zones (from outside to inside): the zona glomerulosa, the zona fasciculata, and the zona reticularis [3]. In all three zones, all cells produce steroids. Zona glomerulosa also secretes the mineralocorticoid aldosterone; zona fasciculate produces the carbohydrate-active steroid, cortisol, and the adrenal sex steroids. The innermost layer, zona reticularis, secretes cortisol, androgens, and estrogens.

The adrenal medulla cells secrete epinephrine and are called chromaffin cells or pheochromocytes. Distributed throughout the medulla, but few in number, are postganglionic sympathetic neurons. Most medullary cells secrete epinephrine, but some secrete norepinephrine instead.

Cholesterol is the common precursor of all steroid hormones synthesized in the adrenal cortex. Steroid synthesis begins with cholesterol being transported in the mitochondria by the acute regulatory protein (StAR) [12]. Cholesterol then undergoes a series of oxidative reactions catalyzed predominantly by cytochrome P-450 yielding the hormonally inactive compound pregnenolone. Further oxidation by the enzyme CYP17, confined to the zona fasciculata and zona reticularis, converts pregnenolone and progesterone into the major adrenal sex steroids dehydroepiandrosterone (DHEA) and androstenedione [13]. Oxidation of pregnenolone and 17-hydroxypregnenolone by 3b-hydroxysteroid dehydrogenase results in the production of the glucocorticoids, corticosterone, and cortisol, with only the latter being active in humans. Aldosterone is generated by oxidation of corticosterone by the enzyme CYP11B2 localized exclusively in the zona glomerulosa.

13.2.1 Glucocorticoids

Glucocorticoids are under the control of a complex mechanism that starts by the release of corticotropin-releasing factor (CRF) by the hypothalamus resulting in secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary [13]. ACTH is able to act on the adrenocortical cell surface and stimulate glucocorticoid secretion. The release of ACTH displays a circadian rhythm and is higher on waking with levels gradually declining throughout the day to reach a nadir in the early evening. Glucocorticoids can downregulate the production of both CRF and ACTH via a negative feedback mechanism.

Glucocorticoid hormones have a wide range of effects on almost all organ systems in the body. They cause an increase in blood glucose concentrations, through upregulation of gluconeogenesis, inhibition of glucose uptake by peripheral tissues, lipolysis stimulation, and a general state of insulin resistance. In the cardiovascular system, glucocorticoids maintain the cardiac contractility and peripheral vascular by sensitizing arterial smooth muscle cells to β-adrenergic stimulation [14]. Finally, glucocorticoids are potent anti-inflammatory and immunosuppressive agents that act at many levels.

13.2.2 Mineralocorticoids

Angiotensin II and blood potassium levels are the primary regulators of the release of aldosterone from the zona glomerulosa. The renin-angiotensin-aldosterone axis is sensitive to the delivery of sodium to the distal convoluted tubule of the kidney; in states such as hypovolemia, shock, renal artery vasoconstriction, and hyponatremia where there is a low sodium delivery, the release of renin from the juxtaglomerular apparatus is stimulated [13]. Aldosterone release is also highly responsive to small changes in the blood potassium level, as previously mentioned. Hypokalemia reduces aldosterone release by suppressing renin secretion and also by acting directly at the zona glomerulosa, while hyperkalemia acts on the opposite way.

Aldosterone's role is to regulate the circulating fluid volume and electrolyte balance by promoting sodium and chloride retention in the distal tubule of the kidney. On the other hand, potassium and hydrogen ions are secreted into the urine. As in the case of glucocorticoids, there is also a negative feedback mechanism that

allows suppressing the release of renin whenever there is an increase in sodium delivery to the distal tubule.

13.2.3 Adrenal Sex Steroids

Secretion of the adrenal androgens androstenedione and DHEA is regulated by ACTH and other incompletely understood mechanisms. The physiologic effects of adrenal sex steroids are generally weak in comparison to the gonadal sex steroids, particularly in males.

13.2.4 Catecholamines

Tyrosine is the substrate used for the synthesis of catecholamines in the adrenal medulla. Dihydroxyphenylalanine (l-dopa) is produced by the hydroxylation of tyrosine, and decarboxylation of l-dopa generates dopamine, which is then taken up by neurosecretory granules and β-hydroxylated to form norepinephrine [13]. Epinephrine is created by the action of phenylethanolamine N-methyl-transferase (PNMT), which is localized to the chromaffin cells of the adrenal medulla and organ of Zuckerkandl.

The stored catecholamines are released in the circulation whenever sympathetic stimulation of the adrenal medulla results in depolarization of the chromaffin cell membrane. Basal levels of adrenal catecholamine secretion are normally low, although major physiologic or psychological stressors can cause large increases in their plasma levels.

13.3 Cortical Tumors (Adenoma-Carcinoma)

13.3.1 Primary Hyperaldosteronism (Conn's Syndrome)

Primary hyperaldosteronism (PHA) is the autonomous aldosterone secretion from one or both adrenal glands and was first described by Jerome Conn in 1954. It is classically manifested as resistant hypertension with hypokalemia, depletion of potassium, retention of sodium, and suppression of plasma/renin activity (PRA). However, the majority of patients may be actually normokalemic [15].

The prevalence of PHA between patients with hypertension was traditionally thought to be around 1 % of the patients with hypertension [16]. The more liberal definition of hyperaldosteronism with the introduction of the concept of normokalemic PHA and the wide application of screening of aldosterone/renin ratio in all hypertensive patients has caused an increase in the prevalence of PHA. Primary hyperaldosteronism usually occurs in individuals between the ages of 30 and 50 years with a mild male predilection.

Most patients are asymptomatic, although those with significant hypokalemia may complain of muscle cramps, weakness, paresthesias, polydipsia, polyuria, nocturia, headaches, and fatigue. Patients typically have moderate to severe hypertension that is refractory to medical therapy.

The most common causes of PHA are unilateral aldosterone-producing adenoma (aldosteronoma) and bilateral adrenal hyperplasia (BAH). Aldosteronoma is present in 30–60 % of cases depending on the pattern of screening (selective versus nonselective) [13]. Adrenocortical carcinoma and glucocorticoid-suppressible hyperaldosteronism are rare, each accounting for less than 1 % of cases [17].

Familial hyperaldosteronism type 1 is a rare autosomal dominant condition which results in abnormal regulation of aldosterone synthesis by ACTH. Patients have a family history of early-onset hypertension, and this condition can be treated medically. Familial hyperaldosteronism type 2 is also a rare condition with autosomal dominant inheritance where patients have autonomous aldosterone hypersecretion, which is not suppressible by dexamethasone. The causes of PHA are shown in Table 13.2 [18].

The ultimate goal of preoperative diagnostic testing is to identify and lateralize aldosteronomas. The first biochemical test performed is to determine the ratio of plasma aldosterone to plasma renin activity. This test is performed after discontinuation of interfering medications such as spironolactone, angiotensin-converting enzyme

Table 13.2 Causes of primary hyperaldosteronism

Etiology	Selective screening	Nonselective screening
Aldosterone-producing adenoma	60 %	30 %
Bilateral adrenal hyperplasia (idiopathic hyperaldosteronism)	35 %	65 %
Aldosterone-producing adrenocortical carcinoma	<1 %	<1 %
Familial hyperaldosteronism		
Type 1 (glucocorticoid-remediable aldosteronism)	<1 %	<1 %
Type 2 (non-glucocorticoid-remediable aldosteronism)	<1 %	<1 %

inhibitors, diuretics, and β-adrenergic blockers. Variable cutoff values have been used in the literature, but a cutoff of 30 yields a sensitivity of approximately 90 % [19]. It is important to note that a positive screening result with A/R ratio is not diagnostic and requires a confirmatory test.

Confirmatory biochemical testing is aimed at demonstrating lack of suppression of aldosterone levels after salt loading. Patients with PHA fail to suppress aldosterone levels with sodium loading. This is done with IV saline loading (2–3 L of isotonic saline given over a 4–6-h period, followed by measurement of plasma aldosterone) or oral salt loading (200 mEq = 5000 mg sodium daily over a 3-day period, followed by measurement of 24-h urine aldosterone excretion) (Fig. 13.1).

Once diagnosis of PHA is confirmed, the next step is to lateralize the source of aldosterone excess production. Anatomic imaging and adrenal venous sampling (AVS) are the initial tests performed, and they help differentiate between adenoma and hyperplasia. Thin-cut (3 mm) adrenal computed tomography (CT) is most accurate for nodules that are larger than 1 cm in diameter [21]. If a solitary adrenal mass 1 cm or greater in size is identified with a normal contralateral adrenal gland and the patient is younger than 40 years old, there is sufficient confidence to proceed to unilateral adrenalectomy surgery [18].

Magnetic resonance imaging (MRI) scans are less sensitive, but more specific, particularly if opposed-phase chemical shift images are obtained. Such scans are very useful whenever CT is contraindicated such as pregnant patients, and in patients who are unable to tolerate intravenous iodine contrast.

New scans currently under evaluation in the armamentarium to lateralize the site of excess aldosterone secretion include 11C-metomidate (MTO), a potent inhibitor of the adrenocortical enzyme 11β-hydroxylase that has been advanced as a positron emission tomography (PET) radiotracer. In a small study, MTO was shown to offer a noninvasive technique to visualize subcentimeter adrenal adenomas and differentiate functional tumors from incidentalomas [22].

In cases where the adrenal CT results are equivocal or the presence of bilateral adrenal nodules is suspected, the next step is to perform AVS, which is 95 % sensitive and 90 % specific in localizing the aldosteronoma in expert hands [2]. This test relies on simultaneous measurement of cortisol, aldosterone, and renin levels in the peripheral circulation, as well as the left and right adrenal veins [13]. Furthermore, cortisol levels are used to correct for differences in dilution secondary to nearby veins, and this has been shown to produce higher accuracy of the test [23].

There are no generally accepted AVS diagnostic cutoffs, largely due to the range of different AVS techniques between centers, and the small number of procedures performed globally. The Endocrine Society guidelines suggest that a cortisol-corrected aldosterone ratio of >4 in the aldosterone to cortisol ratios between the adrenal veins indicates the presence of a unilateral tumor [24]. Ratios between 2 and 3 should be correlated with other clinical, laboratory, and radiographic findings. Aldosterone to cortisol ratios that differ by less than twofold point toward bilateral adrenal hyperplasia if the aldosterone levels are increased bilaterally [23, 25] (Fig. 13.2a). In patients with BAH, AVS allows the identification of the dominant side in case that unilateral adrenalectomy is indicated.

Figure 13.2b shows a CT scan and AVS performed for a patient with a clinical and biochemical diagnosis of PAS to localize the adenoma.

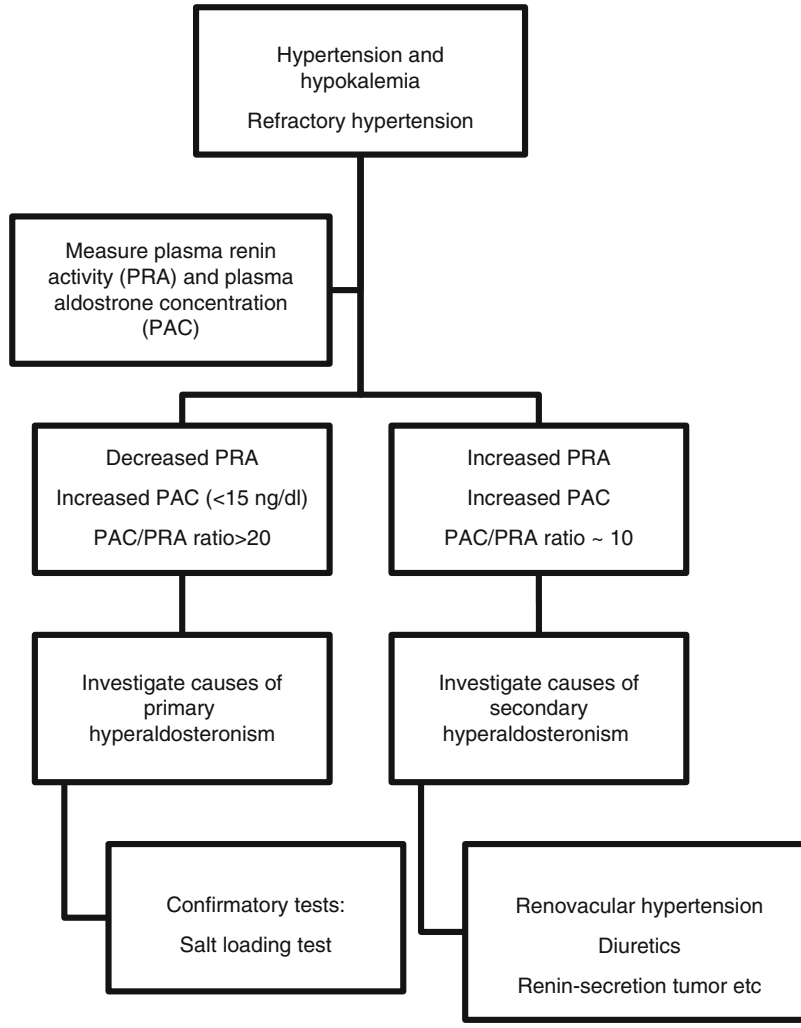

Fig. 13.1 Algorithm for diagnosing aldosteronism with the use of plasma renin activity (*PRA*) and plasma aldosterone concentration (*PAC*) and their ratio (*PAC/PRA*) [20]

AVS	Aldosterone	Cortisol	Adrenal/peripheral vein cortisol ratio	Aldosterone/cortisol ratio
IVC	3820	446		
Left adrenal vein	189400	7470	16.7	25.3
Right adrenal vein	798	482	1	1.6

There is still considerable controversy over which patients should undergo this study as it is an invasive procedure with a 90 % technical success rate in experienced hands [25]. The most common cause for adrenal venous sampling failure to produce valuable results is the failure to cannulate the right adrenal vein due to its very short length (5–8 mm) [26].

Functional scans such as scintigraphy with ^{131}I-6-iodomethyl norcholesterol (NP-59) with dexamethasone suppression have a sensitivity of approximately 90 % [1]. Like cholesterol, this compound is taken up by the adrenal cortex, but unlike cholesterol, it remains in the gland without undergoing further metabolism. Corticosteroids inhibit the uptake of radiolabeled cholesterol by

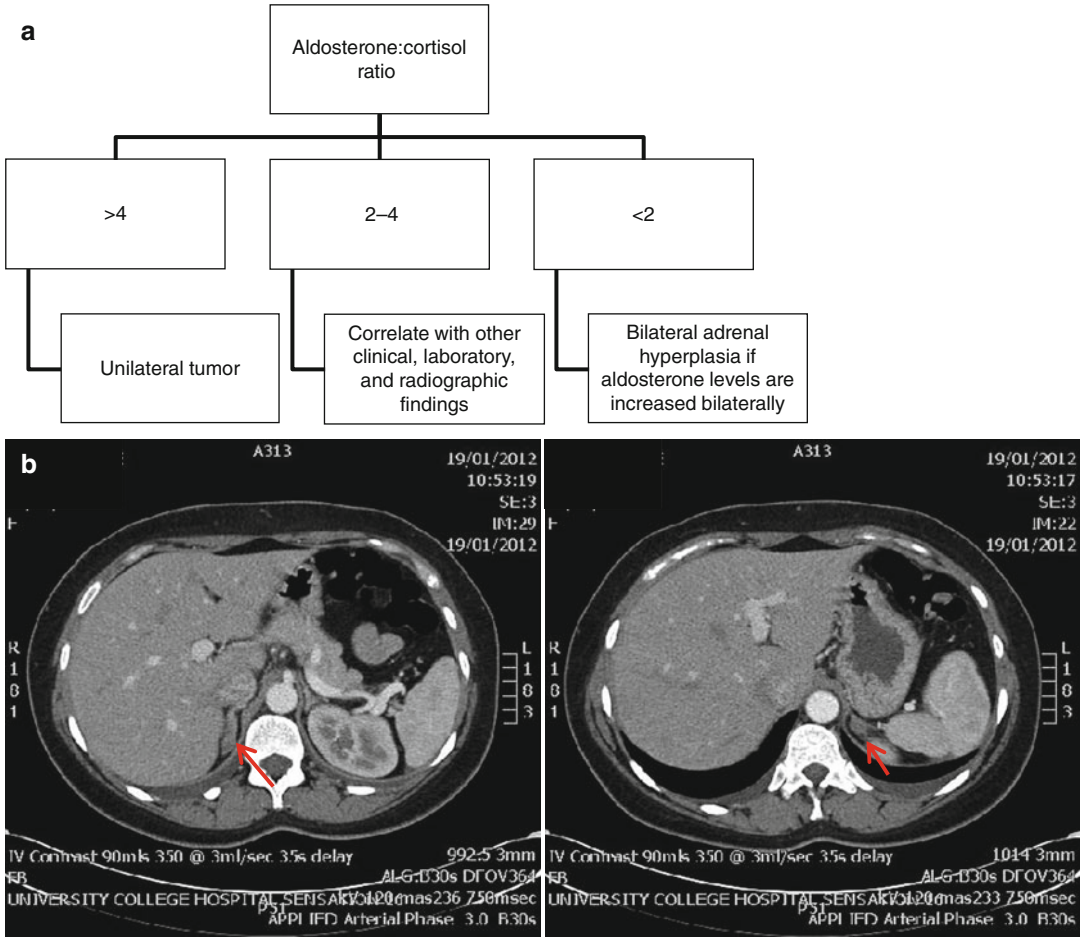

Fig. 13.2 (**a**) Algorithm for the management of adrenal tumors based on adrenal venous sampling results. (**b**) CT scan showed bilateral nodules in the adrenal glands (*Red arrow*) hence the need for AVS. AVS showed adequate cannulation of the left adrenal vein with adrenal/peripheral vein cortisol ratio = 16.7; cannulation of the right adrenal vein was less optimal with adrenal/peripheral vein cortisol ratio = 1. There was a significant aldosterone/cortisol ratio toward the left adrenal vein = 25.3 and the patient had a left laparoscopic adrenalectomy

hyperplastic adrenal glands, and thus dexamethasone increases tracer uptake by aldosterone-producing adenomas thereby improving the sensitivity of their detection. Adrenal adenomas appear as "hot" nodules with suppressed contralateral uptake, whereas hyperplastic glands show bilaterally increased uptake. Disadvantages of NP-59 scanning include higher radiation doses, the need to block the thyroid to prevent radioiodine uptake, and the length of the study, which can take 5–7 days to complete. Functional isotope scanning has largely been abandoned in the UK.

Laparoscopic adrenalectomy (LA) is the treatment of choice for aldosterone-producing adenomas and most other adrenal tumors and has numerous advantages over the conventional open approach, including fewer wound complications, shorter hospitalization, and quicker recovery [27]. Several studies confirmed the superiority of LA over open adrenalectomy (OA), and a recent systematic review largely confined the use of OA for oncological resections in the setting of adrenocortical carcinoma (ACC) [28–31]. Open surgical approaches to the adrenal glands include the posterior, flank, and transabdominal and are usually reserved for large adrenal tumors that harbor a suspicion of adrenocortical carcinoma.

The retro-peritoneoscopic approach evolved as an alternative minimally invasive technique to LA and was popularized by Walz et al. in 2006 [32]. Advantages of this approach include direct access to the adrenal gland without the need for mobilization of intra-abdominal viscera, avoidance of adhesions from previous abdominal surgery, and the ability to perform bilateral adrenalectomy without repositioning the patient. Disadvantages may include the limited working space of the retroperitoneum that can make dissection challenging and limit the size of tumors that can be resected with this technique to less than 6 cm.

Adrenalectomy is greater than 90 % successful in improving hypokalemia and approximately 70 % successful in correcting the hypertension [2]. In patients who continue to be hypertensive in the short term, medications may be added back temporarily as needed until blood pressure gradually reaches a new equilibrium over time.

All patients undergoing adrenalectomy for primary aldosteronism require preoperative medical optimization with control of hypertension and adequate potassium supplementation to keep potassium levels normal. Patients are generally treated with spironolactone (an aldosterone antagonist), amiloride (a potassium-sparing diuretic that blocks sodium channels in the distal nephron), nifedipine (a calcium channel blocker), or captopril (an ACE inhibitor).

13.3.2 Cushing's Syndrome

Cushing's syndrome is a constellation of diseases encompassing obesity, diabetes, arterial hypertension, muscular weakness, and adrenal hyperplasia. It was described by Harvey Cushing in 1932, and the term syndrome includes all hypercortisolism states; one of the most frequent causes of this syndrome is the homonymous disease, Cushing's disease, which is caused by an excess production of pituitary adrenocorticotropic hormone (ACTH) from microadenoma of the adrenal gland [18].

There is a strong female-to-male predilection with the female-to-male ratio in Cushing's syndrome ranging from 3 to 15:1, and the prevalence of Cushing's disease is about 39/million people [33, 34].

Table 13.3 Causes of Cushing's syndrome

Causes	Proportion (%)
ACTH dependent	**80–85**
Cushing's disease	70
Non-adrenal ACTH syndrome	10
Other source of ACTH	5
ACTH independent	**15–20**
Adrenal adenoma	10
Adrenal carcinoma	5
Macronodular adrenal hyperplasia	<2
Primary pigmented nodular adrenal disease	<2
McCune-Albright syndrome	<2

The causes of Cushing's syndrome have been traditionally classified as ACTH-dependent Cushing's syndrome, ACTH-independent Cushing's syndrome, and pseudo-Cushing's syndrome (Table 13.3). The most common cause of Cushing's syndrome (85 % of cases) is excessive production of ACTH, mainly due to autonomous pituitary adenomas. Non-adrenal (ectopic) secretion of ACTH from tumors of the lung, thymus, or pancreas constitutes about 10 % of the ACTH-dependent Cushing's syndromes [34]. ACTH-independent Cushing's syndrome can be due to an adrenal adenoma, carcinoma, or nodular adrenal hyperplasia. Finally, pseudo-Cushing's syndrome is caused by major depressive disorders or alcoholism.

The most common clinical manifestations of Cushing's syndrome are round facies, "buffalo hump" caused by increased fat in the dorsal neck, thin skin, hirsutism, easy bruisability, purple striae, depression, osteoporosis, hypertension, and glucose intolerance [1].

Laboratory investigations used to confirm the diagnosis include:

- 24-h urine collection for measurement of free cortisol
- Overnight 1-mg dexamethasone suppression test which is performed by administration of 1 mg of dexamethasone at 11 pm and determination of a fasting plasma cortisol level between 8 and 9 am the following day [18]

- Late-night salivary cortisol test
- Low-dose dexamethasone suppression test (either as 1 mg p.o. before bedtime or as 0.5 mg p.o. every 6 h for 48 h) [18]

The finding of a raised 24-h urine free cortisol level or a failure to suppress plasma cortisol by dexamethasone signifies loss of physiologic negative feedback and is suggestive of Cushing's syndrome with 95 % accuracy.

The next step is to distinguish between ACTH-dependent and ACTH-independent disease. ACTH-independent Cushing's syndrome is caused by autonomous adrenal cortisol production and is associated with an undetectable ACTH level (<5 pg/mL). The underlying pathology is variable, with a solitary adrenal adenoma found in approximately 90 % of cases, adrenocortical carcinoma in less than 10 %, and bilateral micronodular or macronodular hyperplasia in less than 1 % [35]. Computed tomography with thin sections (3–5 mm) can distinguish between a unilateral adenoma, carcinoma, or bilateral symmetric or asymmetric hyperplasia. Carcinomas tend to be larger than adenomas (>5 cm), inhomogeneous, with an irregular border [1]. Distinguishing adenoma from carcinoma in large tumors can be aided by magnetic resonance imaging. Carcinomas appear brighter than the liver on T2-weighted images.

Hyper-cortisolemia associated with normal or elevated ACTH levels points to ACTH-dependent Cushing's syndrome, which is most commonly caused by a pituitary corticotroph microadenoma (Cushing's disease) [34]. Computed tomography (CT) imaging or magnetic resonance imaging (MRI) of the pituitary gland and a high-dose dexamethasone suppression testing (serum or urine cortisol measurement after the administration of 2 mg of dexamethasone every 6 h over a 48-h period) will confirm Cushing's disease. Corticotroph adenomas will be suppressed in response to high-dose dexamethasone administration, whereas ectopic ACTH sources are completely lacking in feedback inhibition. In case where a clear-cut pituitary tumor is not demonstrable in CT/MRI, bilateral inferior petrosal sinus ACTH sampling with CRF stimulation is used. Other tests to localize an ectopic ACTH source include CT imaging of the chest/abdomen and occasionally somatostatin receptor scintigraphy [2].

The treatment of Cushing's syndrome depends on the subtype causing the hypercortisolism; Cushing's disease requires surgery of the pituitary gland, while adrenal and ectopic tumors call for surgical removal of the adrenal gland and the ectopic tumor, respectively. Adrenalectomy has been shown to be more than 90 % effective in the treatment of primary adrenal Cushing's syndrome [34]. Pituitary microsurgery for Cushing's disease, typically performed via a trans-nasal transsphenoidal approach, is approximately 75 % successful in experienced hands. In case of a failed operation, pituitary irradiation can help in providing remission of the disease. Laparoscopic bilateral adrenalectomy can be considered for patients in whom pituitary surgery has failed, and the disease symptoms are not controlled [18].

Perioperative and postoperative glucocorticoid administration is a critical part of the care of patients with Cushing's syndrome. All adrenalectomy patients for Cushing's syndrome should receive a perioperative dose of hydrocortisone (100 mg i.v. every 8 h for 24 h) [34]. Whenever adrenalectomy is performed for a solitary adenoma, hydrocortisone can usually be tapered to physiologic replacement levels over the course of several weeks. It must be noted that a subset of patients with Cushing's syndrome might have significant HPA axis suppression depending on the duration and the duration of the underlying disease. These patients might require glucocorticoid supplementation for a longer period than usual. Perioperative antibiotics as a single dose or for 24 h to patients undergoing adrenalectomy for Cushing's syndrome can be administered due to their elevated risk for surgical site infection.

13.3.3 Adrenocortical Cancer (ACC)

Cancers of the adrenal gland are rare constituting only 0.05–0.2 % of all cancer deaths [36]. Adrenocortical cancer (ACC) has a bimodal age distribution with the first peak prior to age 5 and

the second peak between the ages of 40 and 50 with no significant gender predilection [37]. Even though many of these tumors are functionally active and secrete steroid hormones, they usually present in an advanced stage, and as a result their prognosis is poor.

Those patients who present before the age of 5 usually do so with virilization symptomatology (>90 %) [38]. In general, men tend to present at an older age. Functional cancers are found more frequently in women, and nonfunctional cancers occur more frequently in men [39].

The exact etiology of these tumors is unknown. There is one rare inherited disorder associated with adrenal cancer, the *Li-Fraumeni* syndrome which is secondary to an inherited mutation in the P53 tumor suppressor gene. This syndrome consists of ACC, breast cancer, osteosarcoma, and/or brain tumor.

The adrenal cortex produces a variety of steroid hormones, and as a result, ACCs frequently produce a similar variety of hormonally active substances, albeit less active than the native hormones. Hormonal symptoms include progressive weight gain, consistent with hypercortisolism, feminization, virilism, or menstrual irregularities, seen in patients with hypercortisolism or excess sex steroid hormone production; weakness; fatigue; and mental status changes, which can be seen with hypercortisolism and hyperaldosteronism [1]. Isolated secretion of mineralocorticoids is rarely seen in patients with ACC.

The other mode of appearance of an ACC is because of tumor size, local invasion, or distant metastasis. Most adrenal cancers are greater than 6 cm when they are diagnosed. These tumor size-related symptoms include abdominal pain or pressure, weight loss, hematuria, left varicocele, dyspnea, or altered gastrointestinal function.

In the absence of metastatic disease or local invasion, the histological diagnosis of ACC remains challenging as many histological features are common in both ACC and benign cortical tumors. A number of histological features are useful in assessing malignant potential in adrenal cortical tumors, and both the Weiss system and modified Weiss system are used in routine practice [40].

Laboratory findings include elevated urinary levels of DHEA in the majority of patients. DHEA has minimal direct biologic activity, but is converted into active androgens in the periphery. Elevated plasma and urinary levels of cortisol are frequently seen. Elevated urinary levels of 17-ketosteroids, the breakdown product of both cortisol and androgens, can be found as well. It is rare to find elevated levels of aldosterone alone in ACCs. It is more common to find a mixed hormonal profile. Those tumors that have no hormonal activity usually present at a later, more advanced stage are usually less differentiated and have a poor prognosis.

Cross-sectional imaging is the most useful radiographic test in the evaluation and diagnosis of adrenocortical cancer. Most patients undergo contrast-enhanced CT scans as they are superior to non-contrast-enhanced scans in regard to addressing issues of invasion or metastases. Invasion of surrounding structures including the ipsilateral kidney, diaphragm, liver, or major blood vessels, if present, indicates the malignant nature of the mass as well as its potential for resection (Fig. 13.3).

The University College London Hospital protocol for histological assessment of cortical adrenal tumors is shown in Table 13.4. Both Weiss and modified Weiss systems are independently validated, and a score of 3 or more in either system indicates malignant potential.

Magnetic resonance imaging (MRI) improves adrenal imaging through the specific tissue characteristics of adrenal tissue on T1- and T2-weighted images. Adrenal tissue appears darker than surrounding adipose tissue on both T1 and T2 images. Although MRI offers information to help tissue-specific diagnosis among adrenal lesions, it is also limited in differentiating benign from malignant masses [34].

Overall, 5-year survival rates are approximately 25–30 %, and 10-year survival rates are around 10 %. Approximately, 70 % of patients present with stage III or IV disease [37, 41].

Treatment of ACC is radical open surgery in an effort to achieve cure. Unfortunately, because of the late diagnosis in many patients, many of these tumors have already metastasized (stage IV) or

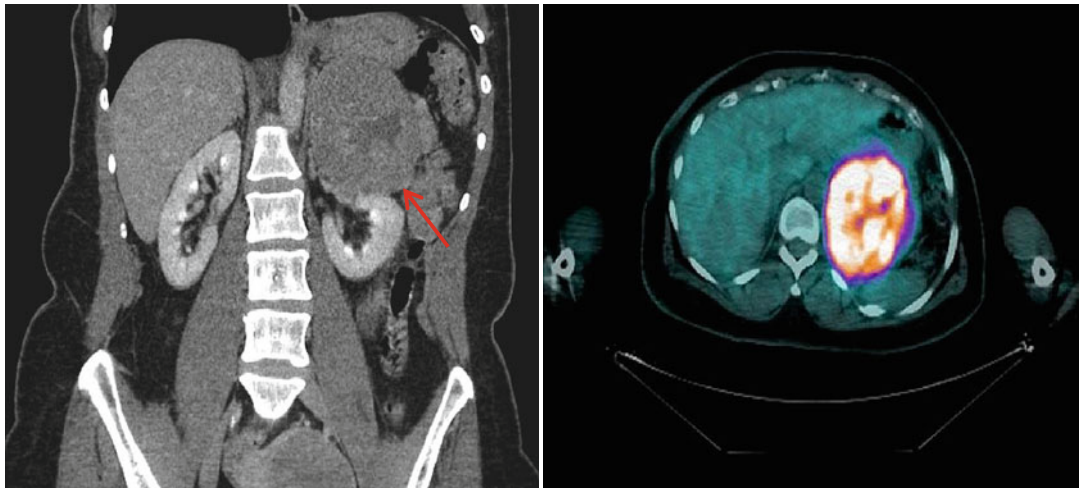

Fig. 13.3 A 49-year-old lady with an axial CT scan (*left*) showing a large 8.7×8.6 enhancing solid mass (*arrow*) arising from the left adrenal compressing the upper pole of the left kidney and stretching out the tail of the pancreas. A FDG whole-body PET/CT shows an intense uptake in the left suprarenal mass suspicious for malignancy

Table 13.4 Weiss and modified Weiss systems

Clear cells comprise <25 % of the tumor	1	2
Diffuse architecture in >1/3 tumor	1	–
Confluent necrosis	1	1
High nuclear grade (Fuhrman grade 3 or 4)	1	–
Mitotic rate >5/50HPF	1	2
Atypical mitoses	1	1
Venous invasion	0	–
Sinusoidal invasion	0	–
Capsular invasion	0	0
Total score	6	6

have invaded nearby structures (stage III), making complete resection impossible. If the patient has advanced local disease but no evidence of metastases, en bloc resection of invaded structures should still be undertaken, if it can be done safely, as resection of even advanced local disease can be curative [41].

Preoperative accurate evaluation of the extent of the disease is paramount. The function of the contralateral kidney should also be assessed since it is not infrequent for the tumor to require en bloc resection with the ipsilateral kidney. The abdominal CT scan can demonstrate if there is direct invasion of surrounding structures and if there is tumor thrombus in the IVC. Needle biopsy to confirm the diagnosis of adrenocortical cancer should not be done as there is always a risk of seeding the tumor through the needle tract.

In the case of ACC, the open approach is advocated over the laparoscopic or the retroperitoneoscopic one. Laparoscopy does not allow the adequacy of exposure, the completeness of lymph node dissection, and the necessary en bloc resection that make complete surgical excision possible [37, 41]. Furthermore, the question of port site recurrence remains real with laparoscopic adrenalectomy.

For much the same reasons that LA is not advocated, the posterior approach is also not a good alternative for the patient with a suspected ACC. The abdomen cannot be adequately evaluated, resection of contiguous structures is difficult, and complete surgical excision is usually not attainable. This approach has limited exposure and makes removal of lesions larger than 5–6 cm technically difficult. It is the authors' opinion that all adrenal cortical tumors larger than 8 cm should be resected via an open approach even in the absence of confirmatory evidence of ACC. This is due to the high incidence of ACC in this cohort of patients and a higher risk of recurrence when these tumors were resected laparoscopically [42].

Open adrenalectomy can be performed via a transabdominal, flank, or thoracoabdominal

approach. All of them are potentially acceptable methods based on location and size of the tumor, invasion of surrounding structures, the patient's body habitus, and finally surgeon preference. If there is direct extension into the kidney, pancreas, spleen, liver, or diaphragm, en bloc resection should still be undertaken, if possible, with either partial or total removal of the involved structure.

The role of adjuvant chemo- or radiation therapy (RT) after complete resection remains undetermined to date [2]. Mitotane (o,p'-DDD) has been used clinically both as an adjuvant to surgery and as primary therapy in individuals with unresectable or metastatic disease [1]. Mitotane inhibits corticoid biosynthesis and causes mitochondrial and cell death [43]. Conventional cytotoxic chemotherapy and external RT is also unclear even in the incompletely resected patient. The main thrust of postoperative management is close follow-up. Common sites of recurrence include the lungs, liver, and adrenal bed. Annual chest X-ray, abdominal CT scan, and urinary steroid hormone measurement should be performed since complete resection of isolated recurrences may lead to long-term survival.

Palliative treatment of the patient with unresectable/metastatic disease is frequently directed at symptom control with mitotane being one of the few effective chemotherapeutic agents for patients with advanced ACC [44]. Doxorubicin and newer agents such as suramin have been used with variable success. The main role of RT is symptomatic relief of bone metastases.

13.4 Pheochromocytoma

Pheochromocytoma is a rare catecholamine-producing tumor. It is often overlooked as a cause of hypertension, resulting in high mortality due to uncontrolled release of catecholamines into the circulation. Early diagnosis and appropriate management are key elements in diffusing this pharmacological time bomb [45].

Pheochromocytoma is embryologically derived from the neuroectoderm. It may arise from the chromaffin cells within the adrenal gland medulla in 80–85 % (pheochromocytoma) or an extra-adrenal site in 15–20 % (paraganglioma). Paragangliomas are located along the paraaortic sympathetic trunk in the neck, mediastinum, or abdomen, in addition to the organ of Zuckerkandl and the urinary bladder. They are more common in children and carry a higher malignant potential [34, 46]. Pheochromocytoma is genetically linked to multiple endocrine neoplasia type 2 (MEN2), neurocutaneous syndromes, especially von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF 1), and the familial paraganglioma syndrome [47, 48].

The tumors are usually composed of small (Zellballen) nests of large pink cells (alveolar/nesting pattern). There is little intervening stroma between tumor cell nests that contains delicate vasculature. They also stain positive for chromogranin A and S-100 which stains the sustentacular cells (black arrows) (Fig. 13.4).

Pheochromocytoma affects approximately 0.2 % of hypertensive individuals [18]. The occurrence is much higher in NF 1 and VHL, 2 and 20 % of such patients, respectively [49, 50]. Almost 40 % of patients with MEN2 can present with a pheochromocytoma [51]. Males and females are affected equally and can occur at any age. Sporadic tumors are more common in the third and fourth decades of life, whereas familial cases tend to be manifested earlier.

A subset of patients has the classic triad of headache, diaphoresis, and palpitations, although almost all patients will display at least one of these symptoms. Hypertension is present in 90 % of cases and may be episodic or sustained. The principal challenge in making the diagnosis of pheochromocytoma arises from the fact that essential hypertension is common and the clinical features suggestive of pheochromocytoma are nonspecific. In fact, only 0.5 % of patients with hypertension and suggestive features will ultimately prove to have the disease.

The measurement of plasma free metanephrines and normetanephrines has the highest sensitivity (97–100 %) and specificity (85–89 %) and appears to be the best initial test for screening patients for pheochromocytoma. A 24-h urine total metanephrines level above 1800 mg in the appropriate clinical setting is almost always diagnostic,

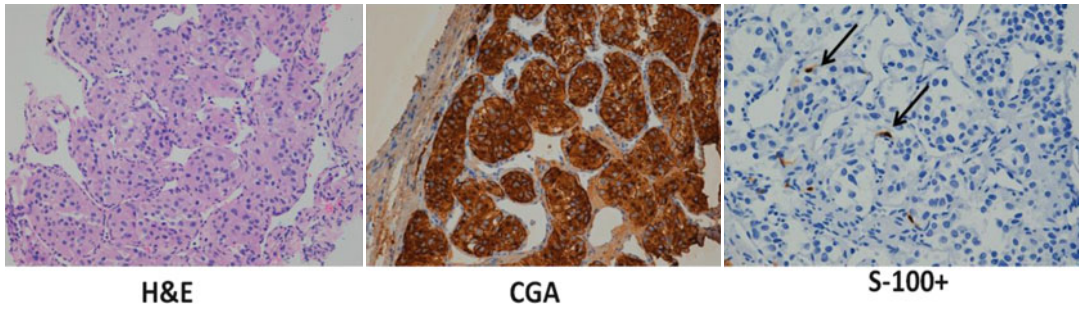

Fig. 13.4 Histopathologic features of paragangliomas and pheochromocytomas. These tumors also stain positive for chromogranin A and S-100 which stains the sustentacular cells (*black arrows*)

and a plasma metanephrines level exceeding 3–4 times normal is highly diagnostic for a pheochromocytoma.

Due to its association with certain familial syndromes, pheochromocytoma patients diagnosed at a young age or with multifocal or extra-adrenal disease should be screened with genetic testing for the VHL gene mutation, mutations in the RET gene, and subunits of the succinate dehydrogenase (SDH) genes. The classical concept of a 10 % rule defining the genetic predisposition of this disease has been valued for several decades; however, since the discovery of the SDH-D mutation in 2000, the 10 % rule has fallen out of practice. Since 2009, at least one new pheochromocytoma/paraganglioma gene has been discovered every year. The current concept is that almost 40 % of patients with pheochromocytoma/paraganglioma have a predisposing genetic mutation [52].

The localization of these adrenal tumors employs the usual cross-sectional techniques such as CT or MRI. The sensitivity of CT scanning with contrast ranges between 85 and 95 %, with a specificity of 70–100 %, while the sensitivity of MRI exceeds 95 %, with a specificity of 100 % [20]. MRI is superior to CT in terms of providing functional confirmation apart from defining anatomic detail and assessing the liver and the retroperitoneum as well as its advantage in pregnant patients. Pheochromocytomas demonstrate a bright enhancement on T2-weighted images [53].

^{123}I-metaiodobenzylguanidine (MIBG) (Fig. 13.5) is used complimentary to CT and MRI as it is taken up and concentrated in the pheochromocytomas, paragangliomas, and any potential metastases, with 80–90 % sensitivity but lower specificity with false-negative results frequently reported especially with paragangliomas, possibly due to a higher SDH-B mutation association [54]. Functional scanning may also be performed with ^{111}indium-labeled pentetreotide (Octreoscan™) or ^{68}Ga-DOTATATE PET/CT especially in patients with paragangliomas and/or suspected to have malignant metastatic disease [55]. Other imaging modalities include the arteriography and the selective venous catheterization which are historical and should not be performed.

The preoperative management of pheochromocytoma patients is focused on minimizing the risk of a hypertensive crisis during surgery. As such, α-adrenergic blockade begins 1–3 weeks preoperatively in order to avoid profoundly unstable blood pressure during surgery. The most commonly used α-adrenergic antagonist is phenoxybenzamine at a dose of 10 mg twice daily, and the dosage is titrated upward to as much as 300–400 mg daily in divided doses until the patient becomes normotensive and the hypertension is well controlled. Alpha-methyltyrosine (metyrosine), whose role is to inhibit tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis, has also been used in combination with phenoxybenzamine. Other selective α_1-blocking agents such as prazosin or doxazosin can be used instead of phenoxybenzamine.

Patients sometimes also require β-adrenergic blockade preoperatively. The indications for

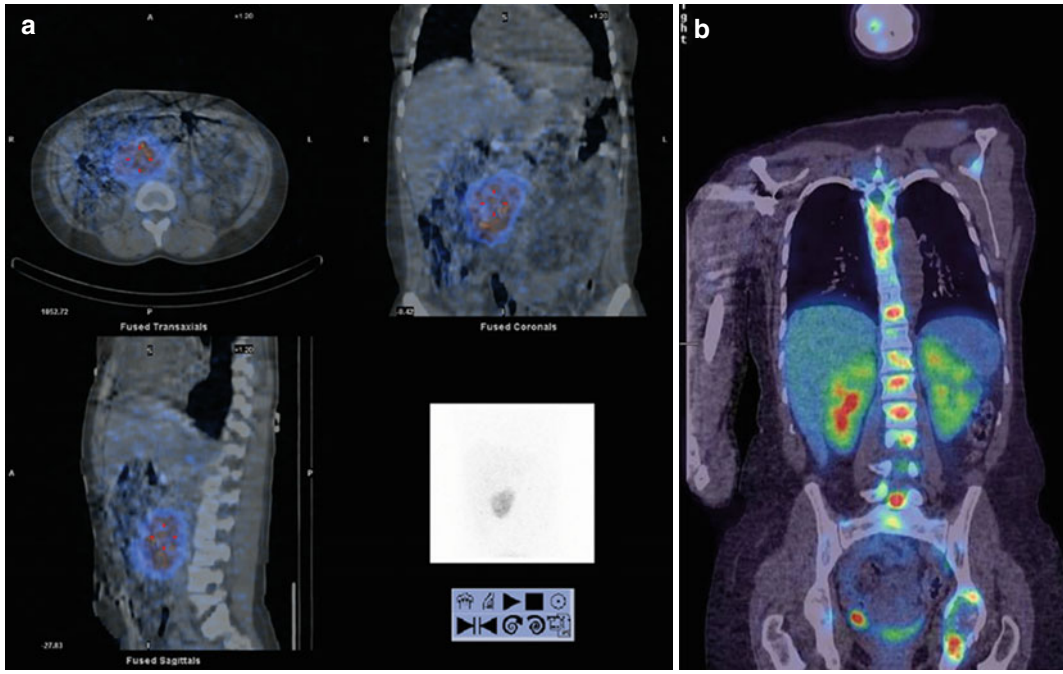

Fig. 13.5 ^{123}I-metaiodobenzylguanidine scan SPECT/CT combining functional and anatomical information in this patient with a large paraganglioma which is helpful in preoperative planning (**a**). 18 F-FDG-PET scan of a patient with metastatic bone disease several years after primary pheochromocytoma resection (**b**)

β-adrenergic blockade (needs to be administered following adequate α-adrenergic blockade) include persistent tachycardia, extrasystoles, or arrhythmias. Propranolol is the most common agent used and is administered in dosages of 10–40 mg every 6–8 h [20].

Patients with pheochromocytomas require close intraoperative monitoring as they are at risk of drastic fluctuations in blood pressure during induction of anesthesia, intubation, or operative dissection of the tumor. As a result, such cases should be undertaken by an experienced anesthesiologist familiar with the particularities of these patients.

The advance of minimally invasive techniques and the increased experience in operating on such cases has allowed laparoscopic adrenalectomy to be the standard of care unless malignancy is suspected [1]. There is still considerable debate regarding MEN2a cases and other familial syndromes, and the decision on the surgical approach should be weighed and tailored to the individual. The transabdominal approach is still the gold standard. Open surgery should strongly be encouraged in large pheochromocytomas or in any paragangliomas due to the difficulty in dissection of these tumors owing to their proximity to major abdominal vascular structures, as well as having a higher malignant potential.

The diagnosis of malignancy in pheochromocytoma patients can prove to be difficult if not impossible on a purely clinical or histopathological basis, and thus long-term follow-up for all pheochromocytoma patients is recommended. The survival rate after the diagnosis of metastatic pheochromocytoma is typically less than 3 years, and the overall 5-year survival rate is approximately 44 % [1].

13.5 Incidentaloma

The incidental finding of an adrenal mass (incidentaloma) occurs in approximately 1 % of patients that have cross-sectional imaging of their abdomen for any reason. Many of these

Table 13.5 The differential diagnosis of incidentally discovered adrenal masses

Causes of incidentalomas	
Functional	Nonfunctional
Adenoma	Myelolipoma
Nodular hyperplasia	Hematoma
Carcinoma	Cyst
Pheochromocytoma	Neurofibroma
Ganglioneuroma	Hamartoma
Ganglioneuroblastoma	Hemangioma
	Teratoma
	Metastases from the breast, lung
	Lymphoma
	Leukemia
	Infections (tuberculosis, fungal, etc.)

masses will be nonfunctioning; thus, a careful strategy is needed to identify the patients that need further investigations and possibly surgical intervention. Only a small percentage of these incidentalomas will prove to be malignant (5 %), and an even less percentage of these are metastases from an occult primary tumor [56]. A significant number will be metastases from a known primary tumor, around 30 % are benign cortical adenomas, and only 5 % are pheochromocytomas (Table 13.5).

The diagnostic work-up for incidentalomas aims to exclude pathologies such as pheochromocytoma, Conn's, and Cushing's syndrome. The relevant tests for each of these pathologies should be employed as described previously. Evidence of androgen secretion is investigated by measuring serum testosterone and dehydroepiandrosterone sulfate levels. In case where the adrenal mass is biochemically proven to be nonfunctioning from an endocrine point of view, further testing is required to identify the cause of the enlarged gland.

Noninvasive tests such as CT and MRI are used alone or in combination with each other. Functional adrenal imaging studies such as MIBG, FDG, and NP-59 may lack the anatomic and structural detail of CT and MRI but exhibit a high specificity and sensitivity for characterizing incidentalomas. Combinations of these scans such as 2-deoxy-2[18f] fluoro-D-glucose positron emission tomography scan (18F-FDG-PET) are used for confirming isolated metastases and to select patients for adrenalectomy [57].

It is important to remember that the actual dimensions of the adrenal masses are usually underestimated when calculated directly in CT scans. The percentage of underestimation varies greatly between 16 and 47 %. To address this, a formula that corrects for the true histological size has been previously proposed and is known as "Linos formula" [58]:

$$\text{Histological size} = 0.85 + \left(1.09 \times \text{CT size}\right)$$

Fine-needle aspiration biopsy (FNAB) or core biopsy is used in cases where there is a past medical history of malignancy in an effort to correlate findings with the original primary tumor. However, FNA can't differentiate between cortical adenoma and carcinoma as the invasion of the capsule can't be assessed [57]. The risk of tumor seeding in the retroperitoneum should always be taken into account. Furthermore there is always the risk that the mass harbors a pheochromocytoma that when punctured by the FNA can result in a hypertensive crisis.

The management of incidentalomas depends on the size of the tumor and on whether the mass is functioning or not. Small (<3 cm), nonfunctioning, adenomas that have radiological features that are consistent with a benign disease can be managed by a watch and wait approach with annual follow-ups with serial CT scans [59]. Patients at the same time need to be asymptomatic and there should be no suspicion of adrenal carcinoma.

Adrenalectomy is recommended when there is laboratory evidence of a functioning tumor and when clinical and radiological evidence of primary or solitary metastatic adrenal carcinoma.

Incidentalomas that are over 3.5 cm in size carry a higher risk of malignancy and should be considered candidates for surgical excision [60]. Adrenalectomy is also advocated in cases where incidentalomas show size progression between follow-ups.

13.6 Bilateral Adrenalectomy

In the event that bilateral adrenalectomy as a one-stage or two-stage procedure is needed, it will have serious consequences on the quality of life as it will result in permanent adrenal failure. Thus the patient will require both glucocorticoid and mineralocorticoid replacement to avert Addisonian crisis. Such procedures are performed for the treatment of pituitary ACTH-dependent Cushing's syndrome.

A special condition can occur following bilateral adrenalectomy after previous pituitary surgery called Nelson's syndrome. In these cases, the ACTH-secreting tumor enlarges and secretes large quantities of ACTH due to the lack of negative feedback mechanism. Clinically, it manifests with hyperpigmentation and mass effects on the pituitary as the tumor enlarges in size. To avoid such issues, radiotherapy to the pituitary is given [61].

13.6.1 Technical Aspects of Adrenalectomy

Open adrenalectomy (OA) techniques have been the standard approach to all adrenal pathologies for decades. It allowed approaching the adrenal gland via a multitude of ways including the open anterior transperitoneal approach and the lateral retroperitoneal approach with various modifications of each. However, OA has been associated with complication rates of up to 54 % and high incisional hernia rates, significant postoperative pain, and lengths of hospital stay of over 1 week [29, 62, 63].

Michel Gagner, in 1992, introduced the laparoscopic approach to the adrenal, and shortly after that numerous other surgeons published their experience in this new technique validating its superiority over the OA [29, 62–64]. A recent systematic review confined the use of open adrenalectomy almost exclusively for oncological resections in the setting of adrenocortical carcinoma (ACC) [28–31].

Perhaps the greatest controversy up to now remains the use of the laparoscopic approach for suspected adrenocortical carcinoma. Studies have confirmed the technical feasibility of LA for larger tumors suspected of being malignant, but there appears to be an association with higher locoregional recurrence rates and shorter disease-free survival [65–67]. More specifically, recurrence in the resection bed as well as peritoneal carcinomatosis was more frequently encountered in the LA group suggesting capsular breaching during dissection and port site seeding as potential causes of the poorer outcomes seen with laparoscopy. Conversely, other recent multicenter studies have found comparable oncological outcomes between LA and OA [68, 69].

All studies however suffer from biases introduced by their retrospective data collection, and the difference in outcomes observed between studies may be explained, in part, by factoring in surgical experience both in LA and oncological ACC resections. It is probably safe to say that until a definitive verdict on LA in ACC can be reached, OA may be regarded as the optimal approach to very large, potentially malignant cortical adrenal tumors and should be performed in specialized high-volume centers with multidisciplinary expertise [70].

Laparoscopic adrenalectomy may be performed via an "anterior" approach with the patient in the supine position or more commonly via an "anterolateral" approach with the patient in the lateral decubitus position as originally described by Gagner et al. [64]. The latter utilizes gravity to assist mobilization of intra-abdominal organs with the side of the adrenal gland to be excised facing upward. Support at pressure points is crucial, and the break in the operating table is positioned just distal to the costal margin to maximize the access. The patient's arms are positioned on armrests, and care is taken to avoid hyperextension at the shoulder to avoid excessive traction on the brachial plexus. Suction beanbags may be used to maintain optimal patient position at all times during the operation with the support of bandage strapping.

Right-sided laparoscopic adrenalectomy is performed using three to four ports 2 cm below and parallel to the costal margin (two 10 mm-sized medial ports and two 5 mm-sized lateral ports) [71]. A 0° or 30° angled camera is used

and the right lobe of the liver is elevated using a fan or triangular articulating retractor. The right lobe of the liver is mobilized, and any attachments of the retroperitoneal fascia to the undersurface of the liver are divided to allow access to the upper pole of the adrenal gland and exposure of the inferior vena cava. This is especially crucial in the case of larger tumors and is one of the steps that defined successful excision of the adrenal gland laparoscopically. This dissection may be performed with hook diathermy, harmonic shears, or an advanced bipolar tissue-sealing device. The use of graspers is avoided and caudal retraction away from the liver is maintained with laparoscopic mounted cotton swabs. Once adequate liver mobilization is achieved, dissection proceeds in a craniocaudal fashion medially to identify the lateral border of the inferior vena cava and adrenal vein. The adrenal vein is skeletonized and ligated with a laparoscopic clip applicator. The adrenal gland is dissected away from the renal hilum, and numerous arterial branches that may be encountered may be safely ligated with the electrothermal bipolar tissue-sealing device and harmonic shears or clipped. Handling of the adrenal gland with graspers should be avoided given its friability. Once the gland has been mobilized away from the upper pole of the kidney, dissection is completed from the medial to the point of attachment of the adrenal gland laterally. The specimen is retrieved with the use of a laparoscopic retrieval bag and may be morcellated if the nodule is too big to be extracted intact.

Left-sided laparoscopic adrenalectomy is performed utilizing three ports (two 10 mm-size and one 5 mm-sized ports). The key to the adrenal access lies with the medialization of the spleen and pancreatic tail. The splenic flexure of the colon is mobilized caudally and the spleen and pancreatic tail medially using a combination of hook diathermy and an electrothermal bipolar tissue-sealing device. The lienorenal ligament is divided and the diaphragmatic attachments of the spleen are freed and the retroperitoneal space is entered. Dissection of the adrenal gland is identical to the right side although the adrenal vein is longer. An accessory adrenal vein is nearly always present, and other anatomical variants of the adrenal vein should be borne in mind.

Another modification of the classic laparoscopic approach employing multiple ports is the insertion of the surgical instruments through a single port. Several techniques have been described that utilize a lateral or anterior approach transperitoneally through a single multichannel port inserted through a 2–3 cm incision either through the umbilicus or in a subcostal position.

Gaur suggested an alternative minimally invasive approach – that of the retro-peritoneoscopic adrenalectomy (RA) that was later refined and popularized by Walz et al. [32] and is now also used in some specialized endocrine surgery centers worldwide [27, 32, 72].

In line with other surgical specialties, robotic adrenalectomy using the daVinci surgical system (Intuitive Surgical, Mountain View, CA, USA) has been introduced with its advocates suggesting advantages over the other minimally invasive approaches, including a three-dimensional working environment, elimination of fatigue, and articulating instruments. The steps of the procedure mimic those of a laparoscopic or retro-peritoneoscopic adrenalectomy with the robotic arms docked in position over the patient and the surgeon performing the operation remotely via the robotic console.

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Pancreatic Neuroendocrine Tumors

14

Mahmoud Sakr

14.1 Introduction

Pancreatic neuroendocrine tumors (P-NETs) are rare tumors having an incidence ranging between 4 and 12 per million of population [1]. They are usually grouped based on malignancy versus benignity, cell of origin, and functional status. On account of malignancy versus benignity, histopathology cannot reliably differentiate between both categories. Distinction is based on demonstrating invasion of nearby organs, nodal, or distant metastasis, undoubtedly marking the tumor as "malignant" [2]. Neuroendocrine carcinomas are exceedingly rare with their incidence accounting for only 1.3 % of pancreatic cancers collectively. However, having a better outcome, they represent up to 10 % of prevalent pancreatic cancers [3].

Regarding the cell of origin, an evident controversy exists. It is well known that islets of Langerhans, which constitute the endocrine pancreas of the adult human, contain only four types of cell, namely, alpha, beta, delta, and PP cells secreting glucagon, insulin, somatostatin, and pancreatic polypeptide, respectively. It is to be noted that gastrin, which is commonly secreted from P-NETs, and vasoactive intestinal peptide (VIP) are not normally secreted by adult endocrine pancreas. In addition, Regitnig and colleagues [4] reported a biochemically confirmed insulinoma with liver metastasis showing cytokeratin-positive ductular differentiation. Such facts have raised doubt on whether Langerhans islets are the origin of these tumors. On the other hand, it has been suggested that endocrine and exocrine lineages develop from common progenitors in the foregut endoderm [5]. The aforementioned facts support the current belief that these tumors – though frequently described as islet cell tumors – originate from multipotent stem cells in the ductal epithelium [2].

Regarding the functional status, functionality is defined as "clinically manifest endocrinopathy related to hormone overproduction by these tumors" [6]. Based on this definition, functional P-NETs include insulinomas, which are the most common of these, closely followed by gastrinomas, while the remainder represents a subset of P-NETS called rare functional P-NETS or RFTs and include VIPoma, glucagonoma, somatostatinoma, and rare others [7]. It is worthy to note that though the tumors are tagged as "pancreatic," considerable proportion of them occurs in extrapancreatic locations. Several other peptides may be overproduced by P-NETs, yet not producing clinical syndromes, hence should be described as nonfunctional P-NETs or NF-PNETs.

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14.2 Insulinoma

14.2.1 Historical and Epidemiological Aspects

The first case of malignant insulinoma was reported in a surgeon who was complaining of episodic unconsciousness for which he underwent an exploratory laparotomy by William Mayo in 1972 and then died 1 month later [8]. The first surgical cure of insulinoma was subsequently reported by Howland in 1929 [9]. Insulinoma occurs at an annual incidence of 0.7–4/million of population rendering it the most common functional P-NET [10] and the second most common functional P-NET in MEN1 [11], constituting 20 % of pancreatic islet cell tumors occurring in association with MEN1 [12], which make up to 7 % of cases of insulinoma while the remaining majority of cases are sporadic [13]. Their importance comes primarily from their bizarre presentations and complex management which frequently bewilder surgeons.

14.2.2 Genetic Basis

Several genetic alterations may be associated with insulinomas. MEN1 gene – located on chromosome 11q13 and encoding the protein menin – is mutated, not only in the majority of MEN1-associated insulinomas but also in some sporadic cases. In addition mutations of tumor suppressor genes VHL (von Hippel-Lindau) and TS (tuberous sclerosis) may be involved in the pathogenesis of these pancreatic lesions [14]. Such knowledge is clinically relevant since testing for these mutations may be recommended if there are clinical findings or family history suggestive of MEN1, VHL, or TS and in the presence of multiple tumors or precursor lesions in the peritumoral pancreatic tissues [7].

14.2.3 Pathological Features

Approximately 90 % of insulinomas are benign; 90 % are solitary [15], though multiplicity is more likely in MEN1-associated cases (Fig. 14.1); and 90 % are intrapancreatic and evenly distributed through the pancreas though pancreatic tail was reported to be the most frequent site in some studies [16]. The rare extrapancreatic insulinomas are most commonly present in the duodenal wall [17]. They are typically small (less than 2 cm); only 8 % are larger than 5 cm [18]. Size criterion is not a determining factor for symptoms of hypoglycemia [19]; however, larger tumors are more likely to be malignant than smaller ones [17]. Malignant ones commonly metastasize to peripancreatic lymph nodes and occasionally to the liver [20]. When describing the pathology of insulinoma, a couple of issues must be addressed in addition to the macroscopic and microscopic evaluation; these are (1) immunostaining for chromogranin A, synaptophysin, and insulin. In this context, it is worthy to emphasize that immunodetection of insulin expression by tumor cells is not a sine qua non for diagnosing an insulinoma since the rapid release of insulin from these cells may result in them not staining positively for insulin and (2) mitotic index using mitotic count and Ki-67 index [21].

14.2.4 Pathophysiology and Clinical Features

In patients with insulinoma, there is continued secretion of insulin despite low blood glucose;

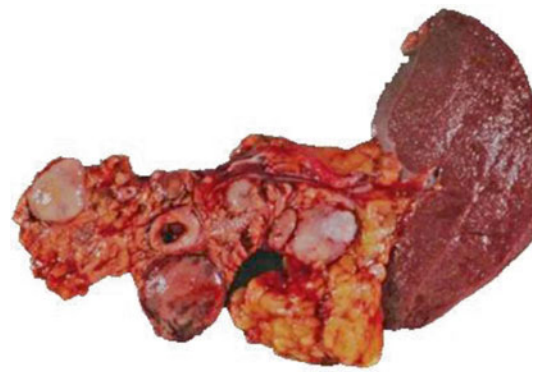

Fig. 14.1 Distal pancreatectomy specimen showing insulinomas in a MEN1 patient

such break of the physiologic negative feedback with the resulting inappropriately excessive insulin secretion is the pathological hallmark of insulinoma [22]. The clinical spectrum of hypoglycemia is attributed to reduced hepatic glucose production rather than increased utilization [23]. Patients present typically at their fourth or fifth decade [24], and the diagnosis is sometimes made years after presentation [16] due to diversity and ambiguity of symptoms. Blood glucose levels below 55 mg/dl induce excessive catecholamine release and subsequently result in appearance of adrenergic symptoms like anxiety, palpitations, tremors, weakness, hunger, nausea, sweating, and warmth. Severe hypoglycemia with blood glucose level dropped below 50 mg/dl causes neuroglycopenia manifested as neurologic dysfunction in the form of visual disturbances (diplopia, blurred vision), amnesia, confusion, convulsions, and even coma [13, 16, 22, 23].

Two points should be emphasized while clinically evaluating these patients. First, timing of symptoms should be confirmed; early morning or post-exercise onset usually favors the diagnosis of insulinoma, while postprandial symptoms, though cannot preclude [15], yet do not favor its diagnosis [13]. Second, given the rarity of the condition and the usually nonspecific presenting symptoms, clinical suspicion should always be kept high.

14.2.5 Biochemical Diagnosis

When clinically suspected, diagnosis is usually suggested by detecting hyperinsulinemia in the presence of hypoglycemia plus reversal of the symptoms by administration of glucose, fulfilling classical criteria of Whipple triad [22]. The current consensus [15] to confirm diagnosis depends on demonstration of six criteria during 72-h fasting test, though some studies declared the adequacy of 48-h fasting [25]. These criteria are (1) documented blood glucose levels ≤2.2 mmol/l (≤40 mg/dl), (2) concomitant insulin levels ≥6 μU/ml (≥36 pmol/l; ≥3 U/l by ICMA), (3) C-peptide levels ≥200 pmol/l, (4) proinsulin levels ≥5 pmol/l, (5) β hydroxybutyrate levels ≤2.7 mmol/l, and (6) absence of sulfonylurea (metabolites) in the plasma and/or urine.

14.2.6 Imaging Localization

Once the diagnosis is biochemically confirmed, localization is sought. Various imaging modalities are available with variable sensitivities. None of them is solely adequate, so more than single modality may be used; however, localization can be accomplished preoperatively in the vast majority of cases. Initially, anatomic imaging modalities are used. Computed tomography (CT) is generally preferred over transabdominal sonography because of reported higher sensitivity in most [26–28] – but not all [24] – studies, in addition to the traditional limitations of ultrasound (US) in obese patients and gaseous abdomen, which are easily overcome by CT scan (Figs. 14.2 and 14.3). Moreover, technical advances in CT enhanced its sensitivity enabling localization of more than 94 % of insulinomas [29]. If the tumor is yet not localized, endoscopic ultrasound (EUS) is the appropriate next step. The disadvantages of EUS, being invasive and requiring expertise, are usually overlooked in light of its very high sensitivity which reached 100 % in some studies [26]; somatostatin receptor scintigraphy (SRS), as a

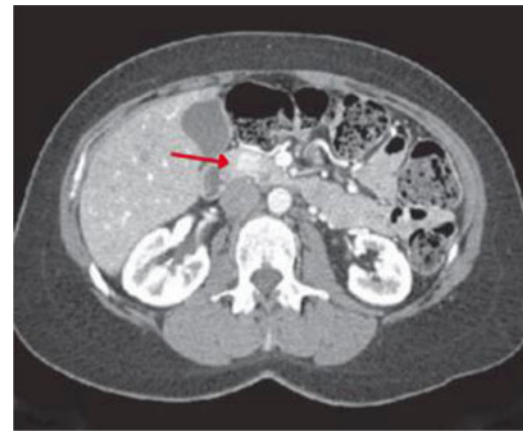

Fig. 14.2 CT scan demonstrating a 1.4-cm hypervascular mass in the head of the pancreas in a patient diagnosed with insulinoma (*arrow*)

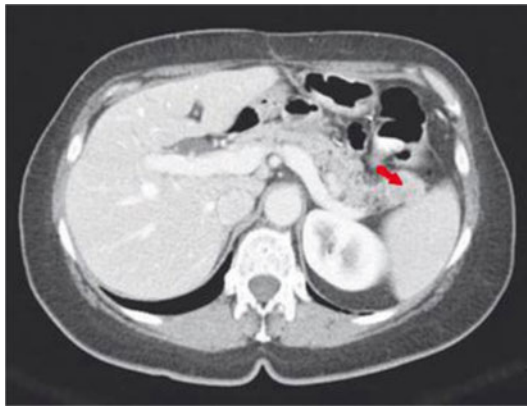

Fig. 14.3 CT scan demonstrating a tumor in the tail of the pancreas (*arrow*)

sole modality, has low sensitivity for the detection of insulinoma owing to the usually small tumor size and low density of somatostatin receptors in the tumor [30].

For the remaining minority of cases, functional imaging is resorted to. Angiography, arterial stimulation venous sampling (ASVS), or selective arterial calcium stimulation (SACS) helps to localize the tumor by verifying hormonal function and thus allowing a more accurate surgical approach [15].

Magnetic resonance imaging (MRI) is an alternative to CT with a higher sensitivity, 50 % versus 30 %, in some studies [31]. However, being much more expensive, it is reserved for patients in whom contrast is contraindicated. Occult insulinomas refer to a minority of tumors which are biochemically confirmed yet cannot be preoperatively localized despite the use of the aforementioned localization studies [11].

14.2.7 Management

In managing an insulinoma patient, two goals should be approached, hypoglycemia control and oncological control, and in fact it is ideal to achieve the first via approaching the second. In addition, given the fact that insulinomas – in the vast majority of cases – are benign and solitary, surgery is usually curative and therefore is indicated. Medical treatment, however, is indicated for preoperative control, for unresectable disease because of metastasis, and for the patient unwilling or unfit for surgery [7]. In order to ameliorate hypoglycemic symptoms in these cases, the following nonoperative strategies may be attempted: (1) dietary modification in the form of slowly absorbed carbohydrates and more frequent meals. Continuous glucose infusion may be needed in some patients with severe hypoglycemia. (2) Antihypertensive agent diazoxide may be used on account of its hyperglycemic potential through a dual action and pancreatic through inhibition of insulin release and extrapancreatic through potentiating glycogenolysis. However, its use may be associated with major adverse reactions like nausea, sodium retention with edema, weight gain, and hirsutism [11]. As previously mentioned, surgery is the only curative treatment for insulinomas. While continuously and carefully monitoring blood glucose level, the tumor is approached through a bilateral subcostal incision followed by complete pancreatic mobilization. An initial exploration is done to exclude metastatic disease. Meticulous examination of the entire pancreas, both bimanually and by intraoperative US, is done to identify the tumor(s) and its (their) relation to major pancreatic ducts (Fig. 14.4). Enucleation is usually done, though distal pancreatectomy or rarely pancreaticoduodenectomy may be performed as indicated by tumor location and size. Blind resection and progressive resections are prohibited. Drainage is generally recommended [13]. With the advent of endoscopic instruments and vascular sealing devices, laparoscopic resection has also been successfully performed [22] albeit with a higher incidence of pancreatic fistulas [23]. Postoperatively, some patients, being transiently hyperglycemic, may require small doses of insulin, avoiding glucose in the first 24-h IV fluids. Drains are removed when the patient resumes oral intake and pancreatic leakage is not suspected [23].

In their series, Hirshberg et al. [32] reported a prolonged survival in nine out of ten patients with malignant insulinoma after appropriate surgical resection. In addition, Starke and colleagues reported the results of follow-up in ten patients

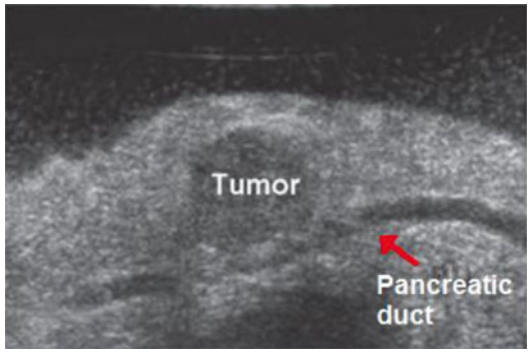

Fig. 14.4 Intraoperative US demonstrates the close proximity of the pancreatic duct (*PD*) just deep to the tumor

with insulinoma and liver metastasis who underwent successful pancreatic surgery and reported the death of four patients from unmanageable hypoglycemia [33]. These reports explain the aggressive surgical approach justified even in metastatic cases. Peripancreatic lymphadenectomy should be performed in case of suspected or proven malignancy [13].

Resection of hepatic metastases, synchronous with the appropriate pancreatic surgery, has been recommended [34]. For patients with insulinoma-induced intractable hypoglycemia, that is not amenable for surgery, continuous glucose infusion pump has been used [16]. An induced apoptotic and antiproliferative effect was reported via targeting glucagon-like peptide-1 receptors on insulinoma cells; this may provide future novel therapy for inoperable cases [35].

14.3 Gastrinoma

14.3.1 Historical and Epidemiological Aspects

Gatrinomas were first described as a distinct clinicopathological entity by Zollinger and Ellison in 1955 [36]. They occur at an annual incidence of 0.5–2/million of population and are the most common functional malignant P-NET [7] and are second in incidence to insulinoma among gastropancreatic NETs associated with hormonal syndrome. They are most frequently located in the duodenum and are the sole functioning duodenal NET [37]. Their clinical importance originates primarily from their ulcerogenic potential and malignant potential [38]. Although 80 % of cases are sporadic, 20 % are familial, occurring in the setting of MEN1 syndrome [39]. While many aspects of the disease are established facts, its management – particularly advanced and familial cases – is a subject of considerable debate.

14.3.2 Genetic Basis

Numerous genetic abnormalities have been identified to be involved in the pathogenesis of gastrinoma. A germline mutation of the tumor suppressor gene MEN1 located on 11q31 was found not only in familial cases [40] but also in sporadic ones [41]. A number of chromosomal deletions, 1q and 22q, have also been identified in 44 and 96 % of gastrinomas, respectively, and may be associated with aggressive growth pattern and higher metastatic rates [42, 43]. A number of tyrosine kinase receptors seem to be also involved. In a small series by Evers, amplification of the HER-2/neu gene was detected in all gastrinoma samples [44]. Similarly, insulin-like growth factors (IGF1 and IGF 2) are expressed in almost all gastrinomas [45].

14.3.3 Pathological Features

Gastrinomas arise from neuroendocrine cells and are well-differentiated tumors. Nevertheless, more than 60 % of them are malignant based on the biologic behavior rather than on histology [13]. The site of the tumor has no effect on the age of diagnosis, nor the severity of disease, but may minimally influence the clinical presentation [46]. The majority of gastrinomas are located in the duodenum, pancreatic head, and lymph nodes within the gastrinoma triangle whose heads are cystic–common bile duct junction, pancreatic head–body junction, and duodenal second–third parts junction. Synchronous occurrence of pancreatic and duodenal gastrinomas was reported in 11 % of gastrinoma cases [38] and in 6 % of all NETs [47]. Ectopic gastrinoma, defined as

extrapancreatic, extraduodenal, and extralymphatic primary gastrinoma, has been reported. In 1997, Wu et al. reviewed 20 reported cases of this rare entity and concluded that such ectopic sites should be carefully examined if no gastrinoma was found in the usual locations [48]. These ectopic sites include the stomach, jejunum, lesser omentum, liver, right kidney, and ovary. Multiplicity and associated islet cell hyperplasia are as well documented, not only in most patients with MEN1[49] but also in up to 15 % of sporadic gastrinoma [47]. In its sporadic type, patients tend to have an isolated duodenal or pancreatic gastrinoma [37]. Although those located in the duodenum are typically small (<1 cm), regional nodal and hepatic metastasis is present in about 60–80 % and 10 % of cases, respectively [50]. The proliferative activity of these tumors ranges from 2 to 10 %, and some may show angioinvasion [37]. On the contrary, pancreatic tumors are larger (>2 cm) with similar incidence of nodal involvement but higher likelihood of hepatic metastasis [51], higher proliferative activity, and higher angioinvasion rate [37]; this explains why pancreatic tumors are more malignant than duodenal ones. On the other hand, almost all gastrinomas, in MEN1 settings, reside in the duodenum, usually small (<1 cm) and, contrary to the sporadic tumors, are multicentric with distant metastasis rarely detected at initial diagnosis [52]. Finally, all gastrinomas are expressing receptors for somatostatin [53].

14.3.4 Pathophysiology and Clinical Features

Overproduction of gastrin by these tumors causes gastric acid hypersecretion which leads to peptic ulcer disease or gastroesophageal reflux disease which are in turn responsible for most clinical features of the disease spectrum known as Zollinger–Ellison syndrome (ZES).

Among 355 gastrinoma patients recorded by Soga et al., seven were asymptomatic. Asymptomatic cases were more likely to be extrapancreatic [54]. The mean age at onset of symptoms is 48–55 years in sporadic form, with slight male predominance (54–56 %). However, the familial type usually presents earlier (mean 32–35 years) [55]. In a series by Roy et al. [46], abdominal pain and diarrhea were the most frequent symptoms occurring in about three-fourths of patients, though pain was less frequently reported in familial cases and diarrhea was more frequently reported in metastatic cases [54]. Heartburn and weight loss were less common presentations, occurring in 44 % and 15 % of patients, respectively, while one-fourth of patients presented with gastrointestinal bleeding [46], melena being more common than hematemesis [54]. Other features are nausea and vomiting occurring in 12–30 % of cases and steatorrhea in 5–10 % [56]. Abdominal tumor and hepatomegaly were also reported, both being significantly more common in metastatic cases [54].

14.3.5 Biochemical Diagnosis

Biochemical assays and imaging are the mainstay of diagnosis since physical examination is usually nonspecific. The diagnosis of ZES is based on the detection of elevated serum gastrin in a fasting patient with raised gastric acid secretion. In this context several points are to be considered. Firstly, patients with pernicious anemia, atrophic gastritis, and those with medically or surgically suppressed gastric acid secretion have elevated serum gastrin level, hence the importance of demonstrating hyperchlorhydria for establishing the diagnosis of ZES and the importance of discontinuing antisecretory medications at least 7 days before the test. Secondly, criteria of basal acid output value more than 15 mEq/h or PH less than 2 are used to define the hyperchlorhydria state [57]. Thirdly, serum gastrin level required to diagnose ZES is a subject of discussion in the literature; this was defined by Harvey and Berber as more than ten times the upper limit of normal [13], while Roy et al. considered a level more than 150 pg/ml [57]. In their large prospective cohort, Berna et al. [58], however, reported normal FSG in up to 3 % of patients in addition to the finding that nearly half of the patients had FSG less than ten times upper

normal, a level that overlaps with more common condition like *Helicobacter pylori* infection and antral G-cell hyperplasia. In case of normal FSG despite clinical suspicion or in case of equivocally elevated FSG, a provocative test is indicated in which secretin, at a dose of 2 mg/kg, is administered intravenously. In gastrinoma patients, serum gastrin level rises above baseline, in 94 % of patients, within three minutes after injection with 100 pg/ml [59]. An alternative but less sensitive provocative test is calcium infusion which, in 84 % of cases of gastrinoma, would result in 50 % rise in serum gastrin above baseline [59].

14.3.6 Imaging Localization

Once diagnosis is biochemically established, imaging localization is the next step. Two types of imaging studies are used for localization: anatomic and functional. In a study by Kisker, sensitivities of the three anatomic imaging modalities were reported to be 44 % for ultrasound, 56 % for CT, and 25 % for MRI [60]. In 1999, Norton et al. [61] found that US, CT, MRI, and angiography localized 24, 39, 46, and 48 % of sporadic gastrinomas. They also noticed that the latter three modalities achieved significantly higher sensitivities for localizing MEN1-associated gastrinomas (70 %, 71 %, and 85 %, respectively). Gibril et al. [62] studied 24 gastrinoma patients with proven liver metastasis, and they reported sensitivities of 46, 42, 71, and 62 for the detection of the metastatic disease by US, CT, MRI, and angiography, respectively. More advanced anatomic imaging like contrast-enhanced spiral CT and high-resolution MRI have been used for MEN1-associated gastrinomas (Fig. 14.5), though their sensitivity for detecting small duodenal tumors is rather low [63]. Collectively, 50–72 % of pancreatic gastrinomas were localized using anatomic imaging, which unfortunately failed to localize 80 % of duodenal tumors [13].

Knowing that almost all gastrinomas express somatostatin receptors on their cells, SRS using somatostatin analogue pentetreotide labeled with a radioactive material – indium^{111} – is being used for the functional imaging of these tumors. SRS was reported to have sensitivity ranging from 58 to 80 % for localization of the primary tumor [13] and 92 % for the detection of metastatic liver disease [63]. Additionally, it detected bone metastasis in all patients [64]. Gibril et al. [62], thus, concluded that SRS, given its sensitivity and cost-effectiveness, should be the initial imaging modality requested for patients with ZES. However, its sensitivity is significantly lower in smaller tumors [65]. In addition, SRS was unable to detect one-third of primary tumors subsequently detected at surgery. Alexander and colleagues [66], therefore, concluded that negative results of SRS in localizing extrahepatic gastrinomas should not be used to decide operability. The EUS was 93 % sensitive for the localization of pancreatic tumors with an average diameter of 1.51 cm [67] though its sensitivity for localizing duodenal tumors was only 40 % [68].

For patients in whom noninvasive modalities prove unable to localize tumor, invasive methods are usually needed. In a prospective study by Sug et al. [69], portal venous sampling was 71 % sensitive, while selective arterial secretin injection was 96 % sensitive for localizing gastrinomas. In a review by Fendrich et al. [63], surgical exploration with intraoperative US was concluded to be the best localizing method.

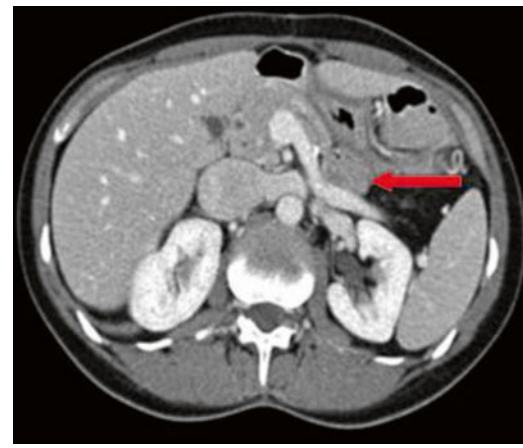

Fig. 14.5 CT scan of the pancreas with intravenous contrast. The *arrow* indicates gastrinoma in the pancreatic tail. The patient had MEN1 and two additional tumors of the pancreas (body and head, <1 cm each)

14.3.7 Management

In managing gastrinoma patients, two goals are to be approached, namely, acid hypersecretion control and oncological control. Control of acid hypersecretion must be accomplished acutely and for long term in order to protect against complications of peptic ulcer disease [70]. Historically, surgery, either vagotomy or gastrectomy, was used. However, control is now commonly adequately achieved medically via antisecretory medications, H_2 blockers, and proton pump inhibitors (PPIs). Generally, PPIs are preferred over H_2 blockers because their longer duration of action allows less frequent dosing conferring better compliance, in addition to their better safety profile even in case of long-term use. Omeprazole 40 mg twice daily is commonly prescribed. Up-titration may be indicated in complicated cases like MEN1 with hypercalcemia [49] and severe gastroesophageal reflux disease (GERD), while down titration has been recommended following initial control and endoscopic documentation of ulcer healing [71].

Medical control is, however, not without cons; long-term use of acid suppression medication was proved to be associated with vitamin B_{12} deficiency [72]. Additionally, two important issues are not addressed through acid-suppressing medications. Firstly, chronic hypergastrinemia with its well-documented predisposition to gastric carcinoids [73] and secondly, the tumor itself, which may prove malignant and may even metastasize. Thus, surgery is the only treatment that can cure gastrinoma [55].

A distinction between sporadic and familial cases is essential to draw an appropriate management plan. For sporadic cases, role of surgery is well established. In a prospective study conducted by Norton et al. [74], they compared survival rates between operated ($n=160$) and nonoperated ($n=35$) patients with *sporadic* gastrinomas and concluded that routine surgical exploration increases survival among ZES patients. Therefore, in the absence of diffuse liver metastatic disease and in the presence of acceptable surgical risk, surgical exploration is routinely recommended for all patients with sporadic gastrinoma [61].

For pancreatic lesions, simple enucleation may be safely performed for solitary well-defined lesion; distal pancreatectomy is indicated for tail lesions, while pylorus-preserving pancreaticoduodenectomy (PPP) is justified for large head lesions [63]. Duodenotomy is routinely indicated while exploring ZES patients [75]. Identified duodenal gastrinomas are subsequently enucleated if smaller than 5 mm or excised with full thickness of the duodenal wall if larger. This is followed by longitudinal suturing of the duodenal opening [63].

For MEN1-associated gastrinoma, the role of surgery is controversial due to multiplicity of the tumor, rarity of cure even after surgery, and the possibility of hepatic metastasis even in surgically managed ZES patients [76]. Firstly, whether or not to operate? Stemming from the fact that surgery never cures ZES, Mignon and Cadiot recommended conservative approach [77]. On the other hand, surgery is recommended by others based on the fact that surgery reduces the incidence of hepatic metastasis [76]. Secondly, when to operate? A selective approach recommending surgery for large-sized tumors was proposed as these were found to be associated with a higher risk of liver metastasis [78, 79]. A more aggressive approach advocating surgery for all patients with sure diagnosis of gastrinomas has also been proposed by other authors [80]. Another controversy exists concerning the management of metastatic gastrinoma. Given the facts that PPIs are extremely effective for controlling symptoms of gastric acid hypersecretion and low rate of prolonged survival reported in cases of gastrinoma with liver metastasis [20], such patients are generally not recommended for surgery. On the other hand, House et al. [81] reported a survival advantage in their series conferred by concurrent hepatic and pancreatic resection in patients with pancreatic islet cell tumors having liver metastasis. Furthermore, acceptable morbidity and mortality were reported with aggressive resection of advanced P-NETs [82]. Consequently, aggressive surgical approach for managing such cases has also been suggested.

14.4 Glucagonoma

14.4.1 Historical and Epidemiological Aspects

A clinical spectrum referring to glucagonoma was described in 1942 by Becker et al. [83]. However, it is not until 1966 when an elevated glucagon level was documented in a similar clinical case by McGavran and colleagues [84]. Glucagonoma is an RF-PNET occurring at an annual incidence of 1 per 20 million of population ranking the third after insulinoma and gastrinoma among functional P-NETs [85] arising from alpha cells of islets of Langerhans in the pancreas and expectedly, from its name and origin, produce an excess of hormone glucagon. Approximately, 60 % of cases are sporadic and the remainder occurs in the setting of MEN1 [86].

14.4.2 Pathological Features

Glucagonomas are generally solitary and large sized (more than 4 cm) [13], located in the pancreas in more than 95 % of cases, and malignant in 50–80 % of cases [6] with higher malignancy rates in larger tumors [87] and lower malignancy rates in MEN1-associated tumors [88]. Metastasis is present in about 90 % of cases, the liver being the most common site with two-thirds of cases having multiple foci usually involving both lobes [89].

14.4.3 Pathophysiology and Clinical Features

Glucagonoma patients characteristically present clinically with 4Ds syndrome: diabetes, dermatitis (Fig. 14.6), deep venous thrombosis, and depression. Other features include cheilitis, glossitis (Fig. 14.7), anemia, weight loss, and hypoaminoacidemia [20].

The diabetic state is a consequence of the glycogenolytic and gluconeogenic effects of glucagon [90]. It develops in about 75 % of patients [89] and is usually mild and effectively controlled with oral hypoglycemic agents, though insulin may sometimes be required. Complications of diabetes do not occur though few cases of diabetic ketoacidosis (DKA) were reported [91, 92].

Dermatitis or necrolytic migratory erythema is a pathognomonic feature occurring in up to 70 % of patients [20], and it may be the presenting sign of glucagonoma [93]. It usually starts in the perigenital, perineal, and perioral areas and subsequently spreads centrifugally to the distal extremities [94], passing through multiple stages: erythema to vesiculation, to crusting, and to resolution over 1–2 weeks [2].

Although the exact pathophysiology has not yet been certainly elucidated, several mechanisms have been postulated, namely, hyperglucagonemia with increased protein catabolism [95], hypoaminoacidemia [86], hypoalbuminemia [90], essential fatty acid, zinc [89], and vitamin B deficiencies [94]. Amino acid hyperalimentation appears to clear this rash [86]. Deep vein thrombosis (DVT) occurs in up to 30 % of glucagonoma patients [20] and is caused by production of a molecule similar to coagulation factor X by tumor cells [90]. Weight loss is present in 62 % of symptomatic patients, may be marked, often associated with anorexia [89], and is attributed to catabolic effect of the chronically elevated glucagon level [86]. Hypoaminoacidemia is due to increased protein degradation stimulated by excess glucagon [85] and usually affecting

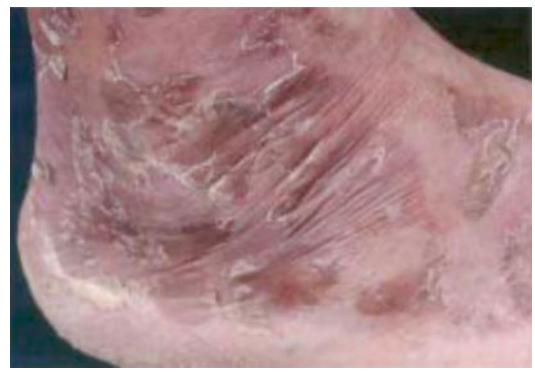

Fig. 14.6 Typical dermatitis in a patient with glucagonoma

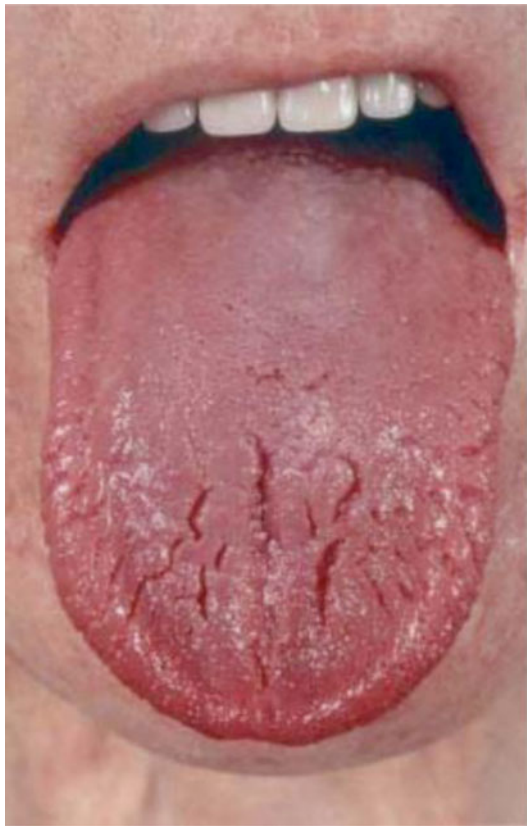

Fig. 14.7 Typical glossitis in a patient with glucagonoma

glucogenic rather than branched-chain amino acid [87]. Anemia may occur in variable proportion of patients, normocytic normochromic in type, and caused by direct suppression of bone marrow by glucagon [89].

14.4.4 Biochemical Diagnosis

When clinically suspected, diagnosis is biochemically confirmed via demonstration of raised fasting plasma glucagon concentration. Levels greater than 1000 pg/mL are diagnostic [2].

14.4.5 Imaging Localization

Once diagnosis is established, localization should be attempted. Abdominal CT with IV contrast is sensitive in 86 % of cases and can detect possible liver metastasis [20]. If the tumor is too small to be imaged by CT, endoscopic US offers a suitable alternative with a comparable sensitivity [96].

14.4.6 Management

Several nonsurgical measures are indicated either for palliation or preoperative preparation; these are (1) aggressive nutritional supplementation [97], (2) somatostatin analogues [98], and (3) prophylactic anticoagulant measures [99]. Surgical resection, however, is the only chance for cure with distal pancreatectomy being the most commonly performed operation [20].

14.5 VIPoma

14.5.1 Historical and Epidemiological Aspects

VIPoma was first described in 1958 by Verner and Morrison [100] and subsequently commonly named after them. It is an RF-PNET occurring at an annual incidence of 0.1 per million of population [86] and overproducing a peptide named vasoactive intestinal peptide (VIP). The majority occurs sporadically; only 5–6 % are MEN1 associated [6].

14.5.2 Pathological Features

Average size at the time of diagnosis is 5.2 cm [101]. Approximately, 70 % are pancreatic. Extrapancreatic sites include the bronchi, colon, adrenal glands, liver, and sympathetic ganglia [102]. Around 60–80 % of VIPomas are malignant, and 75 % have metastasized by the time of surgical exploration [13] with the liver being the most common site. In their comparative study, Soga et al. [103] noted lower malignancy rates in extrapancreatic compared to pancreatic lesions.

14.5.3 Pathophysiology and Clinical Features

VIPomas overproduce VIP, which is known to induce gut smooth muscle relaxation and is a potent vasodilator and is responsible for the pathophysiology of the characteristic clinical triad: watery diarrhea, hypokalemia, and achlorhydria (WDHA). Diarrhea of secretory type is present in all patients and has the following characters: (1) initially intermittent and later becomes continuous and unaffected by fasting; (2) profuse, exceeding 3 L/day; (3) odorless, tea colored; (4) blood-free, mucus-free; (5) results in substantial fluid loss with dehydration, electrolyte disturbance, and even weight loss; and (6) its severity and consequences that impart the name "endocrine cholera" to the condition [2102]. Flushing and hyperglycemia may be also present in some patients [104].

14.5.4 Biochemical Diagnosis and Imaging Localization

When clinically suspected, diagnosis is biochemically confirmed by measuring fasting plasma VIP level, which should be 2–10 times of the upper limit of the normal range [2]. As usual, localization should follow and is accomplished in all cases using CT scan [20] as demonstrated in Fig. 14.8.

Once diagnosis is confirmed, urgent correction of fluid, electrolyte, and acid–base balance is indicated. This usually requires intensive intravenous fluid therapy in addition to a somatostatin analogue and octreotide which can stop diarrhea [2]. Once stabilized, the surgical option should be discussed. Complete resection, usually, guarantees complete cure for patients without metastatic disease. For patients with pre- or intraoperatively detected metastatic disease, surgical debulking is the mainstay of management, to be followed postoperatively by octreotide therapy [20]. Chemotherapeutic agents like Adriamycin and 5-FU may also benefit some patients [104].

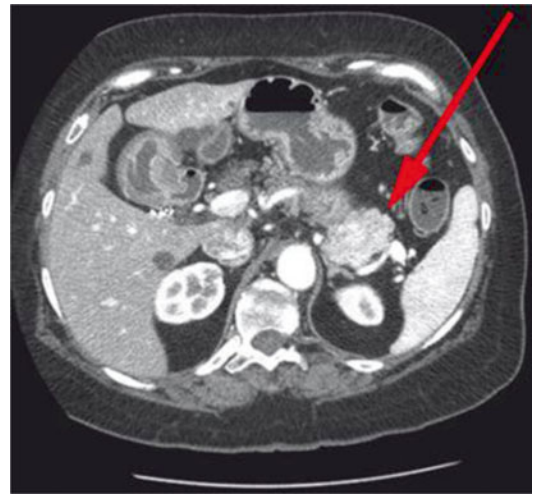

Fig. 14.8 CT scan of a VIPoma in the distal pancreas. The typical hypervascular tumor is indicated by the *red arrow*

14.6 Somatostatinoma

14.6.1 Historical and Epidemiological Aspects

In 1977, Ganda et al. [105] were the first to document elevated somatostatin level in a patient complaining of diabetes and cholelithiasis and having a pancreatic tumor. In the same year, Larsson and colleagues [106] described a similar clinic laboratory scenario. Somatostatinoma is an exceedingly RF-PNET with a reported annual incidence of 1 in 40 million of population [107]. It occurs in MEN1 setting in 45–50 % of cases [6].

14.6.2 Pathological Features

Most tumors are 5 cm or more at the time of diagnosis [86]. Fifty-five to seventy percent of these tumors are located in the pancreas, with the pancreatic head being the most common site [108]. Extrapancreatic somatostatinomas may be located in the remaining bowel, most often in the duodenum. Other sites are the jejunum and biliary tree [20, 86]. Colonic somatostatinomas have also been reported [109]. Duodenal somatostatinomas

are usually located near the ampulla of Vater (Fig. 14.9), usually associated with von Recklinghausen's disease [110], have higher malignancy rates [111], and may occur synchronously with pancreatic head somatostatinoma [112]. Metastasis is present in three-fourths of cases at time of diagnosis, with higher incidence in tumors larger than 2 cm [111] and the liver being the most common site [109].

14.6.3 Pathophysiology and Clinical Features

As their name implies, they secrete excessive amounts of somatostatin which is known to exert inhibitory action on the gut secretory and contractile functions; this subsequently accounts for the clinical features of the disease. Diabetes mellitus and cholelithiasis are the most frequent manifestations and are caused by inhibition of secretion of insulin and cholecystokinin, respectively [86]. Less frequently, diarrhea and steatorrhea are caused by inhibition of pancreatic enzyme and bicarbonate secretion [20]. Additional features include hypochlorhydria due to inhibition of gastrin secretion, weight loss, and anemia due to malabsorption [2]. Duodenal somatostatinomas commonly present with obstructive jaundice [113].

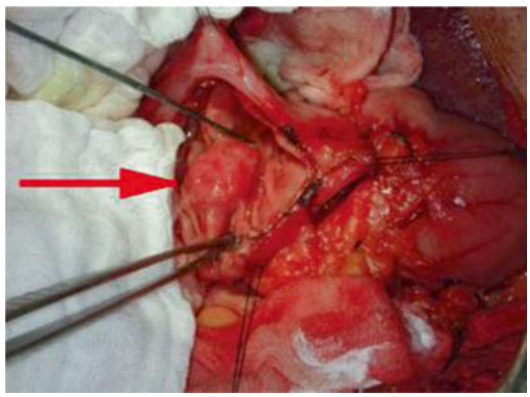

Fig. 14.9 Typical duodenal somatostatinoma (*arrow*) location; in the second portion of the duodenum adjacent to the ampulla of Vater

14.6.4 Biochemical Diagnosis and Imaging Localization

When clinically suspected, fasting plasma somatostatin level should be measured. A level greater than 14 mol/L confirms diagnosis [114]. Localization using CT or MRI should follow and is usually easy since on account of the usually large size of these tumors at time of diagnosis [86].

14.6.5 Management

Surgical resection is the only line of treatment. For patients without metastatic disease, resection is usually curative [20]. For patients with metastasis, surgical debulking usually improves the quality of life [115].

14.7 Nonfunctional Pancreatic NETs

By definition, these constitute a subset of P-NETs lacking clinical syndromes relating to hormone overproduction. However, they may show immunohistochemical positivity for certain hormones or neuropeptides [116]. They represent 10–25 % of all P-NETs [20] and include those secreting pancreatic polypeptide, human chorionic gonadotropin subunits, calcitonin, neurotensin, or other peptides [1].

An important fact is that NF-PNETs are generally regarded as the most aggressive subset among gastroenteropancreatic endocrine tumors [117] with a malignancy rate of 92 % in contrast to, for example, 10 % in case of insulinoma [118]. Symptoms are not related to specific endocrinopathy but are caused by tumor invasion or distant metastasis.

Demonstration of elevated chromogranin A, which may correlate with tumor mass, may aid laboratory diagnosis. In addition, testing for basal and meal-stimulated pancreatic polypeptide may help detect pancreatic involvement in MEN1 [119]. Localization is usually easy accomplished using CT scan (Fig. 14.10), MRI, or EUS as the

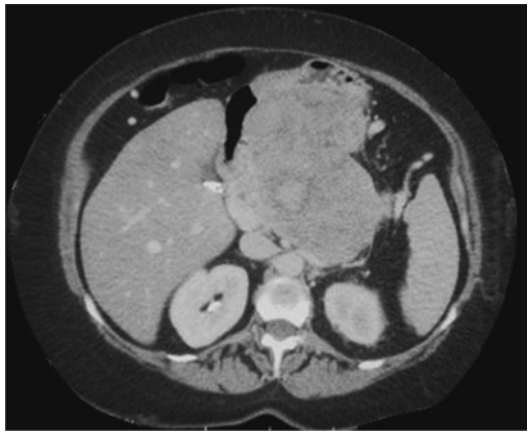

Fig. 14.10 CT scan showing a large nonfunctional tumor of the pancreas

tumor, lacking specific clinical features, is usually large at time of diagnosis [2]. Surgery, either complete resection or bulk reduction, should be always attempted to enhance long-term survival [120].

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Minimally Invasive Surgery in the Head and Neck

15

Mahmoud Sakr

15.1 Introduction

The term minimally invasive surgery (MIS) covers a large spectrum of operations and can be misleading. Surgery may be considered minimally invasive in respect of not only the length of skin incision but also the accessibility of the operative field and extent of dissection. As conventional cervicotomy incisions are 6 cm length or more, it is hardly appropriate to consider any incision over 3 cm to be minimally invasive [1].

Since the early 1980s, minimally invasive techniques have been applied in almost all types of surgery [2–5]. Endoscopic operations were initially limited to regions with naturally occurring cavities such as the peritoneal and pleural cavities. It is not surprising that the pioneers of endoscopic surgery were gynecologists and gastrointestinal surgeons. In the recent years, the range of endoscopically assisted interventions has been expanded to regions where there is no natural cavity [6].

Minimal access surgery was popularized after the introduction of laparoscopic cholecystectomy by Mouret in 1988 [7, 8]. Since that time, a variety of minimally invasive alternative approaches to conventional open surgery have been developed in general surgical, urologic, cardiac, and orthopedic procedures. Minimal access approaches are playing an ever-increasing role in endocrine surgery. Laparoscopic adrenalectomy has become the approach of choice for the treatment of virtually all benign diseases of the adrenal gland.

In 1996, Gagner [9] published the possibility of inflating spaces with carbon dioxide (CO_2) to maintain a pocket for operations on the thyroid and parathyroid. The primary target organs have been the parathyroid and the thyroid glands, although few studies have been reported on its application to other cervical structures. Minimal access parathyroidectomy is finding a role alongside conventional cervicotomy for the treatment of primary hyperparathyroidism (HPT) [8]. In 1998, a new operation called minimally invasive video-assisted thyroidectomy (MIVAT) was set up.

Head and neck endoscopic procedures have extended to the maxillofacial skeleton for reduction and osteosynthesis of malar or subcondylar mandibular fractures [10–12]. Applications in neck soft tissue surgery are growing. Parathyroidectomy, thyroidectomy [13, 14], resection of lateral cervical cysts [15], extraction of epidermal cysts on the face [16], submandibular sialoadenectomy, parotidectomy [17], and even nodal neck dissection [18] have been successfully treated through endoscopic approaches.

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Common to all minimally invasive endoscopic operations is the intention to reduce patient morbidity and hasten recovery [6]. Endoscopic neck surgery minimizes scars which makes it attractive especially for women, young patients, and patients with an increased risk of keloid scars [19].

15.2 Classification of Endoscopic Neck Surgery

The endoscopic neck surgery techniques can be classified in different ways, according to the *position of incision*, the *technique of the operation* either video assisted or pure endoscopic, and according to the *method of obtaining the working space* into carbon dioxide (CO_2) insufflation method or gasless method. The location of the incisions in endoscopic neck surgery is variable; it may be endoscopic trans-oral approach or endoscopic transcervical [20, 21].

Endoscopic surgery of the neck requires that a wide working space be newly created where there is no preexisting cavity. Two methods for providing such a working space have been devised: the *CO_2 insufflation method* (pure endoscopic procedure) characterized by the use of a steady gas flow through trocars and the *gasless skin lifting method* (video-assisted techniques) using external retraction instead of gas insufflation and minimally invasive mini-incision approaches. Each method has its own advantages and disadvantages [20–22].

15.2.1 Gasless Skin Lifting Methods

In 1977, Brunt and colleagues [23] developed a technique for obtaining endoscopic exposure and access to the pretracheal space in the neck with the goal of performing neck exploration and parathyroidectomy and evaluating the safety and efficacy of such an approach experimentally. The technique was developed in eight adult dogs and was further evaluated in a survival dog model and in human cadavers. The pretracheal space was accessed by a 2.5-cm-midline incision in the lower neck. This space was expanded with a balloon dissector; and exposure was maintained with an external lift device.

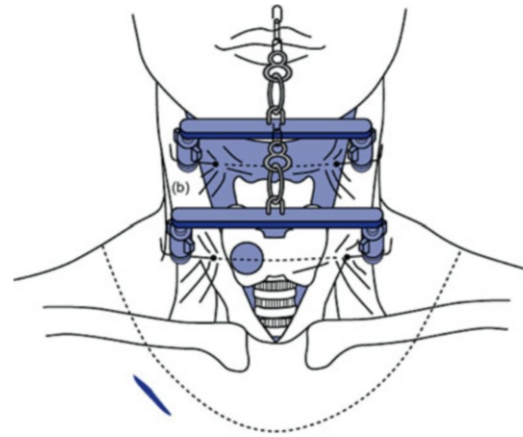

Fig. 15.1 Infraclavicular skin incision in the technique by Shimizu (**a**), with 5-mm incision in the neck (**b**), with application of the retraction system (Shimizu [21])

Shimizuo [21] developed the anterior neck skin lifting method in which the lower layer of the platysma is dissected after the skin incision has been made. The working space is created by pulling the skin away from the body and upwards, opening up the wound (Fig. 15.1).

Miccoli et al. [24] presented a retraction system using conventional surgical retractors, which were used to retract the skin and the strap muscles in order to expose the thyroid gland (Fig. 15.2).

15.2.2 Carbon Dioxide (CO_2) Insufflation Method

The CO_2 insufflation method creates operating space by insufflating a closed area with CO_2. This may cause complications such as severe subcutaneous emphysema, supraventricular tachycardia, and air embolism in case of accidental injury of one of the great vessels [25]. Rubino et al. [26] in their experimental study on pigs observed severe increase in the intracranial pressure with insufflation pressure greater than 15 mmHg, possibly owing to decreased cervical venous flow. These CO_2 insufflation-related

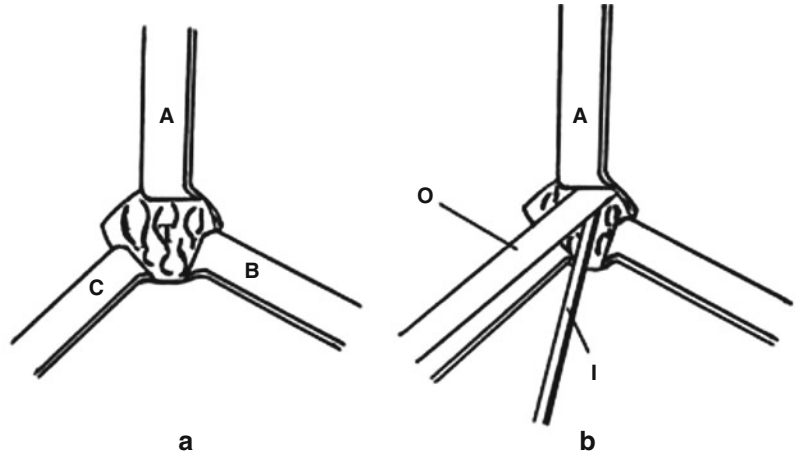

Fig. 15.2 (**a**) Retraction system using conventional surgical retractors (Miccoli et al.). Retractors (*A*, *B,* and *C*) were used to retract the skin and strap muscles to expose the thyroid gland (*T*). (**b**) One retractor (*A*) is also used as a "wall lifter," to allow insertion of a 5-mm 30° laparoscope (*O*) and of 2-mm-diameter laparoscopic and conventional instruments (*I*) through the skin incision [24]

problems have been reported to be alleviated by lowering the CO_2 pressure to 4–6 mmHg [27]. In some procedures, surgeons use short insufflation just to dissect the thyroid space in early phase of the procedure, relying later on, on external retraction only [28]. Ochia et al. [27] performed a detailed study on the safety of this method and used indirect calorimetry to estimate the intraoperative CO_2 absorption from the surgical field, with optimal CO_2 pressure adjusted to 6 mmHg. Hypercarbia was then eliminated.

15.3 Benefits of Endoscopic Neck Surgery

Endoscopic operations have several benefits, including reduced tissue damage, improved cosmesis, and fewer wound-related complications. However, such operations are not yet a standard procedure in the head and neck region [29]. Endoscopic surgery has a smaller wound size and enables the positions of the wounds to be moved to places of cosmetic benefit. This technique may also reduce the amount of bleeding and postoperative pain. In thyroid surgery, it obviates the need for a neck scar. An overzealous pursuit of these objectives must not, however, allow the intrinsic surgical treatment to be compromised [30].

Conventional operative scars in the anterior region of the neck are nearly always exposed and therefore visible to others. Minimally invasive surgery places an emphasis on cosmetic benefits. This criterion was satisfied in a report by Park [31] in which a direct approach was made to the thyroid through a succession of neck wounds without a skin flap [30].

The potential advantages of minimally invasive video-assisted thyroidectomy (MIVAT) are better recognition of the anatomic entities during dissection, improved hemostasis, less postoperative pain, reduction of complications, and higher cosmetic satisfaction [32].

Minimal access surgery has, in the past three decades, evolved to be the standard of treatment in various types of operations such as laparoscopic cholecystectomy. It has the merit of less pain, therefore hastening recovery. Being applied in the head and neck region, minimally invasive parathyroidectomy [33–37] and minimally invasive thyroidectomy [38, 39] have the additional benefit of preservation of functions and improved aesthetic outcome. Actually, minimally invasive parathyroidectomy has become the new standard over conventional bilateral neck exploration [40].

15.4 Obstacles of Endoscopic Neck Surgery

The delay of development of endoscopic neck surgery has been attributed to the relatively narrow field with many vital structures in it and to the lack of a naturally occurring cavity to perform the surgery in contrast to the abdominal, pelvic, and chest cavities. Neck surgery requires fine technique to prevent injuries to important surrounding structures. For endoscopic neck surgery to be feasible, two important points need to be addressed: first, how to create a comfortable working space and second, how to avoid bleeding so that a bloodless and clear operating field can be achieved and maintained [41].

A number of significant obstacles had to be overcome before the performance of endoscopic neck surgery. Although several investigators have described their experience with endoscopic surgery of the thyroid compartment, endoscopic surgery in the other cervical compartments has proven to be more challenging [42]. Carreno et al. [43], in 1999, encountered a series of pitfalls in an experimental model and published an honest report of their unfavorable experience with endoscopic neck surgery. Among the major difficulties were the small size of the potential space and the high pressure required to create this space by pneumatic dissection of fascia layers. The high pressures led to serious complications including air embolism, pneumothorax, and pneumomediastinum [43].

15.5 Video-Assisted Neck Surgery (VANS)

15.5.1 Surgical Technique

The procedure comprises excision of a neck swelling and/or fistula via a video-assisted approach. It is performed under general anesthesia with the patient in the supine position without hyperextension of the neck, but with slight rotation to the opposite side as during conventional lymphadenectomy.

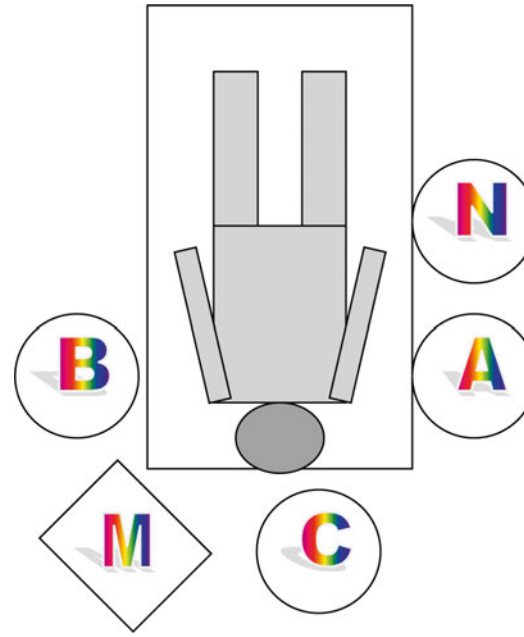

Fig. 15.3 Position of the surgical team in video-assisted neck surgery (VANS) for excision of a right-sided neck swelling through a transcervical skin incision, *A* main surgeon, *B* first assistant, *C* second assistant, *N* operating room nurse, *M* video monitor

15.5.2 Transcervical Approach

The primary surgeon stands on the same side of the swelling. The second and third assistants stand on the opposite side (Fig. 15.3).

Two accesses are used. The first main access is a 1.5-cm central transverse incision situated two fingers above the sternal notch. Through this incision, under direct vision, the fascia on the medial border of the sternocleidomastoid (SCM) muscle is incised, and by blunt dissection, the SCM muscle and strap muscles are progressively separated. Two small retractors are used in this preliminary step to gain the superficial operative space. When the jugular vein and carotid artery come into direct vision, the small retractors are replaced by larger and deeper retractors, which allow maintenance of the operative space for the remainder of the procedure via pulling of the vascular trunk medially and the SCM muscle laterally (Fig. 15.4).

The second access is a 5–7-mm incision along the posterior border of the SCM muscle at the

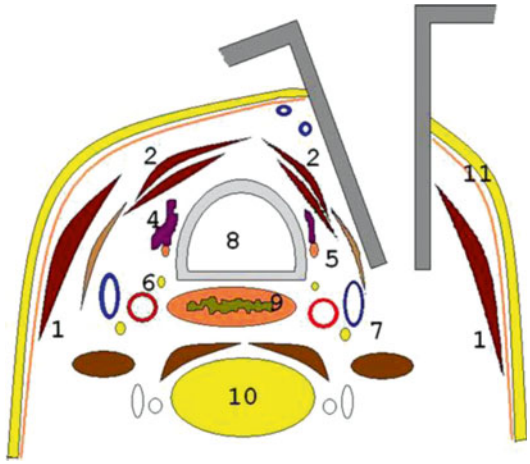

Fig. 15.4 Retractors allow maintenance of the operative space during the entire procedure. By means of these retractors, the SCM muscle is pulled laterally while the strap muscles and vascular trunk are pushed medially. (*1*) SCM muscle, (*2*) strap muscles, (*3*) anterior jugular vein, (*4*) thyroid bed after thyroidectomy, (*5*) parathyroid gland, (*6*) inferior laryngeal nerve, (*7*) neurovascular trunk (internal jugular vein, carotid artery, vagus nerve), (*8*) trachea, (*9*) esophagus, (*10*) vertebra, (*11*) platysma

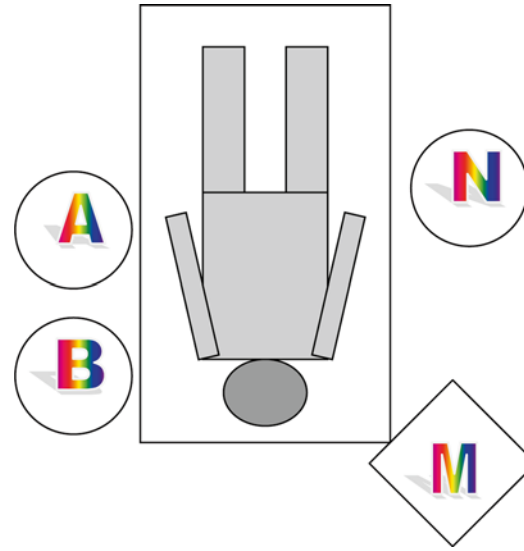

Fig. 15.5 The position of surgical team in VANS through infraclavicular skin incision for a patient with a left neck swelling. *A* the main surgeon, *B* the assistant surgeon, *N* the operating room nurse, *M* the video monitor

median level. All instruments except the endoscope are introduced through the main access, whereas the camera is inserted into the operative space through the second access. At this point, the lateral 5-mm trocar is introduced under direct vision of the endoscope and temporarily held through the main central incision.

The swelling is then grasped by a suitable instrument according to its nature and mobilized all around maintaining a bloodless field by diathermy or harmonic scalpel. After removal of the specimen, the lateral trocar is extracted. No drain is necessary, and wounds are closed by absorbable stitches.

15.5.3 Infraclavicular Approach

Under general anesthesia, the patient is placed in the supine position with the neck slightly extended. The primary surgeon stands on the same side of the swelling. Only one assistant is required to hold the telescope and stands on the same side of the main surgeon toward the head of the patient. The video monitor is placed at the head of the bed to the opposite side of the main surgeon (Fig. 15.5).

An oblique main incision is made for insertion of the harmonic scalpel and grasper, approximately 3 cm below the clavicle, on the chest wall on the ipsilateral side of the swelling. Through the main incision a wide dissection of the subplatysmal plane using long protected tip diathermy is carried out. Two pieces of Kirschner wire are inserted horizontally in the subcutaneous (SC) layer of the anterior part of the neck. These two Kirschner wires are lifted up by the mean of two handles connected and fixed to an L-shaped bar to create a tent-like working space (Fig. 15.6). Moreover, two sutures are inserted, one to the upper edge of the main wound and the second to the skin between the two Kirschner wires, and then pulled up to the L-shaped bar to obtain a wider working space. Another anterior neck skin incision of 5 mm length is then made on the ipsilateral side of the swelling, opposite to the medial border of SCM muscle, for the insertion of a 5-mm telescope through a small-sized trocar to facilitate handling of the telescope by the assistant.

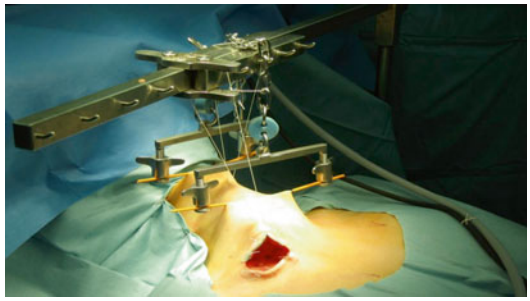

Fig. 15.6 The gasless lifting system for VANS consisting of two Kirschner wires, lifting handles, L-shape bar, two skin sutures with protection of skin edges

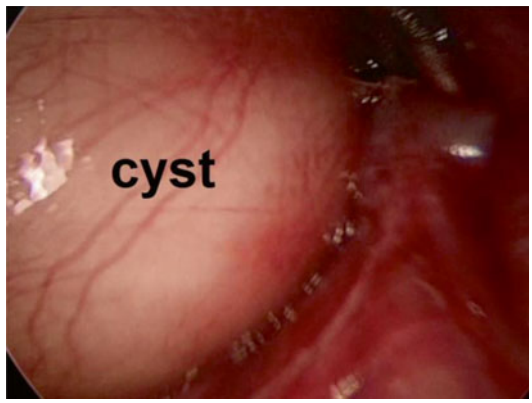

Fig. 15.7 Deep relations of a branchial cyst

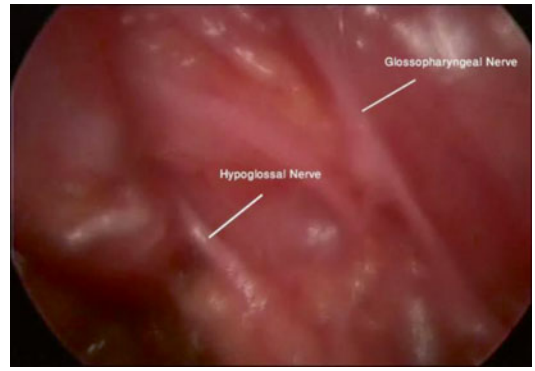

Fig. 15.8 The hypoglossal and glossopharyngeal nerves could be easily identified with the video-assisted technique

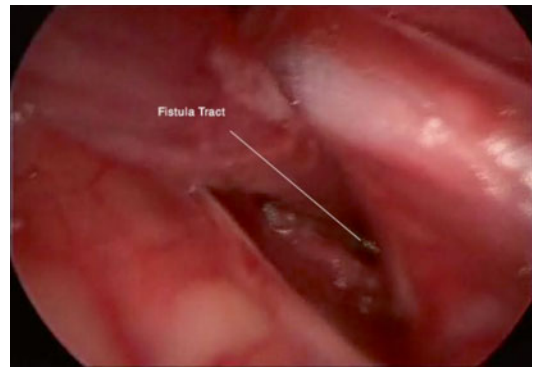

Fig. 15.9 The medial end of a branchial fistula could be identified with illumination and under magnification during VANS

One of the great benefits of using the video-assisted technique is that magnification helps avoidance of injury of important structures. Figure 15.7 demonstrates the medial aspect of the wall of a branchial cyst and its deep relations that are usually invisible during conventional surgery, while Fig. 15.8 shows how easily the hypoglossal nerve and the glossopharyngeal nerve could be identified.

Another benefit is good illumination especially in deep spaces, a benefit that is very useful in identification of fistulous tracts. Figure 15.9 shows the medial end of a branchial fistula.

15.6 Endoscopic Nodal Neck Dissection

Traditional open surgery for lateral neck dissection in patients with head and neck cancers requires a large incision to obtain adequate exposure of the surgical field, leaving an unsightly scar. Over the last decade, surgeons have witnessed dramatic changes in surgical practice as a result of technological advancement.

Several endoscopic modified radical neck dissections (MRND) have been conducted since the introduction of the endoscopic technique to thyroid surgery, attempting at minimizing the extent of dissection, improving cosmesis, reducing postoperative pain, shortening hospital stay, and enhancing postoperative recovery.

Many approaches have been used, mainly in thyroidectomy and neck dissection, either cervical or extra-cervical; the former is applied

through the lateral cervical, retroauricular, and submandibular incisions, while the extra-cervical approach is applied through the axillary, infraclavicular, and breast incisions.

The application and feasibility of the endoscopic approach was given a further boost with the availability of various *robotic systems* such as the da Vinci system. The use of a robot was not tempting at the beginning because of its relatively high cost, bulkiness of the robotic arm, and long operating time. However, since the recent publication demonstrating the feasibility and safety of robotic-assisted thyroidectomy in differentiated thyroid carcinoma, an increasing number of specialized surgical centers worldwide began to accept and perform this procedure. The theoretical advantages of using the robot over the endoscopic approach include the three-dimensional view offered to the operating surgeon, the flexible robotic instruments with seven degrees of freedom and 90° articulation, the increased tactile sensation, and the ability to filter any hand tremors [44].

In a recently published study by Yan and collogues [45], a cervical "scarless endoscopic thyroidectomy" (SET) with ipsilateral levels II, III, and IV dissection via breast approach for papillary thyroid carcinoma (PTC) was performed for 12 female patients. They reported that level II dissection by SET was a feasible and safe procedure, with reasonable costs and satisfactory cosmetic results.

Kang et al. [46] conducted a comparative study of the surgical outcomes of robotic versus conventional open MRND, for PTC with lateral neck node metastasis. They reported that the robotic MRND was similar to conventional open MRND in terms of early surgical outcomes and surgical completeness, but with the additional advantage of leaving no scar on the neck area. Robotic MRND may, therefore, be viewed as an acceptable alternative method in low-risk PTC with LNs. Another study published in 2015 by Sannikorn et al. [18] compared endoscopic-assisted neck dissection via a retroauricular approach versus conventional technique. The study was applied on 70 patients with head and neck cancers. Results were comparable regarding the mean total excised LNs and operative time, but better aesthetic results were in favor of the endoscopic technique.

15.7 Assessment of Minimally Invasive Neck Surgery

After the first endoscopic parathyroidectomy, performed and described by Gagner in 1996 [9], several surgeons reported their experiences with minimally invasive and video-assisted surgery of the neck [47–57]. Much of this change in technique has been technologically driven, in addition to the introduction of high-resolution endoscopy [58, 59] and advanced energy devices [60, 61].

15.7.1 Operative Time

The mean operative time of minimally invasive video-assisted lateral lymphadenectomy (MIVALL) for metastatic papillary thyroid carcinoma (PTC) was 60 min in the two cases reported by Miccoli et al. [62]. In another study, Miccoli and colleagues [63] described total thyroidectomy and central compartment lymphadenectomy via a video-assisted approach of 15 patients with a positive RET proto-oncogene. The mean operative time of the whole procedure was 67.3 min.

In a study done by Wu and Ding [47] evaluating video-assisted selective lateral neck dissection (VASLND) for PTC in 26 patients, the mean operative time was 46 min (range 26–75 min). Lombardi et al. [64] described an approach for lateral neck dissection after resection of PTC via a 4-cm skin incision between the cricoid cartilage and the sternal notch. Dissection of levels II–V were feasible in a time frame of 183 min (total thyroidectomy + central neck dissection + bilateral video-assisted lateral neck dissections) and 125 min (total thyroidectomy + central neck dissection + right video-assisted lateral neck dissection), in two reported cases, respectively.

Ming et al. [65] reported that endoscopic resection of branchial cysts through incisions made in the bilateral areolas and axilla took only

45 min, albeit with longer flaps to reach the neck. Furthermore, Han et al. [66] described video-assisted excision of macrocystic lymphangioma in 6 infants and children through the anterior chest wall and reported a mean operative time of 120 min (range, 90–150 min).

In an early report on MIVAT by Miccoli et al. in 2001 [67], they reported an operative time of 70 min for hemithyroidectomy and 110 min for total thyroidectomy. More recently, Pons and colleagues [68] conducted an analysis of MIVAT learning curve by the number of cases performed. Fifty procedures of thyroidectomy or hemithyroidectomy were performed by a surgeon unfamiliar with MIVAT. For the first 10 patients, an initial mean operative time of 98.5 min that decreased to 50 min after 30 cases was reported. There was no change in operative time thereafter in the remaining patients.

15.7.2 Blood Loss

Han et al. [66] reported a mean intraoperative bleeding volume of 15 ml (range 5–20 ml) for endoscope-assisted excision of cervical macrocystic lymphangioma via an anterior chest approach in infants and children.

Ming et al. [65] stated also that the use of an endoscope facilitated the identification of the surrounding tissue and allowed more elaborate operations for bleeding sites and attached tissues around the mass (branchial cyst) than the conventional surgery. The use of an ultrasonic scalpel was efficient in separating adhesions around the mass and cutting off blood vessels with a small range of thermal injury and no significant intraoperative bleeding.

15.7.3 Complications

Miccoli et al. [62] and Lombardi et al. [64] reported that none of the patients who underwent MIVALL developed nerve palsy, postoperatively. Also, Han and colleagues [66] reported that there were no complications such as local swelling, ecchymosis, subcutaneous fluid, swallowing disorder, hoarse voice, cough, or numbness around ear. They used tube drain in their patients for 36–48 h.

On the other hand, Wu et al. [47] reported that two patients out of 26 (7.7 %) who underwent video-assisted selective lateral neck dissection for PTC developed transient recurrent laryngeal nerve (RLN) palsy, with complete recovery of nerve function in 1 month postoperatively.

The operative scar is one of the most important aspects which head and neck surgeons consider when performing a neck surgery because the neck is always an exposed area. Bad cosmetic results with VANS might be attributed to skin scalding, which usually occurs due to friction of retractors and instruments with skin, a problem that had been overcome by Miccoli et al. [62] by using a sterile film to protect the skin.

Ming et al. [65] in his case report found that endoscopic resection of branchial cysts is a simple and convenient surgical approach, leading to covert incisions, fewer complications, and a faster recovery of patients. Moreover, Han et al. [66] reported that operations were successful and with no conversion of surgery. Postoperatively, all patients were satisfied with the postoperative cosmetic outcomes. However, endoscopic surgery was only performed on subjects with well-defined macrocystic lymphangiomas, without adhesions to nearby tissues.

Guerrissi [68] reported that, in all of his 108 VANS cases, no severe complications were encountered. Hematomas occurred in four patients, wound infection in two, and transitory dysesthesia of the lingual nerve in two other patients.

15.8 Conclusions

Minimally invasive surgery is a viable option in the head and neck and is advisable for young patients particularly concerned with cosmetic outcome. In fact, this procedure could allow avoidance of a long cervical incision otherwise necessary for performance of a traditional surgery. Careful patient selection is necessary; nature, size of the swelling, and its proximity to the site of incision are all factors to be considered to get the optimum results. Subjects with previous radiation or

surgery in the neck and suspected cases of recurrent infection or in the acute inflammatory stage should be excluded from endoscopic surgery.

The anatomy of the head and neck areas is ideal for application of endoscopic principles; its soft tissues can transform in an expandable cavity with avascular planes of dissection. The *advantages* of endoscopic resection are (1) better visualization and magnified view of the dissection areas, such that injury of important anatomic landmarks, nerves, and vessels can be avoided; (2) small incision; (3) an inconspicuous or hidden scar; (4) excellent postoperative comfort; and (5) short hospital stay. The *disadvantages* are that (1) it is necessary to have an endoscope and special instruments and (2) specific surgical training must be undergone by surgeons [69].

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