Well-differentiated Thyroid Carcinoma: Factors Predicting Recurrence and Survival

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ABSTRACT

Aims: 1) Determine the patient and tumour characteristics for well-differentiated thyroid carcinoma – towards developing a unique risk classification for our largely Chinese population. 2) Assess extent of thyroid surgery required. 3) Document prognostic value of UICC and AMES classification.

Methods: Retrospective review of 175 patients treated for primary thyroid epithelial malignancy by the Department of General Surgery at the Singapore General Hospital.

Results: There were 78% papillary carcinomas (PC) and 19% follicular carcinomas (FC). Female: male ratio was 3:1. Patient distribution in the UICC stages I, II, III, IV is respectively 56, 11, 31 and 2%. Twenty-six percent had hemithyroidectomy, and 74% total thyroidectomy. Neck dissections were required in 6% of FC compared to 34% of PC. Mean follow-up was 40 months. Extent of surgery did not affect PC/FC survival nor recurrence rates (p=0.53 and 0.06 respectively). Recurrences occurred in 15% FC and 9% PC. Death occurred in one FC and two PC. Survival correlated with UICC stage I/II and stage III/IV groups (p=0.04), and recurrence correlated with AMES High and Low Risk groups (p=0.004). No statistically significant difference was shown for survival between PC and FC or AMES groups and recurrence between PC and FC or UICC groups.

Conclusions: Extent of thyroid surgery does not significantly affect local recurrences of PC/FC. The characterisation of thyroid carcinoma here is an important step towards developing a risk classification unique to our largely Chinese population.

Keywords: Thyroid carcinoma, Chinese, risk-group classification, extent surgery

Singapore Med J 2002 Vol 43(9):457-462

INTRODUCTION

Thyroid carcinoma is the 9th leading cause of cancer in Singaporean females[1]. In the West, many studies evaluate the controversies surrounding prognostic factors, best mode of investigation and treatment in thyroid carcinoma. However, there may be inaccuracies in applying results of those studies to an Oriental population[2].

Risk-group stratification in thyroid carcinoma is important for choice of extent of surgery, adjuvant therapy and prognosis[3-6]. To be meaningful however, this has to be considered with the patient profile, tumour characteristics, and complication rates of treatment specific to each centre.

This study aims to: 1) Characterise thyroid carcinoma found in our centre, one with a largely Chinese population; 2) assess the adequacy of investigations and extent of surgery required; and 3) compare the prognostic value of UICC and AMES risk stratifications.

METHODS

Medical records of the 175 patients treated for primary thyroid epithelial malignancy at the Singapore General Hospital's General Surgery Department were reviewed (January 1990 to December 1997). Information on race, sex, age, presenting signs and symptoms, investigations, type of operations, operative complications, further management, recurrence and current status was elicited.

Emphasis was on fine-needle aspiration biopsy (FNAC) if malignancy was suspected, rather than thyroid ultrasound or scan. As most patients are euthyroid, serum thyroid function tests were not routine.

Histology followed WHO's classification[7]. Table I shows the age-related TNM staging that was retrospectively assigned based on the International Union Against Cancer classification (UICC)[8]. In a review of 10 different risk-classifications of thyroid cancer by Brierley, no superiority of the other systems over the TNM classification of the AJCC and UICC was found[2,9,10]. Patients were also classified into

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Table I. UICC age-related pTNM staging.

Stage	Papillary/Follicular Carcinoma		Medullary Carcinoma	Anaplastic Carcinoma
	Age <45 year	Age >/= 45 year		
I	T1-4N0, M0	T1N0M0	T1	
II	T1-4N0,1M1	T2-3N0M0	T2-4	
III		T4N0M0 or T1-4N1M0	N1	
IV		T1-4N0,1M1	M1	Any T, N, M

T1 </= 1 cm
T2 >1 cm, </=4 cm
T3 >4 cm
T4 Extrathyroidal
N1 positive neck lymph node
M1 positive distant metastasis

Table II. AMES risk classification.

Low risk

A. Young without distant metastases (Male <41 year, Female <51 year)

B. Older patients with:
   1. Intrathyroidal PC or minor tumour capsular involvement FC and
   2. Primary tumor <5 cm and
   3. No distant metastases

High risk

A. All with distant metastases

B. All older patients with:
   1. Extrathyroidal PC or major tumour capsular involvement FC and
   2. Primary tumour >/= 5 cm regardless of disease extent

Table III. Clinical characteristics of 169 papillary and follicular carcinoma patients by pTNM staging.

	Stage I (n=95) (56%)	Stage II (n=18) (11%)	Stage III (n=52) (31%)	Stage IV (n=4) (2%)	Overall (n=169) (100%)
Age (year)					
Mean	34.7	53.1	56.7	56.0	43.9
SD	10.5	12.8	11.5	11.7	15.2
Range	12-81	30-72	13-83	39-65	12-83
Sex					
Male	19	7	14	1	41
Female	76	11	38	3	128
Ratio	1:4	1:2	1:3	1:3	1:3
Tumor Type					
Papillary	78	11	45	2	136
Follicular	17	7	7	2	33
Ratio	5:1	2:1	6:1	1:1	4:1

AMES High and Low Risk Groups (Table II) for further comparison of the prognostic value of UICC and AMES risk classification[4].

At all times, risk group stratification was an important consideration. Tumour grade is often not specified for papillary carcinoma in our centre; thus this was not considered. We classify our patients into low and high risk groups primarily according to the AMES scores. A third group was classified as intermediate risk. This intermediate risk group consisted of a) low risk tumours (papillary tumours, less than 4 cm diameter) in high risk patients (males, older than 40 years' previous neck irradiation exposure); or b) high risk tumours (poorly differentiated, Hurthle cell, anaplastic, more than 4 cm diameter) in low risk patients (younger than 40 years, females). Total thyroidectomy is usually performed for the intermediate and high risk groups and hemithyroidectomy for the low risk patients. This decision is finalised intraoperatively after frozen section pathology, determining the size of tumour, the likelihood of extracapsular spread, and tumour multifocality. Our intermediate-risk group, a modification of the criteria described by Memorial's classification, provided a challenge[6]. Its operations range from hemithyroidectomy to total thyroidectomy, with or without postoperative radio-iodine, and radiotherapy. Palpable lymph node metastases were subjected to modified neck dissection. Regularly, a search for and clearance of pre-laryngeal and pare-tracheal nodes was done. All patients had adjuvant thyroxine for thyroid suppression or replacement post-surgery. Only high risk patients received radioiodine postoperatively.

Data were analysed using SPSS version 10. To compare the Kaplan-Meier survival and disease free difference the log-rank test was employed. Statistical significance was accepted to correspond to a p value <0.05.

RESULTS

There were 175 patients. Tumour histology was 136 (78%) papillary carcinomas, 33 (19%) follicular carcinomas, 4 (2%) anaplastic carcinomas, and 2 (1%) medullary carcinomas. There was no significant difference in histology with regards sex. Henceforth, only the 169 well differentiated thyroid carcinomas (PC/FC) will be discussed. **Mean follow-up** was 40.3 months (SD 26.5 months).

Age, sex distribution and tumour histology wrt UICC Stages I -IV is shown in Table III. The mean age was 44 years (SD 15) and median age 42, ranging from 12 to 83 years. The race distribution was 82% Chinese, 9% Malay, 5% Indian and 4% Others. **Mean age** for FC and PC was 42 (SD 13) and 44 (SD 16) years respectively (no significant difference). Only 30 patients (18%) were under 30 years. Pathologically confirmed **neck nodes** were documented in 6% of FC and 34% of PC (FC: PC = 1:6). **Distant metastasis** at presentation was found in two FC (6%) and four PC (3%). Extrathyroidal invasion occurred in 17 (30%) PC and 2 (6%) FC.

Univariate analysis showed that the difference of recurrence and survival with regards to histology (PC/FC), sex, age, race, extrathyroidal invasion and neck nodes involvement are not statistically significant. However, tumour size (</= 4 cm vs >4 cm) associated with survival (p=0.008), and distant metastasis with recurrence (p<0.001).

For the FC patients (n=33), the sensitivity for **frozen section** performed (n=23) is 17% and for **fine-needle aspiration cytology** (n=32) 31%. For the FC patients too, the false negative rate for frozen section was 13% and for fine needle aspiration 3%. **Thyroid ultrasounds and scans** were performed in 44 (26%) and 95 (53%) patients respectively. Twenty-five (15%) patients had both. The thyroid scans were reported as 71 (75%) single cold nodule, 1 (1%) single hot nodule, 20 (21%) multinodular goiter and 3 (3%) normal.

Table IV shows the treatment modalities (thyroid surgery, adjuvant radioiodine and radiotherapy) for the PC/FC patients by UICC I-IV stages. Seventy-four percent had total thyroidectomy and 26% hemithyroidectomy (of which 27% were FC and 73% PC). None had only a nodulectomy.

Surgical complications included two wound infections, two haematomas and one seroma. **Recurrent nerve injury** was accidental in four patients (three unilateral and one bilateral), all of which had total thyroidectomy (2.4%). This excludes those who had intentional nerve sacrifice due to tumour involvement. Only one patient had permanent hypocalcemia, of the 123 (0.8%) who had near total/total thyroidectomy.

Table V shows the treatment outcome (recurrence and survival) with regards to UICC Stages I-IV for the 169 PC/FC patients. Overall recurrence was 10% (17 patients). Overall death was 1% (three patients). **Table VI shows the recurrence vs histology (PC/FC), UICC stages, AMES groups and extent of thyroidectomy**. A statistically significant difference was noted only for recurrence vs AMES High/Low Risk groups (p=0.004), as illustrated in Fig. 1 . There were no local **recurrences** in both FC and PC. Twelve (9%) PC had recurrences, of which nine were in neck nodes and three as distant lung metastases. Five (15%) FC had recurrences, of which one was in neck node and four as distant metastases to lung and bone. **Table VII shows the survival vs histology, UICC stages, AMES groups and extent of thyroidectomy**. A statistically significant difference was noted only for survival vs UICC Stage I/II and Stage III/IV groups (p=0.04), as illustrated in Fig. 2.

Table IV. Treatment modalities of 167 papillary and follicular carcinoma patients by pTNM staging.

	Stage I (n=95)	Stage II (n=18)	Stage III (n=50)	Stage IV (n=4)	Overall (n=167) (%)
Thyroid surgery					
HT	36	1	5	2	44 (26)
NTT/TT	59	17	45	2	123 (74)
Ratio HT: NT/TT	1:2	1:17	1:9	1:1	1:3
Adjuvant therapy					
Radioiodine (RI)	14	7	20	2	43 (26)
Radiotherapy (RT)	8	2	13	0	23 (14)
RI + RT	4	2	3	0	9 (6)

Two patients in Stage III out of the total 169 refused surgery.

Key: HT = Hemithyroidectomy,
NTT/TT = Near-total thyroidectomy/Total thyroidectomy

Table V. Treatment outcomes of 169 papillary and follicular carcinoma patients by pTNM staging.

	Stage I (n=95) (%)	Stage II (n=18) (%)	Stage III (n=52) (%)	Stage IV (n=4) (%)	Overall (n=169) (%)
Cancer recurrence					
No. of patients (%)	7 (7)	4 (22)	5 (10)	1 (3)	17 (10)
Time to recurrence					
Mean (months)	39.3	39.5	34.1	33.5	37.6
SD (months)	27.2	28.7	22.0	50.0	26.4
Cancer deaths					
No. of patients (%)	0	0	2 (3.8)	0	2 (1)
Time to recurrence					
Mean (months)	40.8	49.0	36.9	35.0	40.3
SD (months)	27.0	26.6	23.6	48.8	26.5

Table VI. Recurrence – UICC staging, AMES groups, histology and extent of thyroidectomy.

	No recurrences (%)	Total no	p
UICC Stage I/II	11 (10%)	113	
UICC Stage III/IV	6 (11%)	56	0.64
AMES high risk	3 (30%)	10	
AMES low risk	11 (8%)	138	0.004
Follicular carcinoma	5 (15%)	33	
Papillary carcinoma	12 (9%)	136	0.19
Hemithyroidectory	1 (2%)	44	
Total thyroidectomy	15 (12%)	123	0.06

Table VII. Survival – UICC staging, AMES group, histology and extent of thyroidectomy.

	No. of deaths (%)	Total no	p
UICC Stage I/II	0	113	
UICC Stage III/IV	2 (4%)	56	0.04
AMES high risk	0	10	
AMES low risk	0	138	–
Follicular carcinoma	1 (3%)	33	
Papillary carcinoma	1 (1%)	136	0.58
Hemithyroidectory	0	44	
Total thyroidectomy	1 (1%)	123	0.53

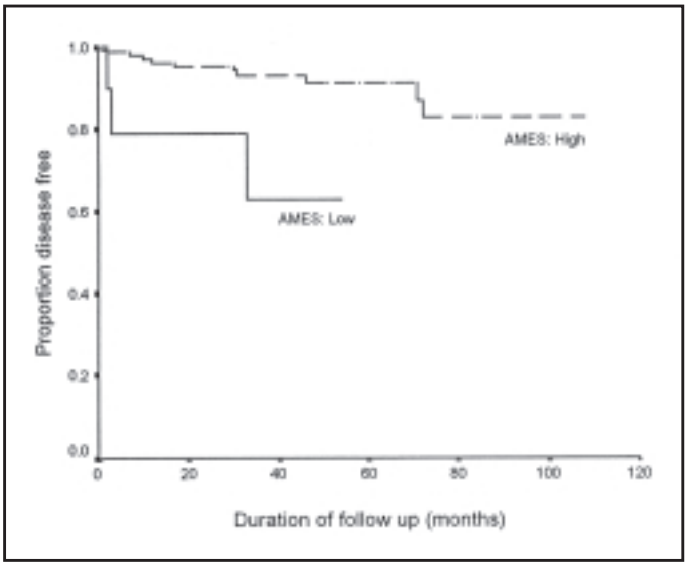

Fig. 1 Kaplan Meier graph of recurrence by AMES risk groups (p=0.004).

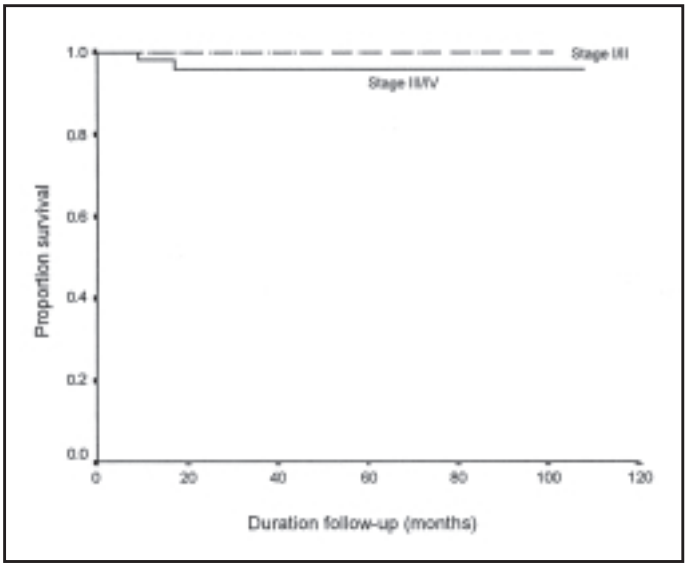

Fig. 2 Kaplan Meier graph of survival by UICC stages (p=0.04).

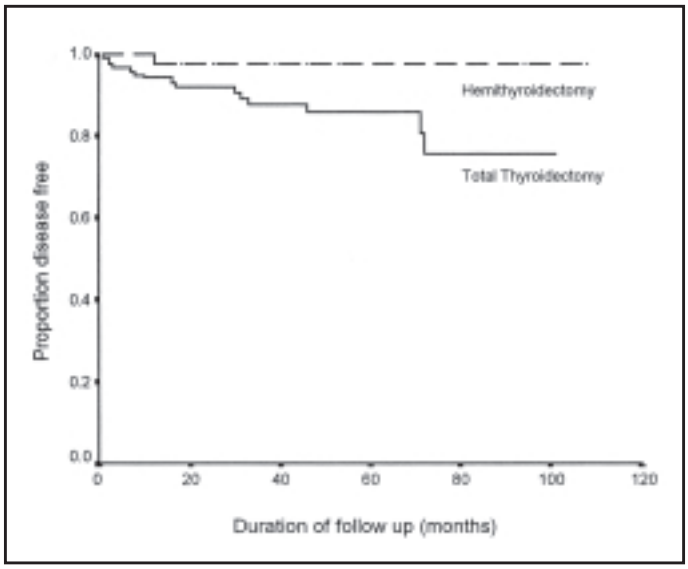

Fig. 3 Kaplan Meier graph of recurrence by extent of surgery (p=0.06).

The extent of thyroid surgery (hemithyroidectomy vs total thyroidectomy) did not affect recurrence (p=0.06, and illustrated in Fig. 3) or survival significantly (p=0.53).

DISCUSSION

The many controversies surrounding investigations, prognostic factors and treatment of thyroid cancer undoubtedly stem from differences in these very aspects between various centres. The results of this study are preliminary, acknowledging the needs for continued follow-up and a larger number of patients studied. However, they are important first steps towards developing a unique risk classification specific to our population. It has characterised the patient and tumour profile, audited the adequacy of investigations, treatment and complications for the well differentiated thyroid carcinomas specific to this centre and our population.

This study's female:male **sex ratio** of 3:1 is similar to that of most studies[11-13]. The **race** distribution of 82% Chinese, 9% Malay, 5% Indian and 4% Others is comparable to Singapore's 1990 resident population (78%: 14%: 7%: 1%). The **mean age** of FC and PC was 42 and 44 respectively. Interestingly, this differs from most studies where FC presents at an older age[11,12,14]. Further observation will be required to document if this places our FC at a lower risk compared to other populations.

We will limit the discussion to the well-differentiated thyroid carcinomas (PC/FC) henceforth. **Papillary carcinoma** accounted for 78% and **follicular carcinoma** 19%, compatible with most studies. Sixty-seven percent of our patients were in the early **UICC stages I/II**, and 33% in stage III/IV. Reports of Stage I/II distribution range from 60% to over 80%, possibly due to differing referral patterns and patient culture specific to each centre[8,15].

Lymph node involvement here for FC: PC is 1:5.8 (6%:34%). In Shaha's study of 1,038 patients, the ratio was 1:2.4 (27%:65%)[16]. All studies however, would agree that lymph node involvement is common for PC. Should patients undergo elective neck dissections, the figures would be even higher, as in De Jong's study of 129 PC patients who had 75% of lymph node involvement[17]. Previous studies like Degroot's had indicated a negative influence of lymph node metastases on survival, but this is now being challenged by long-term retrospective studies like Mazzaferri's[11,13].

Statistical analysis did not show any **predictors of histological type (FC/PC)** wrt sex, age, race, past/family history nor type of operation. **Fine needle aspiration cytology** was the most useful investigation

because of its sensitivity and specificity in differentiating malignant from benign. In our hands, the sensitivity rate is 31% and false negative rate is 3% for FC. **Frozen section** compared poorly, with sensitivity and false negative rate of 17% and 13% respectively. It is not useful for differentiating follicular adenomas and carcinomas.

Extent of thyroid surgery is highly controversial due to the low mortality and long-term survival of the well-differentiated disease, especially for PC. Prospective randomised trials are thus impractical. Meaningful comparison of treatment between studies is further hampered by different risk stratifications used. There are proponents for a less radical operation in the low risk groups. The argument is that some papers have shown no difference between total lobectomy and total thyroidectomy wrt failure rate[14,16,18]. However, opponents would quote reports of disease multifocality reaching 85% and contralateral disease of 30%, with some studies showing that lesser surgical extent leads to increased recurrence with eventual decreased survival. As such, 74% of PC/FC had **near-total or total thyroidectomy**. With our complication rates acceptable at 2% recurrent laryngeal nerve injury and 1% permanent hypocalcemia, total thyroidectomy may seem to be the operation of choice. However, the extent of thyroid surgery (hemithyroidectomy vs total thyroidectomy) has not significantly affected the survival or recurrence of well-differentiated thyroid carcinoma in this study. Furthermore, there were no local recurrences. As such, we consider even a small increase in morbidity unjustifiable when no improvement in outcome has been shown. This consideration assumes increased importance if personally, the surgeon has a higher surgical complication rate.

Surgery was the sole form of therapy in 66%. As adjuvant therapy, **radioiodine** was used in 26% and **radiotherapy** in 14% of patients. Though controversial, like the Mayo Clinic, we would add RI for high risk PC and if there was a thyroid remnant in the FC. Recent reports are increasingly supportive of the routine use of 1,311 ablation[11]. In advocating that, the side-effects of thyroiditis, sialodenitis, facial oedema and male infertility will have to be considered.

Careful analysis of **prognostic factors** avoids the morbidity and expense of more radical treatment without compromising outcome. Prognostic factors of histology, age, sex, extrathyroid invasion, neck node, tumour size and distant metastasis have been given importance in our consideration of type and extent of treatment. Univariate analysis found none of those factors associated with survival and recurrence, with the exceptions of tumour size associating with survival and distant metastasis with survival. Kaplan Meier analysis has only shown a significant difference in survival between the UICC stage groups (p=0.04), and not for survival wrt PC/FC histology nor AMES risk groups. There is a significant difference in recurrence only for AMES High and Low Risk Groups (p=0.004), and not for FC/PC nor UICC Stage groups.

There are many **risk classifications** available. However, a risk classification prepared for one population may not be suitable for application to another[2]. Patient distribution in the UICC stages may differ. For example, our preliminary results have shown that the number of patients in UICC Stage II here is lower than expected compared to Stage III and IV. Even the widespread assumption that females are at lower risk has been challenged. For example, Noguchi et al gave males a lower risk in their Japanese population[4,19,20]. Within one's own centre, the ideal would be to have a unique staging generated via multi-variate analysis, followed by development of a prognostic model and validation. Presently, we are unable to do a multivariate analysis for development of a risk-classification unique to our population. This is due to as yet small numbers and a comparatively short follow-up resulting in few recurrences and deaths for statistical analysis. Until then, a unified classification like the UICC's or AMES can be used, such that comparison of treatment and outcome between different centres is possible.

CONCLUSION

This paper has characterised the patient and tumour profile of thyroid carcinoma found in our largely Chinese population, and contributes towards developing a risk-classification unique to our population. The extent of thyroid surgery has not correlated significantly with the survival nor recurrence of both papillary and follicular carcinomas, and local recurrences have been few. Meanwhile, the UICC and AMES risk classifications may be used for prognosis and reporting.

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