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The Risk of Thyroid Carcinoma in Multinodular Goiter Compared to Solitary Thyroid Nodules: A Prospective Analysis of 207 Patients

Burkan Nasr[1], Mohamed Qubati[2], Sultan Qubati[3], Abdulhakim Al-Tamimi[4], Yasser A Rabo[5], Anwar Jonid[1], Abdullfatah Domini[6] and Abdullkarim Salah[6]*

[1]*Department of Surgery, Saudi Hospital at Hajjah, Yemen*

[2]*Department of Pathology, Taiz University, Taiz, Yemen*

[3]*Department of Pathology, Thamar University, Thamar, Yemen*

[4]*Department of Surgery, Aden University, Yemen*

[5]*Department of Surgery, Thamar University, Yemen*

[6]*Department of Radiology, Saudi Hospital at Hajjah, Yemen*

Abstract

Aim: Assessment of risk of thyroid carcinoma in patients with MNG compared to those with STN.

Methods: Medical files and histopathology reports of 207 patients who underwent thyroidectomy over 5-year period were reviewed. Data including patient' age, gender, presentation, ultrasonography, FNAC, surgical procedures, final histopathologic diagnosis and types of malignant tumors were collected and analyzed.

Results: There were 135 patient's solitary thyroid nodule and 72 patients with multinodular goiter, 193 females and 14 male. Mean age was 36.68 ± 14.5 years (range 13-70). The prevalence of thyroid cancer was 26% (35/135) in STN compared to 24% (17/72) in MNG (Chi-Square = 8.593, p > 0.18). Only male gender (p = < 0.000005) and preoperative clinical, ultrasound finding and fine needle aspiration cytology resulted that impression of malignancy (p = 0.000082) were significantly associated with thyroid carcinoma.

Conclusion: Risk of thyroid carcinoma in STN and MNG is similar. The incidence of malignancy in thyroid nodules in overall is indeed high. For that clinically detected thyroid nodules should be treated with high degree of suspicion. Male patient and Rapid growth by history and hard fixed nodule by clinical examination and hypoechoic, micro calcification and cervical lymphadenopathy on USG were seen more frequently in malignant nodules. While age, number and size of nodules were not. Intraoperative assessment for hardness and fixedity of nodule and decision for total thyroidectomy at that time reducing need to second operation as completion thyroidectomy and its complication.

Keywords

Multinodular goiter, Solitary thyroid nodule, Thyroid cancer

Introduction

Thyroid nodules are common. Prevalence and incidence increases with age. Palpable Thyroid nodules are found in 5% of persons aged an average of 60 years. With the use of imaging techniques, particularly ultrasound, the chance of detection of thyroid nodules has increased many folds about 20%-60% [1].

Thyroid nodules are more common in women than in men [2]. However, the reported incidence of thyroid cancer in general population is low, being only about 1%. Thyroid cancers occur in approximately 5-15% of all thyroid nodules indepen-

***Corresponding author:** Burkan Nasr Rashed Shaif , MD, FEBS, MRCS, FRCS, FACS, Consultant General and laparoscopic surgeon. Department of Surgery Saudi Hospital at Hajjah and Al Thowra Modern General/ Teaching Hospital Sana`a,Yemen, E-mail : burkan.nasr2gmail.com; burkan.naser@yahoo.com, Tel: 00967777407211

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Table 1: Thyroid nodules according sex, age and function of the nodule.

	Solitary thyroid nodule (N = 135)			Multinodular goiter (N = 72)		
	Benign N(100)	Malignant N(35)	Malignant 26%	Benign N(55)	Malignant N(17)	Malignant 24%
Sex						
Female	95	31	89%	51	16	94%
Male	5	4	11%	4	1	6%
Age (year)						
< 20	11	2	6%	4	1	6%
21_30	38	12	34%	12	5	29%
31_40	17	8	23%	8	5	29%
41_50	21	8	23%	19	2	12%
51_60	12	4	11%	6	3	18%
> 60	1	1	3%	6	1	6%
Function						
Euthyroid	93	32	91%	39	17	100%
Hypothyroidism	4	0	0%	7	0	0%
Hyperthyroidism	3	3	9%	5	0	0%

dent of their size [3,4].

The recent data suggest that the incidence of thyroid malignancy is increasing over the years. Worldwide increase incidence of thyroid cancer partly due to increased detection by US and other imaging studies but also to true increase in incidence of papillary thyroid carcinoma (PTC) [5].

The ultrasound for thyroid gland is used in differentiating the true solitary thyroid nodule from those with multinodular gland. Also it classifies the nodule into solid, cystic, or mixed. However it admits a little help in determining the pathological types of the nodule [6].

Fine-needle aspiration cytology (FNA) is regarded as the first diagnostic step to differentiate malignant from benign nodules. FNA has served with high accuracy to diagnose papillary thyroid carcinoma which accounts for 80%-90% of all thyroid cancer [7].

Unfortunately, on the basis of cytological characteristic alone, the pathologist cannot reliably distinguish benign from malignant follicular thyroid lesions, ~20% of Fine-needle aspiration cytology (FNAC) will be given a final diagnosis of follicular malignancy [8].

Methods

Comparative, Descriptive study for 207 patients as 72 patients who diagnosis as multinodular goiter and 135 patients diagnosis as solitary thyroid nodule underwent thyroidectomy over period 5 years April 2015 - October 2020 by single team surgeon, at Saudi hospital at Hajjah Yemen. This hospital considers tertiary referral hospital serving around 1.5 million populations.

Data collected from the patients, medical file and histopathology reports, Data including patient' age, gender, presentation, ultrasonography, FNAC, surgical procedures and final histopathologic diagnosis were collected and analyzed.

Patients were classified into two groups based on the presence of a single (STN) or multiple nodules (MNG) in their thyroid gland by clinical examination and preoperative ultrasonography.

Statistical analysis was performed using Chi-square test and Statistical Package for Social Sciences (SPSS) 21 software. Were used when appropriate to identify independent risk factors of malignancy in patients with thyroid nodules. A p value less than 0.05 is considered statistically significant.

The study Approval by hospital institution ethical committee was obtained for study conduction and publication. Main Aim for study was assessment risk of thyroid carcinoma in patients with MNG compared to those with STN. Second aim demographic and prognostic differences between the two groups.

Results

Over a period of 5 years, 207 patients who underwent 224 thyroid surgery were included in this study. There were 135 patient's solitary thyroid nodule and 72 patients with multinodular goiter, 193 females and 14 male. Mean age was 36.68 ± 14.5 years (range 13-70). In Table 1 the prevalence of thyroid cancer was 26% (35/135) in STN compared to 24% (17/72) in MNG (Chi-Square = 8.593, $p < 0.640$). This correlation was found insignificant. Only male gender ($p = < 0.000005$) and preoperative clinical, ultrasound finding and fine needle aspiration cytology resulted that impression of malignancy ($p = 0.000082$) were significantly associated with thyroid carcinoma.

Thyroid cancer appear 25% (52/207) patients of Thyroid nodule age range between 15-65 years, median age 35 years and mean average 36.53. There were no age difference be-

Table 2: Thyroid nodules according u/s finding.

	Solitary thyroid nodule (N = 135)			Multinodular goiter (N = 72)		
	Benign N(100)	Malignant N(35)	Malignant 26%	Benign N(55)	Malignant N(17)	Malignant 24%
Hypoechoic	15	33	94%	15	12	71%
Lymphadenopathy	2	24	69%	0	15	88%
Calcification	10	28	80%	20	13	76%
Nodules component						
Solid	10	30	86%	30	14	82%
Cystic	10	1	3%	2	2	12%
Mixed	79	5	11%	40	4	24%
Size (cm)						
< 1	1	4	11%	1	0	0%
1-2	22	7	20%	6	5	29%
2.1-4	50	17	49%	28	11	65%
> 4	27	7	20%	20	1	6%

tween patients with benign thyroid diseases and those with thyroid cancer (mean age was 36.72 vs. 36.53 respectively, p = 0.88).

Most Malignant thyroid nodules 94% (49/52) patients were euthyroid. And toxic nodule no significant risk factor for cancer even solitary thyroid nodule or multi nodular goiter.

Hashimoto (autoimmune) thyroiditis (HT) was the primary histopathologic diagnosis in 14 patients (7%) and with hypothyroidism in 11 patients (5.31%).

9% (3/35) patients hypothyroidism with solitary thyroid nodule was developed thyroid cancer. Malignant Solitary thyroid nodule appeared 3/6 (50%) patients was hypothyroidism before operation, results of histopathology was malignant nodule as papillary thyroid cancer on background of hashimotos thyroiditis, one of them with lymph node metastasis. That's mean high risk for malignant transformation especially Papillary Thyroid cancer than lymphoma. In general the correlation between presence of thyroiditis and thyroid cancer was insignificant (p = 0.98).

Before operation for malignant thyroid nodule, History and clinical examination done for all patients, most common presentation of STN was as a swelling in the anterior aspect of the neck. The swelling was noticed by patient's relatives in most instances and in few cases, by patients themselves. Other less common symptoms were pain, hoarseness and dysphagia. The duration of symptoms ranged from one to 24 months. Rapid growth of nodule significantly last 3-6 month 20 cases vs. 12 in MNG, Family history of thyroid nodule was positive in 10 cases vs. 5 in MNG, Hard nodule in 32 cases vs. 15 in MNG.

Clinical diagnosis and Neck Ultrasound showed multi nodular goiter in 72 patients, 41 patients (61.11%) simple multi nodular goiter, multi nodular goiter with retrosternal extension 4 patients (5.5%), 7 patients' (9.7%) toxic nodular goiter, 5 patients' (6.9%) multi nodular goiter hashimotos thyroiditis, multi nodular goiter (huge) with compression symptoms and trachea deviation 10 patients (13.8%), 1(1.3%) recurrent Rt nodular goiter and 1(1.3%) multi nodular goiter with Lt Bronchial cyst and 3 patients with panders syndrome.

Clinical diagnosis and Neck Ultrasound showed solitary thyroid nodule in 135 patients,, 4 of them big nodule with compression symptoms and trachea deviation, recurrent cystic 11 patients (8.14%), and two cases (1.48%) apparent thyroid nodule as supraclavicular mass. One case (0.7%) Recurrent Rt Solitary thyroid nodule after thyroidectomy 15 years ago, and 4 (2.96%) cases as Rt side toxic adenoma.

Ultrasound examination findings were available in 135 clinically detected Solitary thyroid nodule. Clinical diagnosis of Solitary thyroid nodule confirmed on Ultrasound.

In Table 2 thyroid ultrasound show the most of thyroid nodules take size 2.1-4 cm both in solitary thyroid nodule or multi nodular goiter as the benign nodules (n = 78, 50%) and malignant nodules (n = 28, 54%). However, there was no significant correlation between tumor size and the risk of malignancy.

By ultrasound hypoechoic nodule in 45 (87%) patients with malignant nodule and 30 (19%) in benign nodule. By ultrasound nodule was solid in 44 (85%) patients with malignant nodule, cystic nodule 3 patient (6%) with malignant nodule, both solid and cystic (mixed echoic) in 9 (17%) patients with malignant nodule. While solid in 40 (26%) patients with benign nodule, cystic nodule in 12 (8%) was benign nodule, mixed solid and cystic component appeared in 119 (77%) patients with benign nodule.

In addition, Ultrasound detected microcalcification in 41 (79%) patients with malignant thyroid nodules while 30 (19%) patients with microcalcification were reported as benign. Lymph nodal enlargement was detected by Ultrasound in 39 (75%) patients with malignant thyroid nodules. Against only 2 of 155 (1.29%) benign nodules.

Table 3: FNAC Performance in thyroid nodule.

Performance	**Solitary thyroid nodule N(135)**	**Multinodular goiter** N(72)	**Thyroid nodules N(207)**
Sensitivity	61.33%	68%	63%
Specificity	71.66%	89%	79%
Accuracy	64.44%	81.94%	71%
Positive predictive value	73.01%	77.27%	74%
Negative predictive value	59.72%	84%	70%
TP	46	17	63
FN	29	8	37
TN	43	42	85
FP	17	5	22

Table 4: Post-operative Histopathology thyroid nodules.

		Solitary thyroid nodule			**Multinodular goiter**		
Post operative histopathology	**Subtypes**	**(N = 135)**	**%**		**(N = 72)**	**%**	
Benign non neoplastic	Colloid nodule	20	15%		5	7%	
	Adenomatous goiter	13	10%		1	1.3%	
	Hyperplastic nodule	12	9%		31	43%	
	Cystic nodule	5	4%		0	0%	
	Chronic thyroiditis	7	5%		7	10%	
	Toxic adenoma	3	2%		3	4%	
Benign and neoplastic	Follicular adenoma	28	21%		3	4%	
	Hurthle cell adenoma	6	4.4%		3	4%	
	Non invasive Follicular Thyroid Neoplasia with papillary like features (NIFTP)	6	4.4%		2	3%	
Malignant	Papillary thyroid cancer	26	19%	74%	13	18%	76%
	Follicular Thyroid cancer	5	4%	14%	0	0%	0
	Hurthle cell carcinoma	1	0.7%	3%	1	1.3%	6%
	Medullary Thyroid cancer	1	0.7%	3%	0	0%	0
	Lymphoma	1	0.7%	3%	1	1.3%	6%
	Anaplastic cancer	1	0.7%	3%	1	1.3%	6%
	uncertain neoplastic behavior	0	0	0	1	1.3%	6%

Sensitively and specificity and accuracy of FNAC for diagnosis of thyroid nodule show no significant differences between solitary thyroid nodule and multi nodular goiter (Table 3).

Performance of FNAC in diagnosis of thyroid neoplasm calculated by numerous tests is available:

1. TP = The number of cases correctly identified as having thyroid neoplasm.
2. FP = The number of cases incorrectly identified as having thyroid neoplasm.
3. TN = The number of cases correctly identified as not having thyroid neoplasm.
4. FN = The number of cases incorrectly identified as not having thyroid neoplasm.
5. Sensitivity measures the percentage of patient who are correctly identified as having thyroid neoplasm. Thus, sensitivity = TP/(TP + FN).
6. Specificity measures the percentage of patient who are correctly identified as not having thyroid. Thus, specificity = TN/(TN + FP).
7. Accuracy measures ability of fine-needle cytology to correctly identify the cases that having thyroid neoplasm and the cases that not having thyroid neoplasm. Thus, accuracy = (TP + TN)/(TP + FP + TN + FN).
8. Predictive value positive is the proportion of positives

that correspond to the presence of the thyroid neoplasm. Thus, predictive value positive = TP/(TP + FP).

9. Predictive value negative is the proportion of negatives that correspond to the absence of the thyroid neoplasm. Thus, predictive value negative = TN/(TN + FN) (Table 3).

Post-operative histopathology diagnosis of thyroid nodule divided into three categories benign non-neoplastic about 107 (52%) patients, benign neoplastic about 48 (24%) patients and malignant thyroid nodule about 52 (25%) patients (Table 4).

Thyroid cancer prevalence 25% (52/207) patients has thyroid nodule.

The most common tumor was papillary thyroid cancer diagnosed in 39 patients (75%) followed remotely by follicular carcinoma (FTC) in 5 patients (10%), Hurthle-cell carcinoma (HCC) in 2 patients (4%), anaplastic carcinoma in 2 patients (4%), non Hodgkin lymphoma in 2 patients (4%), medullary carcinoma (MTC) in one patient (2%) and uncertain neoplastic behavior in one patient (2%) as follicular pattern thyroid lesion that need histomorphology and immunohistochemistry to exclude malignancy and to avoid aggressive over treatment.

Papillary thyroid cancer appear more in 26 patients with STN (classical papillary thyroid cancer 10 cases, papillary micro carcinoma 3 case and 13 were reported as the follicular variant of papillary carcinoma (FVPTC)) but in 13 patients with MNG as papillary thyroid cancer (5 classical, 7 follicular variant, 1 microcarcinoma). But follicular thyroid cancer appears 5 cases in solitary thyroid nodule but no cases in MNG.

About 71 different surgical procedures for 52 patients with malignant thyroid nodules, 54 operations for 35 patients with malignant STN as 19 patients underwent completion thyroidectomy after resulted of histopathology was cancer, and 17 thyroidectomy for malignant multi nodular goiter (Table 5).

Total thyroidectomy with neck lymph node dissection in 39 patients with malignant thyroid nodule with 10 patients positive lymph node malignant metastasis. Complication after thyroidectomy for multi nodular goiter (Table 6).

8 patients (11%) vs. 12 patients (9%) of solitary thyroid nodule and no significant risk of complication between benign and malignant thyroid nodule.

Temporary hypocalcemia 2 patients (2.7%) vs. 9 patients with STN.

Permanent hypocalcemia 1 patient (1.3%) vs. 0 patients with STN.

Temporary horsnese 3 patients (4.16) vs. 3 patients with STNG Permanent horsnese 2 patients (2.7%) vs. 0 patients with STN.

Discussion

Careful history and thorough clinical examination and thyroid function tests combination with thyroid ultrasound and FNAC becoming essential in the management of thyroid nodules [9,10].

A rapid painless growth of a solid nodule is concerning and

Table 5: Surgical procedure for thyroid nodule.

	Solitary thyroid nodule			**Multinodular goiter**		
Surgical procedure	**Benign** **N = 100**	**Malignant** **N = 54**	**Total** **N = 154**	**Benign** **N = 55**	**Malignant** **N = 17**	**Total** **N = 72**
RT Hemithyroidectomy	60	1	61			
LT Hemithyroidectomy	22	0	22			
Rt Hemithyroidectomy follow by completion thyroidectomy	0	9	9			
Lt Hemithyroidectomy follow by completion thyroidectomy	0	10	10			
Completion thyroidectomy with central lymph nodes dissection	0	17	17		1	
Completion thyroidectomy without central lymph nodes dissection	0	2	2			
Total thyroidectomy with central lymph nodes dissection	0	2	2		9	
Total thyroidectomy	14	8	22	54	2	
Total thyroidectomy with Selective Rt lymph nodes dissection level 2	2	1	3		4	
Total thyroidectomy with Rt Functional Modified neck dissection	0	3	3		1	
Total thyroidectomy with Lt Functional Modified neck dissection	0	1	1			
Subtotal thyroidectomy	1	0	1	1		
Near total thyroidectomy	1	0	1			

Table 6: Common post-operative complication.

	Solitary thyroid nodule (N = 12/135)				**Multinodular goiter (N = 8/72)**			
Complications	**Total (N = 12/135)**	**%**	**Benign N = 6**	**Malignant N = 6**	**Total (N = 8/72)**	**%**	**Benign N = 5**	**Malignant N = 3**
Temporary hypocalcemia	9	7%	5	4	2		2	
Permanent hypocalcemia	0				1		1	
Temporary Horsnese	3	2%	1	2	1		1	
Permanent Horsnese with temporary hypocalcemia	0				2			2
Temporary Horsnese With Temporary Hypocalcemia					2		1	1
Recurrent				1				

also raises the suspicion for thyroid cancer [11]. Similar to this study rapidly growing of malignant thyroid nodule during 3-6 month in 32 (62%).

During our study period, 207 patients with thyroid nodule there were 193 (93%) females vs. 14(7%) males' patients with thyroid nodule. Our study showed that thyroid nodules were 14 times more common in female than male. Similar as noted in the previous study [12-14].

Numerous studies have documented that the risk of malignancy in patients with thyroid nodules is 5%-17%, whether detected by palpation or ultrasonography.

Overall thyroid cancer incidence in our study was high (25%) compared to similar studies on the subject [15-18]. This partly due to our selecting patients With suspicious and malignant thyroid lesions and also pooling more case as our hospital only referral hospital at that region that provide free service also use of diagnostic imaging and fine-needle aspiration biopsy, which has led to enhanced detection and diagnosis of subclinical nodules also early diagnosis of low-risk lesions [19,20].

Male gender was identified as a risk factor for thyroid cancer. Almost 2 out of 4 males (44%) with STN will prove to harbor malignancy and (20%) with MNG. However, age was not found to affect the risk of malignancy. Our results concordance with that of Smith, et al. and Rago, et al. [21,22] who found male gender to be independent risk factors for thyroid carcinoma also concordance with Luo, et al. [23] who reported age as a very weak independent predictor of malignancy (OR 0.97, 95%CI 0.960-0.987, p < 0.001). Thyroid cancer can occur at any age, but the risk peaks earlier for women (who are most often in their 20s or 30s when diagnosed) Mean age of females in this study was 36.21 than for men (who are usually in their 40s) Mean age of males in this study was 39.6 ± 15.6 and this may have contributed to our findings.

Some studies found the malignancy is more in solitary thyroid nodules (STN) compared to multinodular goiter [12,13,15-17,24].

In opposite to that in this study the incidence of thyroid cancer was same or not significantly different in STN compared to MNG (26 vs. 24% respectively, OR = 1.694, 95%CI 1.189-2.412, p = 0.18). Also MNG had the same risk of malignancy as STN when gender and preoperative diagnosis as hard, fixed and rapidly growth nodule also ultrasound finding such as hypoechoic, calcification and lymphadenopathy included in the analysis (OR 1.453, 95%CI 0.842-2.507, p = 0.18). Our results are in concordance with those of several similar studies [25-27].

Some studies found association between increasing nodule size and risk of malignancy [28,29]. Opposite to that in this study malignant and benign nodules were same size either STN or MNG most of nodule between 2.1_4 cm and the average size in these nodules was 2.99. Our findings are similar to those reported by Megwaluand Kamran, et al. [30,31].

Some studies suggest an association between Hashimoto thyroiditis and PTC as well as lymphoma [32,33]. This may partly relate to continuous stimulation by follicular cells by elevated TSH-levels commonly found in autoimmune thyroiditis. In this study, concordance with that although Hashimoto thyroiditis was more commonly found around papillary thyroid cancer compared to lymphoma, the difference was statistically significant level (50% vs. 0%, p = 0.004).

At our institution, FNAC is performed routinely by radiologist under US-guidance. In our study thyroid fine needle aspiration having a sensitivity, a specificity, an accuracy, a positive predictive value, and a negative predictive value of 63%, 79%, 71%, 74%, and 70%, respectively.

The sensitivity of FNA cytology in this study is relative low compared to published studies from outside country where the sensitivity, specificity and accuracy of FNA cytology are more than 94% [18], which had adversely affected the surgical decision making as well as the outcome. In This study proved that aspiration of largest nodules could lead to false negative in 37 (71%) of malignant tumors. This is in concordance with results of Mihailescu, et al. Paksoy, et al. [34,35] who reported in different studies that aspirating only the largest nodule will miss 1/3-2/3 of cancers and As such, aspiration under US-guidance which takes nodule features into consideration is strongly recommended in patients with MNG.

And we have to seriously evaluate the situation and to rethink on how to raise the scale of sensitivity in FNA cytology in the diagnosis of thyroid nodules, and to improve the level

of expertise in cytology.

Type of surgery depending on preoperative evaluation including history, clinical examination, ultrasound, FNAC result, and intraoperative assessment of the nodule. Less complications of thyroid surgery by experience surgeon.

During my study we noted that intraoperative assessment for solitary thyroid nodule was FNAC before operation was benign or follicular neoplasia should be assess for hardness and fixedity of nodule if hard and fixed nodule intraoperative best to make decisions to do total thyroidectomy instead hemithyroidectomy. Because we found hard and fixed nodule intraoperative in 40/52 (77%) patients diagnosed after operation as thyroid cancer.

That means intraoperative assessment for hardness and fixedity of nodule and total thyroidectomy at that time reducing need to second operation, completion thyroidectomy and its complication.

Conclusion

Risk of thyroid carcinoma in STN and MNG is similar. The incidence of malignancy in thyroid nodules in overall is indeed high. For that clinically detected solitary nodules should be treated with high degree of suspicion. Rapid growth by history and hard fixed nodule by clinical examination and hypoechoic, microcalcification and cervical lymphadenopathy on USG were seen more frequently in malignant nodules. FNAC more accurate and helpful for diagnosis Solitary thyroid nodule if aspiration under USG guide and reading by experience histopathologist. Male gender was identified as a risk factor for thyroid cancer while age, number and size of nodules were not. intraoperative assessment for hardness and fixedity of nodule and decision for total thyroidectomy at that time reducing need to second operation as completion thyroidectomy and its complication.

Contributions

Burkan Nasr designed the study and wrote the manuscript; BN, MQ, SQ, AD and AS collected the data; BN, YA, AT and AJ planned the data analysis; And MQ and SQ reviewed the pathological data, AD and AS reviewed the radiological data.

All the authors read, revised and approved the final manuscript.

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Ethics Declarations

Ethics approval and consent to participate

Approval from surgical department Research Committee in Saudi hospital was obtained to perform the study.

Consent for publication

No individual person's data were included in the manuscript.

Competing interests

The authors declare that they have no competing interests.

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