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For debate

Well differentiated thyroid cancer: Are we over treating our patients?

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Over the past 50 years, our understanding of the biology of well differentiated thyroid cancer (WDTC) has improved to the point that clinicians can reliably predict favorable outcome for the vast majority of patients who present for initial treatment. Reports from many large cohorts, both on an institutional and more recently at national level have confirmed the excellent outcomes that can be expected in a majority of patients, along with factors which predict increased rates of recurrence and cancer related death.[1]

We now know that survival rates of over 90% at 10 years can be expected, and low risk cases (young patients with low risk papillary thyroid cancers) rarely if ever die of disease. While this improvement in understanding of the biological behavior, has allowed clinicians to counsel their patients about the excellent outcomes expected, an interesting change in the approach to treatment has developed. Despite the well-recognized indolent nature of WDTC, there has been an emerging trend to employ more aggressive attempts at tumor detection and more aggressive therapy including a significant trend towards total thyroidectomy even for low risk cases.[2] The reasons for this are multifactorial, and the effects have manifest in a number of significant ways.

Initial reports from analysis of large retrospective cohorts from multi-institutional databases dating back to the early 20th century not only demonstrated excellent outcomes, but also found an association between more aggressive primary treatment (total thyroidectomy versus less than total thyroidectomy) and survival.[3] Despite numerous subsequent reports from single institutional cohorts which did not support this association,[4] those early findings carried much weight.

Further evidence linking more aggressive therapy and improved outcome has been reported from large national US datasets.[5] Again, these results are in conflict with the ongoing observations of those large volume centers who continue to analyze their outcomes in great detail.[6]

The difference in the conclusions drawn from analysis of these 2 separate data sources lies in the detail. Where national datasets provide huge numbers of patients, they lack specific details in terms of surgery, pathological features and in some cases oncological outcomes. With such low rates of disease specific death related to WDTC, specific details such as the presence of extra thyroid extension, tumor histology particularly with reference to more aggressive variants of papillary carcinoma, and causes specific death, are critical to interpreting results. Those cases in which limited thyroidectomy is performed due to unresectable disease may be coded as less than total thyroidectomy by data registrars, and without review of case records which is impossible on such a scale, such inaccuracies can unfairly impact on results. Only reports which are clinician collected, with a standardized approach to data collection offer the level of detail required to interrogate subtleties such as the impact of therapy on outcome.

At the same time that the impact of specific tumor factors was being appreciated, the methods used to assess these features evolved. All major staging systems were based upon patient cohorts which pre-dated the routine

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use of pre-operative ultrasound. However, contemporary thyroid practice relies on ultrasound in almost all cases. Accurate assessment of the thyroid gland and the regional nodes has led to significant improvements in the ability to identify potentially adverse features. In particular the ability to identify micro-nodular disease in the contralateral lobe, and micrometastases in the regional lymph nodes has changed our understanding of the thyroid gland in health, and in the presence of malignancy.

It is not only the approach to imaging which has impacted on the management of WDTC, more exhaustive histopathological scrutiny of surgical specimens with whole gland sectioning has resulted in increasing rates of multifocal disease detection and incidental malignancies reported in surgery for benign indications.

It is now clear that a nodular thyroid gland is the norm, particularly in the aging female. Thyroid cancer can be demonstrated in many "normal" thyroid glands at autopsy, suggesting that humans can live with the condition without progression of disease. We now also understand that clinically evident papillary carcinoma metastasizes often and early to lymph nodes, with micrometastases being present in over 40% of those patients considered cN0 on ultrasound.[7] Such occult disease can be demonstrated by elective neck dissection, although this has never been shown to improve survival or rates of recurrence. It is not clear how this change in recognition of disease pattern should be translated in to clinical practice.

Clinicians' understandable response to both the suggestion that more aggressive therapy results in improved outcome, and the more refined ability to identify potentially high risk features has led to a change in practice. This change has been reflected by international guidelines which currently recommend aggressive therapy in all but the lowest risk cases. Indeed the European Thyroid Cancer Task force recommend total thyroidectomy for all tumors >1 cm, and highlight the role of prophylactic central compartment node dissection in staging.[8] It is not surprising therefore that more surgeons than ever recommend total thyroidectomy and elective central neck dissection for even low risk cases.[2]

In addition to the increased aggression from surgeons in managing WDTC, those clinicians involved in adjuvant therapy have also identified increasing numbers of patients who are considered suitable for radioactive iodine (RAI).[9] In part this is linked to the enthusiasm for central neck dissection, which results in previously occult nodal metastases being identified, so upstaging any patient aged 45 years or above and leading to a justification for RAI therapy.

On this backdrop therefore, it comes as a surprise that survival rates for WDTC are unchanged. Increasingly aggressive therapies have not reduced the number of patients dying of disease, which remains static and reflects the small number of high risk patients where current treatment paradigms have made little impact.

Not only has the oncological impact of this change in practice been disappointing, but our understanding of the side effects of aggressive therapy now allow us to comprehend the morbidity related to such an approach. Although centers of excellence have demonstrated low rates of morbidity related to more extensive surgery with total thyroidectomy and elective central neck dissection, this is not true at a wider level. Both European and US studies reveal what all surgeons must truly believe, that all surgery is associated with complications, and that more aggressive surgery which involves total thyroidectomy rather than lobectomy and elective central neck dissection rather than observation of the central neck results in higher rates of complication, including recurrent laryngeal nerve palsy and damage to the parathyroid glands.[10]

Not only have the side effects of aggressive surgery been demonstrated but we now recognize that RAI is not without side effects. Uptake outside the thyroid gland results in salivary and lacrimal dysfunction. Not only does this have theoretical impact but it can be demonstrated in quality of life assessment of those patients who receive RAI.[11] In addition to the quality of life issue, a small but significant increase in the rate of secondary malignancy has been associated with higher doses of RAI.

How then can we provide the best service to our patients? How can we protect patients from the effects of over treatment while maintaining optimal oncological outcomes for all? The answer still lies in the concept of risk prediction. Consideration of patient age, tumor histology and size and features of pre-operative imaging remain critical to appropriate decision making for all patients with WDTC. The promise of risk stratification based upon genetic analysis of pre-operative tissue remains elusive, and is likely to be relevant only in a select few patients who are considered at intermediate risk. At its most basic, those patients who present at advanced age, with large tumors (particularly those with non-papillary histologies), gross extra thyroid extension and distant metastases remain a very high risk group. These patients should be treated aggressively. Total thyroidectomy, neck dissection adjuvant therapy with RAI, and in some cases further adjuvant therapy may be indicated. The role of external beam radiation in those patients with gross extra thyroid extension and either standard chemotherapeutic regimens or more recently targeted therapies for those patients with progressive distant metastases or unresectable disease is evolving. Indeed, it is for this group of patients that our resources must be focused.

The vast majority of patients who are young (<45 years), will however present with tumors limited to the thyroid gland and without aggressive features. It is these patients with PTC who lack extra thyroid extension, and who lack clinical evidence of regional or distant metastases who have low risk WDTC and are being over treated. The ability to demonstrate micrometastases in the central or lateral compartment lymph nodes does not mean one