Controversies and challenges in the management of well-differentiated thyroid cancer

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Abstract The incidence of well-differentiated thyroid cancer has seen a worldwide increase in the last three decades, although whether this is due to a ‘true increase’ in incidence or simply increased detection of otherwise subclinical disease remains undetermined. Nonetheless, this rising incidence has fuelled an interest in early diagnosis, treatment and follow-up of thyroid cancer along with greater public awareness. The treatment of thyroid cancer revolves around appropriate surgical intervention, minimising complications and the use of adjuvant therapy in select circumstances. Prognostic features and risk stratification are crucial in determining the appropriate treatment. There continues to be considerable debate in several aspects of management in these patients, and there is limited prospective data to direct therapy, hence limiting decision-making to retrospective analyses, treatment guidelines based on expert opinion and personal philosophies. The major controversies are related to diagnostic work-up, extent of surgery and postoperative management including the role of radioactive iodine. There are also differences in opinion regarding management of nodal metastases and follow-up protocols. As overall survival in well-differentiated thyroid cancer exceeds 95%, it is important to reduce over-treating the large majority of patients, and focus limited resources on high-risk patients who require aggressive treatment and closer attention. There needs to be a concerted effort on the

part of a multidisciplinary team to recognise the nuances in treating well-differentiated thyroid cancer.

Keywords Thyroid · Surgery · Imaging · Controversy

Introduction

The rising incidence of well-differentiated thyroid cancer is a worldwide phenomenon that has been observed over the last three decades [1, 2]. Whether this is due to a true increase in the incidence of thyroid cancer or merely better detection of smaller, incidental lesions remains unclear. Epidemiological data from the United States alone have shown a 2.4-fold increase between 1973 and 2002, and over 50% of these tumours are below 2 cm [3]. Moreover, there has been no corresponding increase in mortality rates, adding to the speculation that the vast majority of thyroid cancers that have been diagnosed have limited clinical significance. While majority of thyroid cancer deaths are attributable to anaplastic, poorly-differentiated or medullary thyroid cancers, there is a well-recognised subset of patients with well-differentiated thyroid cancer who have poorer outcome. Given this data, there has been increasing interest in early diagnosis and risk stratification, treatment individualised to risk-groups and follow-up strategies based on prognostic factors.

Well-differentiated thyroid cancers represent more than 95% of thyroid cancers, and include two major histological type: papillary and follicular. Despite a number of important clinicopathological differences, these two subtypes are similar in their overall favourable prognosis and ability to be stratified into low, intermediate and high-risk groups based on a number of well-established

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scoring systems. More than 80% of these cancers have an excellent prognosis with a 20-year cause-specific mortality rate of <1% [4].

Management of well-differentiated thyroid cancer has always been controversial, mainly because of the prolonged natural history of the disease in the large majority of patients. The consequent lack of good level 1 or 2 evidence from prospective trials means that most recommendations and guidelines are based on large, retrospective analyses and expert consensus opinion. Hence there is a need to accumulate and analyse carefully documented and detailed retrospective analyses from different centres, before circumstantial associations can be made [5, 6]. The vast amount of information available to physicians and patients can be staggering, with over 140,000 peer-reviewed publications on PubMed and 16 million sites on Google. Access to this large amount of unfiltered information has compounded the problem, with patients and their physicians (primary care physicians or endocrinologists) dictating their own course of treatment, resulting in the widespread use of total thyroidectomies and radioactive iodine (RAI) ablation in the United States. A systematic approach is required to resolve these issues and physicians managing these cancers need to keep abreast of the current developments through well-presented reviews and expert guidelines that are being updated regularly by the National Comprehensive Cancer Network (NCCN) and American Thyroid Association (ATA). In this review, we will discuss some of the controversies and challenges that remain unresolved in managing well-differentiated thyroid cancer.

Diagnosis and evaluation of thyroid nodule

Incidentalomas

The vast majority of thyroid cancers that are being diagnosed are <2 cm and discovered incidentally through clinical examination or other imaging modalities (ultrasound, CT scan, MRI or positron emission tomography [PET] scans). The major debate with these lesions is when to investigate and which patients require surgical intervention [7–9].

As the prevalence of thyroid nodules in the general population is extremely common (50% in population >50-year-old) and only 5% of these nodules are malignant, there is reluctance in investigating nodules <1 cm in size. This is coupled with the fact that microscopic papillary thyroid cancers are common in autopsy studies, and that a minority of these cancers ever achieve clinical significance during a person's lifetime. The issue that arises is our inability to differentiate the clinically relevant nodules from the true incidental lesions that have no bearing on patient outcome. Currently available guidelines suggest that all incidentally discovered nodules should undergo an ultrasound, and lesions that are larger than 1 cm or with sonographic

worrisome features (calcification, irregularity, solid lesion, hypervascularity) should undergo ultrasound-guided needle biopsy [10, 11]. Subsequent management depends on the biopsy result, although even a diagnosis of papillary thyroid cancer may not have any adverse consequence.

PET incidentalomas comprise a unique category of lesions seen in patients undergoing PET scans for a previously diagnosed malignancy or screening evaluation for abnormal tumour markers [12]. Patients with focal PET uptake should be more aggressively evaluated with an ultrasound and ultrasound-guided biopsy, as there is a higher incidence of malignancy (30–50%). Moreover, several series have shown that PET-detected lesions have a more aggressive histologic subtype (tall cell, insular cell, etc.) [13, 14]. Management depends on the diagnosis and natural history of the primary pathology for which the PET was performed.

Imaging

Ultrasound has become the gold standard for evaluating the thyroid nodule and nodal disease in the lateral neck. Ultrasound features suggestive of malignancy include irregular halo, punctate calcification, intra-tumoural hypervascularity and solid nodule [10, 15]. The presence of these features warrants further evaluation regardless of size, with a fine-needle aspiration (FNA) biopsy. Despite the sensitivity of ultrasound scans in detecting thyroid cancer of more than 60–70%, the positive predictive value for each of these features remains <15%, hence the need for further evaluation in the appropriate clinical context. The presence of contralateral thyroid nodules is an important sonographic finding. Even if they appear benign, a total thyroidectomy is usually recommended for bilateral thyroid nodules [16]. Ultrasound is also useful in evaluating the lateral neck compartments for nodal disease. Any abnormal nodes based on size criteria or sonographic appearance should be further evaluated with cross-sectional imaging and needle biopsy. There is limited role for radionuclide thyroid scans in evaluating nodules in the absence of hyperthyroidism. Decisions regarding surgery for thyroid nodules are rarely made based on whether a nodule is 'hot' or 'cold'. Cross-sectional imaging such as CT scans and MRI should be used in patients with compressive or invasive symptoms, especially when a diagnosis of thyroid cancer has already been made. CT scans are more accurate in defining the extent of disease, especially when locally invasive [17]. In fact, cross-sectional imaging usually with CT scans, is mandatory in all patients presenting with locally advanced thyroid cancer for complete evaluation of the extent of disease. This is also crucial in planning extensive surgery. These patients may also require appropriate endoscopy to rule out tracheal, laryngeal and oesophageal invasion. CT scans should also be performed to evaluate lateral compartment nodal disease if ultrasound scans are suspicious. The protocol in most

centres is to perform non-contrast CT scans, although in some circumstance, the benefits of using iodinated contrast to delineate the relationship between the tumour and adjacent major vessels may outweigh the negative impact of contrast on subsequent radioiodine therapy.

Fine-needle aspiration

Fine-needle aspiration biopsy is the most sensitive and specific preoperative indicator of thyroid malignancies. Indications for FNA are well-established and include a number of clinical and imaging criteria as shown in Table 1. More than 60% of FNA biopsies show benign disease, averting a need for surgical intervention [15, 17, 18]. A further 5–10% of biopsies show overt malignancy, necessitating surgery. Interpretation of the remaining 30% of biopsies is more complicated, as most of these are read as suspicious for follicular or Hürthle cell lesions. The diagnosis of follicular cell lesion or neoplasm continues to be a subject of controversy, hence leads to a difficulty in making appropriate treatment recommendations. Biological markers and immunohistochemistry have no definitive role in routine diagnostic purposes. Ultimately surgical decisions should be made based on clinical and ultrasound features, patient anxiety and the comfort level of the treating physician. Both patient and physician should be aware that only 15–20% of these lesions are eventually confirmed to be malignant - either follicular thyroid cancer or follicular variant of papillary thyroid cancer.

FNA biopsy of enlarged lateral compartment nodes should be performed to exclude lymph node metastasis. With regards to lymph node FNA, there has been considerable interest in measuring thyroglobulin levels in FNA washout of lymph node aspirates; a high thyroglobulin

level is virtually diagnostic for metastatic papillary thyroid cancer. Conversely, the presence of well-differentiated follicular, papillary cancer or thyroglobulin-positive cells in neck nodes is diagnostic of metastatic thyroid cancer; lateral aberrant thyroid is a myth and treatment plan should always include a total thyroidectomy together with a neck dissection, even in cases where a thyroid nodule is not appreciated preoperatively. Careful histological examination of the thyroidectomy specimen will reveal a primary thyroid cancer in every case.

Intraoperative management

Total versus less than total thyroidectomy for papillary thyroid cancer

There has been considerable debate as to the role of total versus less than total thyroidectomy (usually lobectomy and isthmusectomy) for well-differentiated thyroid cancers [6, 16, 19]. Proponents of total thyroidectomies have based their argument on large databases showing statistically significant differences in outcome between total thyroidectomy and lobectomy for tumours >1 cm. Furthermore, these patients can then undergo RAI therapy and use thyroglobulin levels as a marker for recurrent disease. At Memorial Sloan-Kettering Cancer Center, we utilise a simplified stratification, dividing patients into low, intermediate and high-risk categories (Table 2) to guide our surgical decision [20]. Patients in the high-risk group or those with aggressive histological subtype undergo total thyroidectomy followed-up by adjuvant RIA ablation. Patients not in the high-risk group, but deemed to require RAI (e.g. <45-year-old with nodal or distant metastasis), undergo total thyroidectomy. Undoubtedly, if pre or intraoperative evaluation shows nodules in the contralateral lobe, patients should undergo a total thyroidectomy. Subtotal thyroidectomy should be abandoned as an option for patients

Table 1 Criteria for FNA biopsy

Clinical features	
History	<ul style="list-style-type: none"> - Previous irradiation - Age <20 or >60 years - Male - History of cancer - Family history of thyroid cancer - Rapid growth
Examination	<ul style="list-style-type: none"> - Hard nodule - Single nodule - Large size >4 cm - Cervical lymphadenopathy - Vocal cord palsy
Imaging	
Ultrasound	<ul style="list-style-type: none"> - Solid nodule - Calcification- micro, macro - Hypoechogenicity - Irregular margins, irregular halo - Central vascular flow

Table 2 Risk-group definition in well-differentiated thyroid cancer as per Memorial Sloan-Kettering Cancer Center [20]

	Low risk	Intermediate risk		High risk
Age (years)	<45	<45	>45	>45
Distant metastasis	M0	M1	M0	M1
Tumour size	<4 cm	>4 cm	<4 cm	>4 cm
Histology and grade	Papillary	Follicular and high grade papillary	Papillary	Follicular and high grade papillary
Five-year survival (%)	100	96	96	72
Twenty-year survival (%)	99	85	85	57

with thyroid cancer. Patients in low-risk group have similar long-term outcome whether they undergo lobectomy or total thyroidectomy. The extent of thyroidectomy in these patients depends on the philosophy of the treating surgeon, the zeal of the endocrinologist and patient preference. Patient preference often has an overriding role to play in these decisions, given the vast amount of information available extolling the virtues of RAI. Nonetheless, patients in the low-risk group derive no benefit from RAI and generally do not require RAI ablation.

Locally invasive thyroid cancer

Extrathyroidal extension is one of the most important prognostic factors in well-differentiated thyroid cancer. Numerous studies have shown that surgical resection of all gross tumour offers the best outcome to patients with locally aggressive thyroid cancer. Hence, it is incumbent on the thyroid surgeon to determine the extent of local invasion prior to and during surgery, and make the appropriate intraoperative decision on surgical extent [21]. Best outcome is achieved when the appropriate procedure is performed during the first surgery.

Local invasion can be anterior, invading the strap muscles, or posterior, invading the recurrent laryngeal nerves, trachea or oesophagus. Excision of the sternothyroid and sternohyoid muscles is not technically demanding, but requires the surgeon to recognise this possibility, especially in anterior or isthmic tumours. Failure to appreciate may result in leaving tumour behind or violating the tumour during surgical exposure. Posterior extension can be more difficult to manage. Recurrent laryngeal nerve invasion with preoperative vocal cord palsy can be managed with resection of the involved nerve, with careful preservation of the contralateral nerve (with or without nerve monitoring). However, in young patients with no preoperative vocal cord paralysis, every effort should be made to dissect the nerve from the tumour. Invasion of the trachea may require tracheal sleeve resection with primary anastomosis. Up to five tracheal rings may be resected and repaired primarily with suprahyoid release procedures, and this may be technically easier to reconstruct than wide, window resections [22]. Shave procedures should be limited to very superficial invasion, as studies have shown high local recurrence rates secondary to incomplete tumour clearance. Invasion of the cricoid and larynx may require more aggressive approaches such as cricotracheal resection and reconstruction or vertical hemilaryngectomies. As there is a higher local recurrence rate, most patients with extensive extra-tracheal extension require adjuvant RAI and external beam radiotherapy in select patients.

Patients presenting with thyroglossal cyst carcinomas generate considerable controversy. This is invariably a postoperative diagnosis that is usually a surprise to the surgeon and patient. Ultrasound evaluation of the thyroid

gland should reveal if there are any gross abnormalities in the remaining thyroid gland or neck nodes. If there are suspicious findings, a total thyroidectomy and appropriate nodal clearance should be undertaken. However, if the thyroid gland is normal based on clinical and imaging criteria, the patient may be kept under close surveillance. Tumours of the isthmic area may require total thyroidectomy and resection of the overlying strap muscles. Central compartment evaluation and clearance may be necessary if there are suspicious lymph nodes in the tracheo-oesophageal groove.

Nodal metastases

Central compartment clearance

One of the major debates in intraoperative management of well-differentiated thyroid cancer revolves around the role of prophylactic or elective central compartment clearance [23–25]. Nodal metastases occur in 40–60% of papillary thyroid cancer; however microscopic disease has minimal impact on overall survival for most patients, although local recurrence rates may be higher. In contrast, bulky nodal disease in high-risk patients may affect long-term survival and loco-regional recurrence. Hence, there is a need to critically evaluate the central compartment intraoperatively in every patient with papillary thyroid cancer. Certainly, the presence of suspicious or palpable nodal disease requires the surgeon to perform a formal central compartment clearance, taking care not to injure the recurrent laryngeal nerve, and either preserve the inferior parathyroid on its pedicle or auto-transplant in the contralateral sternocleidomastoid muscle. However, it is not certain whether the same procedure would be beneficial in the absence of suspicious nodal metastasis. Proponents for elective central compartment clearance argue that it is a safe procedure in expert hands, with meta-analyses showing only an increase in transient hypoparathyroidism rates, and avoids the need for future manipulation of the tracheo-oesophageal groove for recurrent nodal disease [26, 27]. Opponents argue that the presented statistics are from expert centres and do not represent ‘real world’ complication rates which may be much higher. Furthermore, there is probably minimal clinical impact from the small volume or microscopic metastatic disease. Prospective trials to resolve this issue are unlikely, hence surgeon and institutional philosophies will prevail for the moment.

Lateral compartment clearance and disease

Certainly there is no data supporting the routine use of prophylactic lateral neck dissection. If there is clinically apparent disease, patients should undergo a formal modified

radical neck dissection, sparing the accessory nerve, jugular vein and sternocleidomastoid muscle (modified radical neck dissection type III) [27, 28]. There is no role for ‘berry picking’ of enlarged nodes, as this inevitably results in high nodal recurrence rate. However, there is good data to suggest that level I dissection can be avoided as metastatic rates to level I nodes are <3%, and avoiding this region spares the mandibular branch of the facial nerve from inadvertent injury. Metastatic rates to nodes superior to the accessory nerve (level IIB and VA) is also low, hence these levels can be spared, minimising dissecting and skeletonising the accessory nerve. Some surgeons now advocate using ‘compartment-oriented’ dissection and limiting dissections to involved nodal levels only. While this is conceptually appealing and technically not difficult, there is fine line between clearance of nodal levels and ‘berry picking’.

Elective lateral neck dissection is not generally advocated even in patients with locally advanced thyroid cancer. However, if patients present with extensive local invasion and multiple positive paratracheal nodes, due consideration should be given to critically evaluating the jugular nodal chain intraoperatively and selective nodal dissection as indicated.

Postoperative management and long-term follow up

RAI therapy and TSH suppression

Decisions regarding the role of postoperative adjuvant RAI therapy remain controversial. Accurate risk stratification is crucial to determine the value of adjuvant therapy and clinical recommendations should reflect the balance between our best estimate of disease aggressiveness and the risk-benefit profile of available treatment modalities [29, 30]. There are a number of well-established scoring systems, mostly based on factors that have consistently predicted outcome in thyroid cancer: age, grade of the tumour, extrathyroidal extension, size, distant metastasis and histology. The MACIS scoring system proposed by the Mayo clinic is one of the most commonly used schemes, which has been validated in large patient groups (Table 3) [31].

There is no doubt that patients who fall under the category of high-risk require adjuvant RAI therapy and consideration for other therapies such as external beam radiotherapy for aggressive extrathyroidal extension. However, the same scoring system have also suggested that there is limited role for RAI in patients classified as low-risk, who otherwise have survival rates in excess of 98%. The decision is more complex in patients who fall under the intermediate category, where the benefits and risks of RAI should be discussed with the patient and decisions should be made based on institutional philosophies, physician and patient preferences. It should be clear to both the patient and

physician that RAI therapy is not without complications and should not be delivered indiscriminately. With regards to RAI, there is considerable interest in the use of recombinant thyroid stimulating hormone (rTSH) given prior to RAI therapy. The attraction is that patients can avoid the extended period of time (usually 6 weeks) during which they are hypothyroid, which can be distressing. Nonetheless, there are cost considerations that need to be addressed with rTSH, and using tri-iodothyronine (T3) replacement can reduce the period of thyroxine deprivation to 2 weeks.

Data supporting the role of TSH suppression have also shown the maximal benefit in high-risk groups (32, 33). Nonetheless a structured TSH suppression protocol can be used to maximise its benefit while minimising risks in low risk patients. The goal TSH is generally 0.1–0.4 mIU/l in all patients except high risk patients (aim for TSH <0.1 mIU/l) and those at low risk (aim for TSH <1 mIU/l). TSH suppression should always be balanced against symptoms of hyperthyroidism which may require β -blockers to control. Furthermore, extreme TSH suppression increases the risk of developing osteoporosis in the long-term.

Ongoing risk stratification and follow-up

Traditional risk stratification is focused on a single time point, usually postsurgery to determine the risk group that a patient belongs to. Current expert opinion suggests that most patients should be re-assessed after 2–3 years to determine whether they have responded to therapy, the nature of response and hence re-evaluate their risk groups based on treatment response [30]. This approach is important as most patients with thyroid cancer lead long lives and hence have extended periods of follow-up. Given the accuracy and sensitivities of available modalities to detect persistent or recurrent disease and understanding the biological behaviour of these events, the physician needs to make a strategic long-term plan in treating these patients. Quick decisions regarding re-operative surgery for low volume persistent disease, which otherwise has a long natural history, may cause more harm to the patient than a watchful waiting approach.

Table 3 Prognostic factors in thyroid cancer - MACIS scoring [31]

Score = 3.1 (age <40) or 0.8 × age (age >40)
+ 0.3 × tumour size (cm)
+ 1 if incompletely resected
+ 1 if locally invasive
+ 3 if distant spread
20-year survival by MACIS score
• <6 = 99%
• 6–6.99 = 89%
• 7–7.99 = 56%
• ≥8.00 = 24%

There are a number of modalities available to the physician in the long-term follow-up of these patients. Clinical examination, thyroglobulin levels and neck ultrasonography are commonly used in the long-term evaluation of post-thyroidectomy patients. There is also considerable interest in stimulated thyroglobulin levels, although not in widespread use. The predictive values for these modalities are used to modify risk estimates in managing these patients, and divides patients into different treatment response categories: excellent response, acceptable response and incomplete response (Table 4). Thyroglobulin levels shown in Table 4 are most accurate in patients having undergone total thyroidectomy and RAI ablation. In patients who undergo lesser procedure, the trend of thyroglobulin levels over time may be more accurate than a single reading of thyroglobulin level. However, the latter group comprise of patients who have excellent risk profile and hence have low disease recurrence and mortality rates to begin with.

Patients with unmeasurable thyroglobulin levels and no evidence of recurrent disease on imaging are easily managed with routine follow-up. Unfortunately, with increased use and sensitivity of thyroglobulin measurements, we recognise a subset of patients with persistent minimal volume disease, sometimes even seen on cross-sectional imaging as stable paratracheal nodal disease or non-specific changes in the thyroid bed. This group of patients falls under the acceptable response category, with disease that is not easily eradicated with additional surgery or RAI. Most of these patients have long progression-free survival and are best managed with observation, reserving additional therapy when evidence of disease progression is documented. Ultimately, the aim is to determine which of these patients develop disease progression that is clinically relevant, and it is hoped that future studies would help define this subgroup.

The continued use of all detection modalities in all patients is not cost-effective. A risk-stratified follow-up strategy is applied for best utilisation of available resources and should be based on initial risk stratification and secondary response to therapy assessment (Table 5). It is important to note that this approach is mainly directed at patients with complete tumour resection and no evidence of metastatic disease.

PET scan

PET scan has emerged as an important investigational tool for thyroid cancers, especially in patients with high-grade or aggressive thyroid cancers. While routine use of PET scan is not indicated in the long-term follow-up of patients, there are two scenarios where it may be invaluable: first is in patients with rising thyroglobulin levels with no demonstrable disease seen with RAI scans, and second in patients with metastatic disease. FDG avidity is a direct function of histological aggressiveness, and PET positive tumours are usually poorly responsive to RAI therapy [13, 14]. Hence, patients with recurrent thyroid cancer that is PET positive have a worse outcome than PET negative recurrences. Similarly the extent of FDG avidity and standard uptake values are also important prognostic markers both in patients with loco-regional recurrence and distant metastatic disease.

Metastatic disease and targeted therapy

Distant metastasis is rare in well-differentiated thyroid cancer and generally involves the lungs, bones and brain [17]. Pulmonary metastases are the most common, and low-volume, miliary disease detected during RAI scans

Table 4 Variables determined during follow-up that predict response to therapy (Tg - thyroglobulin) (adapted from Tuttle et al. [30])

	Excellent response	Acceptable response	Incomplete response
Suppressed Tg	Undetectable	Detectable but <1 ng/ml	>1 ng/ml
Stimulated Tg	Undetectable	<10 ng/ml	>10 ng/ml
Trend in suppressed Tg	Undetectable	Declining	Stable or rising
Anti-Tg antibodies	Undetectable	Absent or declining	Persistent or rising
Neck examination	Normal	Normal	Palpable disease
Neck ultrasound	No evidence of disease	Non-specific changes in thyroid bed Stable millimetre size nodes	Significant recurrent/persistent disease (>1 cm) in thyroid bed Cervical lymph nodes >1 cm
Diagnostic RAI	No evidence of disease	No evidence of disease Faint uptake in thyroid bed only	Persistent/recurrent RAI avid disease
Cross-sectional imaging (CT, MRI)	No evidence of disease	Non-specific changes	Structural disease in thyroid bed or lymph nodes
PET scan	No evidence of disease	Non-specific changes	FDG-avid disease

Table 5 Follow-up strategy based on risk groups (adapted from Tuttle et al. [30])

	Initial estimate of risk recurrence during first 2 years of follow-up		
	Low risk	Intermediate risk	High risk
Suppressed Tg	Q 6 months	Q 6 months	Q 6 months
Stimulated Tg	Not required	1–2 years	1–2 years
Neck ultrasonography	Q 1 year $\times$ 2	Q 1 year $\times$ 2	Q 1 year $\times$ 2
Diagnostic RAI	Not required	1–2 years	1–2 years
Cross-sectional imaging (CT, MRI)	Not required	Not required	If Tg elevated or high clinical suspicion
PET scan	Not required	Not required	If Tg elevated and RAI scan negative
	Secondary risk stratification based on response to therapy assessment		
	Excellent	Acceptable	Incomplete
Ongoing follow-up	Yearly physical examination and yearly suppressed Tg	Yearly physical examination, yearly suppressed and stimulated Tg, continued assessment of indeterminate structural changes for at least another 2–3 years	Consider additional cross-sectional imaging, possible PET scan and neck for additional therapy

or ablation, is often indolent and associated with a good outcome. Extensive or aggressive metastatic disease is usually detected as structural changes in cross-sectional imaging of the lungs or as FDG-avid lesions in PET scan, and can be more difficult to manage. Palliative procedures may be required to treat persistent pleural effusion. Bony metastases are rare and usually seen in follicular or Hürthle cell cancers. Even if diagnosed early, patients still benefit from a total thyroidectomy and RAI therapy. External beam radiotherapy may be required to palliate symptoms. Brain metastases may be diagnosed with cross-sectional imaging such as CT or MRI scans. Stereotactic procedures may be required to confirm the diagnosis if an isolated lesion is seen. These patients should also be treated with RAI therapy or external beam radiation where applicable.

A small subset of patients with thyroid cancer develop life-threatening, RAI-refractory, progressive metastatic disease. The role of systemic therapy in these patients is not clearly defined. This is mainly due to the fact that conventional chemotherapeutic agents are inadequate in treating thyroid cancers. Anthracyclines (such as doxorubicin, epirubicin) are the most commonly used agents, and these are reported to have response rates of 20–30% at best. As a result, there has been great interest in the use of a targeted approach to treat thyroid cancers [34]. Recent data have suggested that mutations in one of several genes involved in the receptor tyrosine kinase mitogen-activated protein kinase (MAPK) pathway can be detected in up to 80% of well-differentiated thyroid cancers. Specific mutations include those affecting RET (5–30% of cases), ras (10% of cases) and BRAF (40% of cases) has also been identified. Targeting the MAPK pathway has hence been a subject of much investigation in

preclinical and early clinical studies (Table 6). These novel compounds are often used in combination with traditional agents to deliver maximal benefit, although their use is limited to the trial setting. Targeting epigenetic modifiers is an alternative strategy that can be used to re-differentiate thyroid cancer cells and restoring their ability to take up RAI. Clinical trials are also underway to explore the role of DNA methylation and histone deacetylase inhibitors to this effect. Targeting nuclear receptors such as retinoic acid receptors (RAR) and peroxisome proliferators-activated receptors (PPAR) can also re-differentiate cells, which in turn increase NIS expression and uptake of RAI. Apart from these agents, there have been scattered reports of promising clinical response to a range of agents used in desperate settings. With increasing number of clinical trials either underway or soon to be opened, the clinician is faced with having to decide which of the available trials would be most beneficial. Unfortunately, currently available data does not allow us to identify the best agent for a particular patient, although the ultimate aim of these strategies is individualised therapy. These questions can only be answered in time and through careful analyses of well-designed, properly controlled prospective clinical trials, to determine which of the many potential novel agents (or combinations) is most effective in treating patients.

Conclusions

Management of well-differentiated thyroid cancer continues to be a source of debate, predominantly because it is a long-standing disease with good outcome in the majority of

Table 6 Investigational drugs currently in clinical trial and pathways targeted (adapted from Tuttle et al. [34])

Pathways	Specific target	Mechanism	Example (target)
MAPK	TK ligand	Antibody against TK ligand	Bevacizumab (VEGF)
	TK receptor	Antibody against TK receptor	Cetuximab (EGFR) Trastuzumab (EGFR)
		Small molecule inhibitor against TK ligand	Vandetanib (VEGF, EGF, RET) Motesanib (VEGF, PDGF, c-KIT and RET)
		Small molecule inhibitor against TK receptor	Vatalanib (VEGFR), gefitinib (EGFR) sunitinib (VEGFR and others)
	Downstream targets	Ras inhibition	Ras antisense compounds Phenylacetate (also inhibitor of VEGF) Farnesyl transferase inhibitor (tipifarnib)
		Raf inhibition	Sorafenib
		MEK inhibition	PD 98059 AZD6244
Epigenetic modifiers	DNA methylation	Methylation inhibitor	5-aza-2-deoxycytidine
	Histone deacetylation	Deacetylase inhibitor	Suberoylanilide hydroxamic acid/SAHA Valproic acid
Nuclear receptors	Retinoic acid receptors and retinoid X receptors	Vitamin A derived retinoic acids	13-cis-retinoic acid Bexarotene
	Peroxisome proliferators-activated receptors (PPAR)	Thiazolidinediones	Rosiglitazone
Other pathways	COX-2 pathway	COX-2 inhibitors	Celecoxib
	Heat-shock protein-90	HSP inhibitors	Geldanamycin
	Proteasome	Proteasome inhibitors	Bortezomib
	PI3 kinase pathway	Akt-mTOR inhibitors	Rapamycin analogs

patients. The controversies are fueled by increasing range and sensitivities of tests available for diagnosis and follow-up, and the perceived benefits offered by RAI with minimal side effect profile. The consistent increase in the incidence of well-differentiated thyroid cancer, especially in small, incidentally-detected lesions, most with unknown clinical significance adds a further dimension of uncertainty. Lack of prospective data means that practise guidelines are based on large retrospective series and expert opinion. A concerted effort needs to be made to risk stratify and offer treatment according to risk groups. Overtreating low-risk patients offers no benefit to the patient, is a misuse of scarce resources and exposes the patient to unnecessary complications. Treatment of well-differentiated thyroid cancer requires a multidisciplinary approach by endocrine surgeons, endocrinologists, oncologists, radiologists, pathologists and nuclear medicine physician. Sometimes the collective decision of this multidisciplinary team is required to restrain an overzealous patient and avoid over-

treating a low risk patient. Treatment philosophies should follow well-established guidelines offered by NCCN, ATA and other expert organisations rather than personal philosophies. It is therefore incumbent on the treating physician to keep abreast of existing and future treatment options and revisions in these guidelines. In many cases, the most difficult course of action is watchful waiting, hence doing no harm.

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