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Follow-up protocol in differentiated thyroid cancer: Is repeated whole body Iodine scintigraphy necessary? "A 20 years review"

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Abstract

Introduction: Thyroid cancer follow up protocol has recently been reviewed globally, in this study; we present a 20 years descriptive retrospective study from a tertiary hospital.

Method: A total of 106 patients who met the inclusion criteria out of 287 patients treated with radioactive iodine post thyroidectomy for differentiated thyroid carcinoma were reviewed.

Result: There were 91 female and 15 male; M: F of 6:1. The mean age of the patients was 45 years (range: 16-81 years). Papillary thyroid cancer was the most common 58 (55%) then follicular 30 (28%), Hurthle cell 10(9%) and the mixed papillary- follicular 8 (8%) types. The mean ages of occurrence of papillary, follicular, Hurthle and Mixed papillary and follicular cancers were 40, 49, 53 and 49 years respectively More than half of the patients 58 (53.7%) had total thyroidectomy, while 36(34%), and 12(11.3%) patients had near total thyroidectomy and lobectomy respectively. The proportion of patients with negative whole body iodine scan after radioactive iodine ablation (RIA) increased progressively from 57 to 98%, 6-24 months of follow up. The mean iodine dose administered by the 1st 6 month of follow-up was 80mCi (range 30-200mCi) compared to total dose of 429mCi in patients that received multiple treatment (range 220-1160 mCi) At the end of first iodine treatment, 58 patients out 100 were Iodine scan negative. The remaining 42 patients became negative by the 4th treatment. Most patients had undetectable Tg level at 24 months, with a small proportion17 out of 51 (33.3%) with significantly elevated Tg among the Tg >2ng/ml group. Negative iodine scan and Tg level were concordant in 89 (72.1%) of the patients studied at 24 month and discordant in 12 (11.9%) patients. There was no tumour recurrence or rebound serum Tg up till the 24 month follow up period.

Conclusion: Repeated iodine scan is unnecessary in patients who are iodine negative with concordant serum Tg.

Keywords: *Differentiated thyroid cancer, follow up, radioiodine therapy, Iodine scan, review*

Résumé

Récemment, le cancer de la thyroïde suivant le protocole a été revu globalement dans cette étude, nous présentons 20 ans d'étude descriptive et rétrospective d'un hôpital tertiaire. Au total 106 patients qui obéissaient aux critères d'inclusion des 287 patients traits avec de l'idoine radioactive post thyroïdectomie pour des carcinomes de thyroïdes différenciés étaient revues. Ils y avaient 91 femelles et 15 males; M: F 6:1. La moyenne d'âge des patients était de 45 ans (variation: 16-81 ans). Le cancer de la thyroïde papillaire était le plus commun 58 des cas (55%) , suivi de cancer folliculaires 30 cas (28%), les cellules d'Hurtle 10(9%) et les types de follicules papillaires mixes 8 (8%). Les moyennes d'âge de la présentation des cancers papillaire, folliculaires, de Hurtle et de papillaire mixe étaient de 40, 49, 53 et 49 ans respectivement. Plus de la moitie des patients 58 (53.7%) avaient une thyroïdectomie, alors que 36(34%), et 12(11.3%) des patients avaient une thyroidectomie totale et lobectomie respectivement. La proportion des patients avec des résultats négatifs à l'iodine après ablation radioactive a l'iodine (ARI) qui augmentait progressivement de 57 à 98%, 6-24 mois de suivi. La dose moyenne d'iodine administrée dans les premiers 6 mois de sui était de 80mCi (Intervalle 30-200mCi) compare a la dose totale de 429mCi chez les patients qui recevaient multiple traitement (Intervalle 220-1160 mCi).A la fin du traitement à l'iodine, 58 patients sur 100 étaient des résultats négatifs. Le reste des 42 patients ne devenaient negative qu'au 4ieme traitement. Plusieurs patients avaient un taux non détectable de tg à 24 mois, avec une petite proportion de 17 des 51 cas (33.3%) avec un taux significatif élevé de tg >2ng/ml. Les taux d'iodine et de tg étaient concordants chez 89 (72.1%) des patients étudiés en 24 mois et étaient discordant chez 12 (11.9%) patients. Il n'y avait pas de tumeur récurrence ou le sérum Tg pendant les 24 mois de suivi. En conclusion, le scanner de reprise d'iodine n'est pas nécessaire chez les patients qui sont négative à l'iodine avec un taux de sérum Tg concordant.

Introduction

Long term follow-up in patients with differentiated thyroid cancer is mandatory because of lifelong risk of recurrence which could either be locoregional or less commonly distant metastasis [1].

The follow up management include a clinic follow-up with thyroglobulin (Tg) levels and a radioactive I-131(RAI) diagnostic scan months later.

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The follow-up scan and therapy is performed until all functioning tissue is ablated. The upper ceiling dose for cumulative RAI therapy is 37GBq (1Ci) although some authors claim there is no limit to this [2]. Bone marrow suppression is checked before further treatment with a full blood count and renal function test, impairment of which would indicate a lower dose [3]

Recently the management protocol incorporates the use of post ablative therapy whole body scan (WBS) 3-7 days after I-131 administration. The essence of this is to screen for any non-physiologic uptake outside the thyroid bed region that would suggest metastases. This procedure or even a measurement of thyroid uptake may however not be performed before I-131 treatment in patients in whom an experienced surgeon has performed a total thyroidectomy because it may diminish subsequent uptake of a therapeutic dose, an attribute referred to as "stunning effect" [4,5], However when limited surgery has been performed, it may be necessary to measure the neck uptake before treatment, as patients with thyroid uptake >5-15% should be considered for additional surgery [6].

Serum thyroglobulin (Tg) is used as a tumour marker after ablation of residual thyroid tissue. It measured on the day the ablative I-131 is to be administered. A low or undetectable serum Tg then generally predicts a favourable outcome or prognosis. Elevated values have questionable prognostic significance and may be related to persistent disease or lingering leakage from post surgical thyroid residues. It is a sensitive marker checked at each patient's follow-up visit with TSH suppressed with thyroxine replacement and off suppression to help detect functional metastases or recurrence. Serum Tg should be measured by an immunoradiometric assay with a functional sensitivity of 1ng/ml. Tg testing must be accompanied by a Tg antibody assay or by recovery testing. In the absence of this a falsely low or even undetectable values of Tg may be obtained in about 20% of cases with antiTg antibodies [7].

Thyroglobulin Elevated Negative Iodine Scan (TENIS) is a known clinical condition that could exist in a patient that has been treated with high dose radioactive I-131 for differentiated thyroid cancer. The causes of persistent elevated thyroglobulin are myriad but common causes are active thyroid cancer tissue that escaped ablation or a recurrence of malignant tissue. The initial type of surgery performed on the patient following diagnosis of thyroid cancer could also influence serum thyroglobulin (Tg) level post treatment RAI. Serum thyroglobulin is usually the best marker of residual or metastatic disease after treatment of differentiated cancer therefore discordance in serum Tg and diagnostic whole body imaging presents a diagnostic dilemma that warrants an aggressive search for the source of the elevated serum Tg. This study reviews the pattern of thyroid malignancy seen and the modality of follow up over a twenty year period of administering RAI-131 at Johannesburg hospital in South Africa.

Methods

This is a descriptive study based on a retrospective analysis of patients seen at the thyroid clinic of a Nuclear Medicine Department for the management of thyroid carcinoma. The data was analyzed using the SAS version 9 for analysis. Ethical approval was obtained for this study from the human research ethics committee of University of the Witwatersrand.

A total of 106 patients (91 female and 15 male) met the inclusion criterion of complete 24 months of follow up out of 287 patients treated with RAI-131 following thyroidectomy for differentiated thyroid cancer from 1986-2006. Default at any period before the 24 month and inadequate elevation of TSH or unavailable thyroglobulin result were used as exclusion criteria. The patients notes were reviewed to determine the age, gender, type of surgery +/- neck dissection, histopathologic type and the total dose of RAI used as well as the number of times each patient was treated. All the patients had either total, near-total thyroidectomy or lobectomy prior to the radioiodine therapy.

Ablative or repeated therapeutic doses were given to all patients 4–6 weeks after surgery. The dose ranged from 1.1 to 7.4GBq (30–200 mCi) of radioiodine. Serum TSH levels in all patients were above 30 IU/L at the time of ablation and/or therapy. After the ablation therapy, L-thyroxine suppressive therapy was initiated in all patients.

Routine follow-up examinations were performed 6 months after the ablation therapy. Serum Tg measurement and ^{131}I whole body scan (WBS) with 75–185 MBq of radioiodine were performed in all patients in the hypothyroid state. A negative ^{131}I WBS in conjunction with an undetectable serum Tg level was considered complete ablation. Patients were followed subsequently at 12, 24 and 60 months with physical examination and serum Tg measurement and whole body iodine scan on and off suppressive L-thyroxine therapy. An elevated serum Tg level or radioiodine accumulation on diagnostic-WBS or any other positive finding on bone scan was considered as evidence of disease. Patients in this category received further therapeutic doses of radioiodine. During the follow-up examinations, diagnostic WBS

was performed 72 h after oral administration of 74-185MBq of iodine-131. Serum Tg was measured using an immunoradiometric assay. Tg assay at the Johannesburg hospital before 1998 had the limit of detection of 10ng/ml, while from 1998 a new assay with a lower limit of detection of 2ng/ml was instituted. Serum Tg auto-antibody was also measured from all blood samples at the time of Tg measurement.

Result

The mean age of the patients studied was 45 years, age range (16-81 years). There were as many as 6 females to a male. The mean ages of incidence in papillary, follicular, Hurthle and mixed papillary / follicular cancers were 40, 49, 53 and 49 years respectively. Only the age of the patients with papillary cancer differed significantly from the other cancers (p=0.011).

Of the four histopathologic types of cancers, papillary thyroid cancer was the most common 58 (55%) then follicular 30 (28%), Hurthle cell 10(9%) and mixed papillary-follicular 8 (8%) Table 1.

Table 1: Demographic characteristics of patients studied N= 106

Patients		n	Percentage %
Gender	Female	91	(85.9)
	Male	15	(14.1)
Diagnosis	Papillary Ca	58 (51)	(54.7)
(Female n)	Follicular Ca	30 (22)	(28.3)
	Mixed	8 (8)	(7.6)
	Hurthle cell Ca	10 (10)	(9.4)
Surgery type	Total thyroidectomy	58	(53.7)
	Near total	36	(34.0)
	Lobectomy	12	(11.3)

Mean age (SD)44.62 (15.06)

More than half of the patients 58 (54.7%) had total thyroidectomy, while 36(34%), and 12(11.3%) patients had near total thyroidectomy and lobectomy respectively. Majority of the patients with papillary, follicular and Hurthle cell cancer had total thyroidectomy, except the mixed papillary / follicular group Table 2.

Table 2: Patients' diagnosis vs type of surgery

Diagnosis	Total thyroidectomy	Near total thyroidectomy	Lobectomy
Papillary (%)	35 (60.3)	15 (25.9)	8 (13.8)
Follicular (%)	14 (46.7)	13 (43.3)	3 (10)
Mixed(%)	3 (37.5)	5 (62.5)	0
Hurthle (%)	6 (60)	3 (30)	1(10)

The type of surgery seemed not to affect the outcome of iodine therapy. Sixty percent of the patients that had total thyroidectomy had negative iodine scan by the 6th month of follow up compared with 53% and 33% of patients that had near total thyroidectomy and lobectomy respectively (X^2=0.22) Table 3.

Table 3: Relationship between the type of Surgery and negative iodine scan by time

Surgery type	Iodine scan 6	Iodine Scan 12	Iodine Scan 24
T/thyroidectomy (%)	35 (60.3)	51 (87.9)	54 (93.1)
Near total (%)	19 (52.8)	25 (69.4)	33(91.7)
Lobectomy (%)	4 (33.3)	10(83.3)	12 (100)
X^2	0.22	0.082	0.60

**Test of significance between the different sugings andioine scan at various months*

All the patients had complete 24 months follow-up after the first radioactive iodine treatment. However, 32 patients also had follow-up up to 60 months (the full protocol).

Table 4 shows the proportion of patients who were negative for iodine scan at 6 to 60months post ablative/therapeutic radioactive iodine treatment. By the 24th month follow up, 98% (99 of 101) of patients remained negative. Negative iodine scan and Tg were concordant in 48 out of 58 (82.8%) patients at 6th month and in 89 of 99 patients (89.9%) at 24 months.

None of the patients with undetectable Tg at 24 months had significantly elevated Tg antibody levels.

The mean iodine dose administered by the 1st 6 months of follow-up was 88mCi (3.3GBq), range 1.1-7.4GBq (30-200mCi). This contrasted with total dose of 15.9GBq (429mCi) in patients that received multiple treatments, range 8.1-42.9GBq (220-1160 mCi) Table 5. Fifty five (51.9%) patients had their Tg assessed with 10ng/ml cut off point while 51(48.1%) of the patients were assessed with a sensitivity of 2ng/ml. Most patients (89 of 106) recorded undetectable Tg level at 24 months. However the higher sensitivity assay exposed 17 34 of 51 with unsuppressed Tg. Table 6.

Three of the five patients (4F, 1M) with metastasis had papillary cancer while the remaining two had follicular and mixed cancer respectively. The youngest was 16 years and the oldest 63. The metastasis was to the lung in 3 patients and the rest in the lymph nodes. All the patients had remained negative for two years consecutively post becoming Iodine scan negative.

Table 4: Iodine scan finding with corresponding TSH and Tg by months of follow –up

Patients	0	6	12	24	36*	60
n.	101	101	101	101	32	32
Negative (%)	0	58(57.4)	86(85.1)	99(98)	31(96.8)	32(100)
TSH mean mU/L(SD)		77.3 (39.7)	81.6 (43.0)	82.3(44.4)		
Tg suppressed (%)		48(47.5)	71(70.3)	89(88.1)		
WBS –ve (%)		55 (86.2)	74 (82.6)	93 (85.9)		

**Only 32 patients among the iodine scan negative patients had up to 60months scan record.*

Table 5: Profile of iodine treatments and outcome of Scan

Patients	1st Iodine treatment	2nd treatment	3rd treatment	4th treatment
WBS +ve	43	24	11	2
WBS -ve	58	76	89	99
Mean Iodine Dose (mCi)	88 (30-200)	-	-	-
Mean total Dose (mCi)		429* (220 -1160*)		

** For all treatment*

Table 6: Proportion of patients with suppressed Tg with time.

Tg	6 months	12 months	24 months
<10 (%) n= 55	37(67.3)	48(87.3)	55(100)
<2 (%) n = 51	11(21.6)	23(45.1)	34(66.7)
Total (n)	48	71	89

Discussion

The standard of care in management of differentiated thyroid cancer is total thyroidectomy followed by ablation of the thyroid remnant with radioactive iodine-131. The patient is then followed with serial Tg on and off suppression with thyroxine (T_4) and whole body iodine scan (WBS). Prior to every iodine scan, TSH level is expected to be above 30mU/L by withdrawal of T_4 or stimulation with rhTSH. Throughout the period of the study under review only the thyroxine withdrawal method was used.

Among the differentiated thyroid cancers, the papillary type is the commonest [8,9]. This trend was also observed in this study as 55% of the patients had papillary thyroid cancer. The preponderance for women however cannot be explained with certainty as they constituted 88% of the group. The overall female to male ratio of 6:1 in our study was almost twice the findings of El-Haddad et al with a ratio of 2.5:1 and the ratio found in other studies [10,11]. The reason for this could be the random exclusion of men who did not meet the inclusion criteria, it is however generally known that thyroid cancer is more common in women.

The mean age of incidence of thyroid cancer was 45 ± 15 and this was not significantly different from the findings of El- Haddad (46± 37) and others [11,12]. The age range was however unexpectedly high with the youngest patient afflicted being 16 years old and the oldest 81 years. The mean age at presentation for patients with papillary cancer was 40 years. This was significantly younger than the age at presentation for other diagnosis. Among factors that account for poorer prognosis is age ≥45 [13] at presentation which may be responsible for lesser complications observed in the majority of the patients studied.

The use of radioactive Iodine-131 in ablative therapy and in patients who remained positive after diagnostic scan was evaluated in our study. At the end of first iodine treatment at 6th month, 57.4% of the patients were WBS negative. The remaining patients became negative by the fourth treatment. More importantly there was no relapse or rebound serum Tg during their follow-up. This suggests that recurrent whole body iodine scans in these groups of patients was unnecessary. Very recently Schlumberger *et al* [14] pointed that postoperative administration of radioiodine can be avoided in patients with undetectable serum thyroglobulin and no lymph node metastasis detected at surgery. They further recommended low activity radioiodine (1.1GBq) should be administered selectively in low risk patients receiving levothyroxine treatment following injection of recombinant human TSH.

The observation that the type of surgery did not affect the outcome of iodine therapy could be so because risk stratification scoring system such as pathological, Tumour -Node –Metastasis (pTNM) was not used due to non availability of this information on most of the patients. Within 2 years of follow up however more than 90% of all the patients studied were negative for iodine WBS, an indication of favourable outcome. The greater proportion of patients that were still positive for iodine scan

consequently had multiple treatments were from the total and near total thyroidectomy group probably because they were in the majority.

The use of diagnostic iodine scan, T_4 withdrawal and Tg level in monitoring of thyroid cancer patients has recently been reviewed [6]. The recurrent survey of patients with iodine scan has been considered unnecessary in patients that have become negative provided their serum Tg levels are undetectable. As at 24 months, Tg and negative WBS were concurrent in 88% (89 of 101) of the patients studied. In this category of patients follow-up with neck ultrasound is recommended for detection of neck recurrences in conjunction with a sensitive serum Tg assay obtained following TSH stimulation. This modality thus excludes the need for diagnostic iodine scan.

The sensitivity of neck sonar is said to be 97-100% [6]. The neck ultrasound must however employ a probe containing a linear transducer of at least 7.5 megahertz and the report should be done on a diagram [6]. Neck ultrasound can detect lymph node metastases as small as 2-3mm in diameter which cannot be reliably assessed by serum Tg which may remain undetectable even following TSH stimulation. Although this mode of follow-up was not used for our patients, there was however no rebound Tg and WBS remained negative up till 60 months except for the proportion of 10 patients that had elevated thyroglobulin but negative iodine scan. In effect, there was discordance in 10 out of 99 patients (10.1%) at 24th month the so called "patients" with thyroglobulin elevated negative iodine scan (TENIS).

With the trend observed in 20 years it is possible to suggest that with concordant negative iodine scan and undetectable serum Tg at the 6 month follow-up, a WBS may not be mandatory at subsequent follow-ups. There is however need for more prospective long term follow up study of differentiated thyroid cancer patients to rule out recurrence several years later.

The role of laboratory back-up in the follow-up of patients treated for differentiated thyroid cancer cannot be overemphasized. With a more sensitive assay instituted post 1998 at the index hospital, there was increased observation of unsuppressed patients. Adequate preparation of patients for Tg estimation with or without diagnostic scan for TSH elevation could be done by T_4 withdrawal or by the rhTSH method. TSH below 30mU/L means inadequate stimulation of the remnant thyroid tissue or microscopic cancer. An undetectable serum Tg at this point is a false negative finding. Introduction of rhTSH into the protocol obviates the need for T_4 withdrawal with its attendant unpleasant side effects. This protocol has been approved by the European regulatory authority as far back as 2005 [15]. An undetectable Tg obtained this way is more specific. It is therefore important to have a very sensitive and reproducible Tg assay from a reliable laboratory.

Conclusion

This study does not support the continual use of numerous diagnostic whole body Iodine 131scan after a concordant negative scan, undetectable serum Tg and absent Tg antibodies. This submission is further buttressed by the lack of serum Tg rebound in the follow up of our patients with negative whole body iodine scans. It would therefore be safe to propose a yearly follow up of patients with negative scan at 6 month with serum Tg, Tg antibodies and neck ultrasound.

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