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Results of Radioactive Iodine (^{131}I) Therapy in Well Differentiated Thyroid Carcinoma: A Retrospective Study from the Tygerberg Hospital

D. Acullu[1*], A. E. Fourie[2], K. Baatjes[3] and E. J. Opakas[4]

[1]Department of Radiology and Oncology, Gulu Regional Referral Hospital, Ministry of Health, Gulu, Uganda.
[2]Division of Radiodiagnosis, Department of Clinical and Radiation Oncology, Faculty of Medicine and Health Sciences, Tygerberg Hospital and Stellenbosch University, Tygerberg, Cape Town, South Africa.
[3]Department of Surgery, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, Cape Town, South Africa.
[4]Department of Clinical and Radiation Oncology, Eldoret Hospital, Moi University, Eldoret, Kenya.

Authors' contributions

This work was carried out in collaboration between all authors. Author DA designed the study, wrote the protocol, carried data collection and wrote the first draft of the manuscript. Authors AEF and KB managed the literature searches, analyses of the study and performed the manuscript preparation. Author EJO managed the data analysis and literature searches processes. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Well Differentiated thyroid carcinoma (WDTC) represents 80% of all thyroid malignant tumours, with good prognosis and a survival rate higher than 90% at 20 yrs. Total or subtotal thyroidectomy is the treatment of choice, with radioactive iodine (RAI) therapy reserved for adjuvant setting/ablation and/or as a curative treatment modality in patients with local recurrence and/or distant metastases. This retrospective study aimed to investigate the treatment outcome,

**Corresponding author: E-mail: dacullu@yahoo.co.uk;*

survival rate and prognostic factors in our institution over the past half-decade.
Methods: A retrospective study was conducted of 33 patients with WDTC. Data were collected from 1st January 2007 to 31st December 2012 and included: Age at diagnosis, sex, histology, TNM stage, treatment received, indication for ^{131}I therapy, doses of ^{131}I, complication of treatment, follow-up diagnostic scan ^{123}I / Thyroglobulin, time of recurrence since surgery and cause of death. Prognostic factors were analysed using chi-square test and crude mortality rate was used.
Results: Papillary subtype is the most common type of WDTC (63.6%); mean age at diagnosis is 50 years and female to male ratio is cosmopolitan at 3.1:1 with female preponderance. RAI therapy after thyroidectomy (total or subtotal) offers complete remission in 26/33 (78.8%) and the overall mortality rate was 3/33 (9.1%) p=0.023.
Conclusion: RAI therapy is safe and effective in management of patients with WDTC. The initial surgical approach is the cornerstone in the subsequent outcome of RAI therapy with very poor outcome registered in unresectable thyroid tumour and in patients with multiple organ metastases.

Keywords: Radioactive Iodine; well differentiated thyroid carcinoma; ablation; result; Tygerberg Hospital; Stellenbosch University.

1. INTRODUCTION

Thyroid cancer is the most common malignancy of the endocrine system and its incidence has been increasing over the past decades. Histologically this heterogeneous disease is classified into four main groups: Papillary, follicular, medullary and undifferentiated or anaplastic thyroid carcinomas. The vast majority is however differentiated tumours which includes papillary, follicular and the most infrequent hurtle cell subtypes, comprising approximately 90% of all cases of thyroid cancers. Most differentiated tumours are indolent and carry a favourable prognosis. Staging of thyroid cancers is based both on the subtype of tumour and the patient's age [1-4].

Differentiated papillary and follicular thyroid carcinomas are often treated similarly albeit numerous biologic differences. Standard of care consists of total or subtotal thyroidectomy, usually followed by complementary radioactive iodine (RAI) therapy, aimed at ablating any remnant thyroid tissue and potential microscopic residual tumour [5-9]. Therapeutic interventions in persistent (residual disease), recurrent or metastatic differentiated thyroid cancer depend on the type of the initial treatment, the site and the extent of disease. Surgical excision of amenable lesions and radioiodine administration remain the first approach [1,4].

The specific ability of the thyroid follicular cells, including malignant cells of follicular origin to take up iodine, permits the use of radio-iodine for clinical purposes. Once concentrated within the cell, ^{131}I undergoes beta (β) decay, releasing electrons and short path-length (1-2 mm) beta (β) rays that induce localized radiation cytotoxicity as well as emitting γ rays detectable during scanning procures.

These radioactive and highly specific tissue uptake effect then aid to (1) destroy any residual microscopic foci of disease; (2) to increase specificity of subsequent ^{123}I scanning for detection of recurrent or metastatic disease by elimination of uptake by residual normal tissue; and (3) to improve the value of measurements of serum thyroglobulin as a serum marker derived only from malignant thyroid cells [9-13].

Successful ablation is defined by the combination of undetectable serum thyroglobulin levels after thyrotropin stimulation and no uptake after diagnostic ^{123}I whole body scan three (3) months after RAI therapy. In most centers, standard fixed activities of 3700-7400MBq are used for ^{131}I ablation, residual tumour and metastatic disease.

According to the American Thyroid Association (ATA), 2009, guidelines for postoperative radioiodine ablation; RAI is recommended for: (1) all patients with known distant metastases, gross extrathyroidal extension of the tumour regardless of tumour size, or primary tumour size > 4 cm even in the absence of other higher risk features, (2) for selected patients with 1-4 cm thyroid cancers confined to the thyroid who have documented lymph node metastases, or other higher risk features when the combination of age, tumour size, lymph node status, and individual histology predicts an intermediate to high risk of recurrence or death from thyroid cancer.

Effective thyroid ablation requires adequate stimulation by thyroid stimulation hormone

(TSH). The method of choice for preparation to perform a radioiodine ablation is based on the administration of recombinant human TSH (rhTSH), while the patient is on levothyroxine (LT4) therapy [14]. On the basis of several reports the rhTSH administration method is considered the method of choice demonstrating equal efficacy compared with thyroid hormone withdrawal (THW) but better acceptance from the patients [14,15]. In addition, in the recent years, it has become increasingly apparent that successful thyroid ablation may be achieved using low activities of ^{131}I (1110-1850 MBq) [16].

At Tygerberg Hospital (Division of Clinical and Radiation oncology), patients are recruited through the multidisciplinary team meeting at the head and neck/thyroid clinic and their management is based on the departmental protocols. Preparation for ablation entails: 1) informed consent, 2) booking for ^{131}I therapy, 3) thyroid-hormone (Eltroxin) withdrawal to achieve optimal thyrotropin stimulation ≥ 30 μU/mL (20-30) acceptable, 4) isolation of the patient for ^{131}I therapy; the radioiodine dose depends on the indications (ablation, residual disease, recurrence, metastases), 5) re-instate the thyroid –hormone (Eltroxin) treatment after RAI therapy, 6) post ^{131}I therapy scan at the 10th day, 7) three (3) month follow-up, 8) ^{123}I diagnostic scan at three (3) months post ^{131}I therapy, and 8) Routine follow up in the thyroid clinic.

Greater understanding of treatment portfolio and outcomes including risk factors for mortality in our setting (Tygerberg Hospital, Division of Clinical and Radiation Oncology) will translate into optimal treatment individualization, therapeutic approach and improvement of final outcome in our patients with WDTC.

The study was to address the knowledge gap in our setting pertaining treatment response, risk factors and mortality as compared to international guidelines.

1.1 Literature Review

A recent meta-analysis concluded that radioactive (^{131}I) iodine (RAI) therapy decreased the risk of local recurrence and metastases in patients who underwent thyroidectomy for WDTC, but mortality data conflicted between centers [17,18]. The intended benefits of RAI therapy include eradicating any microscopic disease, facilitating the staging of patients with post treatment whole body scans, and increasing the sensitivity of long term screening modalities including ^{123}I whole body scan and thyroglobulin levels.

WDTC has a good prognosis and survival rates are higher than 85%. Many studies have reported overall mortality approximate to 5% and this suggests that the survival rate is high and has improved over the decades [17,18].

In one of the retrospective study reviewed on the role of radioiodine therapy for differentiated thyroid carcinoma in 29 patients that received adjuvant ^{131}I over a period of 2-years, it was found that 35% had local and distant metastases by ^{131}I scan, and 24% had a metastatic lesion not suspected by operative findings or chest radiography. A complete response was obtained in 70% of the patients with metastatic disease [19].

Another study found that radioactive Iodine therapy decreases recurrence in thyroid papillary microcarcinoma and the 5-years RFS for patients treated with ^{131}I was 95% vs 78.6% ($p < 0.0001$) for patients not treated with ^{131}I. The patients with lymph node metastasis who did not receive ^{131}I had a 5-year RFS of 42.9% vs 93.2% ($p < 0.0001$) for patients who received ^{131}I [20].

The third retrospective study on 728 patients treated for well differentiated thyroid carcinoma between 1954 and 1994, found that 17.2% of the patients developed locoregional and /or distant metastases, and 6% mortality related to malignancy of the thyroid [21].

In the fourth retrospective study reviewed on the issue of Differentiated thyroid carcinoma: the survival and prognostic factors of 308 patients with mean follow-up time of 8.9 +/- 6.8yrs: it was found that the thyroid carcinoma related survival was 92.7%. Mortality rate of 4.9% and risk of death significantly increased with distant metastases, follicular histology, age at diagnosis older than 60 years and extrathyroid involvement [22].

Radioiodine therapy is an effective form of adjuvant therapy that is frequently underutilized with a complete response rate of 70-80% in patients with metastatic disease [23]. The conservative attitude towards the treatment of WDTC is supported by the fact that mortality is low in this disease; hence overall survival is not the most appropriate means of judging the efficacy of treatment because the relapses may

occur after a long interval and furthermore there may be another long interval between relapse and death [23,24]. Adjuvant radioiodine therapy augments the already better prognosis.

Retrospective quest for treatment outcome, risk factors, complications of therapy and mortality rate at our treatment center was a virtuous platform. Since there was no similar study done in our setting.

1.2 Rational for the Study

The study generated relevant information on RAI therapy at the Division of Clinical and Radiation Oncology, Tygerberg Hospital. Based on statistical therapeutic outcome, risk factors and mortality data, it will influence the future protocol development and generate prospective researches/trials.

1.3 Aims of the study

To conduct a retrospective analysis to determine the treatment outcome in patients with WDTC that received RAI therapy at Tygerberg Hospital, Division of Clinical and Radiation Oncology from the 1st January 2007 to 31st December 2012.

1.4 Objectives of the Study

1. To determine the various indications for RAI therapy.
2. To analyse prognostic factors and determine the survival rate (mortality).

2. MATERIALS AND METHODS

2.1 Research Design and Methodology

2.1.1 Study design

It was a retrospective observational study

2.1.2 Study site

The Division of Clinical and Radiation Oncology, Tygerberg Hospital

2.1.3 Study population

All patients with WDTC referred, attended and treated with RAI therapy at Division of Clinical and Radiation Oncology, Tygerberg Hospital.

2.1.4 Selection criteria

2.1.4.1 Inclusion criteria

All patients that had thyroidectomy followed by post-operative ^{131}I therapy from the 1st January 2007 to 31st December 2012 were included and also patient that received ^{131}I therapy alone during the study frame without prior thyroidectomy were also included.

2.1.4.2 Exclusion criteria

Patients with incomplete records (data/missing files) on objective outcome, such as response to RAI therapy evaluation at six (6) months with ^{123}I scan and associated adverse toxicities were excluded.

2.2 Sampling

The records of all the patients that received RAI therapy during the study period were reviewed retrospectively. A total of Fifty two (52) patients received RAI within this time frame of which thirty three (33) patients, (63.5%) met the inclusion criteria and nineteen (19) patients, (36.5%) were excluded: seven (7) of these patients, (13.5%) came from neighbouring countries and were loss to follow-up, and twelve (12) patients, (23.1%) had incomplete data/records.

2.3 Data Collection

All relevant data (demographic characteristics, tumour characteristics, details of initial surgery, details of radioactive iodine therapy, post-therapy evaluation data) were collected using a coded questionnaire from the patients' charts/records (files, iSite Enterprise – Laboratory/Histology/ Radiology/ Nuclear Medicine). These were identified from a RAI therapy register, hospital tumour register, hospital and clinic attendance records and patient follow up records from 1st January 2007 to 31st December 2012. Data were collected using patient's folder number only and no names or other discernible information were used.

The demographic characteristics were expressed in ratio of male to female, age of patient at diagnosis capped at 45 years: <45 years and ≥45 years as patient's related prognostic factors.

The initial intervention was considered in terms of resectable (Total thyroidectomy/subtotal thyroidectomy) or unresectable to cover for surgical prognostic factors.

The tumour characteristics were documented based on the histological subtype according to the WHO classification (papillary, follicular and Hurtle cell subtype) for WDTC. The clinical/ histological characteristics of disease (tumour size, extra-thyroidal extension, lymphovascular invasion and lymph node metastases) were documented as tumour related prognostic factors. Distant metastases were considered and documented as stage IV disease. The AJCC 7th edition staging system was used for the WDTC staging for the stage/group documentation.

The indications for RAI per chart and given doses were captured as per record on the file.

Objective tumour responses were documented based on the results of the ^{123}I scan at six (6) months interval and any other clinical/imaging documentation of new lesions, nodes and distant metastases generated in the records within the study frame. Data on mortality was extracted as quoted on the patient chart/file.

2.4 Data Analysis

All data were collected on coded questionnaires and then translated into spread sheet and subsequently analysed using SPSS version 20.0 statistical software.

All data were presented as descriptive statistics. Where applicable data were analysed descriptively by means of the following:

2.4.1 Continuous variables

- Means and standard deviations were used if data were normally distributed
- Medians and interquartile ranges were used for non-normally distributed data
- 95% confidence intervals were used to estimate population parameters
- Pie charts, linear graphs and histograms were used to present data graphically

2.4.2 Categorical variables

- Frequency distributions were presented to show absolute counts and percentages
- 95% confidence intervals were presented for binary variables
- Pie charts, bar graphs, linear graphs and/or histograms were used to present data graphically
- Prognostic factors and survival rate was analyzed using Chi-Square test

2.5 Ethical Considerations

The study proposal was submitted to the research ethics committee at the University of Stellenbosch and approved on the 7th July 2013 (HREC ethic No. S13/05/112) before the study was commenced. The potential risk of confidentiality was maintained by the use of a study number, grouped patient reporting, lock and key and password protection of data sheet.

The patient data was de-identified on chart abstraction. This was a minimal risk study due to the nature of retrospective data collection and thus a waiver of informed consent was granted.

3. RESULTS

3.1 Age and Sex

Of the 33 patients, 25 (75.8%) were women and 8 (24.2%) men (3.1:1). Age at diagnosis ranged from 21 to 78 years (mean of 50 years).Ten (10) patients (30.3%) were aged <45 years at diagnosis and 23 (69.7%) of the patients were ≥45 years of age.

3.2 Surgical Treatment

Twenty six (26) of the patients (78.8%) had total thyroidectomy; 3 (9.1%) had subtotal thyroidectomy and 4 (12.1%) of the patients were unresectable, (Table 1 below).

Table 1. Type of surgery performed

Surgical intervention	Number of patients
Total thyroidectomy	26 (78.8%)
Subtotal thyroidectomy	3 (9.1%)
Unresectable	4 (12.1%)

3.3 Histological Subtype

Papillary carcinoma was reported in 21 (63.6%), Follicular carcinoma in 11 (33.3%) and Hurtle cell type in 1 (3%), (Table 2).

3.4 Histo-pathological Risk Factors

3.4.1 Tumour size

Sixteen (16) of the patients (48.4%) presented with thyroid lesion ≤5 cm and 17 (51.5%) had larger thyroid lesion >5 cm (Table 3).

3.4.2 Extra-thyroid spread

Of the twenty nine (29) patients who had surgical intervention/operation, thirteen (13) of them (44.8%) presented with tumour spread beyond the thyroid capsule and 16 (55.2%) were negative (Table 4): these were documented based on histological findings after resection.

3.4.3 Cervical lymph node metastases

Eighteen (18) of the patients (54.5%) had positive cervical lymph nodes metastasis and 15 (45.5%) were node negative (Table 5): these were documented based on microscopic diagnosis at FNA and/or at histological findings after surgical resection. Important to note were that the number of lymph nodes evaluated and the levels/numbers of the involved nodes were not documented adequately in the clinical and histological reports. Hence, in this particular study only the status of the cervical lymph nodes with or without documented metastases were considered.

Table 2. Histological sub-type of well differentiated thyroid carcinoma reported

Histological sub-type	Frequency	Percentage (%)
Papillary	21	63.6
Follicular	11	33.3
Hurtle cell type	1	3.0

Table 3. Tumour size as measured macroscopically and microscopically

Tumour size (T stage)	No. and percentage
≤ 5 cm	16 (48.4%)
>5 cm	17 (51.5%)

Table 4. The percentage of cases found with extra-thyroid spread

Status	No. and percentage
Present	13 (44.8%)
Absent	16 (55.2%)

Table 5. Cervical lymph node metastases

Thyroidectomy/+/-neck dissection/FNA of the neck lymph node	Results
Cervical lymph nodes present	18 (54.5%)
Cervical lymph nodes absent	15 (45.5%)

FNA=Fine needle aspiration

3.4.4 Lymphovascular invasion

Of the eighteen (18) patients who had metastases to cervical lymph nodes, ten (10) of them (55.5%) at histology had tumour invasion into lymphovascular space and 5 (27.8%) were negative (Table 6): These were documented based on microscopic findings after surgical resection. However, note that three (3) of the eighteen (18) patients (16.7%) developed cervical lymph node metastasis (confirmed on FNA) after the initial surgical intervention/ operation and were referred for RAI therapy.

3.4.5 Prognostic group staging

The majority of the patients presented with late stage disease: 13 (39.4%) of the patients had stage IV disease, 10 (30.3%) had stage III, 8 (24.2%) stage II and only 2 (6.1%) patients were found with stage I disease (Table 7).

3.5 Indications for RAI Therapy

Ablation accounts for approximately sixty four percent (64%) of the indications for RAI treatment, followed by inoperable tumour/locally advanced disease (12%) and lymph node metastases (9%). Local recurrence and distant metastases accounted for 6% each. Post-operative residual disease was uncommon with 3% only (Fig. 1).

Table 6. Lymphovascular invasion

Status	No. and percentage
Present	10 (55.5%)
Absent	5 (27.8%)

Table 7. The prognostic group (TNM) staging according to AJCC 7th edition (Appendix III)

Stage	Frequency	Percentage (%)
I	2	6.1
II	8	24.2
III	10	30.3
IV	13	39.4

TNM= Tumour, Node, Metastasis; AJCC= American joint committee on cancer

3.6 Follow-up at 6 months with Diagnostic ^{123}I Scan

At six (6) month follow up with ^{123}I scan: normal scans were documented in 26 (78.8%) patients, residual disease and lymph node metastases

accounted for 3(9.1%) and 4(12.1%) of the positive scans respectively (Fig. 2).

3.7 The Correlation between the Tumour Response and the Tumour Size in Relation to the Surgical Intervention at 6 Month Follow-up after RAI Therapy

A total of twenty six (26) patients (78.8%) had complete response in the surgical cohorts following RAI therapy/ ablation, while one (1) patient (3.0%) had partial response. Progression of disease contributed to 2/29 (6.9%) in the surgical cohorts and 2/4 (50%) in unresectable tumour (Table 8).

3.8 Retreatment with RAI

After the first RAI, 7/33 (21.2%) of the patients received retreatment. Lymph node metastases accounted 3/33 (9.1%) of the retreatment and incomplete ablation contributed for 2/33 (6.1%), distant metastases and local recurrence each contributed to 1/33 (3%) of the second RAI (Table 9).

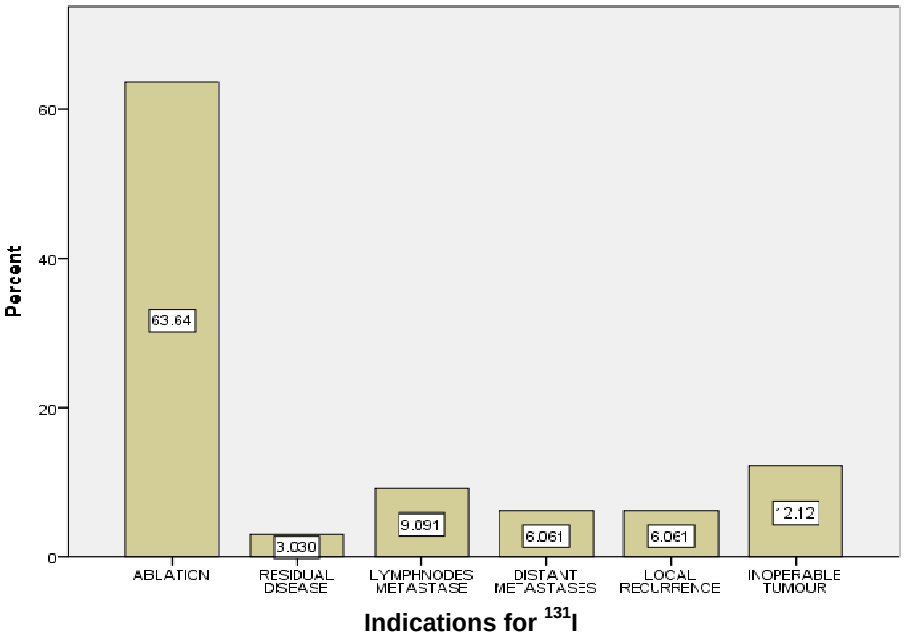

Fig. 1. The percentages (%) of various indications for RAI treatment

Table 8. The correlation between the tumour response and the tumour size in relation to the surgical intervention within the first 6 month follow-up after RAI therapy

Surgical intervention	Tumour response	Tumour size	
		≤ 5 cm (n=16)	> 5 cm (n=17)
Total thyroidectomy (n=26)	Complete response	14	10
	Partial response	1	0
	Progression of disease	0	1
Subtotal thyroidectomy (n=3)	Complete response	1	1
	Partial response	0	0
	Progression of disease	0	1
Unresectable (n=4)	Complete response	0	0
	Partial response	0	1
	Progression of disease	0	2
	Death from disease	0	1

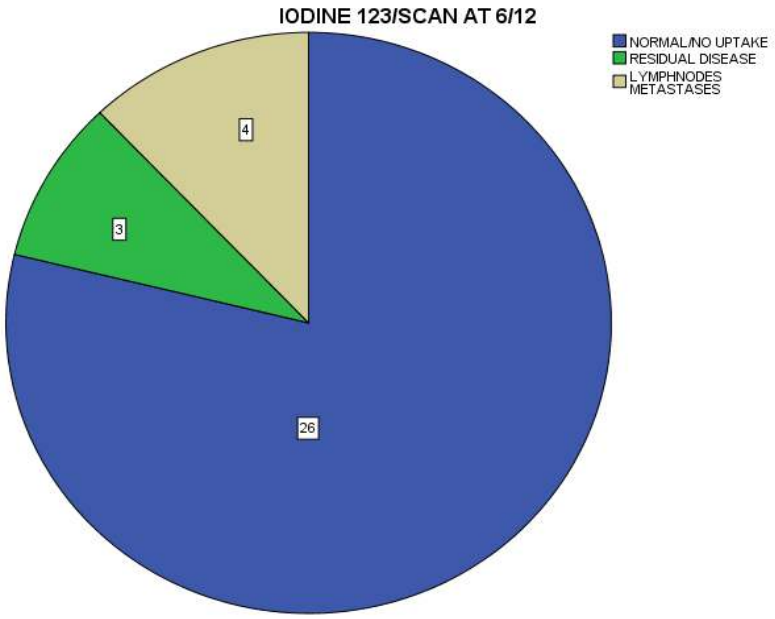

Fig. 2. The results of total body scan with 123I at 6month follow-up

3.9 Correlation between Treatment Outcome and TNM Stage on Follow up at 5 Years

Cases with complete remission were seen in all stages (stage I-IV). However, the stage IV disease carries more risk of local recurrence, distant metastases and mortality from disease, 2/33 (6.0%) and 3/33 (9.0%) respectively (Table 10).

3.10 Correlation between the Treatment Outcome and the Number of Distant Metastases at 5 Years

Eight (8) patients (24.2%) had distant metastases: 4 of the patients (12.1%) had single organ/site metastases and 4 (12.1%) multiple sites metastases. Complete response 2/33 (6%) was depicted in single site metastatic patients and none (0%) in the multiple sites/organ metastases. Worse outcome (death from disease) was associated with the multiple site metastases 3/33 (9.0%) (Table 11).

Table 9. The reasons for retreatment with RAI therapy

Indication for retreatment with RAI	Number of patients retreated (n=7)
Incomplete ablation	2
Lymphnodes metastases	3
Distant metastases	1
Local recurrence	1

3.11 Correlation between age and Distant Metastases at 5 Years Follow up

No death was documented in patients <45 yrs. Distant metastases and death from the disease were associated with advancing age ≥45 yrs (Table 12).

Table 10. Correlation between treatment outcome and TNM stage on follow up at 5 years

Treatment outcome	TNM/stage			
	Stage 1 (n=2)	Stage II (n=8)	Stage III (n=10)	Stage IV (n=13)
Complete remission (n=26)	2	8	10	6
Stable disease (n=3)	0	0	0	3
Local recurrence (n=2)	0	0	0	2
Disease progression (n=2)	0	0	0	2
Death from disease (n=3)	0	0	0	3

Table 11. Correlation between the treatment outcome and the number of distant metastases at 5 years

Number of sites involved	Outcome at 5 years				
	Complete response	Stable disease	Local recurrence	Disease progression	Death from disease
None (n=25)	24	x	1	x	x
Single (n=4)	2	1	1	x	x
Multiple (n=4)	x	x	x	1	3

Single site: (Bone/Lung/ Liver): Multiple sites: (Liver, Lung, Bone) and/or any of the two

Table 12. Correlation between age and distant metastases at 5 years follow up

Five (5) years follow-up		Distant metastases	
		Present (n=8)	Absent (n=25)
Alive (n=30)	<45 yrs	0	10
	≥45 yrs	5	15
Death (n=3)	<45 yrs	0	0
	≥45yrs	3	0

Table 13. The correlation between the gender and type of WDTC on the outcome at 5 year follow up

Outcome at 5 years		Type of WDTC		
Status	Gender	Papillary (n=21)	Follicular (n=11)	Hurtle cell type (n=1)
Alive	Male (n=8)	7	1	0
	Female (n=22)	14	7	1
	Male (n=0)	0	0	0
Death	Female (n=3)	0	3	0

3.12 The Correlations between the Gender and the Type of WDTC on the Outcome at 5 Years Follow up

The follicular subtype carries the worse prognosis with 3/33 (9.1%) mortality rate.

The papillary subtype is the most common, with excellent outcome. One (1) case (3.0%) of Hurtle cell type was documented (Table 13 above).

4. DISCUSSION

Thyroid cancer represents a broad spectrum of disease. The aggressiveness of the lesion varies among individuals, but some general deductions can be drawn.

In our cohort study for WDTC, RAI therapy after thyroidectomy (total or subtotal) offers complete remission in 26/33 (78.78%) patients, stable disease was seen in 3/33 (9.09%) patients, local recurrence and disease progression were 2/33 (6.06%) and 2/33 (6.06%) respectively; the overall mortality was at 3/33 (9.09%) (Tables 8 and 9) p=0.023. These findings were in keeping with the general trend found by other researches: Segal K, et al., Carol S, et al. and Kimberly M, et al. in their studies.

In this cohort, we found that ablation was the most common indication for RAI therapy; accounting for approximately sixty four percent (64%), followed by inoperable tumour/locally advanced disease (12%) and lymph node metastases (9%). Local recurrence and distant metastases accounted for 6% each. Residual disease was uncommon with 1% only. Nonetheless, these were found to be in excess of the International Guideline recommendation by the American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer (appendix II). The subsequent indications of RAI therapy were mainly based on the outcome of the first RAI therapy (Table 9), but the proportion of successful ablation after the first RAI therapy is excellent with a response rate of 26/33 (78.8%).

In WDTC, Simpson et al., Beenken et al. and Segal et al. [25-27] reported that the size of the primary focus (T) is directly related to mortality. In our series, no patient with a tumour measuring less than 5 cm developed recurrence,

progression or death from disease. The progression of disease and mortality rates were significantly higher for patients with a tumour larger than 5.0 cm, 5/17 (29.4%) and 3/17 (17.3%) respectively (Table 8) p=0.023. These were essentially true in the context of extra-thyroid extension, lymph node metastases, extracapsular extension and lymphovascular invasion which are known risk factors of locoregional and distant failure.

The TNM stage is less predictive/prognostic (p=0.064) in WDTC with complete remission seen across the board (stage I-IV); however, the stage IV disease with lymph node metastases carries more risk of local recurrence and distant metastases (Table 10).

The unresectable tumour and multiplicity of distant metastases (Liver, Lung and bone) in a patient carries the worst prognosis (Table 11) p=0.001.

Several studies of prognostic factors in differentiated thyroid cancer have been reported previously, the prognostic significance of age was strongly supported by many investigators. Beenken, et al. found no patient younger than 40 years old who died of thyroid cancer. Simpson, et al. found that an age of 60 years or more highly correlated with death from either papillary or follicular cancer. In our study, (Tables 11 and 12) there was significant differences between patients <45 years and those aged ≥45 years regarding distant metastatic status and thyroid cancer related deaths. There was no incidences of distant metastases and death in the age bracket of <45 years. Five (5) distant metastases with three (3) cancer related deaths in the age bracket≥45 years (crude mortality rate of 0.09), p=0.009 were noted in this cohort study (Table 12).

Tubiana M, et al. and Mazzaferri EL, et al. [26,27] reported that survival was better in women than in men with WDTC. Contrary to these reports, we did not find sex to be a statistical significant prognostic factor (p=0.21), although our study showed a slightly better outcome for males (Table 13). This could be attributed to a number of factors: Fewer male than female 1: 3.1 ratio were captured in this cohort and the three (3) deaths were only female.

When there are distant metastases and locoregional recurrence in patients with functional types of well differentiated thyroid carcinoma, it can often be detected with ^{123}I diagnostic scan and subsequently treated with ^{131}I only if all the normal thyroid tissue has been removed [28-30]. In our series, ten (10) patients in whom locoregional recurrence and/or distant metastases occurred were treated with varying doses of radioactive iodine (3700-5550 MBq). Four (4) of the patients (12.1%) had unresectable disease at index consultation and this could contribute to the high mortality rate after RAI therapy. The issue remains whether there is any benefit for RAI therapy in this sub-group and if the administration of RAI will change the outcome of this already dismal prognostic group. There is no data in international guidelines supporting the use of RAI therapy in this specific subgroup.

It should also be noted that thyroglobulin levels are very important in the follow-up of patients with well-differentiated thyroid cancer; the significance of a high thyroglobulin level is much more specific after radical thyroid surgery and ablation [31,32]. In our centre, thyroglobulin and anti-thyroglobulin antibodies assays are not being used routinely for this purpose because of the logistic problems. However, most of our patients are being followed up with ^{123}I diagnostic total body scan at 6 monthly intervals.

Some investigators state that follicular carcinoma is more aggressive than papillary carcinoma and therefore needs a more aggressive therapeutic approach [32,33]. Others have shown that the prognoses of these two histological types are identical, and the distinction between papillary and follicular thyroid cancer may be of little more than academic interest [33,34]. In our study group, we did find a significant difference in survival rate between patients with papillary and follicular carcinoma p=0.002 (Table 13). All three (3) registered mortalities (9.0%) in this cohort were due to follicular carcinoma.

This study reviewed RAI treatment outcome and determined the various indications for RAI in a small cohort of patients with WDTC (>30) (Figs. 1 and 2) who were similarly treated and followed by the same multidisciplinary team for at least a mean followed-up time >3 years. The experience gained in our department over the last three (3) years has led to the suggestion that an aggressive approach in the treatment of patients with WDTC includes most importantly total and sub-total thyroidectomy (with or without cervical lymph node dissection) followed by

ablative RAI therapy. This correlate with those who advocate that total and subtotal thyroidectomy should be the treatment of choice [32-35].

Administering RAI therapy in patients with unresectable primary tumour in conjunction with extensive, multi-organ metastases has showed no significant benefit.

5. STUDY STRENGTH AND LIMITATIONS

This was a single centre cohort with a small number (33) of patients with low statistical power. Hence, descriptive analyses were more relevant (Chi- Square test).

The retrospective nature of data collection formed the greatest limitation of this study with missing data and non-reporting on the side effects of RAI therapy. Hence no clear deduction could be generated on side effects of RAI therapy, since no data was captured on the treatment related side effects. Nonetheless, RAI therapy is safe and well tolerated and no adverse effects were mentioned.

For the future a prospective up-to-date database to generate a larger cohort will be meaningful accepting that thyroid cancer is not a common malignancy.

6. CONCLUSION

Our retrospective analysis of 33 cases of well differentiated thyroid carcinoma has led to the following observations:

1. Papillary subtype is the most common type of WDTC (63.6%) and female to male ratio is cosmopolitan at 3.1:1 with female preponderance.
2. The RAI therapy response rate is approximating 80%.
3. Significant greater mortality rates (> 9%) were noted especially in the patients with unresectable primary disease and multiple distant metastases to lung, liver and bones.
4. Total or subtotal thyroidectomy is the treatment of choice in well differentiated thyroid carcinoma and radioactive ^{131}I therapy is indicated for ablation therapy after radical thyroid surgery, as well as curative treatment modality for patients who have local recurrence and distant metastases.
5. Tumour size, age of the patient at diagnosis, and the presence of multiple distant metastases are predictors of outcome.
6. No significant clinical response/ benefits of RAI therapy in unresectable primary tumour and/or with multi-organ metastases.
7. No adverse complications of RAI therapy were documented amongst the 33 cases evaluated; this could be because of retrospective data omission or objectively justifying that RAI therapy is a safe procedure without adverse reactions.

CONSENT

Waiver of consent was sort from the institution and HREC of Tygerberg Hospital, Stellenbosch University

ETHICAL APPROVAL

I hereby declare that the research proposal for this study was presented to and approved by the HREC 2 Committee at Stellenbosch University on 07 July 2013. Protocol Number: S13/05/112.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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