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Long term outcomes of simple clinical risk stratification in management of differentiated thyroid cancer

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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 and 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 ± 2.0 cm (mean ± 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

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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 initial radical surgery and radioactive iodine therapy[11] that may represent over-treatment 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. Intra-operative nerve monitoring was not used. Adjuvant RAI was based on risk. Whole Body Scanning (WBS) carried out ten days post- administration of therapeutic 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[8] 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

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