Review Article

Surgical management of cytologically indeterminate thyroid nodules

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Abstract: Nodules in the thyroid are frequent. Preoperative investigations including fine-needle cytology and ultrasound cannot in all patients rule out malignancy. Thus, surgical excision for histopathologic examination is often needed. In this narrative review, we examine aspects of the surgical management of indeterminate thyroid nodules, using a comprehensive review of the available literature. The authors manually searched PubMed for relevant literature, including recently published guidelines. Hemithyroidectomy without lymph node dissection remains the recommended management in indeterminate thyroid nodules, i.e., the complete removal of one lobe of the thyroid, for indeterminate thyroid nodules, defined as nodules with fine-needle cytology fulfilling the criteria of Bethesda III or IV categories. At surgery, it is important to preserve the recurrent and superior laryngeal nerves, and intraoperative neuromonitoring is a useful adjunct. Recent data also suggest that parathyroid autofluorescent techniques are promising tools for parathyroid preservation. There is still lack of specific preoperative investigations to rule in or out central lymph node metastasis. Intraoperative frozen section of lymph nodes can be valuable, but prophylactic or diagnostic central lymph node dissection is not routinely recommended. Outcomes after thyroid surgery are better with high-volume surgeons and institutions. Surgery is probably best performed by high-volume surgeons in institutions with on-site expert pathologists and with technical adjuncts available for nerve and parathyroid preservation. Day-care surgery may be an option for selected patients.

Keywords: Thyroid nodule; surgery; Bethesda; review

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Introduction

Unilateral lobectomy (hemithyroidectomy) remains the gold standard for obtaining a definitive diagnosis for a cytologically indeterminate thyroid lesion atypia/follicular lesion of undetermined significance (AUS/FLUS) or follicular neoplasm (FN)—Bethesda III and IV (1). In this narrative review, we give an overview over existing guidelines, discuss situations where watchful waiting is a valid alternative; we present a summary of how to evaluate and treat potential lymph node metastasis; we review techniques for optimizing outcomes and minimizing risk of damage to recurrent and superior laryngeal nerves and parathyroids; we give an overview of risk of complications and how to manage them; finally we review the literature on volume, experience and issues of centralization of thyroid surgery in this regard.

Guidelines

Several organizations have produced comprehensive, well-researched guidelines for the management of thyroid nodules and/or thyroid cancer. The American Thyroid Association (ATA) published their guidelines in 2015 (2), the German guidelines were published in 2012 (3), the British in 2014 (4), a Korean review and adaptation of the ATA guidelines were published in 2016 (5). The American Association of Endocrinologists together with the Italian Association for Endocrinology also in 2016 updated their previously published guidelines (6). Arguably, the most well-researched and comprehensive of these guidelines is the ATA report (2).

The guidelines agree that the decision if and how to operate for indeterminate (Bethesda III–IV) lesions cannot be made on cytology alone (2,3). It is recommended that clinical factors, such as previous irradiation to the neck, family history, growth rate, associated vocal cord palsy, and sonographic factors (7) such as calcifications and irregular margins are taken into account. The guidelines also mention that molecular testing can be helpful but that evidence currently is too weak to make specific recommendations (8). All guidelines agree that the patient needs to be involved in the decision-making, and that difficult cases can be discussed in a multidisciplinary meeting. Thus, guidelines emphasise a comprehensive work-up for thyroid nodules, and that all available information is taken into account before a decision if and how to operate is made. For FN, Bethesda IV, most guidelines recommend surgery, whereas watchful waiting can be an option in patients with AUS/FLUS, Bethesda III, in the absence of worrisome clinical and ultrasonographic factors.

Guidelines also agree that the surgical procedure of choice for indeterminate thyroid lesions (Bethesda III–IV) is a lobectomy, i.e., the (near) total, complete removal of the entire right or left thyroid lobe. In some circumstances, a total thyroidectomy can be justified; in bilateral lesions or with significant enlargement of the contralateral lobe, if the lesion is large, if the patient has a family history or history of radiation exposure, or if the patient strongly wishes not to undergo a second surgery. Total thyroidectomy has higher complication rates, even when performed by high-volume, experienced surgeons; it is also noted that countries differ in reported complication rate (5)—countries with low complication rates might tend to use a total thyroidectomy more often. Guidelines also advise against the use of frozen section for indeterminate (AUS/FLUS/FN, Bethesda III–IV) lesions during surgery, which generally is too unspecific and cannot reliably distinguish malignant from benign nodules.

Watchful waiting

The purpose of surgical lobectomy in the setting of AUS/FLUS/FN is to reach a definitive diagnosis. However, an appropriate treatment plan for any patient with an AUS/FLUS/FN, Bethesda III–IV lesion strikes a balance between the potential risks and benefits of surgery compared to non-surgical management taking patient preferences, relevant co-morbidities, underlying epidemiological risk and ancillary diagnostic information into account. Depending on these factors, discussed briefly below, the option of watchful waiting must be considered.

Arguably, the most important factor for risk assessment is the underlying epidemiological risk. According to the Bethesda System for Reporting Cytopathology the implied risk of malignancy is 6% to 18% in AUS/FLUS and 10% to 40% in FN (1). However, depending on the practice setting of the diagnostic service the underlying rate of malignancy will vary, e.g., for AUS/FLUS from 8% in a primary (9) to 38% in a tertiary care setting (10). Thus, rates of malignancy for the different Bethesda categories need to be validated individually at each diagnostic service.

With repeat FNA, the diagnosis of indeterminate (AUS/FLUS) nodules will change to benign in some 40% to 58% of cases (11,12). However, in the lesions that are resected, malignancy rates are high (12). These malignancy rates may be both over- and underestimated as histopathological verification is lacking for most lesions that are reclassified as benign on repeat follow-up and resected nodules likely represent a selected group with other suspicious findings. In the AUS/FLUS-group, ultrasound features also help distinguishing benign from malignant tumors (13).

Recently, gene panels to discern malignant from benign lesions have become available, the most common tests in clinical use being the Afirma® Gene Expression Classifier (GEC) and the Thyrosec® V2 (8). Alexander *et al.* reported a high sensitivity (92%) and negative predictive value (93%) for the Afirma® GEC (14) making it a potentially useful adjunct to rule out malignancy. High sensitivity, specificity, positive and negative predictive values were also reported for the Thyrosec® V2 (15,16). However, subsequent validation studies have reported wide variations in test performance (8). Interestingly, the use of molecular tests have been reported to alter clinical management in only 7.9–8.2% of cases (17,18), questioning the impact of these tests in clinical practice. Thus, the role of molecular testing in the management of AUS/FLUS remains to be established.

In conclusion, watchful waiting is an option for selected patients with AUS/FLUS depending on patient preferences, especially in the setting of low epidemiological and sonographic risk. It may also be a valid option for a FN, Bethesda IV, in the elderly patient with relevant co-morbidities and increased surgical risk.

Extent of surgery and central lymph node dissection

In the setting of preoperatively known papillary cancer there has been considerable debate regarding the value of prophylactic central lymph node dissection (pCLND) (19). Those in favour of pCLND argue that pCLND decreases the risk of local recurrence and increases long term survival, while opponents argue that there is no level 1 evidence that pCLND improves survival and that pCLND is associated with a higher risk of postoperative hypoparathyroidism and RLN palsy.

In the setting of AUS/FLUS/FN, the risk of postoperative diagnosis of malignancy is smaller and the case for pCLND correspondingly weaker. To obtain a definitive diagnosis of an AUS/FLUS/FN, a simple lobectomy is the procedure of choice. Intraoperative frozen section of lymph nodes can be valuable, but prophylactic or diagnostic central lymph node dissection is not routinely recommended.

Completion thyroidectomy

Depending on the final histological diagnosis, completion thyroidectomy, i.e., the complete removal of the contralateral thyroid lobe, may be suggested. For small, solitary intrathyroidal papillary cancers, most guidelines do not recommend completion thyroidectomy; however, for larger, multifocal and/or cancers extending outside the thyroid gland, guidelines suggest completion thyroidectomy (2-4). There is an ongoing debate as to whether completion thyroidectomy is needed also in patients with larger intrathyroidal solitary papillary cancers; specifically, many European authors would recommend completion thyroidectomy, whereas the American guidelines state that lobectomy alone can suffice in these situations (20). Proponents of lobectomy cite the low fatality and recurrence rates in differentiated thyroid cancer; lower risk of complications such as hypoparathyroidism, recurrent nerve palsy; and the possibility of avoiding life-long thyroxin replacement. On the other hand, reasons for a complete thyroidectomy are easier follow-up and detection of recurrence through thyroglobulin measurement; and the potential to administer radioiodine, which might lower the recurrence rate. However, a full discussion on the merits of lobectomy *vs.* total thyroidectomy in differentiated thyroid cancer is beyond the scope of this review.

Follow-up after lobectomy

All patients need to have their thyroid status checked with blood tests including at least levels of thyroid stimulating hormone (TSH), possibly also levels of free thyroid hormones T3 and T4; apart from this, benign lesions usually are not followed. For malignant lesions, an individual recommendation regarding further treatment and follow-up, using evidence as summarized in current guidelines (2-4), has to be made. As stated above, this is beyond the scope of this review.

Nerve identification and preservation

Arguably, the most deleterious complication in thyroid surgery is damage to the recurrent laryngeal nerve (RLN) (21). Therefore, the RLN should be identified in all thyroid surgeries (21). The external branch of the superior laryngeal nerve (EBSLN), which innervates the cricothyroid muscle, is also important, especially for high pitch and voice projection (22). Data suggest that intraoperative neuromonitoring, IONM, increases the rate of identification both of the RLN (21) and the EBSLN (23). Studies also imply that IONM is associated with a lower risk of permanent damage to the RLN (24) and the EBSLN (22).

Most instances of damage to the RLN are due to traction. Less common types of injury are transection, heat through diathermy and crushing. These types of injury more often lead to permanent injury, whereby traction injuries sometimes heal (25).

Continuous intraoperative neuromonitoring with automatic periodic stimulation (APS) has been suggested to lower the rate of permanent RLN palsy, presumably by warning the surgeon from imminent damage to the RLN due to traction (26). Traction will lead to lower amplitude and longer latency, which will be detected with APS, making it possible for the surgeon to abort the maneuver that caused the traction.

Parathyroid identification and preservation

The parathyroid glands are at risk of inadvertent injury at thyroid surgery, either through accidental removal or devascularization (27). As stated above, the procedure of choice is a lobectomy (hemithyroidectomy), where only two parathyroids are at risk, and, consequently, the patient cannot have hypoparathyroidism after a lobectomy. Still, a significant proportion of patients will undergo completion hemithyroidectomy, and will then be at risk of hypoparathyroidism (28).

Chronic hypoparathyroidism after total thyroidectomy is more common than previously thought—in population-based studies between 5% (29) and 7% (30), and associated with low quality of life (31), increased costs (32), risk of serious morbidity and even reduced survival (29). Thus, it is imperative to avoid hypoparathyroidism, and since it cannot be known if the patient will have completion hemithyroidectomy, the old adage of viewing "every parathyroid as the patient's last" still holds true.

However, even expert surgeons have difficulties in identifying and preserving the parathyroid glands. Recently, similar to IONM that helps identifying and protecting the nerves, devices to identify parathyroid glands have been introduced. Thus, Fluoptics and PTEye have been approved by the FDA in the US as adjuncts for parathyroid identification. They take advantage of the fact that parathyroid glands fluoresce, i.e., they emit light of a different wavelength when illuminated with near-infra red light. Studies suggest that parathyroid identification increases when these adjuncts are used (33).

Identifying the parathyroids is not enough—their vasculature also needs to be preserved. A promising tool in this regard is parathyroid angiography with the autofluorescent dye indocyanine green (ICG). ICG is injected intravenously and the parathyroids are illuminated with near-infrared light. If well vascularized, the ICG will fluoresce and can be detected with special optical equipment. Studies have shown that having at least one well vascularized parathyroid gland makes the risk for permanent hypoparathyroidism almost zero (34).

Complications

In general, thyroid surgery is safe with low reported complication rates. Adjuncts to minimize the risk of RLN palsy and postoperative hypoparathyroidism have been discussed above. The two other major complications are postoperative hematoma and surgical site infections (SSIs). Bergenfelz *et al.* report a 2.1% frequency of re-bleeding requiring surgical management and SSIs in 1.6% (35).

Postoperative hematoma with airway compromise is a feared but rare complication after thyroid surgery. Several risk factors have been identified including older age (35,36), extent of resection, bilateral procedure and re-operations and an associated mortality of 0.01% (36). Some 80% of postoperative bleedings occurred in the first 6 hours after surgery and 97% within 24 hours. Other authors have found a more stochastic distribution of bleedings without relationship to the extent of surgery (37).

Analyzing a dataset from the Scandinavian Quality Register for Thyroid and Parathyroid Surgery (SQRTPA), the rate of SSIs were 1.2% (38). Independent risk factors for developing an SSI were lymph node dissection and the use of drains. There is no evidence that antibiotic prophylaxis affects the rate of SSIs after thyroid surgery (39) and is not indicated for the surgical management of AUS/FLUS/FN. Established SSI should be managed with antibiotics for skin flora, and occasionally percutaneous drainage.

Volume-outcome relationship and trends in thyroid surgery

The impact of hospital and surgeon volume on postoperative outcomes in thyroid surgery has been a matter of debate for the last decades (40-45). Several investigators have addressed this question by grouping surgeons and hospitals based on annual number of thyroid surgeries performed and associating these volumes to postoperative outcomes. Available data indicate that patients operated by high-volume surgeons have a lower overall complication rate (40,45), less hypocalcemia, infection, postoperative bleeding (46) and shorter length-of-stay (40,45). Not surprisingly, complication rates are lower for hemithyroidectomy than for total thyroidectomy (44).

It should be noted that volume-outcome relationships are most pronounced when comparing very low volume surgeons (less than 5–10 thyroid operations per year to high volume surgeons (varying definitions 30 to more than 100 operations per year) (40,45). The impact of hospital volume on outcomes is less clear, but recent data indicate that a high hospital volume of thyroid surgery is associated with shorter length-of-stay and lower costs (47).

During the last decades, thyroid surgery is increasingly being performed by specialized thyroid surgeons. For instance, the proportion of thyroid surgeries performed by high-volume surgeons in the US increased from 7% in the years 1993 through 2000 to 29% in the period 2001 through 2008 (48). A similar trend has been reported from the UK (45).

Focus on limited healthcare resources, risks with prolonged postoperative immobilization and patient demand have been drivers for the implementation of day-care surgery across surgical disciplines. Whether thyroid surgery can be safely performed in a day-care setting has been a matter of some debate (49). For patients with AUS/FLUS the main constraint for out-patient lobectomy is the risk related to a postoperative hematoma. Even though risk factors for postoperative hematoma have been identified (as reviewed above), the complication is rare, difficult to predict and potentially deleterious, leading for example the British Association of Endocrine and Thyroid Surgeons to advise against day-care thyroid surgery (50). A different analysis was made by the ATA concluding that "*outpatient thyroidectomy may be undertaken safely in a carefully selected patient population provided that certain precautionary measures are taken to maximize communication and minimize the likelihood of complications*" (51). Indeed, a recent meta-analysis show lower complication rates and similar rates of readmissions and reinterventions in out-patient versus in-patient thyroidectomies (52). No mortality due to postoperative hematoma was reported. Furthermore, readmissions or reinterventions were not more likely after out-patient than in-patient thyroid surgery in an analysis of more than 70,000 cases from the American College of Surgeons National Surgical Quality Improvement Program database (53). However, data is limited regarding patient preferences, reported outcomes and experiences.

Clearly, the current trend is towards day-care thyroid surgery with some 1% of thyroid procedures performed as out-patient in the US in 2006 steadily increasing to 24% in 2014 (53). In our view, out-patient lobectomy is a feasible option for selected patients with AUS/FLUS in the proper setting.

When contemplating an out-patient thyroid surgery programme focus needs to be on safety and quality of care. Implementing day-care surgery means not only shortening time to discharge but rather a comprehensive restructuring of the perioperative management involving careful patient selection and communication, reevaluation of surgical and anesthesiological technique, complication surveillance and management including easy access to the surgical team, and a low threshold for (re-)admittance in the immediate postoperative phase.

Conclusions

Hemithyroidectomy without lymph node dissection remains the recommended management in indeterminate thyroid nodules. Care should be taken to preserve recurrent and superior laryngeal nerves and the parathyroid glands. Surgery is probably best performed by high-volume surgeons in institutions with on-site expert pathologists and with technical adjuncts available for nerve and parathyroid preservation.

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Footnote

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