Thyroid cancer

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Thyroid cancer is the fifth most common cancer in women in the USA, and an estimated over 62 000 new cases occurred in men and women in 2015. The incidence continues to rise worldwide. Differentiated thyroid cancer is the most frequent subtype of thyroid cancer and in most patients the standard treatment (surgery followed by either radioactive iodine or observation) is effective. Patients with other, more rare subtypes of thyroid cancer—medullary and anaplastic—are ideally treated by physicians with experience managing these malignancies. Targeted treatments that are approved for differentiated and medullary thyroid cancers have prolonged progression-free survival, but these drugs are not curative and therefore are reserved for patients with progressive or symptomatic disease.

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Introduction

The incidence of thyroid cancer continues to rise worldwide, mostly as a result of increased use of diagnostic imaging and surveillance. Thyroid cancer is the fifth most common cancer in women in the USA, and an estimated over 62 000 new cases occurred in men and women in 2015.[1] Therefore, most practitioners will encounter a patient with this disease at some point in their career. Although incidence is rising steadily, mortality from thyroid cancer has changed minimally over the past five decades. The challenge faced by physicians who treat thyroid cancers is to balance the therapeutic approach so that patients with lower risk disease or benign thyroid nodules are not over treated. At the same time, they need to recognise those patients with more advanced or high-risk disease, who need a more aggressive treatment approach. Thyroid cancers exhibit a broad range of clinical behaviour—from indolent tumours with low mortality in most cases, to very aggressive malignancies, for example, anaplastic thyroid cancer. Therefore, undertaking a proper diagnostic work-up before treatment is started is crucial to appropriately tailor treatment. In this Seminar, we describe the clinical presentation, diagnostic work-up, and standard treatment of thyroid nodules and thyroid cancer, and discuss cutting-edge treatments that could be incorporated into standard care in the future.

Clinical presentation

Thyroid nodules

Thyroid nodules are being identified with increasing frequency in clinical practice, owing largely to the growing use of diagnostic imaging. In studies using new high-resolution imaging techniques, thyroid nodules are being identified that would never have been diagnosed in the past.[2–4] Although over 90% are small, non-palpable, benign lesions that will never become clinically significant tumours,[5,6] some patients have non-palpable or palpable lesions that are malignant. Identification of malignant thyroid nodules is important, especially those that will cause morbidity if not diagnosed early. To distinguish between low-risk and high-risk patient subsets, a thorough history and physical examination, laboratory investigations, neck ultrasonography, and, for appropriately selected patients, fine-needle aspiration (FNA), are needed.[7] Autonomous functioning thyroid nodules that cause hyperthyroidism should be identified before biopsy to avoid complications and ensure appropriate imaging and treatment. A radionuclide thyroid scan should be done only in patients with suppressed thyroid stimulating hormone (TSH).

Follicular-derived thyroid cancers

Differentiated thyroid cancer

Differentiated thyroid cancer is the most common thyroid cancer, accounting for more than 95% of cases,[8] and originates from thyroid follicular epithelial cells. Under the category of well-differentiated thyroid cancers are papillary thyroid cancer, follicular thyroid cancer, and Hurthle cell thyroid cancer. Poorly differentiated thyroid cancer is a more aggressive follicular-derived thyroid cancer than differentiated thyroid cancer.

Papillary thyroid cancer is the most common subtype and carries the best overall prognosis. Metastases most commonly involve cervical lymph nodes and, less commonly, the lungs. Follicular thyroid cancer, Hurthle cell thyroid cancer, and poorly differentiated thyroid cancers are high-risk cancers that have a tendency to metastasise haematogenously to distant sites, in particular, to lung and bones. The staging system for differentiated thyroid cancers depends on age,[9] with older (≥45 years according to the current system) patients faring worse.

Anaplastic thyroid cancer

Anaplastic thyroid cancer is a rare form of thyroid cancer (<1%)[8] that usually presents as a rapidly growing neck

Search strategy and selection criteria

We referred to key publications (including abstracts) and guidelines for the management of thyroid nodules and thyroid cancer. We also searched PubMed (Jan, 2005, to Dec 1, 2015) for the terms "thyroid nodule" and "differentiated thyroid cancer", "medullary thyroid cancer", or "anaplastic thyroid cancer" and cross-referenced these with the following terms: "genetics", "management", and "clinical trials". We also cross-referenced "papillary thyroid cancer" with "surgery" and "lobectomy". We restricted the search to studies done in human beings and published in English. We focused on publications after 2010.

mass. Patients often develop hoarseness, dysphagia, and dyspnoea. On examination, most patients with anaplastic thyroid cancer have a large, firm palpable mass in the thyroid with or without cervical adenopathy. This finding should prompt a rapid assessment and biopsy of the mass. A metastatic work-up often reveals locoregional disease and distant metastases. The most common site of distant metastatic disease is the lungs, followed by bones and brain. Anaplastic thyroid cancer often arises from and can coexist with differentiated thyroid cancer, but can also occur de novo. Clinicians should suspect anaplastic transformation in patients with a history of longstanding differentiated thyroid cancer if they present with the aforementioned symptoms. Referral to a centre with expertise in treating anaplastic thyroid cancer is recommended since these are rare tumours that have poor prognosis because of rapid tumour growth. Promising treatments are being tested in clinical trials (see later) and these might offer the best chance of survival.

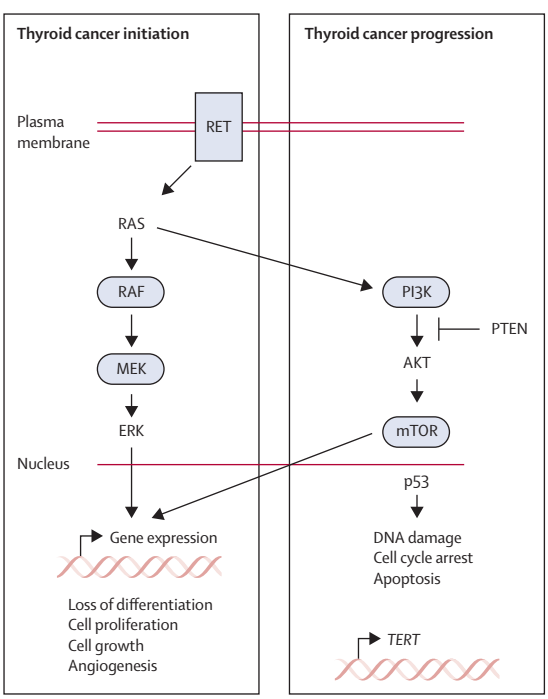

Figure 1: **Thyroid cancer pathways**
Diagram shows the key molecular signalling pathways involved in thyroid cancer. The left box shows the mitogen-activated protein kinase pathway, which is activated by mutation in most thyroid cancers. These events are believed to initiate thyroid cancer development, and lead to altered gene expression, which promotes cell proliferation, cell growth, angiogenesis, and loss of differentiation. The right box shows pathways altered in advanced thyroid cancers, which are believed to promote tumour progression. This includes the PI3K–mTOR pathway, the p53 tumour suppressor, and alterations in the promoter for TERT. Blue boxes represents factors for which targeted treatments are available that have been approved by the US Food and Drug Administration. mTOR=mammalian target of rapamycin. PI3K=phosphatidylinositol-3-kinase. TERT=telomerase reverse transcriptase.

Neuroendocrine C-cell derived thyroid cancer

Medullary thyroid cancer

Medullary thyroid cancer is uncommon, accounting for 1–2% of all thyroid cancers.[8] By contrast with differentiated thyroid cancer, medullary thyroid cancer originates in the parafollicular neuroendocrine cells of the thyroid. It most commonly presents as a solitary thyroid nodule in patients in the fourth to sixth decade of life.[10] Occasionally, neck lymphadenopathy is the first manifestation, because the disease frequently metastasises to cervical lymph nodes. 70% of patients presenting with a palpable medullary thyroid cancer have evidence of cervical node metastases at surgery.[11] Some patients present with the classic case of a thyroid nodule, flushing and diarrhoea, which is suggestive of widespread metastatic disease. A quarter of medullary thyroid cancer cases occur in patients with an inherited multiple endocrine neoplasia syndrome.[10]

Genetics of thyroid cancer

Findings from DNA sequencing studies of thyroid cancer have revealed the genetic basis for most thyroid cancers. Most thyroid cancers harbour mutations along the mitogen-activated protein kinase (MAPK) cellular signalling pathway (figure 1). This pathway transmits growth signals from the plasma membrane to the nucleus and plays a central part in the regulation of cellular proliferation.[12]

Differentiated thyroid cancer and anaplastic thyroid cancer

The most frequent mutation in non-medullary thyroid cancer is the *BRAF*^{T1799A} mutation, resulting in BRAF^{V600E}-mutant kinase, which is exclusive to papillary thyroid cancer[13] and papillary-thyroid-cancer-derived anaplastic thyroid cancer. Mutations in the *RAS* family of oncogenes also occur frequently in thyroid cancer.[14] *RAS* mutations most frequently occur in follicular thyroid cancer and follicular variant papillary thyroid cancer. Chromosomal translocations also occur in thyroid cancers. These genomic rearrangements lead to expression of novel fusion oncogenes that initiate events in many thyroid cancers. PAX8–peroxisome proliferator-activated receptor γ (PPARγ) translocation occurs in about 30% of follicular thyroid cancer cases,[15] and the RET-papillary thyroid cancer family of translocations targeting the *RET* oncogene occur in about 7% of papillary thyroid cancer cases.[13] Less common translocation partner genes include *BRAF*, the *NTRK* gene family, *ALK*, and *THADA*.[13] Although infrequent, these translocation events can directly affect treatment. For example, *ALK* rearrangements might be associated with clinically aggressive thyroid cancers.[16] The availability of small-molecule ALK and *NTRK* gene family inhibitors have shown clinical promise in rearrangement-positive tumours in other cancers;[17,18] therefore, identification of these rearrangements might have direct therapeutic relevance to patients with thyroid

cancer. Debate exists regarding the clinical implications of individual mutations, with findings from some studies suggesting increased propensity for clinically aggressive papillary thyroid cancer in tumours bearing a *BRAF* mutation.[19–23] However, the fact that about 50–70% of papillary thyroid cancers harbour a *BRAF* mutation[13,24] and most of these tumours remain indolent, suggests that other important determinants of clinical behaviour exist. Also, mutations in *TERT* have been identified in more aggressive subsets of papillary thyroid cancer.[25–27]

Findings from DNA sequencing studies of poorly differentiated thyroid cancer and anaplastic thyroid cancer suggest that the acquisition of additional cooperating mutations contributes to tumour progression. Most commonly, a mutation that affects either the phosphatidylinositol-3-kinase or p53 tumour suppressor pathway is present, often in association with an early initiating mutation such as $BRAF^{T1799A}$.[14,28–30]

Medullary thyroid cancer

Mutations in the *RET* proto-oncogene are believed to be the cause of most cases of medullary thyroid cancer, whereas a small proportion are caused by sporadic *RAS* mutations. *RET* mutations can occur sporadically as somatic events or as inherited germline events that exhibit autosomal dominant inheritance.[10,31–33] Germline mutations in *RET* can predispose patients to early development of medullary thyroid cancer as a component of the multiple endocrine neoplasia type 2A and 2B syndromes. As such, patients who present at a young age are likely to have hereditary disease. Strong genotype–phenotype associations exist with specific *RET* mutations, which predict both the age of onset and the clinical aggressiveness of medullary thyroid cancer. Prophylactic thyroidectomy is often indicated, but specific recommendations are based on the age of the patient and the inherited mutation, and have been reviewed elsewhere.[10]

Because 1–7% of patients presenting with apparently sporadic medullary thyroid cancer are carriers of germline *RET* mutations,[10] assessment for a heritable *RET* germline mutation should be recommended to all patients presenting with medullary thyroid cancer, regardless of their family history or age.

Assessment and treatment of thyroid nodules

Sonographic features that require FNA biopsy

Size plays a key part in identifying whether a FNA biopsy is needed for a thyroid nodule, but other sonographic findings can also provide valuable clues regarding the likelihood of nodule malignancy. These include hypoechogenicity, a solid internal structure, irregular margins, microcalcifications, taller-than-wide shape, and evidence of extrathyroidal extension or cervical lymphadenopathy, or both.[34] If a nodule has none of these features, FNA cytology can be deferred as long as the nodule remains small.[19] These considerations apply mainly to papillary thyroid cancer. Follicular thyroid cancers, and follicular variant papillary thyroid cancers,[35] are more often round and isoechoic with regular margins. In these cases, a larger size and increased intranodular vascularity on colour or power doppler imaging are also predictive of malignancy.[36–39] The 2015 American Thyroid Association (ATA) guidelines[19] include ultrasonography-defined risk categories for thyroid nodules, each with specific recommendations for FNA (figure 2).[19] Consideration must also be given to concomitant clinical risk factors for thyroid cancer, which include the presence of a firm mass, neck pain, cough, voice change, and a history of childhood neck irradiation or familial thyroid cancer. In these cases, FNA can be considered regardless of the sonographic appearances.[19] Beyond all these arguments, the 2015 ATA guidelines recommend biopsy only for nodules larger than 1 cm (figure 2).

Use of FNA cytology to tailor treatment

As shown in figure 2, the Bethesda system for reporting thyroid cytopathology includes six diagnostic categories.[40] Diagnostic category 2 includes benign nodules, which can be safely managed with periodic ultrasonography of the neck; nodules that are malignant (diagnostic category 6) or likely to be malignant (diagnostic category 5) generally need surgery.[19] If cytology results are non-diagnostic (diagnostic category 1), the nodule should be re-aspirated. Indeterminate results (diagnostic categories 3 and 4, the latter suggesting a higher probability of malignancy) can be managed surgically or with close monitoring, depending on clinical risk factors, ultrasonography patterns, and patient preferences.[19]

Molecular diagnostics for differentiating between diagnostic categories 3 and 4

A cytological diagnosis of malignancy has a high specificity and positive predictive value, and conversely a cytological diagnosis of a benign nodule has a high negative predictive value and low false negative rate. However, thyroid nodule FNA cytology is confounded in diagnostic categories 3 and 4, in which the diagnosis or exclusion of thyroid cancer is not clear.[19] Two approaches to molecular diagnosis of indeterminate thyroid nodules are in use: gene mutation profiling panels and a 167 gene expression classifier.[41–43] A positive test for a mutation in genotyping panels has a high predictive value for thyroid cancer. By contrast, the 167 gene expression classifier offers a strong negative predictive value, but a suspicious result is predictive of thyroid cancer in only 50% of cases. Therefore, mutation testing is regarded as a good rule-in test, by contrast with the gene expression classifier, which is regarded as a good rule-out test. However, a more recent, expanded mutation panel seems to improve the poor negative predictive value of early seven-gene mutation tests.[43,44] Findings from an initial study[45] showed that use of the 167 gene expression classifier reduced the number of surgeries for benign thyroid nodules, but

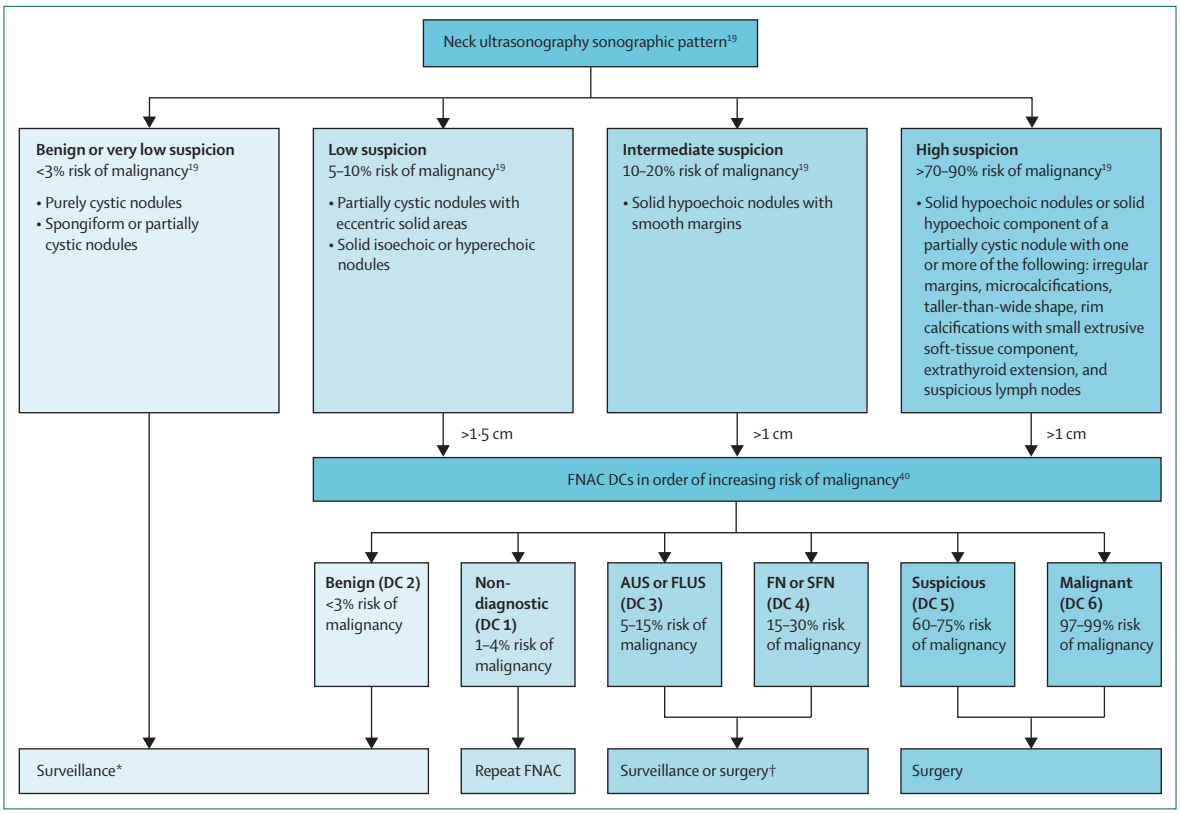

Figure 2: **Management of thyroid nodules on the basis of sonographic patterns and cytology diagnostic categories of the Bethesda system**
AUS=atypia of undetermined significance. DC=diagnostic category. FLUS=follicular lesion of undetermined significance. FN=follicular neoplasm. FNAC=fine-needle aspiration cytology. SFN=suspicious for follicular neoplasm. *Fine-needle aspiration can be considered (1) for nodules with very low suspicion sonographic pattern and the largest diameter greater than 2 cm; and (2) if there are suspicious clinical findings (eg, firm mass, neck pain, cough, voice change, and a history of childhood neck irradiation or familial thyroid cancer), regardless of the sonographic appearances. †Indeterminate results can be managed surgically or with close monitoring, depending on the clinical risk factors, ultrasonography patterns, genetic testing, and patient preferences.

findings from recent reports suggested large inter-institutional variation in the usefulness and cost-effectiveness of this test.[19,46–48] Although expanded mutation profiling panels seem to overcome some weaknesses of the gene expression classifier assay, additional studies validating the mutation panel at several institutions is necessary. Therefore, the use of these tests to improve patient care remains to be established. However, the era of molecular diagnosis in thyroid nodules is underway, and molecular approaches are likely to continue to improve the diagnostics of thyroid nodules.

Treatment of differentiated thyroid cancer

The pretreatment assessment of risk for patients with differentiated thyroid cancer includes neck imaging techniques. Cervical ultrasonography plays a key part, by providing surgeons with fundamental information on the size, location, number of tumours and lymph nodes, and local invasion of surrounding tissues. In up to a third of patients with differentiated thyroid cancer, nodal lesions are identified on the preoperative scan, and in two-thirds of these cases the findings lead to revision of the surgical plan.[49,50]

Surgical approaches

Primary treatment decisions are based on a preoperative risk assessment that includes clinical, imaging, and cytological data. Choices depend on the location or locations and extent of identifiable disease (ie, therapeutic surgery) and the risk that unidentifiable disease foci are also present (ie, prophylactic surgery; figure 3). With increasing emphasis on risk-stratified management, the treatment approaches recommended by the 2015 ATA guidelines[19] are more conservative than in the past. Lobectomy is an option for unifocal tumours smaller than 4 cm with no evidence of extrathyroidal extension or lymph node metastasis. The results of several large database studies[51–54] have shown that unilateral and bilateral resections are associated with similar long-term survival. In these cases, overall survival is also unaffected by the presence of occult lymph node metastases.[55] With one lobe intact, many patients can avoid lifelong thyroid hormone replacement therapy. Complication rates associated with lobectomy are roughly half those reported with total thyroidectomy.[56] In the presence of small, non-invasive, clinical N0 tumours, risk:benefit ratios might favour a plan that includes lobectomy with intraoperative

inspection of the central compartment, and upgrade to total thyroidectomy with compartmental neck dissection should nodal disease be found.[19] The rare recurrences that develop during long-term follow-up of patients treated with lobectomy can be detected readily and controlled appropriately with completion surgery without jeopardising survival.[57,58] However, this evidence is based on findings from case-control and registry database studies, which might give rise to bias, and randomised controlled trials examining the safety and efficacy of lobectomy are needed. For carefully selected patients presenting with papillary microcarcinomas (≤1 cm) without evidence of cervical lymph node metastases, non-surgical management can be an option. Researchers in Japan have found strong evidence of the safety and efficacy of active surveillance in these cases.[59,60] Surgery was done in patients with substantial increases in nodule size. The medical–economic implications of this approach are unknown.

Management after primary surgery

Shortly after surgery, the risk estimate is adjusted based on surgical and pathological findings, and decisions are made regarding the need for radioiodine ablation or TSH suppression, or both. This assessment is conventionally based on the well-known TNM staging system. TNM staging was designed to predict mortality[61,62] and is less effective for estimating the probability of postoperative persistence or recurrence of disease, which is more pertinent to follow-up planning. The need for estimation of risk of recurrence was addressed by the ATA in 2009, with a new system that identifies high, intermediate, and low risk for recurrence.[63] This system is a reliable predictor of the

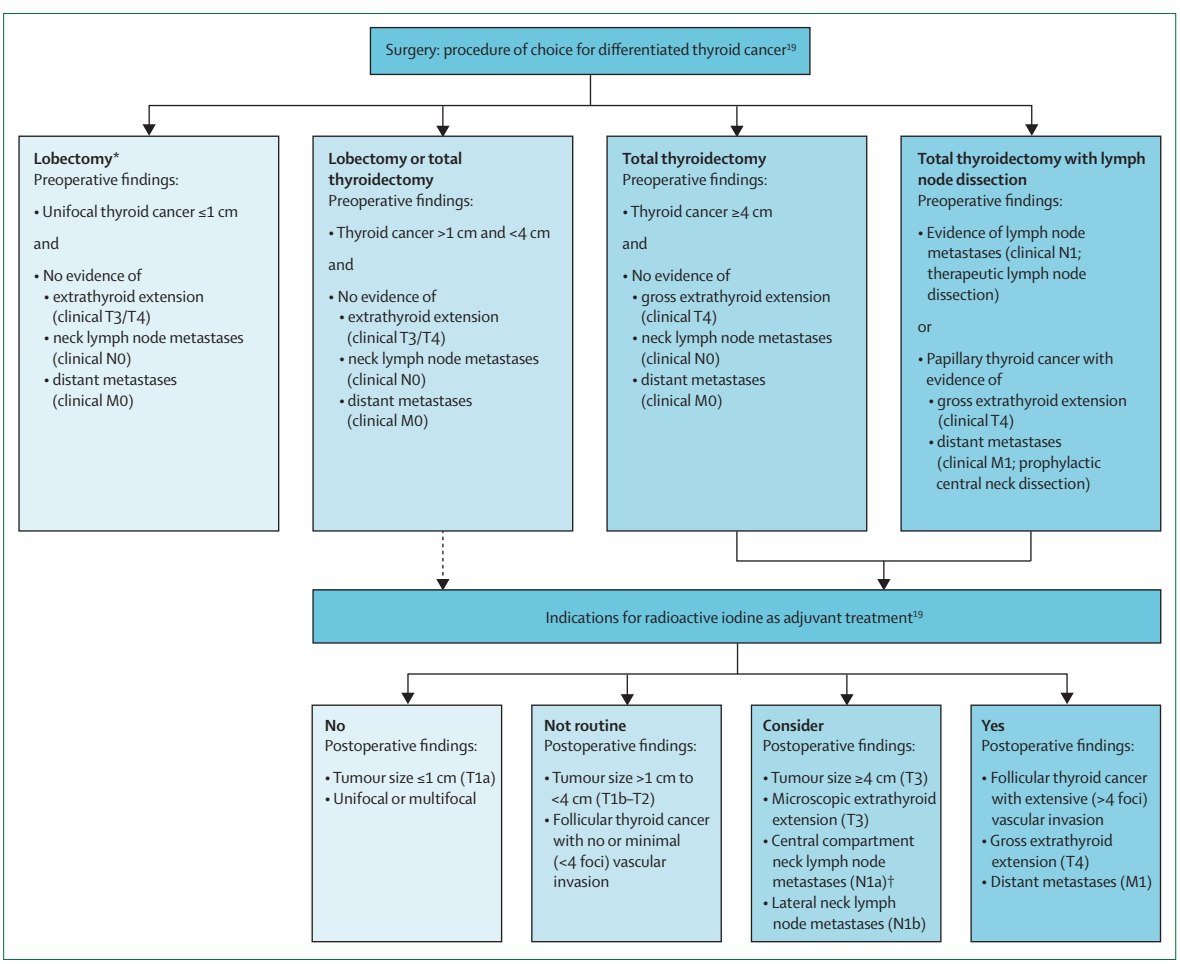

Figure 3: **Primary treatment of patients with differentiated thyroid carcinoma**
*For patients with known clinical risk factors (eg, previous head and neck irradiation or familial thyroid carcinoma), the initial surgical procedure should be total thyroidectomy. Lobectomy can be offered to patients with small, intrathyroidal tumours with no clinical evidence of metastasis. After lobectomy, completion thyroidectomy could be offered to patients with evidence of pathological extrathyroid extension or lymph node involvement, or both. †There is insufficient evidence to recommend radioactive iodine in patients with fewer than five microscopic nodal metastases in the central compartment, without extra-nodal extension. For indications for radioactive iodine, solid lines show pateints for whom we strongly recommended consideration of radioactive iodine based on preoperative finding and the dsashed line shows patients who can be considered for radioactive iodine depending on the pathological postoperative findings.

Panel: **Recurrence risk stratification at the time of primary treatment and over time as a function of the response to treatment**

At the time of primary treatment

ATA low risk (≤5% recurrence)

Papillary thyroid cancer

- Intrathyroid tumour
- Clinical N0 or five or fewer lymph node micrometastases (<0·2 cm in largest diameter)
- ^{V600E}*BRAF*-mutated microcarcinoma

Follicular thyroid cancer

- Intrathyroid tumour
- Capsular invasion and no or minimal (<4 foci) vascular invasion

ATA intermediate risk (5–20% recurrence)

Papillary thyroid cancer

- Minimal extrathyroid extension
- Aggressive histology*
- Vascular invasion
- Clinical N1 or more than five lymph node metastases (<3 cm in largest diameter)
- ^{V600E}*BRAF*-mutated, intrathyroid, 1–4 cm, primary tumour
- ^{V600E}*BRAF*-mutated microcarcinoma, multifocal with extrathyroid extension

ATA high risk (>20% recurrence)

Papillary thyroid cancer

- Gross extrathyroid extension
- Distant metastases
- Lymph node metastasis at least 3 cm in largest diameter

Follicular thyroid cancer

- >4 foci of vascular invasion

During follow-up†

Excellent response (1–4% recurrence)

- Imaging negative for disease recurrence
- Serum thyroglobulin concentration lower than 0·2 ng/mL basal or higher than 1 ng/mL TSH stimulated‡

Indeterminate response (15–20% recurrence)

- Non-specific findings on imaging studies
- Serum thyroglobulin 0·2–1 ng/mL basal or 1–10 ng/mL TSH stimulated, or thyroglobulin antibodies stable or decreasing

Biochemical incomplete response (20% recurrence)

- Imaging negative for disease recurrence
- Serum thyroglobulin concentration higher than 1 ng/mL basal or higher than 10 ng/mL TSH stimulated, or increasing thyroglobulin antibody concentrations

Structural incomplete response (50–85% recurrence)§

- Structural (neck ultrasound, CT, or MRI) or functional (whole-body scan or ^{18}F-fluorodeoxyglucose PET) evidence of disease in imaging studies

ATA=American Thyroid Association. TSH=thyroid stimulating hormone. *Tall cell, hobnail variant, and columnar cell carcinoma. †The initial risk stratification should be updated continually and revised after the primary treatment on the basis of data generated during periodic follow-up visits. This approach is valid soon after surgery (1–3 months) to decide whether or not radioactive iodine should be given for adjuvant or therapeutic purposes. ‡In the absence of interfering thyroglobulin antibodies. §Percentage of patients who will continue to have persistent disease despite additional treatment. Adapted with permission from Haugen and colleagues.[19]

course of differentiated thyroid cancer treated with thyroidectomy alone[64,65] or with radioactive iodine remnant ablation.[64,66–68] The revised system proposed in the ATA's 2015 guidelines[19] includes additional clinical and pathological features, allowing more precise estimates of the risk of recurrence (panel).

See Online for appendix

Primary management with radioactive iodine

The decision to administer radioactive iodine treatment after total thyroidectomy is often justified by the need to eliminate residual clusters of normal thyroid tissue. The ability of this tissue to incorporate iodine and produce thyroglobulin complicates efforts to identify persistent or recurrent neoplastic thyroid tissue with ^{131}I scintigraphy and serum thyroglobulin assays. This rationale is now being challenged. In the past two decades, use of diagnostic whole-body ^{131}I scintigraphy has reduced sharply, and reliance on cervical ultrasonography,[69,70] which is not only more sensitive, but also advantageous in terms of cost, radiation exposure, and absence of adverse effects,[71] has increased. Neck ultrasonography combined with serum thyroglobulin assays are the most sensitive methods for detecting persistent disease and tailoring subsequent diagnostic and therapeutic strategies.[19,69,70]

Radioiodine is also advocated as adjuvant treatment, with the aim of improving long-term outcomes by destroying occult microscopic foci of neoplastic cells within the thyroid remnant or elsewhere in the body. This practice has also been questioned in the past decade.[63] The adverse effects of radioiodine include short-term morbidity and possible increases in the risk of second cancers.[72,73] Guidelines now recommend selective use of radioactive iodine, based on individual risk, with the lowest activity needed to ensure successful treatment (figure 3).[19]

Lastly, radioactive iodine can be used to identify patients with distant metastatic disease that is sensitive to radioactive iodine, and also serves as a treatment. Unfortunately, many patients are refractory to radioactive iodine; in these patients this strategy would not be effective for either detection or treatment of distant disease.

TSH suppression treatment

Circulating TSH stimulates proliferation in normal thyrocytes and most thyroid cancer cells.[74] For this reason, TSH-suppressive doses of thyroid hormone therapy have traditionally been used after surgery. This approach significantly reduces recurrence and cancer-related mortality in patients with differentiated thyroid cancer.[75] However, the amount of suppression needed to attain these goals is unclear. In high-risk patients, reducing TSH concentrations to less than 0·1 mU/L can improve clinical outcomes,[76] but moderate reductions (subnormal to normal TSH) can also improve outcomes.[77] However, the subclinical hyperthyroidism induced by TSH can negatively affect the bone (causing osteoporosis in postmenopausal women) and heart (causing angina in patients with coronary heart disease and atrial fibrillation in elderly patients).[78] The likelihood of complications must be weighed against the risk of increasing tumour cell proliferation, on the basis of ongoing assessments of the individual's risk of persistent or recurrent disease (appendix).[19]

Assessment of individual risk during follow-up

6–12 months after postoperative assessment, the patient's risk status should be revised based on their response to primary treatment, which is classified according to the system shown in the panel.[19,64,66] This checkpoint is mandatory and involves measurement of thyroglobulin concentrations, neck ultrasonography, and other examinations as needed. The results are essential for planning the next few years of follow-up, which are important, since 77% of recurrences are discovered during the first 5 years after surgery.[79] Even so, the risk estimate is updated continually and revised based on data generated during follow-up visits. With this dynamic approach, a substantial proportion of patients with differentiated thyroid cancer—including some whose initial staging revealed a high risk of persistent or recurrent disease—can at some point be reclassified as having a lower risk of recurrence and shifted onto a surveillance programme that is less intensive than originally planned. Recurrences detected during the surveillance period are usually managed with either observation (for small clinically insignificant lesions) or comprehensive compartmental surgery.

Treatment of medullary thyroid cancer

Surgery is the only curative treatment for medullary thyroid cancer; however, few patients with clinically apparent nodal metastases at diagnosis achieve undetectable tumour markers. As with differentiated thyroid cancer, imaging and diagnosis before surgery are crucial to deliver the appropriate surgical intervention. All patients with a preoperative diagnosis of medullary thyroid cancer should undergo comprehensive neck ultrasonography and tumour marker (calcitonin and carcinoembryonic antigen) measurement. Additionally, establishing whether the patient has germline or sporadic disease is crucial because patients with multiple endocrine neoplasia type 2 can have pheochromocytoma or primary hyperparathyroidism, or both. If germline *RET* mutation status is not known or cannot be established before surgery in a patient with medullary thyroid cancer, biochemical testing should be done to rule out pheochromocytoma and hyperparathyroidism. If the patient has primary hyperparathyroidism, thyroid surgery should be tailored to include parathyroidectomy. Adrenalectomy in patients with pheochromocytoma should be prioritised before thyroidectomy. Referral to a genetic counsellor for patients with hereditary medullary thyroid cancer is recommended so that only appropriate family members undergo testing, which reduces the cost. The use of prophylactic thyroidectomy for family members who carry the germline *RET* mutation has been reviewed elsewhere.[10]

Tumour markers in the preoperative setting

If the preoperative calcitonin concentration is higher than 146 pmol/L, further work-up for distant metastatic disease should be done.[10] The recommended imaging for this work-up includes neck and chest CT and three-phase contrast-enhanced MRI of the liver. Skeletal metastases are preferably assessed with axial skeleton MRI. In the absence of substantial distant metastatic disease, the preferred surgery is total thyroidectomy with bilateral central neck dissection. Dissection of lateral neck compartments is recommended only if metastatic disease is suspected by neck ultrasound and confirmed by FNA cytology. The revised ATA guidelines[10] for the management of medullary thyroid cancer recommend contralateral neck dissection in patients with lateral neck disease based on calcitonin concentrations higher than 58 pmol/L; however, this recommendation remains controversial.

Management after primary surgery

The long-term management of medullary thyroid cancer primarily consists of observation. Patients need thyroid hormone replacement but not suppression of TSH, as is done in high-risk differentiated thyroid cancer. Tumour markers (calcitonin and carcinoembryonic antigen) should be checked no earlier than 3 months after surgery to establish whether the patient has persistent disease. External beam radiation should be used sparingly because it can limit future surgical intervention because of the induction of fibrosis. External beam radiation can also reduce the quality of life of the patient. Referral to a centre with expertise in medullary thyroid cancer is recommended for patients for whom external beam radiation is not clearly indicated. Most patients should be managed with active surveillance, whereby both ultrasonography and tumour markers are assessed serially to guide further surgical treatment. Locally recurrent disease can be managed with observation or surgery, depending on the risk of the tumour threatening vital structures and other patient factors.

Use of tumour markers after primary surgery

Patients with undetectable tumour markers and normal imaging after surgery should continue to be followed up annually; those with persistent tumour markers need to be followed up more closely for progression. Calcitonin and carcinoembryonic antigen doubling times are useful measures, because they are predictive of outcomes and aggressive tumour behaviour.[80] Patients with calcitonin and carcinoembryonic antigen doubling times within 6 months have a shorter overall survival. An online calculator can be found on the ATA website.

For **the ATA website** see http://thyroid.org

Systemic treatments for advanced stage differentiated thyroid cancer and medullary thyroid cancer

Identification of patients who should be considered for systemic treatment

Much progress has been made in the treatment of advanced thyroid cancer with the approval of four kinase inhibitors for differentiated thyroid cancer and medullary thyroid cancer. Unfortunately, these drugs are not curative

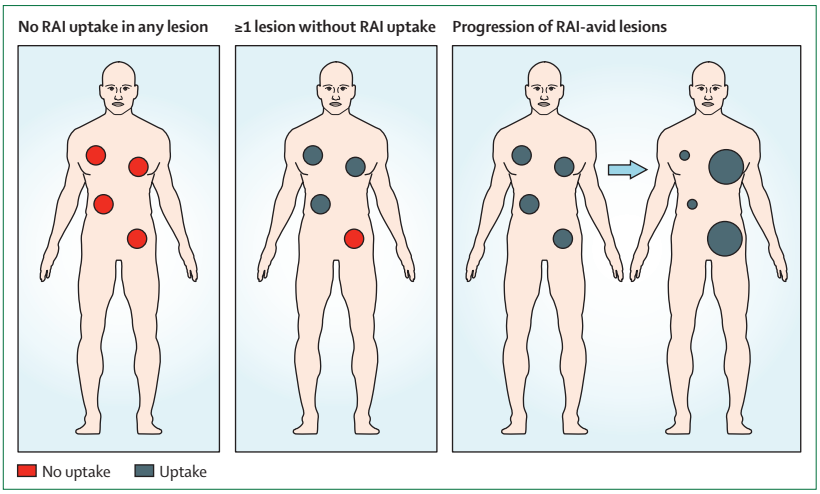

Figure 4: **Definition of differentiated thyroid cancer refractory to radioactive iodine**
The standard definition of patients who are refractory to RAI is those with metastatic lesions that have no RAI uptake, or one or more lesion that does not have any RAI uptake, or progression of lesions that do have RAI uptake. Most definitions also include patients who have received greater than 600 mCi cumulative dose of RAI because those patients do not seem to benefit from additional treatment.[81] RAI=radioactive iodine.

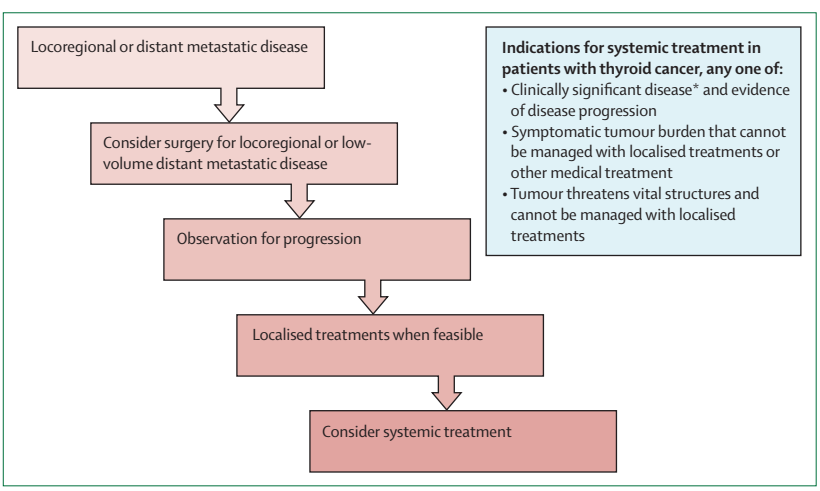

Figure 5: **Treatment approach for a patient with differentiated and medullary thyroid cancer with locoregional or distant metastatic disease and the indications for initiating systemic treatment**
*A tumour that measures at least 1·5 cm. In differentiated thyroid cancer, patients should also have evidence of disease refractory to radioactive iodine.

and patients eventually develop resistance. Furthermore, many patients with metastatic or recurrent differentiated thyroid cancer and medullary thyroid cancer have indolent disease. Thus, these drugs are reserved for patients with progressive disease or those with disease that is threatening vital structures or causing substantial clinical symptoms. Patients with differentiated thyroid cancer should have radioactive iodine-refractory disease (figure 4) before systemic treatments are considered. Figure 5 shows the recommended treatment for a patient with differentiated thyroid cancer or medullary thyroid cancer who has locoregional or distant metastatic disease and the indications for starting systemic treatment. Observation for progressive disease is important because most patients with differentiated thyroid cancer and medullary thyroid cancer have indolent disease. Localised treatments can be considered for patients with progressive disease, thereby delaying the need for systemic treatment. For example, external beam radiation or embolisation for bony or liver metastases in patients in whom these are likely to cause morbidity.[19] In patients with locoregional disease, surgery should be considered in the appropriate setting, and metastasectomy can be used for low-volume metastatic disease if it will delay or prevent morbidity. For example, a patient with a bony metastasis that is threatening function of the limb could be considered for surgery.[19]

Systemic treatments for advanced stage differentiated thyroid cancer

In the past several years, considerable research dedicated to differentiated thyroid cancer has been done, leading to the approval of two kinase inhibitors for use in differentiated thyroid cancer by the US Food and Drug Administration and European Medicines Agency: sorafenib and lenvatinib. These drugs are multikinase inhibitors with antiangiogenic properties. Other classes of drugs have been studied in differentiated thyroid cancer and hold promise for the treatment of patients with advanced, widely metastatic disease.[82–91]

Sorafenib was approved for differentiated thyroid cancer in 2013 on the basis of favourable results of a phase 3 multicentre, randomised, double-blind, placebo-controlled clinical trial (DECISION).[92] The lenvatinib SELECT trial[85] was also a phase 3 multicentre, randomised, double-blind, placebo-controlled clinical trial in patients with differentiated thyroid cancer. The impressive results of this trial led to the approval of the drug in the USA in 2015. The table shows the results and important differences in trial design between the trials that resulted in the approval of these drugs. Neither trial showed a statistically significant difference in overall survival; however, both trials allowed for unmasking and crossover at progression. In a subgroup analysis of SELECT, a significant improvement in overall survival was noted in older (>65 years) compared with younger (≤65 years) patients.[96]

These kinase inhibitors are also associated with adverse effects. Common adverse effects associated with sorafenib and lenvatinib are hypertension, hand–foot skin reaction, diarrhoea, rash, fatigue, weight loss, and stomatitis. Increased TSH concentration is also common and is particularly concerning for patients with differentiated thyroid cancer, who should have TSH suppressed.

Systemic treatments for advanced stage medullary thyroid cancer

Both vandetanib and cabozantinib are approved in the USA and EU for treatment of medullary thyroid cancer. In the phase 3, multicentre, double-blind, placebo-controlled trial of vandetanib (ZETA),[94] adult patients with locally advanced or metastatic medullary thyroid cancer were enrolled. Unmasking and crossover was permitted in

	Trial design				Trial results (drug *vs* placebo)			
	Drug targets	Label indication in thyroid cancer	Notable entry criteria	Randomisation and design (drug *vs* placebo)	PFS, months (HR, 95% CI; p value)	Complete response (%)	Partial response (%)	Stable disease (%)
Sorafenib[92]	VEGFR1, VEGFR2, VEGFR3, RET, BRAF, PDGFR	DTC refractory to radioactive iodine	Adult, DTC refractory to radioactive iodine, treatment naive, progression within 14 months	1:1; crossover allowed	10·8 *vs* 5·8 (0·59, 0·45–0·76; p<0·0001)	0 *vs* 0	12·2 *vs* 0·5	41·8 *vs* 33·2*
Lenvatinib[93]	VEGFR1, VEGFR2, VEGFR3, RET, PDGFR, FGFR1, FGFR2, FGFR3, FGFR4	DTC refractory to radioactive iodine	Adult, DTC refractory to radioactive iodine, one previous VEGF-directed treatment allowed, progression within 13 months	2:1; crossover allowed	18·3 *vs* 3·6 (0·21, 99% CI 0·14–0·31; p<0·001)	1·5 *vs* 0	63·2 *vs* 1·5	23 *vs* 54·2
Vandetanib[94]	VEGFR2, RET, EGFR	MTC	Adult, MTC	2:1; crossover allowed	30·5† *vs* 19·3 (0·46, 0·31–0·69; p<0·001)	0 *vs* 0	45 *vs* 13	NA
Cabozantinib[95]	VEGFR2, RET, MET	MTC	Adult, MTC, progression within 14 months	2:1; crossover not allowed	11·2 *vs* 4·0 (0·28, 0·19–0·40; p<0·001)	0 *vs* 0	28 *vs* 0	48·1 *vs* 50

All trials were randomised, double-blind, placebo-controlled trials in which PFS was the primary endpoint. All trials met the primary endpoint. DTC=differentiated thyroid cancer. HR=hazard ratio. MTC=medullary thyroid cancer. NA=not assessed. PFS=progression-free survival. *For >6 months. †Estimated.

Table: **Phase 3 trial results of the four drugs approved for advanced thyroid cancer**

ZETA at the time of progression. Cabozantinib was studied in a phase 3, multicentre, randomised, double-blind, placebo-controlled clinical trial (EXAM).[95] Patients in EXAM were never unmasked and were not permitted to crossover to open-label drug. This difference in masking and crossover and the inclusion of patients only with progressive disease were the major design differences between EXAM and ZETA. The results of both trials are summarised in the table.

So far, neither trial has shown an overall survival advantage of the drug versus placebo. In the vandetanib trial,[94] overall survival data were immature since only 15% of patients had died at the progression-free survival cutoff. As for the cabozantinib trial,[95] despite not permitting for crossover, overall survival was not statistically different between the two arms. However, in 2015, Schlumberger and colleagues[97] reported a statistically significant difference in overall survival between patients with *RET M918* mutations who received cabozantinib compared with placebo (44·3 *vs* 18·9 months, hazard ratio 0·60, 95% CI 0·38–0·95).

Similar to sorafenib and lenvatinib, diarrhoea, rash, hypertension, fatigue, hand–foot skin reaction, and headaches are common adverse effects associated with vandetanib and cabozantinib.[94,95] Gastrointestinal perforation and fistula formation are rare but serious adverse effects associated with cabozantinib.[98] QTc prolongation was reported in 8% of patients in the ZETA trial,[94] leading to the requirement of a risk assessment and mitigation strategies programme for physicians to be allowed to prescribe the drug.

Treatment of anaplastic thyroid cancer

Anaplastic thyroid cancer is an aggressive form of thyroid cancer, and is both a diagnostic and therapeutic challenge because of the rarity of the disease and because anaplastic thyroid cancer cells lose expression of thyroid and epithelial cell markers.[99] Additionally, these tumours can exhibit diverse histomorphological abnormalities, such as squamoid, spindled patterns, leading to confusion about the organ of origin. This confusion can lead to a delay in diagnosis and initiation of an appropriate treatment plan. Once diagnosis is established, patients should be staged quickly (appendix), and the airway should be assessed by fibreoptic laryngoscopy. A treatment plan must be devised and implemented quickly.

Referral to a centre with experience with anaplastic thyroid cancer is recommended. Treatment of local disease in the neck is multimodal.[100] Patients should be assessed by an experienced head-and-neck surgeon to establish whether the primary tumour is resectable. External beam radiation is recommended soon after resection, preferably with radiosensitising drugs such as some combinations of taxanes with or without platin or anthracyclines (chemo-radiation). Patients with unresectable primary tumours, but without detectable distant metastases, are usually referred for palliative chemoradiation.

The most challenging cases are patients who present with advanced distant metastatic disease (stage IVC). The physician must balance the goal of local control of the primary tumour with treatment of distant metastases. If locoregional disease is an imminent threat then chemo-radiation should be given first. For those patients in whom the airway is not at risk or has already been stabilised by tracheostomy, systemic chemotherapy with cytotoxic drugs or, preferably, enrolment in a clinical trial should be considered.

A recent approach is targeted treatment of the cancer; for example, BRAF inhibitors in patients with $BRAF^{V600E}$-mutated anaplastic thyroid cancer.[101] A trial with the selective BRAF inhibitor dabrafenib and the MEK inhibitor trametinib is accruing patients (NCT02034110). Other interesting drugs being studied are lenvatinib (NCT02657369),[102] second-generation mammalian target of rapamycin (mTOR) inhibitors (NCT02244463), microtubule inhibitors (NCT01240590),

PPARγ agonists (NCT02152137), and immunotherapy (NCT02458638 and NCT02239900). Immunotherapy might be a difficult approach since this class of drugs tends to induce regression of tumour months after starting treatment. In patients who need to respond to treatment quickly, drugs that take effect within weeks rather than months are needed.

As with many advanced, aggressive malignancies, patients and family members need to understand the poor prognosis, and advanced directives and wishes of the patient should be discussed. Some patients should be referred to a hospice if their performance status is poor or they do not wish to pursue treatment.

Summary and future directions

The management of early-stage and late-stage thyroid cancer, as well as approaches to thyroid nodules, has changed markedly in the past decade. Molecular analysis of indeterminate thyroid nodules is beginning to influence disease management; however, no test has so far been able to discriminate malignant from benign nodules reliably. Dynamic risk stratification for patients with differentiated thyroid cancer and the recognition that many differentiated thyroid cancers warrant a more conservative approach should lead to fewer total thyroidectomies, reduce use of radioactive iodine, and relax TSH suppressive treatment in appropriately selected patients.

Prospective randomised clinical trials on management of primary differentiated thyroid cancer have not yet been done, in part because of the overall low mortality and long survival of most patients, which has led to a general paucity of interest by pharmaceutical companies and investigators alike. However, most differentiated thyroid cancer recurrences occur in the first 3 years after initial treatment, and therefore these studies are feasible.[103] One important future direction is execution of prospective clinical trials to address major management decisions including, but not limited to, the use of radioactive iodine for remnant ablation and adjuvant treatment for low-risk or intermediate-risk disease, and optimum initial surgical approaches. Additionally, as molecular markers and analyses are applied to clinical care, prospective studies should integrate these methods into trial designs.

That four antiangiogenic drugs have been approved for advanced thyroid cancer in just 4 years is remarkable. A better understanding of the optimum time to start treatment and which groups of patients warrant treatment will continue to evolve. Other novel treatments have been studied and hold promise in *BRAF*-mutated papillary thyroid cancer, including the selective BRAF inhibitors vemurafenib[82,104] and dabrafenib.[83] As more mutations are being recognised and becoming drug targets (eg, the *NTRK* gene family and ALK molecular abnormalities), more clinical trials are being planned.

One exciting area of active research involves modulation of the differentiation state (ie, how similar the cancer cell remains to the parental cell of origin) of differentiated thyroid cancer. Findings from the large TCGA study[13] of papillary thyroid cancer showed that $BRAF^{V600E}$-like and RAS-like classes of papillary thyroid cancer differ significantly with respect to differentiation state, with $BRAF^{V600E}$-like tumours exhibiting a gene expression profile associated with a less differentiated state. Findings from two proof-of-concept clinical trials[86,87] in patients with thyroid cancers refractory to radioactive iodine have supported this hypothesis. In one trial,[87] selumetinib, a selective MEK inhibitor, was used as a re-differentiating drug, and in the other,[86] dabrafenib, a selective BRAF inhibitor, was used in patients with *BRAF*-mutated papillary thyroid cancer. In both trials, patients with measurable disease were treated over a short timeframe then re-imaged for new or increased radioiodine uptake by the tumour. In each study, most patients exhibited new or increased radioiodine uptake. Future studies should focus on patients with earlier stage disease and those with smaller target lesions, because these patients have the highest chance of a cure with this approach.

New methods to treat patients with medullary thyroid cancer who fail to respond or progress on vandetanib or cabozantinib, or both, are needed. The role of cancer immunotherapies is being studied in medullary thyroid cancer,[105] but no clinical trials are enrolling at the moment. The major limitation to discovering effective treatments for anaplastic thyroid cancer is the rarity of the disease. Patients and their advocates will need to lead the way to push for approval of treatments on the basis of findings from small trials since completion of larger trials are not feasible.

The molecular characterisation of thyroid cancer types has begun to influence the diagnosis and treatment of thyroid cancer. We expect continued improvements in these tests to lead to a reduction in unnecessary treatments for indolent thyroid cancers and to improvements in outcomes in patients with clinically aggressive cancers.

Contributors

MEC, DGM, and CD drafted, revised, and gave final approval of this work.

Declaration of interests

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