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BRIEF ARTICLE

Prevalence of unsuspected thyroid nodules in adults on contrast enhanced 16- and 64-MDCT of the chest

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Abstract

AIM: To determine the prevalence of unsuspected thyroid nodules on contrast enhanced 16- and 64-multidetector computed tomography (MDCT) of the chest, in a population of adult outpatients imaged for indications other than thyroid disease.

METHODS: This retrospective study involved review of intravascular contrast-enhanced MDCT scans of the chest from 3077 consecutive adult outpatients, to identify unsuspected thyroid nodules. Exclusion criteria included history of thyroid cancer, known thyroid nodules or thyroid disease and risk factors for thyroid cancer, as evidenced by their medical records. One of 9 radiologists recorded number of nodules, location and bidirectional measurement of largest nodule, as well as amount of thyroid visualized on the chest computed tomography (CT). Presence of nodule was correlated with age, gender, race and percentage of thyroid imaged.

RESULTS: A total of 2510 (2510/3077 or 81.6%) study subjects were included in the data analysis; among them, one or more nodules were identified in 629 subjects (629/2510 or 25.1%), with 242 (242/629 or 38.5%) having multiple nodules. Patients with nodule(s) were significantly older than those without (64 ± 13 years *vs* 58 ± 14 years, $P < 0.0001$), and female gender was associated with presence of nodule(s) (373/1222 or 30.5% *vs* 256/1288 or 19.9%, $P < 0.0001$). Women were also more likely having multiple nodules (167/373 or 44.8%) compared to men (75/256 or 29.3%, $P < 0.0001$). The majority of nodules (427/629 or 67.9%) were less than 1 cm.

CONCLUSION: This retrospective review revealed a prevalence of 25.1% for unsuspected thyroid nodules on contrast-enhanced chest CT.

Key words: Thyroid nodule; Thyroid cancer; Multidetector computed tomography; Incidental finding; Chest computed tomography

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INTRODUCTION

Thyroid carcinoma is the most frequent endocrine cancer, with 33 500 new cases annually in the United States. Thyroid cancer results in only approximately 1500 deaths each year, mainly due to uncommon, aggressive forms of the disease[1]. The incidence of differentiated thyroid cancers has increased between 1988 and 2005, likely related to increased detection of small nodules on cross-sectional imaging exams[2]. The highest rate of increase is among primary tumors measuring less than 1.0 cm, nearly all of which are treatable, asymptomatic papillary thyroid cancers[2]. Despite this rise in incidence of thyroid cancer, thyroid cancer-specific mortality has remained stable from 1973 to 2002, due to aggressive treatment of even small incidentally detected lesions. For example, approximately 75% of patients with small papillary thyroid cancers (< 1.0 cm) undergo total thyroidectomy[3]. Overdiagnosis and overtreatment are a rising concern due to the relatively benign nature of these small neoplasms.

The likelihood of thyroid nodules increases with age, iodine deficiency, and history of head and neck radiation[4,5]. The exact prevalence of thyroid nodules varies with the population studied and the methods used for detection. Studies show a prevalence of 2%-6% on palpation, 19%-35% with ultrasound, and as high as 65% in autopsy data[4]. The vast majority of nodules detected employing these methods are diagnosed as benign colloid nodules, cysts or adenomas, while only approximately 5% of nodules are malignant[6].

Identification of incidental thyroid nodules at computed tomography (CT) is an area of growing interest. As chest CT is performed more frequently, especially in the emergency room (ER) setting, incidentally detected thyroid nodules can be a challenge for both ER physicians and radiologists. Two recently published studies have reported that 17% of those imaged with neck CT had an unsuspected thyroid nodule[7]. Improvements in image quality resulting from advances in CT technology have increased the frequency with which these lesions are detected. As smaller lesions are discovered, triage algorithms and management protocols must be defined to balance identification of malignant or premalignant lesions with additional imaging studies and/or biopsy that prove unnecessary in patients with benign nodules. As a basis for additional research in this area, our study is a focused investigation designed to measure the period prevalence of unsuspected thyroid nodules using high resolution (current state-of-the-art) intravascular contrast enhanced chest multidetector computed tomography (MDCT) in adult outpatients.

MATERIALS AND METHODS

The institutional review board at Johns Hopkins School of Medicine granted an exemption for this health insurance portability and accountability act compliant retrospective investigation and waived the requirement for informed patient consent.

Subjects

We retrospectively identified all adult patients who underwent contrast enhanced MDCT of the chest at an outpatient center over a 1-year period. The examinations were identified by using an internal coding system for CT scans that included the chest and intravascular contrast. Over the period from April 1, 2008 to April 1, 2009, 3077 adult outpatients were imaged.

To ensure that any nodules discovered were truly unsuspected and previously unknown, we excluded patients with any known thyroid disease or history of head and neck radiation, as evidenced by record review. Exclusion criteria included patients under the age of 18, patients with a known history of either symptomatic thyroid disease or thyroid cysts or masses, indication for CT related to thyroid disease, and patients who underwent prior thyroid surgery. Patients were excluded if no portion of the thyroid was visible on the CT.

CT technique

All CT examinations were performed with a Somatom Sensation 16-MDCT scanner (Siemens Medical Solutions) or Somatom Sensation 64-MDCT. Anatomic coverage was from thoracic inlet to dome of diaphragm. If no portion of the thyroid was visible on the chest CT, the patient was excluded. Depending on the stated indication, the post contrast acquisition was either arterial phase (25-30 s) or venous (50-70 s). If the patient had arterial and venous acquisitions, then the venous was used to perform measurements. Acquisition parameters included detector row configuration of 0.625 mm or 1.25 mm and reconstruction thicknesses ranging from 3 to 5 mm.

Data collection

One of 9 attending radiologists in the division of body CT reviewed each scan, using Ultravisual Software (Emageon) to evaluate the study as axial sections in scroll mode using a soft tissue window. If a patient underwent more than one chest CT examination during the study period, only the first examination was reviewed. The following data were collected for each scan: percentage of the thyroid gland visible on the chest CT, appearance of the gland (normal, enlarged but without nodule, single nodule, multiple nodules without dominant, multiple nodules with dominant). If a nodule (including cyst) was identified, location and size were recorded. Measurements were performed with an electronic caliper measuring tool. Each positive CT was re-reviewed by two experienced attending body CT radiologists in consensus, the purpose being to confirm that the finding represented a true thyroid nodule. Multiplanar reconstructions (MPR) were not reviewed.

All continuous parameters were summarized by means and standard deviations and all categorical parameters were summarized as proportions. To compare between-group differences, the Student's t-test was used for continuous variables, and the χ^2 test was used for categorical variables. The *P*-values reported are two-sided. A *P* -value < 0.05 indicated statistical significance.

RESULTS

Included were 2510 subjects, among them 1222 (48.7%) were women. The race distribution was 72.8% white (1828/2510), 17.6% black (442/2510), 3.0% Asian

(76/2510), 1.2% Hispanic (29/2510), 3.5% other (88/2510) and 1.9% not reported (47/2510). Mean age was 59.3 years with a range of 18 to 94 years. No association was shown between presence of nodule and race (P = 0.5612).

One or more nodules were identified in 629 subjects (629/2510 or 25.1%). More than half of these subjects had only one nodule (61.5%, 387/629), while 38.5% (242/629) had more than one nodule (defined as multiple nodules). The anatomic location of the largest nodule is reported in Table 1. The mean maximum diameter was 8.56 mm, with standard deviation 6.42 mm and range 1.0-62.0 mm. The majority of nodules were less than 1 cm (427/629 or 67.9%), as opposed to 1 cm or greater (202/629 or 32.1%).

The entire thyroid gland was imaged in 55.3% (1389/2510) patients, while more than half of the thyroid gland was imaged in 36.9% (925/2510) patients and less than half in 7.8% (196/2510) patients. The appearance of the gland is reported in Table 2. Of the patients who had the entire thyroid imaged (n = 1389), nodules were identified in 352 (25.3%), compared to 277/1121 (24.7%) whose thyroid was only partially imaged. Presence of a nodule was not associated with percentage of thyroid imaged (P = 0.7165).

Data on 601 patients provided information on location of nodules. Location of a nodule was more likely mid gland or lower pole than upper pole (Table 3). This was the case for all patients as well as those whose entire thyroid was imaged. However, the pattern of nodule distribution was significantly different between patients who had the entire thyroid imaged and those who had only part of the thyroid imaged. The majority of nodules occurred in the interpolar pole for patients who had only partial thyroid imaged (P = 0.0008)

Female gender was associated with presence of nodule(s) (373/1222 or 30.5% *vs* 256/1288 or 19.9%, P < 0.0001). Gender were also found to be correlated with presence of multiple nodules, with women more likely having multiple nodules (167/373 or 44.8%) compared to men (75/256 or 29.3%) (P < 0.0001).

Age was found to be correlated with number of nodules. Patients with nodule(s) were significantly older than those without (64 ± 13 years *vs* 58 ± 14 years, P < 0.0001). There was a significant difference in the mean age of patients with no nodules (mean ± SD: 58 ± 14 years), one nodule (62 ± 13 years) and multiple nodules (66 ± 12 years) (P < 0.0001).

Table 1 Location of the 629 nodules identified on chest computed tomography *n* (%)

	Upper pole	Mid gland	Lower pole	Total
Right	72	120	90	282 (45)
Left	47	138	134	319 (51)
Isthmus				28 (5)
	119 (19)	258 (41)	224 (36)	629 (100)

Table 2 Characterization of the thyroid gland on intravascular contrast enhanced computed tomography in 2510 patients

Characterize	Frequency	Percent
No nodule	1790	71.3
Enlarged but no nodule	91	3.6
Solitary nodule	387	15.4
Multiple nodules (no dominant)	143	5.7
Multiple nodules (dominant)	99	3.9

Table 3 Distribution of nodules in patients who had entire thyroid imaged *vs* all patients *n* (%)

Location	Whole thyroid imaged	All patients
Upper pole	81 (24)	119 (20)
Interpolar pole	124 (37)	258 (43)
Lower pole	131 (39)	224 (37)

The pattern of distribution was significantly different; although, interpolar and lower pole location was most common in both groups.

DISCUSSION

The frequency with which thyroid nodules are detected has varied from as low as 2% to as high as 67%[8-10]. Differences in mode of detection certainly account for variability in prevalence. For example, autopsy is more sensitive than ultrasound, which is more sensitive than CT. Incidental lesions are detected least frequently on positron emission tomography (PET) scans. In a study by Carroll *et al*[8] incidental thyroid nodules were detected by ultrasound in 13% (six women and three men) of 67 patients without known thyroid disease, which is at the low end of the detection spectrum. Woestyn *et al*[11] reported on 300 ultrasound examinations in patients without any signs or symptoms of thyroid disease, asymmetry, or enlargement. Approximately 19% of patients (17% of men and 20% of women) presented with small, incidental echoic nodules. However, improvements of ultrasound technology have led to substantial increases in detection of thyroid lesions. In 2006, Bartolotta *et al*[12] demonstrated thyroid nodularity in 33% of 704 patients without known thyroid disease, using high-resolution ultrasonography (HRUS) and real-time spatial compound sonography. Approximately 60% of the nodules were found in women. Ezzat *et al*[9] examined 100 healthy volunteers without history of thyroid disease and ionizing radiation exposure and reported the highest rate of detection using HRUS at 67%. However, 84% of the subjects were female, which likely contributed to an overestimation of nodule prevalence.

Autopsy data on incidental thyroid lesions is limited. An autopsy study by Mortensen *et al*[13] macroscopically examined 821 thyroid glands from patients with no history of thyroid disease and reported a 50% prevalence of thyroid nodules. Approximately 12% contained a single nodule and 38% had multiple nodules.

Incidental thyroid nodules are also detected on FDG PET. In a study of 4525 patients by Cohen *et al*[10], unsuspected thyroid nodules were demonstrated in 2% of patients. However, these scans were performed for cancer staging which likely introduces selection and population biases. Kang *et al*[14] examined 1330 patients on FDG PET and also reported a prevalence of 2%. This modality is particularly useful for detecting thyroid cancers, with studies reporting sensitivity and specificity of 75%-90% and 90%, respectively[15,16].

A few studies have looked at the prevalence of incidental thyroid nodules on neck CT. In a 2008 study, Yoon *et al*[7] retrospectively reviewed CT scans of the neck in 734 patients without known thyroid disease and reported incidental thyroid nodules in 17% of patients. Their patient population was younger than in our study (mean age 49.8 years compared to our mean age of 59.3 years). This study employed a 16-detector row CT scanner and did not exclude patients with prior history of neck radiation. They also showed that CT features, like calcification, anteroposterior (AP) to transverse (T) diameter ratio, and mean attenuation value, could be used to predict malignancy. This demonstrates the diagnostic value of CT in evaluating thyroid nodules, which may help to avoid extensive ultrasound evaluations.

Youserm *et al*[17] analyzed 123 neck CT scans (HSA or 9800 Quick scanner) and 108 MR images, and reported the prevalence of incidental thyroid nodules at 15%. The lower prevalence probably related to the CT technology, as this study was conducted in 1994. However, this study also did not exclude patients with a history of neck radiation. Given the increased prevalence of thyroid nodules in patients with history of neck radiation[4], we incorporated it in the exclusion criteria. Even though our study evaluated MDCT of the chest, which does not always image the entire thyroid, a prevalence of 25.1% was noted, which is within the range previously reported. Furthermore, there was no difference in the prevalence of those whose entire thyroid was imaged *vs* only a portion of the thyroid included in the acquisition.

The likelihood of having a thyroid nodule and multiple nodules correlated with increasing age, as has been reported previously. Woestyn *et al*[11] found that thyroid nodules were significantly more common on ultrasound scans for patients over the age of 60. Bartolotta *et al*[12] showed that the prevalence of thyroid nodularity on HRUS and real-time spatial compound sonography peaked in the 61- to 70-year-old age group, and then steadily declined. However, this was also the most common age group in their sample. Ezzat *et al*[9] found that there was a tendency toward an increased probability of a thyroid nodule on HRUS with increasing age, but this correlation was not statistically significant. An autopsy based study showed that nodules were significantly more common in women over the age of 40[13]. Both of the previously mentioned CT-based studies did not show any correlation between age and nodule frequency. To our knowledge, our study is the first to show a correlation between age and thyroid nodularity on CT.

Several studies report a higher prevalence of thyroid nodules in females than males[7-9,11,12]. Frequencies range from 20% to 72% in women and 7% to 41% in men. This was also the case in our study, with women more frequently having 1 nodule (16.86% of women *vs* 14.1 % of men) and multiple nodules (13.7% of women and 5.8% of men) ($P < 0.0001$).

The correlation between race and thyroid nodularity still remains unclear. Haselkorn *et al*[18] demonstrated that a greater prevalence of goiter and thyroid nodules accounted for a substantial portion of the higher thyroid cancer incidence rates among Southeast Asian (Filipino, Vietnamese, Thai, Indonesian, Pacific Islander) women living in the United States than among Northern Asian (Chinsese, Japanese, Korean and Asian-Indian) and non-Latino Caucasian women. Our study showed no association with race ($P = 0.5612$).

We also examined the prevalence of solitary and multiple nodules. In our study, one or more nodules were identified in 629 subjects (25.1%). More than half of these subjects had one nodule (61.5%, 387/629), while 242/629 (38.5%) had more than one nodule. Previous studies have examined the relationship between the number of thyroid nodules seen in a patient and the risk of malignancy and thyroid cancer. Sippel *et al*[19] retrospectively reviewed records of 325 patients who underwent thyroidectomy with a fine needle aspiration diagnosis of either follicular neoplasm, Hürthle cell neoplasm, or indeterminate. They showed that the risk of malignancy was lower in patients with multiple nodules as compared to those with a solitary nodule (16% *vs* 28%). Frates *et al*[20] showed that although solitary nodules have a higher per-nodule likelihood of malignancy, the prevalence of thyroid cancer was similar between patients with solitary and multiple nodules. However, that study only considered nodules larger than 10 mm in diameter. These studies suggest that there is a higher risk associated with solitary nodules and approximately two-thirds of thyroid cancers are found in the dominant nodule in patients with multiple nodules[21]. However, non-dominant nodules cannot be ignored because they still comprise a significant portion of carcinomas.

A CT-based study showed that dominant nodules were evenly distributed between lobes, but more commonly detected in the lower pole[22]. In our series, the mid gland was most common (41%), followed by lower pole (36%) for either dominant nodule or solitary nodule. Nearly half (45%) of patients had only a portion of the thyroid imaged, potentially skewing results toward the lower pole. When only those patients whose entire thyroid was imaged are analyzed, the difference between right *vs* left lobe was less pronounced, with 45% in the right lobe and 51% in the left lobe. Our results showed that mean maximum diameter of the largest nodule identified on chest CT was 8.6 mm, and the majority (68%) were less than 1 cm in maximum diameter. The risk of malignancy is difficult to determine using size as a diagnostic criterion. In one study, Papini *et al*[23] correlated sonographic findings with the results of ultrasound-guided FNA biopsy and pathologic staging of resected carcinomas. They examined 494 patients and showed that the prevalence of malignancy was not significantly different between nodules greater or smaller than 1 cm (9% *vs* 7%). Sahin *et al*[24] examined 207 nodular goiter patients and demonstrated that 21% of nodules smaller than 1 cm and 17% of nodules larger than 1 cm were malignant. However, nodules that are larger than 4 cm may carry a higher risk of malignancy than those smaller than 1 cm[25]. Although the clinical importance of nodule size is still controversial, several studies demonstrate that an AP/T diameter ratio greater than 1.0 is more frequent in malignant than in benign nodules[7,26,27], which suggests that nodule shape may be an important diagnostic indicator. In our study, we measured the AP and T diameter of the largest thyroid nodule found on CT for each patient; however we did not perform long term follow up to determine whether nodules were benign *vs* malignant. Future research collecting follow up data will be useful to determine whether the AP/TRV ratio proves to be a valid indicator of malignancy.

Likely owing to improved resolution resulting from advancements in imaging technology, the prevalence of thyroid nodules on CT and MRI has increased dramatically. Although the risk of cancer is quite low (about 5%), most nodules 1 cm or greater are sampled with ultrasound-guided fine-needle aspiration (FNA) biopsy. This has led to a marked increase in the number of patients with papillary microcarcinomas, which measure less than 10 mm in diameter[28]. Treatment strategies remain controversial. In one series, approximately 75% of patients with small papillary thyroid cancers (< 1.0 cm) underwent total thyroidectomy[3], which carries small, but significant risk of complications. Following surgery, many patients are also placed on a lifetime of thyroid replacement therapy. Despite an increase in surgeries to treat these carcinomas, thyroid cancer-specific mortality has not improved[3]. Ito *et al*[29] showed that out of 162 patients with papillary microcarcinomas, more than 70% of tumors either remained stable or decreased in size, even after 5 years or more, suggesting that overtreatment of thyroid disease is a concern, as noted by Black *et al*[30]. Further study to determine the natural history and histologic subtype of the lesions identified will be a great aid in further refining algorithms for cost-effective evaluation and treatment of clinically detectable thyroid nodules.

Management recommendations for thyroid nodules are still under debate because benign nodules are highly prevalent in the population and thyroid carcinoma is relatively uncommon. If we extrapolate from other CT series, we expect that 5% or 32/629 of the nodules that we detected will be cancer. Size has been identified as a discriminatory criteria to guide management. According to guidelines established by the National Comprehensive Cancer Network (NCCN) in 2009[25], solitary nodules measuring greater than 1 cm in diameter in patients with certain risk factors should be further evaluated with measurement of TSH levels, neck ultrasound, and FNA of nodules and clinically suspicious lymph nodes. Risk factors include age below 15 years and above 60 years, male gender, history of head and neck radiation, history of diseases associated with thyroid cancer (eg., Gardner's syndrome, Cowden's syndrome, and Carney Complex), and family history of thyroid cancer. Intranodular hypervascularity, irregular borders, and microcalcification seen on ultrasound are also important factors associated with malignancy[21]. Nodules that are very firm, have exhibited a pattern of rapid growth, and/or are invading other neck structures should be considered for surgery after FNA. NCCN also recommends that unsuspected nodules that measure less than 1 cm in patients without the aforementioned risk factors should be monitored, followed-up clinically as indicated, and a lateral neck ultrasound may be considered. Major sets of guidelines for follow-up and management of incidental thyroid lesions are established by the American Thyroid Association, the British Thyroid Association, and the Society of Radiologists in Ultrasound[21,31,32].

There are certain limitations to our study which should be addressed. First, the retrospective nature of the study is not ideal to obtain a random sample but allowed time efficient review of a large number of cases. Second, since this was a review of all contrast enhanced chest CTs during the selected time period, the data acquisition, contrast administration and reconstruction parameters were not uniform across all subjects. It is possible that more nodules would have been detected if all data sets were reviewed with thin sections or with the addition of MPRs. Third, the entire thyroid was not visible on all patients because the imaging protocol was not standardized to visualize the thyroid. However, there was no significant difference between patients whose entire thyroid was imaged as opposed to partially imaged with respect to percentage of patients who had a nodule, which prompted inclusion of all 2510 patients for analysis. It is also important to note that when the entire thyroid was imaged, the vast majority (76%) of nodules were in the lower and mid-gland regions (Table 3). Scans with partial visualization of the thyroid tended to exclude portions of the upper pole since the protocol was primarily designed for chest imaging. Therefore, the portion of the thyroid with a tendency to be missed on our imaging (i.e., the upper pole) was also the region with the lowest probability of having a lesion. This is likely the reason for insignificant differences in nodule prevalence between patients with fully- and partially-visualized thyroid glands. Nonetheless, our data may slightly underestimate the true prevalence of incidental thyroid nodules.

In patients with multiple scans during the study period we used the first positive CT study rather than choosing one that best visualized the thyroid gland because we wanted to look at truly incidental findings. Thus, by choosing the first study (not optimized for thyroid imaging) our data represents incidental detection of thyroid lesions on routine chest CT imaging.

In conclusion, unsuspected small thyroid nodules are being detected with increased frequency on CT. In this outpatient population the prevalence of unsuspected, asymptomatic nodules identified on contrast enhanced 16- and 64-MDCT of the chest was 25.1%. The presence of a nodule showed a strong correlation with increasing age as well as female gender, but not race. This study serves to highlight some important characteristics of incidental thyroid lesions on chest CT, including patterns of distribution within the gland and patient demographics. Given that nearly one-quarter of our patients had a positive finding on chest CT, this study also emphasizes the clinical relevance of incidental thyroid lesions and the need for standardized protocols for evaluation and follow up.

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COMMENTS

Background

Identification of incidental thyroid nodules at computed tomography (CT) is an area of growing interest. Incidentally detected thyroid nodules can be a challenge for both referring physicians and radiologists. As smaller lesions are discovered, triage algorithms and management protocols must be defined, to balance identification of malignant or premalignant lesions with additional imaging studies and/or biopsy that prove unnecessary in patients with benign nodules.

Research frontiers

Improvements in image quality resulting from advances in CT technology have increased the frequency with which incidental lesions such as small thyroid nodules are detected. Management of incidental findings is an active area of current radiology research.

Innovations and breakthroughs

The incidence of differentiated thyroid cancer has risen, likely related to increased detection of small nodules on cross-sectional imaging exam. Most are smaller treatable, asymptomatic papillary thyroid cancers. Aggressive treatment of these smaller lesions has held stable the mortality rate.

Applications

As a basis for additional research in this area, our study is a focused investigation designed to measure the period prevalence of unsuspected thyroid nodules using high resolution (current state-of-the-art) intravascular contrast enhanced chest modified multidetector computed tomography in adult outpatients.

Peer review

This is a well written manuscript including many patients (more than 3000). It contains, however, not much new information. After exclusions for different reasons 2510 exams are left for this retrospective study. In only 55% (1389) of these cases the whole thyroid has been visualized. In the rest (1121) only part of the thyroid was visible but still these patients are included and reviewed in this study. They should have been excluded as it is impossible to tell the number of nodules, if any, in this group.

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