Differentiated thyroid carcinoma recurrence: patterns and participating factors

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Received: 9 November 2022
Revised: 23 November 2022
Accepted: 27 November 2022
Published: 9 June 2023

The Egyptian Journal of Surgery 2023, 42:10–19

Background
Surgery for recurrent differentiated thyroid carcinoma is technically difficult, is demanding, and carries a higher risk for complications than de novo cases, so understanding the precipitating factors and patterns of recurrence will help in practicing maneuvers that can help in decreasing the recurrence. In this study, we examined these factors and patterns of recurrence.
Patients and method
A total of 40 patients with recurrence after differentiated thyroid carcinoma surgery were subjected to redooperations after clinical evaluation and all needed preoperative investigations. Preoperative and operative data and postoperative surgical and pathological outcomes were collected and analyzed.
Results
Our results revealed that the size of the primary tumor had a negative or inverse significant relationship with time passed till occurrence of recurrence or relapse (P=0.044). However, postoperative radioactive iodine therapy, postoperative thyroxine replacement therapy, unifocal tumors, and total thyroidectomy in primary procedure all were associated with a wider range of recurrence time with a higher mean±SD but did not reach a statistically significant level. Central compartment lymph nodes are the most affected group (95%) followed by level IV nodes, which had a 100% correlation with central group, and all lateral groups summed 82.5%.
Conclusion
The primary tumor size has a significant inverse relationship with time till occurrence of relapse. However, other factors did not reach a statistically significant level. Central compartment lymph nodes, which are very difficult for safe dissection in recurrent cases, are the most affected group, confirming being the first echelon nodes followed by level IV nodes. Therefore, prophylactic routine meticulous central dissection in the primary cases is advised for being much easier and safer.

Keywords:
differentiated thyroid carcinoma, lymph nodes, metastasis, neck dissection, recurrence

Egyptian J Surgery 42:10–19

1110-1121

Introduction

Thyroid cancer is a universally relatively rare neoplasm, accounting for nearly 1–5% of all female cancers and less than 2% of male cancers. In spite of this relatively low incidence, it occupies the first rank among the most common endocrinal malignancies, with a consistent male to female ratio of 1 : 3 observed in nearly all ethnic groups and geographic areas, despite the considerable variation in its incidence internationally [1,2].

Differentiated thyroid cancer (DTC) is rated as slowly growing disease with a fairly good outcome where the five-year survival rate for localized tumor is 99.8%, whereas for tumors with regional metastases, it is 97%, and 57.3% for tumors with distant metastases [3,4]. DTC accounts for nearly 90–95% of total thyroid cancers, with papillary thyroid carcinoma (PTC) for more than 85%, and follicular thyroid carcinoma and Hürthle cell cancer account for 2–5% or more [5,6].

The incidence of DTC is increasing with a rising trend in different ethnicities and health systems. In the last few decades, it dramatically increased three to 15 times, and it is expected to occupy the fourth rank among the most common cancers by 2030. This increase may be owing to more detection of small, low-risk tumors or real increase in its incidence [4,7–9].

With a 10-year survival rate of more than 90%, the DTC is considered to have excellent prognosis. Unfortunately, there is a risk of recurrence within these 10 years of 5–30%. The outcome of DTC is often valued by postoperative complications, locoregional recurrence, and disease-specific survival. In most of instances, the regional recurrence happens in the cervical lymph nodes (LNs), which is a clue for persistent disease. This can be detected during follow-up visits by increased levels of serum thyroglobulin (TG) and follow-up neck ultrasound (US). Recurrence carries an increased risk of more morbidity and mortality especially in high-risk groups; here, the surgical management in the form of neck dissection is considered the cornerstone modality of treatment [10,11]. There are many documented risk factors that affect DTC recurrence, like tumor size, histological tumor features, age, and presence of regional or distant metastasis. Regional metastasis to the cervical LNs is considered a separate recurrence risk factor. The concentration of the serum TG usually is used as a marker for thyroid tissue recurrence or persistence after near-total thyroidectomy [12,13].

Objectives

Our objectives from this study were to evaluate the possible precipitating factors and the pattern of tumor and locoregional LN recurrence.

Patients and methods

Preoperative work

During the period from December 2017 to September 2022, a prospective study was performed on 40 patients who have recurrence after differentiated thyroid carcinoma surgery. The study was carried out at the Department of General Surgery in Menoufia University hospitals after approval of the hospital ethical committees and in accordance with the Code of Ethics of the World Medical Association. The included patients were those who gave a history of total or near-total thyroidectomy that revealed a diagnosis of papillary, follicular, or Hurthle cell carcinoma by surgical pathology. However, patients with medullary and anaplastic thyroid carcinoma, patients with distant metastases, patients with other head and neck tumors, those with incomplete or missing operative or pathological data of the primary procedure, patients with poor general condition that precludes major surgery, or those who were unable to provide consent were excluded from this study.

A detailed medical and surgical history with special concentration on the previous procedure was taken from all patients in addition to complete general and local clinical examination, full laboratory, and radiological investigations, including thyroid function tests, serum TG, head and neck US or computed tomography for evaluation of the tumor and the LN states, and radioactive iodine thyroid scanning. All patients were subjected to a fine-needle aspiration biopsy cytology to select the patients who have been histologically confirmed to have recurrent thyroid lesions, and sometimes tissue blocks were done from the aspirate if the diagnosis was doubtful.

An informed consent was obtained from all the patients to be enrolled in the study with full explanation of the steps of the operation and the possible complications or postoperative sequelae.

Procedure

Strict antibiotic and anticoagulation policies were followed for all patients. All surgeries were performed under general anesthesia in supine position (Fig. 1). Then, all patients were subjected to either modified radical neck dissection in most instances or to simple excision of the recurrent mass with completion of neck dissection with central neck node dissection in cases that had previous incomplete neck dissection. Great care was taken in all cases during dissection regarding the blood supply of parathyroid glands and recurrent laryngeal nerves (RLNs), as in recurrent situations with adhesions of previous

Figure 1

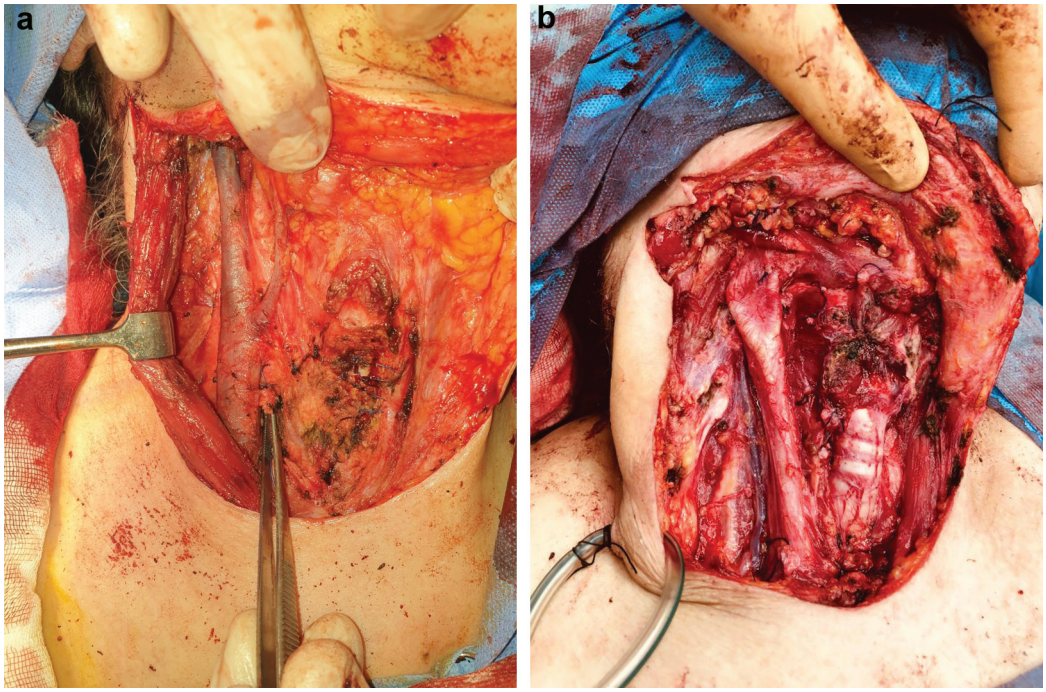
Scar of previous operation.

operations, the condition mostly needs special care and meticulous dissection. Believing that central group of LN is the first echelon for locoregional metastasis, its dissection was done for all cases, and even for those who had previous neck dissection, meticulous revision of it was done.

Central neck dissection

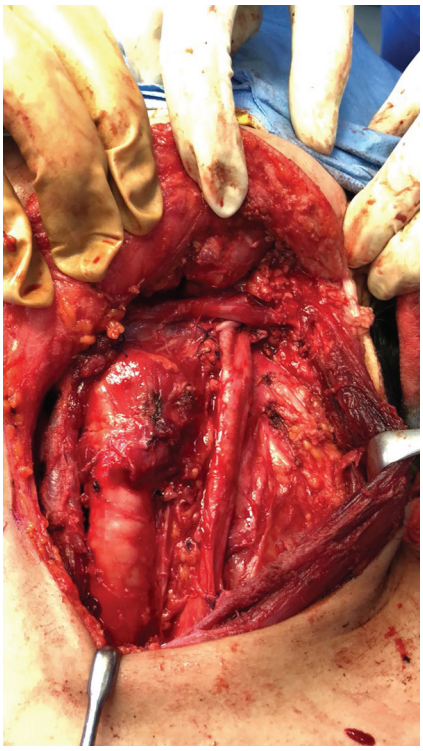
(1) After defining its boundaries, which extend from the innominate vein inferiorly to the hyoid bone superiorly, and to the carotid sheath laterally on either side, with the paravertebral fascia making its dorsal boundary, it is then divided into three distinct node sites: first the ipsilateral level VI, second the contralateral level VI, and lastly, the pretracheal LNs.
(2) The pretracheal LNs were the first nodes that we searched, and dissect it if present, as it may have been dissected with the previous thyroidectomy.
(3) After that, we cautiously identified the RLNs and then separation of the carotid sheath and the lateral side of the paratracheal LNs took place, continuing the dissection line reaching the brachiocephalic vein or to the innominate artery.
(4) Then, we dissected right and left central compartments, which differed from each other because of difference in the RLN course.
(5) The right RLN returns after looping the right subclavian artery, so it does not ascend in the tracheoesophageal groove. Herein, the nerve divides the right paratracheal LNs into anterior and posterior compartments or superficial and deep nodes. The superficial or anterior LNs are dissected cautiously from the nerve and then the posterior or deep LNs were anteriorly mobilized with its division along the right RLN. This dissection may extend inferiorly in some cases to the superior mediastinum reaching the thymus gland that may be excised also in bloc with the deep or posterior right RLN LNs. The LNs and the fibrofatty tissue superficial to the right RLN below the level of the inferior thyroid artery are then dissected from the prevertebral fascia and esophagus reaching the level of the brachiocephalic vein or the innominate artery to ensure complete dissection of the anterior compartment LNs (Fig. 2a, b).
(6) The left RLN returns after looping the aortic arch, and then it ascends in the tracheoesophageal groove with the esophagus lying just behind the nerve making only anterior or superficial compartment of LNs, with no space for deep or posterior one. Therefore, after dissection of the paratracheal LNs, from the carotid sheath, medial and lateral LNs, dissection to the left RLN and reaching the level of the brachiocephalic vein or the innominate artery without division is usually sufficient to be done in the left side (Fig. 3).

Figure 2



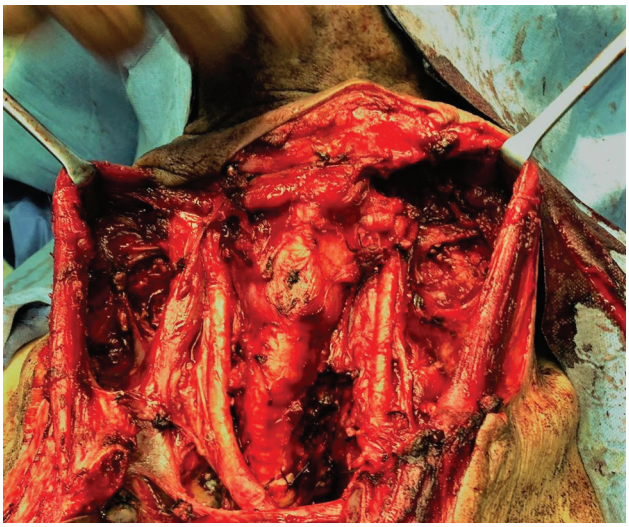
(a) Right central and lateral neck dissection. (b) Bilateral neck dissection, showing right central and lateral groups.

Figure 3



Left central and lateral neck dissection.

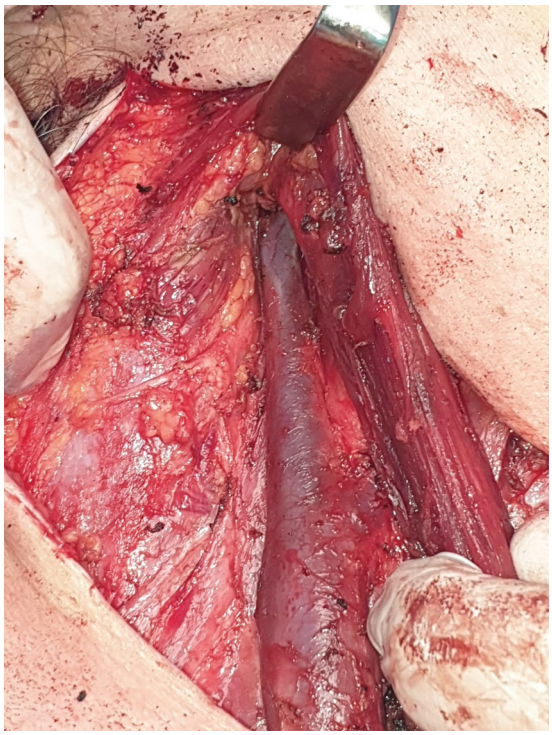
Figure 4



Bilateral central neck dissection.

(7) Great care is always taken if any parathyroid gland is removed with no clue for infiltration or its viability is questioned; it is minced to 1-mm slices and implanted in the sternomastoid or the brachioradialis muscles with marking the site by a surgical clip.
(8) Then, the central dissection (Fig. 4) is kept in a separate container for subsequent pathological examination.

Figure 5



Right lateral neck dissection.

Completion of neck dissection

Completion of the neck dissection was then done in the usual known procedure from level II till level V with preservation of both internal jugular vein or at least one in bilateral cases, spinal accessory nerve, sternocleidomastoid muscle, and great auricular nerve whenever possible (Fig. 5).

Then, perfect hemostasis was done with insertion of drains and good wound closure in layers (Fig. 6).

Postoperative course and follow-up

Routine laryngoscopy was done immediately after completion of operation before exit from operation room for all cases for checking if any nerve palsy was found.

Labeling of the specimens was done for each group separately for histopathological evaluation (Fig. 7).

All patients received medications in the form of analgesic, antibiotic, anti-edematous, and prophylactic neurotronic treatment. Prophylactic oral calcium, supplement by combined fortified formula of calcium, magnesium, florin, and vitamin D3, was given to all patients. They were given at least 1 g of oral calcium daily for nearly 1 month postoperatively. Great care was taken for early discovery of postoperative

Figure 6

Wound closure with drains inserted.

Figure 7

Labeling of LNs separately according to their site and groups. LNs, lymph node.

hypocalcemia which was diagnosed by either clinically or by routine daily, measuring its values according which appears first, and subsequent management was done if any case was found.

Patients were observed in the immediate postoperative period to detect any complications such as hemorrhage, infection, and seroma, which were managed if they occurred. The patients were discharged when the drain stopped, mostly 3–5 days postoperatively.

Follow-up laryngoscope was done for patients who experienced temporary vocal cord dysfunction.

Data collection

Patients' demographic data and any preexisting comorbidities were identified and recorded. All preoperative, operative, and postoperative data were recorded, tabulated, and statistically analyzed.

Statistical analysis

Data collected through history, basic clinical examination, laboratory investigations and outcome measures were coded, entered, and analyzed using Microsoft Excel software.

The data collected was tabulated and analyzed by SPSS (statistical package for the social sciences), version 25 (IBM Corp., Armonk, New York, USA).

The data were tested for normality using Kolmogorov–Smirnov test and Shapiro–Wilk test.

Two types of statistics were done:

Descriptive statistics

Qualitative data were represented as number and percentage, and quantitative data were represented by mean±SD (for parametric data), median, and interquartile range (for nonparametric data)

Analytic statistics

(1) χ^2 test was used to study association between two qualitative variables.
(2) Student's t test was used for comparison between two groups having quantitative variables with normal distribution (for parametric data).
(3) Analysis of variance test for independent measures is designed to compare the means of three or more independent samples (treatments) simultaneously.
(4) Spearman's correlation test a nonparametric test used to measure the strength of association between two variables, where the value $r=1$ means a perfect positive correlation and the value $r=-1$ means a perfect negative correlation.
(5) A P value of less than 0.05 was considered statistically significant and less than 0.001 for high significant result for two-tailed tests.

Data were collected and subjected to statistical analysis. The following statistical tests and parameters were used.

Results

The study was performed on 40 patients with recurrence after previous surgery for DTC. Patients comprised 18 (45%) males and 22 (55%) females, and their ages ranged from 23 to 69 years, with mean±SD of 42.95±12.34 years. Time elapsed till recurrence to occur ranged from 4 to 180 months, with mean±SD of 23.25±31.60 months, as shown in Table 1. Other clinical data and comorbidities are also reported in Table 1. The operative and postoperative course and tumor and pathological characteristics of the studied group in the primary procedure are documented in Table 2. It illustrates the types of the primary procedure and sites and side of local recurrences, pathological focality of the tumors, and condition of postoperative thyroxine replacement therapy or radioactive iodine therapy. The size of primary lesion in centimeters had an inverse relationship with the time passed till recurrence occurred and had a statistically significant negative correlation with it (P=0.044). However, the age and postoperative TG level did not affect significantly such timing (Table 3 and Fig. 8). Patients with unifocal thyroid tumors and those who received postoperative thyroxine replacement therapy had a better rate of recurrence timing than multifocal one or patients who did not receive postoperative thyroxine respectively. However, both did not reach a statistically significant level (Tables 4 and 5). There were wider range of recurrence timing with less mean ±SD between patients who received postoperative radioactive iodine therapy and who did not receive respectively but it did not reach a statistically significant level (Table 6). Regarding the association between recurrence timing and type of previous operation, a wider range and higher mean±SD time of recurrence was seen with total thyroidectomy among previously done operations, but also it did not reach a statistically significant level (Table 7). The types of current operation are documented in Table 8. All postoperative complications as mentioned in Table 9

Table 1 Preoperative patient, tumor, and pathological characteristics of the studied group

Study (N=40)		
Sex of patients	Males=18 (45%)	Females=22 (55%)
Age (years)	Range=23–69	Mean±SD=42.95 ±12.34
Clinical data of patients	Range	Mean±SD
Size of primary lesion (cm)	1–7	3.29±1.507
Postoperative thyroglobulin level.	1.10–364.00	67.65±84.77
Time elapsed to recurrence (months)	4–180	23.25±31.60
Comorbidity		n (%)
None		18 (45)
DM		10 (25)
HTN		11 (27.5)
DM+HTN		1 (2.5)
Chronic liver disease		2 (5)

DM, diabetes mellitus; HTN, hypertension.

Table 2 Operative, postoperative course, tumor and pathological characteristics of studied group in the primary procedure

Study (N=40)	
Previous primary operation	n (%)
Total thyroidectomy	25 (62.5)
Near-total thyroidectomy	11 (27.5)
Total thyroidectomy+MRND	2 (5.0)
Total thyroidectomy+tracheostomy	1 (2.5)
Total thyroidectomy+CND	1 (2.5)
Primary pathology	
Multifocal papillary carcinoma	12 (30.0)
Unifocal papillary carcinoma	28 (70.0)
Receiving postoperative radioactive iodine therapy	
Yes	32 (80.0)
No	8 (20.0)
Receiving postoperative thyroxine replacement therapy	
Yes	37 (92.5)
No	3 (7.5)
Side of local recurrence	
Ipsilateral side	30 (75)
Contralateral side	10 (25)
Site of local recurrence	
Right cervical LN	8 (20.0)
Left cervical LN	16 (40.0)
Bilateral cervical LN	7 (17.5)
Right thyroid operative bed	2 (5.0)
Left thyroid operative bed	4 (10.0)
Left operative bed mass+left cervical LN	3 (7.5)

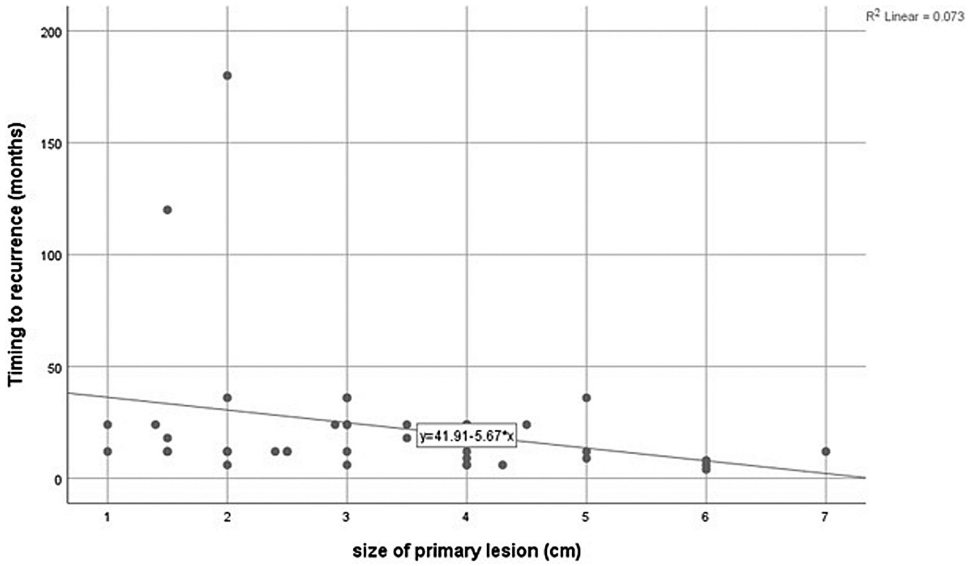
CND, central neck dissection; LN, lymph nodes; MRND, modified radical neck dissection

Table 3 Correlation between recurrence timing and age, size of primary lesion (cm), and thyroglobulin level postoperative

	Recurrence timing (months) Mean ±SD=22.68±31.69 months Range=2–180 months	
	r	P value
Age	0.239	0.137
Size of primary lesion (cm)	–0.320	0.044*
Postoperative thyroglobulin level	0.031	0.848

According to Spearman's rho's rank correlation coefficient analysis, the recurrence timing was statistically significantly negatively correlated with size of primary lesion (cm). r, Spearman's rho correlation. P value greater than 0.05, insignificant. *P value less than equal to 0.05, significant.

Figure 8



Correlation between recurrence timing and size of primary lesion (cm).

Table 4 Association between timing till recurrence and primary pathology

Primary pathology	Multifocal papillary carcinoma	Unifocal papillary carcinoma	*t*	*P* value
N	12	28		
Recurrence timing (months)			0.694	0.492
Minimum–maximum	4–180	6–120		
Mean±SD	28.58±48.85	20.96±21.26		

t, Student's *t* test. *P* value for comparing between the studied groups.

Table 5 Association between recurrence timing and postoperative thyroxine replacement therapy after primary operation

Postoperative thyroxine	Yes	No	*t*	*P* value
N	37	3		
Recurrence timing (months)			0.409	0.685
Minimum–maximum	4–180	6–36		
Mean±SD	32.84±32.84	16.00±17.32		

t, Student's *t* test. *P* value for comparing between the studied groups.

were of mild form and were all treated conservatively according to each one, with fair outcome, except for one case of reactionary hemorrhage, which necessitated operative ligation of slipped ligature, and another two cases of permanent vocal cord dysfunction due to complete cut of RLN which was totally infiltrated by the recurrent mass and was already paralyzed preoperatively. The postoperative pathological results showed that recurrence in central compartment (VI) was found in 95% of patients, whereas recurrence in the lateral neck nodes occurred in 82.5% of cases either alone or accompanied by central compartment recurrence which was present in all cases with level IV affection. Lastly, actual PTC recurrence was found in 15% of cases, as documented in Table 10.

Discussion

The incidence of DTC has increased significantly in the last decades. Authors have proposed many theories for this marvelous increase, including may factors like use of neck ultrasonography, which was associated with fivefold increase, and use of thyroid fine-needle aspiration cytology, which was associated with up to sevenfold increase. Other factors like exposure to radiation, changes in thyroid tumor pathological classifications, or even the increased obesity incidence and changing reproductive patterns in women were also accused in this issue [14,15].

The optimal management of DTC is the risk-adapted multimodal therapeutic approach; it decreases the

Table 6 Association between recurrence timing and postoperative radioactive iodine therapy

Postoperative radioactive Iodine therapy	Yes	No	*t*	*P* value
N	32	8		
Recurrence timing (months)			0.346	0.750
Minimum–maximum	4–180	2–120		
Mean±SD	21.5±30.4	27.38±38.97		

t, Student's *t* test. *P* value for comparing between the studied groups.

Table 7 Association between recurrence timing and type of the previous operation

Previous operation	Total thyroidectomy	Total thyroidectom+MRND or tracheostomy or CND	Near-total thyroidectomy	ANOVA test	*P* value
N	25	4	11		
Recurrence timing (months)				0.648	0.723
Minimum–maximum	4–180	9–18	2–36		
Mean±SD	27.3±39.1	12.75±3.77	16.91±11.43		

ANOVA, analysis of variance; CND, central neck dissection; MRND, modified radical neck dissection. *P* value for comparing between the studied group.

Table 8 Distribution of the studied cases according to current operation

Current operation	*n* (%)
Right MRND	10 (25)
Left MRND	16 (45)
Bilateral MRND	7 (17.5)
Left MRND+left operative bed excision	2 (5)
Excision+central neck dissection	2 (5)
Excision of recurrent mass+left MRND	1 (2.5)
Excision of recurrent mass+bilateral MRND	2 (5)
Total	40 (100.0)

MRND, modified radical neck dissection.

Table 9 Postoperative complications

Postoperative complications	*n* (%)
Hemorrhage	1 (2.5)
Seroma	4 (10)
Mild wound infection	5 (12.5)
Temporary hypocalcemia	4 (10)
Permanent hypocalcemia	0
Temporary vocal cord dysfunction	6 (15)
Permanent vocal cord dysfunction	2 (5)
Mild partial superficial skin flap necrosis	1 (2.5)

Table 10 Distribution of the studied cases according to postoperative pathology

Postoperative pathology	*n* (%)
Left level 2a,3	1 (2.5)
Left level 2a,3,4,6	17 (42.5)
Left level 2a,3,6	1 (2.5)
Left level 6	1 (2.5)
Left level 2	1 (2.5)
Recurrent papillary ca+bilateral level 6 LNs	4 (10)
Recurrent papillary ca+left level 2,3,6+right level 6	2 (5)
Bilateral level 6 LNs	1 (2.5)
Right level 2a,3,4,6	8 (20)
Right level 2a,3,4,5,6	1 (2.5)
Right level 4,6	2 (5)
Right level 6	1 (2.5)
Total	40 (100.0)

LN, lymph nodes.

treatment-related morbidity and offers the patients an excellent prognosis. The European Association of Nuclear Medicine and the American Thyroid Association guidelines for standard treatment usually includes surgical procedure total or near-total thyroidectomy followed by ablation of the remanent by radioactive iodine [16].

Previously, radical neck dissection was considered the best choice modality of treatment before recognition of the importance of histology as an outcome predictor. However, radical neck dissection was associated with significant morbidities. At these times, the excellent results of DTC raised a question about the need for this aggressive procedure. Synchronous development of high-resolution US over the last decades changed the practice significantly. With a reported 83.5% sensitivity and 97.7% specificity, it become a reliable tool for assessing the metastatic LNs. Nodal metastases now can be preoperatively identified accurately. This gives the surgeons a golden chance to plan for the extent of surgery guiding the extent of neck dissection, particularly the lateral neck region [17,18]. Unfortunately, the US sometimes cannot assess the central compartment nodes easily, so in suspicious conditions, computed tomography should be done. It also has an added value by assessing the mediastinal LNs. [19–21].

Differentiated thyroid carcinomas, especially papillary thyroid carcinoma metastases to cervical LNs, are very common. They occurs in nearly 20–50% of patients, and micrometastases less than 2 mm may reach up to 90% [22]. Although these microscopic nodal metastases slightly affect the survival rate, they increase the recurrence rate [17]. Stulak *et al.* [18] documented that cervical recurrences occur in 14–30% of patients mainly in the LNs especially with PTC; this is compatible with our results, where all our recurrent cases were PTC.

PTC recurrence can happen in three forms: distant metastasis, 'true' local recurrence, and disease within LNs. The LN recurrence was estimated by nearly 90% of the total relapse; it is discovered in the first 36 to 48 months postoperatively. In fact, this mostly represents persistence and enlargement of unexcised part of the primary pathology rather than true recurrence. This can be explained by the slow growing nature of the primary tumor [10,19]. In this study, we got similar results, where the recurrence was purely in LNs, which occurred in 85% of cases, and remaining 15% were recurrent PTC in thyroid operative bed associated with LN metastasis also. Moreover, the recurrence timing was similar, where we had mean±SD of 23.25±31.60 months.

Believing that the first echelon nodes are the central compartment nodes, we had done dissection for it in all study cases. Even those who underwent previous neck dissection, the central compartment was revised carefully. It was divided into anterior or superficial compartment and posterior or deep compartment, which may extend to the superior mediastinum in the right side, whereas only superficial compartment in the left side due to difference in RLN course in the neck as described before. This matches with many authors [11,19–21,23], who documented that the central compartment nodes are the first echelon nodes. In the same context, Grant [19] mentioned in his study eight points for why prophylactic central neck dissection should be done routinely for de novo cases. Our study confirms his point of view where really the dissection was very demanding especially in previously dissected central compartment with a higher rate of temporary vocal cord dysfunction than usual, and also, with our results where we found recurrence in compartment VI in 38 (95%) of 40 patients. This high rate even with cases that were already subjected to neck dissection may be due to difference in anatomical presentations between the right and left RLN as mentioned before. Moreover, the posterior group right RLN should be paid great attention especially that it may extend to the superior mediastinal nodes and many recurrent cases occur there. Lastly, we should emphasize that surgeons should be aware of these anatomic variations, and meticulous central neck dissection should be done by an experienced surgeon, especially in recurrent cases.

The lateral neck nodes are considered the second echelon nodes; however, some authors reports that they are involved as frequently as the central compartment nodes [23,24]. In this study, we found recurrence in the lateral neck nodes in 82.5% of cases, but only 5% was alone and the central compartment was not affected. It should be noted that this ratio represents the whole LN groups compared with central one only. Moreover, we noticed that all cases where level IV was affected there was affection of level VI with a ratio of 100%. This means that level IV is the first step in the lateral group affection followed by level III, II, and lastly level V. This is very compatible with what had been documented by Na'ara *et al.* [11] in their results.Big debates, many conflicting results, and controversies about the real factor that has a significant effect on chance of recurrence are present between published studies, with the size of the tumor being the only agreed one between all authors [12,13,25,26]. This was very compatible with our results, where only size of the tumor showed a statistically significant result, whereas all other parameters did not reach statistically significant value in affecting the recurrence time.

Hypocalcemia is one of the most important outcomes of thyroid operations. Fortunately, we got temporary hypocalcemia in only 10% of patients, which is slightly higher than El-Foll *et al.* [21] but similar and slightly lower than other authors, who described values between 15 and 27.9% [27–29]. This may be because most of the cases for central dissection were de novo cases and extreme care was taken during all of the procedures, as we knew that we were working on recurrent cases, which pressurized us and made us very meticulous during all dissection steps, plus great care was taken for early implantation of any questionable parathyroid gland as mentioned before.

Finally, our experience in this study documents that surgery on recurrent DTC is technically difficult, is demanding, and carries a higher risk for complications than de novo cases, so understanding the precipitating or participating factors and patterns of recurrence will help in practicing maneuvers that can help in decreasing the recurrence. In this study, we had examined these factors and patterns of recurrence.

Conclusion

The size of the primary tumor has a significant negative or inverse relationship with time till occurrence of relapse. However, postoperative radioactive iodine therapy, postoperative thyroxine replacement therapy, unifocal tumors, and total thyroidectomy in primary procedure all had a wider range for recurrence time, with a longer mean±SD, but did not reach a statistically significant level. Awareness of anatomic variations of RLN helps in central compartment LN dissection, which is very difficult for safe dissection in recurrent cases. It is the most affected group, confirming being the first echelon nodes followed by level IV nodes. Therefore, prophylactic routine meticulous central dissection in the primary cases is advisable to be much easier and safer.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P (eds). Cancer incidence in five continents; vol IX. Lyon: IARC Scientific Publications 2007. 160.

2 Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, *et al.* International patterns and trends in thyroid cancer incidence. Cancer Causes Control 2009; 20:525–531.

3 Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2018; 68:7–30.

4 Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. CA Cancer J Clin 2012; 62:118–128.

5 Fagin JA, Wells SA Jr. Biologic and clinical perspectives on thyroid cancer. N Engl J Med 2016; 375:1054–1067.

6 To K, Nixon IJ. The surgical approach to managing differentiated thyroid cancer. Indian J Med Res 2016; 143:689–695.

7 Furuya-Kanamori L, Bell KJL, Clark J, Glasziou P, Doi SAR. Prevalence of differentiated thyroid cancer in autopsy studies over six decades: a meta-analysis. J Clin Oncol 2016; 34:3672–3679.

8 Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014; 74:2913–2921.

9 Sanabria A, Kowalski LP, Shah JP, Nixon IJ, Angelos P, Williams MD, *et al.* Growing incidence of thyroid carcinoma in recent years: factors underlying overdiagnosis Head Neck 2018; 40:855–866.

10 Durante C, Montesano T, Torlontano M, Attard M, Monzani F, Tumino S, *et al.* on behalf of the PTC study group. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. J Clin Endocrinol Metab 2013; 98:636–642.

11 Na'ara S, Moran A, Eran F, Ziv G. Contemporary management of recurrent nodal disease in differentiated thyroid carcinoma. Rambam Maimonides Med J 2016; 7:e0006.

12 Sharifi A, Shojaeifard A, Soroush A, Jafari M, Abdehgah AG, Mahmoudzade H. Predictors of regional lymph node recurrence after initial thyroidectomy in patients with thyroid cancer. J Thyroid Res 2016; 2016:4127278.

13 Leung AM, Dave S, Lee1 SL, Campion FX, Garber JR, Pearce EN. Factors determining the persistence or recurrence of well-differentiated thyroid cancer treated by thyroidectomy and/or radioiodine in the Boston, Massachusetts area: a retrospective chart review. Thyroid Res 2011; 4:9.

14 Zevallos JP, Hartman CM, Kramer JR, Sturgis EM, Chiao EY. Increased thyroid cancer incidence corresponds to increased use of thyroid ultrasound and fine-needle aspiration: a study of the Veterans Affairs health care system. Cancer 2014; 121:741–746.

15 Corsten MJ, Hearn M, McDonald JT, Stephanie Johnson-Obaseki SJ. Incidence of differentiated thyroid cancer in Canada by City of residence. J Otolaryngol Head Neck Surg 2015; 44:36.

16 Schmidbauer B, Menhart K, Hellwig D, Grosse J. Differentiated thyroid cancer-treatment: state of the art. Int J Mol Sci 2017; 18:1292.

17 Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, *et al.* Revised American Thyroid Association Management Guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19:1167–1214.

18 Stulak JM, Grant CS, Farley DR, Thompson GB, van Heerden JA, Hay ID, *et al.* Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. Arch Surg 2006; 141:489–494.

19 Grant CS. Recurrence of papillary thyroid cancer after optimized surgery. Gland Surg 2015; 4:52–62.

20 King AD. Imaging for staging and management of thyroid cancer. Cancer Imaging 2008; 8:57–69.

21 El-Foll HA, El-Sebaey HI, El-Kased AF, Hendawy A, Kamel MM. Pattern and distribution of lymph node metastases in papillary thyroid cancer. J Clin Exp Pathol 2015; 5:204.

22 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, *et al.* American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26:1–133.

23 Ducoudray R, Trésallet C, Godiris-Petit G, Tissier F, Leenhardt L, Menegaux F. Prophylactic lymph node dissection in papillary thyroid carcinoma: is there a place for lateral neck dissection? World J Surg 2013; 37:1584–1591.

24 Machens A, Hinze R, Thomusch O, Dralle H. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg 2002; 26:22–28.

25 Bardet S, Malville E, Rame JP, Babin E, Samama G, De Raucourt D, *et al.* Macroscopic lymph-node involvement and neck dissection predict lymph-node recurrence in papillary thyroid carcinoma. Eur J Endocrinol 2008; 158:551–560.

26 Chen X, Zhong Z, Song M, Yuan J, Huang Z, Du J, *et al.* Predictive factors of contralateral occult carcinoma in patients with papillary thyroid carcinoma: a retrospective study. Gland Surg 2020; 9:872–878.

27 Alessandro P, Lodovico R, Nadia I, Giulio O, Nicola A, Giuliani P, *et al.* Hypocalcemia following thyroid surgery: incidence and risk factors. A longitudinal multicenter study comprising 2,631 patients. Endocrine 2014; 47:537–542.

28 Wang YH, Bhandari A, Yang F, Zhang W, Xue LJ, Liu HG, *et al.* Risk factors for hypocalcemia and hypoparathyroidism following thyroidectomy: a retrospective Chinese population study. Cancer Manag Res 2017; 9:627–635.

29 Nair CG, Babu MJC, Menon R, Jacob P. Hypocalcaemia following total thyroidectomy: an analysis of 806 patients. Indian J Endocrinol Metab 2013; 17:298–303.