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Thyroid

Risk of thyroid carcinoma in patients treated surgically with assumed benign cytology in Riyadh, Saudi Arabia

Il rischio di carcinoma tiroideo in pazienti con citologia preoperatoria di benignità a Riyadh, Arabia Saudita

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SUMMARY

Objectives. This study aimed to report the rate of thyroid malignancy in benign fine-needle aspirations (Bethesda II) at King Abdulaziz Medical City and evaluate the factors that affect false-negative outcomes of FNA.

Methods. All patients referred for thyroidectomy from 2009 to 2019 were reviewed (n = 1968). Only patients with a benign FNA, corresponding to the Bethesda II, were included (n = 384). Information on age, gender, body mass index (BMI), serum thyroid-stimulating hormone, type of surgery and histopathological outcomes were retrieved.

Results. Of the sample (n = 384) with an initial benign FNA, 63 patients had a malignancy on postoperative pathological examination, yielding an overall false-negative rate of 16.4%. The most frequently reported histopathological type was papillary thyroid microcarcinomas (n = 52). For the false-negative group, the mean age was 43.8 years (range 21-70 years) with an 84.1% female predominance. The surgical choice for 74% (n = 46) of cases was total thyroidectomy. Age, gender, thyroid function and BMI did not affect the false-negative rate of benign FNA ($p > 0.05$).

Conclusions. This study found a higher risk of malignancy compared to the literature related to benign FNA. The risk of malignancy should be considered, even with benign FNA.

KEY WORDS: thyroid carcinoma, benign cytology, malignancy, fine-needle aspiration

RIASSUNTO

Obiettivi. *Questo studio analizza il rischio di cancro della tiroide in pazienti con citologia preoperatoria di benignità (Bethesda II) sottoposti a chirurgia presso la King Abdulaziz Medical City, valutando i fattori che determinano i risultati falsi negativi agli agoaspirati preoperatori (FNA).*

Metodi. *Sono stati revisionati i dati di tutti i pazienti sottoposti a tiroidectomia dal 2009 al 2019 (n = 1968). Sono stati inclusi solo i pazienti con un FNA benigno, corrispondente al Bethesda II (n = 384). Sono state recuperate informazioni su età, sesso, indice di massa corporea (BMI), TSH sierico, tipo di intervento chirurgico ed esiti istopatologici.*

Risultati. *Del campione (n = 384) con FNA benigno iniziale, 63 pazienti presentavano un tumore maligno all'esame patologico postoperatorio, ottenendo un tasso complessivo di falsi negativi del 16,4%. Il tipo istopatologico più frequentemente riportato è stato il microcarcinoma papillare della tiroide (n = 52). Per il gruppo dei falsi negativi, l'età media era di 43,8 anni (range 21-70 anni) con una predominanza femminile dell'84,1%. La scelta chirurgica per il 74% (n = 46) dei casi è stata la tiroidectomia totale. Età, sesso, funzione tiroidea e BMI non hanno influenzato il tasso di falsi negativi di FNA benigno ($p > 0,05$).*

Conclusioni. *Questo studio ha indicato un rischio più elevato di malignità rispetto alla letteratura relativa all'FNA benigno. Il rischio di malignità dovrebbe essere considerato, anche con FNA benigno.*

PAROLE CHIAVE: *carcinoma tiroideo, citologia benigna, malignità, aspirazione con ago sottile*

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Introduction

Thyroid nodules are common with a suggested prevalence of 8-65% in autopsy data, 19-35% with ultrasound and 2-6% with palpation [1]. Thyroid cancer is the most frequent endocrine carcinoma, constituting 90% of all endocrine malignancies, and is considered to be one of the fastest-growing cancers [2,3]. The rate of thyroid cancer has increased during the last 30 years, with an average increase of 48.0% in males and 66.7% in females [4]. The most likely explanation for this is the extensive employment of ultrasonographic and cytological techniques, which ensures early diagnosis of occult thyroid nodules [1,5]. According to the last Saudi Cancer Registry Report, thyroid cancer is the second most prevalent malignancy in females, and the ninth in males. A 26-fold increase in the incidence of thyroid cancer has been reported in Saudi Arabia, ranging from 71 new cases in 1990 to 1900 new cases in 2016 [6].

Fine-needle aspiration (FNA) has become the procedure of choice to differentiate benign from malignant thyroid nodules and guide surgical treatment of patients with FNA-proven carcinoma. The routine use has led to an increase in cancer detection in surgical specimens from 15% to more than 30% and a decrease in the number of surgical interventions by 25% [7]. The Bethesda scoring system classifies the results of FNA specimens according to the cytopathologic features and estimates the risk of malignancy for each category as follows: (I) non-diagnostic or unsatisfactory, 5-10%; (II) benign, 0-3%; (III) atypia of undetermined significance/follicular lesions of undetermined significance (AUS/FLUS), 10-30%; (IV) follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), 25-40%; (V) suspicious for malignancy (SM), 50-75%; and (VI) malignant, 97-99%.) [8].

Although FNA is considered the gold standard for preoperative diagnoses, it has some limitations in that false-negative and false-positive results can occur [9]. Accurate FNA cytology diagnosis is dependent on various factors, including skills of the operator, specimen preparation, FNA techniques and cytology interpretation [10]. The study aimed to report the rate of thyroid malignancy in cases of benign FNA (Bethesda category II) at King Abdulaziz Medical City (KAMC).

Materials and methods

Study design and population

This retrospective study was conducted at KAMC. All patients referred for thyroid surgery were reviewed from January 1st, 2009, to December 31st, 2019 (n = 1968). Only patients with benign FNA, corresponding to the Bethesda category II were included (n = 384), using a non-probability sampling technique. All the patients with benign thyroid disease, Bethesda category II with an FNA, who had thyroid surgery and a final pathology report were included. Patients with another Bethesda category or who did not have surgery and no final pathology report were excluded.

Data collection

We used a structured data collection sheet to retrieve information from the outpatient surgery clinics. Demographic information and disease characteristics were retrieved from the "BestCare" electronic health record system. The medical files and histopathology reports of patients who had thyroidectomy for benign thyroid disease were reviewed. Data including age, gender, body mass index (BMI), fine-needle aspiration cytology (FNAC), serum thyroid-stimulating hormone (thyroid function), type of thyroidectomy and final histopathologic diagnoses and features were collected. The identified thyroid cancer cases were classified based on size as microcarcinoma, defined as a papillary thyroid cancer measuring 1.0 cm or less in the largest diameter. Macrocarcinoma was defined as any thyroid cancer measuring more than 1.0 cm. The thyroid function results were classified as hypothyroid, euthyroid and hyperthyroid. Patient data were reviewed to establish an association between FNA results and histopathological outcomes.

Statistical analysis

The data were entered in Microsoft Excel 2019, and the Statistical Package for Social Sciences (SPSS) version 21 was used for data cleaning and analysis. A P-value of < 0.05 was considered statistically significant in all tests. The quantitative data were analysed with descriptive statistics. The categorical variables, such as the type of thyroid disease, are described as percentage and frequency. The continuous variables, such as body mass index, are reported as mean ± standard deviation (SD). Inferential statistics were used to describe the comparative variables using chi-square and t-test.

Results

Of the 1968 files reviewed, the sample size was 384 patients, with Bethesda category II thyroid FNA results. The majority (81%) were female, and the mean age was 44.3 ± 18.85 years. The demographic and clinical variables of patients who underwent surgery are illustrated in Table I. The post-surgical histopathological examination identified 63 cases of thyroid cancer in the group with a preoperative benign FNA. The mean age of the group with thyroid cancer was 44.7 years (range 21-70 years) with a female predominance (84.1%). Of the 63 cases, 52 (82.5%) were papillary thyroid microcarcinoma, and 9 (14.3%) were papillary thyroid macrocarcinoma (diameter range, 1.1-4.1 cm). Folli-

Table I. Demographic and clinical variables associated with the presence or absence of thyroid cancer post-thyroidectomy (n = 384).

	Overall (n = 384)	Benign (n = 321)	Thyroid cancer (n = 63)	P-value
Mean age, years	44.3 ± 12.9	44.4 ± 0.7	43.7 ± 1.4	0.71
Gender, n (%)				
Female	311 (81%)	258 (80.4%)	53 (84.1%)	0.48
Male	73 (19%)	63 (19.6%)	10 (15.9%)	
Mean BMI (kg/m^2)	30.9 ± 6.4	30.6 ± 0.36	32.3 ± 0.81	0.057
Thyroid function status, n (%)				
Hypothyroidism	43 (11.2%)	31 (9.7%)	12 (19%)	0.08
Euthyroid	301 (78.4%)	255 (79.4%)	46 (73%)	
Hyperthyroidism	40 (10.4%)	35 (10.9%)	5 (7.9%)	

cular carcinoma was found in 2 (1.6%) cases, with one case having both follicular thyroid carcinoma and papillary thyroid microcarcinoma. The false-negative rate was 16.4%. If microcarcinomas were excluded, the false-negative rate was 2.9%. The histopathological outcomes of thyroid cancer cases are presented in Table II. The surgical choices for the group with thyroid cancer were a total thyroidectomy in 46 (73%) patients, hemithyroidectomy in 14 (22.2%) and 3 (4.8%) who underwent completion hemithyroidectomy. Of the 14 patients that underwent hemithyroidectomy, 5 had an initial diagnosis of papillary macrocarcinoma. Subsequently, those 5 patients needed a second surgery and malignancy was identified in only 1 case following completion hemithyroidectomy. The remaining 9 patients had an initial diagnosis of papillary microcarcinoma, but only 3 needed a completion hemithyroidectomy and all turned to be negative for malignancy. In total, 8 patients needed a completion hemithyroidectomy out of 14 patients. Table III shows the ultrasonographic and clinical features of the 11 patients who were found to have macrocarcinoma.

Discussion

The presence of malignancy in patients operated for benign thyroid disease is frequently reported the literature, which is also supported by the current observational retrospective study findings [11]. Fine needle aspiration (FNA) is the gold standard diagnostic test to evaluate and categorise thyroid nodules. It is an accurate, safe, rapid and minimally-invasive diagnostic tool to manage thyroid nodules. However, the American Thyroid Association guidelines recommend that FNA should be done for nodules greater than 1 cm or nodules with a suspicious ultrasound (US) pattern. Microcarcinomas, defined as malignant lesions < 1 cm in size, can be missed and found incidentally following thyroidectomy [12,13]. Since most patients with benign FNA cytology, without any other indications, do not undergo resection of the thyroid nodules, false-negative FNA cytology is problematic as it can adversely affect the patient's outcome and delay treatment. It is imperative to explore the potential of underlying thyroid malignancy in a benign FNA [14].

In this study, 63 of 384 patients with a benign FNA had thyroid cancer in the post-surgical histopathological examination, translating to a false-negative rate of 16.4%. The literature frequently reports a false-negative rate of benign FNA lower than 16.4%. The post-surgical histological analysis of preoperative benign thyroid in a study identified thyroid cancer in 14.5% [14]. Other studies reported rates of incidental thyroid cancers in a preoperative benign FNA cytology as 11, 10.4 and 10.8% [5,11,15].

Table II. Postoperative histopathological outcomes of the identified thyroid cancer in patients with a benign FNA (N = 63).

Histopathological outcomes	Total (N = 63) n (%)	Microcarcinoma (N = 52) n (%)	Macrocarcinoma (N = 11) n (%)
Multifocal	10 (15.9)	8 (15.4)	2 (18.2)
Lymphovascular invasion	2 (3.2)	1 (1.9)	1 (9.1)
Positive margin	5 (7.9)	3 (5.8)	2 (18.2)
Extracapsular extension	2 (3.2)	1 (1.9)	1 (9.1)
Extrathyroidal extension	11 (17.5)	6 (11.5)	5 (45.5)
Diameter (cm), mean ± SD	0.72 ± 0.84	0.41 ± 0.22	2.16 ± 1.17

Table III. Ultrasonographic and clinical details for patients found to have macrocarcinoma.

Patient no.	Sex	Age	Surgical procedure	Ultrasonographic features		
				Microcalcification	Increased vascularity	Echogenicity
1	F	70	TT	-	-	-
2	F	38	HT	Yes	No	Isoechoic
3	F	29	HT	No	Yes	Hypoechoic
4	F	40	TT	No	Yes	Hypoechoic
5	F	40	HT	Yes	Yes	Hypoechoic
6	F	54	TT	No	Yes	Isoechoic
7	F	32	TT	No	Yes	Heterogenous
8	F	41	HT	No	No	Hypoechoic
9	F	33	TT	No	No	Hypoechoic
10	M	28	TT	No	Yes	Heterogenous
11	F	29	HT	No	No	Hypoechoic

TT: total thyroidectomy; HT: hemithyroidectomy.

Multiple factors can be the reason for the incidence of false-negative FNA results. Studies have indicated that using a combination of experienced technologists, ultrasound-guided FNA and accurate interpretation of the final cytological results can significantly decrease false-negative results [16]. The literature frequently reports papillary thyroid carcinoma (PTC) and especially micro PTC as the most prevalent types of thyroid cancer [17]. Studies indicated that micro PTC accounted for 30% of all thyroid carcinoma [18]. Similarly, a meta-analysis conducted in 2008 stated that micro PTC accounts for an average of 22.9% of malignant tumours [19]. These studies confirm the current findings with micro PTC as the highest type of thyroid carcinoma in 52 of 63 patients treated surgically with benign FNAs, followed by 9 cases of macro PTC; however, follicular carcinoma was reported in only 2 cases, one of which had both follicular thyroid carcinoma and micro PTC.

Papillary microcarcinomas have been described as being less aggressive than the well-differentiated thyroid cancers, with a shallow frequency of distant metastases and a favourable prognosis. Although papillary thyroid microcarcinomas have an excellent prognosis, they are associated with a 1% disease-related mortality rate, a 2.5% distant metastasis rate and a 5% lymph node recurrence rate [20]. In a Chinese study investigating incidental thyroid carcinoma (mostly micro PTC's), 28.75% were multifocal, 18.5% had thyroid capsular invasion, with 6.2% associated with vascular invasion [20]. Similarly, in the current study, multifocality was found in 8 (15.4%) cases of microcarcinoma, extrathyroidal extension in 6 (11.5%), extracapsular invasion in 1 (1.9%), lymph vascular invasion in 1 (1.9%) and a positive surgical margin in 3 (5.8%) cases.

Due to the increasing prevalence of incidental thyroid cancer, the optimal surgical procedure for benign thyroid disease remains debatable. Some authors support total thyroidectomy for benign thyroid disease as the most appropriate procedure, considering the risks associated with cancer multifocality and second surgery [2,21,22]. In the current study, total thyroidectomy was the surgical choice for 46 (73%) cases, and hemithyroidectomy and completion hemithyroidectomy were performed in 14 (22.2%) and 3 (4.8%) cases, respectively. Of the 14 patients who had a hemithyroidectomy, 8 had completion thyroidectomy.

Knowing the risk of malignancy is critical for decision-making and for patient counselling regarding the most appropriate management. The possibility of having a malignancy despite a benign FNA result should be discussed with the patient when a non-surgical intervention is chosen. The patient should be aware of the need for regular follow-up. A higher rate of false-negative FNA results was reported in this study, stressing the importance of an appropriate sampling technique when performing the FNA and improved ultrasonography methods for detecting thyroid carcinomas [25]. Different characteristics of thyroid malignancy on ultrasound have been reported in the literature, such as ill-defined margin, presence of calcification, irregular shape, invasion to adjacent organs, hypoechogenicity and heterogeneity. In this study, we reported some ultrasonographic feature of the 11 cases that were found to have macrocarcinoma. Two of 11 patients were found to have microcalcification, 6 had hypoechoic nodules and 2 had heterogenous nodules. Other clinical factors should be taken into consideration when assessing the risk of malignancy, including but not limited to age, gender, nodule size and surrounding lymphadenopathy [1,24].

The main limitation of this study is its retrospective design. Also, the fact that it was conducted in a single centre limited the sample size. We encourage more multicentric studies with a larger sample size to evaluate more data to be able to approach patients appropriately. In the current study, only patients who had surgery were included, which may have resulted in selection bias as it is likely that the patients who were selected for surgery were deemed clinically suspicious by their treating physicians compared to non-surgical candidates.

Conclusions

A higher risk of thyroid malignancy in a patient with a benign FNA was reported in the current study compared to the literature. The overall false-negative rate of benign FNA was 16.4%; most of the identified cancer cases had papillary thyroid microcarcinoma accounted for 82.5%. The risk of malignancy should be considered and discussed with the patient, even with a benign FNA. The patient's presentation, as well as their individual risk factors, should not be ignored.

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

MAlessa: concepts, design, definition of intellectual content, manuscript review, guarantor. AD: concepts, design, definition of intellectual content, literature search, manuscript editing, manuscript review. LA: concepts, design, definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review. AAlkhaldi and MMA: concepts, design, definition of intellectual content, literature search, data acquisition, manuscript preparation, manuscript editing, manuscript review. MAlsadi: literature search, data acquisition, manuscript preparation, manuscript editing, manuscript review. AAlsalem: concepts, design, definition of intellectual content, manuscript editing, manuscript review.

Ethical consideration

Because it is a chart review, informed consent was not needed. However, the patient's privacy and confidentiality would be insured. The data would be saved on password-protected computers.

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