TOO MUCH MEDICINE

Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours

Juan P Brito instructor of medicine1 2, John C Morris professor1, Victor M Montori professor1 2

1Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, 200 First St SW, Rochester, Minnesota 55905, USA ; 2Knowledge and Evaluation Research Unit, Mayo Clinic

This article is part of a series on overdiagnosis looking at the risks and harms to patients of expanding definitions of disease and increasing use of new diagnostic technologies.

Thyroid cancer is the most common endocrine malignancy.1 Worldwide, its incidence has increased substantially over the past 50 years. The Cancer Incidence in Five Continents report showed that the age standardised incidence of thyroid cancer in women rose from 1.5 cases/100 000 population in 1953 to 7.5 cases/100 000 in 2002, with a similar relative increase in men (fig 1⇓).2 Behind these averages hide important and surprising differences between and within countries. In the US, the incidence of thyroid cancer has tripled in the past 30 years, increasing from 3.6 cases/100 000 in 1973 to 11.6 cases/100 000 in 2009,3 making it one of the fastest growing diagnoses. By contrast, in Sweden, Japan, and China, the increase in incidence has been minimal.2

Not all thyroid cancers are equal

Malignant cells are detected in only 10% of patients who present with thyroid nodules.4 To identify which nodules are malignant, current guidelines recommend that patients with thyroid nodules have thyroid ultrasonography followed by fine needle aspiration biopsy if ultrasonography shows suspicious features (microcalcifications, hypoecogenecity, infiltrative margins) or if the patient has a family history of thyroid cancer or has had significant radiation exposure (box).

The histology of malignant thyroid nodules provides the most important prognostic information. Thyroid cancer is divided into four types: papillary (comprising 85% of the total detected), follicular (11%), medullary (3%), and anaplastic (1%).5 6 Anaplastic thyroid cancer is associated with the worst prognosis, with most patients dying within a year of diagnosis (table⇓). This contrasts with the excellent prognosis of papillary cancers, especially in patients with nodules <20 mm in diameter; 99% of these patients will be alive at 20 years.6 Patients with small (<15-20 mm) lesions, no family history of thyroid cancer or personal history of radiation exposure, and no evidence of extraglandular invasion on ultrasonography are considered to be at low risk of progression.9 10

Autopsy series have shown a large reservoir of subclinical papillary thyroid cancers. One study found that a third of people who died from other causes had this type of thyroid cancer. These tumours (most <1 mm) were discovered through interval sectioning every 2 to 3 mm,11 raising the possibility that many more may have been missed between interval cuts. The presence of this subclinical reservoir is consistent with the asymptomatic nature of most diagnosed cases of papillary thyroid cancer.

Increased imaging has fuelled epidemic in diagnosis

Small papillary thyroid cancers account for 90% of cases in countries in which the incidence is increasing rapidly.12 Until two decades ago most thyroid cancers were found in patients who presented with nodules causing compression symptoms on the neck, visible neck masses, or through regular physical examinations in patients with no thyroid complaints. Nodules bigger than 20 mm were assessed by palpation and biopsy. The advent of neck ultrasonography in the 1980s and ultrasound guided biopsy in the late 1990s enabled detection and biopsy of nodules as small as 2 mm. Ready access to portable ultrasound machines together with policies which reimburse physicians for imaging have promoted the routine use of neck ultrasonography, which has increased by 80% in general endocrinological services over the past few decades.13

Increased diagnosis has also resulted from greater use of new imaging technology for other indications. In the US computed tomography (CT) more than tripled between 1995 and 2005 (rising to 173/1000 Medicare beneficiaries) and magnetic resonance imaging more than doubled (547/1000 Medicare beneficiaries).14 Nearly 16% of CT and magnetic resonance images show incidental thyroid nodules, of which around three quarters are <15 mm.15 16 This imaging (mostly chest CT to investigate cough and exclude pulmonary embolus and head...
and neck MRI to evaluate cervical radiculopathy has contributed to a 2.4-fold increase in the reported incidence of thyroid nodules over the past 30 years and a threefold increase in biopsies between 1995 and 2005. Today, more patients receive a diagnosis of thyroid cancer after an evaluation of an incidentally found thyroid nodule than after evaluation of a symptomatic or palpable nodule. More women than men are diagnosed (ratio 3:1) and most are in their 40s or 50s at the time of diagnosis.

The link between imaging and increased incidence is supported by a correlation with access. In an analysis across 18 regions in the US markers for higher levels of healthcare access, both sociodemographic and age based, were associated with higher incidences of papillary thyroid cancer. In New Jersey, Los Angeles, and Wisconsin, thyroid cancer incidence rates were higher among people with higher socioeconomic status. In Wisconsin, for each 5% rise in the population covered by health insurance, the incidence of thyroid cancer increased, on average, by 1.4 cases/100,000 people for the years 1980-2004. In the same population, for each increase of $10,000 ($6400; $7500) in county median income, thyroid cancer incidence increased on average 0.5 cases/100,000 a year. Counties in Wisconsin with a higher percentage of residents with a college degree also tended to have higher incidences of thyroid cancer.

Evidence suggests overtreatment

Detection of small papillary thyroid cancers in patients without a family history of thyroid cancer or exposure to radiation usually triggers intensive treatment, even though these are unlikely to cause morbidity or premature mortality. In an observational study conducted between 1993 and 2004, 1395 patients with low risk papillary thyroid cancer were given the choice of surgery or active surveillance. Less than a quarter (340) opted for active surveillance with ultrasonography. Patients in the surveillance group had repeat ultrasonography at six months and a year and then annually for an average of 74 months. Nodules enlarged by >3 mm in only 31 patients during follow-up. Of these, 18 subsequently had surgery and 13 chose to continue surveillance. In seven of the 13, the tumour shrank. No one died in the surveillance group. This suggests that small papillary cancers may never progress to cause symptoms or death. To back this view, analysis of the US National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) database, which includes 32 years of data, showed no significant difference in the death rate from thyroid cancer in patients who did not receive immediate surgery (n=440) for low risk papillary thyroid cancers compared with those who did (n=35 663).

The most compelling evidence that patients with low risk cancers are being overtreated is that despite a threefold increase...
in incidence of papillary thyroid cancer over the past 30 years, the death rate has remained stable (0.5/100 000 in 1979 and 0.5/100 000 in 2009, fig 2).}

**Unnecessary thyroidectomy is costly and harms patients**

The number of thyroidectomies for thyroid cancer in the US has risen by 60% over the past 10 years, from 16 377 in 1996 to 27 493 in 2006. The increase has been associated with costs estimated at $416m (£270m; €316m) in 2006.  

Thyroidectomy requires hospital admission and carries a 1-6% risk of complications, including permanent hypoparathyroidism and hypocalcaemia requiring calcium supplementation and laryngeal nerve injury. The risk of complications depends on whether the patient has total or partial thyroidectomy (more risk with the former, which is the recommended procedure) and on the skill of the surgical team. Patients who have had total thyroidectomy and some who have had partial thyroidectomy, also require lifelong thyroid replacement therapy, which carries its own burden of monitoring and treatment, costs, and the risk of complications from over-replacement and under-replacement.

Despite recommendations against using radioactive iodine in patients with low risk thyroid cancer, its use increased from one in 300 patients to two in five patients between 1973 and 2006 in the US, perhaps because of a suggestion that it makes it easier to follow-up patients because the tumour markers are more reliable. The short term side effects of radioactive iodine include altered taste and inflammation of salivary glands in a third of patients, and dry eyes and transient fertility reduction in a fifth. In the long term, it is associated with reduced quality of life and a risk of secondary malignancies. Among 14 589 patients who received radioactive iodine from 1973 to 2007, there was a 13% increase in the risk of salivary gland malignancies and a 5.7-fold increase in the risk of leukaemia compared with a reference cohort without thyroid cancer.

**Limitations of the evidence**

The evidence supporting overdiagnosis and overtreatment of low risk papillary thyroid cancer is drawn from epidemiological and observational evidence. Such evidence is often affected by confounding and selection and reporting biases. Large randomised trials are required comparing immediate thyroidectomy with surveillance. Although trials in patients with low risk thyroid cancer might be challenging to plan, fund, and execute, the example from prostate cancer, shows us that it is possible.

**How to do better**

Cancer raises fear and anxiety in patients and clinicians, and labelling indolent lesions as papillary thyroid cancer causes unnecessary distress. We suggest renaming low risk lesions (< 20 mm in patients with no family history or radiation exposure and no ultrasound evidence of extraglandular invasion) as micropapillary lesions of indolent course (microPLICs) to convey their favourable prognosis. A change in nomenclature could frame the care of these patients and avoid their overtreatment. It might also improve recruitment into trials in which one arm entails active surveillance rather than immediate treatment. Renaming has already occurred in other “cancers”: papillary urothelial neoplasia of low malignant potential (from grade 1 papillary transitional cell carcinoma of the bladder), atypical lipomatous tumour (from well differentiated liposarcoma), and cervical intraepithelial neoplasia (from cervical cancer).

Patients with low risk lesions should be offered the option of surveillance to detect changes suggestive of progression (for example, tumour growth causing compression symptoms, lymph node metastasis). Although there is currently no evidence based surveillance schedule, it might follow a similar path to the one used after thyroidectomy, including yearly neck ultrasonography and physical examination. Patients with lesions that are stable or shrink could then be followed up less often than those whose nodules increase in size (change in volume >20%).

**What to discuss with patients**

Uncertainty about the benefits and harms of immediate treatment for low risk papillary thyroid carcinoma should spur clinicians to engage patients in shared decision making. This will ensure treatment is consistent with the evidence for the subtype of cancer that they have and with their preferences. Some patients may prefer not to have aggressive treatment of small, low risk thyroid cancers, especially those patients where the risk clearly outweighs the benefits of treatment (for example, older patients, patients with other malignancies, or patients with severe comorbidities). Patients can be reassured that if nodules later show more aggressive behaviour the evidence suggests no additional harm from delayed surgical treatment.

**Unresolved questions**

The proportion of the gap between thyroid cancer incidence and mortality that is explained by overdiagnosis remains unclear. Part of the discrepancy may be due to new risk factors for thyroid cancer such as radiation exposure from CT, nutritional factors, and menstural and reproductive factors. While the association between these risk factors and the incidence of thyroid cancer is weak and inconsistent, further research should clarify their relative contribution. Furthermore, the differing rates of thyroid cancer between countries (fig 1) suggest that other factors (such as healthcare system coverage, access to care, or expenditure per capita) may have a role in the incidence of thyroid cancer and warrant investigation. Why, for example, do Ecuador and Iceland have high rates but not Norway, Sweden, and Japan? The role of new biomarkers (such as the BRAF V0600E mutation) in identifying and monitoring indolent thyroid cancers also needs to be clarified.

**Conclusion**

The incidence of small and indolent thyroid cancer is increasing at different rates among countries. The incongruity between the increased incidence and stable mortality is most likely an effect of overdiagnosis. This is exposing patients to treatments inconsistent with their prognosis. Both the overdiagnosis and overtreatment of this form of cancer need to be fully recognised. A change in nomenclature for low risk cancers, as we have suggested, here, could help this and make it easier to give patients the choice of active surveillance.
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<table>
<thead>
<tr>
<th>Thyroid cancer</th>
<th>Proportion of all thyroid cancers</th>
<th>Change in incidence over past three decades</th>
<th>Change in mortality over past three decades</th>
<th>Mortality</th>
<th>Type of intervention</th>
<th>Benefits</th>
<th>Harms</th>
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<tbody>
<tr>
<td>Papillary</td>
<td>85%</td>
<td>3-fold increase</td>
<td>Unchanged</td>
<td>1-2% at 20 years</td>
<td>Thyroidectomy/radioactive iodine/thyroid hormone replacement</td>
<td>Unclear, possible decrease in mortality from 0 to 2/1000 patients compared with active surveillance</td>
<td>Anxiety, insurability, need for lifelong thyroid replacement, cost, burden of follow-up, complication from surgery and radioactive iodine</td>
</tr>
<tr>
<td>Follicular</td>
<td>11%</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>10-20% at 10 years</td>
<td>Thyroidectomy/radioactive iodine/thyroid hormone replacement</td>
<td>Clear benefit in mortality (50% reduction in cancer death rate on average)</td>
<td></td>
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<tr>
<td>Medullary</td>
<td>3%</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>25-50% at 10 years</td>
<td>Thyroidectomy/thyroid hormone replacement</td>
<td>Some patients can be cured with surgery</td>
<td>Anxiety, insurability, need for lifelong thyroid replacement, cost, burden of follow-up, complication from surgery</td>
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<tr>
<td>Anaplastic</td>
<td>1%</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>90% at 5 years</td>
<td>Thyroidectomy/chemotherapy/thyroid hormone replacement</td>
<td>Some benefit (prolongs survival by months)</td>
<td>As above plus side effects from chemotherapy</td>
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Figures

Fig 1 Incidence of thyroid cancer by country. Countries above the dotted line experienced a rise in incidence between 1985 and 2002.

Fig 2 Incidence of and mortality from thyroid cancer in the US, 1975-2009 and advent of new technologies.