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Consensus-based management of differentiated thyroid cancer in a tertiary care set-up

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ABSTRACT

Introduction: This study describes the experience of a tertiary care hospital in the management of differentiated thyroid cancer. Thyroid cancer accounts for less than 1% of all human malignancy. Nevertheless, it is the commonest endocrine malignancy constituting 90% of endocrine cancers. It is the commonest cancer in Saudi Arabian women second to breast cancer. This fact makes differentiated thyroid cancer an important tumor and a challenging disease.

Methods: The medical records of patients diagnosed to have differentiated thyroid cancer in King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia between 1st January 2000 and 30th September 2006 were reviewed retrospectively. The data included patient's demographic details, clinical diagnoses, co-morbid conditions, relevant investigations, imaging studies, medical and surgical treatment offered, types of surgeries performed, radioactive iodine therapy given, and the complications and outcome of management. Management of these patients follows a clinical care pathway set up by the hospital Thyroid Cancer Group representing various multidisciplinary team members.

Results: One hundred and eight medical records were reviewed. Of these, 72 (66.7%) patients were females and 36 (33.3%) were males. Median age for the females was 40 years, and for males 45 years. Ninety patients (83.3%) had a papillary carcinoma, four patients (3.7%) had a follicular carcinoma and fourteen patients (13%) had other types, namely medullary thyroid carcinoma, anaplastic carcinoma and lymphoma. A total of 78 patients underwent various forms of surgery in our hospital and the remaining patients underwent operation in the district hospitals before they were referred to our centre for further management. Complications included bleeding (1.8%), voice changes (4.5%), and hypocalcaemia (3.8%). The overall outcome showed that 99 patients (91.7%) were alive and well at the time of analysis, 4 patients (3.7%) died and 5 patients (4.6%) were lost to follow up.

Conclusions: This hospital-based epidemiological study, the largest one done in the western part of Saudi Arabia, showed that differentiated thyroid cancer behavior and the management approach we adopt is not different from other centres of excellence. In spite of the relatively higher number of redo surgery we performed in these patients, yet the incidence of recurrent laryngeal nerve injury and hypocalcaemia are similar to what is published in the literature.

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1. Introduction

Thyroid cancer (TC) is a heterogenous group of diseases with different tumor behavior and tumor biology. It includes differentiated thyroid cancer (DTC), medullary thyroid carcinoma, anaplastic carcinoma, thyroid lymphoma and rarely secondary deposits from other tumors. TC is the most common malignancy of the endocrine system as it accounts for 90% of all endocrine malignancies. Its incidence has been increasing over the past 20 years.¹ DTC is the

most common thyroid malignancy that includes the major types, papillary carcinoma, follicular variant, Hurthle cell carcinoma as well as rare subtypes. Several classifications and staging systems have been proposed for DTC. However, no clear consensus has emerged so far favoring any one over the other. As a prognostic scoring system developed in one particular group of patients has often performed poorly when applied to other groups of patients with the same disease.

For the United States population the life time risk of being diagnosed with DTC is about 1% (0.84% for women and 0.30% for men) and with the incidence increasing by 6.2% per year, thyroid cancer is currently the 8th common malignancy diagnosed in women in the United States of America.^{2–4} Although it can occur at

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any age, its peak incidence is around 50–54 years in women and 65–69 years in men.⁵ Among patients aged 15–24 years of age, DTC accounts for 7.5–10% of all diagnosed malignancies.⁶ Despite that it occurs commonly in women yet the mortality rates are higher for men probably because males are affected at an older age than women.⁷ DTC is the most common solid organ malignancy in Saudi Arabian women second to breast cancer.⁸ This fact probably renders DTC an important and challenging disease requiring more research and studies in this country. By and large DTC has a good outcome and a good prognosis, as it is usually indolent and when identified at an early stage is almost always curable. On the other hand the five year disease specific survival of patients with DTC with distant metastases is less than 50%.^{9,10}

2. Methods

The medical records of patients diagnosed to suffer from DTC in the King Faisal Specialist Hospital and Research Centre Jeddah Kingdom of Saudi Arabia between January 2000 and September 2006 were abstracted. The patients included those who were referred from other centres (non-virgin-neck) to this tertiary care facility and those who were primarily seen in this institution (virgin-neck patients). This distinction is made because most of the referred patients had received initial treatment and/or an intervention been performed in their hospitals, including surgical procedures and then referred to our institution for further management. Both groups of patients were managed according to a standard management protocol made and agreed upon by the hospital's Thyroid Cancer Group (TCG). The TCG consists of members representing the services which have direct involvement and interest in the management of thyroid cancer, namely; endocrinology, surgery, radiology, nuclear medicine, and histopathology. The protocol is applied to all patients accordingly to which the patients' cases are discussed during the TCG's weekly meeting. A dedicated team shares a common interest, enthusiasm and perseverance that are vital to achieve and positively adds to the outcome and prognosis of DTC compared to other malignancies. The current consensus-based-guidelines for the treatment of DTC include; adequate surgery, optimization of TSH suppression, radioactive iodine therapy, excision of residual tissue and resection of selected metastases and the use of bisphosphonates for bony metastases. We use a staging system derived from the Ohio State University System, which was developed following; retrospective analysis of tumor registry of 1355 patients, on the basis of a staging scheme derived from a multivariate analysis.⁵ According to this system patients are classified as follows:

- Stage 1 — primary tumor smaller than 1.5 cm in diameter
- Stage 2 — primary tumor 1.5–4.4 cm, or presence of cervical lymph node metastases, or more than three intra-thyroidal foci of tumor
- Stage 3 — primary tumor at least 4.5 cm or presence of extra-thyroidal invasion
- Stage 4 — distant metastases

The meetings are attended by all the concerned units. It simultaneously serves as a teaching forum and for decision making regarding every individual patient. The patients' history, clinical findings, various images and histopathology records are discussed and their disposition is decided by consensus. The final decision is documented. The decision is then conveyed to the patient and his/her family by the treating physician before he/she signs the informed consent for treatment.

Patients are either diagnosed locally (*virgin-neck patients*) or had been referred from other secondary care hospitals in the catchment area of our centre and they would usually have been subjected to

some form of surgical treatment (*Non-virgin-neck patients*). These patients would have their other investigations including the histopathology slides reviewed at our centre. Other tests are requested according to the patient's clinical and co-morbid status, which include complete blood count, renal profile, TSH, Free T4, serum calcium and phosphate, parathyroid hormone (PTH), thyroglobulin and antithyroglobulin antibodies, as well as high resolution neck ultrasonography to assess any residual thyroid tissue and/or cervical lymph nodes. The same will be done for those patients seen primarily at our hospital (*virgin-neck*) except that they will be subjected for an ultrasound guided fine needle aspiration cytology (FNAC) for the thyroid swelling detected clinically or by ultrasound.

Non-virgin-neck patients' treatment depends on the results of the outside histopathology review. If it was positive for malignancy they will have an ultrasound to look for the size of the residual thyroid tissue and for cervical lymph nodes. Patients with residual thyroid tissue of more than 1 cm with an elevated thyroglobulin level will have a total body isotope scan to detect distant metastases. These patients will subsequently have a remnantectomy (excision of remnant thyroid tissue) followed one month later by radioactive iodine therapy after hormone withdrawal. The long term follow up of our patients is decided along the protocol guidelines.

The data were entered in a case record form (CRF), that included the clinical and demographic details, clinical diagnoses, presence of co-morbid conditions, biochemical and radiological investigations. Details of surgery(ies) performed and radioactive iodine ablation, complications of surgery, and the ultimate outcome of patients on subsequent follow up visits.

Statistical analysis: Data were analysed by using the Statistical Program for Social Sciences version 12.0 (SPSS Inc. Chicago, Illinois, USA). The appropriate measures of central tendency and variation were used and Chi-square test was used to test independency and *t*-test was used to compare means. *P*-value ≤ 0.05 was considered as significant.

3. Results

One hundred and eight medical records of patients diagnosed to have DTC were reviewed. Seventy two patients (66.7%) were females and 36 (33.3%) were males. The median age for females was 40 years (range 14–87 years) and that for males was 45 years (range 14–77 years). Ninety patients (83.3%) had papillary thyroid carcinoma, four patients (3.7%) had follicular carcinoma and fourteen patients (13%) were diagnosed with other thyroid cancers, namely medullary, anaplastic, and thyroid lymphoma. Females were more affected by differentiated thyroid cancer compared to male patients, with females constitute 60.19% while males were only 26.85% of the total number of DTC. However; there was no statistical association between sex and type of thyroid cancer (Chi-square = 1.24; *df* = 1; *P*-value = 0.167) (Table 1).

The other types and number of malignant tumors of the thyroid gland in this study included medullary carcinoma (5 cases), anaplastic carcinoma (5 cases) and lymphoma (4 cases). They all together

Table 1
Pathological types, number and percentage of thyroid carcinoma by gender at KFSH&R-J, January 2000 to September 2006.

Type of tumor	Sex		Total
	Female	Male	
Papillary	62 (57.4%)	28 (25.92%)	90(83.3%)
Follicular	3 (2.8%)	1 (0.93%)	4 (3.7%)
Others	7 (6.5%)	7 (6.5%)	14 (13.0%)
Total	72 (66.7%)	36 (33.3%)	108 (100%)

constituted 13.0% (14 cases) of the total number of the cases reviewed. In this group of patients the gender distribution is equally shared at a rate of 6.5% each.

The commonest mode of presentation was the presence of a neck swelling in 99 patients (91.7%) the remainder had their neck swelling discovered on ultrasound examination. Only one patient (0.9%) in this series gave a positive family history of thyroid cancer in a first degree relative. A second patient (0.9%) gave a history of exposure to radiation at an early stage of his life. Seventy patients (68.0%) had ultrasound guided fine needle aspiration cytology (FNAC) at our hospital. The sensitivity of FNAC at our institution is 74% (95% CI 64–84%), with specificity of 94%. The other 38 patients (32.0%) had an FNAC done in an outside facility with or without subsequent surgical procedures, and brought histopathology slides for review in our institution. All patients with an FNAC positive for malignancy (51%) were subjected for surgery.

The total numbers of patients operated in our hospital were 80 patients, and the total number operated elsewhere were 28 patients. Of those 80 patients, 23 patients underwent lobectomy, 21 patients had completed thyroidectomy, 19 patients had total thyroidectomy. The remaining 20 patients were those who had recurrence and they undergo redo surgery (15 patients from outside and 5 patients who were primarily managed at our institution). So the total number of patients who had total thyroidectomy were 40 patients (50% of all treated patients).

The patients who were primarily operated outside our institution and who were referred to our Centre for further treatment were 28 patients. Of those, 14 patients had total thyroidectomy, and 8 patients had lobectomy. Of the later, 6 patients had to undergo completion thyroidectomy in our institution. Further 11 patients had to undergo a second operation in our institution make the total number of the 'non-virgin-neck patients' 17 patients.

In the whole group, postoperative complications included bleeding, hoarseness of voice, and transient hypocalcaemia. The number of each complication and its percentage is shown in Table 2.

The tumor size, multi-centricity, the presence of vascular and/or capsular invasions in DTC have a lot of bearing on the prognosis. In addition, the rate of local recurrence and the need for adjuvant radioactive iodine ablative therapy affect the prognosis. In our study we found that the tumors size varies between less than 1 cm and more than 5 cm. Of the above 80 patients operated upon in our institution, twenty three patients had a tumor size of less than 1 cm, 22 patients had tumor size between 1 and 2 cm, 21 patients had tumors between 2 and 5 cm, and only 8 patients their tumor size was more than 5 cm, the data of the remaining six patients were missing. Of those treated surgically elsewhere ($n = 28$) before referral to our centre, no data regarding tumor size were available to present.

From our first group 'Virgin-neck Group', 14 patients had a histology positive for vascular invasion, 28 patients had a positive capsular invasion and 33 patients had multi-centric tumor, the remaining 5 patients did not show features of invasiveness. Thus patients who have overall features of histological invasiveness represents 93% of patients treated primarily at our institution.

Table 2

Documented complications following thyroid surgery for thyroid cancer patients at the King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia, between January 2000 & September 2006.

Complication	Frequency	Percentage
No complication	95	88.0%
Bleeding	2	1.8%
RLN ^a dysfunction	5	4.5%
Hypocalcaemia	6	3.6%
Total	108	100%

^a RLND (Recurrent Laryngeal Nerve Dysfunction).

The total number of patients who received adjuvant radioactive iodine therapy (RAI) following surgery for differentiated thyroid cancer, were 68 (63%) and 40 patients (37%) did not receive any RAI therapy.

The main tool of follow up was a soft tissue neck ultrasound scan, 72 (66.7%) patients had an ultrasound scan which was positive in 35 (32.4%) patients when it diagnosed a recurrence in the neck or remnant thyroid tissue. Patients with positive ultrasound were submitted to a diagnostic radioactive iodine whole body scan to rule out secondary deposits. Sixty nine patients (63.9%) with a positive radioactive iodine scan received radioactive iodine ablation therapy.

The mean age of patients who were still alive at follow up was 41.4 ± 17 years. In contrast, the mean age of those who died was 53 ± 12 years. This difference in the mean age between the two groups was not statistically significant (t -test, $p = 0.185$). The overall outcome of our patient cohort is shown in Table 3.

4. Discussion

This is the largest epidemiological study on thyroid cancer performed in the western part of Saudi Arabia. The study emphasizes the need for a dedicated team which follows a consensus-based protocol or a pathway for the management of DTC. Such an approach, we believe, is very much required because DTC is a unique and interesting disease in many aspects. Our study confirmed previous reports from Saudi Arabia and the Gulf region about incidence and behavior of thyroid cancer. Ahmed et al.¹¹ (1995) who presented one of the largest series in the world showed that papillary carcinoma represents 79% of all thyroid cancer in their series with follicular cancer accounting for 4.3% in that series. Alzahrer et al.¹² (2008) reported similar figures from the United Arab Emirates, a fact been reproduced from the review by Alzahrani and Ravichandran¹³ (2007) on thyroid cancer in the Gulf States.

There is a considerable debate and controversy about the management of differentiated thyroid cancer in the literature. Although most patients do well, there is still considerable contention related to the extent of thyroidectomy and the postoperative management of these patients. There are vigorous proponents of routine total thyroidectomy, whereas other authors recommend less than total thyroidectomy depending on the prognostic and risk factors.¹⁴ The existing controversy and contention inspired us to develop the TCG consisting of members from all the disciplines involved in the management of thyroid cancer. This consensus-based style of management has made the challenge imposed by managing DTC much easier, specially that there are no prospective randomized trials of treatment been done in this area and the results from the ongoing randomized trials will not be available for many years, given the typically prolonged course and relative infrequency of these tumors. Most of the information about the treatment comes from studies of large patients' cohorts in which therapy has not been randomly assigned. This accounts for much of the disagreement about managing differentiated thyroid cancer.

Table 3

Overall outcome of patients with Differentiated Thyroid Cancer at the King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia, between January 2000 & September 2006.

Outcome	Frequency	Percentage
Alive	99	91.7%
Died	4	3.7%
Missing	5	4.6%
Total	108	100%

Nonetheless, most patients can be cured of this disease when properly treated by experienced physicians and surgeons as part of a team.¹⁵ Surgery is the primary treatment of choice for patients with DTC followed in many patients by radioactive iodine ablation and suppressive thyroxin therapy. Established in the year 2003 the TCG adopted a protocol of management which is a product of our local experience and the guidelines set for the management of DTC in adults published by the British Thyroid Association in 2002.¹⁶ The protocol provided our clinicians with universal standards of management, applicable to the vast majority of patients with DTC. In the majority of controversial areas (e.g. controversy of lobectomy vs. total thyroidectomy in follicular neoplasia), one of the dilemmas is the extent of surgical procedure in case of a cytological diagnosis of follicular cancer. In our institution we treat them with a lobectomy and isthmusectomy.

Total thyroidectomy is the standard of care in our institution for DTC except for a unifocal micro-papillary carcinoma (less than 1 cm) (*with no evidence of invasiveness or regional/distant spread*) when a lobectomy and an isthmusectomy would be enough without radioactive iodine ablation. We follow the recommendations of the ATA guidelines regarding performing central compartment lymph node dissection in a lesion with an FNA suspicious of papillary thyroid cancer and Hürthle cell cancers.¹⁷ However the European consensus states that the benefits of an 'en-bloc' central node dissection in the absence of pre- or intra-operative evidence of nodal disease is controversial. In the case of a micro-PTC, few surgeons advocate lymph node dissection, thereby reflecting the positive relationship between tumor size and lymph node metastasis.¹⁸ Lymph node invasion is recognized as a risk factor for local recurrence, as indicated by the large cohort study of Lundgren et al.¹⁹ (2006) which showed significantly higher mortality rates in DTC with lymph node involvement even after adjusting for the TNM stage. Sywak et al.²⁰ (2006) demonstrated that in papillary thyroid cancer of more than 1 cm, the addition of routine lymph node dissection of the central compartment of the neck resulted in lower post-ablation thyroglobulin levels and higher rates of 'athyroglobulinaemia' when compared to total thyroidectomy alone.²⁶ In their experience, the risk of permanent hypoparathyroidism or recurrent laryngeal nerve dysfunction was not different between the two approaches. Similarly, in our institution, despite the fact that the incidence of recurrent laryngeal nerve dysfunction and transient hypocalcaemia is higher in redo surgery and in total thyroidectomy for malignant thyroid disease, yet we have an incidence of 4.8% for recurrent laryngeal nerve dysfunction, and 3.8% for transient hypocalcaemia which is in line with international literature.

In our institution, when a patient has a diagnosis of follicular neoplasm we go for lobectomy and isthmectomy, the final permanent pathology comes back as follicular carcinoma we then go back to complete the thyroidectomy. i.e. that is to say when the diagnosis DT cancer diagnosis is made in retrospect. Remnantectomy (resection of a remnant thyroid tissue in the thyroid bed) is carried out when a patient has undergone total thyroidectomy and on follow up when a high thyroglobulin (TGB) level is elucidated and a neck ultrasound shows remnant thyroid tissue in the thyroid bed of more than one cm. If less than 1 cm of remnant tissue with elevated TGB we would then subject the patient to RAI, specially if the remnant in an anatomical site endangering the recurrent laryngeal nerve.

We follow the American Thyroid Association (ATA) guidelines for radioiodine ablation for patients with thyroid cancer.¹⁷ The appropriate dose of radioactive iodine for thyroid ablation has been a source of continuing controversy. Although the low dose radioactive iodine ablation is advocated by some authorities,²¹ yet the high fixed dose of 100–200 mCi has been advocated by most authorities.^{22,23} This we believe has contributed to the high overall survival of 91.7% shown in Table 3.

Comparing our centre outcome from this relatively modest number of patients, were not different from results obtained in centres of excellence in the developing world, with approximately 92% of our patient alive at the time of the analysis of a follow up period of 7 years. A recent retrospective series from Italy showed a disease free state of 94% after 48 month following surgery.²⁴ We seem to be ahead of other centres in the region. Bhargav et al.²⁵ (2010) from India reported the 10 year overall survival rate of their low and high risk patients as 80% & 54% respectively. Our group are mostly of high risk, with significant proportion of them had larger tumor size, features of histological invasiveness and evidence of locoregional spread. Our finding confirms the earlier report of Al-Nuaim et al.²⁶ (1996) who showed that papillary thyroid cancer in Saudi Arabia present in an advanced stage.

Regarding long term follow up it has been well documented in the literature that most recurrences of DTC occur within the first five years after initial treatment, but recurrences may occur many years or even decades later, particularly in patients with papillary carcinoma. As most recurrences in DTC occur in the first 5 years after treatment,²⁷ we adopt the approach for long term follow up for our patients, with all patients seen at 6 monthly interval in the first year, then yearly following that for the first five years, but long term follow up is always stressed to patients.

In conclusion; our overall results, management and outcome of DTC match what has been published from other institutions. DTC though not a very common disease yet it is unique in its biological behavior, prognosis and thence its management. Once the diagnosis of DTC is established, several treatment options may be considered, depending upon the extent of the disease, the patient's age, and the presence of co-morbid conditions. In the absence of prospective trials, conclusions regarding the optimal selection of treatments must be based upon retrospective analyses and expert consensus opinions augmented by consensus-based teams like our TCG interested and dedicated to the management of each and every case upon its own merits. Despite the controversy on the extent of thyroidectomy and the limits of lymph node dissection surgery still remains the primary mode of therapy for patients with DTC. Our own experience highlighted in this paper is very much in accord with this.

Conflict of interest

None declared.

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Ethical approval

The study has been approved by IRB (Institutional Review Board) in King Faisal Hospital and Research Jeddah.

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