Long Term Outcomes of Simple Clinical Risk Stratification in Management of Differentiated Thyroid Cancer

W L Craig[1] MPH FRCS L Smart[2] FRCP, S Fielding[3] PhD, C Ramsay[4] PhD & Z H Krukowski[1] PhD FRCS FRCP

Department of Surgery[1]

Department of Pathology[2]

Medical Statistics Team, Institute of Applied Health Science[3]

Health Services Research Unit, Institute of Applied Health Science[4]

University of Aberdeen, UK.

Correspondence to:

Professor Z H Krukowski, East Lodge, Balmoral, Ballater AB35 5TB UK

Telephone: +447551323430 email: profzhk@gmail.com

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Key Words

Thyroid cancer, surgery, risk management, conservative therapy

ABSTRACT

Objective: To establish the long term outcomes of risk stratified management of differentiated thyroid cancer (DTC).

Background: Guidelines for management of DTC lack a strong evidence base and expose patients to overtreatment. This prospective study of patients diagnosed with DTC between 1977-2012 describes the long term outcomes of a conservative risk stratified (AMES) management policy .

Methods: Outcomes were analysed around patient and tumour characteristics, primary intervention (surgery +/- radioiodine (RAI)), in terms of mortality, recurrence and reintervention.

Results: Median follow-up in 348 patients was 14 years: mean age 48 (range 10-91) years, 257 (73.9%) female, 222 (68.3%) papillary cancer, tumour size 3.4 $\pm$ 2.0 cm (mean $\pm$ SD). 89 (25.6%) AMES high risk, 116 (33.3%) TNM stage III/IV and 16 (4.6%) had distant metastases. Primary surgery comprised lobectomy in 189 (54.3%): 11 (5.8%) patients had subsequent completion total thyroidectomy with cancer present in five. Primary nodal surgery was performed in 142 (40.8%) patients. 35 (13.5%) low and 43 (48.3%) high risk patients received RAI following initial surgery. Overall disease specific survival (DSS) was 92.1% at 10 years and 90.7% at 20 years. DSS at 20 years was 99.2% in low risk cases. AMES risk scoring predicted both survival and recurrence. Patients receiving RAI and AMES high risk were significantly associated with increased risk of death and recurrence.

Conclusions: Routine total thyroidectomy and RAI are not justifiable for low risk DTC. Treatment should be tailored to risk and AMES risk stratification remains a simple reliable clinical tool.

INTRODUCTION

Differentiated thyroid cancer (DTC) although rare, with a UK annual incidence of 4 per 100,000 population, is the commonest endocrine cancer and the incidence is increasing[1]. The British age-standardised incidence has more than doubled between 1975 and 2008 with a particular increase in small tumours[1]. The reasons for this increase include coincidental detection and increased population awareness – particularly, but not exclusively, for this group of small tumours[2]. Countries, with the most liberal access to diagnostic imaging and screening, such as the USA and South Korea, have the largest increase in incidence[3,4].

Although thyroid cancer comprises a heterogeneous range of diseases, including some anaplastic tumours and lymphomas, the majority are indolent. The two main histological types, papillary (PTC) and follicular (FTC) have differences but share an inherently good prognosis and long natural history[5]. Although there is an increase in high quality observational studies there is a virtual absence of randomised trials to properly inform surgical options; thus controversy remains about the optimum treatment for DTC and potential for harms from over-treatment.

There are reports of large case series, some comprising thousands of patients[6], from tertiary centres with an international referral base and remote long

term follow-up[7], heterogeneous national databases[8], Far Eastern centres with large numbers and cultural aversion to radiotherapy[9], with variable primary thyroid and nodal surgery[8], with relatively short follow-up and proxy outcomes variously managed by radiation oncologists[10], surgeons or endocrinologists. Furthermore although management related to risk is now being advocated this follows inital radical surgery and radioactive iodine therapy[11] that may represent overtreatment for many patients.The resulting confusion makes formulation of guidelines problematic.

The Grampian region of North East Scotland is geographically remote with a stable population of around 500,000 and a single combined medical/surgical thyroid unit in the Aberdeen Royal Infirmary since the 1950s. The multidisciplinary clinic was the first in the UK to introduce and analyse the impact of Fine Needle Aspiration Cytology (FNAC) on the management of thyroid swellings[12],[13] and prospectively collected data on thyroid cancer since 1977.

The underlying treatment philosophy was conservative avoiding overtreatment with both surgery and radioactive iodine (RAI). This prospective population based cohort study provides a perspective on the long-term outcome of a simple risk based approach to the management of DTC.

METHODS

This manuscript was prepared to conform to the STROBE statement on cohort observational studies[14].

All patients diagnosed with thyroid malignancy in the North East of Scotland between January 1977 and December 2012 were entered in a customised database. Information on preoperative investigation, operative procedure, pathology, adjuvant treatment and follow-up were collected. All patients were routinely consented for inclusion within the database; NHSG R&D did not require separate ethical permission for this analysis. All pathology was reported and reviewed by pathologists with an interest in thyroid cancer on at least three occasions with problematic cases sent elsewhere for further opinions.

Preoperative investigation evolved and included routine thyroid function, autoantibody status and FNAC (post 1981). Chest radiography and CT scanning were used selectively after FNAC or other investigation, e.g. node biopsy indicating DTC. Ultrasound[15] and MRI[16] scanning were evaluated in the 1980s and 90s and abandoned as routine first line investigations. After 2000 ultrasound scans were used to assess lymph nodes in patients scheduled for surgery for nodules confirmed to be, or suspicious for cancer. The minimum investigation necessary to formulate a treatment plan was used.

The surgical strategy until 2000 was to remove all macroscopic disease including involved or suspicious lymph nodes. The majority of patients had a total thyroid lobectomy with bilateral near/total thyroidectomy reserved for patients with bilateral disease, or deemed likely to require RAI. Completion total thyroidectomy following a diagnostic or therapeutic lobectomy was not routine. Post 2000 all patients with a preoperative diagnosis of cancer underwent imaging of the lateral cervical nodes with ultrasound, although some already had CT, MRI and/or latterly

PET/CT, to permit directed compartmental nodal dissection. After 2001 diagnostic central compartment node sampling was carried out in patients with no other indication for nodal removal but abandoned with a return to selective surgery after 2010[17]. Limited lateral nodal surgery was defined as removal of macroscopically abnormal lateral lymph nodes within or comprising a single lateral level. lntra-operative nerve monitoring was not used. Adjuvant RAI was based on risk. Whole Body Scanning (WBS) carried out ten days post- administration of theraputic RAI to identify areas of uptake. Low dose RAI diagnostic scans were not used routinely.

Since 2000 all cases were reviewed at an expanded multidisciplinary meeting (MDT) comprising endocrine surgeons, medical endocrinologists (licensed to administer RAI), pathologists, radiologists, ENT surgeons and medical oncologist. The MDT included the Highlands and Islands and Tayside regions of Scotland covering a population of one million although this study comprises only the North East cohort.

Follow-up comprised one month postoperative, six months for two years then annual review thereafter. All patients received levo-thyroxine to suppress endogenous TSH production: serum thyroglobulin was measured at each review except in patients with high anti-thyroglobulin antibody titres. Re-imaging and repeat FNAC were carried out if a new swelling was detected on examination or thyroglobulin increased. Thyroglobulin can be used for follow-up in patients who have not undergone total thyroidectomy[18]. Patients were seen at a dedicated thyroid clinic unless they left the region when follow-up continued by postal review by a local specialist.

Sufficient information was recorded to permit risk stratification using AMES[19] high/low risk (Table 1), MACIS[7] score and the sequential iterations of TNM staging, currently Version 7[20]. Outcomes assessed included overall and disease specific survival (DSS) and recurrence stratified by primary surgery, pathological type, RAI, AMES risk and TNM (V7) stage.

Statistical analysis:

Categorical variables were described using number and percentage, with normally distributed continuous variables as mean (standard deviation, SD), or median and inter-quartile range (IQR) if skewed. Kaplan-Meier plots were created to compare survival/recurrence for primary surgery, pathological type, RAI, AMES and TNM stage. Cox regression was used to assess the factors influencing DSS with results presented as adjusted hazard ratios and 95% confidence intervals.

RESULTS

Between January 1977 and December 2012, 348 patients were diagnosed with DTC (Table 2). All patients were followed up to the end of 2014, 96.0% in Aberdeen. In terms of primary therapy the majority of patients were treated with lobectomy 189 (54.3%) of 348, which included 30 (33.7%) of 89 AMES high risk patients (Table 3). Eleven (5.8%) of 189 lobectomy patients required subsequent completion total thyroidectomy: 5 (2.6%) had malignancy in the second lobe. The majority 206 (59.2%) of patients had no nodal surgery, 87 (25.0%) having only central compartment or limited nodal surgery, 55 (22.4%) had lateral neck node dissections, RAI was given to 78 (22.4%): 46 (53.9%) AMES high risk and 35 (13.5%) low risk patients following initial surgery.

With a median follow up of 14 years 75 (21.6 %) of 348 patients had died: 24 (6.9%) of DTC. 22 (24.8%) of 89 AMES high risk and 2 (0.8%) of 259 low risk patients died of DTC. DSS was 92.1% at 10 years and 90.7% at 20 years. DSS was better following initial thyroid lobectomy (Figure 1a), absence of RAI administration (Figure 1b) and AMES low risk (Figure 1c). Improved DSS according to the individual components (age, gender, size, spread and metastases) of the AMES score was confirmed. A similar striking relationship between initial lobectomy, RAI and AMES low risk and recurrence was found (Figure 2). The expected relationship between DSS and recurrence according to TNM stage was also seen (Figure 3) but there was no difference in DSS or recurrence according to histological type (Figure 4). Total thyroidectomy increased from 71/228 (31.0%) before 2000 to 88/120 (73.3%) post 2000 and RAI from 41/228 (18.0%) to 52/120 (43.3%) with no improvement in survival (Figure 5) or recurrence.

The results of multivariate analyses are shown in Table 4. Administration of RAI and AMES high risk were statistically associated with significantly increased risk of DTC death. The risk of recurrence was related to whether the patient had a total thyroidectomy and AMES high risk. MACIS scores were calculated retrospectively for all patients and prospectively for those diagnosed after 2010 and conformed to the risk groups described,

DISCUSSION

This prospective study with long term (mean follow up 14 years) outcomes following treatment of DTC in the UK and is based on a stable population in an isolated geographic region with complete follow-up. There has been a combined

medical/surgical thyroid clinic throughout with a commitment to evaluation of process and outcomes in thyroid cancer. We were the first in the UK to introduce and systematically analyse the impact of fine needle aspiration cytology (FNAC) on the management of thyroid swellings.[12,13] Studies of imaging modalities including ultrasound[15] and MRI[16] scanning also influenced the development of efficient local protocols.

Of particular relevance has been a consistently conservative approach to the management of DTC. Although this evolved and became more explicit over the 35 years of patient recruitment, the underlying philosophy was to tailor treatment to risk. Initially the surgical approach was to remove all macroscopic disease with total thyroidectomy reserved for bilateral disease, high risk tumours and adjuvant RAI likely to be required. Following the publication of the first British Association of Endocrine Surgeons guidelines diagnostic central compartment node sampling, with preservation of the thymus where possible and without skeletonisation of the recurrent nerves, was carried out in patients with no clinical or radiological evidence of nodal involvement. We reverted to selective dissection based on clinical assessment at operation after 8 years.[17] Lateral neck dissections became more frequent with levels resected guided by imaging. Frozen section was used intra-operatively to assess questionable nodal involvement. Completion total thyroidectomy was not routine following thyroid lobectomy (Table 3) and TSH was routinely suppressed. Decisions around treatment were made amongst a group comprising surgeons, endocrinologists (responsible for RAI administration) and pathologists until the larger MDT was established in 2000 when ENT surgeons, radiologists and oncologists also contributed. Indications for more radical therapy

including RAI and (completion) total thyroidectomy were influenced by adverse pathological features. Follow-up was six monthly for two years then annually thereafter following any surgical procedure. Review comprised examination, measurement of serum TSH, free T3 and T4, and thyroglobulin. Any new symptoms, clinical findings or rise in thyroglobulin triggered further investigation.[18] Elimination of serum thyroglobulin was not a therapeutic objective and a stable (low) serum thyroglobulin was accepted. Patients with serum antithyroglobulin antibodies were managed on an individual basis depending on risk.

Weaknesses of this study include the relatively small population studied, the number of new cancers diagnosed annually and, some will argue, not using ultrasound as a first line investigation. The incidence of DTC in Grampian is the second lowest in Scotland[21] and it can be argued that our practice is missing occult and minimal cancers by not carrying out routine ultrasound, total thyroidectomy and more extensive prophylactic nodal surgery[22]. These criticisms are valid only if such tumours were of clinical significance. The reduction in operation rate in thyroid swellings which followed the introduction of FNAC[12,13] has been sustained over the years with no evidence of late presentation of “missed” cancers[23]. Similarly failure to detect occult disease in the contralateral lobe following lobectomy, in macroscopically normal lymph nodes and distant metastases because prophylactic node dissection and WBS were not used should result in excessively high recurrence rates. This has not happened over the time scale of this study. Furthermore the cohort of patients managed prior to 1977 and not included in the prospective study has been followed up to death in the same clinic with no evidence to support this hypothesis. Therefore, internal study control negates these possible arguments.

TSH suppression has conventionally been used to reduce the risk of recurrence, particularly in PTC. Routine complete suppression is associated with potential for adverse cardiovascular outcomes (increased left ventricular mass, tachycardia atrial fibrillation) and osteoporosis[24] and there is now evidence that this is unnecessary in low risk cases[25]. Without a clear contraindication, routine suppression was carried out, and it may be that this practice makes a rise in serum thyroglobulin more meaningful. We do not have data to comment on possible increased cardiac or bone issues related to this policy: it may be timely to review this policy for low risk patients although it will be many years before any change in outcome would be become apparent.

Patients requiring RAI had a WBS ten days post therapy with subsequent doses tailored to uptake, response and thyroglobulin level. Although the proportion of patients receiving RAI increased over time it has remained low compared to most Western guidelines. It would be virtually impossible to improve upon the excellent outcome in terms of both survival and recurrence observed in those not receiving RAI (Figure 1b & 2b) with more liberal use.

The proportion of FTC (36.2%) in this cohort is higher than normally reported but consistent with an earlier comparative study in 1977[26]. The histology was reviewed on at least three occasions: initially by a pathologist with a thyroid interest, on review at a clinico-pathological conference or MDT and subsequently as part of a comprehensive review of all DTC. When there was debate about classification, opinions were obtained from nationally recognised thyroid pathologists. A number of

cancers were reclassified as follicular variant of PTC as diagnostic criteria evolved. The high proportion of FTC was consistent with four other UK university teaching hospital datasets which reported a range of 20.7 -31.1% FTC[27]. This indicates a different pattern of DTC distribution in the UK, within specialist units, compared to other locations.

The reliability of the AMES classification in identifying patients at risk of dying of DTC is confirmed beyond doubt (Figure 1c). It is notable that the cut-off point in terms of size in AMES is 5cm whereas much contemporary debate is around 1-2cm. Two AMES “low risk” patients died: Male, 35 years diagnosed in the 1980’s with an 8cm minimal follicular cancer treated by lobectomy presented with cerebral metastatic disease 14 years later which was treated by completion thyroidectomy and RAI but died 15 years after diagnosis: Female, 60 years 3.5cm histologically aggressive papillary cancer treated with total thyroidectomy and RAI but developed early local recurrence and metastases and died 9 years after diagnosis. Both these patients had features which increase perception of risk and the first patient would now also be treated with immediate total thyroidectomy and RAI as was the second. Whether this would have influenced the outcome is speculative. There is compelling evidence that mortality is related to the biological aggression of the tumour as exhibited in DNA ploidy[28],[29] regardless of therapy. Although AMES risk was devised to determine mortality it also proved a reliable indicator of the risk of recurrence (Figure 2c).

Contrary to the influential paper by Mazzaferri[8] thyroid lobectomy was not associated with worse outcomes than total thyroidectomy. In fact the converse was demonstrated (Figure 1a & 2a). Mazzaferri’s paper derived from a heterogeneous

national dataset from a mixture of specialist and non-specialist centres and surgeons with no risk stratification recorded or applied. The excellent outcomes in this series following lobectomy alone reflect correct case stratification for low risk of death and, as it transpired, of recurrence. This is entirely consistent with other series reporting a large experience of lobectomy alone for low risk tumours[10,30,31]. By converse, there is no implication that total thyroidectomy affords an increased risk of poor outcome - simply that biologically aggressive disease was treated maximally, whilst those avoiding maximal treatment came to no harm.

It is very striking that a similar effect is apparent in relation to the use of RAI (Figure 1b & 2b). Whilst our use of RAI has increased over the years, particularly in patients with TNM Stage III disease (age > 45 years, N1, M0), it remains at a low level and much less than contemporary guidelines and many publications advocate. There is no evidence from the HiLo trial[32] that routine RAI influences even short term proxy outcomes in low risk cases and we predict the current IoN trial[33] comparing none with low dose RAI in low risk cases will show a similar lack of effect.

We calculated MACIS scores for patients but since this depends on knowledge of the histology of the tumour it was not a useful tool for deciding operative strategy. It is a reliable indicator of long-term risk but as a continuous scale rather than a binary value there is more potential for debate in decision making. Categorical analysis produced similar results to those for TNM staging (Figure 3).

The overall and TNM stage related outcomes in terms of survival are comparable to all series with similar long-term follow-up despite the conservative treatment policy. The adverse outcomes observed following total thyroidectomy and RAI are not the consequence of more radical surgery or adjuvant RAI but statistical constructs, reflecting that patients at higher risk received more aggressive therapy. The virtual absence of DTC related death or recurrence in patients deemed at low risk and not undergoing total thyroidectomy or receiving RAI validates the treatment policy based on individual risk. The level of risk is easily estimated from simple parameters known at the time of primary surgery[7]. More extensive thyroid resection and prophylactic nodal dissection may disclose other foci of DTC but the clinical relevance of such incidental disease is inconsequential, consistent with autopsy studies demonstrating population prevalence of over 30% in asymptomatic individuals[34]. Much depends on the confidence of the MDT making these decisions: lack of exposure to the long-term outcomes of a conservative policy and adherence to guidelines with a poverty of evidence leads to over-treatment.

Over-treatment of DTC is increasingly recognised as both financially and clinically detrimental[35]. Medical bankruptcy in the USA is 3.5 times more likely with thyroid than other cancers[**36**] and many patients could be spared the cost of excessive surgery, RAI and imaging by recognising the benign nature of their DTC. This is particularly relevant in view of the dramatic increase in the rate of diagnosis of low risk DTC cancer over the last two decades[2,37]. The disadvantages of total thyroidectomy over lobectomy are the doubling of the risk of nerve injury, to both recurrent and superior laryngeal nerves, voice change and hypoparathyroidism. Although there are many selected series reporting extremely low rates of these complications following routine total thyroidectomy these are not representative of

unselected results reported in national registries[38] even amongst high volume surgeons[39].

Of concern is the potential for long-term effects of therapeutic RAI; apart from acute inflammation in salivary glands due to high uptake. There is a higher rate of malignancy in salivary gland, bowel and bone marrow amongst patients treated with RAI[40]. Whilst this association may be serendipitous the possibility exists that a second potentially more lethal malignancy may be induced by a high dose of radiation administered unnecessarily for a tumour with a negligible risk of death. This is especially relevant when the patient is young. Even if the second malignancy is not caused by RAI there is a cogent argument for avoiding unnecessary irradiation to patients with an apparent increased predisposition to develop cancer compared to the normal population.

Elimination of serum thyroglobulin as a therapeutic objective and proxy for long-term survival is problematic for a number of reasons. In many centres detectable thyroglobulin is considered to represent recurrence and Increasingly sensitive assays lower the threshold for such detection, When this initiates a search for recurrence occult disease may be found or suspected with the potential for further, more risky surgery and which may not impact on survival or clinically relevant recurrence. Only one third of tissue resected for such ‘recurrence’ is subsequently histologically confirmed[41] - the concept of overtreatment may apply beyond that of the primary intervention.

The uncertainty around recommendations for optimal management for low risk cancers remains manifest in guidelines; the 2014 British Thyroid Association guidelines state " The evidence for an advantage of total thyroidectomy compared to hemithyroidectomy in patients with unifocal tumours >1– ≤4 cm in diameter, age <45 years, with no extrathyroidal spread, no familial disease, no evidence of lymph node involvement, no angioinvasion and no distant metastases, is unclear"[42]. This study clarifies the position. The AMES criteria for defining risk may appear liberal to practitioners accustomed to a policy of total thyroidectomy and RAI for all but are justified not only in terms of mortality but also, and previously unreported, recurrence. The debate on the optimal management of DTC will continue but the movement away from routine aggressive multimodal therapy for all DTC manifest in early guidelines is already clear[43] and will continue. In practical terms no patient with papillary thyroid cancer selected to receive only thyroid lobectomy and no RAI died of thyroid cancer. Simple clinical risk stratification based on information available at the time of the primary surgery avoided the cost and complications of overtreatment in many patients with no demonstrable detriment over 37 years of this study. Radical surgery and adjuvant RAI therapy based on the risk of death and recurrence can be restricted to those at higher risk with the proviso that neither of these major outcomes may be affected in those with the most aggressive cancers.

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TABLE LEGENDS

Table 1: AMES risk stratification adapted from Cady et al Cancer 1979

Table 2: Demography, pathology, risk and stage in 348 patients

Table 3: Primary management of 348 DTC patients 1977-2014

Table 4:Multivariate analysis

FIGURE LEGENDS

Figure 1: Kaplan-Meier plots of DSS according to primary surgical procedure, administration of RAI and AMES Risk

Figure 2: Kaplan-Meier plots of recurrence according to primary surgical procedure, administration of RAI and AMES Risk

Figure 3: Kaplan-Meier plots of DSS, recurrence and TNM stage

Figure 4: Kaplan-Meier plots of DSS, recurrence and histological type

Figure 5: Kaplan-Meier plots of DSS according to TNM stage before or after 2000.

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Table

Table 1

HIGH risk		**LOW risk**
Male	age >40 years	All other patients
Female	age >50 years	
and	tumour size > 5cm	
or	extrathyroidal spread	
or	distant metastases	

Table

Table 2

Gender	male	91	*26.1%*
	female	257	*73.9%*
Age (years)	mean	48	
	range	10 - 91	
Follow-up (years)	mean	13.0	
	range	2 - 37	
Pathology	mean size	3.4 cm	
Papillary		222	*63.8%*
	mPTC	32	*9.2%*
Follicular		126	*36.2%*
	mFTC	71	*20.4%*
AMES risk	High	89	*25.6%*
	Low	259	*74.4%*
TNM stage	I	181	*52.0%*
	II	51	*14.7%*
	III	64	*18.4%*
	IV	52	*14.9%*
mPTC: micropapillary thyroid cancer <1 cm			
mFTC: minimal follicular thyroid cancer			

Table

Table 3

AMES	Low Risk		High Risk		Total	
	259		89		348	
First operation						
Lobectomy	159	*61.4%*	30	*33.7%*	189	*54.3%*
Subsequent completion	*8*	*3 +ve*	*3*	*2 +ve*	*11*	*5 +ve*
Total thyroidectomy	100	*38.6%*	59	*66.3%*	159	*45.7%*
Nodal surgery						
none	157	*60.6%*	49	*55.1%*	206	*59.2%*
central / limited	62	*23.9%*	25	*28.1%*	87	*25.0%*
lateral neck	40	*15.4%*	15	*16.9%*	55	*15.8%*
Radio-active iodine	35	*13.5%*	43	*48.3%*	78	*22.4%*
+ve: malignancy present in second lobectomy specimen						

Table

Table 4

Disease specific survival				
	Hazard Ratio	Adjusted Hazard Ratio	95% confidence interval	p
Histology PTC	0.8	1.1	0.40 – 3.26	0.81
RAI - any	18.9	6.3	1.81 – 21.61	0.004
Total thyroidectomy	3.3	0.6	0.19 – 1.57	0.27
AMES High Risk	41.8	22.0	4.65 – 103.60	<0.001
Nodal Surgery (major)	2.8	2.1	0.53 – 8.48	0.29
Recurrence				
Histology PTC	1.0	2.6	1.1 – 5.9	0.03
RAI - primary	7.1	1.6	0.79 – 3.38	0.19
Total thyroidectomy	7.2	4.2	3.29 – 13.30	<0.001
AMES High Risk	10.4	6.6	1.76 – 10.22	<0.001
Nodal Surgery (major)	3.6	3.0	1.11 – 8.09	0.03

Figure 1a: Primary surgical procedure

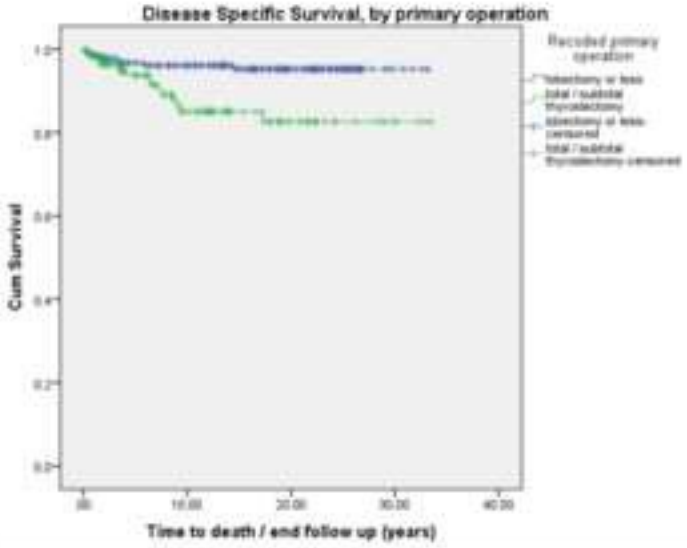

Figure 1b: RAI administration

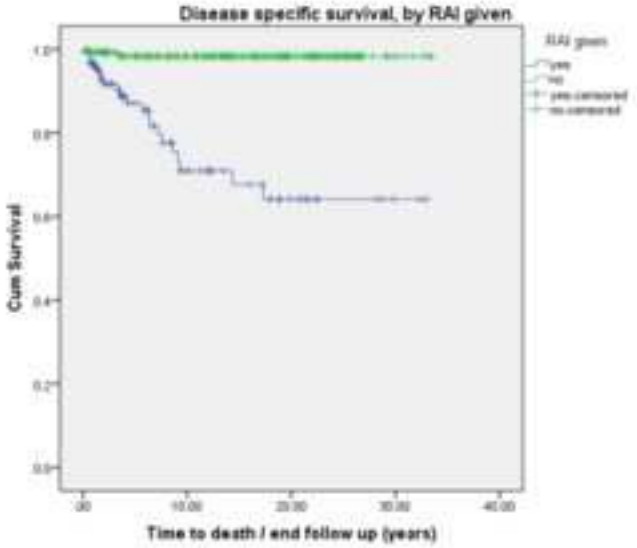

Figure 1c: AMES risk

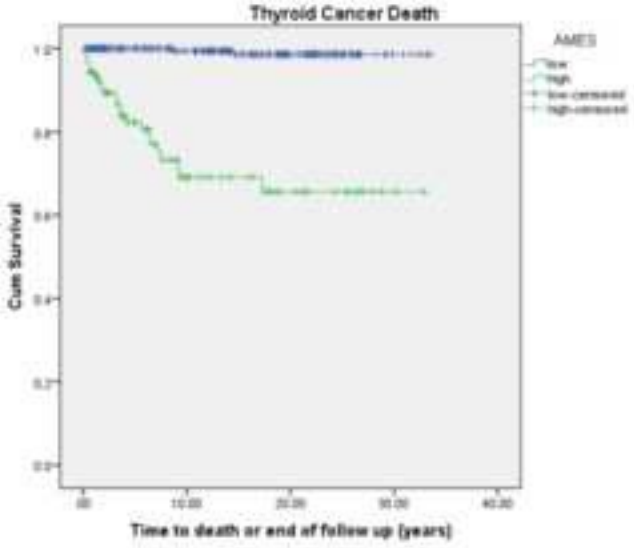

Figure 2a: Primary surgical procedure

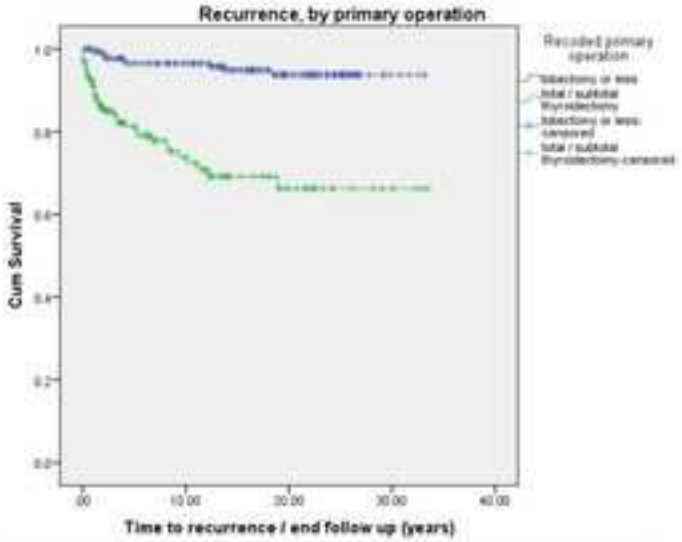

Figure 2b: RAI administration

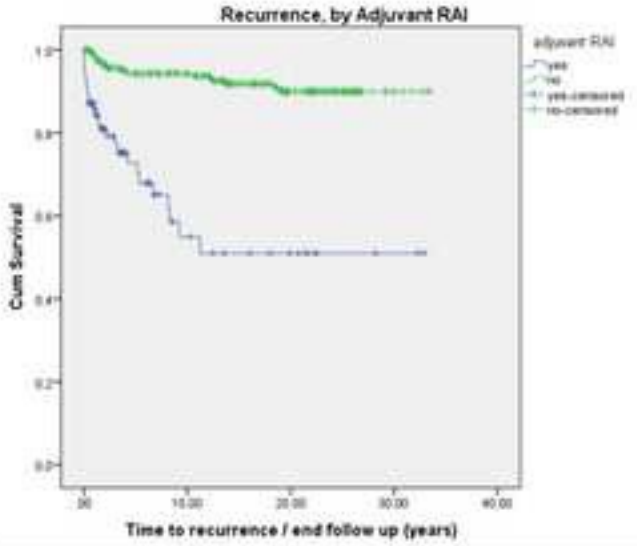

Figure 2c: AMES risk

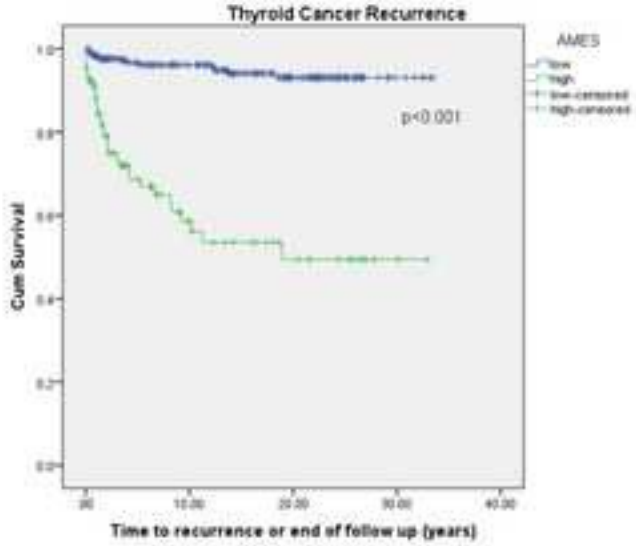

Figure 3a : DSS and TNM stage

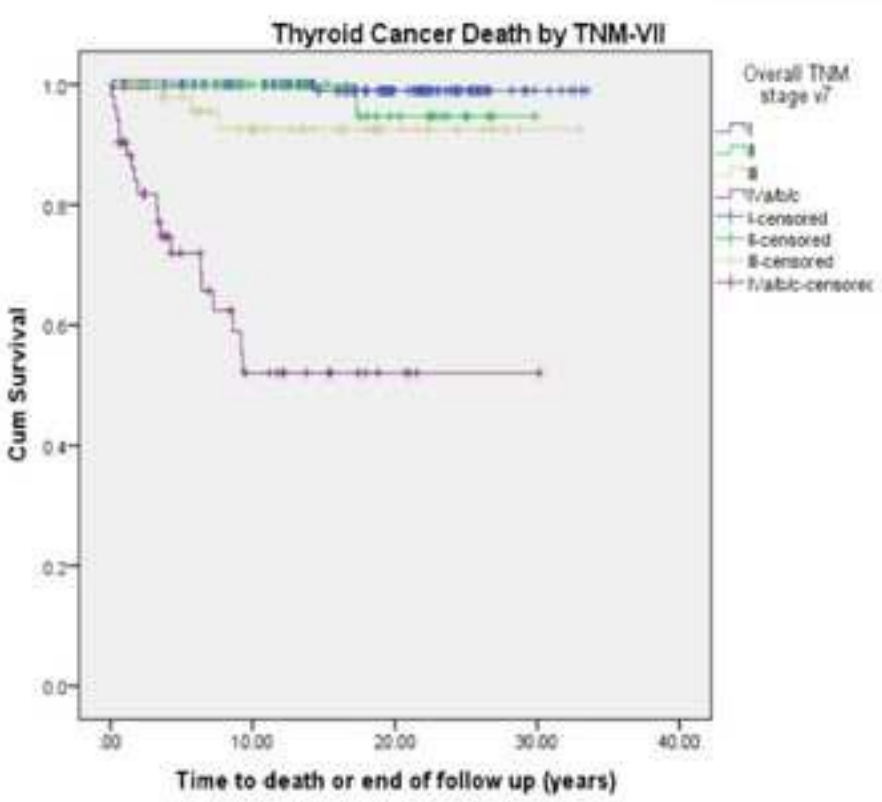

Figure 3b: Recurrence and TNM stage

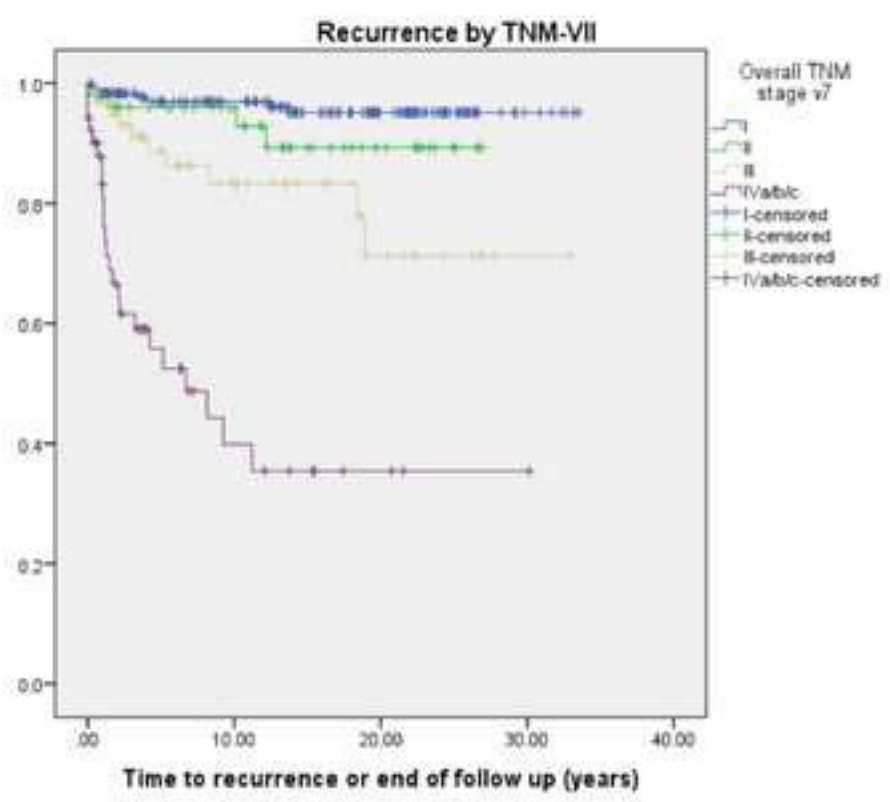

Figure 4a : DSS and histological type

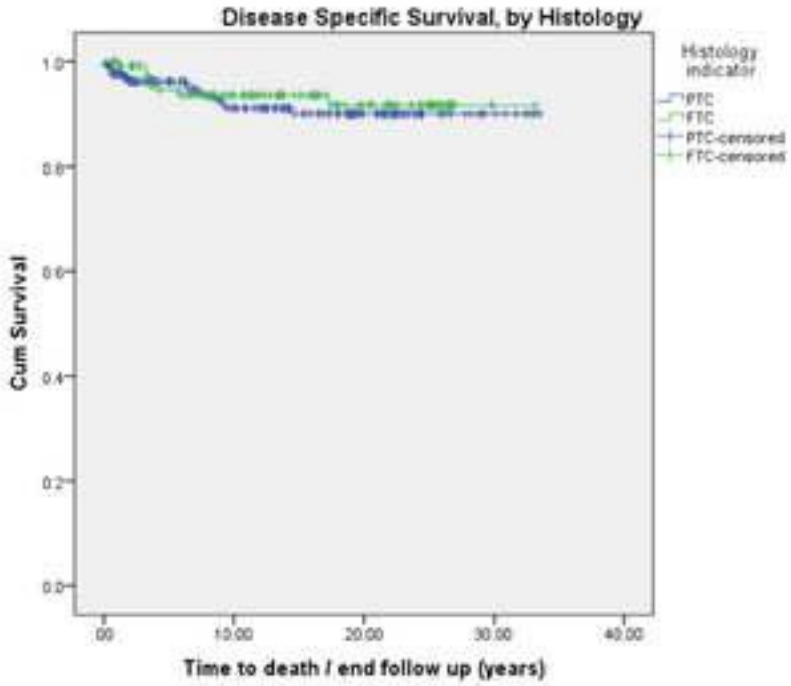

Figure 4c: Recurrence and histological type

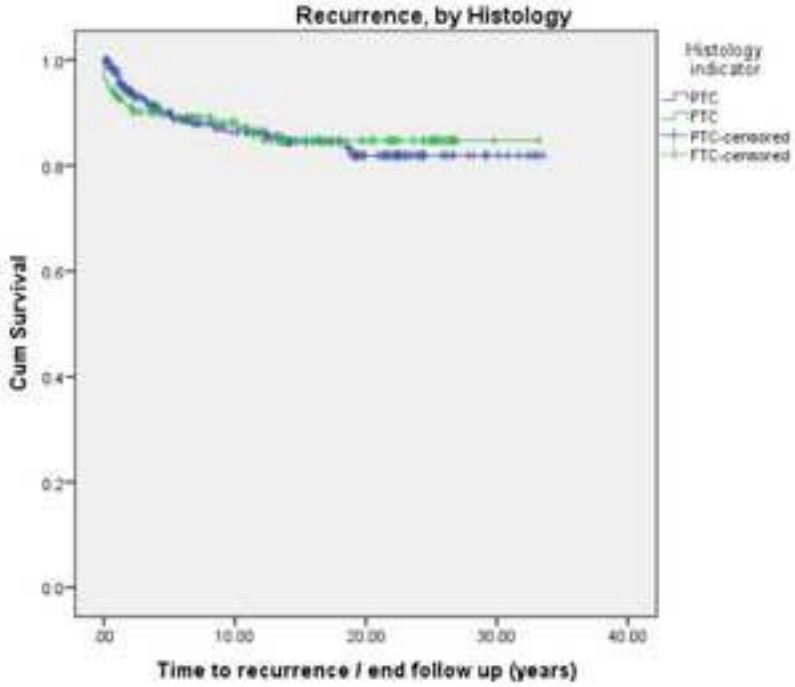

Figure 5a: DSS for TNM stages I & II before and after 2000

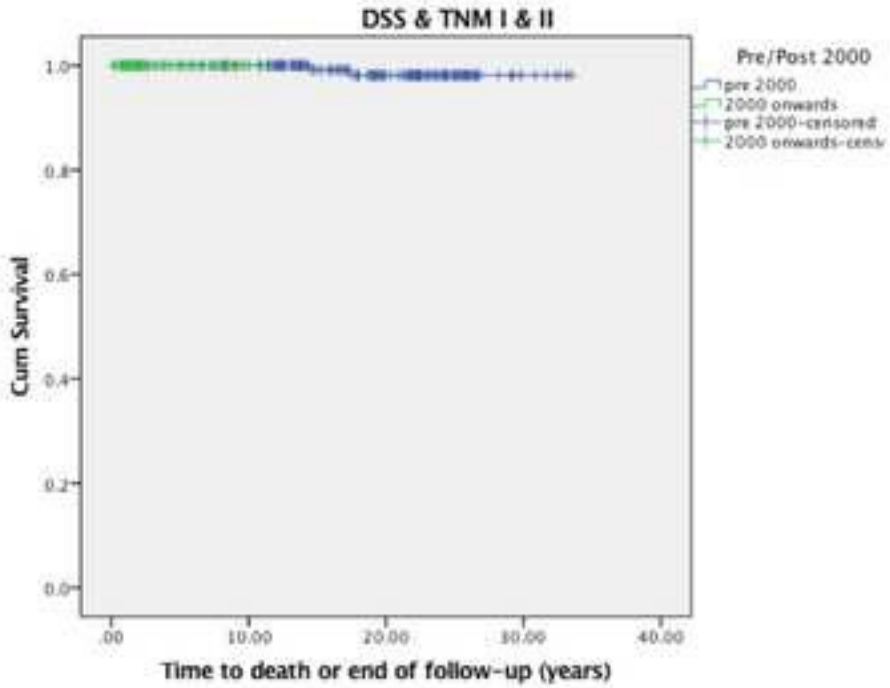

Figure 5b: DSS for TNM stages III & IV before and after 2000

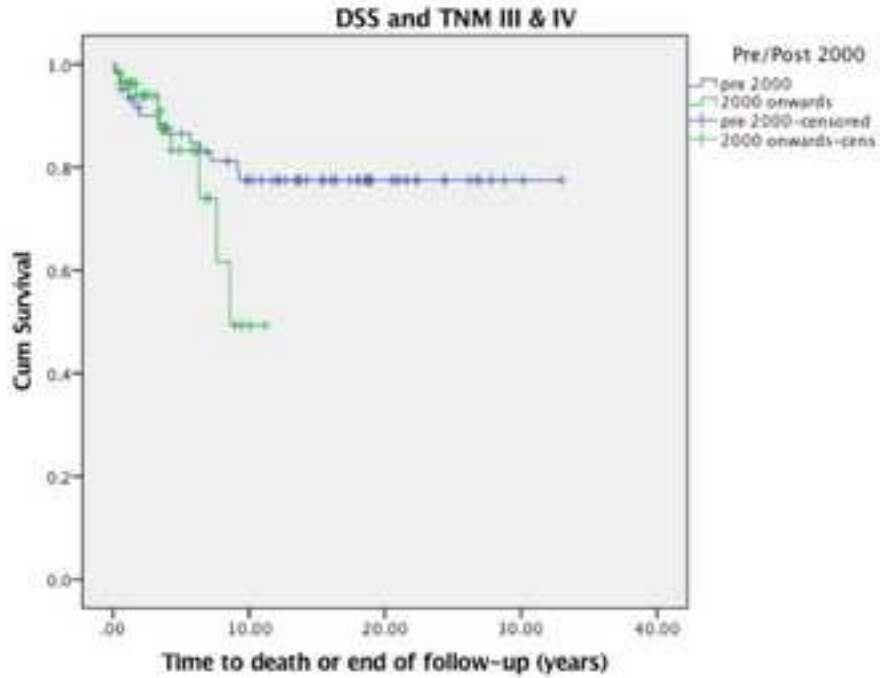

FIGURE LEGENDS

Figure 1: Kaplan-Meier plots of Disease Specific Survival (DSS) according to

a: primary surgical procedure

b: administration of RAI

c: AMES Risk

Figure 2: Kaplan-Meier plots of Recurrence according to

a: primary surgical procedure

b: administration of RAI

c: AMES Risk

Figure 3: Kaplan-Meier plots of DSS, Recurrence and TNM stage

Figure 4: Kaplan-Meier plots of DSS, Recurrence and histological type

Figure 5: Kaplan-Meier plots of DSS according to TNM stage before or after 2000.

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There are no declared conflicts of interest.

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