COLLEGE OF HEALTH SCIENCE, SCHOOL OF MEDICINE, DEPARTMENT OF INTERNAL MEDICINE,
NUCLEAR MEDICINE UNIT(NMU)

Graduate Study Program

Assessment of Complete response rate of Post-Thyroidectomy Radioactive Iodine Therapy for Differentiated Thyroid Cancer at Nuclear Medicine center of CHU de Bab El Oued, Algiers, Algeria

Investigator: Mariya Jemal (MD)-Final Year Nuclear Medicine Resident

Advisors:

Beyene Assefa(MD), Assistant professor of Nuclear Medicine, Department of Internal Medicine, CHS-AAU

Hagos Tesfay(PhD), Assistant professor, NMU, Department of Internal medicine, CHS-AAU

Bouyoucef salah-eddine(MD)- Proffesor of Nuclear Medicine, CHU de Bab El Oued,Algiers, Algeria.

Lydia Cherhome(MD), Assistant professor of Nuclear Medicine CHU de Bab El Oued,Algiers, Algeria.

Thesis submitted to Addis Ababa University, College of Health Sciences, post graduate studies, in partial fulfillment of the requirements for the specialty certificate in clinical nuclear medicine.

April 2025

Approved by the Examining Board

This thesis by Dr. Mariya Jemal is accepted in its present form by the board of examiners, fulfilling the thesis requirements for the Specialty Certificate in Clinical Nuclear Medicine.

Title of project: Assessment of Complete response rate of Post-Thyroidectomy Radioactive Iodine Therapy for Differentiated Thyroid Cancer at Nuclear Medicine center of CHU de Bab El Oued, Algiers, Algeria

Examiner 1 Name _____ Signature _____Date _____

Examiner 2 Name_____ Signature _____Date_____

Advisor Name_____ Signature _____Date _____

Advisor Name_____ Signature _____Date _____

Chairperson of the Department or Graduate Program Coordinator

Acknowledgments

Foremost, I would like to express my sincere gratitude to Addis Ababa University, College of Health Sciences Department of Internal Medicine Nuclear Medicine Unit, and Nuclear Medicine center of CHU de Bab El Oued, Algiers, Algeria for giving me this chance to do this research.

I would also like to acknowledge and give my warmest thanks to my advisors who made this work possible. Their guidance and advice carried me through all stages of completing my research.

Table of Contents

Table of Contents

List of tables

List of Figures

List of annexes–

Abbreviations/Acronyms

ATA	American Thyroid Association
CA	Cancer
CHU	Center Hospitalo- University
DTC	Differentiated thyroid cancer
EBRT	External Beam Radio Therapy
HR	Hazard Ratio
KHCC	King Hussein Cancer Center
NCD	Non Communicable Disease
OS	overall survival
PFS	progression-free survival
RAI	Radioactive iodine
RAIT	Radioactive Iodine Treatment
ST	Survival Time
TC	Thyroid Cancer
TCSS	Thyroid Cancer Specific Survival
Tg	Thyroglobulin
WHO	World Health Organization

Abstract

Background: -. Thyroid cancer is the most common endocrine cancer globally, with a rapidly increasing incidence rate. Since the most common subtype of thyroid cancer is DTC, which includes papillary and follicular ca, it has a good prognosis with more than 90% survival rate. RAI treatment of thyroid cancer is a well-evaluated therapeutic model and is given in combination with surgery for the purpose of thyroid tissue ablation, adjuvant therapy, and distance metastatic treatment. Even though the complete response rate of RAI is high, it is affected by different factors, including histology type, age, lymph node involvement, and so on. Also, the dose and outcome depend on these factors. Patient can have low risk, intermediate risk, or high risk thyroid cancer disease category.

Objective: To assess the complete response rate of post thyroidectomy RAI therapy for differentiated thyroid cancer patients treated in 2021GC (and follow up from January 2021 to november2024) by using a retrospective study at the Service de Medicine Nucleaire-CHU de Bab El Oued, Algeria

Methods: Retrospective study in 164 different thyroid cancer patients who underwent thyroidectomy and took treatment of radioactive iodine in Service de Medicine Nucleaire-CHU de Bab El Oued, Algeria from January 1/2021 to december31/2021 and follow up from January 2021 to november2024.Chi- square ($\chi 2$) test was used for comparisons categorical variables. To identify significant predictor univariate logistic regression was conducted at a 25% significance level. Subsequently, multivariate regression analysis was performed on these variables, with a 5% significance level.

Result :-A total of 159 patient were included in the study, out of these 144(90.6%) were female and 15(9.%)Were male .Majority of patient were in the age range of 30 to 45 years old (45.9).Complete response rate of patients was 88%, by which majority of patient reach to this state with in the 1st 2 years of follow up (82%).lymph node involvement, high base line Tg level, sex, RAI dose was found to have significant association with complete response outcome but the only independent predictor factor was found to be having higher baseline Thyroglobulin level.

Conclusion and recommendation: in this study it is found that patients who have low and intermediate risk characteristics have good complete response rate, and since there was incomplete data for some patient who have high risk disease characteristics, it is difficult to conclude about the complete response rate of high risk patients. The only associated factor which is found to have independent predictive factor to have low complete response rate is having high baseline thyroglobulin level. Based on this assessment, since patient with high baseline Tg level has lower response rate, we recommend giving emphasis to these patients, which might bring better complete response rate.

Key Words: - RAIT, Thyroid Cancer, DT

1.Introduction

According to the 2023 WHO report, non-communicable diseases account for 74% of all deaths globally, resulting in 41 million fatalities annually, with 17 million occurring before the age of 70. In Algeria, from WHO report which is done in 2018, non -communicable disease accounted for 76% mortality rate and 144,000 deaths per year (1). Out of this NCDs, mortalities from cancer holds one of top three diseases (1). From Algerian cancer registry report of 2006, revised in 2020, thyroid cancer, which account for 88% of all cancer of the endocrine organs, shows a significant increment in new cases, which makes the rank to increase from fifteen to fifth place with regards to frequency of all cancers (2).

According to various research studies, since the most common subtype of Thyroid cancer is differentiated thyroid cancer, which include papillary and follicular thyroid cancer, it has good complete response rate if treated appropriately. One of the treatment modality for thyroid cancer is RAI therapy which is found to have significantly reduced disease specific deaths (adjusted HR=0.65, $p=0.017$) and overall deaths (adjusted HR=0.54, $p<0.001$) (3). The major risk factor for the disease include sex(women), age between 22-65, family history, obesity, genetic condition like MEN, Cowden Syndrome and iodine deficiency (4).

Thyroid cancer is treated by combining surgical and medical treatment with RAI therapy. Surgery is often the first step in successful therapy of thyroid cancer and is usually combined with RAI Therapy for the purpose of thyroid tissue remnant ablation, adjuvant therapy, and treatment of known metastatic disease. RAI therapy is given based on patient risk category which is classified as low risk, moderate risk and high risk. According to 2015 American Thyroid Association, for low risk thyroid cancer, even though there is controversy over giving RAI therapy, the risk to benefit ratio is in favor of not giving the treatment.

The standard recommended dose of RAI treatment for differentiated thyroid cancer is in the range of 30- 100mci for postoperative thyroid remnant ablation, 150mci for presumed thyroid cancer in neck or mediastinum, and 200mci for distant metastasis. Due to possible bone marrow suppression cumulative

activity from repeated treatments above 800mCi should be given with extreme caution. (4)

In addition to this, RAI treatment has short-term and long-term adverse effects, which include neck pain or swelling, gastrointestinal symptoms, pain or swelling of salivary gland, headache and vertigo, insomnia, vocal cord paralysis, fatigue or general malaise, and foreign body sensation, xerostomia, dental caries, reduced taste, dry eyes, and <1% there is possibility of radiation-induced neoplasms. Due to total removal of thyroid, the patient has to be on long term hormone replacement and follow-up is required.

Follow-up with whole body imaging, TSH suppression test, and serum thyroglobulin is crucial for the response assessment of the treatment which could be complete response and persistent thyroid cancer. According to 2015 American Thyroid Association, treatment response is classified as excellent response, biochemical incomplete response, structural incomplete response and indeterminate response. Depending on the incomplete response type the patient is going to have different risk of progression to complete response or persistent disease.

1.1 Statement of the problem

As described above, RAI has a significant impact on the treatment and prognosis of thyroid cancer, resulting in a better survival rate of the patients. Even if it might not be comparable with the advantages, it has its own side effects as there is high radiation exposure to the patient. Since there is no published research which was done in Algeria, to our knowledge, over this area, i.e. assessment of complete response rate of RAI treatment or assessment of outcome of RAI treatment in general, it would be difficult to objectively assess the outcome of the RAI therapy and the factors that have a negative impact on the complete response rate of the therapy. As it is well known, the outcome of thyroid Ca treatment depends on different precondition in addition to standard.

RAI, which include –advancement of the center with regard to the quality of surgery and the amount of remnant thyroid tissue left, which is going to vary from developed country to upper middle income country like Algeria, because of this, the disease response pattern might differ from that of developed countries which has well studied Thyroid cancer response rate to RAI treatment. In addition to this, assessment of the specific effective dose which is going to be effective for different type of patients having different pattern of disease based on difference in demography, stage of disease, histology and pathological characteristics of those patients who are living in this area would be difficult, which might result in unnecessary increased or decreased radiation exposure.

1.2 Significance of the Study

This study will provide information about the complete response rate of the RAI therapy in general for patients who have different sociodemographic, pathologic characteristics and who underwent different surgical procedure and assessment of patient response rate for different range of RAI doses for different types of patients who were treated in this hospital. So this would support more individualized treatment plan and treatment protocol development which is going to be best suited for the center by taking different sociodemographic, disease pattern and facility factor into account .Since it also gives some information on the factors which are linked to have low complete response rate , it would also give base for further treatment planning or hospital based protocol development which would be useful to target those patient who have these factors leading to lower complete response .So the aim of this research is to evaluate the complete response rate of RAI therapy for the given different range of RAI (I-131) dose in patients presenting with different demography and pathological characteristics of differentiated thyroid and to assess factors which are linked to incomplete response rate of RAI therapy.

2. Literature review

1 in 3 premature deaths from NCD worldwide is caused by cancer, which is responsible for 1 in every 6 deaths, affecting every household (5). There were an estimated 20 million new cases of cancer and 9.7 million deaths in 2022, which is a significant increment from 2012 with new cases of 14.1 million, resulting in 41% increment in new cases from 2022(6).

From the study that was done in the Arab world, cancer is the fourth leading cause of death in the Eastern Mediterranean region, with approximately 419,000 deaths in 2018(7).

Different research shows that there is similarity between Middle East and North Africa, even though there is not much research found in Algeria, one study which was done in a Western Algeria, U.C.M. Telcan Hospital shows thyroid cancer is one of the most frequent endocrine cancers, also one of the cancers that is increasing in number significantly (8).

"Globally, in 2020, the age-standardized incidence rate of thyroid cancer was 10.1 per 100,000 in women and 3.1 per 100,000 in men, with a mortality rate of 0.5 per 100,000 and
0.3 per 100,000," (9) comparing higher and very high development index country with low and medium human index country, it shows five times higher incidence rate. (9)

From the research that was done in Algeria, assessment of epidemiology of thyroid cancer for 3 years, from 2013 up to 2015, 1376 cases of thyroid CA were taken from the UTC nuclear medicine center, and the peak age group shows 40 to 60 years (45.8%), followed by 60 to 80 years (31.04%), and group 20 to 40 years (21.75%). (10)

It also shows women hold higher rates than men, representing 94.75% of the thyroid CA and men hold only 5.24% of thyroid CA. (10) ''Radioiodine (I-131) treatment of well-differentiated thyroid carcinoma is a well-evaluated therapeutic model for nuclear medicine which has never been equaled by subsequent developments" (11)

In one systematic review and meta-analysis study which was done in USA with 3103 patients at intermediate to high-risk thyroid ca patients, it shows successful ablation rates in the range of 51 to 94%, with 71% pooled successful ablation. (12)

In a retrospective analysis which was done in turkey, 588 low risk thyroid ca patients were taken which are divided in to, patients who took high dose (100mci) RAI and those who only receive total thyroidectomy. After 24 months follow up, it shows 86% excellent response rate in those patients who took RAI compared to 74 % excellent response rate who only underwent total thyroidectomy. Long-term follow up also shows 99.3% of patients who took RAI show no evidence of disease (NED) versus 90.6% in non RAI group. (13)

In a retrospective comparative analysis that was done in Spain, an excellent response rate of 79.8% in the low-dose group and 85.7% in the high-dose group was observed. 174 patients with low- and intermediate-risk thyroid cancer were taken, 90 treated with low-dose ablation, and 84 treated with high-dose ablation. As a conclusion, low-dose ablation seemed to be less effective than the high dose. Stimulated thyroglobulin at the moment of ablation and positive ant thyroglobulin antibodies were indicated as independent predictive factors for no excellent response, and young age, intermediate initial recurrence risk, and low-dose ablation ($p = 0.004$) were independent predictive factors for recurrence. (14)

In another study which was done to assess the effectiveness of RAI for distant metastasis was done, comparing patients who had RAI and those who received EBRT, a different study that examined the efficacy of RAI for thyroid cancer in DTC with distant metastases, revealed that the 5-year rates of TCSS were 45.5% and 91.7%, respectively. Patients over 45 who had RAI had a 5-year TCSS rate of 69.1%, while those who got EBRT had a 5-year TCSS rate of 20.0%. RAI increased survival for patients with lung metastases in the higher grade group, but it had little effect on the better grade group. According to this conclusion, patients with young, well- or moderately differentiated thyroid carcinoma who have distance metastasis should be specifically treated with RAI. (15)

In one research which was done in South Korea to assess subsequent incidence of cancer in children and young people who took RAI therapy, a sample of 18617 children and young adults (0-29years old) were taken and 9548(51.3%) had at least one RAIT session, initially the dosage was 4.35 ±2.19 GBq but subsequently decreased from 64.2% to 36.5%. During the 120,474 person-years of follow-up, 124 cases of secondary cancer arose. (16)

2.1. Literature review in Middle Eastern population

A retrospective analysis of 528 patients with a 10-year primary DTC diagnosis was conducted from a study conducted in Arabic patients at the King Hussein Cancer Center (KHCC) with the goal of evaluating the 5- and 10-year overall survival (OS) and progression-free survival (PFS). The results indicate that the 10-year OS was 96.5%, while the 10-year PFS was 85%. All patients in the group had an average progression-free time (PFT) of 129.4 months and an average estimated survival time (ST) of 140.1 months.

They also came to the conclusion that while RAI therapy was successful in extending ST, the prognosis was negatively influenced by the male gender, age ≥55, ATA high-risk category, and TNM metastatic status. (17)

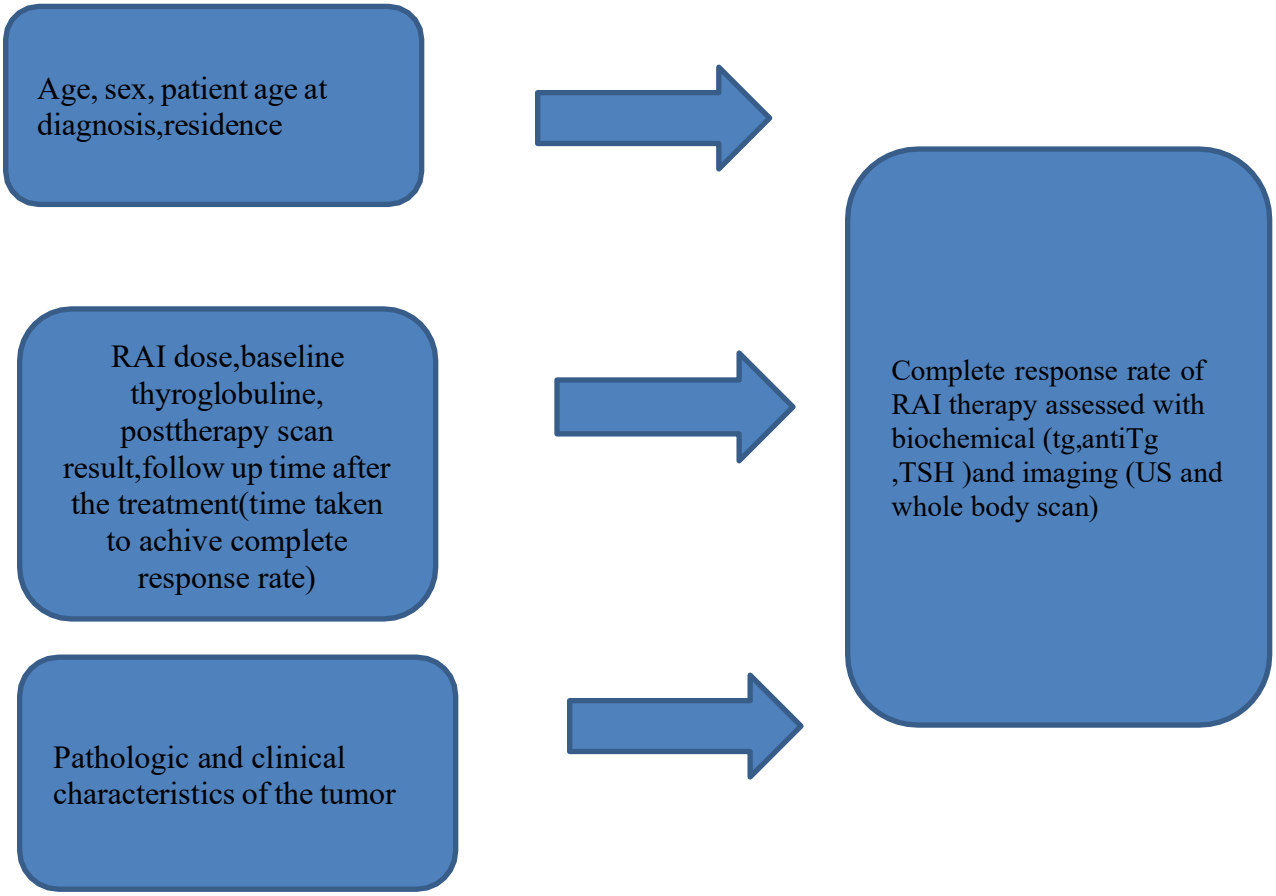
In one Iranian study which was done to assess predictors of response to Radioactive Iodine Therapy in Intermediate and high risk patients with papillary thyroid carcinoma, they took 333 patient record for analysis and it concludes TSH-Stimulated serum Tg greater than 15.7 ng/ml was associated with response failure even after multiple RAI therapy ($P < 0.001$) .The other finding was, the chance of ER(excellent response) was decreased by 74% if initial post-operation ultrasound imaging confirmed the presence of loco regional involvement, OR 0.26, (95% CI: 0.12–0.55), $P < 0.001$.(18)

Another study from Palestine was conducted to assess the effectiveness of RAI-131 therapy following the use of high cumulative doses of I-131, at Al-Ahli Hospital in Hebron. It is a retrospective analysis of 141 post-operative patients with histologically confirmed thyroid cancer. There were 141 TC patients in all, with 114 (80.15%) being female and 27 (19.85%) being male (b). In the current study, the overall efficacy of I-131 therapy was 87.9%. Although the fifth age group (60–70) was the least affected, the middle-aged patients (30–40) had noticeably lower outcomes than the other groups.

I131 offered a useful therapeutic approach for thyroid cancer patients with distance metastasis (19) Lastly, according to an Egyptian study that examined 70 patients with DTC with distant metastasis, the median overall survival (OS) from a well-defined diagnosis of DTC with distant metastases was 79.06 months, and it was much lower in the case of male sex and T4 stage, Because RAI therapy lowers the number of adverse events while preserving a good standard of living and improving OS, it has been found to be an effective treatment for DTC with distant metastases. (20)

The path of patient taking the treatment is- initially thyroidectomy (which could be total thyroidectomy, total thyroidectomy with lymph node dissection or lobectomy) would be done, then RAI scan will be taken and estimation of the dose of the therapy would be done based on the patient condition (age,sex,stage,remenant thyroid tissue amount after surgery, histology of the cancer, lymph node involvement-ATA risk category) then the patient will take the treatment and follow up with Tg,anti Tg ,TSH,and ultrasound will continue every 6 month to 1 year. If the patient did not respond to the therapy, additional dose would be given.

Conceptual Framework of the Study



3. Objectives of the study

3.1 General objective

- To assess the complete response rate of Post Thyroidectomy Radioactive Iodine Therapy in Differentiated Thyroid Cancer Patients Treated in 2021GC (having follow up from January 2021 to December 2024) by using a retrospective study at the Service de Medicine Nucleaire-CHU de Bab El Oued, Algeria

3.2 Specific objectives

- To assesses the complete response rate of post thyroidectomy RAI therapy (I131) in Differentiated Thyroid Cancer patients.
- To examine the impact of patient demographic and clinical characteristics. (Such as age, gender, and disease stage and pathological characteristics) on complete response rate of the diseases
- To assess the complete response rate of RA I-131 depending on different doses (low, medium and high) correlating with biochemical response and imaging result in differentiated thyroid cancer.
- To assess factors which are associated to incomplete response rate of the RAI therapy.

4. Methods

4.1. Study design

Retrospective complete response rate study of post thyroidectomy RAI therapy for patients taking the RAI treatment in the year 2021 and follow up to December 2024 at Service de Medicine Nuclear-CHU de Bab El Oued, Algeria.

4.2 Study area and period

4.21 Study area

- Service de medicine nucleaire-CHU de Bab El Oued, Aljiers, Algeria

4.22 Study period

- From January 2021 to December 2024

4.3 Source and study population

4.31 Source population

All differentiated thyroid cancer patients who come to the nuclear medicine center (Service de medicine nucleaire-CHU de Bab El Oued, Algiers Algeria) for RAI therapy.

4.32 Study population

All differentiated thyroid cancer patients who took the RAI treatment and fulfilled the inclusion criteria.

4.4 Sample size determination.

Since there is no previous study, up to our knowledge, which was done in this country, so the sample size was calculated by using the study in Palestine as a reference (19): the effectiveness rate was 87.9%=0.879=q; P=1-q

P=1-0.879=0.121

The formula used to determine the sample size is:

$n = [Z^2 p (1 - p)]/ C^2$

$n = (1.96)^2 (0.121) (1-0.121)/ 0.05)^2 = 164$

n=164

4.5 Sampling procedure

Appropriate systemic random sampling procedures was applied

4.51 Inclusion criteria

All differentiated thyroid cancer patients who had full clinical assessment and laboratory and imaging investigations (data on tumor size, extension, lymph node, and distant metastases, Tg, TSH). Who had regular follow up for 3 year- 4year.

4.52 Exclusion criteria

- Patients missing data on outcome measure
- Patients who received external radiation treatment.
- Patient who lost follow-up

4.6 Variables of the study

4.61 Independent variables

- Age, sex, patient age at diagnosis, cumulative RAI dose, baseline thyroglobulin, follow up time until they reach complete response.
- Pathologic and clinical characteristics: histology, type of surgery (TT or NTT/STT,status of lymph node metastases (negative, positive)

4.62 Dependent variable

Post thyroidectomy RAI therapy Complete response which is measured by thyroglobulin, anti- thyroglobulin, TSH (sensitized or unsensitized, imaging (thyroid US)

4.7 Operational definitions

- Complete response - is defined as negative imaging and a non-suppressed thyroglobulin level <0.2 ng/ml or stimulated tg <1 ng/ml.

- Incomplete response or indeterminate response - is defined as positive imaging or a non- suppressed thyroglobulin level >0.2 ng/ml or stimulated Tg >1 ng/ml.

I-131 therapy outcome definition (ATA guideline)

- **Excellent response/complete response:** is defined as negative imaging and a non-suppressed thyroglobulin level <0.2 ng/ml or stimulated tg <1 ng/ml.)

- **Indeterminate response** is defined as nonspecific findings on imaging studies, faint uptake in thyroid bed on therapy scan, no stimulated Tg < 1 ng/mL, stimulated Tg < 10 ng/mL, or anti-Tg antibodies stable/declining. (30 % spontaneously progress to NED (no evidence of disease, 20% achieve NED after additional therapy, 20% develop structural diseases)

- **Biochemical incomplete response**: negative imaging, suppressed Tg ≥ 1 ng/mL, or stimulated Tg ≥ 10 ng/mL, or rising anti-Tg antibody levels. 50%-85% continue t have persistent disease

- **Structural incomplete response:** structural or functional evidence of disease with any Tg level, with or without anti-Tg antibodies.

4.8 Data development and collection procedures

4.81 Data development procedures

The data development starts with identifying and recording patients from registered and documented patients' files from year 2021 data (who took RAI treatment from January1, 2021to December 30, 2021)

4.82 Data collection procedures

The data was collected by data collectors who had knowledge on how to assess the chart and fill the data collection format which is found on annex 1.

4.9 Data quality assurance

The professionals who were assigned on data collecting performed according to data collecting Format (annex 1) and it was cross-checked by another independent personnel.

4.10 Date management and analysis

The data was coded and entered to SPSS software version 27.0. Descriptive statics was presented by frequency table and graphs. Chi square test was used for assessing association of variables, Bi variable and multivariable logistic regression analyses were conducted to identify factors associated with complete response rate of RAI therapy

4.11 Ethical consideration

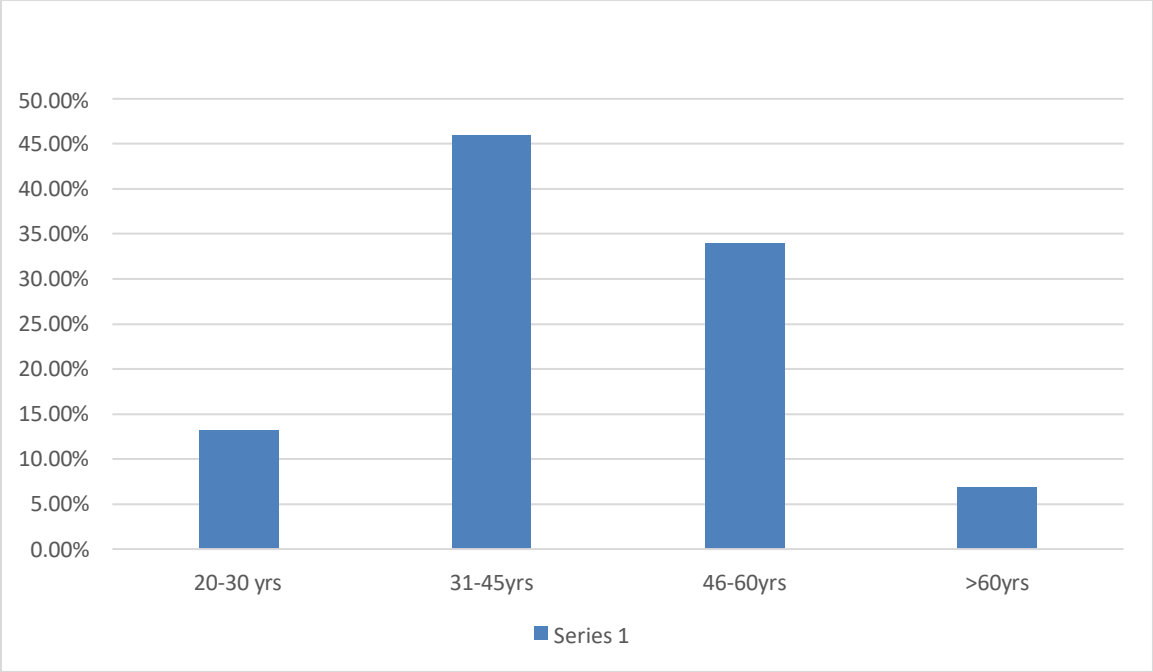
The study was conducted after obtaining permission from the department of Nuclear medicine at CHU de Bab El Oued and AAU nuclear medicine unit internal medicine department. The patient data was kept confidential. The study was conducted under the basic principles of ethics.

5. Results

5.1 Demographic characteristics

Five of the 164 patients who were taken as a sample were eliminated due to insufficient data. 159 patients in all were examined. There were 15/159 (9.4%) men and 144/159 (90.6%) women. Among them, the majority of patients (45.9%) were between the ages of 31 and 45, 34% were between the ages of 46 and 60, 13.2% were between the ages of 20 and 30, 6.9% were above 60, and no patient was younger than 20. Figure 1 shows the result of the age range of the patients in this study.

Figure 1 Age range of patient who took RAI tx



5.1.1. Disease (Thyroid cancer) characteristics of the patients

Almost all of the patients who were admitted to the center for the RAI treatment had papillary thyroid cancer (97.5) the rest 2.5 %(4/159) patients had follicular thyroid ca. 153 of 159 patients (96.2 %) had stage 1 thyroid cancer,3 patients were stage 2 ,2 of the patients were stage 4b and 1 patient had stage 4a thyroid cancer, and there was no patient who was stage 3.

Of the patients, 24% (39/158) had lymph node involvement, while the remaining patients (119/158) had no involvement. The lymph node status was not specified in one patient.

Four patients had metastases, of which two had spread to the lung, one to the bone, and one to both the lung and the bone. The majority of patients (155 out of 159, 97.5%) did not have metastatic thyroid cancer.

A total thyroidectomy without lymph node dissection was performed on 59.7% of patients, while a total thyroidectomy with lymph node dissection was performed on 37.7% of patients. Lobectomies were performed as a form of surgical care for three patients.

The majority of patients (47.2%) had baseline thyroglobulin levels in the range of less than 1 ng/dl, 35.2% had baseline Tg levels in the range of 1–10, and 12.6% (20/159) had baseline Tg levels greater than 10 ng/dl. The baseline Tg level in seven cases was not specified.

The specific amount of RAI dose given to the patients was comparable with the dose recommended by American Thyroid Association, but, since complete response rate of the patients depend on the quality of surgery and amount of remnant tissue remained during surgery, in some cases the dose recommendations of ATA were not applied in the center, and it was personalized to the specific patient case scenario based on the physician decision. Most of patients took RAI once (94.3 % or in 150/158 of patients) with cumulative dose range of 30-50mci given for 62 patients (39%), 51-100mci for 48 patients (30.2%),101-150 given to 31(19.5%) of patients,>200 for 13 patients (8.2%) and 1patient took 151- 200mci range of RAI.

With the aforementioned management, the complete response rate for 144 of the 159 patients was determined; the data for the other 15 patients was incomplete, so they were excluded from the complete response rate analysis. 16 patients had an incomplete/indeterminate response rate, whereas 127 patients (88%) had a complete response.

Of the patients who achieve complete response, the majority (51.9%) attain this state within a year or two years, 30.7% do so from six months to a year, and 13.2% require more than two years. Figure 4 shows response of patients for RAI therapy in the patients of this study. Table 1 depicts the complete response of patients with different demographic and disease character.

Figure 2 -response of patients for RAI therapy

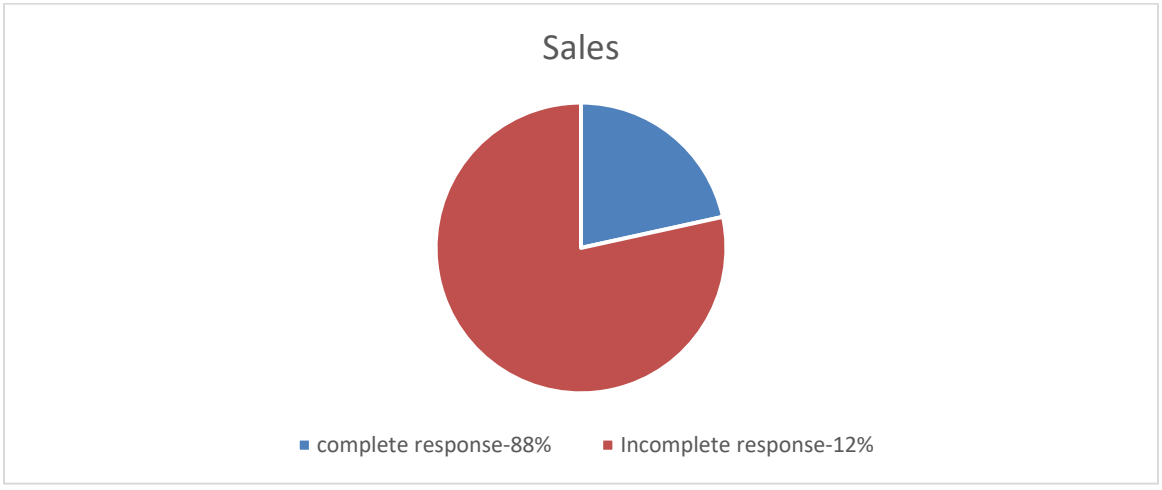


Table 1 – complete response rate of patient having different demographic and disease characteristics

Variables		**Complete response rate**		**p-value**
		Complete response (n=127)	**Incomplete/indeterminate** (n=16)	
Base line Tg level	<!ng/ml	65/69(94.2%)	4/69(5.7%)	**0.01**
	1-10ng/ml	50/52(96%)	2/52(3.8%)	
	>10ng/ml	8/17(47%)	9/17(52.9%)	
Age	20-30	18/20(90%)	2/20(10%)	0.309
	30-45	60/64(93.7%)	4/64(6%)	
	46-60	40/48(83.3%)	8/48(16.6%)	
	>60	9/11(81.8%)	2/11(18%)	
Sex	Female	116/129(89.9 %)	13/129(10%)	0.201
	Male	11/14(78.5%)	3/14(21.4%)	

Table 2– complete response rate of patient having different demographic and disease characteristics (continued)

Variables		Complete response rate		p-value
		Complete response (n=127)	**Incomplete/indeterminate** (n=16)	
Stage	1	125/139(89%)	14/139(10%)	**<0.01**
	2	2/2(100%)	0/2(0%)	
	4	0/2(0%)	2/2(100%)	
Type of DTC	Papillary	125/140(89.2 %)	15/140(10.7%)	0.203
	Follicular	½(50%)	1/2 (50%)	
	Other	1/1(100%)	0/1(0%)	

Chi-square test with CI=95% used in these categorical variables P-values of ≤0.05 were considered statistically significant (*)

Table 3– complete response rate of patient having different demographic and disease characteristics

Variables		Complete response rate		p-value
		Complete response (n=127)	**Incomplete/indeterminate** (n=16)	
Lymph node	Involved	25/143(17.4	7/143(4.8%)	

involvement		%)		**0.03**
	Not involved	102/143(71.3%)	9/143(6.2%)	
	30-50	55/58(94.8%)	3/58(5.1%)	
RAI dose	50-100	38/41(92.6%)	3/41(7.3%)	
	100-150	26/31(83.8%)	5/31(16%)	
	150-200	1/1(100%)	0/1(0%)	<0.01
	>200	7/12(58%)	5/12(41.6%)	
	Chi-square test with CI=95% used in these categorical variables P-values of ≤0.05 were considered statistically significant (*).			

Table 4– complete response rate of patient having different demographic and disease characteristics (continued)

		Complete response (n=127)	**Incomplete/indeterminate** (n=16)	
metastasis	Yes	1/2 (50%)	½(50%)	
	No	126/141(89.3%)	15/141(10.6%)	<0.01
	Total thyroidectomy without LN dissection	78/85(91.7%)	7/85(8.2%)	

Type of surgery	Total thyroidectomy with Lymph node dissection	47/54(87%)	7/54(12.6%)	<0.01
	Lobectomy	1/3(33.3%)	2/3(33.3%)	
	Chi-square test with CI=95% used in these categorical variables P-values of ≤0.05 were considered statistically significant (*).			

5.1.2 Relation of demographic and disease characteristic with complete response rate

A significantly reduced complete response rate (47%) was observed in patients with baseline Tg levels greater than 10, 94.2% in those with baseline Tg levels between 1 and 10, and 95.6% in those with baseline Tg levels less than 1, additionally, a P value of less than 0.001 indicates a significant association between the baseline Tg level and the complete response rate.
Patients with lymph node involvement achieve a 78% (25 of 32) complete response rate, while 102 out of 111 patients with no lymph node involvement achieve a complete response (91%) rate. With a p-value of 0.03, the relationship between lymph node involvement and full response was significant

The majority of patients (89.9%) with stage 1 thyroid cancer get a complete response rate; two patients with stage 2 thyroid cancer also achieve a complete response rate; and out of two patients with stage 4 (a &b) thyroid cancer both of them did not reach a complete response rate. The significant association was indicated by the P value of less than 0.01.

There was some difference in the complete response rates of male and female patients; the men`s complete response rate was 81.15% (13/16), while the females were 91% (116/127). The p-value of 0.201indicates that there was no significant association between sex and the entire response rate.

Out of two patients who had lobectomies, one patient developed an incomplete/indeterminate response.

The complete response rate for patients who had a total thyroidectomy was 92.9%, and the complete response rate for patients who had a total thyroidectomy with lymph node dissection was 83.3%. There is a significant association, as indicated by the P value of 0.016.

A higher dose was administered to high-risk patients, and although the complete response was still low, the effectiveness of the dose cannot be deemed ineffective, because since the patient is also high-risk, the measure of effectiveness is different from those with low risk and intermediate risk. Instead, a separate study for high risk patients (patient with metastatic disease-advance stage) with different measure of effectiveness must be conducted. But for patients who took low and intermediate dose, the complete response rate was high, 94% for those who took dose 30-50 mci, 92% for those patients who took
50-100mci and 83% for those who took 100-150mci, p value for association of RAI dose excluding Higher dose is 0.199, showing no significant association.

Four patients had metastatic thyroid cancer, and one of them passed away early in the follow-up, two had incomplete charts, and one responded well to treatment, with her Tg declining from thousands in the early follow-up to less than 100mci in three to four years. She received four cycles of RAI with a total dose of 800mci.

5.2 Factors affecting the complete response rate of patients

Factors affecting the complete response rate of patients were analyzed by using Bivariate analyses using logistic regression to assess the relationship between demographic and disease characteristics of patients in relation to attaining complete response rate. From this analysis, sex of patients, lymph node involvement, baseline thyroglobulin level and dose of RAI were significantly associated with referral of patients at 25% level of significance.
However, from the multivariate analysis only baseline thyroglobulin level was found to be significantly associated with complete response rate at 5% level of significance. Since the number of patient having baseline Tg level >10ng/ml was less than 10 further analyses was not possible.

Table 5: Factors affecting complete response rate

Predictors	**Complete response rate**		**A0R (95%CI)**	**P value**
	Complete Response	Incomplete/indeterminate		
Lymph node Involvement				
Involved	25/143(17.4%)	7/143(4.8%)	1.178(0.225-6.179)	0.846
Not involved	102/143(71.3%)	9/143(6.2%)		
Sex				
Female	116/129(89.9%)	13/129(10%)	0.361(0.61-2.138)	0.262
Male	11/14(78.5%)	3/14(21.4%)		

Logistic regression done to identify possible independent predictors. P-values of ≤0.05 were considered statistically significant (*)

Table 6: Factors affecting complete response rate (continued)

Predictors	**Complete response rate**		**A0R (95%CI)**	**P value**
	Complete Response	Incomplete/indeterminate		
Baseline Thyroglobulin				
<1ng/ml	65/69(94.2%)	4/69(5.7%)		**<0.01***
1-10ng/ml	50/52(96%)	2/52(3.8%)	0.437(2.055-0.334)	
>10ng/ml	8/17(47%)	9/17(52.9%)	0.078(0.17-0.357)	
RAI dose				
30-50	55/58(94.8%)	3/58(5%)		
50-100	38/41(92.6%)	3/41(7%)	0.929(0.147-5.884)	
100-150	26/31(83.8%)	5/31(16%)	0.629(0.76-5.235)	**0.670**
>200	7/12(58%)	5/12(41%)	0.225(0.27-1.899)	
150-200	1/1(100%)	0/1	--------	

Logistic regression done to identify possible independent predictors. P-values of ≤0.05 were considered statistically significant (*)

6. Discussion

This research assesses the complete response rate of the RAI therapy for patients who have different demography, disease characteristics and surgical management by measuring the complete response rate of the patient in 3-4 year period .I- 131 RAI therapy is a well-studied therapy modality which shows high complete response rate all over the world(11) .According to various research works the response of the therapy is dependent on factors which are associated to the patients characteristics ,the surgical management type and quality ,which is assessed by remaining thyroid tissue ,and other factors(23) .Because of this reason assessment of the response of the patients to the given therapy has to be assessed and treatment guideline or protocol has to be developed. Since the above described factors result in a discrepancy in treatment outcome between various treatment centers throughout the world, treatment guideline which best suit the treatment center is crucial. And in order to develop a protocol a study which deals with patients who got treated in the same center is important. In this study, we assess the complete response rate for the given therapy and factors which have negative impact to the outcome of patients was assessed.

In our study, complete response rate was found to be 88% which is comparable with study done in Turkey, showing 86% excellent response rate, which was done in low risk thyroid ca patients .In this Turkish study, the dose given to this low risk patient was high dose (100mci) for all of the patients taking the treatment(13), in our study the dose given to the low risk patients was comparable with ATA guideline, but in some of patients increased RAI was given based on assessment of patient surgical condition. This high compete response rate was also seen in a study done in Pakistan which shows effective rate of 87.7
%(19).

In another study in USA ,which was done for the assessment of successful ablation rate, it shows51%-94% success rate with pooled successful ablation rate of 71 %(12).In our study the result is comparable with the finding in this study ,but since there was limitation of data completeness especially in high risk patients(15 patient from total of 159 patients had incomplete data ,majority being high risk patients)estimation of effectiveness in high risk patient is compromised but still majority of patients having intermediate risk and low risk has high success rate.

Similarly, in one Saudi Arabian study, which assesses the effectiveness of the treatment with regard to overall survival and progression free survival ,it shows the prognosis was negatively influenced by the male gender, age ≥55, ATA high-risk category, and TNM metastatic status (17).This was also evidenced in our study , male gender ,ATA high risk category evidenced by higher stage (metastatic)disease ,who took high RAI dose for having high risk features ,who have lymph node involvement ,and those patients having higher baseline thyroglobulin level have lower outcome for the therapy but the only independent associated factor found to result lower complete response rate was having high base line Tg level (>10ng/dl).

Majority of patients who have lower stage disease, younger age group, female sex, lower baseline tg level and those patient who has no lymph node involvement has better complete response rate.

Patient who have lower baseline Tg level which is <10ng/ml has good complete response rate (94%) but those patients whose baseline Tg level >10ng/ml has significantly lower (47%) complete response rate. This result is also the same with one Iranian study which was done to assess predictive factor for incomplete response, it shows having higher baseline Tg level >15ng/ml is associated with higher incomplete response rate (18).

Even though those patient who had lymph node involvement had higher response rate (91%) than those who have lymph node positive disease, still the compete response rate is high (78%)for lymph node positive diseased patients.

The complete response rate of the patient who underwent different type of surgery between total thyroidectomy without lymph node dissection and with lymph node dissection was not significant but those patient who has lobectomy has lower complete response rate.

In another Egyptian study which assessed the effectiveness of the treatment with regard to overall survival, RAI lowered adverse events and it preserved a good standard of living and improved overall survival (20). .In our study ,the number of patients who had metastatic disease was small (4) and out of these patients 2 had incomplete data ,but the other 1 patient showed significant improvement in Tg and antiTg level ,which was initially very high ,in thousands ,and after 3-4 yr. follow-up it become <100ng/ml,which shows the effectiveness of the treatment .But because of the above described limitation of the study in metastatic patient ,and since assessment and evaluation of metastatic thyroid cancer is different than that

of other low and intermediate thyroid ca patient ,separate study which solely study metastatic patients with the measure of overall survival and disease progress free survival is needed.

Our study also showed most of patients responded to 1 cycle of RAI and majority of them responded within 2 years of treatment (82.6%), of those patient who took the treatment twice, most of them responded to the treatment. Even though the RAI dose vary based on the patient condition, majority of them were treated with dose less than 100 mci (69.2%) and responded well. But, since the dose depend on the patient risk category, deep analysis of different range of dose for same risk category has to be done in order to objectively assess the effective range of dose for specific risk type of patients. In this study we tried to

evaluate patients' response based on their different demographic, surgical management and disease pathological characteristic for the given dose of RAI, which can be used as source of information for more personalized treatment planning

.

7. Limitation and strength of the study

Since the study was retrospective study and medical chart review was done to collect data, and there was chart incompleteness. In addition to this, some of the patients discontinue their follow-up in the middle and majority of them were -metastatic thyroid ca patients, who had lymph node involvement and other high risk features, so this would limit the study complete analysis of patients who had high risk thyroid cancer. The other limitation is, since all patients are post-surgical patients, and evaluation of complete response rate of patients who were unfit for surgery and took RAI was not possible.

Despite the limitation, since there is no research, i.e. to our knowledge, which assesses the complete response rate of RAI treatment and the factors which negatively affect the complete response rate in Algeria, it will help to develop more personalized treatment approach and protocol development which could be best suited for the patients who are going to be treated in the center.

8. Conclusion and recommendation

Thyroid cancer is one of commonest endocrine tumor which has increasing incidence rate, making it to be one of the top 10 cancers in women worldwide. Unlike majority cancers, thyroid cancer has good prognosis if treated well.

This study shows that the complete response rate of low and intermediate risk patient was high and the only independent associated factor which is found to have negative predictive factor for the complete response rate is having high base line thyroglobulin level. Because of the aforementioned limitation, i.e. incomplete data for high risk patients, assessment and conclusion of complete response rate for high risk patient was not possible.

In order to achieve high complete response rate, appropriate RAI dose has to given based on the patient disease characteristics and the type and quality of surgery undertaken. Different facility whether in developed, developing or high middle income
/emerging country, all has different response to the RAI dose based on the associated factors that the patient has. In addition to this Sociodemographic characteristics of patients, factors associated to facility practice and patient disease characteristics affect the outcome of the patient response. So, we recommend, in order to have higher complete response rate, developing treatment protocol which best suit the therapy center and which consider patient baseline thyroglobulin level would be beneficial.

We recommended the nuclear medicine department to work on further research in this area, which is going to be helpful for the development of thyroid cancer RAI treatment
protocol which is going be used in treatment center.

References

1. World Health Organization (WHO) https://www.who.int › Publications › m › item, Non communicable diseases Algeria 2018 country profile

2. National Institute of Public Health (Algeria). Algeria - Algiers Cancer Registry Report2006. Alger, Algeria: National Institute of Public Health (Algeria).

3. Wang X, Zhu J, Li Z, Wei T. The benefits of radioactive iodine ablation for patients with intermediate-risk papillary thyroid cancer. PLoS One. 2020 Jun 15;15(6):e0234843. doi: 10.1371/journal.pone.0234843. PMID: 32542018; MCID: PMC7295195.

4. Mettler, Fred A., and Milton J. Guiberteau: *Essentials of Nuclear Medicine and Molecular Imaging*. 7th edition. Philadelphia, PA: Elsevier; 2019 **https://nls.ldls.org.uk/welcome.html?ark:/81055/vdc_100064933823.0x000001.**

5. Pham BN, Jorry R, Abori N, Silas VD, Okely AD, Pomat W. Non-communicable diseases attributed mortality and associated sociodemographic factors in Papua New Guinea: Evidence from the Comprehensive Health and Epidemiological Surveillance System. PLOS Glob Public Health. 2022 Mar 25;2(3):e0000118. doi: 10.1371/journal.pgph.0000118. PMID: 36962128; PMCID: PMC10021879.

6. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024 May-Jun;74(3):229-263. doi: 10.3322/caac.21834. Epub 2024 Apr 4. PMID: 38572751.

7. Al-Muftah M, Al-Ejeh F. Cancer Incidence and Mortality Estimates in Arab Countries in 2018: A GLOBOCAN Data Analysis. Cancer Epidemiol BiomarkersPrev. 2023 Dec 1;32(12):1738-1746. doi: 10.1158/1055-9965.EPI-23-0520.PMID: 37733340; PMCID: PMC10690144

8. Benouis, A. & Bekkouche, Z. & Merad, M.s & Loudjedi, L. & Khelil, H. & Berber, N.. (2017). Thyroid Cancer in Western Algeria: Histopathological and Epidemiological Study.Journal of Cancer Therapy. 08. 672-682. 10.4236/jct.2017.87058

9. Pizzato M, Li M, Vignat J, Laversanne M, Singh D, La Vecchia C, Vaccarella S. The epidemiological landscape of thyroid cancer worldwide: GLOBOCAN estimates for incidence and

mortality rates in 2020. Lancet Diabetes Endocrinol. 2022 Apr;10(4):264-272. doi: 10.1016/S2213-8587(22)00035-3. Epub 2022 Mar 7. PMID: 35271818.

10. Benouis, A. & Bekkouche, Z. & Merad, M.s & Loudjedi, L. & Khelil, H. & Berber, N.. (2017). Thyroid Cancer in Western Algeria: Histopathological and Epidemiological Study. Journal of Cancer Therapy. 08. 672-682.10.4236/jct.2017.87058

11. Beierwaltes WH. The treatment of thyroid carcinoma with radioactive iodine. Semin Nucl Med. 1978 Jan;8(1):79-94. doi: 10.1016/s0001-2998(78)80009-9. PMID: 345448.

12. Klain M, Nappi C, Zampella E, Cantoni V, Green R, Piscopo L, Volpe F, Manganelli M, Caiazzo E, Petretta M, Schlumberger M, Cuocolo A. Ablation rate after radioactive iodine therapy in patients with differentiated thyroid cancer at intermediate or high risk of recurrence: a systematic review and a meta-analysis. Eur J Nucl Med Mol Imaging. 2021 Dec;48(13):4437- 4444. doi: 10.1007/s00259-021-05440-x. Epub 2021 Jun 18. PMID: 34142215; PMCID: PMC8566414

13. Bilgic S, Meral R, Sağer MS, Sönmezoğlu K. RAI therapy in low-risk papillary thyroid cancer: recurrence reduction and long-term outcomes in the Turkish population. BMC Cancer. 2024 Oct 14;24(1):1273. doi: 10.1186/s12885-024-12986-0. PMID: 39402494; PMCID: PMC11475254.

14. Gómez-Pérez AM, García-Alemán J, Molina-Vega M, Sebastián Ochoa A, Pérez García P, Mancha Doblas I, Tinahones FJ. Efficacy of Low-Dose Radioiodine Ablation in Low- and Intermediate-Risk Differentiated Thyroid Cancer: A Retrospective Comparative Analysis. J Clin Med. 2020 Feb 21;9(2):581. doi: 10.3390/jcm9020581. PMID: 32098039; PMCID: PMC7074446 .

15. Li C, Wu Q, Sun S. Radioactive Iodine Therapy in Patients With Thyroid Carcinoma With Distant Metastases: A SEER-Based Study. Cancer Control. 2020 Jan-Dec;27(1):1073274820914661. doi: 10.1177/1073274820914661. PMID: 32292051; PMCID: PMC7160783.

16. Seo GH, Kong KA, Kim BS, Kang SY, Moon BS, Yoon HJ, Kim HO. Radioactive Iodine Treatment for Children and Young Adults with Thyroid Cancer in South Korea: A Populationbased Study. J Clin Endocrinol Metab. 2021 Jun 16;106(7):e2580-e2588. doi: 10.1210/clinem/dgab192. PMID: 33755732.

17. Al-Ibraheem A, Al-Rasheed U, Mashhadani N, Abdlkadir AS, Al-Adhami DA, Ruzzeh S, Istatieh F, Mansour A, Hamdan B, Kheetan R, Al-Shatti M, Mohamad I, Juweid ME, Abu Sheikha A, Al-Rabi K, Sykiotis GP, Kreissl MC, Ismael T, Sultan I, Abdel-Razeq H. Long-Term Survival Analysis and Prognostic Factors of

Arabic Patients with Differentiated Thyroid Carcinoma: A 20Year Observational Study at the King Hussein Cancer Center (KHCC) Involving 528 Patients. Cancers (Basel). 2023 Aug 15;15(16):4102. doi: 10.3390/cancers15164102. PMID: 37627130; PMCID: PMC10452119

18. Keshavarzi A, Alaei-Shahmiri F, Fallahi B, Emami Z, Malek M, Khamseh ME. Predictors of response to Radioactive Iodine Therapy in Intermediate and high risk patients with papillary thyroid carcinoma. BMC Endocr Disord. 2024 Jul 15;24(1):112. doi: 10.1186/s12902-024-01648-8. PMID: 39004697; PMCID: PMC11247765.

19. Rumman, Mysara & Sabarna, Khaled. (2021). The Radioactive Iodine I-131 Efficiency in Thyroid Cancer Treatment At Al-Ahli Hospital, West Bank-Palestine.
10.13140/RG.2.2.29266.07365

20. Walaa Asaad Faheem Abd El Rahman, Hanem Abdel Fattah Sakr, Azza Elsaid Abdel Naby, Sherif Mahmoud Elhadidy, The Effectiveness of Radioactive Iodine for Treatment of Well Differentiated Thyroid Carcinoma with Distant Metastases (10 Years Study), The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90 (2), Page 3695-3702.

21. Eilsberger F, Kreissl MC, Reiners C, Holzgreve A, Luster M, Pfestroff A. Application of the American Thyroid Association Risk Assessment in Patients with Differentiated Thyroid Carcinoma in a German Population. Biomedicines. 2023 Mar 15;11(3):911. doi: 10.3390/biomedicines11030911. PMID: 36979890; PMCID: PMC10045624.

22. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016 Jan;26(1):1-133. doi: 10.1089/thy.2015.0020. PMID: 26462967; PMCID: PMC4739132.

23. Cancer Tomorrow tool.

International Agency for Research on Cancer.

24. World Health Organization; 2023.cancer fact sheet

25. Cancer Epidemiol Biomarkers Prev (2016) 25 (1): 3–5 Freddie Bray, International Agency for Research on Cancer, https://doi.org/10.1158/1055- 9965.EPI-15-1109

ANNEXES

Table 1 -Thyroid ca patient risk category according to American Thyroid Association (3)

Patients With Low Risk	○ individuals with papillary carcinoma who have undergone a gross total thyroidectomy without distant metastases, lymph node involvement, invasion of adjacent structures or blood vessels, or aggressive histology,lack RAI uptake outside the thyroid bed, palpable lymph nodes, and pathological nodal micrometastases. ○ Other low-risk conditions encompass the encapsulated intrathyroidal follicular variant of papillary thyroid cancer and well-differentiated intrathyroidal follicular carcinoma with capsular invasion, whether or not fewer than 4 foci of vascular invasion are present.
Patients With Intermediate Risk	○ Who have aggressive histology types such as Hurtle cell cancer, follicular thyroid cancer, columnar cell or tall cell variants, and insular carcinoma. ○ individuals with multifocal papillary micro carcinoma exhibiting extra thyroidal extension and patients with clinically positive lymph nodes less than 3 cm in the largest dimension or more than 5 pathologically positive lymph nodes less than 3 cm in the largest dimension.

Patients With High Risk	High-risk patients include those with incomplete resection, gross extra thyroidal extension, pathologically positive lymph nodes where at least 1 is greater than 3 cm in the largest dimension, distant metastasis, and follicular carcinoma with more than 4 foci of vascular invasion.

ANNEX 2

1. Data collecting format for DTC thyroid cancer patient who took RAI treatment

I. Demographic characteristics of the patient

1. Age -1. <20 2. 21-30 3. 31-45 4. 46-60 5.>60

2. sex 1. female 2. male

4. Type of DTC 1 papillary. 2. Follicular 3. Other variant of differentiated thyroid ca

5. Stage A. stage 1 B. stage 2 C. stage 3 D. stage 4.

6. Lymph node status 1. Involved 2. not involved

7. Metastasis 1. Yes 2.no

8. If metastatic to where 1. Lung 2. Bone 3. brain 4. other 5. multiple site

9. Management taken, surgical management A.Total thyroidectomy Lobectomy Near total thyroidectomy D. debunking E.Not done

10. Duration taken to achieve complete response rate 1. 6 months 2. 6 months to 1 year
3. 1 year to 2 years 4. >2 years

11. Cumulative RAI dose 1.30-50 2. 51-100 3.101-150 4.151-200 5.>200

12. Response to RAI treatment 1. Complete response 2. indeterminate response 3. biochemical incomplete response 4. structural incomplete response

13. Total number of RAI given 1. once 2 .2 times 3.3 times 4. more