Review Article

Current Concepts and Future Directions in Differentiated Thyroid Cancer

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Abstract
This paper provides an overview on the biology, monitoring and management of differentiated thyroid cancer (DTC), with particular attention to issues of relevance to clinical chemistry. The incidence of DTC appears to be increasing and management strategies are evolving as we learn more about its natural history and response to therapy. Clinical chemistry techniques play a central role in these protocols. Technical limitations inherent in current monitoring tools can hamper follow-up, although progress is being made. The molecular basis of DTC is being delineated with the potential to develop new strategies for diagnosis, monitoring and management of this condition.

Introduction to Thyroid Cancer

Understanding the assessment and management of differentiated thyroid malignancy requires an appreciation of the biologic properties and behaviour of its variants.

Basic Biology

There are two major forms of differentiated thyroid cancer (DTC): papillary and follicular. These account for approximately 90% of all thyroid cancer.[1] Both arise from follicular thyroid cells. They are distinguished by cytology and histology, and display minor differences in behaviour. However, their similarities outweigh differences, and for the most part they are considered together.

Papillary Thyroid Carcinoma

Papillary thyroid cancer accounts for 90% of DTC.[1] Classical papillary cancers are unencapsulated with complex arrangements of malignant cells on a fibrostromal background.[2] The nuclei are characteristic. Psamomma bodies are common as is lymphocytic reaction. These tumours are often multifocal and bilateral in one-third.[3] Papillary cancers are slow growing, and thus ten-year survival rates are high. However, they commonly metastasise, initially to the cervical lymph nodes. The next most common site of metastasis is lung.[4] Papillary cancers have several well-described variants: the most common are follicular variants of papillary cancer, which behave as per normal papillary cancer. Several rare variants (e.g. tall cell, columnar cell) have more aggressive courses.[2]

Follicular Thyroid Carcinoma

Follicular thyroid cancers can have a variable appearance histologically; most are encapsulated although they do invade the capsule at least to a small degree. While they are invasive locally, follicular cancers metastasise distantly rather than to regional lymph nodes, with propensity for lung or bone (where they cause lytic disease).[3] They are generally unifocal. Like papillary cancer, follicular cancers also have variant forms, including insular and Hürthle cell tumours. Insular tumours are known for their more aggressive course and variable uptake of radioiodine. Hürthle cell tumours do not usually accumulate radioiodine, limiting therapeutic options when they recur.[5]

Incidence and Epidemiology

Thyroid cancer rates appear to be rising steadily, with estimates of a 240% increase in the 30 years to 2002.[6] Australian data is consistent with the worldwide trend.[7,8] The American Cancer Society estimates there were 37,340 cases in America in 2008, with approximately 75% occurring in women.[9]

Pertinent questions arising from these observations include: (1) is the increase real?; and (2) if real, why is it occurring? Regarding the first question, all analyses demonstrate that the greatest rise in incidence has occurred in cancers of the smallest sizes.[6,9-13] This suggests that diagnosis of previously subclinical disease is playing a role in the rising incidence via increased utilisation of diagnostic procedures such as fine-needle aspiration (FNA) and ultrasound, and/or possibly

more diligent pathological scrutiny.[14] However, several sophisticated studies have recently concluded that while the above explanation is a contributor, it does not completely account for the rise in incidence.[9-11,15] These studies conclude that larger tumours as well as smaller ones are becoming more frequent; an observation that cannot be solely explained by increasing incidental diagnosis. It is unknown what other causes may be impacting. While some risk factors have been well defined (for example female sex, age, family history and radiation exposure), none adequately account for a real increase in disease over such a short space of time.[3]

Genetics

The genetics of DTC is an evolving area, with investigation holding the potential for improved assessment of prognosis and also rational therapeutic targets.[16]

Papillary Thyroid Cancer

Papillary cancers often display genetic alterations in the mitogen-activated protein kinase (MAPK) system.[17] The MAPK system is a serine/threonine phosphorylation signalling cascade implicated in, amongst other things, cell differentiation, proliferation and survival. There are several components of the MAPK system that are usually activated in turn: receptor tyrosine kinases that act as growth factors; RAS, a small membrane bound G-protein; RAF, a serine/threonine kinase; MEK, a serine/threonine kinase, and MAPK (known in mammalian cells as ERK), the effector kinase that translocates from the cytosol to the nucleus and leads to alterations in gene expression.[18] Evidence that this pathway is very important in papillary cancer pathogenesis lies in the observation that the majority of papillary cancer cells carry mutations in genes expressed for this pathway, and that mutations rarely overlap or coexist in the same tumour line.[17] The implication here is that one mutation leading to constitutionally active MAPK cascade elements may set the cell on the path towards oncogenesis.

BRAF: The most commonly mutated gene is the B-type RAF gene (*BRAF*), especially a T→A transversion at position 1799 leading to a V600E substitution, which occurs in approximately 45% of papillary cancers.[16] In the majority of studies (but not all) $BRAF^{V600E}$ is associated with negative clinical features such as extra-thyroidal invasion, lymph node metastasis, advanced tumour stage at presentation and cancer recurrence,[19] and in one study, higher mortality.[20] These clinical correlations are supported by evidence of high prevalence of BRAF mutations in advanced thyroid cancers as defined by histological and imaging features including positron emission tomography (PET) positivity and loss of radioiodine uptake.[21] The mechanism by which the MAPK system interacts with the other well-known thyroid follicular cell growth factor, thyrotropin (TSH), is still to be elucidated. However, it is known that BRAF mutations are associated with impaired iodine trapping through the sodium iodine symporter (NIS), decreased thyroid hormone synthesis and increased TSH in vivo.[17]

RET/PTC: While RET is not usually highly expressed in follicular thyroid cells, a variant form of the gene product can lead to tumourigenesis. The genetic alteration is a chromosomal rearrangement with the *RET* gene fusing with one of a number of unrelated genes (collectively called Papillary Thyroid Cancer [*PTC*] genes). The PTC genes are expressed in follicular thyroid cells, with the fusion gene product (dubbed *RET/PTC*) leading to ligand-independent activation of the MAPK system, and papillary thyroid cancer.[18] *RET/PTC* rearrangements are found in approximately 20% of papillary cancers.[22] Genetic correlation studies suggest that these rearrangements are associated with younger age, classic papillary histology, and possibly better prognosis, although a high rate of lymph node metastases.[23] The frequency is much higher in those thyroid cancer patients exposed to ionising radiation.[24]

Follicular Carcinomas

RAS: *RAS* mutations are common in follicular adenomas and carcinomas, anaplastic carcinomas, and follicular variants of papillary carcinomas.[22] These appear to be associated with aggressive tumours.[25]

PAX8/PPARγ: The *PAX8*/*PPARγ* fusion gene is associated with follicular carcinoma only slightly less commonly than *RAS* mutations.[22] The pathologic event is a (2q:3p)(13:25) translocation.[26] Exact mechanisms of oncogenic function are not yet understood.[27]

Other pathways related to DTC currently being investigated include PI3K/AKT pathway,[28] epigenetic phenomena,[29] and pathways of other kinase families.[30]

Management of DTC

Management and assessment strategies have evolved considerably over the last decade.[31] Important considerations that influence management practices include:

- Overall, DTC has a high 10-year survival rate, of the order of 90% or greater for papillary cancer,[4,32-34] although not as high for follicular carcinoma.[4,32,33] Survival rates approach 100% for patients with stage I disease.[32] This knowledge should be combined with the recognition that there are potential harms of therapy, such as salivary gland injury or risk of distant second tumour development with radioiodine,[3] or atrial fibrillation or osteopaenia with overly aggressive TSH-suppression.[35] Historical

data suggests significant numbers (approaching one-third) will have recurrent or persistent disease, with attendant morbidity and potentially mortality.[36] This can occur many years distant to the original diagnosis.
- Mechanisms to stratify patients for risk of adverse outcomes from thyroid cancer, while imperfect, are available.[31]
- Assessment for recurrent disease in an enlarging population of thyroid cancer survivors has its own costs, with financial and adverse-event implications.
- Current treatment for patients with persistent radioiodine resistant disease is unsatisfactory, with the need to develop new approaches into the future.

Increasing recognition of these factors has led to management approaches that emphasise risk assessment for adverse outcomes. The major difficulty in making management recommendations lies in the fact that for most aspects of care, a lack of randomised studies exists to guide therapy (i.e. most data has been derived from retrospective observational studies).

Risk Assessment

Currently the pathological Tumour-Node-Metastasis (pTNM) classification system[37] is recommended to classify the stages of thyroid cancers, in order to allow standardisation of assessment, and because it is useful in predicting mortality.[31] Numerous other clinicopathologic systems have been devised to address limitations of the pTNM system, with some evidence suggesting MACIS (Metastases, Age, Complete resection, Invasion, Size) has some advantage.[38]

Surgical Management

Initial management is surgical. The extent of surgery is governed by consideration of mortality risk, although absolute consensus is lacking.[39] In papillary and Hürthle cell tumours, central-neck compartment dissection may be of benefit, but is controversial.[31] Where lymph node disease is suspected or evident, these should also be excised.[31] Recurrent or metastatic disease should be treated by resection or palliative surgery if possible (for example internal fixation of weight-bearing bones).[31]

Radioiodine Therapy

Radioiodine therapy can be divided into radioiodine ablation following near-total thyroidectomy and radioiodine treatment of loco-regional or metastatic disease.[40]

The aims of ablation therapy are as follows:
- Destroy any remaining normal thyroid tissue
    - Increases sensitivity of later radioiodine total-body scans
    - Increases specificity of measurements of thyroglobulin
- Destroy occult microscopic carcinoma
    - Hopefully decreases the long-term risk of recurrent disease
- Permit post-ablative total-body scanning (sensitive imaging modality for radioiodine sensitive disease)

Controversies exist for both the indications for radioiodine ablation and the dose of therapy. Careful long term follow-up studies appear to support radioiodine ablation, especially for high risk tumours;[36] more recent reviews do not demonstrate benefit for lower risk disease.[34,41,42] Current consensus guidelines reflect this evidence.[40]

Uptake of radioiodine occurs under the influence of TSH; satisfactorily elevated TSH may be achieved by either thyroid hormone withdrawal or use of recombinant human TSH (e.g. rh-TSH, Thyrogen®, Genzyme). In Australia rh-TSH is available through the Pharmaceutical Benefits Scheme (PBS) under strict criteria on a once-per lifetime basis for radioiodine ablation.[43]

TSH Suppression

Thyroid hormone (L-thyroxine) therapy may have dual roles following initial thyroid cancer treatment: hormone replacement and TSH suppression.[44] The rationale for suppressive therapy is that TSH acts as a growth factor of follicular-derived thyroid cells, and thus depriving DTC cells of this influence may decrease tumour growth, complications of disease and death.[45] DTC cells also express TSH receptors, and early case reports suggested tumour responsiveness.[46] The most robust evidence for improved clinical outcomes is derived from retrospective cohorts,[36] meta-analyses of cohorts,[47] and prospective registries.[32,48] These studies support the overall principle of TSH suppression, although all have limitations. The best quality evidence originates from the National Thyroid Cancer Treatment Cooperative Study Group[32] which suggests that patients with higher initial stage disease (i.e. stage III/IV) have improved overall survival from near complete TSH suppression, while patients who were initially stage II had improved survival from more modest suppression. Good prognosis patients (i.e. stage I) did not appear to gain any benefit from TSH suppressive therapy.

Risks of L-thyroxine therapy are principally cardiovascular (especially atrial fibrillation), demineralisation of bone, and overt thyrotoxicosis.[35]

Current guidelines therefore suggest that patients with persistent disease should have their TSH suppressed to less than 0.1 mU/L indefinitely,[31,45] while high-risk patients should

be maintained with serum TSH between 0.1–0.5 mU/L for 5–10 years.[31] Clinical euthyroidism should be maintained. Uncertainty remains regarding targets in lower risk groups, with some authorities postulating low normal values.[31,44]

Other Treatment

A number of other agents have been used in thyroid cancer, although their usefulness has been restricted to small percentages of patients. Much excitement has been generated regarding novel therapies, based on recent improvements in understanding of thyroid cancer biology.

Established or Traditional Therapies:

- For symptomatic bony disease, intravenous bis-phosphonates or embolisation of lesions can be considered.[31]
- External beam radiotherapy (EBXRT) for some metastatic disease, or for adjuvant therapy in the neck in the setting of gross residual disease or extensive extrathyroidal extension.[49]
- Chemotherapy: chemotherapy has no role in the adjuvant treatment of DTC, with the possible exception of doxorubicin acting as a radiosensitiser for EBXRT. Single agent doxorubicin is also the most widely studied cytotoxic agent for advanced metastatic disease, but benefits are at best modest and as such, enrolment in clinical trials should first be considered.[31]

Novel and Emerging Therapies:

- Kinase inhibitors: Recently a number of phase II clinical trials have been reported, based on the developing understanding of molecular mechanisms underpinning DTC. Most agents thus far studied affect multiple kinases, including those of the MAPK system, but also signalling involved in angiogenesis amongst others.[50] So far, studies have revealed modest objective responses such as some partial responses and tumour stability,[51-54] which may be related to the lack of apoptotic effect of these agents on thyroid cancer cells,[16] leading to the suggestion that other pathways may need to be targeted simultaneously.
- Other agents: early phase studies are planned or have commenced for multiple other classes of agents, including histone deacetylase inhibitors, demethylating agents, immunomodulatory agents and proteasome inhibitors.[55]

Assessment Tools for Follow-up

Thyroglobulin

Thyroglobulin is a 670 kDa glycoprotein made up of two identical subunits,[56] and acts as a scaffold for thyroid hormone synthesis. It is specific for follicular-derived thyroid cells.[57] More than 95% of papillary and follicular carcinomas are thyroglobulin positive, even those that are metastatic. Well-differentiated tumours generally express more thyroglobulin than poorly differentiated tumours. This can help distinguish these from other lesions such as medullary, anaplastic or non-thyroidal cancers using immunohistochemistry.[56]

Thyroglobulin is also useful for recurrence monitoring because small amounts of total protein escape from cells into the systemic circulation and can thus be detected in the sera. This correlates with the volume of differentiated thyroid tissue.[58] Just as tumour growth in DTC is under TSH control, so is thyroglobulin. Thus, serum thyroglobulin is decreased by TSH suppressive therapy.[59]

Immunometric assays for thyroglobulin have come to dominate the commercial market and have advantages of sensitivity, speed, the potential for full automation, wider concentration range and stability.[56] However, several technical limitations can be identified with current immunometric methods. Sensitivity, imprecision and 'hook effects' are amongst these.[60] Another issue is standardisation between methods, even with widespread adoption of the CRM-457 international reference preparation (BCR, Brussels).[56] This is possibly due to heterogeneity between thyroglobulin molecules at varying degrees of malignant de-differentiation, leading to slightly variable epitopes presenting to monoclonal antibodies of commercial assays. A recent Australian paper detailed dissonance between various methods, highlighting the need for standardisation between assays (now being addressed via External Quality Assurance).[61] From a clinical standpoint, it is sensible to use the same laboratory for serial measurements. This issue also highlights the need for caution in directly applying recommended cut-off values in day-to-day management.[57]

Of high clinical interest is the issue of thyroglobulin interference by autoantibodies, which occurs with all immunometric methods (although radioimunoassays are somewhat more resistant).[60] Approximately 25% of patients display anti-thyroglobulin antibodies, compared to 10% of the general population.[62] These cause measured thyroglobulin levels to be falsely low, likely due to thyroglobulin-antibody complexes not being detected.[57] Persistence or rising thyroglobulin antibodies may be a marker for antigenic stimulation and thus ongoing disease.[62] Thyroglobulin antibodies should thus be quantitatively measured with each serum thyroglobulin request.[31]

Heterophile antibodies are another source of interference in immunometric assays, despite commercial assays' attempts to minimise their impact.[63] The use of commercially available

'blocking tubes' is useful for investigation of this potential problem.

Thyroglobulin assessment also has clinical utility for diagnosis from tissue specimens, specifically the washout of FNA samples of non-thyroidal neck masses or adenopathy. The idea that thyroglobulin could provide a sensitive differentiator for metastatic thyroid cancer as opposed to other lymphadenopathy is not new,[64] although it has achieved renewed interest over recent times.[65-70] Thyroglobulin washout fluid measurement does not appear to be affected by thyroglobulin antibodies.[67] A major problem at present is a lack of standardisation between normal and abnormal cut-offs.[70]

TSH and Thyroid Hormone

TSH is routinely measured using third generation ultrasensitive assays. Given that Thyroid Function Testing reporting is automated, laboratories should ideally have mechanisms to identify and flag patients with DTC, so that the usual comments regarding euthyroid TSH levels can be altered to reflect potential requirements for TSH-suppressive therapy. Clinical history or, in its absence, serial thyroglobulin estimations are two such measurements. It is not uncommon for thyroid cancer physicians to find that other well-meaning but inexperienced clinicians have reduced their patient's L-thyroxine dose in response to a "subnormal" TSH result, and as such pathology reports encompassing management suggestions can play an important role in preventing this occurrence.

Rh-TSH

Rh-TSH is an alternative to thyroid hormone withdrawal for both radioiodine ablation and TSH stimulation testing (see below). It is well tolerated, has comparable efficacy for thyroglobulin-stimulation tests and has the advantage of avoiding hypothyroidism.[71] However, in direct financial terms it is costly, and at present is not subsidised by the PBS for this indication. In Australia rh-TSH is available under the Medicare Benefits Scheme where thyroid hormone withdrawal is contra-indicated (unstable coronary artery disease or psychiatric disease with risk of deterioration) or not effective (co-existing pituitary disease).[72]

Imaging

Cervical ultrasound is now the dominant technique for identification of loco-regional recurrence, with advantages of absence of radiation exposure, excellent sensitivity and the possibility of adjunctive assessment with FNA for suspicious lesions.[73] Radioiodine diagnostic whole body scans were traditionally the imaging of choice, although they add little information to that provided by stimulated thyroglobulin and ultrasonography scan in the majority of low-risk patients.[74] Computed tomography (CT) scans are generally performed without contrast to prevent iodine uptake 'stunning' should radioiodine therapy be contemplated, and are especially helpful in detecting pulmonary metastases.[75] 18F-fluoro-deoxy-glucose (FDG)-Positron Emission Tomography (PET) (especially CT/PET) is emerging as an important tool for the future for localisation of recurrent disease, with PET positivity also acting as a harbinger for poorer prognosis because it is associated with de-differentiation and increased metabolic activity.[73]

Follow-up Protocols

DTC can recur at any time (although two-thirds recur in the first 10 years), and therefore life-long follow-up is recommended.[1] As discussed above, the surveillance protocol over that period is increasingly being determined by measures of risk of recurrence.

The detection of thyroglobulin in the serum following ablative therapy signifies presence of follicular-cell derived tissue, most likely residual disease or recurrence. Current clinical guidelines are based on immunometric assays with a functional sensitivity of 1 ng/mL.[74] Using assays of this sensitivity, a detectable thyroglobulin on suppressive therapy reliably indicates ongoing disease, although a negative result does not.[76] Stimulation of latent thyroid cancer cells to produce and secrete thyroglobulin (so-called stimulated thyroglobulin) by either thyroid hormone withdrawal[76] or rh-TSH[77] can therefore alert the clinician to the need for further diagnostic evaluation or empiric treatment. For patients with a negative stimulated thyroglobulin one year after initial treatment, the chance of a subsequent positive result during follow-up is low – thus one stimulated test may be adequate in this group.[78,79] In those with detectable stimulated thyroglobulin, serial evaluation may be useful.

The combination of stimulated thyroglobulin and ultrasound has been shown to have the highest diagnostic accuracy for identification of persistent disease in low-risk patients, obviating the need for radioiodine diagnostic whole-body scans in those patients.[80] Consensus guidelines support the use of stimulated thyroglobulin and ultrasound in patients with low risk disease.[74] Stimulated levels greater than 2 ng/mL should trigger diagnostic assessment – this level is chosen because while detectable levels below this point probably indicate residual disease, it is rarely able to be localised because of the small volume of tissue involved, and should simply be re-evaluated serially. Six- to twelve-monthly evaluation of non-stimulated thyroglobulin thereafter is recommended.[31]

Specific Situations

Follow-up of Patients Not Requiring Thyroid Ablation Therapy

Those who have not undergone near-total thyroidectomy plus ablative therapy will continue to demonstrate detectable serum thyroglobulin levels. This negates the usual cut-off levels for diagnosis, although current guidelines point out that high or increasing thyroglobulin levels in this setting may represent recurrent disease, and as such, periodic thyroglobulin measures are still worthwhile.[31] Ultrasound may be especially useful in this setting because these patients are usually low-risk and recurrence most likely will occur in the neck.[59]

Anti-thyroglobulin Antibody Positive Disease

Usual follow-up protocols must be modified for this patient group, although laboratory investigations may reveal important clues. A detectable thyroglobulin level in the presence of thyroglobulin antibodies generally indicates persistent disease.[81] Thyroglobulin antibody titres should decline over time,[62,82] and persistent or rising levels may indicate ongoing antigenic stimulation as mentioned previously. Monitoring should comprise a careful clinical examination, neck ultrasound and radioiodine diagnostic whole body scans.[81]

Positive Serum Thyroglobulin, Negative Scan Disease

Some patients have recurrent disease as defined by detectable serum thyroglobulin, although negative localisation studies. Optimal treatment is controversial. An empiric therapy dose of radioiodine may be both diagnostic and therapeutic, although in patients with a negative post-therapy scan there is little advantage to further therapy.[83] Further, serum thyroglobulin may decline or remain stable without treatment,[84] and empiric doses of radioiodine may exceed tolerable radiation exposures, especially in elderly patients.[85] FDG-PET scan may be a method of distinguishing who will have benefit from radioiodine therapy, with PET avid lesions much less likely to respond.[86]

Future Approaches for Assessment and Monitoring of DTC

Impact of Highly Sensitive Thyroglobulin Assays

As stated above, current clinical guidelines for serum thyroglobulin assessment are based on assays that display a functional sensitivity of 1 ng/mL.[74] Improvements in immunometric technology now allow several commercial assays to claim much more sensitive specifications, for example to below 0.1 ng/mL.[87] A number of studies demonstrate that undetectable thyroglobulin levels using these highly sensitive assays correlate with stimulated thyroglobulin of less than 2 ng/mL, a situation that could make stimulation testing redundant.[88-91] There does appear to be a trade-off with specificity in some cases,[90] although serial measurements assessing for small increments in serum thyroglobulin may be a useful method of predicting recurrence.[92] Further work is needed to define the long-term prognostic implications for patients with undetectable and low-level thyroglobulin levels while on L-thyroxine therapy.[87]

Molecular Diagnosis of Persistent or Recurrent Disease

The problem of anti-thyroglobulin antibodies could potentially be overcome either by development of thyroglobulin assays resistant to interference, or via novel assays for circulating thyroid cancer markers. One such candidate is thyroglobulin mRNA.[58] Following the initial report in 1996 using thyroglobulin mRNA detected by reverse-transcription nucleic acid amplication,[93] much interest has been generated in this area. However results of subsequent studies have ranged from very promising to disappointing. Of particular concern has been the lack of specificity of thyroglobulin mRNA, even in athyreotic individuals without thyroid cancer.[94] Factors that may account for these results include pre-analytic specimen handling, ectopic thyroglobulin expression especially via splicing variants, and assay standardisation issues. Several groups have reported methods to overcome these problems including stable collection systems,[95] and careful primer selection.[96,97]

TSH receptor mRNA has also been the subject of investigation as a relatively specific thyroid marker. It also shows promise both for the serum monitoring of thyroid cancer recurrence[96-98] and as well as diagnostic assessment prior to surgery.[99,100]

It is early days for the technology associated with these markers, and their place in routine management is still sometime away. However, further research may overcome some of the current barriers, and lead to new mechanisms for surveillance of DTC.[58,94,101]

Molecular Genetics for Risk Stratification and Diagnosis

The emerging understanding of molecular mechanisms underlying DTC holds promise for widespread applications in the diagnosis, risk stratification and management of DTC.

FNA Diagnosis

FNA of thyroid nodules has problems of frequent inadequate sample collection and indeterminate cytology.[31] While inadequate cellular material is a difficult challenge to overcome, use of mutational analyses could prove useful where cytology is indeterminate. A great step forward would be the identification of a molecular marker that distinguishes follicular adenoma from carcinoma on cytology. Many of the genetic alterations discussed previously have been assessed, although most literature concentrates on BRAF for this purpose. Retrospective[102-105] and prospective studies[106-109] have

concluded that addition of BRAF testing to cytology increases the diagnostic yield, without false positives. This exciting development over time could reduce repeat FNA, improve diagnostic accuracy and limit unnecessary surgery.

Risk Stratification and Management

Not only could pre-operative identification of genetic alterations improve FNA diagnosis, it could also be used as a marker of risk to guide extent of surgery and future monitoring for recurrence.[19] BRAF again holds most appeal because of its relation to adverse outcomes.[109] To date, no prospective data exists for this possibility.[110]

While current clinical studies of kinase inhibitors have been a major advance, these likely represent the tip of the iceberg in terms of therapeutic developments for refractory thyroid cancer. Exciting prospects include discovery of novel agents and pathways, or combinations of therapies that could achieve improved outcomes for patients.[55]

Conclusions

DTC is a disease with a rapidly rising incidence and prevalence. This presents a challenge for appropriate surveillance of recurrent disease. Follow-up protocols in recent times have altered to reflect a growing knowledge of the disease's natural history and risk factors for recurrence. Clinical chemistry techniques play a central role in these protocols, and as technical limitations are overcome, will have increasing utility. Modern advances in the understanding of the basic biology and genetics of DTC have led to the promise of exciting new developments in molecular diagnosis, monitoring and therapy that will benefit patients into the future.

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