COLLEGE OF HEALTH SCIENCES

INTERNAL MEDICINE DEPARTMENT

NUCLEAR MEDICINE UNIT

Recurrence Rate of Differentiated Thyroid Cancer in Patients Underwent Post-Radioactive Iodine Ablation Therapy at the Service de Medicine Nucleaire, Centre Hospital-Universitaire De Bab El Oued, Algiers, Algeria.

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Declaration

This thesis is my original work and has not been presented for a degree in any other University

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May 02/2025

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This thesis has been submitted for examination with my approval as University Supervisors

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Abbreviations

AAU: Addis Ababa University

AJCC: American Joint Cancer Committee

ALARA: As Low As Reasonably Achievable

ATA: American Thyroid Association

BRAF: B Proto oncogene, Serine/Threonine Kinase

CHS: College of Health Sciences

CND: Complete Nodal Dissection

COVID-19: Coronavirus Disease 2019

DTC: Differentiated Thyroid Cancer

GY: Gray

LND: Local Nodal Dissection

NIS: Sodium Iodine Symporter

PET/CT: Positron Emission Tomography/Computed Tomography

RAI: Radioactive Iodine

RhTSH: Recombinant Hormone Thyroid Stimulant Hormone

SPSS: Statistical Package for the Social Sciences

Tg: Thyroglobulin

TNM: Tumor size Nodal involvement Metastasis

TSH: Thyroid Stimulant Hormone

UAE: United Arab Emirates

U/S: Ultrasound

Abstract

Introduction: Differentiated thyroid cancer (DTC) is primarily derived from follicular cells and accounts for over 90% of thyroid malignancies. Despite a high disease-free survival rate (98%) following radioactive iodine (RAI) ablation therapy, recurrence rates vary significantly globally.

Objective: This study aimed to assess the recurrence rate of DTC through a retrospective cross-sectional analysis of patients who underwent RAI therapy.

Methods: A sample size of 100 patients with DTC treated at the Service de Médecine Nucléaire was analyzed using specific inclusion/exclusion criteria.

Result: The recurrence rate post-RAI therapy was 11% with 6/11(55%) cytological confirmed and 5/11(45%) not confirmed. The study show no associated risk factor for recurrence.

Conclusion: the study shows recurrence rate was in the low-risk group but higher than the local region. No predictor associate with recurrence.

Recommendation: revise management principle and risk stratification. PET/CT must be included in the follow-up

Keywords: Differentiated thyroid cancer, Radioactive Iodine, recurrence

1. Introduction

1.1 Background

The cancer of the thyroid is increasing disease worldwide, Chung, J.-K., & Cheon, G. J. (2014). There are many histologic variants of thyroid cancer among these the most commonly classified are papillary, follicular, medullary, and anaplastic, Benouis et al. (2017). Some histologic variants are well differentiated like classic papillary and follicular, Fawzya et al. (2022). Nowadays thyroid cancer is primarily treated by total thyroidectomy (but also by some practices like lobectomy and subtotal thyroidectomy) with or without nodal dissection and RAI ablation.

The most frequent thyroid cancers (papillary and vesicular) are cured in 80% to 90% of cases if the treatment is appropriate which means total thyroidectomy plus RAI ablation with or without nodal dissection, Benouis et al. (2017). DTC which includes papillary and follicular cancers, comprises greater than 90% of all thyroid malignancies, Sherman's (2003). At the same time, to be ablated the tumor must be well differentiated which has NIS, and able to organify iodine as normal thyroid follicular cell, Liu J.et al. (2019).

Even though the curability is good there is a risk of recurrence mostly within the first five years after therapy, Haugen et al. (2016). The definition of recurrence is different from institution to institution. But most institution has a common definition grossly. Recurrent DTC can be divided into biochemical recurrence (abnormal Tg without rising anti-Tg antibody levels in the absence of localizable disease), which carries an excellent prognosis; imaging-detected recurrence, which is a structurally recurrent disease (persistent or newly identified loco-regional or distant metastases); or clinical recurrence (detected on physical examination) which was disease free for one year, Shaha, A.R. (2012). Disease-free status is defined as no clinical evidence of a tumor, no evidence of a tumor based on RAI imaging or ultrasound, unstimulated Tg < 0.2 ng/mL or stimulated Tg < 1 ng/mL in the absence of antibodies, Haugen et al. (2016).

The long-term study on over 1300 patients with DTC, reported a recurrence rate of 30% after 30 years, Mazzaferri & Jhiang, (1994). The ATA risk stratification criteria can estimate the hazard of structural recurrence. Based on this risk classification, DTC recurrence is not uncommon, occurring in 3–13% of low-risk patients, 21–36% of intermediate-risk patients, and approximately

68% of high-risk patients, Haugen et al. (2016). Applying these three categories, most patients (80%) are classified as low-risk. In UAE Dubai there was one study which was conducted in a tertiary center that showed a recurrence rate of 3%, Al-Haideri et al. (2024). In Egypt one study shows, there is a risk of recurrence within these 10 years of 5–30%, Fawzya et al. (2022). There is also one study which was conducted in Morocco Casablanca which shows persistent/recurrence 6.12%, Hodé et al. (2020).

1.2. Statement of the Problem

The epidemiology of thyroid cancer, worldwide, 586,202 new cases of thyroid cancer were estimated in 2020; the estimated number of deaths for that same year was 43,646, World Health Organization. (2023). Worldwide the highest rates are observed in the French and Italian registries, whereas the lowest ones are in the United Kingdom, the Netherlands, Denmark, Sweden, and some registries in Germany, Hammouda et al. (2006). The global incidence of thyroid cancer is 6.7 per 100,000, and the number of newly diagnosed likely cases in China has exceeded 190,000 (194,232 cases), Ferlay et al. (2019). This low case-fatality rate, mostly due to the indolent nature of DTC, is another reason to emphasize the importance of adequate patient management.

In UAE, thyroid cancer represents the third most common malignancy in the population mostly occurring in the 3rd-4th decades of life and presenting as a localized disease, Statistics, Research Center. (2015). It is increasing in all countries of the world, including Algeria. Thyroid cancer holds the 5th place in order of frequency, Hammouda et al. (2006). It occupied only the 15th row in 1980 with the age-adjusted international incidence rate has increased fivefold in men and tenfold in women, Lalmi, Sadoul, & Rohmer (2015). In Algeria, the incidence standardized according to the world population is 7.7/100,000 in women and 2.9/100,000 in men, Abid, (2008).

The management of TC has significantly changed in the last decade with several guidelines advocating for a conservative approach in the majority of patients, Perros et al. (2014) and Haugen et al. (2016). Although most thyroid cancers have favorable prognoses with appropriate treatment, disease recurrence poses a challenge, Jayarangaiah et al. (2019). Persistent clinical around 5-30% of patients experience recurrent thyroid cancer depending on initial tumor characteristics and treatment modalities, Medas et al. (2019) and Guo & Wang, (2014).

In Algeria, the nuclear medicine practice has a long-standing history compared to other African country. Thus has been treating the DTC with surgery plus RAI management since 1995 in Algeria Algiers Centre Hospitalo Bab el Oued service de medicine nucleaire. Currently, DTC is an approximately curable disease by reducing or eliminating the recurrence by using RAI ablation or treatment by identifying the responsive histologic type. The most frequent thyroid cancers (papillary and vesicular) are cured in 80% to 90% of cases if the treatment is appropriate, Benouis et al. (2017). Even though there is a recurrence, in Africa there is no sufficient research data which was done for DTC recurrence. And also there is no sufficient risk factor assessment for recurrence.

There is a recurrence rate even in a well-advanced treatment center, Mazzaferri & Jhiang, (1994) and Haugen et al. (2016). In addition to the presence of a significant recurrence rate, there are some risk factors which was studied by some scholars worldwide but there is no uniform risk factor association with recurrence in different study papers. In some scholars, age has an association with recurrence but not others. The locoregional and distant metastasis has a strong association with recurrence in most scholars' papers. In general, there is no clear and persistent association between variables and recurrence rate. Even though Service de Medicine nucleaire has a long-standing history of the practice, there is no published paper on the recurrence rate of DTC in PubMed, Cureus, Google Scholar, and Scopus. So the magnitude and association are important to know the recurrence rate and identify the risk factor for recurrence respectively.

1.3. Significance of the study

Knowing recurrence is important in order to improve or revise the management principle as well as help to identify the risk stratification response. Identifying the recurrence with associated factors which used to stratify the patient to apply the management principle. The research on the recurrence rate of DTC post-RAI ablation therapy aims to fill the gap that has insufficient data about the prevalence of recurrence even though there is a growing usage of the management principle. Assessing the recurrence rate and the risk factor for recurrence is crucially important for pre-cautions to incorporate in the management protocol for those who will undergo RAI ablation or treatment.

Knowing the associated risk factor for recurrence has great significance for treating DTC patients by RAI ablation based on the risk factor and its association with recurrence. The presence of associated risk factor and way of dependence is very important to apply the RAI ablation management principle to a specific patient. And also it helps for policy maker as information to develop risk stratification model.

2. LITERATURE REVIEW

Thyroid cancer is the most increasing endocrine malignancy, Fawzya et al. (2022). Currently, the best approach for treating thyroid cancer is total thyroidectomy with or without nodal dissection plus RAI ablation therapy. The most frequent thyroid cancers (papillary and vesicular) are cured in 80% to 90% of cases if the treatment is appropriate, Benouis et al. (2017). RAI ablation therapy helps to destroy the remnant normal tissue for follow-up and detect recurrence and also adjuvant therapy for suspected malignant tissue to reduce recurrence, J R. Hurley (2000).

As the study showed the prognosis of DTC is very good 20 years overall free survival is greater than 90% but there is also a significant percent of recurrence worldwide. A long-term study on over 1300 patients with DTC, reported a recurrence rate of 30% after 30 years, Mazzaferri & Jhiang, (1994). Even if the recurrence is significant, there is no sufficient study worldwide as well as in Africa in a separate way. In addition, there is no study which was conducted in Algeria. So when came, the literature review on the study conducted on incidence and risk factors of DTC recurrence after thyroidectomy plus RAI management.

Retrospective cross-sectional study were conducted in Brazil of 86 patients with clinical nodal-involved papillary type for 8 years duration with collected data, by Furtado, Rosario, & Calsolari, (2015). The study was on patients who underwent total thyroidectomy plus RAI ablation and also nodal dissection on patients who were identified intraoperative. The research focused on nodal recurrence who was clinical nodal involved or not involved papillary type retrospectively. Tumor recurrence was defined as structural disease diagnosed more than one year after ablation in patients without persistent disease. The patient followed with serum thyroglobulin (in two different methods), RxWBS, and neck U/S. The study had three times female predominance with an overall recurrence of 2.4 %(2/83) (both with cervical metastases: one with positive cytology and the other with non-diagnostic cytology, but Tg in the needle washout > 400 ng/mL). There was no association between predictive factors like gender, age, nodal involvement, and tumor size and recurrence except pre-ablation Tg level. The paper had received ethical approval.

A multispecialty group conduct retrospective study on 431 patients from collected data for 29 years by chart review in America Boston, Massachusetts area, Leung et al. (2011). It focused on persistent/recurrence in combined manner to identify the predictive factor association with

persistent/recurrence. All patients underwent total thyroidectomy plus RAI ablation with or without nodal dissection. Recurrence or persistence of tumor, following total thyroidectomy and radioiodine ablation, was defined as serum thyroglobulin levels greater than 0.5 μg/L (unstimulated) or >2 μg/L (following rhTSH stimulation or thyroid hormone withdrawal) with negative thyroglobulin antibodies. The patient followed with serum thyroglobulin (using a chemiluminescence immunoassay), RxWBS, and neck U/S. It had approximately three times female predominance with age at initial surgery being 45.8 $\pm$13.5 years and papillary predominant 91%. The persistent/recurrence was 12% without the significant association of patient-associated and tumor-associated predictive factors but the study excluded local and distant metastasis.

The scholars conducted a retrospective cross-sectional study on 836 patients among those 71 underwent reoperation with 7 years duration of collected data in a well-established tertiary center, Al-Haideri et al. (2024). The study was conducted on total thyroidectomy and RAI ablation (with or without nodal dissection). Recurrence was defined as the development of disease after a patient had undetectable thyroglobulin and negative radiological scans within one year of the first surgery. The patient was followed by serum thyroglobulin and antithyroglobulin, RxWBS, and neck U/S. The mean age of the patients was 44.4 years with three times female predominance. The paper showed 98.6% of papillary type with recurrence of 2.8% (2/71 reoperated patients) with onset duration 15 and 44 months from the initial surgery. Also, the study showed no significant association of predictor factors of recurrence like gender, age, histology, surgery, serum thyroglobulin level, and local metastasis but there was an association on distant metastasis. The research was ethically approved by the ethical committee.

In Casablanca Morocco, a descriptive and retrospective study was conducted on 392 patients in a single center, Hodé et al. (2020). The data was collected for 30 year study period. All underwent total thyroidectomy but half underwent nodal dissection and RAI ablation. However, the study focused on both persistence and recurrence. The recurrence of differentiated thyroid cancer specifies itself as the appearance of the clinical biological or radiological manifestations of differentiated thyroid cancers after a year of initial treatment. The patient was followed by serum thyroglobulin and antithyroglobulin, RxWBS, and neck U/S. The paper shows females are three times more predominant than males as well as the papillary variant is four times more predominant than the follicular variant. The average age during diagnosis is 48 ± 7 years and also the average duration of relapse after initial surgery is 43.89 months. The persistent/recurrence of the study was 6.12%. The paper concluded the persistence/recurrence was low with late detection.

All the above-reviewed papers had a recurrence of DTC lower than the global recurrence of 30% and also within the low-risk category of ATA. The patient also followed for a long period relatively, at the same time the onset of recurrence was within the first fourth year of follow-up. The socio-demographic data was similar worldwide in those papers. The predictive factor of recurrence had no strong association. Even though most of the reviewed papers exclude the poor prognostic factor, had a correlation with the recurrence rate of patients who had high risk. Most recurrences are detected by radiologic imaging.

In general, all the above reviewed studies had limitation on differentiating recurrence from persistent. The limitation also on the data recording habit, lost follow-up due to economy case, single-center, and multiple recurrence definition with variable risk stratification. Although the recurrence rate was low in those studies, it was significant. However, in Algeria, there was no data about the recurrence rate of DTC after thyroidectomy plus RAI management. And also there was no recent study on recurrence especially in a separate manner globally.

3. Conceptual/Theoretical Framework

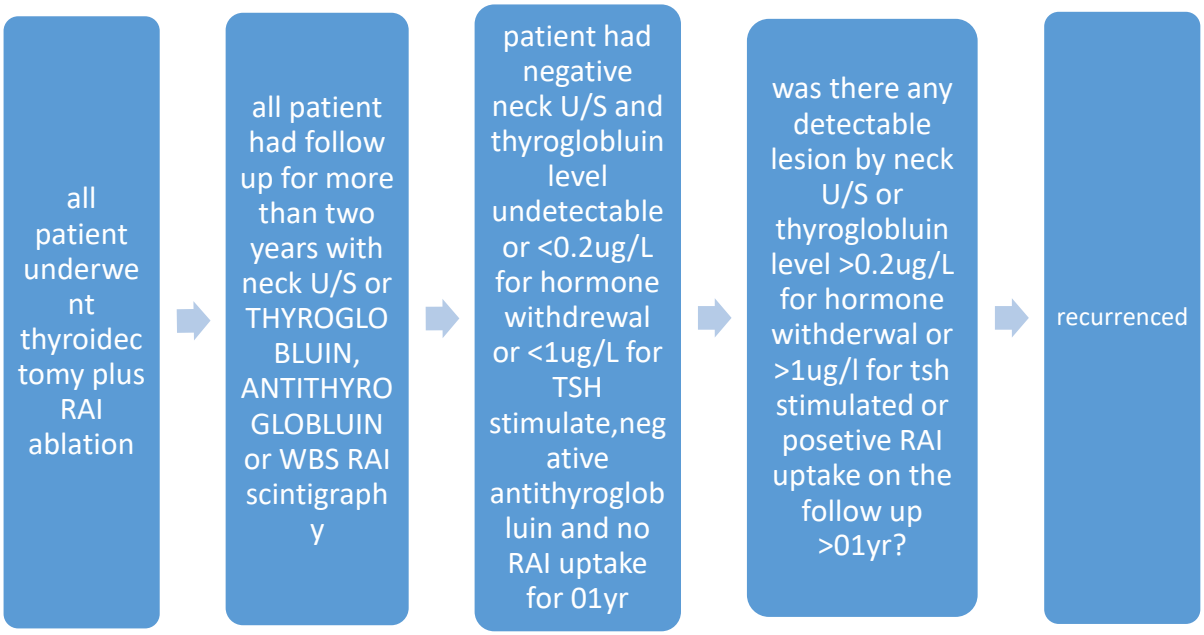

Figure 3.1 conceptual/theoretical framework of the study

4. Objective of the study

4.1 General Objective

To assess the recurrence rate of differentiated thyroid cancer (DTC) in patients who underwent post-radioactive iodine (RAI) ablation therapy and identify factors contributing to recurrence

4.2 Specific Objectives

1. To determine the recurrence rate of DTC in patients who received post-RAI ablation therapy
2. To assess the association of lymph node dissection at initial surgery to recurrence
3. To assess the association of distant metastasis at initial surgery to recurrence
4. To assess the association of age at initial surgery to recurrence
5. To assess the association of histologic variant at initial surgery to recurrence
6. To assess the association of gender to recurrence

5. Methodology

5.1. Study Design

Retrospective cross-sectional study with recurrence rate of patients treated with post RAI ablation who had been treated from January 2021 to December 2022 period on follow up at Service De Medicine Nucleaire Centre Hospitalo Bab El Oued Algiers Algeria.

5.2. Study area and period

5.2.1. Study area

Since 1995, Algeria's nuclear medicine department has been practicing RAI management for thyroid cancer for a considerable amount of time. Service De Medicine Nucleaire at Centre Hospitalo Bab El Oued in Algiers, Algeria, is the first facility. The service was first provided under the endocrinology department before being moved to the nuclear medicine service in 2004.

5.2.2. Study period

From November 01/2024 – March 31/2025

5.3. Source and Study population

5.3.1. Source population

All patients who were diagnosed with DTC and underwent post-radioactive iodine (RAI) ablation therapy during 2021 to 2022.

5.3.2 Study Population

All patients post RAI ablation therapy from January 2021 to December 2022 who had no evidence of disease of DTC for one year and on follow up more than one year and six months from initial RAI ablation time.

5.4. Sample size determination and Sampling procedures

5.4.1 Sample size

The proportion of the population was taken from the low risk prevalence of ATA guidelines and also the Casablanca prevalence of recurrence, Hodé et al. (2020).

Outcome = DTC disease recurrence(Y/N)

Best guess of expected prevalence (p) =6.12 % (0.0612)

Desired width of 95% CI = 10% (i.e. +/- 5%, 1.12% - 11.12%)

The formula used to determine the sample size is:

$$N=p\,(1-p)\,(Z/E)^2$$

Where: $Z1-\alpha 1/2 = 1.96$

N is the required sample size

P is the expected proportion

E is margin of error

Z is the value corresponding to level of confidence required

According to this formula:-

$$N = 0.0612(1-0.0612)\,(1.96/0.05)^2$$

$$N = 88$$

For more precise and near to accurate the sample size was 100.

5.4.2 Sampling procedure

Appropriate random sampling procedure applied.

5.5. Eligibility criteria

5.5.1 Inclusion Criteria

- All patient who underwent surgery plus RAI management
- All patient who had Serum thyroglobulin or Radiologic scan during follow up which was negative within one year follow up from the initial RAI ablation and had >01 year and 6 month follow up from the initial RAI ablation

5.5.2 Exclusion Criteria

- Patient who didn't meet the above criteria
- Patient who had histologic type other than papillary and follicular type
- positive thyroglobulin antibody titers

5.6. Study Variables

5.6.1. Independent variables

Tumor and patient-associated factors were the two independent variables. Socio-demographic variables such as age, sex, ethnicity, and thyroid size are connected with the patient. The histologic type, nodal involvement, distant metastases, tumor size, type of operation (total or subtotal thyroidectomy), CND, LND, and thyroglobulin were the variables linked to the tumor.

5.6.2. Dependent Variables

Disease recurrence response.

5.7. Operational definitions

Recurrence = evidence of disease after one year of disease-free (no evidence of disease) follow-up of DTC patient who underwent post-RAI ablation therapy. According to the recent ATA guidelines, disease-free status is defined as no clinical evidence of a tumor, no evidence of a tumor based on RAI imaging or ultrasound, unstimulated Tg < 0.2 ng/mL or stimulated Tg < 1 ng/mL in the absence of antibodies. Biochemical recurrences are defined as recurrences occurring in patients with negative imaging and thyroid hormone discontinue Tg >0.2 ng/mL or stimulated Tg >1 ng/mL (both in the absence of anti-Tg antibodies). A structurally incomplete response is defined as clinical, radiological (US), or functional evidence of disease (RAI scan, 18-FDG-PET) occurring as loco-regional or distant metastases, with any Tg level. The prognosis was better after surgery plus RAI ablation therapy with 90% free overall survival for twenty years with no evidence of local and distant metastasis

5.8. Data development and collection procedures

5.8.1. Data development procedure

The data development started identifying and recording patients from registered and documented patients' files within 2021-2022

5.8.2. Data collection procedures

For the retrospective cross-sectional DTC recurrence rate post RAI ablation therapy which was disease free for one year by neck U/S, Thyroglobulin, Anti thyroglobulin and Thyroid scintigraphy at 06th month and 12th month.

5.9. Data quality assurance

The data was collected by professionals who were assigned on data collecting and it was cross-checked by another independent personnel.

5.10. Data processing and analysis

The data collected within one month from November 01/2024 to November 23/2024 in files which was recorded in Service De Medicine Nucleaire Centre Hospitalo Bab El Oued Algiers Algeria. The patient documented in the file with confirmed DTC and underwent surgery plus RAI with eligible criteria of no evidence of disease for one-year follow-up by using the parameter neck U/S, serum thyroglobulin, serum anti-thyroglobulin, and RAI scan at post-RAI therapy, 06th month and 12th month. And also the patient socio-demographic included. The data was analyzed by using p-value, chi-square statistics, Pearson's correlation coefficient, and binary logistic regression to demonstrate whether or not there was a relationship between these two variables. In general, the data is analyzed as proportion. The data collected was tabulated and analyzed by SPSS (statistical package for the social sciences), version 25 (IBM Corp., Armonk, New York, USA).

5.11. Ethical Considerations

The ethical considerations were given after the proposal was completed and presented at Service De Medicine Nucleaire Centre Hospitalo Bab El Oued Algiers Algeria and Internal Medicine Department CHS AAU Addis Abeba Ethiopia.

5.12. Result dissemination

After completion, the findings prepared in three copies and disseminated to TASH, the School of Medicine and the Internal Medicine Department, the Nuclear Medicine Unit, and Service De Medicine Nucleaire Centre Hospitalo Bab El Oued Algiers Algeria. The thesis will be published and presented at national and international conferences.

6. Result

The data was evaluated using SPSS software, employing proportion, chi-square tests, p-values, and binary logistic regression. The findings indicated an 11% recurrence rate of differentiated thyroid cancer (DTC) following radioactive iodine (RAI) ablation among a cohort of 100 patients. The average age of patients with recurrence was 36.4 years (ranging from 25 to 50), whereas the average age of those without recurrence was 45.5 years (ranging from 23 to 75), with a higher prevalence in females (figure 6.1). In this study, all patients exhibited the classic papillary histological type, and all individuals with recurrence had undergone total thyroidectomy, while most of those without recurrence also had total thyroidectomy, although a few underwent other types of surgical procedures. None of the patients who experienced recurrence underwent lymph node dissection (LND). Similarly, the majority of patients without recurrence also did not have LND, though some had central or lateral LND (table 6.1).

Every patient, regardless of recurrence status, did not have a pre-radioactive iodine therapy scan. Four patients experienced recurrence with SPECT/CT scans at 18 months, but the remainder had no imaging aside from ultrasound scans. Among them, one patient had a positive finding confirmed by ultrasound and cytology, while another had a negative scan but elevated serum thyroglobulin levels alongside cytological confirmed recurrence. The other two patients had negative scan outcomes, but positive ultrasound results with negative cytological findings. The remaining 7 out of 11 (64%) patients did not undergo any follow-up scans post-radioactive iodine ablation, whether or not cytological confirmation was achieved (table 6.3). Of the 11 patients who experienced recurrence, 9 out of 11 (82%) had positive ultrasound results, and 3 out of 11 (27%) showed elevated thyroglobulin levels after one year of follow-up (table 6.4).

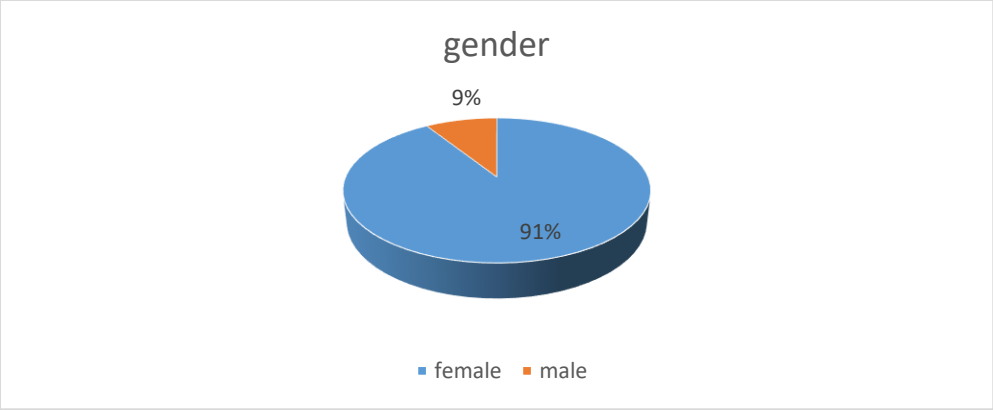

Figure 6.1. Socio-demographic (gender) result of the patients who underwent post-RAI ablation therapy from 2021 to 2022 in service de medicine nucleaire, CHU Algeria

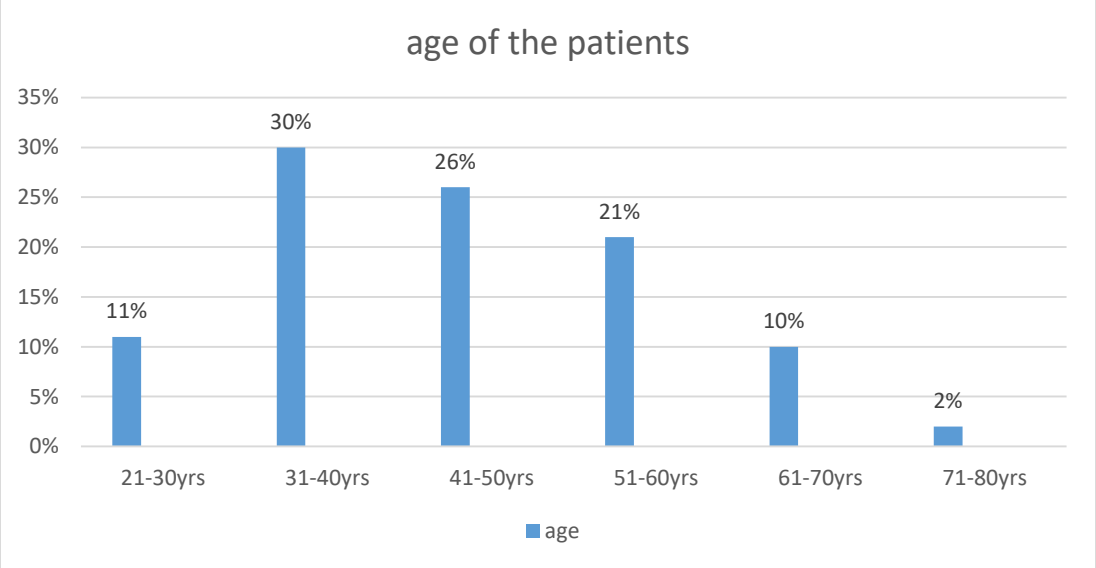

Figure 6.2. Socio-demographic (age) analysis of the patients who underwent post-RAI ablation therapy from 2021 to 2022 in service de medicine nucleaire, CHU Algeria

Table 6.1: Subject demographics, tumor characteristics, and surgery type analysis of the patients who underwent post-RAI ablation therapy from 2021 to 2022 in service de medicine nucleaire, CHU Algeria

Characteristic	n (%)
Gender	
Female	91/100 (91%)
Male	9/100 (9%)
Age	
21-30 yrs.	11/100 (11%)
31-40 yrs.	30/100 (30%)
41-50 yrs.	26/100(26%)
51-60 yrs.	21/100 (21%)
61-70 yrs.	10/100 (10%)
71-80 yrs.	2/100 (2%)
Ethnicity	not determined
Histologic type	
Classic papillary	100/100 (100%)
Follicular and others	0/100 (0%)
Surgery type	
Total thyroidectomy	97/100 (97%)
Lobectomy	3/100 (3%)
Nodal dissection	
Central type	21/100 (21%)
Lateral type	6/100 (6%)
No dissection	73/100(73%)

To evaluate the relationship between predictive factors such as sex, age, histologic type, type of surgery, lymph node dissection, and tumor size in relation to DTC recurrence, a multivariate analysis approach could be employed. However, in this study, no predictors of statistical

significance were identified. Therefore, bivariate binary logistic regression was not utilized. The study for age, yielded a chi-square test result of 0 and a p-value of 0.639, indicating a lack of statistical significance. According to the Chi-Square Tests, the correlation between lymph node dissection and recurrence resulted in a chi-square statistic of 4.57 and a p-value of 0.99, suggesting no statistically significant relationship ($p > 0.05$). Analysis of surgical procedures revealed a p-value of 0.99 and a chi-square statistic of 0.382, denoting statistical insignificance. The chi-square statistic for histologic type was 0, with a p-value of 1.0, showing that there is no association between the histologic type (e.g., classic papillary) and the likelihood of recurrence. The gender of the patients exhibited a chi-square test result of 0 and a p-value of 0.99, indicating no statistically significant findings (table 6.2).

Table 6.2: Overall analysis of predictor associations with recurrence of DTC post-RAI ablation therapy of the patients who underwent post-RAI ablation therapy from 2021 to 2022 in service de medicine nucleaire, CHU Algeria

predictors	Chi square test	p-value
Sex of the patients	0	0.99
Age of the patients	0	0.639
Surgery type	0.382	0.99
Histology type	0	1
Lymph node dissection	4.57	0.99

Table 6.3: Subject recurrence rate, follow up laboratory, and imaging result analysis of the patients who underwent post-RAI ablation therapy from 2021 to 2022 in service de medicine nucleaire, CHU Algeria

Characteristic			n (%)
WBS			
Pre RAI ablation			0/100 (0%)
Post RAI ablation	SPECT/CT		52/100 (52%)
	SPECT		48/100 (48%)
	PET and PET/CT		0/1100 (0%)
At 6th months &12thmonths of follow up			0/100 (0%)
At 01yr&6thmonths of follow up			
	SPECT/CT		1/100 (1%)
Beyond 1yr &6thmonths of follow up			
	SPECT/CT		4/100 (4%)
Imaging finding			
Post RAI ablation	positive		95/100 (95%)
	Negative		5/100 (5%)
At 01yr &6thmonths of follow up			
	Negative		1/1 (100%)
Beyond 1yr &6thmonths of follow up	positive		1/4 (25%)
	Negative		3/4 (75%)
Serum thyroglobulin level at follow up			
Is serum thyroglobulin at 6th month elevated?		No	92/100 (92%)
		Not done	8/100 (8%)
Is serum thyroglobulin at 12th month elevated?		No	96/100 (96%)
		Not done	4/100 (4%)
Is serum thyroglobulin at 1yr& 6th month elevated?		Yes	1/100 (1%)
		No	43/100 (43%)
		Not done	56/100 (56%)
Is serum thyroglobulin beyond 1yr&6th month elevated?		Yes	2/100(2%)

	No	80/100(80%)
	Not done	18/100(18%)
Neck U/S finding at follow up		
Has positive finding on neck U/S at 6th month follow up? Yes		1/100(1%)
	No	92/100 (92%)
	Not done	7/100 (7%)
Has positive finding neck U/S at12th month follow up? No		83/100(83%)
	Not done	17/100(17%)
Has positive finding neck U/S at 1yr&6th month follow up? Yes		5/100(5%)
	No	40/100(40%)
	Not done	55/100(55%)
Has positive finding neck U/S beyond 1yr&6thmonth follow? Yes		8/100(8%)
	No	70/100 (70%)
	Not done	22/100 (22%)
For recurrent		
Nodal involvement at initial diagnosis	local	3/11 (27%)
	Loco regional	1/11(9%)
	No involvement	7/11(64%)
Metastasis at the initial diagnosis	no involvement	11/11(100%)
Cytological finding		
Is the recurrence Cytological confirmed?	Yes	6/11 (55%)
	No	5/11 (45%)

According to the recurrence definition stipulated by the American Thyroid Association guidelines, the study found that the majority of recurrences were structurally detected through imaging within the thyroid bed and surrounding areas, accounting for 9 out of 11 (82%). The remaining 3 out of 11 (27%) were identified as biochemical recurrences (table 6.4).

Table 6. 4: Incidence of recurrent disease in patients with DTC.

Characteristic	recurrent disease n (%)
Structural by imaging	
Regional metastasis include thyroid bed	9 (82%)
Loco regional lymph node metastasis	0
Distant metastasis	0
Biochemical	3(27%)

7. Discussion

This research aimed to assess the recurrence rate of DTC following RAI ablation therapy, as well as to investigate the relationship between age at initial surgery and recurrence among other factors. The results underscore several important observations that both agree and disagree with the current literature regarding DTC recurrence. The analysis indicated an 11% recurrence rate among patients who had a total thyroidectomy followed by RAI ablation therapy, with 6 out of 11 cases (55%) being cytological confirmed and 5 out of 11 cases (45%) not confirmed. This recurrence rate aligns well with previous studies that report recurrence rates ranging from 3% to 30%, influenced by tumor characteristics, treatment methods, and duration of follow-up. The recurrence rate observed in this cross-sectional study is similar to findings from comparable settings, such as research conducted in Morocco, which documented a recurrence rate of 6.12%, as noted by Hodé et al. (2020). It also aligns with results from areas such as the UAE, where a tertiary care facility in Dubai noted a 3% recurrence rate, according to Al-Haideri et al. (2024). However, other regions of the world have reported significantly higher recurrence rates. For example, a study from Egypt found recurrence rates reaching as high as 30%, especially among high-risk patients, as discussed by Fawzya et al. (2022).

From the recurrence data, 82% (9 out of 11) were identified through neck ultrasound, while 27% (3 out of 11) were detected by elevated thyroglobulin levels. Among the 11 patients who experienced a recurrence, 4 underwent SPECT/CT scans, with only one scan showing a positive finding. If a papillary or follicular tumor loses its ability to take up iodine, but there is an increase in serum thyroglobulin, FDG-PET may be able to reveal metabolically active tumors. Therefore, for those patients with negative scan results, PET/CT can assist in detection. This variation underscores that the recurrence of tumors is affected by numerous factors, such as treatment protocols, the criteria for inclusion, genetic differences, the duration of follow-up, how recurrence is defined, and potentially the quality of follow-up care. Despite advances in the treatment of DTC, including the common practice of using RAI ablation therapy following total thyroidectomy, recurrence continues to pose a challenge.

The recurrence rate highlighted in the cross-sectional study, although modest, emphasizes the necessity for long-term observation and personalized patient management to identify and address recurrences promptly. Age does not serve as a prognostic factor in DTC, aligning with certain

studies, as discussed by Al-Haideri et al. (2024). Nevertheless, it plays an essential role in various risk stratification systems, including the ATA guidelines and the AJCC TNM staging system. The average age of patients with recurrences was 36.4 years, compared to 45.5 years for those without recurrences. The chi-square test result of 0 with a p-value of 0.639 indicates there is no statistically significant relationship between age and recurrence. However, older patients seem to have an increased risk of recurrence, which correlates with findings from some studies, including that of Haugen et al. (2016).

Although advanced age is typically linked to a poorer prognosis concerning mortality, findings from various studies regarding its connection with tumor recurrence have been inconsistent. Older patients tend to have higher rates of recurrence, especially when dealing with larger or more invasive tumors, Schlumberger et al. (1998). These results imply that, within this cross-sectional study, age is not a predictive factor for recurrence. Furthermore, older patients could have undergone more comprehensive initial treatment (such as total thyroidectomy followed by radioactive iodine therapy), potentially decreasing recurrence likelihood.

All patients in the recurrence group had total thyroidectomy without LND, which may suggest that the presence of lymph node involvement could affect recurrence rates. However, the study's analysis did not reveal a statistically significant relationship (p-value = 0.99) between LND and recurrence. The findings indicated no significant association between LND and recurrence (p-value = 0.99), implying that the implementation of prophylactic or therapeutic LND did not substantially impact recurrence rates in this cohort. This is consistent with other research that suggests prophylactic LND may not lead to a reduction in recurrence rates among low-risk DTC patients, although it may be advantageous for high-risk patients with clearly visible nodal metastasis. Selective use of LND is recommended, particularly for patients exhibiting high-risk characteristics, but prophylactic dissection is not universally advocated for low-risk DTC, as discussed by ATA Guidelines (2015). This targeted approach corresponds with the lack of a significant relationship found in this study, suggesting that routine dissection may not be necessary for every patient.

The absence of LND in cases of recurrence is a topic that requires deeper exploration, as lymph node metastasis has been identified as a recurrent risk factor in various studies. Individuals with

micro metastatic nodal disease, which may remain undetected during initial surgery, are susceptible to recurrence, Ito et al. (2011). These patients could potentially gain from more extensive nodal dissection. Although total thyroidectomy is the standard treatment for DTC, the absence of LND might have elevated the risk of recurrence in this cross-sectional analysis. The ATA guidelines advises considering LND for patients with established lymph node metastasis during surgery. The observation that none of the patients who experienced recurrence in this study had received LND suggests that hidden lymph node metastases may have gone unnoticed, resulting in disease recurrence. Recurrence rates were greater among patients who did not have LND performed, as discussed by Mendelsohn et al. (2013.

However, they indicated that undetected metastases could be responsible for some recurrences when dissection was not performed, implying that LND might be more advantageous for individuals with subclinical nodal disease. This outcome corresponds with some research that has emphasized the significance of thorough nodal dissection in lowering recurrence rates, especially in patients with aggressive or advanced tumors. Conversely, studies that adopted a conservative stance on LND, particularly in low-risk patients, have reported comparable recurrence rates. Patients who had prophylactic central neck dissection experienced lower recurrence rates, but this benefit was primarily observed in those with high-risk characteristics, Barczynski et al. (2017). In patients with low-risk DTC, recurrence rates were similar whether or not LND was conducted. The choice to perform LND continues to be a subject of debate, and this study contributes to the ongoing discussion regarding its necessity in DTC management.

The complete removal of the thyroid gland eliminates the possibility of any residual microscopic disease in the remaining thyroid tissue. RAI therapy is utilized more effectively, often after surgery, to eliminate any leftover thyroid tissue or microscopic cancer cells. Long-term monitoring of serum thyroglobulin (Tg) levels becomes simpler, as Tg serves as a marker for any remaining thyroid tissue or cancer; after a total thyroidectomy, Tg levels should be undetectable, which simplifies the detection of recurrence. It's important to recognize that a subset of patients may still experience recurrence even after RAI ablation therapy. This indicates that while RAI ablation generally achieves long-term remission for the majority of patients, there is still a group that might not fully respond to this treatment, possibly due to RAI resistance or other influencing factors. Total thyroidectomy resulted in significantly lower recurrence rates compared to partial thyroidectomy, especially among patients with nodal metastases and larger tumors, Mazzaferri and Jhiang (1994). Patients who have total thyroidectomy followed by RAI therapy usually display higher disease-free survival rates due to the more thorough removal of cancer and the use of adjunctive therapy.

Patients with RAI-refractory thyroid cancer generally face worse outcomes and increased rates of recurrence, as discussed by Furio Pacini, Yasuhiro Ito, Markus Luster, Fabian Pitoia, Bruce Robinson, and Lori Wirth (2012. This highlights the necessity for additional research to find predictive markers for RAI resistance and to customize treatment strategies accordingly. The implementation of RAI ablation therapy in this cross-sectional study is consistent with international guidelines for treating DTC. The proven effectiveness of RAI in diminishing recurrence has been well documented, with long-term disease-free survival rates reaching as high as 98% in patients who respond favorably to this treatment. RAI ablation considerably reduces the risk of recurrence in patients at high risk for DTC, particularly those with nodal metastasis, Mazzaferri et al. (2001). These findings imply that while RAI therapy is very effective, there exists a small but significant group of patients who might still face recurrence despite undergoing comprehensive management.

8. Strength and limitation

The strength of the study may be the first study for the area and able to provide recurrence information to revise management principles and risk stratification. And also the study focus on recurrence separate way. The limitations of the study are being retrospective, small sample size, single-center, short duration of follow-up, unable to include all predictor factors and data documentation.

9. Conclusion and recommendation

The recurrence is in the low risk category of ATA guidelines but it is significant comparing to the regional prevalence. While no significant associations were found between gender, age, surgery type, histologic type, and LND with recurrence in this cross-sectional study, existing literature suggests that these factors play critical roles in high-risk patient populations.

Most of the recurrence detected by neck U/S but the sensitivity and specificity is lower than SPECT/CT. thus, for the patient who has either positive neck U/S or elevated serum thyroglobulin level, SPECT/CT must be done. In this study not all recurrence was confirmed by cytological. And also there is negative SPECT/CT finding and PET/CT not done for those patients.

PET/CT which is useful for dedifferentiated thyroid cancer. So PET/CT scan must be included in follow-up. The recurrence is higher than in the local region but within the low-risk stratification of ATA, so the management principle may need to be revised and also serious follow-up. Use ATA guidelines as risk stratification and apply the management based on it unless having own risk stratification guidelines. It may help for future study as information and also needs further study by multidisciplinary with large sample size. The government can use it for policy making.

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11. Annex

Annex 1. Patient age analysis

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	23	3	3.0	3.0	3.0
	24	2	2.0	2.0	5.0
	25	1	1.0	1.0	6.0
	27	2	2.0	2.0	8.0
	28	1	1.0	1.0	9.0
	29	1	1.0	1.0	10.0
	30	1	1.0	1.0	11.0
	31	4	4.0	4.0	15.0
	32	4	4.0	4.0	19.0
	33	3	3.0	3.0	22.0
	34	1	1.0	1.0	23.0
	35	3	3.0	3.0	26.0
	36	2	2.0	2.0	28.0
	37	2	2.0	2.0	30.0
	38	3	3.0	3.0	33.0
	39	4	4.0	4.0	37.0
	40	4	4.0	4.0	41.0
	41	1	1.0	1.0	42.0
	42	2	2.0	2.0	44.0
	43	6	6.0	6.0	50.0
	44	4	4.0	4.0	54.0
	45	4	4.0	4.0	58.0
	46	3	3.0	3.0	61.0
	47	1	1.0	1.0	62.0
	48	2	2.0	2.0	64.0
	49	1	1.0	1.0	65.0
	50	2	2.0	2.0	67.0
	51	3	3.0	3.0	70.0
	52	2	2.0	2.0	72.0
	53	4	4.0	4.0	76.0
	54	1	1.0	1.0	77.0
	55	2	2.0	2.0	79.0

	56	3	3.0	3.0	82.0
	57	2	2.0	2.0	84.0
	58	2	2.0	2.0	86.0
	59	2	2.0	2.0	88.0
	61	2	2.0	2.0	90.0
	62	3	3.0	3.0	93.0
	63	1	1.0	1.0	94.0
	64	1	1.0	1.0	95.0
	65	1	1.0	1.0	96.0
	66	2	2.0	2.0	98.0
	72	1	1.0	1.0	99.0
	75	1	1.0	1.0	100.0
	Total	100	100.0	100.0	

Annex 2. Binary logistic regression on age, surgery type & lymph node dissection type

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	@2.Ageofthepatientnumber			3.394	5	.639	
	@5.Surgerytypewhichwasdone(1)	-18.293	23138.432	.000	1	.999	.000
	@6.typeoflymphnodedissection			.000	2	1.000	
	@6.typeoflymphnodedissection(1)	-19.477	8317.946	.000	1	.998	.000
	@6.typeoflymphnodedissection(2)	-19.428	16107.341	.000	1	.999	.000
	Constant	1.361	1.368	.990	1	.320	3.902

a. Variable(s) entered on step 1: @2.Ageofthepatientnumber, @5.Surgerytypewhichwasdone, @6.typeoflymph Node dissection.

Annex 3. Crosstab on histologic type

Crosstab

			Is the recurrence Cytological confirmed?		
			Yes	No	Total
Histologic type of differentiated thyroid cancer	classic papillary	Count	11	89	100
		Expected Count	11.0	89.0	100.0
Total		Count	11	89	100
		Expected Count	11.0	89.0	100.0

Annex 4. Crosstab on surgery type

			Is the recurrence Cytological confirmed?		
			yes	No	Total
Surgery type which was done	total thyroidectomy	Count	11	86	97
		Expected Count	10.7	86.3	97.0
	others	Count	0	3	3
		Expected Count	.3	2.7	3.0
Total		Count	11	89	100
		Expected Count	11.0	89.0	100.0

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.382[a]	1	.536		
Continuity Correction	.000	1	1.000		
Likelihood Ratio	.711	1	.399		
Fisher's Exact Test				1.000	.702
N of Valid Cases	100				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .33.

b. Computed only for a 2x2 table

Annex 5. Crosstab on age analysis

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.fo Lower
Step 1[a]	age of patient			3.394	5	.639		
	age of patient(1)	-19.006	28420.679	.000	1	.999	.000	.000
	age of patient(2)	-20.147	28420.679	.000	1	.999	.000	.000
	age of patient(3)	-18.718	28420.679	.000	1	.999	.000	.000
	age of patient(4)	.000	29743.274	.000	1	1.000	1.000	.000
	age of patient(5)	.000	31133.302	.000	1	1.000	1.000	.000
	Constant	21.203	28420.679	.000	1	.999	1615473310.817	

a. Variable(s) entered on step 1: age of patient.

Annex 5. Data extraction tool

1. Patient sex

   A. Male B. Female

2. Age of the patient , number
3. Ethnicity of the patient

   A. Arab B. Amazighs C. Arabized Berbers D. Others

4. Histologic type of differentiated thyroid cancer

   A. Classic Papillary B. Follicular C. Others

5. Surgery type which was done

   A. total thyroidectomy B. partial thyroidectomy C. hemi thyroidectomy D. lobectomy

6. type of lymph node dissection

   A. central neck dissection B. Lateral neck dissection C. no

7. Which type of pre RAI ablation therapy of scan?

   A. SPECT B. SPECT/CT C. PET/CT D. no

8. If the scan has, the scan value? A. positive B. negative
9. Which type of post RAI ablation therapy WBS within a week?

   A. SPECT B. SPECT/CT C. PET/CT D. no

10. If the scan has, the scan value? A. positive B. negative

11. Does has WBS at 6^{th} month of post ablation?

A. SPECT B. SPECT/CT C. PET/CT D. no

12. If the scan has, the scan value? A. positive B. negative

13. Does has WBS at 12^{th} month of post ablation?

A. SPECT B. SPECT/CT C. PET/CT D. no

14. If the scan has, the scan value? A. positive B. negative

15. Does has WBS at 01 year and 6^{th} month of post ablation?

A. SPECT B. SPECT/CT C. PET/CT D. no

16. If the scan has, the scan value? A. positive B. negative

17. Does has WBS at beyond 01 year and 6^{th} month of post ablation?

A. SPECT B. SPECT/CT C. PET/CT D. no

18. If the scan has, the scan value? A. positive B. negative

19. Does has elevated serum thyroglobulin at 6^{th}month?

A. yes B. no

20. Does has elevated serum thyroglobulin at 12^{th}month?

A. yes B. no

21. Does has elevated serum thyroglobulin after 01year and 6^{th} follow up?

A. yes B. no

22. Does has elevated serum thyroglobulin beyond 01year and 6^{th} follow up?

A. yes B. no

23. Does has positive finding on neck U/S after 6^{th} follow up?

A. yes B. no

24. Does has positive finding on neck U/S after one year follow up?

A. yes B. no

25. Does has positive finding on neck U/S after one year and 6th follow up?

A. yes B. no

26. Does has positive finding on neck U/S beyond one year and 6th follow up?

A. yes B. no

27. Is there nodal involvement at initial diagnosis?

A. yes B. no

28. Is there distant metastasis involvement at initial diagnosis?

A. yes B. no

29. Is the recurrence cytological confirmed?

A. yes B. no