Published in final edited form as:

J Surg Res. 2012 May 15; 174(2): 207–210. doi:10.1016/j.jss.2011.11.1035.

Are there predictors of malignancy in patients with multinodular goiter?

Jie Luo, B.S., Catherine McManus, B.S., Herbert Chen, M.D., and Rebecca S. Sippel, M.D.
Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, WI

Abstract

Background—Multinodular goiters (MNG) have recently been shown to have an incidence of cancer that approaches that of solitary thyroid nodule. However, fine needle aspiration (FNA) of a MNG is limited due to the presence of multiple nodules. Therefore we sought to identify risk factors for malignancy in patients with MNG.

Methods—1791 consecutive patients underwent thyroidectomy at a single academic institution between May 1994 and December 2009. 838 patients had a MNG, which we defined as ≥ 2 nodules on pre-operative ultrasound. The medical records of these patients were reviewed and analyzed.

Results—A final pathologic diagnosis of malignancy was found in 260 of 838 (31%) of MNG patients. Of the 260 patients with malignancy, 113 (44%) had a focus of cancer < 1 cm. Of the patients with malignancy on final pathology, pre-operative FNA detected only 46% ($n=120$). Of the 140 cancers not recognized pre-operatively, 61 (44%) were > 1 cm in size. On univariate analysis risk factors for malignancy were younger age and male gender. Patients with malignant nodules also had smaller nodules, smaller thyroids, and fewer nodules than those patients with benign findings on pathology. On multivariate analysis all predictors remained independently associated with malignancy with the exception of thyroid weight.

Conclusion—Risk factors for malignancy in a MNG included male gender, younger age, fewer nodules, and smaller nodule size. The low predictive value of FNA in our population suggests there needs to be better ways to predict malignancy in patients with MNG. Therefore, these clinical risk factors should be considered when consulting patients with MNG in regards to their risk of malignancy.

Keywords

thyroid; multinodular goiter; malignancy; risk factor

Introduction

Thyroid nodules are a very common finding, present in at least 4% of the population in iodine-sufficient countries upon palpation, and in over 50% of patients using

© 2011 Elsevier Inc. All rights reserved.

Corresponding Author: Rebecca Sippel, M.D., F.A.C.S. 600 Highland Avenue, Clinical Science Center K3/704, Madison, WI 53792-7375, Phone: 608-263-1387, Fax: 608-252-0912, sippel@surgery.wisc.edu.

This research was presented in oral form at the Academic Surgical Congress in Huntington Beach CA in February of 2011.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ultrasonography¹⁻³. Thyroid nodules may lead to a variety of clinical sequelae including compressive symptoms, hoarseness, dysphagia, and importantly, cancer^{1,4}. Thyroid cancer is one of the most prevalent endocrine cancers in the United States, most commonly found in women of middle age⁵. Multinodular goiters (MNG), defined as an enlarged thyroid gland with multiple nodules, have historically been thought of as a benign condition with a low risk of associated malignancy, and may be present in up to 4% of the population in iodine sufficient countries⁶. However, recent studies have suggested that the incidence of malignancy in patients with MNG approaches that of patients with a solitary thyroid nodule⁷.

Pre-operative diagnosis of thyroid cancer is commonly done through fine-needle aspiration (FNA)^{4,8}. While it remains one of the best pre-operative methods of determining nodule malignancy, large studies have found FNAs to be non-diagnostic in up to 25% of the cases⁹. Previous work by our group had shown that up to half of the FNAs taken of thyroid nodules 4 cm and larger were falsely reported as benign¹⁰. Furthermore, the presence of multiple nodules can present difficulties in adequately evaluating the entire thyroid because sampling every nodule is not practical¹¹. The presence of multiple nodules also creates challenges in following individual nodules for growth overtime, which is an additional factor that is used to increase the suspicion for malignancy.

Because a negative FNA finding cannot be used definitively in determining benign versus malignant MNG, other clinical factors must be taken into consideration when assessing patients' risk for malignancy. Such factors include but are not limited to radiation exposure, suspicious ultrasonography, surrounding adenopathy, age, gender, and nodule size. Past studies have shown a correlation between thyroid cancer and female gender, middle-age, and single nodularity⁹. Therefore, the purpose of this retrospective study is to identify risk factors for malignancy in patients with MNG.

Methods

Patients were identified from our prospectively maintained Endocrine Surgery Database between May 1994 and December 2009. All consecutive patients who underwent thyroid surgery were identified. Patients were defined as having MNG if they had 2 or more nodules on pre-operative ultrasound. Indications for surgery included compressive symptoms, nodule growth, nodule size >4 cm, hyperthyroidism, and suspicion of malignancy. We retrospectively reviewed the database to identify a number of patient and gland factors including age, gender, pre-operative thyroid function, nodule size, number of nodules, and mean gland weight. Additionally, we looked at the FNA findings of patients prior to surgery to determine the efficacy of diagnostic testing. The final diagnosis was determined by final pathology of the surgical specimen.

The medical records of these patients were reviewed and then analyzed with statistical software (SPSS, Inc., Somers, NY) using χ^2 and student t-test, when appropriate. A multivariate logistic regression was performed using all the variables identified in the univariate analysis. Findings with a p-value of ≤ 0.05 were considered statistically significant.

Results

1791 consecutive patients underwent thyroid surgery at our institution during the study period. Of those patients, a total of 838 patients underwent surgery for a multinodular goiter during the study period. A final pathologic diagnosis of malignancy post-surgery was found in 31% (n=260) of MNG patients (Table 1). The cancer was in the largest nodule in only

37% (n=95) of cases. Of the 260 patients with malignancy, 113 (44%) had a foci of cancer <1 cm.

Malignancy was identified pre-operatively in 47% (123) patients. Of the 137 cancers not recognized pre-operatively, 61 (45%) were >1 cm in size. Pre-operative FNA was performed on 204 patients with malignancy on final pathology, and malignancy was suspected or confirmed by FNA evaluation in only 60% (n=123) (Figure 1). Of the 81 cancers that FNA evaluation missed, 44% (61) were greater than 1 cm in size. Excluding patients with malignancy that was known pre-operatively, unexpected malignancy was found in 16% of our overall MNG population.

Demographically, the majority of patients in both the malignant and non-malignant groups were female, however the percentage of males was higher in the malignant group than in the non-malignant group (28% vs. 17%, $P<0.001$). The mean age of patients in the malignant group was younger than those in the non-malignant group (47 ± 0.9 vs. 53 ± 0.6 , $P<0.001$).

The presence of malignant thyroid nodules was negatively correlated with the thyroid gland weight. The mean thyroid gland weight was lower in the malignant group compared to the non-malignant group (31 ± 2.5 gm vs. 50 ± 2.8 gm, $P<0.001$). There were also fewer nodules in the malignant group. The percentage of patients having 5 or more nodules was much less in the malignant group than that in non-malignant group (20.9% vs. 42.6%, $P<0.001$). In addition, the largest nodule size was smaller in malignant group (2.32 ± 0.09 cm vs. 3.05 ± 0.09 cm, $P<0.001$). Pre-operative TSH and free T4 levels did not differ significantly between the two groups.

Risk factors for malignancy identified in the univariate analysis are displayed in Table 2 and include younger age and male gender. Patients with malignant nodules also had smaller nodules, smaller thyroids, and fewer nodules than those patients with benign findings on pathology (Table 2). A multivariate logistic regression analysis was performed and all variables, with the exception of gland weight, identified in the univariate analysis remained statistically significant (Table 3). However, the odds ratio for age, while statistically significant, approached 1, making it a very weak independent predictor of malignancy.

Discussion

Malignancy was present in nearly a third of patients with a MNG in our study. While many of these patients came to surgery with a cancer diagnosis, cancer was not suspected pre-operatively in 16% of patients that were ultimately found to have malignancy on final pathology. This data supports the fact that our current methods for the detection of malignancy pre-operatively are not adequate.

FNA still remains the best diagnostic tool to screen for malignancies; however it is important to note that a negative finding does not exclude the possibility of cancer. FNA is usually performed on a number of factors such as nodule size and suspicious features on ultrasonography¹². However, in our population, less than 37% of the cancers were found in the dominant nodule, therefore limited FNA evaluation of the thyroid based on size alone would have missed most of the malignancies. This, coupled with the presence of multiple nodules suggests that patients with a MNG need a more comprehensive evaluation that includes a risk factor analysis, and will need FNA of more than just the dominant nodule.

While overall the incidence of malignancy in our series was 30%, when we excluded patients with known malignancy, our rate of unsuspected malignancy was still 16%, many of which were clinically significant cancers, not just microcarcinomas. This shows that MNG is not a benign condition and is associated with a significant rate of thyroid malignancy. The

significance of these tumors is unknown and our study does not allow us to determine the natural history of these tumors if they had not been resected. However, since over 50% of the cancers identified were >1 cm in size we presume that at least some of these would have behaved in a non-indolent manner and that there was some benefit to surgical resection of these tumors.

Since FNA has its limitations in this population, we need to look for other factors which may increase a patient's risk. We examined our series to identify risk factors for malignancy. We found that younger age, male gender, smaller nodules, and fewer nodules were all associated with a significantly higher risk of malignancy. While thyroid weight was associated with malignancy in our univariate analysis this association was lost in the multivariate analysis. This is likely due to the fact that larger glands tend to have more nodules and most of the risk is related to that factor. In addition, age, while it remained statistically significantly protective of malignancy on the multivariate analysis, the odds ratio approached 1, suggesting that age is not a very strong independent factor for malignancy and will likely not be helpful in predicting the risk of malignancy in a given patient.

Our results are confirmed by work performed by Erbil et al.² who showed a positive correlation between a smaller thyroid volume and a higher detection rate of suspected malignant thyroid nodules in patients with MNG. They found that thyroid gland volumes less than 38 ml had a 48-fold increase in the rate of detecting suspected thyroid cancer. Additionally, they found correlation between larger tumor sizes and increased malignancy rate detection. Our results indicate that a smaller tumor size is associated with a higher risk of malignancy as demonstrated in final pathology. The reasons for the negative correlation between tumor size and malignancy rate are not clear, but it is likely do to a selection bias as all of the patients underwent thyroid surgery and in the absence of suspected malignancy, patients with smaller nodules do not routinely undergo surgical intervention. The reason that the presence of more nodules is associated with a lower risk of malignancy may be that growth stimulating factors that lead to large goiters do not necessarily stimulate the formation of malignancy.

A previous study by Mihailescu et al.¹³ showed that the number of nodules found didn't influence the risk that a particular nodule was malignant. However, the likelihood that cancer was present was increased in patients with multiple nodules. They hypothesized that this finding may be due to the different pathogenesis of multiple nodularity in patients with and without a history of radiation exposure. Taking these results into consideration, it can be seen that FNA may be inadequate in determining the risk of malignancy in these patients. These findings further emphasize the important role that clinical evaluation plays in determining the risk of malignancy in patients with multinodular goiters.

Ultrasound findings are increasingly used to help distinguish malignancy in patients with MNG. Features such as microcalcifications, hypoechoic appearance, irregular borders, and increased vascularity have all been associated with a higher risk of malignancy^{14,15}. Some clinicians use radioactive iodine scan to help identify "cold" nodules in order to better discern which nodules should undergo biopsy. Unfortunately due to retrospective nature of our study we were unable to determine if those features were present or not in each nodule and if they were used to help determine which nodules to biopsy. Because of the high false negative rate of FNA in our study, it is essential that clinicians use a combination of clinical and imaging information to help determine how to optimize the use of FNA in this population. The clinical variables identified in our study can identify higher risk groups within a population, but are difficult to apply to an individual patient therefore individual

data that can be provided from imaging characteristics may have the greatest potential to optimize the detection of malignancy in this population.

Another limitation of our study is that not every patient underwent a pre-operative FNA evaluation. Earlier in the study some patients with other indications for surgery (such as compressive symptoms) may have undergone surgery without a pre-operative FNA. However, in the more recent half of our study FNA has become the standard of care. Interestingly, when we exam the rate of undetected malignancy in only those that had a pre-operative FNA, the rate remains high, suggesting that our current method of FNA evaluation remains inadequate for the evaluation of a MNG.

In conclusion, our study shows that assessing patients with a MNG using FNA alone is insufficient, and several other risk factors such as male gender, younger age, fewer overall nodules, and smaller nodule size should be considered for a risk of malignancy.

Acknowledgments

Research was supported by the UW-Madison SMPH Shapiro Summer Research Program and the NIH T35 DK062709 Grant

References

1. Polyzos SA, Kita M, Avramidis A. Thyroid nodules - stepwise diagnosis and management. *Hormones (Athens)*. Apr-Jun; 2007 6(2):101–119. [PubMed: 17704042]
2. Erbil Y, Barbaros U, Salmaslioglu A, et al. Effect of thyroid gland volume in preoperative detection of suspected malignant thyroid nodules in a multinodular goiter. *Arch Surg*. Jun; 2008 143(6):558–563. discussion 563. [PubMed: 18559748]
3. Leclerc J. Multinodular goiters. *Rev Prat*. Jan 31; 2005 55(2):167–173. [PubMed: 15825997]
4. Pelizzo MR, Merante Boschini I, Toniato A, Sorgato N, Marzola MC, Rubello D. Surgical therapeutic planning options in nodular goiter. *Minerva Endocrinol*. Sep; 2010 35(3):173–185. [PubMed: 20938420]
5. Wartofsky L. Increasing world incidence of thyroid cancer: increased detection or higher radiation exposure? *Hormones (Athens)*. Apr-Jun; 2010 9(2):103–108. [PubMed: 20687393]
6. Pinchera A, Aghini-Lombardi F, Antonangeli L, Vitti P. Multinodular goiter. Epidemiology and prevention. *Ann Ital Chir*. May-Jun; 1996 67(3):317–325. [PubMed: 9019982]
7. Gandolfi PP, Frisina A, Raffa M, et al. The incidence of thyroid carcinoma in multinodular goiter: retrospective analysis. *Acta Biomed*. Aug; 2004 75(2):114–117. [PubMed: 15481700]
8. Ogilvie JB, Piatigorsky EJ, Clark OH. Current status of fine needle aspiration for thyroid nodules. *Adv Surg*. 2006; 40:223–238. [PubMed: 17163105]
9. Rago T, Fiore E, Scutari M, et al. Male sex, single nodularity, and young age are associated with the risk of finding a papillary thyroid cancer on fine-needle aspiration cytology in a large series of patients with nodular thyroid disease. *Eur J Endocrinol*. Apr; 2010 162(4):763–770. [PubMed: 20083557]
10. Pinchot SN, Al-Wagih H, Schaefer S, Sippel R, Chen H. Accuracy of fine-needle aspiration biopsy for predicting neoplasm or carcinoma in thyroid nodules 4 cm or larger. *Arch Surg*. Jul; 2009 144(7):649–655. [PubMed: 19620545]
11. Rios A, Rodriguez JM, Galindo PJ, et al. Utility of fine-needle aspiration for diagnosis of carcinoma associated with multinodular goitre. *Clin Endocrinol (Oxf)*. Dec; 2004 61(6):732–737. [PubMed: 15579188]
12. Hurley DL, Gharib H. Evaluation and management of multinodular goiter. *Otolaryngol Clin North Am*. Aug; 1996 29(4):527–540. [PubMed: 8844728]
13. Mihailescu DV, Schneider AB. Size, number, and distribution of thyroid nodules and the risk of malignancy in radiation-exposed patients who underwent surgery. *J Clin Endocrinol Metab*. Jun; 2008 93(6):2188–2193. [PubMed: 18381575]

14. Kim JY, Lee CH, Kim SY, et al. Radiologic and pathologic findings of nonpalpable thyroid carcinomas detected by ultrasonography in a medical screening center. *J Ultrasound Med.* Feb; 2008 27(2):215–223. [PubMed: 18204012]
15. Lu ZH, Zhu HQ, Dou JT, et al. Predictive value of sonographic features in preoperative evaluation of malignant thyroid nodules. *Zhonghua Yi Xue Za Zhi.* Dec; 2010 90(46):3272–3275. [PubMed: 21223785]

Figure 1. Flowchart demonstrating the use of FNA for the detection of thyroid malignancy. Malignancy was not picked up in 40% of the cases that underwent an FNA evaluation.

Table 1

Incidence of Malignancy

	Database (n=1791)	MNG (n=838)
% Malignancy	30% (n = 537)	31% (n = 260)
% Cancer < 1 cm	30% (n = 162)	44% (n = 113)

Table 2

Patient and Gland Characteristics

	No Malignancy (n=578)	Malignancy (n=260)	P-value
% Female	83%	72%	<0.001
Mean Age (years)	53±1	47 ±1	<0.001
Pre-op TSH	1.65	2.22	0.30
Pre-op T4	1.17	1.23	0.39
% 5+ nodules	43%	21%	<0.001
Mean gland weight (gm)	50 ±2.8	31±2.5	<0.001
Largest Nodule Size (cm)	3.1±0.1	2.2±1	<0.001

Table 3

Multivariate Logistic Regression

	Odds ratio	95% Confidence Interval	p-value
Age	0.97	0.960–0.987	<0.001
Gender (female)	0.40	0.251–0.647	<0.001
Number of nodules	0.86	0.809–0.908	<0.001
Gland weight	0.99	0.986–1.000	0.07
Nodule size	0.81	0.711–0.930	0.002
Pre-op TSH	1.02	0.971–1.062	0.50