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Comparative Study between Total Thyroidectomy and Hemithyroidectomy in Treatment of Solitary Thyroid Nodules Diagnosed as Follicular Lesions by Fine-Needle Aspiration Cytology

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ABSTRACT

Background: Thyroid nodular (TN) lesions are a common clinical problem in the world. These are more common in women and in areas of iodine deficiency. Exposure to ionizing radiation in childhood and adolescence increases the risk of solitary thyroid nodule and thyroid carcinoma.

Objective: Determination of the optimal surgical approach for individuals undergoing thyroidectomy for solitary thyroid nodule identified as indeterminate follicular lesion on preoperative fine needle aspiration cytology (FNAC) diagnosis and to estimate the long term outcome of patients treated by lobectomy for solitary follicular thyroid nodule.

Patients and methods: From June 2017 to June 2019, 50 patients having a solitary thyroid nodule with a cytological diagnosis of "indeterminate follicular lesion" were selected prospectively.

Results: There were 26 women and 24 men with a mean age of 56 years (range: 28-83). Hemithyroidectomy (HT) was performed in 25 patients (50%) and a total thyroidectomy (TT) in 25 (50%). Postoperative morbidity was 3.50% in patients who underwent HT and 9.75% in those who underwent TT. At the histological analysis 3 (12%) patients of hemithyroidectomy group had a malignant lesion.

Conclusions: Considering the high rate in which HT represents the adequate treatment, and the low rate of re-operation morbidity, HT seems to be the preferable initial surgical approach for indeterminate follicular lesions. Long-term ultrasonographic follow-up seems advisable.

Keywords: Fine-needle biopsy, Follicular lesion, Hemithyroidectomy, Total thyroidectomy.

INTRODUCTION

Follicular adenoma and follicular carcinoma of the thyroid gland are tumors of follicular cell differentiation that consist of a microfollicular architecture with follicles lined by cuboidal epithelial cells**.** The ratio of follicular adenoma to follicular carcinoma in surgical specimen is approximately 5 to 1. Follicular carcinoma has microscopic features that are similar to a follicular adenoma. Most patients with a follicular adenoma are clinically and biochemically euthyroid. Approximately 1% of follicular adenomas are "toxic adenomas", which are a cause of symptomatic hyperthyroidism. Fine needle aspiration cytology (FNAC) is the most important test for diagnosing follicular thyroid lesion however FNAC cannot distinguish follicular adenoma from follicular carcinoma on the bases of cytological analysis as it cannot detect capsular and vascular invasion [(1)].

Follicular carcinoma has microscopic features that are similar to a follicular adenoma. However, a follicular carcinoma tends to be more cellular with a thick irregular capsule and often with areas of necrosis and more frequent mitoses. A follicular carcinoma cannot be distinguished from a follicular adenoma based on cytological features alone. It is distinguished from a follicular adenoma on the basis of capsular invasion, vascular invasion, extrathyroidal tumor extension, lymph node metastases or systemic metastases. Capsular invasion is defined as tumor extension through the entire capsule. A follicular neoplasm with tumor invasion into but not through the entire capsule is considered a follicular adenoma [(1)]. Vascular invasion is defined as tumor penetration into a large caliber vessel within or outside the capsule. Tumor invasion of a large vessel with an identifiable wall and an endothelial lining is definitive morphologic evidence of vascular invasion. Vascular invasion is the most reliable sign of malignancy [(2)]**.**

Follicular carcinoma is divided into minimally invasive and invasive variants based on morphologic criteria. Minimally invasive follicular carcinoma is an encapsulated tumor with microscopic penetration of the tumor capsule without vascular invasion [(3)]. Follicular carcinoma accounts for ~10% of all cases of thyroid malignancy in iodine sufficient areas and 25%–40% of thyroid malignancies in areas of iodine deficiency. It occurs more often in women and older patients with a female-to-male ratio of 3:1 and a mean age of 60 years at the time of diagnosis. Most follicular cancers are nonfunctional, but there are rare cases of functioning follicular cancers. Ten to 15% of patients with follicular carcinoma present with metastatic disease, most commonly involving the lung followed by bone. The brain, liver, and skin are less common sites of systemic metastases [(1, 4)].

AIM OF THE WORK

To determine the optimal surgical approach for individuals undergoing thyroidectomy for solitary thyroid nodule identified as indeterminate follicular lesion on preoperative FNAC diagnosis and to estimate

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the long-term outcome of patients treated by lobectomy for solitary follicular thyroid nodule.

PATIENTS AND METHOD

This is a prospective study which included 50 patients with solitary follicular thyroid nodule diagnosed by FNAC as indeterminate follicular nodule was conducted in Al-Azhar University Hospitals. The indeterminate solitary follicular nodule was diagnosed on the basis of clinical symptoms and signs, serum level of thyroid hormones and thyroid stimulating hormones, neck ultrasound and FNAC.

The patients were divided into two groups on randomized basis by closed envelope technique:

The first group (group A): This group included 25 patients with indeterminate solitary follicular nodule who underwent total thyroidectomy.

The second group (group B): This group included 25 patients with indeterminate solitary follicular nodule who underwent Hemi-thyroidectomy.

The clinical symptoms, signs and investigations of indeterminate follicular nodule were recorded.

Inclusion criteria:

- Patient with solitary thyroid nodule.
- Patient with age below 50years (males or females) or more than 20y.
- NAC shows indeterminate follicular lesion.
- Patient with good general condition.

Exclusion criteria:

- Patients less than 20 and more than 50 years old.
- Chronic debilitating disease (liver cell failure, chronic renal failure).
- Patient with multinodular goiter.
- Patient with pathology other than indeterminate follicular lesion.
- Any patient with preoperative affection of vocal cord mobility.
- Any patient with preoperative diagnosis of malignancy.
- Presence of enlarged lymph nodes in the neck observed ultra-sonographically or distant metastases.
- Bilateral or diffuse disease.
- History of radiotherapy and presence of Hashimoto's thyroiditis.
- All surgeries were done by a consultant expert in neck surgery.

FNA interpretation

Fine needle aspiration cytology (FNAC)

Although FNA is a very sensitive test false-negative results are sometimes obtained. Therefore, a reassuring FNA should not override worrisome clinical or radiographic findings.

Molecular diagnostic testing to detect individual mutations or pattern recognition approaches using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate to assist in management decisions [(5)].

The BRAF V600E mutation occurs in about 45% of patients with papillary carcinoma and is the most common mutation. Although, controversial data suggest that BRAF V600E mutations may predict for increased recurrence of papillary carcinoma [(5)].

The crucial test in determining the management of thyroid nodules is FNAC, which should be the first diagnostic test performed. The FNAC will assist in deciding whether the patient needs surgical intervention or may be followed without surgery. It has a high degree of accuracy exceeding 95 %, sensitivity and specificity [(6)]. Effective use of FNA is operator-dependent and requires an experienced multidisciplinary group including radiologists, cytopathologists, and surgeons [(7)]. FNAC is best performed with image guidance via ultrasound which increases the accuracy, sensitivity, and specificity. Obtaining insufficient specimen for diagnosis is minimized by having immediate cytopathologic interpretation of the results [(7)]. It is however, important to understand the pitfalls of needle biopsy and avoid carte blanche decisions based on the results of the needle biopsy alone [(6)]. FNA should be performed on nodules larger than 1 cm, as any nodule harboring a carcinoma smaller than 1 cm is clinically insignificant with the exception being those with clinical symptoms and lymphadenopathy or in patients with a history of ionizing radiation exposure [(7)].

Cytological analysis is performed according to the Bethesda System for Reporting Thyroid Cytopathology. The findings are graded into six categories:

I: Nondiagnostic/unsatisfactory,
II: benign,
III: Atypia of undetermined significance/follicular lesion of undetermined significance,
IV: Follicular neoplasm/suspicious for follicular neoplasm,
V: suspicious for malignancy,
VI: malignant.

If the FNA biopsy is graded non-diagnostic/unsatisfactory, biopsy should be repeated. Numerous molecular tests can be applied to distinguish malignant from benign lesions, such as BRAF (V600E), PIK3CA and TERT promoter, AKT1 and TP53, although there is no explicit recommendation in the current guidelines. Accordingly, adjustments are to be expected in the future. For more non-diagnostic biopsies in a row, the decision for close surveillance without intervention or for surgery should be made in dependence of the sonographic pattern [(8)].

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.

- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)
- P-value < 0.05 was considered significant.
- P-value < 0.001 was considered as highly significant.
- P-value > 0.05 was considered insignificant.

Ethical approval and written informed consent:

An approval of the study was obtained from Al-Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

RESULTS

HT was performed in 25 patients (50%) and a TT in 25 (50%). In the HT group there were 9 women and 16 men a mean age of 52 years (range 28 to 76 years) and the TT group comprised 16 women and 9 men (p < 0.37) with a mean age of 63 years (range 38 to 83 years) (p < 0.002). Table (1) showed that the two groups were well matched for preoperative diagnosis, gender and nodule size. There was a significant difference regarding patients' age in the two groups (p<0.002). Preoperative diagnoses were all thyroid adenomas in both groups (p < 0.97).

Patients having HT had a significantly (p < 0.00006) less operative time than patients undergoing TT: mean operative time for hemithyroidectomy was 92 minutes (range 55 to 130 minutes) and 118 minutes (range 85 to 180) for total thyroidectomy. Mean postoperative hospital stay was respectively 2.26 days (range 2 to 3 days) in the HT group and 3.11days (range 2 to 3 days) in the TT group.

Postoperative complications in HT group included 2 (8 %) temporary laryngeal nerve palsies (complete recovery after 3 months). Neither permanent recurrent laryngeal nerve palsy nor permanent hypoparathyroidism occurred after either procedure. The laryngeal nerve was identified in all cases. In the TT group, mean postoperative complications included 2 (8 %) transient hypocalcemia and 2 (8%) temporary laryngeal nerve palsies (p < 0.31). Patients having HT experienced significantly (p < 0.001) less pain than patients undergoing TT, as evaluated by VAS. The mean postoperative pain evaluated by VAS at 4 and 24 hours after operation was, respectively 2.53 (range 0 to 6) for TT versus 1.57 (range 0 to 6) for HT with no statistically difference was found between the two groups.

Table (1): Patients characteristics in two groups.

Characteristic p value	Hemi HT	total TT
Male/Female (p<0.37)	9/16	16/9 7/34
Mean age in years p<0.002	52 years (range 28 to 76)	63 years (range 38 to 83)
Major diameter of the dominant nodule p<0.97	34,3 mm (range 8-80)	30,6 mm (range 34-80 mm)
Mean operative time p<0.00006	92 minutes (range 55 to 130)	118 minutes (range 85 to 180)
Postoperative pain (mm) by VAS p<0.001	1.57 (range 0 to 6)	2.53 (range 0 to 6)
Mean hospital stay (p<0.07)	2.26 days (range 1 to 6 days)	3,11 days (range 1 to 7) days)
Postoperative morbidity: p<0.13	2/57	4/41
– Transient hypocalcemia (p<0.31)	0	2 (4.87 %)
– Temporary laryngeal nerve palsy (p<0.31)	2 (3.50 %)	2 (4.87 %)

Table (2): Preoperative diagnosis and histological results in the two groups

Preoperative FNAC diagnosis	HT	TT	**Histology of malignancy**	**REINTERVENTION (Completion Thyroidectomy)**
Follicular neoplasms (N=28) (14%)	12	21	4	2
MicroFollicular neoplasms (N=2)	1	1	0	0
Hürthle cell neoplasm (N=20) (5%)	12	8	3	1
Total = 50 (6%)	25	25	7	3

Concerning preoperative diagnosis, length of hospital stay and morbidity. Overall, after histological evaluation, carcinoma was found in 7 (14 %) patients of the 50 indeterminate cases. Particularly, of the 50 patients with a preoperative cytological diagnosis of follicular neoplasm, carcinoma was found in 4 (16%) patients. Among the 20 patients with a preoperative diagnosis of Hürthle cell neoplasm, definitive histology demonstrated malignant lesions in 3 (15%) patients. Of the 2 patients with a preoperative cytological diagnosis of microfollicular neoplasm, carcinoma was found in 1 (4%) patient (follicular carcinoma). Total thyroidectomy was performed as the initial surgical procedure in 4 of the 7 patients whereas thyroid lobectomy was performed in the other 3 patients who returned to the operating room for completion thyroidectomy (Table 2).

Considering the total follicular lesions populations, hemithyroidectomy was considered adequate treatment for 22 patients (88%) while the 3 patients who underwent HT (12%), a completion thyroidectomy was necessary. Furthermore, we observed that TT was an over-treatment in 84% of cases.

In one patient, central lymph nodes were removed. Only enlarged lymph nodes were removed and sent for frozen section (FS) examination. The number of lymph nodes removed was 2.

At mean 12 months follow-up (range: from 6 to 12 months) among patients who underwent lobectomy, single case developed a recurrence: one had a nodular hyperplasia and two had an adenoma.

DISCUSSION

A majority of studies have shown that up to 20% of the thyroid lesions classified as such are found to be malignant on surgical excision (low to intermediate risk of malignancy 20-30%). This percentage may be higher in Hurthle cell lesions if the nodule is equal to or larger than 3.5 cm in greatest dimension [(9)].

In order to improve therapeutic strategies of indeterminate cytological findings on FNA of thyroid nodules, these can be subdivided into groups with different malignant risks. The Papanicolau Society of Cytopathology recently proposed six diagnostic categories for the classification of thyroid FNA cytology. These categories were beneficial for triaging patients for either clinical follow-up or surgical management [(10)]. Some studies have suggested that clinical criteria such as nodule size (>4 cm), fixation and age of the patient may be associated with increased risk for malignant potential whereas others have not confirmed these observations and that was not observed in our series of patients [(11)].

The correct diagnosis can be obtained only at histology. Follicular and Hürthle cell neoplasms should undergo thyroidectomy and if so, it should be decided what extent of thyroid resection (hemithyroidectomy versus total thyroidectomy) is necessary to be performed. Numerous reports in the literature support either approach [(12)].

In our study, we included only patients having a solitary thyroid nodule with a cytological diagnosis of "indeterminate follicular thyroid lesion", whereas patients with preoperative cytological diagnosis of non diagnostic, negative for malignancy, and positive for malignancy, thyroiditis and history of irradiation were excluded.

In our study, there was a significant difference regarding patients' age in the two groups. This difference could be explained because the younger patients chose to undergo the upfront hemithyroidectomy to have less risk to necessity of thyroid hormone replacement therapy.

In fact, the treatment for solitary follicular neoplasm will differ between various surgeons and pathologists. Some patients will elect to have a less extensive initial operation with the realization that a second operation, if thyroid cancer is the final pathological diagnosis, may be necessary in about 25% of all cases. Other patients may not want to face the prospect of a second surgical procedure and elect to have a total thyroidectomy done at the time of initial surgery [(13)]. Hemithyroidectomy and frozen-section analysis appear to be a suitable solution. However, frozen-section histopathologic analysis may miss vascular or capsular invasion due to the limited number of sections examined in centers not equipped for high-volume, more complete frozen-section analysis [(13)].

Recent studies revealed the incidence of hypothyroidism after thyroid lobectomy is based upon risk factors such as preoperative TSH or having Hashimoto's. Up until recently, it was common practice for physicians to place post-hemithyroidectomy patients on thyroid suppression therapy during the immediate postoperative period. That practice began to fall out of favour as a result of two developments: the publication of data that put into question the efficacy of thyroxine therapy for preventing recurrent disease or thyroid growth and a heightened awareness of the morbidity associated with thyroxine [(14)].

Regarding the postoperative complications, the risks involved in thyroid surgery clearly depends on many factors, such as the extent of surgery, whether this is the first or second operation, the nature of the thyroid disease present, the presence of co-existing medical conditions and the skill and experience of the surgeon [(12)].

A second operation to remove the remainder of the thyroid and the extent and type of additional surgical procedures required the setting of thyroid cancer treatment depending on the initial pathology report and other associated clinical features. Patients should be aware that the risks and potential complications associated with a second operation are still low, but generally higher than for the first operation [(15)].

In our series, total thyroidectomy was not associated with clinically significant additive morbidity ($p < 0.13$) and no differences were found in terms of length of hospital stay ($p < 0.075$).

A review of the selected Toronto experience for patients undergoing total thyroidectomy vs initial hemithyroidectomy followed by completion thyroidectomy, analyzed the complication rate for the different surgical approaches. In relation to our data, the rates of recurrent laryngeal paralysis were not significantly different for the three procedures, however patients having a completion thyroidectomy had a slightly longer stay in hospital **(16).**

Some patients will also require a second operation for benign thyroid disease, perhaps due to recurrence of a large goiter or hyperthyroidism. In our series, 5.26% of patients developed a benign recurrence **(17).**

Nevertheless, the detection of small amounts of thyroid cancer in the other thyroid lobe after a second operation is unlikely to have any adverse prognostic implications **(18)**. A unilateral resection, such as lobectomy plus istmusectomy can be performed with satisfactory long-term results in low-risk patients, those with small (less than 1.5 cm) unilateral lesion and in those with no evidence of metastatic disease.

On the other hand, we should consider that the diagnosis of incidental thyroid carcinoma in patients operated on for a benign disease is recurrent. Incidental thyroid carcinoma results more frequently in euthyroid patients than in thyrotoxic patients **(19).**

CONCLUSIONS

- The management of patients with indeterminate follicular lesions, and no evidence of autonomous function, remains controversial.
- In our series, hemithyroidectomy was considered adequate treatment for a majority of the 50 FNA patients in our study population.
- In our opinion, hemithyroidectomy seems to be the preferred initial surgical approach for the management of individuals presenting with solitary nodular thyroid disease and a cytological diagnosis of indeterminate neoplasms because of its significant advantages, especially in terms of shorter operative time and less postoperative pain. Long-term ultrasonography follow-up seems advisable.
- The major challenge in the management of the solitary thyroid nodule remains the assessment as to which nodules require surgical excision and which can be followed conservatively. New diagnostic tools are needed to reduce the number of operations performed for benign pathology in patients with a needle biopsy diagnosis of indeterminate follicular lesions.

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