Recurrent Differentiated Thyroid Cancer

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Abstract

Despite high prevalence of malignancy of the thyroid, recurrent thyroid cancer remains a poorly understood entity. This paper aims to consolidate research and literature specifically on recurrent disease by discussing its epidemiology, genetics, surveillance, treatment and outcomes. Mutations in the BRAF and RET genes predispose to recurrent disease. Currently utilized surveillance methods include thyroglobulin monitoring, radioiodine body scanning, PET/CT, and neck ultrasound. Surgical reoperation is optimal treatment of choice. Long term outcomes still remain poorly described.

Keywords: Thyroid; Cancer; Thyroid cancer; Recurrent differentiated thyroid; Thyroid cancer; Recurrent; Differentiated; Ultrasound; PET-CT; Review

Epidemiology

Thyroid cancer is the most common endocrine malignancy. In 2010 there were 44,670 new cases and 1,690 deaths from all thyroid cancers [1]. Between 5-15% of all thyroid nodules are discovered to be malignant. Thyroid follicular epithelial cells give rise to follicular carcinomas, hurthle cell carcinoma, papillary carcinoma, and less often, undifferentiated carcinomas such as anaplastic or poorly differentiated carcinoma [2]. Ninety percent of thyroid cancers are of the differentiated types, papillary or follicular [3], while less than 5% are anaplastic. Often, recurrent disease retains identical histological characteristics as the primary malignancy, but also may recur with a less differentiated histology [2]. Literature exists on rates of recurrence but it is limited and dated. Published rates range from a 5-25% recurrence rate in papillary cancer and 25-61% for various stages of follicular carcinoma [2, 4-7]. A further confounding issue is that most published literature lumps both persistent and recurrent disease as a single entity despite these being entirely distinct forms of disease.

Risk factors and prognostic criteria for recurrent thyroid cancer differ from those of primary disease. Survival in primary well differentiated thyroid cancer is inversely related to both patient age and tumor size [8, 9]. Studies have shown that only extrathyroidal extension either via surgical pathology or lymph node involvement at the time of resection is actually a risk factor for developing recurrent disease [10]. One such study (N = 246), higher pTNM staging, age, and primary tumor size were not significantly associated with recurrence [8]. Primary cases of aggressive or highly invasive histological variants are at an increased risk for recurrence [2, 11]. Raef et al. followed 100 consecutively diagnosed patients with differentiated (papillary 76%, follicular variant 14%, hurthle 4%, tall cell and sclerosing 2%, pure follicular 4%) thyroid cancer. Nine of these cases recurred within the year after remission was achieved. Fifty patients had either recurrent or persistent disease in this cohort, and they tended to be older, had a higher TNM stage, and higher post surgery thyroglobulin levels as compared to patients who remained in remission. Gender was not determined to be a significant factor for recurrence in this study [12]. While there is no definitive answer on the effect of nodal metastasis on survival, it is generally agreed that nodal involvement increases rates of recurrent disease [13]. Locoregional recurrence in papillary thyroid cancer more often occurs in the lateral neck compartment (8.2%, N = 342) [10].

In a study of multicentric papillary thyroid carcinoma, Lin et al demonstrated higher rates of recurrence (20.2%) than that of those patients with unifocal disease (n = 1682). Of those with multicentric disease with greater than 5 foci, 45.8% recurred [14].

Tuttle et al devised a recurrence risk stratification scheme for patients with thyroid cancer. Low risk patients are defined as individuals at any age with PTC and primary tumor size of < 1 cm without lymph node involvement. Intermediate risk patients are between 20 - 60 years of age with PTC with extrathyroid or vascular extension. The primary tumor size of must be between 1 and 4 cm with or without lymph node involvement. High risk patients are classified as < 20 or > 60 years old with variants other than PTC or gross extrathyroid extension or vascular invasion. These patients have a primary tumor size of > 4 cm and are positive for lymph node involvement [15].

Mutations and Recurrent Thyroid Cancer

BRAF mutations and RET/PTC rearrangements are often found in papillary thyroid carcinomas. Rarely, BRAF mutations can initially be absent in primary disease but then occur in the process of PTC recurrence [16]. Recurrence is more likely in the presence of a BRAF mutation and some authors suggest total thyroidectomy if FNA genetic analysis are positive for such [17-21]. BRAF mutated PTC was associated with at 23% recurrence rate in one study as compared to 9% in PTC without BRAF mutation [22]. In another examination of 54 cases of recurrent PTC, BRAF mutations were detected in 77.8% of cases. Only 16.7% of these cases exhibited RET/PTC rearrangement. Both mutations were simultaneously present in 9.3% of patients with recurrent disease, a much higher percentage than the prevalence of dual mutations in primary disease. These findings support the idea that BRAF mutations, as well as dual mutations, are significantly associated with recurrent papillary thyroid carcinoma [23]. A BRAF V600E mutation in patients older than 65 with papillary thyroid cancer has been associated with a higher incidence of recurrence than in younger patients (10% and 2%, respectively). This mutation itself also predisposed to recurrence in 13% of cases as compared to 2% of BRAF negative patients [24]. BRAF mutations may also be associated with recurrent disease lacking radioiodine avidity [16]. Cradic et al developed a PCR-based blood test to detect BRAF mutations. This technique may be useful for detecting recurrence of PTC although this has not yet been validated [18].

Both VEGF and VEGF-C (a lymphangiogenic factor) are elevated in cases of recurrent papillary thyroid carcinoma and, like in other cancers, are proposed to play a role here in growth, metastasis and recurrence [25]. Papillary thyroid carcinomas with recurrence appearing in the contralateral lobe expressed identical genetic mutations in both the primary and recurring tumor. This suggests that local metastasis plays an important role in recurrent disease [26].

Far less is described about the role of genetics in recurrent follicular thyroid cancer. Primary disease is usually associated with a mutation in either RAS or in PAX8/PPAR γ [20, 21].

Surveillance and Diagnosis

The 2009 ATA Guidelines define absence of persistent tumor as an undetectable serum Tg and negative imaging studies post-thyroidectomy or near-total thyroidectomy with remnant ablation [3]. One study showed that cases of multicentric papillary thyroid carcinoma that exhibited disease recurrence were diagnosed within one year post thyroidectomy 52.9% of the time [14]. Recurrent thyroid cancer typically appears with metastatic disease in the cervical lymph nodes (85%), with 32% having thyroid bed recurrence and 12% having distant metastasis [27].

The two methods to detect recurrence or metastasis are by measurement of serum thyroglobulin (Tg) or by I-131 whole body scans (WBS). Certain patients test negative for serum Tg but are I-131 WBS positive despite the higher sensitivity of serum Tg. Patients with this paradoxical finding were more likely to have local disease recurrence or metastasis, and thus it is recommended that patients receive an iodine WBS post-ablation therapy regardless of postoperative serum Tg [28]. Serum Tg may not be an adequate test to predict recurrent disease [9] although a stimulated Tg may be more useful for this purpose [29].

One study examined patients deemed disease free after thyroidectomy and radioiodine ablation and who were taking levothyroxine. They were challenged with recombinant human TSH (rhTSH) and stratified into 3 groups based on their measured thyroglobulin (Tg) response. Rates of cancer recurrence were measured amongst these groups and it was found that those with higher rhTSH stimulated thyroglobulin levels exhibited more recurrence. Challenged Tg values of 2.5 ng/mL or higher predicted recurrence with sensitivity and specificity of 80 and 97 respectively [30]. Patients who are post-thyroidectomy with ablation may have undetectable stimulated thyroglobulin levels. A marker of recurrent thyroid cancer may be a previously undetectable thyroglobulin level which has become measurable again. Nascimento et al showed that repeating TSH-Tg measurements 6 - 18 months post surgery in patients with undetectable postoperative stimulated Tg does not yield information on recurrence [11].

The presence of Anti-thyroglobulin antibody (TgAb) further complicates serum Tg measurements as a screening tool for recurrence. The presence of TgAb is higher in patients with differentiated thyroid cancer than in the general population and thus may cause falsely lowered measured Tg concentration. TgAb levels should be measured especially in patients with initially undetectable serum Tg values post surgery and ablation. Downward trending serial TgAb measurements are a marker of good prognosis and

conversely an increasing trend raises the risk of recurrence. Taken together, values of 4.45 ng/mL and 27.81 U/mL for Tg and TgAb respectively were found to be significantly more sensitive and just as specific for detecting recurrence as single Tg measurements (Sensitivity increased from 52.5% to 78.3%, whereas specificity decreased from 91.7% to 90%) [31].

Imaging modalities such as neck ultrasound, CT, MRI, and FDG-PET have all been evaluated as tools in the detection of thyroid cancer recurrence. Neck ultrasound, according to the 2009 American Thyroid Association guidelines, should be used to survey the thyroid bed and cervical lymph node compartments at 6 - 12 months and beyond. Neck US is now a preferred detection modality along with serum Tg over diagnostic whole body scanning (DxWBS) [3]. Neck US is able to detect both differentiated and undifferentiated (not typically radioiodine avid) thyroid cancers, whereas DxWBS detects only radioiodine avid cancers [32]. DxWBS can be performed after 3 weeks of thyroid hormone therapy withdrawal [33].

Patients with intermediate or high recurrence risk may benefit from DxWBS 6 - 12 months after ablative therapy. Isotopes such as I-123 or I-131 should be used to perform DxWBS. DxWBS is not indicated in patients on thyroid hormone replacement with undetectable serum Tg and TgAb, and an unrevealing neck ultrasound [3]. Administration of a diagnostic I-131 dose may cause thyroid stunning and a therapeutic follow-up dose of I-131 will not be adequately absorbed for proper imaging. I-123 imaging is of better quality but its greater expense and short half life makes its usage more difficult [32].

Some differentiated thyroid cancers may lose their ability to take up radioactive iodine, but concurrently begin taking up more FDG (2-Deoxy-2(18F)-fluoro-D-glucose). This "flip-flop" phenomenon is taken advantage of by FDG-PET scanning in Tg positive yet WBS and ultrasound negative recurrence [34-39]. Sensitivities of PET and PET-CT in the detection of recurrent PTC were calculated to be 77-85% and 82-84% in a meta-analysis [40]. Choi et al calculated the sensitivity and specificity of PET scanning to be 56.6 and 52.2% in detection of recurrent PTC in a series of 76 cases [35]. PET scanning is not effective as a first line diagnostic for detection of recurrent disease, but there may be a yet to be defined role for concurrent WBS and PET scans [41-44].

Ultrasound-guided fine needle aspiration (US-FNA) is a safe and effective tool to diagnose and characterize recurrence of DTC [45]. Examination of the thyroid bed and the internal jugular chain lymph nodes should be conducted, and when suspicious of an aggressive recurrence, examination should extend to the supraclavicular, lateral cervical and submandibular lymph nodes. Inferior pretracheal lymph nodes should be scanned in patients who had isthmic or lower pole cancer [46]. Some research has demonstrated a 27% recur-

rence rate of DTC diagnosed by US-FNA and these recurrences were associated with elevated Tg levels as well as with ultrasound abnormalities such as irregular margins or non-ovid lesion shape. This modality may be less useful in patients without such characteristics [47]. The drawback of ultrasound is that it inadequately visualizes the paravertebral, retrotracheal and retropharyngeal regions as well as nodal chains close to the skull. Fortunately most recurrence does not present in these areas [27].

Tuttle et Al recommend different postoperative surveillance for each of his risk strata for the first 1 - 2 years post treatment. Low risk patients should have suppressed Tg measured every 6 months and a neck ultrasound yearly for two years. These patients do not need stimulated Tg measured, nor do they need DxWBS [48], MRI/CT or FDG-PET. Intermediate risk patients need a suppressed Tg measured every 6 months and a stimulated Tg measured 12 - 24 months after treatment. They should undergo neck US yearly for 2 years and should receive radioactive iodine (RAI) DxWBS at 12 - 24 months. They do not require MRI/CT, or FDG-PET. High risk patients should receive the same surveillance as intermediate risk patients with the addition of cross sectional imaging such as CT/MRI if their Tg measurements are elevated or if there is clinical suspicion. Furthermore, they should receive FDG-PET scanning if a Tg measurement is elevated but their RAI DxWBS is negative [15].

Treatment Modalities

Surgical therapy is widely regarded as definitive treatment for recurrent thyroid carcinoma. Central compartment dissection for recurrent PTC, while carrying an increased risk for hypoparathyroidism and recurrent laryngeal nerve injury, remains the treatment modality of choice for regional recurrent or metastatic disease [13, 49]. Central neck dissection entails removal of all soft tissues in level VI and VII neck compartments in a patient who previously underwent thyroidectomy or central lymph node dissection. It is recommended to obtain cross sectional imaging such as CT or PET-CT for operative planning because physical examination and ultrasound can miss pathological mediastinal lymphadenopathy [50]. Recurrent laryngeal nerve identification and monitoring as well as retention of parathyroid gland vascular pedicles reduce reoperative morbidity in central compartment dissection [51] although the risk of nerve injury is greater in reoperation than primary surgery. Early visual identification of the nerve is of utmost importance and is the gold standard measure to prevent nerve injury in both primary surgery and reoperation. Preoperative laryngoscopy should be performed to evaluate for RLN injury as this may influence the operative approach [50]. Intraoperative nerve monitoring may be particularly helpful in revision surgery [52]. It is particularly important

that all fibroadipose tissue posterior to the strap muscles be removed in central compartment reoperation because this tissue contains paratracheal lymph nodes which may harbor cancer [53].

Recurrence in a remnant thyroid is far more often operable than recurrence within the thyroid bed. Reoperation should be done through the prior operative site and efforts to should be undertaken to maintain as much of the anatomy undisrupted, despite the presence of fibrosis and scar tissue from the previous surgery. Identification of the recurrent laryngeal nerve is of utmost importance and may be difficult intraoperatively without the use of nerve monitoring devices due to the possibility that the nerve is encased in fibrotic tissue. Dissection along the carotid artery inferiorly may allow access to undisrupted tissue planes and may assist in locating and identifying the nerve. The dissection should include all remnant lymphatic tissue from the trachea to the carotid artery. The superior and inferior borders of the dissection should extend from the cricoids to the superior edge of the clavicle. Picking out individual lymph nodes which appear diseased is highly discouraged. Due to the fibrosis and scarring, intraoperative ultrasound can be very useful for identifying disease < 20 mm [54].

Preservation of the inferior thyroid artery is recommended as it reduces parathyroid devascularization. Due to increased scar tissue and fibrosis, liberal frozen section pathology should be utilized to ensure that parathyroid glands are not inadvertently removed [53]. Patients with low intact serum PTH are associated with postoperative hypocalcemia [55, 56]. Reoperative central lymph node dissections (CLND) were found to have a lower rate of transient postoperative hypocalcemia as compared to initial dissections. Inadvertent removal of parathyroid tissue is common in reoperation but is not associated with postoperative hypoparathyroidism [57]. No comparison has yet been done of the risk of transient or permanent hypoparathyroidism post lateral versus central compartment dissection. The role of prophylatic CLND for unenlarged central compartment nodes remains controversial due to operative risks [4]. Most importantly, reoperation is effective at treating recurrent disease [29].

Recurrence in the lateral neck discovered by US should be further evaluated with FNA to identify regional metastasis. Recurrent disease most often occurs in levels II-V involving the transverse cervical and spinal accessory lymph nodes [58]. Lateral compartment dissection carries its own set of complications, which include thoracic duct injury, internal jugular vein injury, carotid artery damage, spinal accessory nerve damage and brachial plexus injury, among others [13, 59]. Nononcologic structures such as the jugular vein, spinal accessory nerve, and sternocleidomastoid should be retained unless directly invaded by tumor recurrence. Lymph node resection should include the highest affected node along with its drainage basin inferiorly. Again,

selection of individual diseased lymph nodes is discouraged in lateral dissection and proper technique is to remove an entire nodal basin [54].

Central or lateral lymph node dissection (LND) for recurrent PTC may result in cure (defined as total or near total Tg reduction) in 72% of cases [60]. There is no difference in the rate of central versus lateral recurrence after a primary or reoperative central lymph node dissection [4]. Critics of the trend towards prophylactic neck dissection put forth that extrathyroidal extension (ETE) and lymphovascular invasion are independent predictors of regional recurrence and may be of little benefit to patients without these findings. In those with gross ETE there may be an additional role for contralateral central compartment dissection as well as dissection of ipsilateral level III and IV [10, 61].

Laryngotracheal involvement can occur in up to 16% of cases. Adherence to the trachea resulting in a shaving resection or more significant involvement requiring tracheal resection with end to end anastomosis are both appropriate as long as the tumor is completely excised. It is critical implement a resection which offers the lowest perioperative morbidity as well as the best quality of life. More significant laryngotracheal involvement requiring complex reconstruction suffer from increased rates of complications and perioperaive death [54].

Radioguidance is emerging as a tool in revision thyroid surgery that can be particularly useful after normal anatomy has been disrupted or there has been incomplete resection of tissues. As most recurrent disease is not iodine avid, radiopharmaceuticals such as ^{99m}Tc sestamibi or ^{18}F-FDG can be used to tag remnant tissues in difficult or previously undetected locations [62].

The use of same-day US along with preoperative imaging in resection of recurrent PTC leads to greater chance of success without impacting mean operating time. Preoperative US-guided injection of blue dye into a focus of recurrent thyroid cancer has also been successfully used to intraoperatively localize disease recurrence [63-65].

Aggressive histological variant cancers should have surgical treatment followed up with radioiodine ablation. Ablation does not need to be implemented in patients postoperatively when their measured Tg is undetectable and they have a normal neck ultrasound [11]. Ablation may be less effective in PET positive lesions as they often have reduced ability to take up radioiodine [66].

External beam radiation can be used on non-radioiodine avid tumors, painful bony metastasis, and tumors in regions that may cause significant anatomic complications but cannot be surgically treated. Recurrence is more often treated with radiation, particularly when there is extracapsular extension from the remnant thyroid [54]. Stereoctactic body radiotherapy [33], radiofrequency ablation, ethanol injection, and chemoembolization have been used in certain cases although as of yet chemotherapeutic treatment of DTC has

shown little to modest response [67].

Molecular Strategies

The mainstay of medical treatment of DTC is thyroxine replacement, which negatively feeds back on TSH thus inhibiting TSH-dependent tumor growth. Poorly differentiated cancers may not be as responsive to this modality [33].

Both VEGF and VEGF-C (a lymphangiogenic factor) are elevated in cases of recurrent papillary thyroid carcinoma and, like other cancers, are proposed to play a role in growth, metastasis and recurrence [25]. Anti-VEGF antibodies and other antiangiogenic therapies are currently in phase III clinical trials and a search is underway for good predictive markers of cancer response [68, 69].

Metastatic DTC cells express a somatostatin receptor subtype which can be tagged using a somatostatin analogue and detected via PET scanning. (68Ga) DOTATOC is one such somatostatin analogue. PET scanning with this molecule has not been shown to be more effective than (18F) FDG scanning. Higher affinity analogues exist but have not yet been studied in context of PET detection of recurrent thyroid cancer [36].

Outcomes and Conclusions

Well differentiated thyroid cancer recurs in 5-20% of patients. Cancer-related mortality has been estimated at 6.5% [2, 70]. Survival of primary disease is arguably excellent with 10 year survival rates of 98% and 92% in papillary and follicular cancers respectively [71]. Forty-year survival rates are 94% and 84% [72].

Life expectancy for persistent disease is dependent on tumor characteristics, but has been shown to be only 60% that of the general population [3]. Roughly half of all patients with recurrent thyroid cancer will eventually die from disease [73]. Cancer-related mortality from multicentric recurrent papillary thyroid carcinoma was found to be 27.8% in one study [14]. An older study by Rossi et al puts forth treatment success rates at 73% for patients with nodal recurrence, 53% for local recurrences, and only 27% for distant recurrences [7]. Extrathyroidal extension may be a negative prognostic factor in survival of recurrent papillary cancer [10]. Thorough resection of primary disease decreases the risks of recurrence and secondarily decreases the risk of death from recurrent disease. Recurrence in the remnant thyroid or subcutaneous tissue has better outcomes than recurrence in the thyroid bed or surrounding tissue [74]. Primary disease staged T1-T3 has excellent 5, 10, and 15 year survival rates (96%, 93%, 87% respectively). Both T4 and distant disease have increasingly worsened survivability [54]. Despite this handful of studies, there is no definitive answer yet on the long-term survivability of recurrent differentiated thyroid cancer.

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