Non-toxic Thyroid Nodules and Multinodular Goitre

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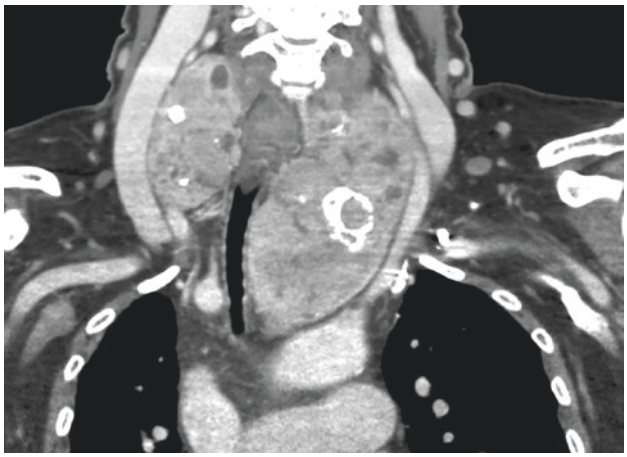
Case Presentation

A 60-year-old lady presents with a 12-week history of dyspnoea, worse on exercise and when she lies down in bed. She has no hoarseness or dysphagia. There is no family history of goitre. She is previously fit and well aside from controlled essential hypertension (furosemide). She has had a known goitre for many years.

On examination, she has a ruddy complexion and stridor at rest. Palpation reveals a large diffuse nodular goitre, and it is not possible to palpate a lower limit on either side. The images below show a lateral profile of her neck and two representative scans from her CT neck and thorax.



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Questions

1. Which of the following statements are true?
    1. Goitre is more common in women.
    2. Goitre is more common in the elderly.
    3. Diffuse goitre is more common than nodular in iodine-sufficient areas of the world.
    4. Smoking is a risk factor for the development of goitre.
    5. Multiple genes are responsible for the pathogenesis of goitre.
        (a) All are correct.
        (b) 1, 2 and 3 only are correct.
        (c) 2, 3, 4, 5 only are correct.
        (d) 1, 2, 4 and 5 only are correct.
        (e) 1, 2 and 4 only are correct.
2. Regarding blood tests
    1. Thyroid function tests are likely to be normal.
    2. A high TSH is associated with malignancy.
    3. A raised thyroglobulin is diagnostic of malignancy.
    4. An elevated anti-TPO titre predicts myxoedema.
    5. Thyrotoxicosis must be excluded.

(a) All are correct.
(b) 1 and 3 only are correct.
(c) 1 and 5 only are correct.
(d) 1, 2 and 5 only are correct.
(e) 2 and 4 only are correct.

3. The following ultrasonographic features are suggestive of malignancy:
   1. The presence of a halo
   2. Microcalcifications
   3. A low elasticity measure
   4. Cervical lymphadenopathy
   5. A nodule greater than 4 cm in maximum diameter
      (a) 1, 2 and 4 only
      (b) 2, 3 and 4 only
      (c) 2, 3, 4 and 5 only
      (d) 2 and 4 only
      (e) 2, 4 and 5 only
4. Regarding biopsy
   1. Ultrasound determines whether to perform an FNAB.
   2. Core biopsy can be used to diagnose thyroid lymphoma.
   3. FNAB of the dominant clinical nodule is the next best step.
   4. Biopsy should not be undertaken for anaplastic cancer.
   5. Biopsy is not necessary for long-standing goitres.
      (a) All are correct.
      (b) All are incorrect.
      (c) 3 and 5 are correct.
      (d) 2 and 5 only are correct.
      (e) 1, 2 and 3 are correct.
5. Regarding dysphagia
   1. It is more likely with retrosternal goitres.
   2. It is more likely with bilaterally enlarged goitres.
   3. It can be secondary to gastro-oesophageal reflux.
   4. It is suggestive of a malignant process.
   5. Upper intestinal endoscopy must be undertaken.
      (a) All are correct.
      (b) 1 only is correct.
      (c) 1 and 2 only are correct.
      (d) 1, 2 and 3 only are correct.
      (e) 1, 2, 3 and 4 only are correct.
6. Which of the following statements are true regarding the goitre in the clinical images above?
   1. This goitre could be treated with 131 iodine ablation.
   2. This goitre could be treated with thermal ablation.
   3. A median sternotomy may be required to excise this goitre.
   4. Preoperative vocal cord inspection is mandatory.
   5. This goitre might be extracted using the cervical approach alone.

(a) All are correct.
(b) 4 and 5 only are correct.
(c) 3 and 4 only are correct.
(d) 1 and 5 only are correct.
(e) 3, 4 and 5 only are correct.

7. Which of the following statements are true?
   1. Unilateral nodular disease is best treated by hemithyroidectomy.
   2. A hemithyroidectomy carries a 50% risk of permanent hypothyroidism.
   3. A Dunhill operation has fewer complications compared with total thyroidectomy.
   4. Prescribing levothyroxine after hemithyroidectomy may reduce the risk of contralateral 'recurrence' in a subgroup of patients.
   5. Hemithyroidectomy avoids the risk of hypoparathyroidism.
      (a) 1, 2, 4 and 5 only are correct.
      (b) All are correct.
      (c) 1, 3 and 4 only are correct.
      (d) 1, 4 and 5 only are correct.
      (e) 1, 2, 3 and 4 only are correct.
8. Indications for a median sternotomy for retrosternal goitre include
   1. Pre-existing recurrent laryngeal nerve palsy
   2. Previous median sternotomy
   3. Working in a hospital with thoracic surgeons
   4. A preoperative diagnosis of papillary thyroid carcinoma
   5. Severe stridor
      (a) All are correct.
      (b) 1, 3 and 5 are correct.
      (c) 5 only is correct.
      (d) 3 only is correct.
      (e) None are correct.
9. For retrosternal goitre, the following complications are more common:
   1. Hypoparathyroidism
   2. Recurrent laryngeal nerve injury
   3. Postoperative haemorrhage
   4. Tracheomalacia
   5. Venous thromboembolic disease
      (a) All are correct.
      (b) 1, 2 and 3 only are correct.
      (c) 1, 2, 3, and 4 only are correct.
      (d) 1 and 2 only are correct.
      (e) 2 and 3 only are correct.
10. For a euthyroid benign solitary nodule, indications for surgical management include
    1. A nodule with a maximum diameter >4 cm
    2. The presence of dysphagia

3. In the case of significant cosmetic concerns
4. Tracheal deviation
5. A positive family history of thyroid cancer
   (a) All answers correct.
   (b) None of the answers are correct.
   (c) 2 and 3 only are correct.
   (d) 1 and 4 only are correct.
   (e) 1, 2 and 4 only are correct.

2.1 Introduction

The normal thyroid cannot be seen by inspection nor palpated. A visible or palpable thyroid gland is called a goitre (latin *guttur* = *throat*). A goitre may be large or small, hyper-, eu- or hypothyroid and can either be benign or malignant. So the term *goitre* tells us nothing about the aetiology; it is simply a short-hand term for an enlarged thyroid. Goitres can be *nodular* (solid or fluid-filled) or *diffuse*. A single thyroid nodule can also be called *solitary*. This chapter deals with euthyroid goitre.

2.2 Clinical Presentation

Patients present with a painless lump and are often unsure as to its duration. The increased size of the goitre can lead to symptoms related to pressure effects on adjacent structures such as dysphagia (from pharyngeal and/or oesophageal compression), globus sensation, hoarseness (from laryngeal or recurrent laryngeal nerve compression) or shortness of breath (from tracheal deviation and compression).

An incidental thyroid nodule (ITN) is one of the most common incidental findings on imaging studies that include the neck. Guidelines have been developed to assist the medical provider in deciding when and how to investigate ITN [1].

2.3 Natural History

The presence of goitre was originally determined from autopsy studies that weighed the thyroid gland, but this was superseded by the use of ultrasound by which a goitre is diagnosed if the size of the thyroid gland is greater than three standard deviations of the median (volume 18 ml for women and 25 ml for men). Goitre is more common in iodine-deficient regions of the world, where endemic goitre affects 10% of the population [1, 2]. In Framingham, clinically apparent nodules (palpation) were present in 6.4% of women and 1.5% of men [3]. The presence of single thyroid nodules was 3%, and multinodular goitre was 1%. In an autopsy study in 1955, 50% of people

had thyroid nodules and the majority were multiple [4, 5]. Like autopsy, imaging frequently reveals subclinical thyroid nodules and, when ultrasound is used in epidemiological studies, the estimate of goitre prevalence is 19–67% [4]. Incidental thyroid nodules are seen in up to 25% of contrast-enhanced chest CT scans [6]; 16–18% of CT and MR scans of the neck [7, 8] and 1–2% PET scans [9]. In patients under 40 years, the goitre is typically a solitary nodule, whereas diffuse goitre is more common over the age of 65 years. The female to male ratio is 4:1 [10].

2.4 Aetiology

It is generally believed that the development of goitre depends on complex interactions amongst genetic, environmental and endogenous factors. Studies on monozygotic and dizygotic twins provide evidence to suggest that there is a genetic component to the aetiology of goitre [11]. Whilst various candidate genes have been associated with familial goitre, it appears that there is a considerable heterogeneity in familial goitre [11, 12]. The genetic contribution to goitre formation is more pronounced in areas of borderline iodine deficiency compared with areas of endemic goitre. Moreover, goitre with multiple nodules (multinodular goitre, MNG) is clearly influenced by genetic markers, whereas goitre with a solitary nodule most likely develops as a result of environmental exposures [13]. The most important risk factors associated with the genesis of goitre are smoking and iodine deficiency. In iodine-deficient areas of the world, people suffer from nodular goitre, whereas in iodine-abundant areas, diffuse goitre is more common [14]. Tobacco smoking increases the risk of goitre formation probably via iodine-mediated mechanisms. Thiocyanate from the metabolism of cyanide in tobacco smoke is a likely candidate [13].

2.5 Pathogenesis

The genetic development of goitre appears to be polygenic with no single gene being either necessary or sufficient for goitre development. A number of loci (MNG-1, and 3) have been identified on various chromosomes including 14, 19 and the X chromosome [13]. Iodine deficiency triggers hyperplasia and hypertrophy probably via the mutagenic effects of free oxygen radicals generated in the iodine-deficient thyroid and this process is independent of TSH [15]. Both diffuse and nodular goitre may occur secondary to subtle arrangements in thyroid hormonogenesis and TSH overproduction [15]. In smoking,

thiocyanate from the metabolism of cyanide in tobacco smoke is a likely mediator for goitre formation [13].

2.6 Diagnosis

The goals from the history, clinical examination and special investigations are as follows:

- To confirm that the patient has a goitre
- To identify patients with thyroid cancer
- To identify patients with benign disease and compressive effects that would benefit from thyroid surgery

When present, growth of the lump is slow unless there has been haemorrhage into a cyst, in which case there is a very sudden onset/expansion. There will be an absence of symptoms of thyroid dysfunction and symptoms to suggest malignancy (rapid growth and hoarseness). A positive family history is common. It is important to enquire about the geographical background – does the patient come from a geographical area with endemic goitre?

2.7 Clinical Examination

Whilst taking the history it will become apparent if the patient has any audible hoarseness of the voice, stridor or breathlessness at rest. Inspection will allow you to form an impression about the patient's thyroid endocrine status. In the neck, any obvious mass is seen and the patient is asked to swallow a cup of water to determine if the mass rises. The examiner should look for dilated veins coursing over the anterior chest wall which would raise the suspicion of mediastinal venous hypertension (◘ Fig. 2.1).

Palpation can be performed standing behind the patient. The mass is confirmed as a goitre by palpation as the patient swallows water (as seen on inspection). The goitre is palpated and the size (cm), extent (solitary or diffuse), surface (smooth or nodular) and consistency (hard, rubbery or soft) are determined. You should examine for the lowest extent of the goitre on swallowing to determine if there is retrosternal extension. The trachea should be palpated (is it palpable and central?) and the lateral neck must be palpated for the presence or absence of lymph nodes. The sternum may be percussed to determine retrosternal dullness (an unreliable physical sign). In the presence of retrosternal extension, ask the patient to elevate their upper limbs to narrow the thoracic inlet and elicit Pemberton's sign (inducing facial plethora). With the arms elevated listen again for the presence of stridor.

Fig. 2.1 Dilated veins over the chest wall in the presence of significant retrosternal extension

2.8 Thyroid Function Tests

All patients presenting with a goitre should undergo thyroid function tests. If abnormal, auto-antibody titres are measured. An elevated TSH is associated with a higher chance of malignancy [16].

2.8.1 Thyroid Ultrasound

Thyroid ultrasound can
- Confirm the patient has a thyroid lump
- Accurately measure its dimensions

- Provide information about the ultrasound characteristics of the goitre
- Determine the presence of suspicious cervical lymphadenopathy

The pattern of sonographic features confers a risk of malignancy and guides decision making about which nodules should undergo FNAB [17]. For example a hypoechoic solid nodule with calcifications and irregular margins requires a biopsy, whereas a purely cystic or spongiform lesion is less likely to need cytologic evaluation [17, 18]. Elastosonography is a relatively newer technique and nodules with high elasticity have a low probability of malignancy. This can further guide which nodules require FNAB [19].

2.8.2 Fine-Needle Aspiration Biopsy (FNAB)

Most thyroid nodules are benign (95%). The main goal in assessing a patient with a goitre is to identify those patients who require thyroid surgery. FNAB is the most useful preoperative tool to diagnose malignancy. The nodules that should undergo biopsy include the following:

- Nodules >10 mm with high-risk sonographic features (hypoechoic solid nodule with microcalcification, irregularity, taller than wide shape, evidence of extrathyroid extension (ETE))
- Nodules >10 mm with intermediate sonographic suspicion (hypoechoic, solid nodule with smooth margins without microcalcifications, irregularity, ETE, wider than tall shape)
- Nodules >15 mm with low sonographic suspicion (isoechoic or hyperechoic solid nodules, partially cystic nodules with eccentric solid area) [17]

The biopsy result is classified according to the Bethesda (USA) or Thy (UK) classification system.

2.8.3 Precision Medicine

Precision medicine is defined as 'the right treatment for the right patient at the right time'. For the indeterminate thyroid nodule this translates to the 'right clinical decision for the right cytology, with the right test'. A vast amount of effort has been invested in trying to identify cancers in the population of patients with indeterminate cytology. The approach can either be to try and identify cancers by searching for the presence of somatic mutations (rule-in approach) or to try and identify patients with benign nodules (rule-out).

Rule-in tests are designed to drive the clinician to recommend surgery in the case of a positive result. Rule-in searches for a number of mutations simultaneously (*BRAF, NRAS, HRAS* and *KRAS* mutations and *PAX8*/*PPARG*- and *RET*/*PTC* rearrangements) and to be successful a high positive predictive value is required. Rule-out tests are designed to identify patients who have benign disease and do not require follow-up. To be successful, it requires a high negative predictive value. The drawback to the test is the lack of long-term outcome data on patients excluded from surgery.

Currently, no test is wholly reliable and the greatest barrier to their use is cost [20, 21].

2.8.4 Cross-Sectional Scans

CT scanning is indicated for retrosternal goitre and can provide information on the following:

- Confirmation of the presence and determination of extent of retrosternal extension
- A 'road map' for the anaesthetist (tracheal deviation and compression)
- Oesophageal compression
- At-risk anatomical structures in the impending surgical field
- An assessment of malignancy (not accessible by ultrasound)
- Anterior versus posterior mediastinal extension
- The likelihood that the goitre can be extracted without the need for a sternotomy (the 'shape' of the goitre)

2.8.5 Laryngeal Examination

Despite a thorough patient history, subtle voice changes are not easily volunteered by patients and may be difficult for clinicians to detect. Also, there is a significant divergence between voice symptoms and objective vocal cord function. Indeed, the sensitivity of voice change in predicting VCP can range from 33% to 68% [22, 23]. Thus, vocal cord paralysis may be present without significant vocal symptoms (and vice versa). Goitres can directly compress the recurrent laryngeal nerve which provides a rationale for the inclusion of a preoperative glottic examination in these patients to facilitate surgical planning, aid intraoperative decision making and optimize patient counselling.

2.9 Management

Indications for treatment include the following:

- Suspicion of malignancy
- Compression of trachea
- Compression of oesophagus
- Quality of life

The patients at particular risk for these symptoms are those with a retrosternal component. When the goitre is confined to the neck, the overlying skin and subcutaneous tissues are stretched and the patient may only notice a visible lump in the neck. However, when the goitre plunges behind the bones (clavicular head and manubrium), the confined space causes adjacent soft tissue structures to become compressed, principally the trachea and oesophagus (Fig. 2.2). Tracheal involvement can either result in deviation or narrowing. Tracheal deviation is typically asymptomatic and does not require surgery (Fig. 2.3). Tracheal compression results in upper airway obstruction (UAO) with suppression of the inspiratory capacity which can be detected on flow loop volume analysis. The patients may have stridor and/or complain of exertional dyspnoea.

Oesophageal compression is less common than tracheal and more difficult to quantify. Contrast swallowing radiologi-

Fig. 2.2 Coronal plane of CT scan showing retrosternal right goitre with deviation and compression of the trachea (arrow)

Fig. 2.3 Cross-sectional CT scan of the neck at the level of the manubrium in a patient with dysphagia to solid food. A goitre can be seen to be sited between the trachea and the oesophagus (arrow)

cal studies are often unhelpful and the surgeon should rely on the history and cross-sectional imaging to determine whether surgery is likely to be of benefit (Fig. 2.3). In severe cases, large vessel venous compression may manifest as superior vena cava syndrome.

There are three options for management.

2.9.1 Conservative

Many patients with goitre have no or only a few symptoms. In the absence of any concern about malignancy (either by ultrasound and/or biopsy) or compressive symptoms, it is very reasonable to manage patients with goitre conservatively. Treat the patient, not the X-ray. Be aware that some apparent retrosternal goitres on CT scan may be exaggerated by a patient's flexed neck at the time of the scan. When looking at the CT scan, take note of where the chin is, in relation to the thyroid. Some 'retrosternal goitres' can be cured by neck extension! Most goitres (90%) do not progress in size and those that do, do so slowly [24]. It is reasonable to offer to review the patient after a 6–12-month period and if there has been no progression and the patient is happy to avoid surgery, then the patient can be discharged. Note that there is a poor correlation between goitre size and symptoms. Be aware that some symptoms may be unrelated to the goitre. This is especially so for patients with neck discomfort. Care must be taken in attributing symptoms to a goitre when the patient has an underlying lung condition (e.g. COPD) or gastro-oesophageal reflux disease.

2.10 Non-surgical (Means to Debulk the Thyroid)

2.10.1 Radio-iodine Therapy

Surgery has the uncontested advantage that it provides a rapid and comprehensive removal of the goitre. However, there are certain situations when a non-surgical approach might be considered:

- Previous thyroid surgery
- Severe co-morbidity
- Intrathoracic location

131I therapy reduces the volume of non-toxic nodular goitres by 35–50% within 1 year [25]. A prerequisite is sufficient radio-iodine uptake in the target tissue which can be evaluated qualitatively by thyroid scintigraphy.

Complications can be classified as early and late. A radiation-induced thyroiditis is occasionally seen in the early days after treatment. Adjuvant glucocorticoids might be considered in patients with significant tracheal compression. Patients may also experience a transient hyperthyroid state, but this is usually subclinical. In the longer term, about 20% of patients may develop hypothyroidism. The risk of malignancy remains unproven [25, 26]. For patients requiring a rapid debulking and for those with a larger goitre (>100 ml), surgery remains the preferred option.

2.10.2 Thermal Ablation

There are a number of 'minimally invasive techniques' performed under local anaesthesia. They all induce thermonecrosis via a local circumscribed damage of tissue when temperatures rise to between 65 and 100 degrees Celsius. The cells are irreversibly destroyed and degraded by the body, resulting in a reduction in volume of thyroid tissue over subsequent months. The variety of techniques include the following:

- Laser ablation
- Microwave ablation
- High intensity focused ultrasound
- Mono- and bi-polar radiofrequency ablation

Prerequisites to these forms of treatment include exclusion of malignancy (FNAB), vocal cord assessment and informed consent [27]. These techniques are relatively new, and long-term data is not available. However, the published outcomes suggest that these techniques offer an alternative to surgery especially for the smaller benign nodules. Relative contraindications include diffuse enlargement, larger nodules (>30 ml) and nodules with far caudal extension [28].

2.11 Surgical

2.11.1 Thyroid Surgery

The details of thyroid surgery are covered in ▶ Chap. 11. However, there are different approaches to the treatment of the euthyroid nodular goitre that deserve special consideration.

2.11.2 Hemithyroidectomy

Multinodular goitre is often asymmetric and only one half of the thyroid is affected in about one half of all patients [29]. In this scenario, a hemithyroidectomy is a reasonable option as it avoids the possibility of hypoparathyroidism, halves the risk of recurrent laryngeal nerve injury and reduces the risk of hypothyroidism (22%) [30]. The disadvantage of this approach is the potential for contralateral progression of the goitre and the later need for a second completion operation. This can be mitigated with the prescription of levothyroxine which reduces the risk of progression from 16.7% to 1.4% [31]. All of these issues must be discussed with the patient before a management plan is agreed.

2.11.3 Subtotal Thyroidectomy or Total Thyroidectomy

Historically, the approach for diffuse multinodular goitre was a unilateral total lobectomy and contralateral subtotal lobectomy (Dunhill operation). A total thyroidectomy was proposed in order to abolish the risk of recurrent goitre and the need for re-operative surgery with its much higher morbidity [32]. The concern about shifting to a total thyroidectomy is the higher risks of permanent recurrent laryngeal nerve injury and hypoparathyroidism. However, more recent data suggests that these risks are not greater when the surgery is undertaken by higher volume surgeons [17]. In a randomised study comparing Dunhill with total thyroidectomy, the recurrent goitre rate was 8.6% versus 0.6% with a subsequent re-operative rate of 2.8% versus 0.6% [33]. For bilateral multinodular goitre, total thyroidectomy is the operation of choice.

2.11.4 Retrosternal Goitre

It is desirable to avoid a median sternotomy with its associated morbidity whenever possible. The majority of retrosternal goitres (90%) can be extracted via a cervical excision [34]. Risk factors for a non-cervical approach include involvement of multiple mediastinal compartments, iceberg morphology,

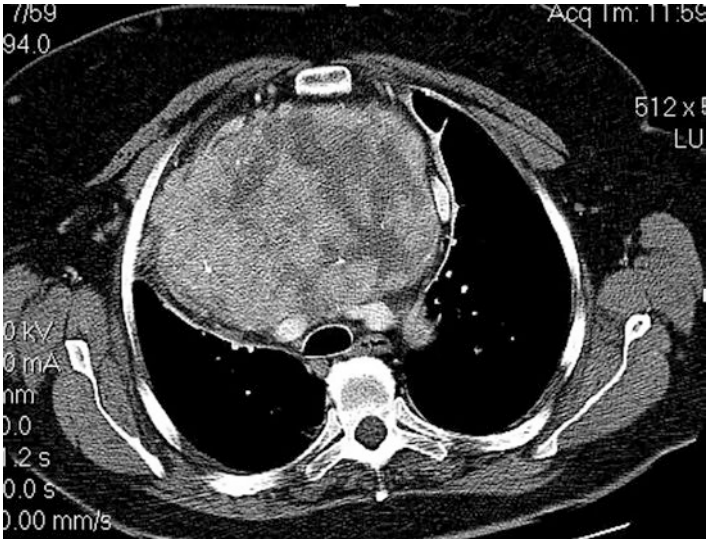

Fig. 2.4 Cross-sectional CT scan demonstrating a huge anterior mediastinal goitre for which a cervical extraction is not possible

extension to the posterior pleura and goitre with separate components (Fig. 2.4) [35]. All of these can be determined by cross-sectional imaging of the neck and thorax. Where there is a risk for an extracervical access, a thoracic surgeon should be engaged early in the planning stage. It is equally important that an anaesthetist with experience in the 'difficult airway' is a member of the multidisciplinary team. There is an increased risk of injury to the recurrent laryngeal nerve due to a combination of distorted anatomy, a longer length of nerve dissection and at times a suboptimal view of the nerve [36]. Intermittent intraoperative nerve monitoring can assist in nerve localisation and continuous monitoring may help prevent traction related nerve injuries. Equally, identification of the inferior parathyroid glands may be more demanding and so, the surgeon must be obsessive in identifying the superior glands to minimise the risk of hypoparathyroidism. Retrosternal goitre is an independent risk factor for postoperative haemorrhage [37]. Whilst tracheomalacia is a justifiable concern in patients with tracheal compression, this complication is very rarely observed in the Western World. Owing to the large dead space at the end of the resection, drains are often deployed.

2.11.5 Video-Assisted Thoracoscopic Thyroidectomy

This minimally invasive approach has been adopted by some thoracic surgeons with less morbidity compared to median sternotomy. Several ports are placed into the chest between the ribs. The conversion rate to open surgery is less than 10% [38].

2.11.6 Transoral Thyroidectomy

The minimally invasive approach to thyroidectomy via the oral vestibular route has been developed and is currently under evaluation. It adheres to the principles of minimally invasive surgery using an endoscopic approach anterior to the mandible between the mentalis muscles. Contraindications to this approach are thyroid volume: >45 ml or a dominant nodule size >50 mm [39]. The sole benefit of this novel approach is cosmetic. The technique is very demanding and is yet to be adopted as a mainstream approach by thyroid surgeons.

Answers to the Questions

1. (a); 2. (d); 3. (b); 4. (e); 5. (d); 6. (e); 7. (d); 8. (e); 9. (b); 10. (c)

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