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Thyroglossal Duct Remnant Carcinoma: Beyond the Sistrunk Procedure

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Abstract

Thyroglossal duct remnants (TGDRs) account for more than 70% of anterior neck masses in children and 7% in adults; however, cancer is identified in only 1–2% of the cases. The diagnosis of a TGDR is based on clinical manifestation of a painless, anterior neck swelling, which elevates with swallowing. Cytological evaluation with fine needle aspiration and biopsy (FNAB) may facilitate the pre-operative diagnosis of malignancy, as the majority of TGDR cancers are of papillary histotype. The recommended treatment for symptomatic TGDR without evidence of malignancy is a Sistrunk procedure, which entails *en bloc* resection of the remnant and the mid-portion of the hyoid bone. The optimal management of patients with diagnosed malignancy is controversial, and in the past, additional total thyroidectomy was recommended for all of these patients. The purpose of this study is to review the literature on TGDR carcinomas, present the evidence on the available diagnostic tools, identify the surgical and post-operative medical management strategies, discuss current controversies, and conclude with a management algorithm.

Keywords

thyroglossal duct; remnant; cancer; thyroid; review

Introduction

During the third week of fetal life, the thyroid gland arises embryologically from a midline endodermal invagination of the foregut, at the level of the *foramen caecum*. Its tract of descent from the base of the tongue to its final resting place in the anterior neck involutes by the ninth week of gestation [1]. Approximately 7% of the general population has a thyroglossal duct remnant (TGDR) which fails to involute, and more than 50% of these TGDRs contain ectopic functional thyroid tissue [2, 3]. TGDRs, most notably presenting as

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cysts, are the most common congenital anomalies of the neck. They represent over 70% of childhood midline neck masses, and are three times more common than branchial cleft remnants [4].

TGDR carcinomas are rare tumors that occur in 1–2% of TGDRs [3, 4]. This rare cancer was first reported in the medical literature by Brentano in 1911 and by Owen and Ingelby in the English literature in 1927 [5, 6]. Initially suspected to be metastases from cancers of the main gland, these *de novo* tumors can exhibit a biological behavior similar to their primary gland relatives. Even though all histologic types can occur at any age, anaplastic, squamous, and concurrent squamous and papillary carcinomas are extremely rare [7–9]. A malignant diagnosis can be made on fine needle aspiration biopsy (FNAB) or intra-operative frozen section (FS); however, the majority of TGDR carcinomas are diagnosed after definitive pathological examination of the excised remnant. The current treatment for a symptomatic or infected TGDR cyst is a Sistrunk procedure, which involves an *en bloc* cystectomy and central hyoidectomy, with tract excision up to the *foramen caecum*. However, the controversy for the treatment of this malignant neoplasm evolves regarding the optimal surgical management with regard to the main thyroid gland and the cervical lymph nodes. The main controversies include: 1) diagnostic strategies to provide a definitive diagnosis and enable a single neck exploration, 2) the need for additional therapies after completion of the Sistrunk procedure, and 3) what that further management includes. The purpose of this study is to review the literature on TGDR carcinomas, present the evidence on the available diagnostic tools, identify the surgical and post-operative medical management strategies, discuss current controversies, and conclude with a management algorithm.

Incidence

Thyroglossal duct remnant

TGDRs are the most common congenital cervical anomaly. The majority (50–60%) of cases are found in children under 5 years of age; however, up to one-third appear in patients 20 years or older [10, 11]. Nevertheless, the cyst can be observed at any age and as many as 25% are present at birth [4]. The patients of most concern are those who present with a TGDR after the age of 20, due to the increased incidence of malignancy in this subgroup [4].

Thyroglossal duct remnant carcinoma

TGDR carcinomas are extremely rare and are identified in only 1–2% of all TGDR [2, 3, 12–14]. Originally described by Brentano in 1911, only a little over 250 cases have been reported in the relevant literature [15–17]. These rare malignancies account for less than 1% of thyroid cancers. Despite TGDRs being very common in children and adolescents, carcinomas of the TGDR are rarely present in this age group [16–19]. The peak incidence for women occurs in the fourth decade, whereas men peak later, during the sixth decade of life. Nearly 70% of these rare cancers are diagnosed in adults over the age of 20 [4, 16–19]. Unlike other thyroid disorders, the prevalence of this cancer is equivalent amongst males and females [4].

Embryology and Pathophysiology

Thyroglossal duct remnant

TGDRs arise from the failure of the thyroglossal tract to obliterate *in utero*. Occurring concurrently with duct lumen atrophy, from the fifth through seventh weeks of gestation, mesoderm from the second and third branchial arches condense and undergo chondrification, to form the hyoid bone, growing from posterior to anterior, and divides the thyroglossal duct tract into suprahyoid and infrahyoid portions [12, 20, 21]. The thyroid gland reaches its final position, just below the thyroid cartilage, by the eighth gestational week [22]. In normal fetal development, the tract of migration persists until the tenth week of fetal development, at which time it begins to obliterate. Failure of the tract to obliterate results in TGDRs: ducts, cysts, fistulas, and ectopic thyroid tissue [10]. Despite being congenital deformities, these remnants are often noticed in the first two decades of life, anywhere along the tract of descent, from the submental region to the suprasternal notch. Formation within the hyoid bone, tongue or mouth floor, are extremely uncommon [4]. The most common site of occurrence is juxtaposed to the hyoid bone (80%) [23].

The tract consists of stratified squamous, pseudo-stratified ciliated columnar epithelial cells, and thyroid cells. The TGDRs may be lined by squamous or respiratory epithelium, and small accumulations of normal thyroid tissue have been identified and reported within the wall of the cyst or tract in 1.6 to 40% of cases [24–26]. It has been suggested that TGDRs are caused by mutations in genes responsible for follicular cell development (the thyroid-restricted transcription factors TITF1, TITF2, and PAX8, and thyroid-stimulating hormone receptor (TSHR) [27]; however, to date, there is no definitive proof for this concept.

Thyroglossal duct remnant carcinoma

TGDR carcinomas arise from TGDRs. The majority of these malignancies share a common histology with those of the main thyroid gland. Two thirds of all TGDRs have normal thyroid cells, hence the belief that papillary carcinomas arise *de novo* from the TGDR, as opposed to representing metastatic spread from the main gland. The absence of parafollicular cells in the ectopic thyroid tissue present in these malignancies provides further evidence for this theory [28, 29]. The duct consists of ciliated squamous epithelial cells, and hence squamous cell carcinoma can also be diagnosed. Papillary carcinoma (PTC) is the most common, as it is in the thyroid gland, ranging between 85.5%-94% [10, 17]. However, mixed papillary/follicular (4.4%), follicular thyroid (1.1%), squamous cell (6.6%), adenocarcinoma (2.2%), Hürthle cell, and anaplastic thyroid carcinomas can be diagnosed [16, 18, 30–33]. A case each of concurrent papillary thyroid with squamous cell carcinoma and adenosquamous carcinoma, have been reported in the literature [34, 35].

The squamous cell carcinomas consist of squamous epithelial cells, which arise from the cyst wall. These malignancies can arise *de novo* in older adults, being reported in patients in their sixth and seventh decades of life (55 and 65 years old), or as squamous cell metaplasia of thyroid papillary histotype, in children under 15 years old [7, 8, 18]. The rare case reported of anaplastic thyroid carcinoma of the TGDR in an 84-year-old woman was associated with a benign follicular neoplasm [9]. The one thyroid malignancy that does not

occur as a TGDR carcinoma is medullary thyroid cancer, as C cells are not located in the medial aspect of the thyroid gland.

Diagnosis

Clinical Presentation

Patients with TGDR can be asymptomatic with a “lump in the throat”, or report dyspnea or a choking sensation. A history of pain, sudden enlargement of a neck mass, hoarseness, weight loss, or airway compromise is extremely rare, but one that should raise suspicion for malignancy. Up to 60% of patients present with a firm, non-tender, mobile midline mass at, or just below the level of the hyoid bone [29, 36]. In addition to this common location, up to 25% of TGDR are found to the left of the midline, usually along the thyroid cartilage [28, 37]. Other locations along the tract include: suprahyoidal (24%), suprasternal (13%), and intralingual (2%) [38]. The history and physical examination can eliminate other diagnoses, including: dermoid cyst, branchial cleft cyst, cystic hygroma, a Delphian lymph node with cystic papillary thyroid carcinoma, and ectopic thyroid tissue [17, 30].

Recurrent infections, sinus or fistula formation, malignant change, or cosmetic appearance, are all indications for resection. One should have a high index of suspicion for carcinoma, when the remnant is hard, fixed, irregular, or associated with lymphadenopathy [29, 39].

Imaging Studies

Radiologic evaluation of the TGDR for the presence of features suggestive or suspicious of a malignancy begins with ultrasound examination. The cyst presents as an anechoic, hypoechoic, or complex heterogeneous lesion [39–41]. The cancer will appear along the duct wall, as a mural lesion, and may have microcalcifications. Main thyroid gland sonographic examination may confirm an eventual multifocal cancer. On computed tomography (CT) or magnetic resonance imaging (MRI), the malignant component is seen as a peripheral mass within the cyst, as a solid mass along the thyroglossal tract, or as a complex invasive midline mass [36, 42]. Calcifications within the primary tumor or a metastatic lymph node can also be revealed on ultrasound or CT scans. Ultrasound, CT, or MRI imaging studies can be used to evaluate the lateral and central neck for nodal metastases [42, 43]. Anaplastic or squamous cell carcinomas are best evaluated by cross-sectional imaging (CT or MRI).

In euthyroid patients, radioiodine scans may be able to determine if the only functioning thyroid tissue in the patient is within the TGDR (or lingual thyroid). Such findings will avoid inappropriate resection.

Fine Needle Aspiration Biopsy

The gold standard diagnostic tool of TGDR carcinoma is fine needle aspiration biopsy (FNAB) performed under ultrasound guidance to ensure sampling of the cyst/duct wall, under direct visualization. This is especially critical in elderly patients, due to their higher incidence of malignancy [42, 44]. When a sufficient yield of cells is obtained, the diagnostic criteria for a cancer diagnosis are the same as those for a malignancy arising from a thyroid

nodule. The accuracy of FNA is 90–95% for all thyroid nodules [45, 46]. The incidence of malignancy in a FNAB interpreted as benign is 0–3% [45]. Because the recommended management is different for TGDR carcinomas >1 cm, as compared to a benign TGDR, having a diagnosis at the time of the first neck exploration, can minimize the morbidity of subsequent neck explorations [47].

There is no controversy that every patient with a TGDR should undergo cervical ultrasound to evaluate the thyroid gland and the presence of cervical lymphadenopathy. However, the low prevalence of malignancy (1–2%) does not make performing FNAB in every patient cost-effective or appropriate, especially in children [13, 48]. In a small series, Miccoli et al. reported a 100% sensitivity and specificity, supporting it as a low-cost, operator-dependent test [47]. FNAB is a simple procedure, which would add little cost to the scan; hence, performing it only in adult patients with a residual mass after emptying the TGDR cyst, and in patients in whom there is a high suspicion of TGDR malignancy, may improve its efficacy. Up to 50% of patients can be diagnosed pre-operatively, and this can dictate correct surgical management [29].

Histology

The definitive criteria for a primary TGDR carcinoma are: 1) the carcinoma is in the wall of the TGDR; 2) the cancer must be differentiated from a cystic lymph node metastasis by histological demonstration of a squamous or columnar epithelial lining and normal thyroid follicles in the wall of the TGDR; and 3) there is no malignancy in the thyroid gland or any other possible primary site [49]. The difficulty in meeting these criteria is two-fold. First, the majority of main gland papillary thyroid cancers are multifocal, and some may consider the remnant as part of the entire gland. Secondly, the diagnosis of TGDR malignancy is usually made post-operatively on pathology. When a cancer is only diagnosed in the remnant, this is indeed a TGDR carcinoma; however, when a cancer focus is also present in the main gland it is impossible to distinguish between synchronous *de novo* TGDR carcinoma and multifocal disease originating from the thyroid gland lesion. Simultaneous TGDR carcinoma and papillary thyroid carcinoma has been reported in 11–40% of cases [3].

Intra-operative Frozen Section

Intra-operative frozen section may play a role in determining the diagnosis at the time of the initial surgery, hence minimizing the necessity for neck re-exploration. Intra-operative frozen section can be performed after completion of the Sistrunk procedure, and if a malignancy is confirmed surgical management of the main thyroid gland can be addressed at that time; as opposed to subjecting the patient to the increased risk of morbidity during a second operation. As with cancer in the thyroid gland, the role of intra-operative frozen section for indeterminate lesions on FNAB is controversial, as the diagnosis of malignancy is not always possible and it may only result in prolonged surgery time [50]. Opponents of frozen section claim that it has been shown to add very little to intra-operative decision-making in thyroid gland surgery [51]. Haymart et al. demonstrated its benefits as a useful diagnostic tool, when FNAB is suspicious for PTC [52]. As literature is lacking clear evidence for both arguments, it is reasonable to recommend that frozen section be utilized in

highly suspicious cases, in centers that perform it for thyroid surgery and where there is established such cooperation between the surgeons and the pathologists.

Management

Thyroglossal Duct Remnant

The key parts of the Sistrunk procedure are removal of the central portion of the hyoid bone and any proximal cyst (which may include some portion of the tongue base - *the foramen caecum*) along with the tissue surrounding it [20].

Thyroglossal Duct Remnant Carcinoma

There are four practiced surgical management strategies for TGDR carcinomas: 1) Sistrunk procedure alone [10]; 2) Sistrunk procedure with thyroid lobectomy or pyramidal lobe resection [53]; 3) Sistrunk procedure and total or near total thyroidectomy in all patients [54, 55]; and 4) Sistrunk procedure and selective addition of total or near total thyroidectomy to high-risk patients [3, 56]. The rationale for adding thyroid resection to every patient with a TGDR carcinoma is based on three aspects: the presence of concomitant thyroid malignancy in the main thyroid gland, the utilization of radioactive iodine (RAI) as an adjuvant treatment, and the role of thyroglobulin, as a follow-up marker [11, 54].

Concomitant main thyroid gland malignancy has been reported to be present in 11–45% of cases [2, 3, 16, 18, 28, 29]. Synchronous papillary thyroid carcinomas in the TGDR and the thyroid gland are multifocal tumors, and hence this risk should be carefully evaluated. Noting the potential for serious complications, Plaza et al. make the argument against the addition of total thyroidectomy [3]. The literature contains several case reports with too few patients treated with a diversity of operative procedures, and hence evidence-based conclusions are difficult to establish. None of the studies describing TGDR carcinomas specifically are case controlled and therefore all management recommendations regarding patients with TGDR carcinomas are Grade C, because they rely on case reports, case series, and expert opinion (level V) [57].

The recommended surgical management of patients with TGDR carcinoma is based on the risk assessment. Similar to well differentiated thyroid gland malignancies, patients are stratified from low- to high-risk based on the revised 2009 American Thyroid Association (ATA) guidelines on differentiated thyroid cancer and the National Comprehensive Cancer Network (NCCN) guidelines. This stratification is modified to fit TGDR carcinoma based on the literature [54, 58–60]. Low-risk patients have the following characteristics: 1) patient – age over 15 and younger than 45 years, no radiation history; 2) tumor – less than 4 cm in size,; and 3) metastases - no distant or nodal metastases. The majority of the patients fall into low-risk category and for these patients when there are no thyroid abnormalities or suspicious findings a Sistrunk procedure suffices. These patients will have a 95% cure rate with Sistrunk procedure alone and 95–100% long-term survival. High-risk patients are rare and should be treated with Sistrunk procedure and resection of the main thyroid gland via a total or near total thyroidectomy (Figure 1). [54]. Rare patients diagnosed with a squamous cell or anaplastic thyroid cancer of the TGDR, should also be treated aggressively, with a total or near total thyroidectomy, if possible [33, 34, 61].

In the majority of the cases, the carcinoma is identified on final pathology following a Sistrunk procedure performed for presumed benign disease. If not previously performed, a cervical ultrasound with careful evaluation of the thyroid gland as well as the central and lateral compartments should be performed. Suspicious thyroid nodules or cervical lymph nodes should be biopsied. Positive work-up warrants total thyroidectomy and involved compartment lymph node dissection. If work-up is negative, completion of thyroid gland resection should be offered only to high-risk patients or patients with the following findings: not all macroscopic disease resected, microscopic tumor locoregional or cyst wall invasion, aggressive histology (e.g. tall cell, insular, columnar cell carcinoma) [3, 28, 29].

There is a consensus on the surgical management of the more aggressive tumors that present with lymph node involvement. Cervical lymph node metastases have a prevalence of 7.7 to 15% [17, 47, 48, 55] and the presence of lymph node metastases warrants the addition of neck compartment dissection. Usually only the central compartment (level VI) requires dissection; however, lateral lymph node dissection may be required if involvement is proven on biopsy or pathology [3, 54, 59]. The role of prophylactic elective lymph node dissection was not investigated in TGDR carcinomas and therefore routine prophylactic central lymph node dissection cannot be recommended.

Adjuvant Therapy

Staging systems used for the differentiated thyroid cancer of the main gland may be applied to TGDR carcinomas and we recommend using the TNM (tumor, nodes, metastasis) staging system, for uniformity. Low-risk patients treated with Sistrunk procedure alone do not require any adjuvant therapy. In contrast, some intermediate and high-risk patients are candidates for thyroid gland remnant ablation following total or near total thyroidectomy. The decision on RAI remnant ablation should follow the considerations of the ATA or NCCN guidelines for the management of well-differentiated thyroid carcinomas [58, 60].

As with the controversy over the extent of thyroidectomy, the benefit of radioactive iodine for low-risk patients remains unclear [62]. Recently, some studies have shown an increase in the risk of developing secondary malignancies after RAI therapy [63, 64]. The most recent ATA guidelines for well-differentiated thyroid gland malignancies recommend remnant ablation for all patients with known distant metastases, gross extra-thyroidal extension, tumor size > 4 cm, or tumor size 1–4 cm who have documented lymph node metastases or other high risk features [58]. These recommendations can also be adapted to TGDR carcinomas. It is thus reasonable to conclude that radioactive iodine may be beneficial for patients with larger tumors and metastatic disease, but the increased risk of secondary malignancies in low-risk patients, including children, where the long-term benefit of radioactive iodine is questionable, means that careful patient selection for RAI treatment is necessary [53, 56, 61].

Follow up

For those patients with a TGDR malignancy, follow-up is required for recurrence surveillance. Annual physical examination, cervical ultrasound, and an unstimulated thyroglobulin level, are sufficient surveillance in the majority of patients diagnosed with a

TGDR malignancy. The histopathologic type and extent of disease are used to tailor surveillance to the individual patient. Patients taking thyroid hormone supplementation should be followed, to maintain appropriate TSH suppression [59].

Prognosis

The prognosis of TGDR malignancy is excellent and depends on the extent of surgery, tumor stage, and histology. Since more than 90% of the cancers are confined to the thyroglossal duct itself, a Sistrunk procedure results in a 95% cure rate and 95–100% long-term survival [3]. Patel et al. concluded that for well differentiated thyroid carcinomas the only significant prognostic predictor of outcome is the extent of surgery [55]. Hence, in TGDR carcinomas simple local excision of the TGDR is no longer acceptable. The minimum operation is a Sistrunk procedure, as simple TGDR excision has a significantly lower (75% vs. 100%) 10-year survival [55]. That being said, death is also very rare, even for those patients with extra-ductal extension or lymph node metastases [61, 65].

As expected, patients with papillary or follicular thyroid cancer have a 5-year survival that exceeds 95% [3]. Squamous cell and anaplastic thyroid carcinomas are more aggressive and hence portend a worse prognosis. In the small number of cases described with adequate follow-up, a 36.3% disease related mortality was reported in patients with squamous cell carcinoma [42, 61].

Conclusion

TGDR carcinomas are rare tumors, usually presenting as well differentiated thyroid cancers confined to the TGDR. A Sistrunk procedure is the gold standard for management. As these well-differentiated cancers have similar biological behavior and prognosis as cancers that originate in the main thyroid gland, additional management should be the same for higher-risk TGDR cancers: total or near total thyroidectomy, radioactive iodine remnant ablation, and thyroid hormone suppressive therapy. Anaplastic thyroid and squamous cell carcinomas are very rare and warrant aggressive initial surgical management, including total thyroidectomy with lymph node dissection.

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Highlights

- Thyroglossal duct remnant (TGDR) carcinomas are rare and occur in 1–2% of all TGDRs.
- Over 90% of patients are low-risk and require Sistrunk procedure alone.
- Total thyroidectomy should be added only to high-risk patients.
- Adjuvant therapy with radioactive iodine should be reserved for high-risk patients.
- Sistrunk procedure results in a 95% cure rate and 95–100% long-term survival.

Figure 1.
Suggested management algorithm for TGDR:

Low Risk:

Patient – age over 15 and younger than 45 years, no radiation history.

Tumor – less than 4 cm in size. Metastasis - no distant or nodal metastases.

* Total thyroidectomy should be performed after the SP when the following findings are evident: not all macroscopic disease resected, microscopic tumor locoregional or cyst wall invasion, or aggressive histology (e.g. tall cell, insular, columnar cell carcinoma).

Abbreviations:

US – ultrasound, FNAB – fine needle aspiration biopsy, SP – Sistrunk procedure, CT – computed tomography, MRI – magnetic resonance imaging, TT – total thyroidectomy, LND – lymph node dissection, RAI – radioactive iodine, TSH – thyroid stimulating hormone, Tg – thyroglobulin