Primary hyperparathyroidism and Non-Medullary Thyroid Cancer

REVIEW

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Abstract

Background: The association of thyroid disease and primary hyperparathyroidism is well described, with thyroid carcinoma being reported in 2-15% of cases. The most commonly associated carcinoma is non-medullary thyroid cancer. While the association of PHPT and medullary thyroid cancer (MCT) is well known, that of NMTC, despite its increasing incidence, is still not established. Our study is a review of incidence and underlying mechanisms of non-medullary thyroid cancer associated with PHPT. Also, best imaging tools for concomitant diagnosis is reviewed to ensure an adequate plan of care.

Methods & findings: A search was done using two databases: Medline & Embase. The search conducted from the period of 2008 until April 2018 yielded a total of 142 studies. After an adequate screening, 26 studies were reviewed.

Incidence of DTC in association with PHPT in the literature ranged between 0.91% and 17.6%. The main histological thyroid malignancy found is micropapillary carcinoma. Despite its less aggressive presentation, these microcarcinomas may grow or develop nodal metastases on follow up. Although bilateral neck exploration with hemi/total thyroidectomy carries the risk of temporary recurrent laryngeal nerve injury or hypoparathyroidism, permanent complications are rare especially when compared to re-do neck surgery. Recently, parathyroid surgeries are going towards minimal invasive procedures, requiring an adequate imaging tool to ensure diagnosis of both diseases. Multiple risk factors for concomitant diseases were hypothesized, the more robust are the common embryologic origin and activation of angiogenic growth factors.

Conclusion: NMTC is frequently associated with PHPT especially in endemic goiter areas. With the high prevalence of micropapillary carcinoma and its risks, a partial/total thyroidectomy in addition to

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parathyroidectomy may be warranted. With the recent need of adequate diagnostic tools, combining both Technetium Sestamibi scintigraphy and thyroid ultrasound improved sensitivities and accuracy of diagnosis, but dual-isotope scintigraphy (I-123 sodium iodide/99mTc-sestamibi) seems an attractive modality in hyperparathyroid patients with concomitant suspicious thyroid nodules. However, further studies for validation may be needed.

Keywords

Primary Hyperparathyroidism; Non-Medullary Thyroid Carcinoma; Micropapillary Carcinoma; Thyroidectomy; Parathyroidectomy; Sestamibi Scan; Thyroid Ultrasound.

Introduction

Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders, with a prevalence of around 0.1% of the general population [1] and an annual incidence of up to 82 cases per 100,000 having increased by fivefold early on after initiating routine screening and diagnosing asymptomatic cases [2]. It is more prevalent among women, with a peak during the 5th and 6th decades of life [2, 3]. PHPT is caused by a single adenoma in around 80-85% of cases, followed by hyperplasia in 10-15%, and rarely parathyroid carcinoma in around 1% of cases [4]. The standard management of PHPT is surgical and bilateral neck exploration had been the usual approach. However, the modern practice changed toward minimally invasive approaches and intra-operatively parathyroid hormone (PTH) testing with a high success rate [5, 6] These approaches involves the resection of the single parathyroid adenoma without neck exploration, reducing the length of the surgery and post-operatively complications [4].

On the other hand, thyroid disease is becoming increasingly more frequently diagnosed after the

wide spread use of ultrasound, with occult thyroid nodules being prevalent in up to 68% of the general population [7, 8]. It is also found incidentally on diagnostic imaging done for purposes not related to thyroid, such as computed tomography (CT scan) or magnetic resonance imaging (MRI) and fluoro-deoxy-glucose (FDG)- positron emission tomography (PET) [8]. Around 10% of patients presenting with thyroid nodules are at risk for malignancy, the most common being differentiated thyroid cancer (DTC), with papillary thyroid cancer (PTC) accounting for around 95% of cases [7, 8].

The association of thyroid disease and PHPT is well described [7, 9]. Benign goiter and thyroid nodules are commonly found, followed by Hashimoto thyroiditis [9]. With thyroid nodules being frequently encountered (20-60%) [7], thyroid carcinoma is reported in 2-15% of PHPT cases [9, 10]. The most commonly associated carcinoma is non-medullary thyroid cancer (NMTC) [7, 10].

While the association of PHPT and medullary thyroid cancer (MCT) is well known [11, 12], that of NMTC, despite its increasing incidence, is still not established [10].

PHPT is treated surgically, when indicated, and surgery is also indicated whenever thyroid malignancy is present [2, 13]. With the current shift towards minimal invasive parathyroidectomy (MIP), detection of thyroid pathologies becomes difficult [14]. Thus, a need for diagnosing concomitant diseases prior to primary surgery seems advisable [7, 14].

Aim

The incidence of non-medullary thyroid cancer in association with PHPT will be reviewed. The underlying mechanisms and the best imaging tools to diagnose both diseases will also be reviewed in order to ensure an adequate plan of care.

Methods

A search was done using two databases: Medline & Embase. The search was conducted from the period of 2008 until April 2018. It was limited to human studies, using "primary hyperparathyroidism" and "thyroid neoplasms" as *Mesh* terms. "Primary hyperparathyroidism", "papillary", "follicular", "non-medullary", "thyroid carcinoma", "thyroid neoplasm", "thyroid tumor" or "tumour", "thyroid malignancy" & "thyroid neoplasia", were all used as *keywords*. These terms were used in mixed combinations. Boolean operators and truncations were used to expand our search results, and only English articles were selected. Medline search yielded 142 studies, while Embase 131 results. Articles were screened by title and abstract and the most relevant articles to our review were selected. Case reports, articles that included parathyroid carcinoma cases only and medullary thyroid cancer cases in the setting of MEN2A syndrome were excluded. Finally, 26 studies were included of which 5 articles are prospective cohorts of patient undergoing concomitant parathyroidectomy and thyroidectomy. One cross-sectional study was included.

Differentiated thyroid cancer incidence in PHPT

The association between thyroid disease and primary hyperparathyroidism was first described in 1947 by Kissin *et al* [14, 15]. In 1982, Prinz *et al* studied 351 cases who underwent parathyroidectomy (PTX), and 70 patients (20%) were found to have nodular thyroid disease at time of surgery, of whom 14 (20%) had a DTC [15]. Thereafter, several studies were published describing intraoperative finding of thyroid nodular disease and thyroid cancer in patients evaluated for PHPT, with incidence reaching 54% and 17.6%, respectively [15, 16].

The first study to evaluate concomitant thyroid disease in patient undergoing PTX preoperatively was by Morita *et al* [15]. In their retrospective study, around half of PHPT patients (102/200) had concomitant nodular thyroid disease of whom 12 patients were diagnosed with thyroid cancer on final pathology, with all cases being PTC, with a mean size of 5.1mm, and a range of 1-13 mm. A third were multifocal and one microcarcinoma of 2mm had nodal metastases [15]. Micropapillary thyroid carcinoma was also the most common malignant pathology associated with PHPT in several other studies [3, 14-18], showing multifocality in more than half of cases [17], and presence of concomitant lymph node metastases in other cases [17, 19].

The recent case series evaluating concomitant diseases included 849 patients primarily treated for hyperparathyroidism (HPT), with PHPT being the most common diagnosis in 95.6% of cases [13]. 224 patients (26.4%) had concomitant thyroid disease, of whom 10% were found to have thyroid cancer with PTC in 91% of cases. The malignancy rate of concomitant thyroid nodules with PHPT was higher in a study by Xue *et al*, being as high as 20.7%, after excluding cases of multiple endocrine neoplasia (MEN) or familial HPT [3].

The malignancy rate of thyroid nodules in PHPT appears to be similar [13, 16, 18, 20] or even higher

[3, 21] than that in general patients (5-15%) [22], and while some authors found this association to be coincidental [23], others consider PHPT patients with thyroid nodules “extra suspicious” for thyroid malignancies [24]. The latter was shown in 4 cases of PHPT with sub-centimetric thyroid nodules, benign on fine needle aspirate, that were found to be micropapillary carcinoma intra-operatively by frozen section, leading to an extensive surgery and radio-active iodine therapy [24]. However, according to the latest guidelines, these patients had been treated aggressively since pathology examination showed absence of aggressive features [25].

Another study by Weiss *et al*, also demonstrated a false negative fine needle aspirate (FNA) in 2/5 patients with PHPT that were found to have PTC on final pathology [26].

Regarding parathyroid pathology, the main diagnosis is parathyroid adenoma, as expected in patients with PHPT. However, the prevalence of parathyroid hyperplasia is high ranging between 20 to 40% of PHPT with concomitant DTC [16, 17]. It is higher than the reported prevalence in patients with primary hyperparathyroidism (8.5%) [27]. In one study, the prevalence of parathyroid hyperplasia (33.3%) was higher in patients with papillary thyroid cancer as compared to those with benign nodules (15.21%) and those with no concomitant thyroid diseases (20.61%) [3]. DTC seems frequently associated with parathyroid hyperplasia and hyperplasia appears to be 4 times more present in DTC versus PHPT [17].

As shown in **Table 1**, the mean age for concomitant diseases is in the fifth decade, and the majority are female. The highest prevalence of concomitant thyroid cancer in patients with PHPT reached 17.6% in a study conducted by Kösem *et al*. in Turkey [21], a known endemic goitrous regions [16]. Similarly, Kutluturk *et al*, reported the highest prevalence (76.1%) of concomitant thyroid disease in patients with PHPT, with 10.9% of all patients having papillary thyroid cancer, primarily microcarcinoma [16].

Clearly, the main thyroid malignancy associated with PHPT is micropapillary carcinoma (**Table 1**).

The reported incidence of papillary microcarcinoma in patients undergoing total thyroidectomy for benign goiter is 27.4%. It can be multicentric in 9.5 to 24.9% of cases, with presence of regional lymph node metastasis in 14-64% of lesions [16, 28].

There is no agreement on the treatment of incidental thyroid papillary micro-carcinoma. While bilateral total thyroidectomy was advocated in the past to prevent tumor recurrence [29], recent studies conducted in Japan suggest only observation of micropapillary PTC in the absence of unfavorable features [28, 30, 31]. In their most recent study, Ito *et al* showed papillary microcarcinoma enlargement in 6.4% and 15.9% of patients at 5y and 10y follow up respectively with novel nodal metastases occurring in 2.1% of cases. Of patients who underwent surgery on follow up, no tumor recurrence was noted. Clinically apparent lateral lymph node metastases, in addition to male gender, were found to be independent prognostic factors of disease-free survival in patients with papillary microcarcinoma [28].

A study looking at cost effectiveness showed that non-surgical approach for micropapillary PTC was less costly in elderly patients with life expectancy being $\leq 16y$, whereas surgery was preferable, in term of cost, for younger and healthier patients [33].

As for the actual plan of care of endocrine surgeons operating patients with primary hyperparathyroidism, a cross-sectional survey investigated their management in the setting of concomitant incidental finding of thyroid nodules. Responders were divided into high volume surgeons, (performing 5 or more parathyroidectomies monthly) and low volume surgeons with less than 5 parathyroidectomies per month [34]. In case of incidental thyroid nodule diagnosed before parathyroidectomy, the vast majority of respondents would assess a thyroid nodule ≥ 0.8 cm (91%) and do FNA for those > 1 cm (89%). High volume MIP were more likely to rely on-

Table 1. Summary of the data regarding the incidence of non-medullary thyroid carcinoma in patients with PHPT.

Study		PHPT patients	F	M	Mean Age	Thyroid cancer		F	M	Mean Age	PTC		MICRO-PTC		FTC		MTC	
Autor	Year	No				N	%				N	%	N	%	N	%	N	%
Bentrem BJ	2002 [28]	580	N	A	N/A	12/580	2.1	N	A	N/A	12/580	2.1	9/12	0.75	0		0	
Kosem M	2004 [21]	51	44	7	47.8 ± 12.7	9/51	17.6	8	1	46.8±11.1	9/51	17.6	2/9	22.2	0		0	
Morita SY	2008 [15]	200	NA		51.9	12/200	6	F>M		61	12/200	6	Mainly	+++‡	0		0	
Heizman	2009 [20]	30	17	13	65	2/30	6.6	N	A	N/A	½	50	0		½	50	0	
Arciero CA	2012 [6]	94	71	23	56 ± 13	6/94	6.4	N	A	N/A	5/94	5.3	N/A		1/94	1.1	0	
Ghorra	[17]	384	N	A	N/A	5/384	1.3	5	0	58	5/384	1.3	4/5	80	0		0	
Kutluturk	2014 [16]	46	39	7	52.8	5/46	10.9	4	1	50.6	5/5	100	5/5	100		0	0	
Yazici	2015 [18]	228	228	0	N/A	6/228	2.6	6	0	51 ±11.9	6/228	2.6	4/6	66.6		0	0	
Emirikçi	2015 [15]	550	N	A	N/A	5/550	0.91	N	A	N/A	5/550	0.91	4/5	80		0	0	
Riss	2015 [19]	1065	853	212	N/A	86/1065	8.1	N	A	N/A	81/86	94.2	57/81	70	1/86	1.16	2/86	2.32
Xue Y	2016 [3]	155	117	38	55±14	12/155	7.7	8	4	55±18	12/155	7.7	7/12	58.3	0		0	
Wright	2017 [7]	103	74	29	55.06± 15.56	7/103	6.8	N	A	N/A	N/A		N/A		N/A		N/A	
Jovanovic	2017 [14]	849*	724	125	57.6 ± 14.9	22/849	2.6	201	23	N/A	20/22	91	N/A	1/22	1/22	4.5	1/22	4.5

*: Including primary, secondary and tertiary hyperparathyroidism. ‡: Mean size of PTC 5.3mm, range 1-13mm. F: Female; M: Male; N/A: not available

sonographic features to decide on thyroid nodules workup. On the other hand, low volume MIP would plan elective thyroidectomy with parathyroidectomy for thyroid nodules less than 1cm more frequently than high volume surgeons (78% versus 59%, respectively, $p < 0.05$) [34].

For nodules identified intra-operatively, thyroid lobectomy or nodule biopsy would be performed more likely during open parathyroidectomy as compared to minimal invasive procedure (30% versus 9% respectively for lobectomy, $p < 0.001$; 32% versus 20% for nodule biopsy, $p < 0.01$) [34]. Thyroid lobectomy was less likely performed by high volume surgeons during open parathyroidectomy, for an incidental thyroid nodule regardless of its size, as compared to low volume surgeons (24% versus 40%, $p < 0.05$). This was similar for intra-operative nodule workup (by fine needle biopsy or frozen section), but the difference was not statistically significant ($p = 0.07$) [34]. Finally, taking into account both volume and technique, high-volume MIP surgeons were significantly more likely to ignore thyroid nodules of less than 1 cm and were infrequently performing a planned thyroidectomy [34].

Concomitant procedures safety and advantages of MIP

Regarding the safety of both procedures, Panarese *et al.* looked at elderly patients undergoing bilateral neck exploration for PHPT with total thyroidectomy in those having both diseases. Concomitant surgeries, as compared to only parathyroidectomy, did not expose them to higher risk and was safe when done by experienced surgeons [35].

However, recent trend is toward a minimal invasive parathyroidectomy (MIP) for parathyroidectomy [14]. It has several advantages including a high success rate, a low complication rate with better cosmetic results and a reduction in length of surgery, hospital stay and total hospital charges [5, 20]. Several approaches of MIP were described over the last ten years, including: total endoscopic parathyroi-

dectomy, video-assisted techniques, radio-guided explorations and focused parathyroidectomy using mini-incisions over the adenoma [20]. But these procedures necessitate an adequate localization study preoperatively [20] and lack adequate visualization and diagnosis of thyroid nodules if present concomitantly [7].

A prospective, non-randomized study by Heizmann *et al.*, evaluated the outcome of focused open MIP in patients with PHPT in respect to coexisting thyroid findings. All patients had preoperative localization imaging with both ultrasound and ^{99m}Tc -MIBI scintigraphy with intraoperative PTH measurement [20]. Of 30 patients, MIP was possible in 18 (60%) patients, the remainder with either concomitant thyroid nodules or negative localization studies underwent bilateral neck exploration. Only one case of conversion rate to a four gland exploration was needed (1/18) in a case of an ectopically paroesophageal located parathyroid adenoma falsely localized on imaging [20]. During a median follow-up of 40 months, none of the patients developed persistent or recurrent hypercalcemia, resulting in a 100% cure rate with both procedures. None of the patients undergoing MIP had hypocalcemia postoperatively versus 4 cases of transient hypocalcemia with the traditional bilateral neck exploration. Early discharge at 24h postoperatively was possible in those undergoing MIP [20].

A large analysis of 1065 patients compared complication rates after different surgical approaches, either open minimal invasive parathyroidectomy (OMIP), unilateral or bilateral neck exploration (UNE or BNE), while half of patients required concomitant thyroid surgery. The majority of patients (36.6%) underwent OMIP. The probability for recurrent laryngeal (RLN) nerve palsy was 0.9 % with OMIP and 5.3% with all the other procedures together. UNE with hemi-thyroidectomy and BNE, alone or with total thyroidectomy, were significantly associated with increased risk of transient RLN paresis (OR=5.827, 7.16, 8.047, respectively, $p < 0.01$). A

non-significantly higher probability was seen with UNE alone and BNE with hemithyroidectomy. A significantly higher probability for temporary hypoparathyroidism was seen with BNE either alone (OR= 2.36, $p=0.0058$), with hemithyroidectomy (OR= 2.38, $p= 0.0223$) or with total thyroidectomy (OR= 7.23, $p< 0.001$) as compared with OMIP. As for UNE alone or with hemithyroidectomy, there was no increased risk for temporary hypoparathyroidism as compared to OMIP [36]. At 6months, only 1 patient had permanent RLN paresis, and 3 patients only (0.3%) had permanent hypoparathyroidism [36].

There is still no consensus for the management of incidentally discovered thyroid pathology in the patient with PHPT undergoing MIP. Despite the prevalence of non-medullary thyroid cancer in these patients, studies evaluating long-term outcomes in these patients are lacking [34]. When looking at concomitant thyroid and parathyroid disease, it is important to balance the pros and cons of diagnosis and intervention. With the advances in imaging, incidental thyroid disease diagnosis is increasing, and this is similar for microcarcinoma detection [7, 26]. While micropapillary carcinoma can be managed conservatively, these may grow or develop metastases on follow up [28], needing a re-do neck surgery, with an increased risk of RLN injury and permanent hypocalcemia secondary to scar tissue formation obscuring the visualization of adjacent structures [7]. As for intervention outcomes, although bilateral neck exploration with total thyroidectomy was associated with a higher risk of temporary RLN paresis and hypoparathyroidism as compared with OMIP, but the overall risk of permanent diseases was low. In addition, the risk of transient RLN paresis was lower with hemithyroidectomy and that of hypoparathyroidism was even non-significant [36]. As noted previously, since endemic goitrous regions are at highest risk for concomitant thyroid cancer [16, 36], a thyroid ultrasound may be warranted in those undergoing parathyroidectomy, and subsequent evaluation and

management of eventual thyroid nodules according to the latest American Thyroid Association guidelines should follow.

Hyperparathyroidism in patients presenting for thyroid surgery

In 1983, Lever *et al* reported concomitant parathyroid disease at time of thyroidectomy in 0.4% of cases. Thereafter subsequent authors reported association varying between 0.3 up to 8.7%. A large study conducted by Wagner *et al* between 1992 and 1998 demonstrated that PHP was three fold more prevalent in patients with thyroid disease as compared to those with normal thyroid gland, the highest being with patients with thyroid cancer [1, 37]. Ghorra *et al* reported the association of PHPT with differentiated thyroid cancer in 3.5% of cases [17]. Interestingly, all patients who underwent concomitant parathyroidectomy were normocalcemic preoperatively and 29% of the resected parathyroids were cases of hyperplasia [17].

Morita *et al* checked serum calcium levels $\pm$ PTH levels in all patients planned for thyroidectomy. Of 326 patients, 10 (3.1%) were found to have PHPT [9]. In their study, Jovanovic *et al* investigated patients undergoing thyroidectomy for concomitant diagnosis of hyperparathyroidism preoperatively and found both diseases in 2.8% of cases. These patients were older than those undergoing thyroidectomy alone (55.8 vs 51.8y) [13].

Out of 114 patients undergoing thyroidectomy, 37 % had normocalcemic HPT and 26% of cases were parathyroid hyperplasia. 17 % of patients planned for thyroidectomy with concomitant PHPT had renal calculosis, similar to general population. Thus renal calculosis cannot be considered a predictive factor for concomitant diseases. Preoperative calcium and PTH measurement is necessary [13].

Regarding normo-calcemic hyperparathyroidism, Lowe *et al* followed 37 patients with normocalcemic PHPT for a median of 3y. Seven patients (19%) became hypercalcemic, all within the first 3y of ob-

servation. A total of 16 patients required surgical management after developing either hypercalcemia (19%), marked hypercalciuria (5%) or progressive cortical bone loss (29%) [38].

Risk factors for concomitant diseases

Radiation induction theory

In 1975, Tisell first reported about the significant increase in coexistent parathyroid and thyroid disease in patients who had received childhood low-dose therapeutic irradiation. Out of 170 patients with parathyroid adenomas, coexistent non-medullary thyroid carcinoma developed in 17% of those with irradiation history as compared to 1.3% of the non-irradiated patients [39]. A more recent study conducted by Wilson *et al* on patients undergoing parathyroidectomy showed that those with a history of neck and head irradiation have a marked increase in nodular thyroid disease in 95% of cases. Nearly 1 out of 2 patients had a concomitant thyroidectomy and nearly 1 out of 4 were found to have thyroid carcinoma [40]. In 1981, Prinz *et al* identified 35% of patients who had a history of irradiation exposure to have unsuspected parathyroid disease while undergoing total thyroidectomy [41].

However other studies refuted this association [3, 15-17, 34], and in most of the reviewed studies, none of the included patients had a history of radiation treatment [3, 16, 17].

Similar embryogenic origin

Thyroid gland starts around the fourth week of gestation as an endodermal thickening between the 1st and 2nd pharyngeal pouches, with parts originating from 4th and 5th pharyngeal pouches. By the end of the seventh week of gestation, thyroid gland reaches its final destination, being able to function by the end of the 3rd gestational month [10].

The parathyroid glands start their development during the fifth and sixth weeks of gestation from the 3rd and 4th pharyngeal pouches. The superior parathyroid glands are the one originating from 4th

pharyngeal pouches along with part of the thyroid gland [10].

Multiple genes have been implicating in the development of pharyngeal organs, including our main focus, thyroid and parathyroid glands. Inactivation of *Hoxa3* gene was associated with absence of parathyroids and thymus in mice [10]. *Pax1* and *Pax9* are related to the paired-box gene family, and their inactivation also leads to failure of thymus and parathyroid glands formation [10].

- *Gene 1 Eyes absent (Eya1)* is involved in morphogenesis of thymus, parathyroid and thyroid glands [10].
- *Gcm2*, similar to the *Drosophila Glial cells missing gene* encodes a transcription factor crucial for the organogenesis of parathyroid glands. [10]. In addition to these, retinoid signaling was shown essential for the formation of 3rd and 4th pharyngeal arches [10].

To note that PTC is associated with RET mutation in 11-40% of cases [17].

A high PTH level was reported to have tumor-promoting effect with genetic predisposition to new malignancies. PTH has shown to increase cellular proliferation in bone marrow and liver *in vivo*, affecting phagocytosis, and altering both humoral (B-cell function) and cellular (T-cell sensitivity) immune function, thus increasing cancer incidence [3, 10]. Therefore, exposure to high parathyroid hormone levels may initiate a step in the cancer process by altering the DNA [10]. Several studies showed that HPT was associated with the development of urinary tract cancer, colonic cancer, squamous cell skin cancer, breast cancer and thyroid cancer [42-44]. The increase in cancer risk remains beyond 15y after parathyroidectomy [44].

In one study, primary HPT was associated with significantly increased risk of hematologic malignancies, while secondary hyperparathyroidism had insignificantly higher risk for overall malignancies [42]. This can be explained by the lower levels of active form 1,25 vitamin D in patients with chronic kidney

disease (CKD), since active vitamin D appears to suppress cell proliferation and stimulate differentiation of neoplastic cells [10].

However, in the reviewed articles, there was no significant difference in PTH levels between HPT and thyroid cancer as compared with benign thyroid disease.

Calcium & phosphorus levels

Hypercalcemia is reported to be goitrogenic, which is due to inhibition of thyroxine synthesis as a result of increased iodine clearance by the kidney. Also excessive production of calcitonin in response to hypercalcemia has been proposed as a common pathogenic mechanism for the coexistence of thyroid carcinoma and PHPT [41].

However, in their study, Xue et al demonstrated a significantly lower levels of serum Ca levels in patients with DTC as compared with those with benign thyroid nodules [3]. They reported an albumin corrected serum calcium levels $< 2.67\text{mmol/L}$ with a sensitivity of 63.6% and a specificity of 77.3% for predicting DTC in PHPT patient with thyroid nodules [3]. This correlates with studies on colon cancer where serum ionized, total and albumin-corrected calcium levels in patients with colorectal cancer were significantly lower than those of controls. Also there was an inverse relation between serum calcium levels and blood Ca^{19-9} concentration, concluding that lower serum Ca level can be both a pathogenic and prognostic factor in colorectal cancer [45].

Interestingly, patients with PHPT and concomitant PTC were found to have significantly higher preoperative serum phosphorus level as compared to those with PHPT & benign thyroid diseases in 2 studies [3, 16].

Angiogenic growth factors

Angiogenic growth factors like basic Fibroblast Growth Factor (bFGF) and Vascular Endothelial Growth Factor (VEGF) ensures vascularisation and

growth of tumor tissue. Follicular cells of thyroid gland carcinomas and parathyroid adenoma produces higher levels of bFGF, stimulating cell growth. It has mitogenic effects, and is a very strong activator of angiogenesis [10].

TSH activates the VEGF production in Thyrocytes resulting in initiation of angiogenesis. VEGF is a mitogenic factor and activates neovascularisation. Importantly, VEGF is involved in the lymphatic vessel formation and affects malignant cells spreading to regional lymph nodes [10].

Imaging: Sestamibi versus thyroid ultrasound in the evaluation of parathyroid & concomitant thyroid diseases

The minimally invasive parathyroid surgery requires an accurate preoperative localization imaging. High resolution ultrasound (US), Technicium ($^{99\text{m}}\text{Tc}$)-sestamibi scintigraphy (SS), CT scan, and MRI are the methods performed. With a sensitivity as high as 87%, sestamibi has become a standard technique in preoperative parathyroid imaging [34]. However, due to its capacity to detect thyroid nodules in addition to parathyroid adenomas, a special interest was given to thyroid US as an additional preoperative modality.

In a retrospective study by Kwon et al, high-resolution ultrasound was similar to $^{99\text{m}}\text{Tc}$ -sestamibi scintigraphy in localizing parathyroid adenoma in 105 patients with sensitivities of 93.1% and 90.4%, respectively. As for positive predictive value, it was 96.9% for both modalities [5]. Importantly, both imaging were complimentary for diagnosing parathyroid adenoma where Sestamibi found 7/10 adenomas missed by thyroid US, and US detected 9/12 missed by sestamibi. 3 cases were missed by both. The advantage of US was the concomitant diagnosis of thyroid nodules in 46.9% of patients, of whom 14.89% were found to have PTC [5]. Heizmann et al followed prospectively 30 patients with PHPT in Switzerland, an endemic region for thyroid

disease, and found that sensitivities of both imaging decreased substantially in case of concomitant thyroid pathology (66.6% versus 94.4% for Sestamibi scan with versus without thyroid nodules, respectively, similarly, it was 58.3% versus 88.9% for US). To note that in their study, combination of both modalities failed to improve sensitivities in adenoma detection, as opposed to previous study, despite a lower prevalence of thyroid diseases (33%). Apart from being a prospective study, it is limited by the small number of patients, and characterized by

the high proportion of male patients included (43.3% versus 26.7% in the former) [20].

Gómez-Ramírez *et al.* confirmed the results of Heizmann *et al.*, and showed decrease sensitivities of Tc-MIBI for localization of parathyroid adenomas in patients with thyroid nodular disease requiring thyroidectomy and those not requiring thyroid resection, compared to patients without thyroid nodules. Sensitivities were respectively 54.5%, 73.1 and 78.5% [46].

Adenomas missed by Tc-sestamibi could be due to low weight of the enlarged gland, superior adenomas or those formed mainly from chief cells with a low rate of oxyphil cells [1, 5]. MIBI false-positives could be related to radioactive tracer accumulation in thyroid nodules or to Hashimoto's thyroiditis [1].

As for ultrasound, despite being not influenced by the histopathology of the adenoma or thyroid lesion, it has its own limitation. It includes difficulty detecting deep seated or ectopic adenomas, and it is operator dependent. However, the convenience, availability, lack of radiation, and better detection of concomitant thyroid diseases make it an appealing choice [5].

Almost all endocrine surgeons (98%) use preoperative parathyroid localization study prior to MIP [34]. Eighty-five percent of surgeons use sestamibi/sestamibi-SPECT imaging, whereas fifty-five percent use preoperative ultrasonography. The majority of them (69%) utilize more than one localization imaging. When comparing management of high

volume surgeons performing MIP to low volume surgeons, the former were more likely to use sestamibi scans (44% vs 24%) and PTH intra-op (75% vs 48%) as compared to low volume surgeons [34].

The accuracy of 99mTc-MIBI SPECT/CT in detecting concomitant thyroid carcinoma was studied in 222 consecutive patients with clinically suspected parathyroid adenoma and was compared to ultrasonography [4]. Overall, 29 (13.06%) cases with concomitant thyroid carcinoma were diagnosed. The sensitivity, specificity, and accuracy for thyroid carcinoma detection were 35.71, 88.16, and 80.49% for SPECT/CT and 73.81, 95.10, and 91.99% for ultrasonography, respectively. As compared to SPECT/CT, ultrasonography enhanced diagnosis in 10 (23.8%) lesions, where seven cases were not detected, and three nodules misread by SPECT/CT. SPECT/CT improved localization, compared to ultrasonography, in five (11.9%) patients; one being an intra-thyroidal parathyroid lesion. Regarding parathyroid disease, both modalities falsely localized adenomas in six patients (14.3%) [4]. 99mTc-MIBI SPECT/CT appears to be less effective than ultrasound in detecting concomitant thyroid carcinoma, thus the necessity of both modalities.

In a large prospective database at Mayo Clinic, 470 patient underwent concomitant thyroidectomy and parathyroidectomy. In these patients, dual-isotope scintigraphy (I-123 sodium iodide/ 99mTc-sestamibi) was performed preoperatively in the majority of cases, and detected parathyroid adenomas with a sensitivity of 67% and a positive predictive value of 66% [47]. Interestingly, false positive results occurred significantly more in cases of thyroid malignancies as compared with benign nodules [47]. Forty-six percent of patients with PTC had a Tc-MIBI Hot and I-123-Cold phenotype and seventeen percent had a Tc-MIBI Cold and I-123-Cold phenotype. Twenty three percent of these tumors were not detectable with both Tc-MIBI and I-123 [47]. They concluded that patients with Tc-MIBI-Hot/I-123-Cold phenotype, were highly specific for

thyroid malignancy, and FNA should be considered. On the second hand, patients found intraoperatively to have a false positive Tc-MIBI study, were more likely to have malignant nodules, suggesting either a bilateral neck exploration or a frozen section intra-operatively [47]. Thus, dual-isotope imaging was recommended as a primary modality for parathyroid localization, in addition to improving detection of suspicious thyroid nodules [47]. However, it may not be applicable currently because of lack of availability and high cost.

Conclusion

NMTC is frequently associated with PHPT especially in endemic goiter areas. With the high prevalence of micropapillary carcinoma, the need for preoperative workup to detect concomitant thyroidal disease is questionable. However, since microcarcinoma can present with nodal metastases or progress during follow up, a partial/total thyroidectomy in addition to parathyroidectomy may be warranted. Both procedures showed low risk for permanent complications, and may avoid the morbidity associated with the redo neck surgery. As for imaging modalities, thyroid ultrasound is an effective tool for diagnosing both diseases, but needs operator expertise. Both Tc-MIBI and ultrasound have decreased sensitivity in the presence of thyroid nodules, thus combining both modalities may be beneficial. Dual-isotope scintigraphy is a promising imaging tool for concomitant diagnosis preoperatively but further studies for validation may be needed.

Abbreviations:

bFGF: basic Fibroblast Growth Factor
BNE: bilateral neck exploration
CKD: chronic kidney disease
CT: computed tomography
DTC: differentiated thyroid cancer

FDG: fluoro-deoxy-glucose FNA: fine needle aspirate
FTC: follicular thyroid cancer HPT: hyperparathyroidism
MEN: multiple endocrine neoplasia
MIP: minimal invasive parathyroidectomy
MRI: magnetic resonance imaging MTC: medullary thyroid cancer
NMTC: non medullary thyroid cancer
OMIP: open minimal invasive parathyroidectomy
PET: positron emission tomography PHPT: primary hyperparathyroidism
PTC: papillary thyroid cancer
PTH: parathyroid hormone
PTX: parathyroidectomy
RLN: recurrent laryngeal nerve
SPECT: single photon emission computed tomography
Tc-MIBI: technetium methoxyisobutylisonitrile
UNE: unilateral neck exploration
US: ultrasound
VEGF: Vascular Endothelial Growth Factor

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