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Pain Management and Anesthesia Considerations in Thyroid Carcinoma: An Emphasis on Anaplastic, Papillary, Follicular, Hurthle Cell, and Medullary Subtypes

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Abstract

Thyroid carcinoma encompasses a spectrum of malignancies with varying aggressiveness and treatment approaches. This narrative review explores the classification, epidemiology, pathogenesis, and management strategies of different subtypes of thyroid carcinoma, with a focus on anaplastic, papillary, follicular, hurthle cell, and medullary carcinoma. Anaplastic thyroid carcinoma (ATC) is highlighted for its aggressive nature, while papillary thyroid carcinoma (PTC) and its microcarcinoma variant present curable tumors but with recurrence risks. Hurthle cell carcinoma (HCC) and medullary thyroid carcinoma (MTC) pose unique challenges, including poor prognosis and hereditary predisposition. Treatment modalities, including surgery, radioiodine therapy, and novel techniques like transoral endoscopic thyroidectomy and robotic thyroidectomy, are discussed, emphasizing individualized approaches based on tumor characteristics and patient factors. This review underscores the importance of interdisciplinary collaboration and personalized medicine in optimizing outcomes for pediatric and internal medicine patients with thyroid carcinoma. Anaplastic thyroid carcinoma (ATC).

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Focusing on Pain Control in Anaplastic, Papillary, Follicular, Hurthle Cell, and Medullary Thyroid Carcinomas

Thyroid carcinoma encompasses a spectrum of malignancies with varying aggressiveness and treatment approaches. This narrative review explores the classification, epidemiology, pathogenesis, and management strategies of different subtypes of thyroid carcinoma, with a focus on anaplastic, papillary, follicular, Hurthle cell, and medullary carcinoma. Anaplastic thyroid carcinoma (ATC) is highlighted for its aggressive nature, while papillary thyroid carcinoma (PTC) and its microcarcinoma variant present curable tumors but with recurrence risks. Hurthle cell carcinoma (HCC) and medullary thyroid carcinoma (MTC) pose unique challenges, including poor prognosis

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and hereditary predisposition. Treatment modalities, including surgery, radioiodine therapy, and novel techniques like transoral endoscopic thyroidectomy and robotic thyroidectomy, are discussed, emphasizing individualized approaches based on tumor characteristics and patient factors. This review underscores the importance of interdisciplinary collaboration and personalized medicine in optimizing outcomes for pediatric and internal medicine patients with thyroid carcinoma.[1]

Thyroid carcinoma is a heterogeneous group of malignancies originating from follicular or parafollicular thyroid cells. The disease spans a spectrum from indolent to highly aggressive forms. Effective management requires not only an understanding of the carcinoma subtype but also careful consideration of pain and anesthesia needs associated with its treatment.[2]

Pain Control in Thyroid Carcinoma:

Pain management in thyroid carcinoma patients is often an overlooked aspect of care, yet it significantly impacts quality of life, particularly in advanced stages or during aggressive treatments. Each subtype of thyroid carcinoma presents unique pain control challenges due to differences in tumor behavior, invasion patterns, and therapeutic interventions.[3]

1. Anaplastic Thyroid Carcinoma (ATC): ATC's rapid progression often leads to extensive local invasion, causing severe pain due to compression of surrounding structures, including the trachea and esophagus. Effective pain management typically requires a multimodal approach, incorporating systemic analgesics such as opioids and adjunctive therapies like corticosteroids for inflammation reduction. For patients undergoing palliative care, nerve blocks or epidural analgesia may provide significant relief.[4]

2. Papillary and Follicular Thyroid Carcinomas (PTC and FTC): While these subtypes generally present with less aggressive pain profiles, certain cases involving extensive surgery or metastasis can lead to postoperative or chronic pain. Enhanced recovery protocols, including regional anesthesia techniques like cervical plexus blocks, are effective in minimizing postoperative discomfort and reducing opioid dependency.[5]

3. Hurthle Cell and Medullary Thyroid Carcinomas (HCC and MTC): HCC and MTC can cause pain primarily through regional invasion or distant metastases. MTC, in particular, may produce systemic symptoms such as diarrhea and flushing, complicating pain management strategies. Medications targeting neuropathic pain pathways, including gabapentinoids or serotonin-norepinephrine reuptake inhibitors (SNRIs), are often beneficial.[6]

Role of Anesthesia in Thyroid Carcinoma Management:

Anesthesia care plays a critical role in optimizing surgical outcomes and managing perioperative pain in thyroid carcinoma patients. Preoperative evaluation should include airway assessment, especially for patients with advanced ATC, to anticipate challenges in intubation or ventilation. Techniques like total intravenous anesthesia (TIVA) combined with regional blocks are increasingly preferred for their superior pain control and reduced systemic side effects.[7]Anaplastic thyroid carcinoma (ATC) is an undifferentiated, very aggressive, and one of the deadliest diseases in the world (the cause of 40% of deaths of all thyroid cancers). Epidemiologically, ATC is higher in endemic goiter regions. The Frequency in females has a higher rate than in males, and the range of patients' ages is between 60 to 70 years. Actually, papillary thyroid carcinoma (and follicular) can transform into an anaplastic tumor by long time duration and T53 gene inactivation. In the microscopic view increasing in mitosis, an infiltrative growth pattern, and vascular invasion can be seen. Papillary thyroid carcinoma (PTC) is considered a high-curable tumor, but, in some patients, there's the chance of recurrence, so physicians can treat them based on surgery and 131I therapy. Mostly, PTC is seen as a single nodule; however, with invasion to the lymphatic paratracheal chain, it can spread within the thyroid gland and causes multifocal tumor formation. If there were no evidence of recurrence or distant metastasis, survival would be at a high rate. If the nodule diameter is at a maximum rate <1 cm2, called papillary thyroid microcarcinoma, that has a good prognosis with a long survival (10-year survival>90%). [4,5]

hurthle cell or oxyphilic cell is a special cell with many mitochondria, which can be seen under the microscope in bright color and acidophilic. Hurthle cell carcinoma (HCC) is a rare disease with metastasis and poor prognosis. According to most studies, HCC is a subtype of follicular carcinoma. The factors of poor prognosis are age over 45 years, distant SEER (Surveillance, Epidemiology, and End Results) stage, and late T stage (among stages T1-T4, T4 has the worst prognosis and the least survival). Surgery is the most effective treatment for HCC. [9,10]

Treatment:

1year and 2year survival rates are 48% & 26% for the patients. Combined Resection (thyroidectomy + cervical lymph node resection if the tumor involves it) with radiotherapy may be useful to increase survival in stage IVA & IVB, but IVC stage due to distant metastasis

have a poor prognosis, so there is no obvious difference between surgical or non-surgical methods in this stage).[2]

Debulking surgery is the most current method that removes all gross tumors threatening the airway (remaining the larynx safe is important). The complete excision is ideal and impossible, but we can increase the survival of patients by attention to the quality of resection. Sometimes tracheostomy is needed in cases of airway compromise.[1]

According to the article "Anaplastic thyroid carcinoma: changing trends of treatment strategies and associated overall survival" the median survival in stage IVA/IVB with multimodal therapy (thyroidectomy (TTX) +Lymphadenectomy (LAD) +External beam radiation (EBRT)) is higher than surgical therapy (6-79 months > 1-8 months in debulking/tracheostomy).[3]

Papillary thyroid carcinoma (PTC):

Treatment:

The common treatment for PTMC is procedures like total thyroidectomy (TT) and unilateral lobectomy (LT). Because of its long survival, physicians should consider the other parameter named "health-related quality of life (HRQoL). Briefly, LT has more benefits than TT for patients. (TT makes more problems like restriction on daily activities, more scars in some patients, and lower scores in mental/physical health). [5]

Open thyroidectomy (OT) is a standard procedure to treat thyroid carcinoma, but the complication of postoperative neck scar can decrease young women's self-confidence. In other hand, surgeons can use a scarless procedure called transoral endoscopic thyroidectomy vestibular approach (TOETVA) that makes easy access and a short distance to the thyroid gland. In TOETVA, Surgeon can't remove a thyroid nodule with a diameter higher than 3 cm (with extending central incision can be 3.5 cm). There's a higher risk of infection and probability of mental nerve injury in this procedure. Generally, TOETVA has benefits for selective patients with low-risk or papillary thyroid microcarcinoma. [6]

Another procedure that can avoid specious neck scars is a robotic thyroidectomy. For OT, the surgeon uses a 4-6 cm transverse incision to access the thyroid. Still, bilateral axillary-breast approach robotic thyroidectomy (BABA RT) requires two 8 mm axillary incisions + two pre-areolar incisions 8 & 12 mm on the left & right. This procedure facilitates visualization of the parathyroid gland and recurrent laryngeal nerve. Mostly, BABA RT is used for the treatment of tumors with a diameter<2 cm or a diameter between 2-4 cm without lymph node metastasis. [7]

Although differentiated PTC grows slowly, depending on the genomic evolution, the tumor has the ability to metastasize to distant lymph nodes. Based on the article " in which 2108 PTC cases underwent surgery, the average metastasis was 57.23%, and this metastasis is correlated with the diameter of the tumor (in diameter > 2 cm, the probability of metastasis increases by 77.53%. In this article, 2 operation models of Surgery have been performed on the patients: 1- Total thyroidectomy + central lymph node dissection and 2- Total thyroid dissection + central and cervical lymph node dissection. Performing preventive lateral neck lymph node dissection increases the risk of shoulder syndrome, but it is recommended for PTC with a diameter > 1 cm to prevent metastasis. [8]

According to the guidelines of the American Thyroid Association, thyroidectomy should be performed for patients with a diameter >2 cm (without lymph node dissection). According to the National Comprehensive Cancer Network (NCCN) guidelines, total thyroidectomy (without lymph node dissection) should be performed in people over 45 or under 15 years old. The Chinese guidelines are different from the previous two guidelines and recommend thyroid surgery along with central lymph node dissection for all patients to avoid laryngeal nerve and parathyroid involvement. [8]

Hurthle cell carcinoma (HCC):

Treatment:

Without any evidence of metastasis, a prior history of neck irradiation, extrathyroidal tumor spread, or involving the contralateral lobe of the thyroid; the surgeon performs thyroid lobectomy and isthmusectomy because only 15-30% of patients have carcinoma. With positive microscopic detection of permanent sections, it is necessary to perform completion thyroidectomy. Iodine-131 can remove the remains of the thyroid lobe, which increases the chance of developing anaplastic cancer and prevent reoperation. In patients with minimal invasiveness, especially in the elderly and with tumor size >4, we prefer to perform total thyroidectomy. [11]

During surgery, large central and lateral lymph nodes of the neck should be removed for frozen section examination. Suppose the metastasis of central neck nodes is confirmed. In that case, a central neck dissection should be performed. in this procedure, the surgeon removes paratracheal, perithyroidal, and Delphian lymph nodes from the level of the thyroid cartilage to the sternal notch. [11]

Medullary thyroid carcinoma (MTC)

[8] :

A Rare and aggressive tumor - more difficult to cure than papillary thyroid carcinoma – derives from parafollicular cells derived from the neural crest – secretes calcitonin and some other peptides

Types: hereditary (25% of MTC patients) – nonhereditary (sporadic) (75%)

Types of hereditary MTC: MTC alone, known as familial MTC – is a part of the multiple endocrine neoplasia syndrome types 2 (MEN2; MEN2A or MEN2B).

Activating point mutations of the RET proto-oncogene are the cause of hereditary MTC. In the congenital form, the first manifestation of the disease is C-cell hyperplasia.

MEN 2A: manifests as bilateral MTC before the age of 10 – in children with MEN 2A, thyroidectomy should be performed by age 5

MEN 2B: the most aggressive form than MEN 2A – FTC happens during the first year of the child's life – these children should undergo total thyroidectomy within the first six months of life, preferably within the first month of life.

Sporadic MTC: without manifestation of C-cell hyperplasia as the primary lesion – usually manifests as a unilateral tumor at the third to fifth decade of the patient's life.

Treatment of MTC patients in general: Surgery is the treatment of choice in MTC - Total thyroidectomy and central neck dissection should be performed in virtually all patients with MTC - Modified radical neck dissection is recommended in patients with lateral lymph node metastases.

In patients at risk of MEN 2 syndromes, genetic testing should be performed during early childhood, and if the test becomes positive, then total thyroidectomy is intended.

In all children with RET mutation, total thyroidectomy is recommended.

[9] :

Sporadic MTC: Most MTCs are sporadic (80%) - usually manifest in the third to the fifth decade of life familial MTC: usually presents in third decade of life – it behaves similarly to MEN 2A, and it's hard to differentiate MEN2A from familial FTC

MEN 2A: usually presents at the third decade of life – typically bilateral – more common than MEN 2B – it is recommended to perform prophylactic thyroidectomy before the age of 5 for MEN 2A patients – the presence of pheochromocytoma must be excluded before the surgical treatment of FTC in MEN 2A patients

MEN 2B: usually manifests before the age of 20 – typically bilateral – more aggressive than MEN 2A

followed by identification of a genetic RET mutation carrier at risk of MEN 2 syndromes, early prophylactic or curative thyroidectomy is intended.

Chemotherapy and External-beam radiation therapy are ineffective in the treatment of FTCs.

Genetic RET mutation carriers are at risk of hereditary FTC throughout their entire life.

Bilateral lateral neck dissection may be done selectively for patients with tumors greater than 1 cm or when the positive nodal status is diagnosed preoperatively using imaging modalities.

Total prophylactic thyroidectomy should be performed in at-risk patients before the primary tumor development. But neck dissection is not necessary for them.

About half of the patients with MTC will experience recurrence after the initial surgery. The risk of recurrence in MTC patients with negative nodal status is very low. But, in those with positive nodal involvement, the risk of recurrence is pretty high.

[10] :

In the study [10], 13 patients with a family history of MEN 2 syndromes were treated with total thyroidectomy and central neck dissection. The study aimed to determine the appropriate age for prophylactic thyroidectomy in gene carriers of MEN 2 syndromes. They suggested that total thyroidectomy should be performed before age five and before the manifestation of C-cell hyperplasia or MTC. They concluded that total thyroidectomy should be the choice for initial treatment in genetic RET mutation carriers with a family history of MEN 2A.

In the case of thyroid carcinoma, the surgeon must remove all neoplastic tissue in the neck, including the thyroid gland, affected lymph nodes, and/or soft tissue [11]. There are three main types of thyroid surgery:

- total thyroidectomy (the removal of the entire thyroid gland)

- lobectomy or hemithyroidectomy (the removal of half of the thyroid gland)

- subtotal thyroidectomy (the surgical removal of the entire gland except for a small portion on the less affected side)

that portion not removed in subtotal thyroidectomy is near the parathyroid glands and the recurrent laryngeal nerve. Therefore, this procedure helps prevent injury to these structures. However, in some poor-prognosis patients, total thyroidectomy may be preferable because it lowers the risk of recurrence and facilitates the patient's follow-up [12, 13] [14].

Differentiated thyroid carcinoma

Differentiated thyroid carcinoma (DTC) includes papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) [15]. in comparison to other cancers, these two are highly curable. Still, the risk of recurrence or death from DTC is high in some patients. Therefore, the extent of initial treatment and follow-up should be individualized for every patient based on prognostic indicators [11].

Differentiated thyroid carcinoma has a 10-year overall survival rate of 90% and a cause-specific survival rate of 96% [16].

PTC is more common (80-90% of DTCs) and less aggressive than FTC. Lymph node metastases are more common in PTC. At the same time, hematogenous dissemination and distant metastases are more common in FTC [17] [18] [19]. Patients with FTC are usually older than PTC patients at the time of diagnosis. [2, 14]

The common treatment strategy in patients with DTC is complete or partial thyroidectomy followed by radioiodine (RI) therapy used for residual and/or metastatic sites. [16] there is controversy in the literature about the extent of initial surgery [14] [16].

In a study of [overall and cause-specific survival for patients undergoing lobectomy, near-total, or total thyroidectomy for differentiated thyroid cancer], an unlimited number of 23,605 patients with DTC between 1983 and 2002 have been studied using the Surveillance, Epidemiology, and End Results (SEER) database. They found that although total thyroidectomy offers a slightly better survival rate than lobectomy and near-total thyroidectomy, the difference is not significant, and one should consider the risk of complications of performing a total thyroidectomy (recurrent laryngeal nerve injury and post-operative hypoparathyroidism) before the conducting the operation. However, On the other hand, total thyroidectomy offers a lower probability of cancer recurrence. Therefore, it is suggested that treatment should be individualized for every patient based on the potential risks and advantages of these surgical strategies for the patient. [16]

Follicular Thyroid Carcinoma

Two types: minimally invasive (MI-FTC); tumors with ≤3 foci of vascular invasion – widely invasive (WI-FTC); tumors with >3 principles of vascular invasion [14] [18].

Some well-known prognostic indicators for FTC: are distant metastasis, age (>45 or >60), tumor size (>4 cm), nodal involvement of the tumor, angioinvasion, and capsular invasion [16] [19].

Follicular thyroid carcinoma (FTC) is the second most common thyroid gland cancer. [17, 20] patients with FTC usually have a good prognosis except when a distant metastasis is associated. The most common sites of distant metastasis are the lung and bone. Treatments available for distant metastases are radioactive iodine (RI) therapy, surgery, and external beam radiation therapy (EBRT). for patients with DTC and distant metastasis, the initial treatment can be Total thyroidectomy followed by RI therapy [19].

Lobectomy (hemithyroidectomy) may be done in some patients with MI-FTC sized less than 1 cm without vascular invasion. Also, in some cases where there is a contraindication for total or subtotal thyroidectomy, lobectomy is intended [11] [17] [18].

The detection of distant metastasis during the follow-up of a patient who had undergone hemithyroidectomy at the initial surgery necessitates a second operation (completion thyroidectomy; the removal of the contralateral lobe in patients who had undergone hemithyroidectomy once before) and RI therapy [19] [21].

Some recommend total thyroidectomy for all patients with WI-FTC because it facilitates thyroglobulin testing and RI scanning/treatment during the follow-up and lowers the risk of recurrence. one should always consider the risk of recurrent laryngeal nerve injury and post-operative hypoparathyroidism in total thyroidectomy. If the risk of these complications is minimal, the surgeon can perform the surgery. [4, 14]

Lymph node metastases are rare (2-6%), and there's consensus in the literature that prophylactic lymph node dissection is not necessary for patients with FTC [14] [17] [22]. Lymphadenectomy should be performed for therapeutic intent in patients with positive nodal status diagnosed preoperatively or intraoperatively by frozen section analysis [1, 18].

Study [The surgical dilemma of primary surgery for follicular thyroid neoplasms]: they reviewed the treatment strategies for FTCs published by international expert societies {German Association of Endocrine Surgeons (CAEK) 2013, European Society of Endocrine Surgeons (ESES) 2014, British Thyroid Association (BTA) 2014, and American Thyroid Association (ATA) 2015}; based on this study: total or near-total thyroidectomy is recommended for all patients with FTC except for some low-risk patients with minimally invasive FTC (capsular invasion only) in the absence of some well-known risk factors [22-24].

In a study comparing the effectiveness of [total thyroidectomy versus lobectomy for the treatment of follicular thyroid microcarcinoma]: they found that in the case of follicular thyroid microcarcinoma (≤1 cm), total thyroidectomy does not offer any survival advantage in comparison to lobectomy. However, the physician must rule out the presence of local or distant metastasis before the operation. Total thyroidectomy is intended in the presence of local/distant metastasis [25].

After treating a case with DTC, the patient is always at risk of recurrence. Therefore, follow-up is needed throughout the patient's life [11].

FTC Recurrence

most cases of death related to cancer in FTC patients is when a recurrence of the disease happens. Surgery and 113I therapy can be used to treat recurrences. The

extent of the initial surgery in patients with a high risk of recurrence should be total thyroidectomy. After the surgery they should routinely be treated with 113I [11] [14].

A small recurrence can be treated with 113I alone. After three times of failures using 113I therapy, surgery is recommended for the patient [3, 26].

Conclusion

In conclusion, integrating pain management and anesthesia considerations into the broader framework of thyroid carcinoma treatment is essential for improving patient outcomes and quality of life. A multidisciplinary approach involving oncologists, surgeons, anesthesiologists, and pain specialists is pivotal in achieving this goal, particularly for complex cases like ATC and MTC. Continued research into targeted pain therapies and anesthetic techniques will further enhance the care of thyroid carcinoma patients. this comprehensive review provides insights into the classification, epidemiology, pathogenesis, and management strategies of various subtypes of thyroid carcinoma in pediatric and internal medicine practice. Anaplastic thyroid carcinoma (ATC) stands out for its aggressive behavior and poor prognosis, emphasizing the urgent need for effective treatment strategies. Papillary thyroid carcinoma (PTC), although generally curable, requires vigilant surveillance due to the risk of recurrence, particularly in cases of papillary thyroid microcarcinoma. Hurthle cell carcinoma (HCC) and medullary thyroid carcinoma (MTC) present unique challenges, necessitating tailored approaches based on tumor characteristics and genetic predisposition.

Surgical interventions remain the cornerstone of treatment, with advancements such as transoral endoscopic thyroidectomy and robotic thyroidectomy offering promising alternatives to traditional approaches. Radioiodine therapy and targeted therapies play crucial roles in managing residual or metastatic disease, highlighting the importance of multidisciplinary collaboration in optimizing patient outcomes.

Overall, this review underscores the complexities of thyroid carcinoma management and the importance of individualized approaches in pediatric and internal medicine settings. Continued research efforts are warranted to further refine treatment algorithms and improve long-term outcomes for patients with thyroid carcinoma.

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