Research Article

Treatment, Clinicopathologic Patterns, and Survival of Patients Diagnosed with Thyroid Carcinoma at Tikur Anbessa Specialized Hospital Radiotherapy Unit, Addis Ababa, Ethiopia: A Retrospective Cohort Study

Abstract

Background: Thyroid carcinoma is the most common malignancy of the endocrine system, with a steadily increasing global incidence over the past three decades. According to the Addis Ababa City Cancer Registry, it is the seventh most common cancer among women. This study aimed to describe the treatment patterns, clinicopathologic features, and survival outcomes of patients diagnosed with thyroid carcinoma in Ethiopia. Materials and Methods: A retrospective cohort study was conducted involving 118 patients diagnosed between January 2016 and June 2019 at the Radiotherapy Unit of Addis Ababa University Hospital. Survival data were collected through telephone interviews. The coprimary endpoints were median survival time and associated prognostic factors.

Results: The majority of patients were female (68.6%). Papillary thyroid carcinoma (PTC, 49.2%) and Follicular Thyroid Carcinoma (FTC) were the most common histologic subtypes. Among 74 patients with Differentiated Thyroid Carcinomas (DTCs) who had an indication for radioactive iodine (RAI) therapy, only two received it. The median survival time was 41 months. Kaplan-Meier survival analysis showed that the absence of surgery, advanced T stage, and Anaplastic Thyroid Carcinoma (ATC) histology were significantly associated with reduced survival (Mantel-Cox p-values: 0.006, 0.002, and 0.041, respectively).

Conclusions: PTC and FTC are the predominant histologic subtypes of thyroid carcinoma in Ethiopia. Limited access to RAI therapy represents a significant gap in care. Poor survival was associated with lack of surgery, advanced tumor stage, and ATC histology. Efforts to improve early detection, access to high-quality thyroid surgery, and establishment of nuclear medicine facilities are urgently needed in Ethiopia.

Keywords: Thyroid Carcinoma, Retrospective Cohort Study, Survival Time, Ethiopia, Africa.

Introduction

Thyroid Carcinoma (TC), the most common cancer of the endocrine system, occurs two to three times more frequently in women than in men and is the fifth most commonly diagnosed malignancy among women globally, accounting for 5.1% of new cancer cases [1]. While the incidence of many malignancies is declining in the Western world, the incidence of TC has continued to rise globally over the past three decades—except in Africa, where detection may be inadequate [2]. Despite the rising incidence, TC-related mortality has remained stable at approximately 0.5 deaths per 100,000 individuals [3]. Thyroid cancers include Papillary Thyroid Carcinoma (PTC), Follicular Thyroid Carcinoma (FTC), and Hürthle Cell Carcinoma (HTC), collectively classified as Differentiated Thyroid Carcinomas (DTCs), along with Medullary Thyroid Carcinoma (MTC) and Anaplastic Thyroid Carcinoma (ATC). In the United States, PTC accounts for 89.8% of all thyroid malignancies, followed by FTC (4.5%), MTC (1.6%), and ATC (0.8%) [4]. In Sub-Saharan Africa, studies report PTC in 59.6% of female patients with thyroid cancer—an unexpected finding given the region's high prevalence of iodine deficiency, which is typically associated with increased FTC rates [5]. In Ethiopia, national-level data on thyroid carcinoma incidence are lacking. However, according to the Addis Ababa City Cancer Registry, TC is the seventh most common cancer among women [7]. A study conducted in Gondar, northwest Ethiopia, found that PTC was the most frequent subtype, although FTC accounted for 29% of cases-significantly higher than reported in more developed countries—likely reflecting endemic iodine deficiency [7]. Differentiated thyroid carcinomas (DTCs) generally have a favorable prognosis, whereas ATCs are highly aggressive, with disease-specific mortality nearing 100% [8]. Poor prognostic factors related to the patient include older age (>40 years) and male sex [8-10], while tumor-related factors include histologic type, tumor size, local invasion, necrosis, vascular invasion, BRAF V600E mutation status, and the presence of metastasis

> Citation: Bezabih SH, Tigeneh W, Kantelhardt EJ. Treatment, Clinicopathologic Patterns, and Survival of Patients Diagnosed with Thyroid Carcinoma at Tikur Anbessa Specialized Hospital Radiotherapy Unit, Addis Ababa, Ethiopia: A Retrospective Cohort Study. Collect J Oncol. Vol 2 (1) 2025; ART0079.

OPEN ACCESS

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Received Date: 09 Apr 2025 Accepted Date: 16 May 2025 Published Date: 24 May 2025

Citation:

Bezabih SH, Tigeneh W, Kantelhardt EJ. Treatment, Clinicopathologic Patterns, and Survival of Patients Diagnosed with Thyroid Carcinoma at Tikur Anbessa Specialized Hospital Radiotherapy Unit, Addis Ababa, Ethiopia: A Retrospective Cohort Study. Collect J Oncol. Vol 2 (1) 2025; ART0079.



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[11]. Among DTCs, FTC and HTC with vascular invasion are more aggressive than PTC [12,13]. Tumor size and local invasion are particularly important; small (<1.5 cm) tumors confined to the thyroid rarely metastasize distantly, while tumors with local invasion are associated with a twofold increase in recurrence and are the cause of death in up to 33% of cases [15]. Distant metastasis remains the leading cause of death in both PTC and FTC, with patient age, metastatic site, and iodine-131 (¹³¹I) uptake being key prognostic indicators [14-16]. Surgical resection remains the cornerstone and most critical component of thyroid carcinoma management. In a study conducted at the Mayo Clinic Cancer Center, patients with an AGES score of 4 or higher had poorer survival outcomes when treated with lobectomy alone compared to those who underwent bilateral resection [17]. Postoperative administration of Radioactive Iodine (RAI) therapy with Iodine-131 has been shown to reduce recurrence and disease-specific mortality in patients at intermediate or high risk in several studies [9,18-21]. Additionally, Thyroid Hormone Suppressive Therapy (TST) with levothyroxine has been associated with decreased recurrence rates and improved cancer-specific survival [18,22,23]. Thyroid carcinoma is the seventh most common malignancy in Ethiopia, according to data from the Addis Ababa City Cancer Registry. Ethiopia, a country in East Africa with a population exceeding 100 million, treats numerous thyroid cancer patients across various hospitals. Tikur Anbessa Specialized Hospital (TASH) serves as the main referral center, where many patients undergo surgery and are referred to the radiotherapy unit for follow-up, adjuvant treatment, or palliative care. Adjuvant treatment options for Differentiated Thyroid Carcinomas (DTCs) typically include TST and RAI therapy. However, RAI is currently unavailable in Ethiopia, and radiotherapy is often used as a palliative measure rather than a definitive treatment. This study describes the treatment modalities and clinicopathologic patterns of thyroid carcinoma in Ethiopia. It is the first to report survival outcomes and prognostic factors among thyroid cancer patients in the country and also highlights the critical gap in adjuvant care—specifically, the unavailability of RAI therapy for patients with DTCs.

Methods and Materials

Study design, area and setting

This is a retrospective cohort study conducted in Tikur Anbessa Specialized Hospital Radiotherapy center between January 2016-June 2019 G.C. It was established in 1998 with the help of International Atomic Energy Agency (IAEA), and currently has two Cobalt-60 Teletherapy units one out of order since the past few years and one HDR Brachytherapy unit and a LINAC on installation process. The hospital consists of several general surgeons who are capable of performing various thyroid surgeries as well as one endocrine surgeon who constantly engages in multi-disciplinary discussion in patients with thyroid carcinoma. Eight full time consultant oncologists, three medical physicists and five radiotherapists are currently working in the radiotherapy center. The center has started training of clinical oncology in 2013 and currently 41 residents are enrolled. Activities include inpatient admission for chemotherapy, radiotherapy treatment and outpatient clinics for new patient evaluation and follow-ups.

Population

All patients with newly diagnosed thyroid cancer that were registered at the radiotherapy unit of Tikur Anbessa hospital between January 2016-June 2019 G.C were eligible for this study.

Exclusion criteria

Patients whose phone number was not available on the patient medical record chart for contacting the patient or his relatives was excluded from the study. In addition, those patients who cannot be reached out on three repeated phone calls over seven consecutive days are excluded from survival analysis.

Sample size and sampling procedure

HMIS logbooks was used to identify all cases of thyroid cancer that were documented after evaluation at the radiotherapy unit. And every case that fulfilled the inclusion criteria was included in the study. In the current study a total of 118 patients with pathologically confirmed thyroid carcinoma patients were identified from January 2016 to June 2019 and included in this study.

Operational definitions

T stage – refers to the size of the tumor at presentation (T ≤ 2 cm, T2 > 2cm but ≤ 4 cm, T3 > 4cm or gross extrathyroidal extension invading only strap muscles, T4 gross extrathyroidal extension beyond the strap muscles) [24].

N stage – refers on lymph node status based on the pathologic report of the submitted specimen (N0 no evidence of regional lymph node metastasis, N1 metastasis to regional nodes) [24].

Metastatic disease (M1) - the presence of the disease outside of the remnant thyroid and regional lymph nodes at presentation or follow-up [24].

Variables

Rscope

The dependent variables were time to death due to thyroid cancer measured in months. Accordingly, those patients died were events and those who were alive were censored. The explanatory variables were sociodemographic factors (age, sex), surgery-related factors (type of surgery, history of surgery, vascular invasion, capsular invasion), and tumor-related factors (T stage, N stage, metastasis, pathological subtypes, adjuvant Thyroxine, serum TSH level, post operation serum thyroglobulin level).

Data collection tools and procedures

Medical record charts were collected based on the HMIS record and all the cards that were not in accordance with the inclusion criteria were returned by the primary investigator/supervisor. The supervisor discussed the goal and purpose of the study as well as the questionnaire with the other data collectors. The data collectors filled sample/pilot charts together so that there was common understanding as well as interpretation of the parameters and data. There were regular meetings with primary investigator/supervisor and data collectors concerning the process.

Data management and quality assurance

The principal investigator gave training on the relevance of the study and standard operating procedures to the data collectors; followed closely the data collection procedures and kept hard copy of the completed forms in a protected place. During telephone call of patients' detail information was asked and efforts were made to get quality data by approaching the respondents in good manner. To avoid overstated loss to follow up and to decrease non response rate, telephone calling was made repeatedly three times per day for 7 consecutive days.

Data analysis

Data was entered, cleaned and analyzed using SPSS version 22. The main findings were described by using mean, median, frequencies, percentages, tables and graphs. COX Regression Model and Log rank (Mantel-Cox) was used to assess explanatory variables significantly associated with outcome variable. In multivariable analysis variables with P value < 0.05 were considered as statistically significant and median overall survival was calculated by Kaplan Meier method.

Ethical consideration

Ethical clearance was obtained from the Ethical review board of Addis Ababa University College of Health Sciences (AAU CHS). During telephone call, verbal consent was obtained from each participant prior to data collection. Each participant was informed about the aim of the study as it contributes necessary information for the study and their permission was asked to give the response.

Results

Demographic characteristics

A total of 118 patients with pathologically confirmed thyroid carcinoma patients were identified from January 2016 to June 2019 and included in this study. Majority of the study participants were female 81 patient (68.6%) and about 74 patients (62.7%) of them were in 21-55 years of age interval with a mean age of 47.8 years (\pm 14.9 SD) followed by age above 55 with 44 patients (33.9%). Most 41(33.6%) of the study participants were from Addis Ababa followed by Oromia 40(32.8%) (Table 1).

Descriptive statistics of presentation and risk factors

From a total of 118 patients, about 88(72.10%) of study participants had history of goiter and only 3 patients had history of irradiation to the neck or chest wall. For almost all 118 (99.2%) of the respondents the nodule was not detected by ultrasound. Only 8(6.6%) of the study participants had history of previous surgery for benign thyroid disease and about 35(28.7%) of the study participants were suffering from shortness of breath at presentation. Similarly, about 25(20.5%) of study participants had history of dysphagia at presentation. On 29(23.8%) individuals, hoarse of voice at presentation occurred and obesity and family history of thyroid malignancy was not found at all in the study (Figure 1).

Surgical and clinicopathologic characteristics

Clinical and surgical characteristics

51(43.2%) of patients had T4 lesion followed by T3 lesion in 19 patients (16.1%). T1 and T2 lesions combined occurred in 17 patients (14.3%) while unknown or unassessed tumor size (Tx) and recurrent lesions occurred in 20 patients (16.8%) and 11 patients (9.2%), respectively. For 63 patients (53.4%) surgery was not done at all while the type of thyroidectomy was not identified for 21 patients (17.8%). Subtotal thyroidectomy was the commonly performed thyroidectomy among patients for whom the type of surgery was specified. It was done in 18 patients

Table 1: Demographic characteristics of patients diagnosed with thyroid carcinoma at Tikur Anbessa Specialized Hospital, radiotherapy unit.

Variable	Category	Frequency	Percentage
Sex	Female	81	68.6
	Male	37	31.4
Age	less than 20	4	3.4
	21-55	74	62.7
	More than 55	40	33.9
Region	Addis Ababa	41	33.6
	Somalia	1	0.8
	Tigre	3	2.5
	Afar	0	0.0
	Amhara	30	24.6
	SNNPR	6	4.9
	Harari	1	0.8
	Oromia	40	32.8

Table 2: Clinical and surgical characteristics of patients diagnosed with thyroid carcinoma at Tikur Anbessa Specialized Hospital, radiotherapy unit.

Variable	Category	Frequency	Percent
T stage	T1 and T2	17	14.3
	Т3	19	16.0
	T4	51	42.9
	ТХ	20	16.8
	Recurrent	11	9.2
Type of surgery	Total thyroidectomy	10	8.5
	Subtotal thyroidectomy	18	15.3
	Lobectomy	1	0.8
	Debulking	2	1.7
	Unspecified type of thyroidectomy	21	17.8
	Not done	63	53.4
	Lobectomy and Isthmesectomy	3	2.5
Lymph node dissected	yes	4	3.4
	no	27	22.9
	Not known	23	19.5
	Surgery not done	64	54.2
Metastasis at first presentation	Yes	45	38.1
	No	73	61.9

(15.3%) and 10 patients (8.5%) had total thyroidectomy. Lobectomy alone was done in only 1 patient while lobectomy plus isthmesectomy was done 3 patients. Debulking was done in 2 patients. Lymph node dissection was done in only 4 patients of the entire cohort. About 45 patients (38.1%) had metastatic disease at first presentation. The most common site of metastasis were the lungs followed by the bone (Table 2).

Histopathologic characteristics

About 86 patients (72.9%) had differentiated thyroid carcinoma. Among the DTCs; PTCs and its variants that includes papillary microcarcinoma, follicular variant PTC and Hurthle cell variant PTC occurred in 58 patients (49.16%), while patients with FTC and HCC were 28 (23.7%). Undifferentiated anaplastic thyroid carcinomas and poorly differentiated thyroid carcinomas occurred in 16 patient (13.6%) and 10 patients (8.5%) respectively. Capsular invasion was reported on 19 patients (37.3%) out of the 51 patients for whom it ought to be; and 11 patients had capsular invasion, while vascular invasion was reported in 6 patients out of 51 patients and 5 of them had positive vascular invasion (Table 3).

Table 3: Histopathologic characteristics of patients diagnosed with thyroid carcinoma at Tikur Anbessa Specialized Hospital, radiotherapy unit.

Variable	Category	Frequency	Percent
Histology	Papillary thyroid cancer	55	46.61
	Papillary micro carcinoma	1	0.85
	Follicular variant	1	0.85
	Hurthle cell variant	1	0.85
	Follicular thyroid cancer	21	17.80
	Hurthle cell cancer	7	5.93
	Medullary thyroid cancer	3	2.54
	Anaplastic thyroid cancer	16	13.56
	Poorly differentiated thyroid cancer	10	8.47
	Carcinoma/fibrosarcoma/suspicious of SCC	3	2.54
Capsular invasion	Yes	11	9.3
	No	8	6.8
	Not reported	32	27.1
	Not applicable (surgery not done)	67	56.8
Vascular invasion	Yes	5	4.2
	No	1	0.8
	Not reported	45	38.1
	Not applicable (surgery not done)	67	56.8

 Table 4: Prognostic factors of survival time for thyroid carcinoma patients.

Variables	Status		Kaplan Meier Log-rank (Mantel-Cox)		
Variables	Alive n= 86	Death n=32	χ^2	df	р
Female	63()	18	1.31	1.00	0.25
Male	23()	18	1.51	1.00	0.23
Age	23()	14			
Less than 20	2	2	0.08	2.00	0.96
21-55	53	21	0.00	2.00	0.00
More than 55	32	9			
T stage	02				
T1 and 2	17	0	16.59	4.00	0.002
T3	13	6			
Τ4	29	22			
Tx (unknown)	18	2			
Recurrent	9	2			
Histology group		1	1		1
Differentiated thyroid carcinoma	29	18	8.27	3.00	0.041
Medullary	3	0			
Anaplastic	7	9			
Poorly differentiated carcinoma	5	5			
Subtypes of DTCs (n=32)		1			
Papillary	19	0	7.757	5	0.170
Follicular variant	1	0			
Follicular	6	3			
Hurthle cell	3	0			
Type of surgery					
Total thyroidectomy	10	0	18.12	6.00	0.006
Subtotal thyroidectomy	15	3			
Lobectomy	1	0			
De bulking	2	0			
Unspecified type of thyroidectomy before 7 years	16	5			

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Not done	39	24			
Lobectomy and Isthmesectomy	3	0			
Vascular Invasion			· · ·		
Yes	3	2	19.35	3	0.00
No	1	0			
Not supported	36	9			
Not applicable	48	19			
Capsular Invasion		1			
Yes	7	4	17.35	3	0.001
No	8	0			
Not supported	22	10			
Not applicable	49	18			
Metastasis at first presentation					
Yes	17	14	0.88	1	0.35
No	38	18			

Survival

Survival status was successfully confirmed via telephone for all 118 patients included in the cohort. A total of 32 patients (27.1%) had died, with a 95% confidence interval (CI) of 17.1% to 36.8% (Figure 2). The median survival time was 41 months (Interquartile Range [IQR]: 36–60 months). Histologic subtype, absence of surgery, and T stage were found to significantly affect patient survival time. However, factors such as sex, age, DTC subtypes, presence of metastasis at diagnosis, and TSH suppression levels were not significantly associated with survival. Kaplan-Meier survival analysis showed that patients who did not undergo surgery had significantly shorter survival times, with a log-rank (Mantel-Cox) p-value of 0.006. Histologic subtype was also significantly associated with survival (p = 0.041), as was T stage (p = 0.002). While vascular and capsular invasion were initially found to be statistically significant, further analysis was limited. Many patients either did not undergo surgery or had pathology reports that did not assess or mention vascular and/or capsular invasion. A separate analysis including only patients with documented presence or absence of vascular and capsular invasion showed no significant difference in survival time, with p-values of 0.17 and 0.85, respectively (Table 4).

Patients with DTC had better survival time than poorly differentiated carcinoma and ATC. MTC fared best. From the multiple comparisons, there was a significant difference between differentiated thyroid carcinomas and anaplastic thyroid cancer by average survival time difference of 7 months which was longer in differentiated thyroid carcinomas with a P-value of 0.007. Similarly, there was also a significant survival time difference between ATC and MTC with 10 months longer survival time in patients with medullary thyroid carcinoma with a P-value of 0.045. But there was no significant survival difference among the 3 variants of DTCs i.e. PTC, FTC, and HCC with a P-value of 0.17. (Figure 3) Patients with T4 lesion had significantly less survival time as compared to those patients in with smaller tumor size (T1 and T2 lesions) (Figure 4).

Discussion

Thyroid carcinoma incidence has increased in the western world over the last three decades mainly due to increased detection rates of smaller thyroid nodules with the use of frequent ultrasound [3,5]. The most common presenting manifestation in this study is a progressively enlarging anterior neck swelling (goiter) occurring in 72.1% of patients which might imply the presumed iodine deficiency in Ethiopia; no patient being identified on routine neck ultrasound and only 3 patients had previous history of irradiation to the neck or chest wall which is stated as the predominant risk factor in patients with PTC [17]. 38.1% of patients in this study had metastatic disease at presentation: the lungs and bone being the most common site of metastases with a frequency of 17% and 12% respectively in line with a meta-analysis by Ruegemer et al [25]. DTCs occurred in 75.4% of patients, among which patients with PTC predominated with 49.2% followed by FTC in 17.8% and HCC in 5.9% of patients in this study. This is very much lower than those reported in the U.S study, in which PTC accounted for ~90% of DTC cases [10], yet in comparison to studies done in sub-Saharan Africa where PTCs accounted for 59.6% and 45.2% of patients with DTC in Accra, Ghana and Gondar, Ethiopia respectively [13,15]. The rates of FTC were higher similar to other Sub-Saharan Africa studies compared to the western world possibly because of endemicity of iodine deficiency resulting in increment of TSH level, a major growth factor for thyroid follicular cells. The most important prognostic features in patients with DTCs apart from tumor histology (worse in FTC and HCC) are tumor size, local (capsular) invasion, necrosis, vascular invasion, BRAF V600E mutation status, and metastasis [11]. In the current study, out of 86 patients with DTC, majority (30 patients) presented with a T4 disease followed by T3 lesion and unknown tumor size (17 patients) in each). Only 16 patients presented with T1 and T2 disease in contrast to the study done by Mazzaferri et al [11]in which majority (972 out of 1114) of patients with DTC

presented with T1 or T2 lesions. In this study, ATCs occurred more frequently (13.6% of patients with thyroid carcinoma) compared to rates reported in other studies in the range of 1-3% [10,13]. This may be due to this study is conducted in a radiotherapy unit where more patients would be referred for palliative RT. There were 3 patients with medullary thyroid carcinoma (2.5%), which arises from parafollicular C cells of the thyroid gland accounting for 1.6% of thyroid carcinomas [10]. Surgery is the first and the most important management of thyroid carcinoma with various extent of thyroid resection based on tumor risk [26]. In the current study, any kind of surgery was not done in 53.4% of the patients due to the higher frequency of T4 lesions in the DTCs and the increased proportion of patients with ATCs. Unspecified type of thyroidectomy, subtotal thyroidectomy and total thyroidectomy were the 1st (17.8%), 2nd (15.3%) and 3rd (8.5%) most common types of surgery performed respectively. Lobectomy alone was done in only 0.8% of the patients which might be reasonable considering the infrequency of early lesions in this study unlike patients in the western world [27,28]. The death rates in patients with anaplastic and poorly differentiated thyroid carcinoma were 60% and 42.9% respectively which are lower than reported in other study that has a 100 % disease-specific mortality rate [29], yet significantly higher than patients with differentiated thyroid carcinomas with a significant p value of 0.007 but the difference in survival time between poorly differentiated and DTCs is not statistically significant. There was no significant survival difference among the subtypes of differentiated thyroid carcinomas (i.e. PTC, FTC or HCC) with a non-significant Log-rank p value of 0.17. And the survival time for PTC is generally good like those patients in the literature [10,18,30]. Patients with T4 lesions which imply local invasion directly into adjacent structures had less survival time than early lesion tumors in this study with a significant p value of 0.002. Tumor stage is one of the most important prognostic factors, and its influence on survival among papillary and follicular carcinomas increased when only thyroid carcinoma deaths were considered. In this study 74 patients were identified for whom RAI was indicated for the presence of T3 or T4 lesion, post-operative serum thyroglobulin level between 5 and 10 ng/ml, presence of capsular or vascular invasion, bulky nodal disease and presence of metastatic DTC but only 2 patients afforded to go abroad to get this treatment which is known to be an invaluable treatment modality for postoperative thyroid remnant and metastatic disease ablation [21]. In the current study a total of 71 patients with DTCs were put on TSH suppression therapy (thyroxine) and a simple linear regression result showed that as a dose of thyroxine increased by 1 microgram, the TSH will drop significantly by 0.083microU/L. Even though data are lacking on optimally suppressed level of a recommended target TSH level, a measure of < 0.05 was met in only 4.6% of patients who had TSH value determination for at least 50 % of their follow up period to compensate for possible laboratory and technical variations in TSH measurement across different lab centers in the country. But a mean TSH measurement of < 0.1 was met in 49.2 % of the patients and a measure < 1 was achieved in about 92% of patients. Since the proportions of patients with high risk DTCs in the current study is high, it would be reasonable to keep the serum TSH level as low as possible watching for potential levothyroxine toxicities simultaneously based on evidences from different literatures [22,23,31].

Limitations of the Study

The study is a retrospective cohort intrinsically exposed to biases from poor documentation, non-uniform patient evaluation, and missing patients from follow-up and it had a short follow-up period considering the special characteristics of patients with differentiated thyroid carcinoma who are known to live longer, unlike most cancers. The sample size is also small.

Conclusions

The health system of the country should strongly consider establishing a nuclear medicine treatment facility to have proper use of established diagnostic and therapeutic benefits from radioisotopes including the radioablative iodine therapy. A well-organized health informative registry system will help to document patients' health information enabling health professionals to do a long-term prospective cohort study which is the most widely used study design for studying outcomes of differentiated thyroid carcinomas.

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