FINE-NEEDLE ASPIRATION OF THYROID NODULE: CORRELATING MALIGNANT HISTOLOGY OUTCOMES WITH CYTOLOGY RESULTS IN HOSPITAL SULTANAH NUR ZAHIRAH (2011 – 2015).

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IV. LIST OF ABBREVIATIONS AND NOMENCLATURES

FNAC	Fine Needle Aspiration Cytology
ATA	American Thyroid Association
USG	Ultrasonography
FNAC	Fine Needle Aspiration Cytology
AUS	Atypia of Undetermined Significant
FLUS	Follicular Lesion of Undetermined Significant
TSH	Thyroid Stimulating Hormone
STN	Solitary Thyroid Nodule
MNG	Multinodular Goitre
ROC	Receiver Operation Characteristics
AUC	Area Under Curve
AOR	Adjusted Odd Ratios
HSNZ	Hospital Sultanah Nur Zahirah
RLN	Recurrent Laryngeal Nerve
OR	Odd Ratio
CI	Confidence Interval
LR	Likelihood Ratio

TFT	Thyroid Function Test
SD	Standard Deviation
AACE	American Association of Clinical Endocrinologist
AME	Associazione Medici Endocrinologi
ETA	European Thyroid Association
FPR	False Positive Rate
FNR	False Negative Rate
PTC	Papillary Thyroid Carcinoma

V. ABSTRAK

Pengenalan:

Benjolan kelenjar tiroid adalah penting terutama sekali dalam kes yang dicurigai seperti kanser. FNAC adalah prosedur paling utama atau "gold standard procedure" untuk mengesahkan benjolan tiroid adalah kanser atau sebaliknya. Ia juga penting untuk menentukan bahawa rawatan pembedahan adalah tepat bagi rawatan kanser tiroid dan mengelakkan pembedahan yang tidak perlu sekiranya benjolan yang dimaksudkan adalah bukan kanser. Ultrasound boleh bertindak sebagai nilai tambah untuk mengetahui dan memberi gambaran lebih lanjut tentang nodul tiroid terutamanya apabila ianya kecil (<1 cm) dan tidak dapat dirasa melalui pemeriksaan klinikal biasa.

Objektif:

Objektif utama adalah mengkaji persetujuan antara sitopathologi dan histopatologi dalam pesakit yang menjalani pembedahan thyroidectomy dan untuk mengenal pasti risiko yang berkaitan dengan kanser tiroid.

Kaedah:

Antara Januari 2011 hingga Disember 2015, pesakit yang menjalani pembedahan tiroid dengan keputusan pra-pembedahan sitologi di Hospital Sultanah Nur Zahirah, Kuala Terengganu telah dikaji. Data demografi dikumpul dan direkodkan. Histopatologi akhir telah dianalisis dan

dibandingkan. Kajian spesifisiti dan sensitiviti FNAC tiroid dikira dan direkodkan. Risiko yang berkaitan dengan kanser termasuk umur, jantina, bangsa, status tiroid, nodul simtomatik dan penemuan ultrasound pra-pembedahan telah dikaji semula.

Keputusan:

Seramai 301 pesakit (274 perempuan 27 lelaki) telah menjalani pembedahan tiroid. Diagnosis sitologi telah dibuat mengikut kategori berikut: Benign, Atypia of unsignificance (AUS), folikular, malignan dan sample tidak mencukupi untuk diagnosa. 141 kes benign, 34 kes daripada kategori folikular, 19 pesakit dari kumpulan malignan dan 62 orang pesakit dari kumpulan sampel tidak mencukupi. Persamaan antara sitopatologi dan histopatologi adalah K = 0.44 dengan 95% CI = (0.35, 0.53). Nilai kappa menunjukkan bahawa sitopatologi dan histopatologi mempunyai persetujuan sederhana dalam menentukan malignan dan tidak malignan dalam kajian ini. Hasil keseluruhan menunjukkan kepekaan 63%, spesifisiti 81%, dan nilai ramalan positif 61%, nilai ramalan negatif 82% dan ketepatan diagnostik 75%.

Kesimpulan:

Kami membuat kesimpulan bahawa FNAC adalah satu prosedur yang sangat bernilai dan sangat baik untuk penilaian pesakit dengan nodul tiroid. FNAC mempunyai sensitiviti tinggi dalam mengesan kanser tiroid dan juga mempunyai ketepatan diagnostik yang tinggi dalam penilaian nodul tiroid.

VI. ABSTRACT

Introduction:

Thyroid nodule is increasingly important especially in a case of suspicious for malignancy. FNAC is a gold standard for assessment of thyroid nodule. It also imperative as a tool to 'rule in' malignancy as proper surgical excision can be planned and to 'rule out' malignancy to prevent unnecessary surgery. US can act as adjunct to further evaluate the thyroid nodule especially when nodule is small (<1cm) and not palpable.

Objective:

The main objective is to study the agreement between cytopathology and histopathology in thyroidectomy patients and to identify the associated risks of malignancy in patients with thyroidectomy.

Methods:

Between January 2011 and December 2015, patients who underwent thyroidectomy with pre-operative FNAC in Hospital Sultanah Nur Zahirah, Kuala Terengganu were reviewed. The demographic data were collected and documented. Analysis and comparison of final histopathology were conducted and the specificity and sensitivity study of thyroid FNAC were calculated and recorded. The discussion for associated risk for thyroid malignancy including age, gender, race, thyroid status, symptomatic nodule and pre-operative ultrasound finding.

Results:

301 patients (274 female 27 male) had thyroid surgery. The pre-operative cytological diagnosis was made according to following categories: Benign, AUS, Follicular lesion, Malignant and Inadequate sampling. There are 141 cases in benign cytology category, 34 cases from follicular category, 19 patients from malignant category and 62 patients from inadequate sampling group. The agreement between cytopathology and histopathology was K = 0.44 with 95% CI = (0.35, 0.53). Kappa value shows that cytopathology and histopathology has moderate agreement in determining malignant and non-malignant in this study. The overall results showed a sensitivity of 63%, specificity of 81%, and positive predictive value of 61%, negative predictive value of 82% and diagnostic accuracy of 75%.

Conclusion:

We conclude that FNAC is a valuable and minimally invasive procedure for pre-operative assessment of patients with thyroid nodules. FNAC has high sensitivity in picking up thyroid malignancy in thyroid and has high diagnostic accuracy in the evaluation of thyroid nodules.

Introduction

Thyroid diseases are common problem in surgical practice and being managed at different level and involving multidisciplinary teams. However, the problem comes in managing thyroid nodules whereby we have to have high degree suspicious towards malignancy. In the era of technology, the treatment of thyroid problem especially in a group of well differentiated tumour give a good prognosis and overall survival. In view of this, early detection of thyroid nodule is imperative for early evaluation and treatment. The initial evaluation should always include complete history and physical examination focusing in features suggestive of malignancy. Tissue biopsy and imaging modalities should thoroughly be done to improve the pre-operative diagnosis and provide appropriate treatment options for patients with thyroid nodules.

A nodule is a mass, rounded lump which could be cyst, carcinoma or lobule of normal tissue. Thyroid nodule represents a wide range of different disease. According to American Thyroid Association (ATA) thyroid nodule is defined as a discrete lesion within the thyroid gland and radiologically distinct from surrounding thyroid parenchyma. It usually found during a routine general physical examination due to patients' concern and awareness. However non-palpable nodule has been incidentally found with radiographic studies performed for other medical evaluations which termed incidentally discovered nodules or "incidentalomas"(Cooper *et al.*, 2009).

From our study, we review the relation between demographic data, clinical symptom and sign and biochemical value with thyroid carcinoma. Hopefully, the similarities and difference between local data with other published literature regarding risk associated with thyroid malignancy would benefit us in future.

Literature review

A thyroid nodule represents abnormal growth of cells which form a lump within the thyroid gland. Iodine deficiency and Hashimoto's autoimmune thyroiditis is associated with an increased risk of thyroid nodules (Gharib *et al.*, 2010; Haugen *et al.*, 2016) twenty percent of thyroid nodules are benign and vast majority of nodules will diminish in size during their natural course. Although thyroid cancer is the most common endocrine malignancy, its only constitutes less than 1% of all human cancers. A thyroid carcinoma is met in 7–15% of patients with thyroid nodules, depending on the age, gender, family history and history of radiation exposure. In general, nodules >1 cm present greater potential to be clinically significant cancers (Hegedüs, 2004) .

Thyroid nodules constitute by far the most common abnormality of the endocrine system. Epidemiological studies have indicated that approximately 5% of women and 1% of men resident in iodine-sufficient areas have palpable thyroid nodules. The 'incidentalomas' prevalence is up to 70% when neck/carotid artery ultrasonography (USG), computed tomography (CT) or magnetic resonance imaging (MRI) is performed for other indications (Guth *et al.*, 2009; Tan and Gharib, 1997) . A study was done in Framingham, of 5234 subjects aged more than 60 years in clinically apparent thyroid nodules were present in 6.4% of women and 1.5% of men (Vander *et al.*, 1968). The prevalence of single thyroid nodules was 3% and multinodular goitre was 1%. From early autopsy surveys, up to 50% of patients had thyroid nodules and using ultrasonography between 20 and 76% of women have at least one thyroid nodule(Vanderpump and Tunbridge, 2005). According to the SEER (November 2011) report, thyroid cancer contributes for only 0.4% of all cancer deaths, with an incidence of 11 cases and about0.5-0.6 deaths per 100,000 population in the United States each year. In Malaysia, according to National Cancer Registry from year 2007-2011, thyroid malignancy was ranked 17th among male and 9th among female population. The incidence was highest among elderly

in both sexes. In Kelantan, it was reported that the incidence was 1.5 in male and 4.9 in female per 100,000 population. (National Cancer Registry,2011)

From ATA guidelines, ultrasound neck should be done in all patient with suspected thyroid nodules, nodular goitre or any abnormal radiological imaging which accidentally detected. Many information can be obtained from ultrasound, namely size, location, thyroid parenchyma (homogenous/heterogenous), margins, presence or type of calcifications, shape if taller than wide and vascularity.(Haugen *et al.*, 2016) Its features is associated with risk of malignancy like microcalcifications, irregular or microlobulated margins, hypoechogenicity, taller-than-wide shape, and increased intranodular vascularity plus nodule size is a guide for FNAC decision making(Papini et al., 2002; Rago et al., 1998). Thyroid ultrasound has been widely used to stratify risk of cancer. Wharry et al has done a study to see a reliability of ultrasound in excluding thyroid cancer in large thyroid nodule (>4cm). It was a retrospective study where 361 patients with pre-operative ultrasound who underwent thyroidectomy. It was concluded that the suspicious ultrasound features did not discriminate malignant from benign nodules and the absence of ultrasound features did not exclude malignancy.(Wharry *et al.*, 2014) Several authors have suggested stratification risk for malignancy based on the constellation of sonographic appearance (Horvath *et al.*, 2009; Tae *et al.*, 2007). In the absence of sonographically suspicious cervical lymph nodes, features associated with the highest risk for thyroid cancer can be used to triage smaller nodules for fine-needle biopsy, whereas nodules with sonographic appearance suggesting lower risk might be considered for fine-needle biopsy at a larger size as determined by maximal diameter

A large series of study which involved 5469 sample from January 1980 till December 2004 was done in Italy. This retrospective study was conducted by Sangalli et. al is to compare between final histological diagnosis with pre-operative cytology for thyroid nodules. It was concluded that FNAC has proved to be the most accurate method for diagnosis of nodular

thyroid lesion. The sensitivity and specificity was 93.4% and 74.9% respectively with positive predictive value for malignancy is 98.8% (Sangalli *et al.*, 2006). JC young et al has discovered the significance of ultrasound in benign cytology thyroid nodule. It was a multicenter retrospective study with approximately 700 patients who underwent initial ultrasound and cytology examination with final histology result. It was concluded that there is 4.7 % of samples with benign cytology and suspicious ultrasound finding is truly malignant as compared to 0.8% of patient with benign cytology and benign ultrasound findings. The suggestion was to repeat cytology with suspicious ultrasound finding to reduce false negative cases.

To date, the difference between prevalence of STN with thyroid cancer and MNG with thyroid cancer still unclear. A study done by Brito et al, a meta-analysis study to compare prevalence of thyroid cancer in STN versus MNG. A total of 20723 from 14 studies including observational, cross sectional and longitudinal studies were analyzed. It was concluded MNGs found to have lower risk for thyroid cancer (Brito *et al.*, 2013).

A study in Pakistan showed there is slightly increase prevalence in solitary nodule as compare to multinodular goiter (24.32% vs 14.27%) (Anwar *et al.*, 2011). However overall prevalence of malignancy in nodular goiter is 16.18% which are comparable to those of Baloch MN and colleagues which found 14% malignant case in overall nodular goiter. However, a study in Iran did not show any statistically significant difference between the frequency of malignant and benign nodules in single and multiple thyroid. (Shojaiefard *et al.*, 2015)

Rationale for study

To analyze correlation between FNAC and final histopathology and associated risk that contributed towards thyroid malignancy.

Study protocol

Fine-Needle Aspiration of Thyroid nodule: Correlating Malignant Histology outcomes with Cytology Results in Hospital Sultanah Nur Zahirah (2011 – 2015).

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Introduction

American Thyroid Association (ATA) has defined Thyroid nodules have as a "discrete lesions within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma."(Cooper *et al.*, 2009) It usually discovered on general physical examination or with imaging studies performed for medical evaluations, such as ultrasound (US), computed tomography (CT) scans or magnetic resonance imaging (MRI) studies. There is a term called "thyroid incidentalomas" where thyroid nodule was found on these imaging studies but impalpable on examinations. However, some palpable lesions may not correspond to distinct radiologic abnormalities. Such abnormalities do not meet the strict definition for thyroid nodules.Palpable thyroid lesions that have negative radiological entities would not be defined as thyroid nodules.(Marqusee *et al.*, 2000) Generally, nodules larger than 1 cm should be evaluated because for malignant potential. Occasionally, there may be nodules smaller than 1 cm that require evaluation, because of suspicious ultrasound findings, a history of head and neck irradiation, or a positive family history of thyroid cancer.

Thyroid disorder is a spectrum of disease which include hormone imbalance, thyroid mass and carcinoma. Thyroid disorders are amongst the most common endocrine diseases in Malaysia(Zainudin *et al.*, 2012). Epidemiologic studies have shown the prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in men living in iodine-sufficient parts of the world. (Haugen *et al.*, 2016). Thyroid nodules are clinically important for several reasons. the most important is to exclude malignancy. Others it can cause dysfunction like hormone imbalance and to extend compressive symptom which may obstruct respiratory system. The reported prevalence of malignancy in thyroid nodules evaluated by biopsy ranges from 4.0% to 6.5% and is largely independent of the nodule size.(Hegedüs, 2004)

A complete history and physical examination particularly on the thyroid gland and adjacent cervical lymph nodes should be performed. Pertinent historical factors predicting malignancy include a history of head and neck irradiation, total body irradiation for bone marrow transplantation(Curtis *et al.*, 1997), family history of thyroid carcinoma in a first-degree relative, and rapid growth and hoarseness. Pertinent physical findings suggesting possible malignancy include vocal cord paralysis, ipsilateral cervical lymphadenopathy and fixation of the nodule to surrounding tissues

Fine-needle aspiration cytology (FNAC) is a well-established diagnostic adjunct in the assessment of a thyroid nodule. The overall sensitivity of FNAC is up to 98 %(Cooper *et al.*, 2009) with a specificity up to 99 %.There is a false negative rate for malignancy of 0.7–5 %. This technique has resulted in improved assessment of preoperative likelihood of malignancy, reduces the number of diagnostic thyroidectomies for thyroid nodules, increases the proportion of cancers in resected specimens, and guides operative management if a definitive diagnosis is made. It is cost effective, has a low morbidity, and is well tolerated by patients. Based on the recent Bethesda System for Reporting Thyroid Cytopathology(Baloch *et al.*, 2008) diagnostic FNAC results are divided into 5 categories, benign (70%), malignant (5%), suspicious for malignancy (50% to 75%), follicular or Hurthle cell neoplasm (20% to 30%), and follicular lesions of undetermined significance or atypia. (5% to 10%) (Baloch *et al.*, 2008) The last 3 cytologic diagnoses, which represent 25% of the total cases, have been previously classified as indeterminate lesions.

Nowadays, ultrasound (US) is an important tool widely used in the detection and evaluation of thyroid nodules. It has advantages compare to other modalities such as widely available, non-invasive and inexpensive procedure that provides information with regard to nodule dimensions, structure, and thyroid parenchymal changes. As small as 2 to 3 mm lesions may detect by the use of brightness-mode US and high-frequency transducers, which raises the

question of which thyroid nodules are clinically relevant for further evaluation. Several US features have been found to be indicative of malignant potential. Microcalcifications, irregular or microlobulated margins, hypoechogenicity, taller-than-wide shape, and increased intranodular vascularity were found to be independent risk factors for malignancy.(Papini *et al.*, 2002; Rago *et al.*, 1998) Even though these suspicious features are characterized by high specificity, their positive predictive value is lowered by their relatively low sensitivity. It is important to know that none of these US features alone is sufficient to differentiate benign from malignant tumors, but a combination of at least 2 of them better succeeds in pointing out a subset of lesions at high risk for malignancy.(Frasoldati and Valcavi, 2004; Papini, 2003)

Surgery, with lobectomy or total thyroidectomy is the treatment of choice for malignant and suspicious lesions.(Cooper *et al.*, 2009) The same is true for follicular lesions, unless the nodule is found to be autonomous on a 123-I scan in the setting of low-normal TSH. Thyroid nodules larger than 3 cm with mixed cystic/solid components should be strongly considered for surgery for diagnostic purposes, as FNA yields a high rate of false-negative results in these lesions.(Meko and Norton, 1995)

A retrospective study done to review the final histology with preoperative cytopathology of patient diagnosed with thyroid nodule who underwent thyroidectomy with in the year 2011 through 2015. The aims were to review the agreement between cytopathology report and final histopathology in patients underwent thyroidectomy, which to detect the accuracy of FNAC in the diagnosis of thyroid abnormalities within local geographical area. Another purpose is to determine the predictable risk factors on patient with suspicious cytology with malignant histopathology detected post-surgery. We also want to review the prevalence of thyroid nodule among our studied population and rate of malignancy detected. We hope from this study the result will benefit us more in managing patient especially those with thyroid

nodule and possible malignant nodule which may prevent the patient from unnecessary surgery and face further more complication.

Literature review

Sinna et al (Sinna and Ezzat, 2012) have concluded FNA cytology is a sensitive, specific, and accurate initial diagnostic test for the evaluation of patients with thyroid swellings. The study included 296 cases presented with thyroid nodules who underwent diagnostic thyroid FNAC. Female to male ratio was 5.2:1, and the median age was 44 years. Ninety-eight cases (33.1%) were diagnosed as benign, 40 cases (13.5%) as follicular lesion of undetermined significance, 49 cases (16.5%) as follicular neoplasm, 30 cases (10.1%) as suspicious for malignancy, 58 cases (19.5%) as malignant, and 21 cases (7.1%) as unsatisfactory. Nodular hyperplasia represented the majority of benign cases (89.8%), while papillary carcinoma was the most frequent malignant lesion (72.4%). Cytologic diagnoses were compared with their corresponding final histologic ones. FNAC achieved a sensitivity of 92.8, a specificity of 94.2%, a positive predictive value of 94.9%, a negative predictive value of 91.8%, a false positive rate of 7.2%, a false negative rate of 5.8%, and a total accuracy of 93.6%.(Sinna and Ezzat, 2012)

In another study by Wesley et al (Giles *et al.*, 2015), they concentrate on false negative rate of large thyroid nodule despite benign initial cytology. A total of 323 nodules with benign preoperative cytology were identified. Eighty-three nodules were <3 cm, 94 nodules were 3–3.9 cm, and 146 nodules were >4 cm in size. It was found that the false negative rate was 11.7% for all nodule > 3cm and 4.8% for <3cm. It was concluded that, patients with large thyroid nodules demonstrate a modest, yet significant, false-negative rate despite initial benign

aspiration cytology. Therefore, thyroid nodules >3 cm may be considered for removal even when referred with benign preoperative cytology.(Giles *et al.*, 2015)

Andrea et al (Baynes *et al.*, 2014) from Annals of Surgical oncology meanwhile do a study to see correlation of suspicious cytology result with final histopathology. A total of 2,692 patients underwent FNAC for investigation of a thyroid nodule. The five cytological categories for the total study and their relative proportions. 94 (3.5 %) patients had cytology suspicious for malignancy (C4), with a mean age of 55 (range 20–98) years. Of the 94 patients with suspicious for malignancy cytology, 53 (56.4 %) were malignant on definitive histopathology, the majority being papillary thyroid cancer 44 (83.0 %). The malignancy rates for benign (C2) and indeterminate follicular (C3) nodules were 2.9 and 14.9 %. It was concluded that suspicious cytology has a high risk for malignancy (Baynes *et al.*, 2014)

Bagga et al(Bagga and Mahajan, 2010) meanwhile had a study in accuracy of FNAC. A total of 252 FNACs of thyroid lesions were done during the study period. The results of the FNA cytological diagnosis showed that four (1.6%) were inadequate for cytological assessment, 228 (90.5%) patients had benign lesions, 17 (6.7%) had lesions that were suspicious for malignancy, and three (1.2%) had malignant neoplasms. 32 of the patient underwent surgery and 24 of the patient had benign disease and the rest turn to be malignant. A sub-analysis was done and correlation of the FNAC findings with the histopathological diagnosis, showed that FNAC diagnostic accuracy rate was 96.2%, with a sensitivity of 66%, and specificity of 100%.(Bagga and Mahajan, 2010) The results are comparable with the current published data and demonstrate that FNA cytology is a sensitive, specific and accurate initial diagnostic test for the preoperative evaluation of patients with thyroid swellings.

Melina et al(Flanagan *et al.*, 2006) concentrate on repeat thyroid nodule fine-needle aspiration in patients with initial benign cytology results. 402 patients underwent thyroid

surgery during a recent 22-month period. Of these patients, 267 had at least 1 satisfactory FNA and 70 had 2 or more (up to 5). After an initial benign FNA, 1 repeat FNA correctly identified an unsuspected malignancy in 2 of 70 patients and was indeterminate in 17; of these, 7 of 17 were identified as malignant in the final pathologic diagnosis. the use of 1 repeat FNAC increased the sensitivity for malignancy from 81.7% to 90.4% and decreased the false-negative rate from 17.1% to 11.4%. With more than 1 repeat FNAC, there was no improvement in performance characteristics. These data make a strong argument for 1 repeat FNAC following an initial benign FNA diagnosis.

Objective

1. To study the correlation between malignant histopathology and preoperative cytopathology

2. To study the predictive value of malignancy in patients with suspicious thyroid nodule who underwent thyroidectomy.

Specific objectives

1. To determine the prevalence of thyroid malignancy in patients with thyroid nodule.
2. To determine the correlation between cytopathology and histopathology of thyroid nodule.
3. To determine sensitivity, specificity, diagnostic accuracy, positive predictive value and negative predictive value of FNAC in thyroid nodule evaluation.
4. To identify the risk factors of malignancy in suspicious nodule.

Research design

This is retrospective study involving patients that underwent thyroidectomy in Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu between January 2011 to December 2015.

Sample size estimation

Sample size calculation for objective 1- 3:

The data will be calculated using Sample Size Calculation v1.7.1 by Dr Wan Nor Arifin, available at medic.usm.my.

Using 95% CI test, proportion (p) = 20.00%, precision (Δ) = 10.00%, significance level (α) = 0.05,

Sample size (n) = 62, with 10% drop out, corrected sample size = 69

Sample size calculation for objective 2:

Using Kappa agreement test, lowest limit of kappa (k0) = 0.6, expected kappa (k1) = 0.9, proportion of outcome (p) = 0.2, significance level (α) = 0.05, power (1-β) = 0.8, non-centrality parameter 7.849,

Sample size (n) = 86, with 10% drop out, corrected sample size = 96

Sample size calculation for objective 3:

By using sensitivity and specificity test, expected sensitivity = 85.00%, expected specificity 50%, prevalence of disease (p) = 20.00%, acceptable precision (W) = 10.00%, significance level (α) = 0.05, with drop out 10%

Sample size for sensitivity = 245

Sample size for specificity = 121

Final sample size = 245

Corrected sample size = 273

Sample size calculation for objective 4:

By using multiple logistic regression test, calculated Using G*Power v3.1.9.2,

1/ Gender[14]

Input:	Tail(s)	= Two
	Pr(Y=1|X=1) H1	= .43
	Pr(Y=1|X=1) H0	= 0.22
	α err prob	= 0.05
	Power (1-β err prob)	= .8
	R^2 other X	= 0
	X distribution	= Normal
	X parm μ	= 0
	X parm σ	= 1
Output:	Critical z	= 1.9599640
	Total sample size	= 60
	Actual power	= 0.8039350

2/ Indeterminate nodule (Suspicious Nodule vs Suspicious for papillary cancer)[21]

Input:	Tail(s)	= Two
	Pr(Y=1|X=1) H1	= 0.76
	Pr(Y=1|X=1) H0	= 0.15
	α err prob	= 0.05
	Power (1-β err prob)	= .8
	R^2 other X	= 0
	X distribution	= Normal
	X parm μ	= 0
	X parm σ	= 1
Output:	Critical z	= 1.9599640
	Total sample size	= 23
	Actual power	= 0.8124232

Sampling frame

There are inclusion and exclusion criteria in this study

Inclusion criteria:

- All patients who have undergone thyroidectomy with preoperative cytology within duration of study period.

Exclusion criteria

- Patients underwent completion thyroidectomy with prior history of surgery for thyroid cancer (only the first surgery will be recruited).
- Patient that underwent cervical nodal biopsy prior to surgery.
- Incomplete documentation of patient's case note.

Study area

The study includes all patients who have undergone thyroidectomy from 1st January 2011 to 31st December 2015. The data collection will be started after ethical approval.

Research tool

After ethical approval, a list of patients who underwent thyroidectomy in between January 2011 to December 2015 will be obtained from the record in Hospital Information System (HIS). Patients who fulfill the inclusion and exclusion criteria will be included in the study. The data of patients will be obtained by retrospective study of patients' medical records. The data will be entered in a data collection form (Appendix 1). Cytopathology of each sample

will be classified according to Bethesda criteria and comparison, associated risk factors in indeterminate group will be determined.

Data collection

Data collection will be recorded in a data collection form (Appendix 1). The following information was recorded: patients' demographic, thyroid function test prior to surgery, cytopathological diagnosis, date and type of surgery performed and histopathological report of resected specimen

Proposed data analysis

Data entry and analysis will be done by using SPSS version 22. Descriptive analysis will be done using mean and standard deviation for numerical variables and frequency and proportion for categorical variables.

Each specific objective will be analyzed using different methods:

Sample Size Calculation v1.7.1 by Dr Wan Nor Arifin, available at medic.usm.my.

1. 95% Confidence Interval test
2. Kappa agreement test
3. Sensitivity and specificity studies

Ethical Issues

1. Declaration of Conflict of Interest

There is no conflict of interest in this study.

2. Handling Privacy and Confidentiality Issues

Throughout this study, all personal information and data will not be disclosed unless required by law. Subject's confidentiality will be protected; no name or identifiable information will be collected. Data will be protected through password setting to access the database and securely locked. The data is only accessible by researchers involve in this study.

The data will be used and remain directly available up to completion of the study. Thereafter, the data will be compressed with encryption and archived in a flash drive after proper documentation. This is to be destroyed by formatting the flash drive after a 5-years maintenance period determined by the date of its formal closure. We define the formal 15 closure as the submission of a closure report to the National Medical Research Registry of Malaysia. Subject's data and information will be kept confidential and will be known by research team only. Only aggregated (grouped) results will be presented and submitted to local or international peer-reviewed medical journals and relevant government ministries

3. Publication and Presentation

The data and results from this study will be presented either in poster format or published in any upcoming conference without revealing any subjects' private information.

4. **Community Benefits**

Hopefully the information and the result from this study can be beneficial for the researcher to evaluate regarding management of thyroid nodules and the risks factors that contribute to malignancy among patient in Terengganu and will enable us to formulate steps that can enhance the quality of service given by health facilities in the future.

Flow chart

List of patients underwent thyroidectomy from January year 2011 to December 2015 is obtained from HIS.

↓

Recruitment of patients who fulfilling the inclusion and exclusion criteria

↓

Review of medical records of patients that recruited in the study

↓

Data from medical records entered in the data collection form

↓

Data collection and statistical analysis

↓

Report and manuscript write up

Gantt Chart of Research Activities:

PROJECT ACTIVITIES	2016						2017								
Month	J	A	S	O	N	D	J	F	M	A	M	J	J	A	N
	Year 3						Year 4								
Proposal presentation	→														
Ethical community approval		→	→	→											
Data collection					→	→	→	→	→						
Discussion with supervisor	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Data analyses & writing							→	→	→	→	→				
Draft submission to supervisor											→	→	→		
Final paper submission													→	→	→

Milestone of Research Activities:

1. June 2016 : Proposal presentation
2. October 2016 : Ethic community approval
3. March 2017 : Complete Data collection
4. May 2017 : Complete analses and writing
5. July 2017: draft submission to supervisor
6. November 2017: Final paper submission.

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Fine-Needle Aspiration of the Thyroid nodule: Correlating Cytology Results with Histological outcomes in Hospital Sultanah Nur Zahirah

Data Collection Form

Sample no : ____ HSNZ no:_____

Demographic:

Age: _____ Sex: M/ F Ethnic: _____

Pre-operative information:
Thyroid Function Test before surgery:

TSH _____ T4_____ T3_____

Status of patient before surgery:
- Euthyroid
- Hypothyroidism
- hyperthyroidism

Goiter:
- Diffuse
- Single nodule
- Multinodular

Pressure symptoms:
- Discomfort in throat
- Hoarseness of voice
- Difficulty breathing/ stridor
- Dysphagia
- Others: _____

FNAC before surgery:
- Not done
- Inadequate/ unsatisfactory
- Benign
- Atypia
- Follicular
- Suspicious for malignant
- Malignant _____
- Others _____

Us finding

- Benign malignant

Operative information:

Date of surgery: _____ Duration of surgery: _____ mins

Indication for surgery:

- Compression
- Risk of malignancy
- Hyperthyroidism
- Cosmesis
- Substernal goiter
- Others: _____

Surgical procedure:

- Total thyroidectomy
- Hemithyroidectomy

Weight of resected specimen: _____g

Surgeon:

- Endocrine surgeon
- Trainee surgeon

Histopathological diagnosis after surgery:

- Diffuse hyperplasia
- Benign MNG
- Single colloid nodule
- Follicular adenoma
- Hurthle cell adenoma
- Hashimoto's thyroiditis
- Carcinoma
- Others: _____

If carcinoma:

- Papillary
- Follicular
- Hurthle cell
- Anaplastic
- Medullary
- Micropapillary
- Lymphoma
- Others: _____

Complication:

- Temporary hypocalcaemia
- Permanent hypoparathyroidism
- Recurrent laryngeal nerve palsy
- Re-operation for haemorrhage
- Wound infection
- Haematoma
- Death
- Others: _____

Ethical approval letter

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
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Tarikh : 28 Oktober 2016

DR YUSRI RAHIMI BIN JUSOH @ MOHD YUSOFF
HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU

Tuan/Puan,

NMRR-16-1733-32202 (IIR)
Fine-Needle Aspiration of Thyroid nodule: Correlating Malignant Histology outcomes with Cytology Results in Hospital Sultanah Nur Zahirah (2011 - 2015).

Lokasi Kajian:

HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) tiada halangan, dari segi etika, ke atas pelaksanaan kajian tersebut. JEPP mengambil maklum bahawa kajian tersebut hanya melibatkan pengumpulan data melalui :

i. **Rekod Perubatan**

3. Segala rekod dan data subjek adalah **SULIT** dan hanya digunakan untuk tujuan kajian ini dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi.

4. Kebenaran daripada Pegawai Kesihatan Daerah/Pengarah Hospital dan Ketua-Ketua Jabatan atau pegawai yang bertanggungjawab disetiap lokasi kajian di mana kajian akan dijalankan mesti diperolehi sebelum kajian dijalankan. Dato'/Dr/ Tuan/ Puan perlu akur dan mematuhi keputusan tersebut. Sila rujuk kepada garis panduan Institut Kesihatan Negara mengenai penyelidikan di Institusi dan fasiliti Kementerian Kesihatan Malaysia (Pindaan 01/2015) serta lampiran *Appendix 5* untuk templet surat memohon kebenaran tersebut.

5. Adalah dimaklumkan bahawa kelulusan ini adalah sah sehingga **27 Oktober 2017**. Dato'/Dr./ Tuan/ Puan perlu menghantar perkara-perkara berikut kepada JEPP selepas mengikut kesesuaian. Borang-borang berkaitan boleh dimuat turun daripada laman web MREC (http://www.nih.gov.my/mrec).