EDITORIAL
96 Watch and wait policy in advanced neuroendocrine tumors: What does it mean?
Fazio N

100 Translating new data to the daily practice in second line treatment of renal cell carcinoma: The role of tumor growth rate
Grande E, Martinez-Sáez O, Gajate-Borau P, Alonso-Gordoa T

FRONTIER
106 Leptin signaling and cancer chemoresistance: Perspectives
Candelaria PV, Rampoldi A, Harbuzariu A, Gonzalez-Perez RR

REVIEW
120 Targeted therapies in breast cancer: New challenges to fight against resistance
Masoud V, Pagès G

MINIREVIEWS
135 How best to manage gastrointestinal stromal tumor
Lanke G, Lee JH

145 Immunotherapies in sarcoma: Updates and future perspectives
Ghosn M, El Rassy E, Kourie HR

ORIGINAL ARTICLE
Retrospective Study
151 Bethesda System for Reporting Thyroid Cytopathology: A three-year study at a tertiary care referral center in Saudi Arabia

Clinical Trials Study
158 Study of recombinant human interleukin-12 for treatment of complications after radiotherapy for tumor patients

Observational Study
168 Gastric and duodenal polyps in familial adenomatous polyposis patients: Conventional endoscopy vs virtual chromoendoscopy (Fujinon intelligent color enhancement) in dysplasia evaluation
Editorial Board Member of World Journal of Clinical Oncology, Hua-Feng Wei, MD, PhD, Research Associate, Cancer Center Lab, General Hospital of Chinese PLA, China and Second Military Medical University, International Joint Cancer Institute, Beijing 100853, China

World Journal of Clinical Oncology (World J Clin Oncol, WJCO, online ISSN 2218-4333, DOI: 10.5306) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCO covers a variety of clinical medical topics, including etiology, epidemiology, evidence-based medicine, informatics, diagnostic imaging, endoscopy, tumor recurrence and metastasis, tumor stem cells, radiotherapy, chemotherapy, interventional radiology, palliative therapy, clinical chemotherapy, biological therapy, minimally invasive therapy, physiotherapy, psycho-oncology, comprehensive therapy, and oncology-related nursing. Priority publication will be given to articles concerning diagnosis and treatment of oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to WJCO. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

World Journal of Clinical Oncology is now indexed in PubMed, PubMed Central and Scopus.

World Journal of Clinical Oncology

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Bimonthly

EDITOR-IN-CHIEF
Godefrius J Peters, PhD, Professor, Department of Medical Oncology, Cancer Center Amsterdam, VU University Medical Center, Amsterdam 1081 HV, Netherlands

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://www.wjgnet.com/2218-4333/editorialboard.htm

EDITORIAL OFFICE
Xia-Xia Song, Director

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.bpgpublishing.com/helpdesk
http://www.wjgnet.com

COPYRIGHT
© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non-commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/genericinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

Responsible Assistant Editor: Xiang Li
Responsible Electronic Editor: Ye-Jing Lw
Proofing Editor-in-Chief: Lian-Sheng Ma

Responsible Science Editor: Feng-Feng Ji
Proofing Editorial Office Director: Xia-Xia Song
Bethesda System for Reporting Thyroid Cytopathology: A three-year study at a tertiary care referral center in Saudi Arabia

Mohamed Abdulaziz Al Dawish, Asirvatham Alwin Robert, Aljuboury Muna, Alkharashi Eyad, Abdullah Al Ghamdi, Khalid Al Hajeri, Mohammed A Thabet, Rim Braham

AIM
To stratify the malignancy risks in thyroid nodules in a tertiary care referral center using the Bethesda system.

METHODS
From January, 2012 to December, 2014, a retrospective analysis was performed among 1188 patients (15-90 years) who had 1433 thyroid nodules and fine-needle aspiration at Prince Sultan Military Medical City, Saudi Arabia. All thyroid cyto-pathological slides and ultrasound reports were reviewed and classified according to the Bethesda System for Reporting Thyroid Cytopathology. Age, gender, cytological features and histological types of the thyroid cancer were collected from patients' medical charts and cytology reports.

RESULTS
There were 124 total cases of malignancy on resection, giving an overall surgical yield malignancy of 33.6%.
Majority of the thyroid cancer nodules ($n = 57, 46\%$) in Bethesda VI category followed by Bethesda IV ($n = 25, 20.2\%$). Almost 40\% of the cancer nodules in 31-45 age group in both sex. Papillary thyroid carcinoma (PTC) was the most common form of thyroid cancer among the study population ($111, 89.6\%$) followed by 8.9\% of follicular thyroid carcinoma (FTC), 0.8\% of medullary carcinoma and 0.8\% of anaplastic carcinoma. Among the Bethesda IV category 68\% thyroid nodules were PTC and 32\% FTC.

CONCLUSION
The malignancy values reported in our research were constant and comparable with the results of other published data with respect to the risk of malignancy. Patients with follicular neoplasm/suspicious for follicular neoplasm and suspicious of malignancy categories, total thyroidectomy is indicted because of the substantial risk of malignancy.

Key words: Bethesda; Total thyroidectomy; Thyroid nodules; Risk of malignancy; Fine needle aspiration

Core tip: The purpose of this study was to stratify the malignancy risks in thyroid nodules in a tertiary care referral center using the Bethesda system. The study found that there were 124 total cases of malignancy on resection, giving an overall surgical yield malignancy of 33.6\%. Majority of the thyroid cancer nodules in Bethesda VI category followed by Bethesda IV. Almost 40\% of the cancer nodules in 31-45 age group in both sex. Papillary Thyroid Carcinoma was the most common form of thyroid cancer among the study population followed by follicular thyroid carcinoma, medullary carcinoma and anaplastic carcinoma.

INTRODUCTION
According to epidemiological and clinical studies thyroid nodules are commonly encountered in clinical exams, palpable in 5\% of the population on thyroid examination and detectable in nearly 60\% of those subjected to thyroid ultrasound. While the majority of the nodules are benign (non-cancerous), they are normally the first indicators of thyroid cancer; therefore, further investigations are required to identify the cancerous nodule\(^1\).\(^2\).

The last decades have revealed a constant and remarkable rise in the occurrence of thyroid cancer across the world, including Saudi Arabia\(^3\)-\(^5\). The Saudi Cancer Registry (SCR) report has registered 890 thyroid cancer cases, in nearly 8.1\% of all the newly diagnosed cases in 2012. However, studies revealed variations in the incidence of thyroid cancer globally. Thyroid cancer is the 5\(^{th}\) most common cancer among females in the United States, whereas in Saudi Arabia it is the 2\(^{nd}\) commonest identified cancer in females, and 8\(^{th}\) among males\(^6\). However, compared with the developed countries, research regarding the malignancy risks in thyroid nodules is still insufficient due to lack of appropriate studies being conducted in these specified areas.

One of the most widely used diagnostic tools is fine-needle aspiration (FNA) cytology with ultrasound imaging to determine the necessity for the surgical excision of a thyroid nodule. Today, molecular genetic biomarker analyses are employed to increase the diagnostic accuracy of the FNA biopsies, and can at times drastically change clinical decision procedures as they become more commonly available and better assessed. FNA cytology (FNAC) continues to remain the initial investigation mode for malignancy in patients with thyroid nodules and the selection of patients for thyroid surgery\(^7\). This minimally invasive and useful method is highly effective in identifying a large percentage of thyroid nodules as benign and eliminating unnecessary surgery for patients with benign disease\(^8\). However, because a standardized reporting system is still unavailable, pathologists have been employing varying terminologies and diagnostic criteria, thus causing misunderstanding among the referring clinicians while interpreting cytopathology reports, resulting in non-definitive clinical management\(^9\)-\(^11\). In 2007, the National Cancer Institute (NCI) established guidelines employing a standardized nomenclature to interpret thyroid FNAS called the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) which is now accepted as the proposed diagnostic categories for thyroid cancer\(^12\). This study attempts to stratify the malignancy risks in thyroid nodules in a tertiary care referral center in Saudi Arabia utilizing the Bethesda system.

MATERIALS AND METHODS

Study design and setting
From January, 2012 to December, 2014 (36 mo), a retrospective analysis was performed among 1188 patients (15-90 years old) who had 1433 thyroid nodules and FNA at Prince Sultan Military Medical City (PSMMC), a 1200 bedded tertiary care center, Riyadh, Saudi Arabia. The PSMMC caters to the patients referred from different regions of Saudi Arabia and considered a worthy representative of Saudi Arabia in general. The study protocol was approved by the Research and Ethics Committee of PSMMC, Riyadh, Saudi Arabia.

Data collection
All thyroid cytopathological slides and ultra sound
reports were reviewed and classified according to the BSRTC system. Age, gender, cytological features and histological types of the study population were collected from patients’ medical chart and cyto-pathology reports.

Bethesda system
Currently, the Bethesda system of reporting thyroid cytology (TBSRTC) is used for reporting FNAC specimens of thyroid. According to Cibas[13], this system was innovated in 2007 and consists of six categories: (1) Unsatisfactory (UNS) or nondiagnostic (ND); (2) Benign and nonneoplastic; (3) Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS); (4) Follicular neoplasm or suspicious for follicular neoplasm (FNS/SFN); (5) Suspicious for, but not diagnostic of, malignancy; and (6) Malignant (Table 1).

All FNAs were performed by one of five interventional radiologists under ultrasound (US) guidance, performing 3-5 passes by using 25 gauge needles. On-site FNAs stained with the Diff-Quik stain and adequacy assessment was performed for all samples. All slides interpreted by among of five accredited cyto-pathologists.

Histological diagnoses
The histological diagnoses of thyroid nodules were classified into two types: Benign and nonneoplastic and malignant. For papillary thyroid carcinoma (PTC), subtype variants were documented such as the follicular variant, classical variant, conventional variant and tall cell variant. Also were follicular thyroid carcinoma (FTC) subdivided to minimally invasive follicular thyroid carcinoma (MIFTC) and Widely Invasive follicular thyroid carcinoma (WIFTC).

Statistical analysis
All statistical calculations were performed using IBM SPSS Statistics (IBM SPSS Statistics for Windows, Version 22, SPSS Inc. an IBM Company) program and Microsoft Excel 2010 (Microsoft Corporation, Seattle, WA, United States). The descriptive analysis of the epidemiological data presented as frequencies, percentages and mean ± standard deviation (SD). χ² test was performed to find out the variables associated with cancer among the surgical patients.

RESULTS
A total of 1188 patients (range 15-90 years) included in this study. The mean age of the study population was 46.3 ± 15.1 (SD), median 45 years, and mode 49 years. Of the 1188 (212 male; 976 female) patients, 245 patients had two thyroid nodules, which resulted in a total of 1433 FNA cases (nodules). Among the study population, a total of 311 patients underwent surgery and 877 patients did not undergo surgery. Of the 311 patients who underwent surgery, 58 patients had two thyroid nodules, which resulted in a total of 369 cases (245 benign and 124 malignant) (Figure 1). Among patients who underwent surgery, no statistically significant differences were observed on the presence of cancer among both gender (P = 0.463), and different age groups (P = 0.928).

As shown in Table 2, the distribution of all cases in the six Bethesda diagnostic categories were as follows: 46 cases (3.2%) of category I, 1080 cases (75.3%) of category II, 131 cases (9.1%) of category III, 71 cases (5%) of category IV, 32 cases (2.2%) of category V and 73 cases (5.1%) of category VI.

The distributions of follow-up diagnoses for each initial Bethesda diagnostic classification are shown in Table 3. There were 124 total cases of malignancy on resection, giving an overall surgical yield of malignancy of 33.6%. Eight of (2.2%) 369 thyroid nodules were diagnosed as ND, 181 (49.1%) diagnosed as benign, 42 (11.4%) diagnosed as AUS/FLUS, 53 (14.4%) as FNS/SFN. Category V (SM) diagnoses (26 cases) reminded benign in 8 cases, but histologically confirmed as carcinoma in 18 case (69.2%). Finally, category VI diagnoses (59 cases) reminded benign in 2 cases, but histologically confirmed as carcinoma in 57 cases (96.7%).

Table 4 shows the comparison rates of malignancy on surgical resection for FNA diagnostic categories and malignancy risk of the present findings and previously published data. Table 5 shows the age and sex distribution of thyroid cancer: Majority of the thyroid cancer nodules (n = 57, 46%) in Bethesda VI category followed by Bethesda IV (n = 25, 20.2%) and Bethesda V (n = 18, 14.5%). Among the Bethesda IV category 17 (68%) were PTC and 8 (32%) were follicular carcinoma. Almost 40% of the cancer nodules in 31-45 age groups in both sex.

Type and variants of thyroid cancer among histopathological diagnosis are shown in Table 6. Papillary carcinoma was the most common form of thyroid cancer among the study population (111, 89.6%). Among PTC (n = 111), four histologic variants exist, with classic variant PTC accounting for 51.4% of PTC followed by follicular-

---

Table 1 The Bethesda system

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Cytological diagnosis</th>
<th>Risk of malignancy, %</th>
<th>Usual management</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Nondiagnostic or unsatisfactory</td>
<td>1-4</td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>II</td>
<td>Benign</td>
<td>0-3</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>III</td>
<td>AUS/FLUS</td>
<td>5-15</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>IV</td>
<td>FNS/SFN</td>
<td>15-30</td>
<td>Surgical lobectomy</td>
</tr>
<tr>
<td>V</td>
<td>Suspicious for malignancy</td>
<td>60-75</td>
<td>Near-total thyroidectomy or surgical</td>
</tr>
<tr>
<td>VI</td>
<td>Malignant</td>
<td>97-99</td>
<td>Near-total thyroidectomy</td>
</tr>
</tbody>
</table>

FNA: Fine-needle aspiration; AUS/FLUS: Atypia of undetermined significance or follicular lesion of undetermined significance; FNS/SFN: Follicular neoplasm or suspicious for follicular neoplasm.

---
variant PTC (30.6%). Furthermore, 8.9% of malignancies were FTC (including 0.8% of the highest risk widely invasive phenotype), 0.8% of medullary thyroid carcinoma (MTC) and 0.8% of anaplastic thyroid carcinoma (ATC).

Among the Bethesda Ⅳ category 17 (68%) thyroid nodules were PTC and 8 (32%) were FTC.

**DISCUSSION**

Over the last few decades thyroid cancer has been on the rise considerably, globally, while mortality has steadily dropped, including in Saudi Arabia[14]. This reduction in the mortality resulting from thyroid cancer reflects the variations in the exposure to risk factors and alters the diagnosis and treatment of the disease, while the rise in the incidence is probably due to the improvement in the identification of this neoplasm[14]. However, in comparison with the developed countries, research on the incidence, prevalence and type of thyroid cancer in Saudi Arabia is still inadequate due to the lack of suitable studies being done on this specific aspect.

Therefore, the objective of the current study is to stratify the risk of malignancy in the thyroid nodules based on the Bethesda system, which enhances the interpretation of the FNAC reports and enables a more accurate study and diagnosis of such thyroid nodules[13,15]. In this study, the total number of patients is 1188, of which 943 (79.4%) patients with one nodule, 245 (20.6%) patients with two nodules, 311 (26.2%) underwent surgery, 311 (26.2%) patients with one nodule, 877 (73.8%) no surgery, 253 (81.3%) patients with one nodule, 311 (26.2%) underwent surgery, 58 (18.7%) patients with two nodules, 245 (66.4%) Benign, 124 (33.6%) malignant.

**Table 2** Age and sex distribution of thyroid lesion (based on fine-needle aspiration cytology according to Bethesda system)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Total number of patients</th>
<th>Gender F/M</th>
<th>Bethesda Ⅰ</th>
<th>Bethesda Ⅱ</th>
<th>Bethesda Ⅲ</th>
<th>Bethesda Ⅳ</th>
<th>Bethesda Ⅴ</th>
<th>Bethesda Ⅵ</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-30</td>
<td>176 (14.8)</td>
<td>159/17</td>
<td>9 (4.5)</td>
<td>149 (74.9)</td>
<td>17 (8.5)</td>
<td>12 (6)</td>
<td>4 (2)</td>
<td>8 (4)</td>
<td>199</td>
</tr>
<tr>
<td>31-45</td>
<td>420 (35.4)</td>
<td>362/58</td>
<td>12 (2.4)</td>
<td>375 (74.7)</td>
<td>41 (8.2)</td>
<td>28 (5.6)</td>
<td>14 (2.8)</td>
<td>32 (6.4)</td>
<td>502</td>
</tr>
<tr>
<td>46-60</td>
<td>374 (31.5)</td>
<td>301/73</td>
<td>15 (3.3)</td>
<td>347 (75.1)</td>
<td>40 (8.8)</td>
<td>22 (4.8)</td>
<td>9 (2)</td>
<td>23 (5)</td>
<td>456</td>
</tr>
<tr>
<td>61-75</td>
<td>175 (14.7)</td>
<td>126/49</td>
<td>10 (4.5)</td>
<td>162 (72.3)</td>
<td>33 (14.7)</td>
<td>7 (3.1)</td>
<td>4 (1.8)</td>
<td>8 (3.6)</td>
<td>224</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>43 (3.6)</td>
<td>28/15</td>
<td>0</td>
<td>47 (90.4)</td>
<td>0</td>
<td>2 (3.8)</td>
<td>1 (1.9)</td>
<td>2 (3.8)</td>
<td>52</td>
</tr>
<tr>
<td>Total</td>
<td>1188</td>
<td>976/212</td>
<td>46 (3.2)</td>
<td>1080 (73.5)</td>
<td>131 (9.1)</td>
<td>71 (5)</td>
<td>32 (2.2)</td>
<td>73 (5.1)</td>
<td>1433</td>
</tr>
</tbody>
</table>

FNA: Fine-needle aspiration; F: Female; M: Male.

**Table 3** Cyto-Histopathological correlation of thyroid lesion

<table>
<thead>
<tr>
<th>Cytopathology</th>
<th>Histopathological diagnosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign</td>
<td>Malignant, n (%)</td>
</tr>
<tr>
<td>Bethesda Ⅰ</td>
<td>6</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Bethesda Ⅱ</td>
<td>165</td>
<td>16 (8.9)</td>
</tr>
<tr>
<td>Bethesda Ⅲ</td>
<td>36</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>Bethesda Ⅳ</td>
<td>28</td>
<td>25 (47.2)</td>
</tr>
<tr>
<td>Bethesda Ⅴ</td>
<td>8</td>
<td>18 (93.3)</td>
</tr>
<tr>
<td>Bethesda Ⅵ</td>
<td>2</td>
<td>57 (96.7)</td>
</tr>
<tr>
<td>Total</td>
<td>245</td>
<td>124 (33.6)</td>
</tr>
</tbody>
</table>

Figure 1 Flowchart of thyroid nodules description among 1188 patients and the risk of malignancy among 311 surgically excised nodules during January, 2012 to December, 2014. FNA: Fine needle aspiration.
The malignant rate was 33.6% which exactly matches the percentage (33.8%) of 25445 thyroid FNAs used in the meta-analysis done by Bongiovanni et al[17], as well as Jo et al[18] who reported 30.9%. However, this high malignancy rate is not unusual if it is understood that the FNAC is consistently being performed today for most patients with thyroid nodules. This has resulted in a drop in the number of unwarranted surgeries and thereby to an increase in the percentage for reported malignancies[1]. It is noteworthy that the number of FNA

Table 4  Comparison rates of malignancy (%) on surgical resection for fine-needle aspiration diagnostic categories and malignancy risk of recent studies

<table>
<thead>
<tr>
<th>Published year</th>
<th>Comparison of diagnostic categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (ND)</td>
</tr>
<tr>
<td>Present study</td>
<td>3.2</td>
</tr>
<tr>
<td>Park et al[22]</td>
<td>2014</td>
</tr>
<tr>
<td>Mondal et al[10]</td>
<td>2013</td>
</tr>
<tr>
<td>Mufti et al[29]</td>
<td>2012</td>
</tr>
<tr>
<td>Wu et al[30]</td>
<td>2012</td>
</tr>
<tr>
<td>Bongiovanni et al[31]</td>
<td>2012</td>
</tr>
<tr>
<td>Recent studies</td>
<td></td>
</tr>
</tbody>
</table>

ND: Nondiagnostic; AUS/FLUS: Atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN: Follicular neoplasm/suspicious for follicular neoplasm; SM: Suspicious for malignancy.

Table 5  Age and sex distribution of thyroid cancer

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Total number of nodules</th>
<th>Gender</th>
<th>All FNAs (n = 124) n, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F/M</td>
<td>Bethesda I</td>
<td>Bethesda II</td>
</tr>
<tr>
<td>15-30</td>
<td>18 (14.5)</td>
<td>3/15</td>
<td>0</td>
</tr>
<tr>
<td>31-45</td>
<td>49 (39.5)</td>
<td>39/10</td>
<td>1</td>
</tr>
<tr>
<td>46-60</td>
<td>43 (34.7)</td>
<td>35/8</td>
<td>1</td>
</tr>
<tr>
<td>61-75</td>
<td>12 (9.7)</td>
<td>8/4</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>2 (1.6)</td>
<td>2/0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>87/37</td>
<td>2 (1.6)</td>
</tr>
</tbody>
</table>

FNA: Fine-needle aspiration; F: Female; M: Male.

Table 6  Type and variants of thyroid cancer among histopathological diagnosis

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Total = 124 (n, %)</th>
<th>Bethesda I</th>
<th>Bethesda II</th>
<th>Bethesda III</th>
<th>Bethesda IV</th>
<th>Bethesda V</th>
<th>Bethesda VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTC</td>
<td>111 (89.6)</td>
<td>2</td>
<td>15</td>
<td>5</td>
<td>1</td>
<td>17 (68)</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Classic variant</td>
<td>57</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>Follicular variant</td>
<td>34</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>11</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Conventional</td>
<td>19</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Tall-cell variant</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total PTC</td>
<td>111 (89.6)</td>
<td>2</td>
<td>15</td>
<td>5</td>
<td>1</td>
<td>17 (68)</td>
<td>17 (55)</td>
</tr>
<tr>
<td>FTC</td>
<td>11 (8.9)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MIFTC</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>WIFTC</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total FTC</td>
<td>11 (8.9)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>8 (32)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>FTC</td>
<td>11 (8.9)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>8 (32)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MTC</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ATC</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

PTC: Papillary thyroid carcinoma; MTC: Medullary thyroid carcinoma; ATC: Anaplastic thyroid carcinoma; FTC: Follicular thyroid carcinoma; MIFTC: Minimally invasive follicular thyroid carcinoma; WIFTC: Widely invasive follicular thyroid carcinoma.
cases in this study steadily rose from 2012 (n = 357) to 2014 (n = 449). From various studies it was evident that the percentage of cases that were subjected to surgery differed widely among different institutions, reporting a range from 11.8% to 45.1% with an average rate of 25%[17]; the current study identified 26.2% of the study population who had surgical outcome.

Each Bethesda category showed a malignancy rate ranging from 1%-10% (“benign category”) to 94%-100% (“malignant” category). This comprehensive range highlights the ability of the Bethesda system to differentiate and determine the likelihood of malignancy. The results recorded in our research concurred closely with the results reported in the American Thyroid Association Management Guidelines and other studies: 25% vs 9%-32% (“non-diagnostic or unsatisfactory” category), 9.3% vs 1%-10% (“benign and non-neoplastic” category), 14.3% vs 6%-48% (AUS/FLUS), 69.2% vs 53%-97% (“suspicious for malignancy” category), and 96.7% vs 94%-100% (“malignant” category)[13,17]. Among Bethesda, category IV found 47.2% malignancy risk, a value higher than the meta-analysis results of 14%-34% (FNS/SFN), published recently by Bongiovanni et al[17]. However, many studies revealed the greatest variation in the risk of malignancy class IV, some of which are higher (malignancy rate 50%-67%) than the present values[21-23].

The current study reported PTC (89.6%) as the commonest type of thyroid cancer in the population under study. Studies also reported that overall PTC as the commonest kind of thyroid cancer represents 80% of all the thyroid malignancies and more than 90% of the differentiated thyroid cancers[13,24,28]. A spurt in the occurrence of PTC over the past decades has triggered greater interest in this disease. This is one of the fastest growing kinds of cancer recording over 20000 new cases annually. Although individuals are susceptible to papillary carcinoma irrespective of age, most patients will show the disease prior to 45 years of age[28], a fact corroborated by the current findings (42% PTC between 31-45 years of age). Unfortunately, FTC is not being diagnosed as often, although there is an increasing incidence of well-differentiated thyroid carcinomas everywhere else[27,28], concurring with the results of the current study.

There are a two limitations to this study, mainly the retrospective design and performance in a single center. As the PSMMC is a tertiary center for thyroid lesions, the retrospective design and performance in a single center . More research is warranted to overcome the limitations of the study.

In conclusion, 33.6% of the cases overall among the surgically excised nodules, showed malignancy. The malignancy values reported in our research were constant and comparable with the results of other data with respect to the risk of malignancy. For the FN/SF patients and those with suspicions of malignancy, total thyroidectomy is indicated because of the substantial risk of malignancy. It is clear, that reviewing the thyroid FNAs with the Bethesda system allowed a more precise cytological diagnosis. However, the impact of Bethesda application may vary among different institutions. Clinicians are advised to be aware of the malignancy rate in the Bethesda categories in their respective institutions to improve the investigation and decision regarding patients with thyroid nodules.

COMMENTS
Background
The National Cancer Institute, United States, established guidelines employing a standardized nomenclature to interpret thyroid fine-needle aspirations (FNAs) called the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) which is now accepted as the proposed diagnostic categories for thyroid cancer.

Research frontiers
Compared with the developed countries, research regarding the malignancy risks in thyroid nodules is still inadequate due to lack of appropriate studies being conducted in these specified areas in Saudi Arabia. Hence, this present study attempts to stratify the malignancy risks in thyroid nodules in a tertiary care referral center in Saudi Arabia utilizing the Bethesda system.

Innovations and breakthroughs
The study found that there were 124 total cases of malignancy on resection, giving an overall surgical yield malignancy of 33.6%. Majority of the thyroid cancer nodules in Bethesda VI category followed by Bethesda IV. Almost 40% of the cancer nodules in 31-45 age group in both sex. Papillary thyroid carcinoma was the most common form of thyroid cancer among the study population followed by follicular thyroid carcinoma, medullary carcinoma and anaplastic carcinoma.

Applications
Reviewing the thyroid FNAs with the Bethesda system allowed a more precise cytological diagnosis. However, the impact of Bethesda application may vary among different institutions. Clinicians are advised to be aware of the malignancy rate in the Bethesda categories in their respective institutions to improve the investigation and decision regarding patients with thyroid nodules.

Terminology
PTC: Papillary thyroid carcinoma; FTC: Follicular thyroid carcinoma; SCR: Saudi Cancer Registry; FNA: Fine-needle aspiration; FNAC: Fine-needle aspiration cytology; NCI: National Cancer Institute, United States; BSRTC: Bethesda System for Reporting Thyroid Cytopathology; PSMMC: Prince Sultan Military Medical City; TBSRTC: The Bethesda system of reporting thyroid cytology; UNS: Unsatisfactory; ND: Nondiagnostic; AUS/FLUS: Atypia of undetermined significance or follicular lesion of undetermined significance; US: Ultrasound; MIFTC: Minimally invasive follicular thyroid carcinoma; WIFTC: Widely Invasive follicular thyroid carcinoma; ATC: Anaplastic thyroid carcinoma.

Peer-review
The study shows a very exhaustive analysis of the throughput of thyroid cytology over a three-year period. The manuscript contains a detailed exposition of the results, including comprehensive tables and a comparison to other recent studies. In my opinion, this manuscript fulfills all the requirements to be published.

REFERENCES
Al Dawish MA et al. Thyroid nodules and risk of malignancy

Year 1 at an academic institution. Thyroid 2009; 19: 1215-1223 [PMID: 19888859 DOI: 10.1089/thy.2009.0155]


Wu IH, Rose C, Elsheikh TM. The Bethesda system for reporting thyroid cytopathology: An experience of 1,382 cases in a community practice setting with the implication for risk of neoplasm and risk of malignancy. Diagn Cytopathol 2012; 40: 399-403 [PMID: 21681976 DOI: 10.1002/dc.21754]


