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Title: Clinical guidance for Radioiodine Refractory Differentiated Thyroid Cancer

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Declarations of Interest

B.H., D.J.T., B.G.R., F.P., J.T. and R.C-B have served on an advisory board for Eisai. B.H. and B.G.R. have served on the advisory board of AstraZeneca. D.J.T., R.C-B. and B.G.R have served on an advisory board for Bayer. D.J.T has received honoraria for lectures on thyroid cancer, including use of kinase inhibitors, and use of rhTSH, from Eisai and

Genzyme. R.C.-B. has received honoraria for lectures on thyroid cancer, including use of kinase inhibitors, from Eisai. D.J.T and B.G.R were principal investigators for the SELECT trial of lenvatinib, and for ongoing trials of lenvatinib in thyroid cancer. Other authors had no conflicts of interest to declare.

Summary

Prognosis from differentiated thyroid cancer is worse when the disease becomes refractory to radioiodine. Until recently, treatment options have been limited to local therapies such as surgery and radiotherapy, but the recent availability of systemic therapies now provides some potential for disease control. Multi-targeted kinase inhibitors (TKIs) including lenvatinib and sorafenib have been shown to improve progression free survival in Phase III clinical trials, but are also associated with a spectrum of adverse effects. Other TKIs have been utilised as "redifferentiation" agents, increasing sodium iodide symporter expression in metastases and thus restoring radioiodine avidity. Some patients whose disease progresses on initial TKI therapy will still respond to a different TKI and clinical trials currently in progress will clarify the best options for such patients. As these drugs are not inexpensive, care needs to be taken to minimize not only biological but also financial toxicity. In this review we examine the basic biology of radioiodine refractory disease, and discuss optimal treatment approaches, with specific focus on choice and timing of TKI treatment. This clinical field remains fluid, and directions for future research include exploring biomarkers and considering adjuvant TKI use in certain patient groups.

Background

Differentiated thyroid cancer (DTC) is derived from aberrant follicular cells within the thyroid gland. It encompasses both papillary (PTC) and follicular (FTC) subtypes that make up the bulk of the prevalence (Figure 1). These epithelial-derived cancers are grouped together as they behave similarly despite biologic differences. Follicular cells are stimulated by thyroid stimulating hormone (TSH) to produce and secrete the thyroid hormones, thyroxine (T4) and triiodothyronine (T3). The follicular cells have a unique machinery to take up iodine from blood and ‘organify’ it to generate these hormones. It is this mechanism that is exploited with radioactive iodine treatment.

The incidence of thyroid cancer has increased in the past few decades. In Australia and the United Kingdom, there has been a surge in new diagnoses that is mostly - but not completely

- explained by overdiagnosis [1,2]. Cancer projection rates by the Australian Institute of Health and Welfare predict in 2020, 3,435 new cases of thyroid cancer will be diagnosed every year [3]. In the UK, incidence rates for thyroid cancer are projected to rise by 74% between 2014 and 2035 [4]. Irrespective of whether overdiagnosis plays a role in incidence, there are now *more* patients who need nuanced risk stratification of their disease. Most cases are associated with excellent prognosis: overall, the 5 year survival rate is 95.8% [5]. More reassuringly, the 5 year conditional survival, for those who have already survived 1 year after diagnosis, is 98% [5]. However, in aggressive DTC, 25% of cases will develop locally recurrent disease requiring additional treatments [6]. Distant metastases are rare on presentation but are found in 6-20% of patients in follow up and this markedly increases the risk of cancer-specific mortality [7].

Paramount to thyroid cancer management is determining the appropriate scale of therapy. Treatment can range from none at all (active surveillance), through to combinations of surgery, radioactive iodine (RAI), external beam radiotherapy, and systemic therapies. The most recent American Thyroid Association (ATA) guideline now includes four classifications of DTC risk (very low, low, intermediate, high) and reflect changing attitudes to minimise treatment recommended for very low- and low-risk disease[8]. Moreover, even for intermediate- and high-risk disease there has been increasing use of so-called *dynamic risk stratification* that takes into account response to first therapy, which better correlates with long-term outcomes[9]. These categories are excellent response, biochemically incomplete response, structurally incomplete response, and indeterminate response [8].

Scott et al recently reviewed a tailored approach to thyroid cancer risk from an Australian perspective [10]. Our purpose here is to extend this by providing specific guidance on management of radioiodine-refractory disease: i.e. a small subfraction (~5%) but with the poorest prognosis (10% 10-year survival) of all thyroid cancer cases (Figure 1) [11]. Therapeutic options have improved since The British Thyroid Association guidelines published in 2014 which promoted largely supportive care and clinical trial enrolment [2]. Of note, the Phase III clinical trials discussed below were not in press at the time those guidelines were published.

Patients identified with RAI-refractory disease (RAIRD) will have already undergone total thyroidectomy, RAI ablation, and suppressive dose thyroxine as their first line treatment, and many will have had repeated doses of RAI. Some will have had external beam radiotherapy

to prevent local recurrence. Early recognition of RAIRD is important to avoid further unnecessary RAI treatment, and to prompt consideration if or when systemic therapy is appropriate. RAIRD can present with an indolent course for which active surveillance is reasonable [12]. Optimising the balance between quality and quantity of life is prudent in treatment decisions. In patients with stable or slowly progressive disease, systemic therapies should be deferred. However, for patients with rapidly progressive and/or symptomatic RAIRD, the recent availability of effective systemic therapies offers potential for disease control [13].

Biological mechanisms for radioiodine-refractory disease

Genetic mutations and distortions of signalling pathways underpin the initiation and propagation of thyroid cancer [14]. The Mitogen Activated Protein Kinase (MAPK) pathway is overexpressed in thyroid cancer and upstream mutations are pivotal to tumorigenesis. Constitutive activation of the MAPK pathway leads to dedifferentiation of PTC cells in pre-clinical models [15]. Subsequent stimulation of downstream targets lead to transcription of genes involved in cell proliferation.

Tumour-stromal interactions are also important for thyroid cancer progression, and in particular tumour expression of Vascular Endothelial Growth Factor (VEGF) and Platelet Derived Growth Factor (PDGF) and their interactions with cognate receptors on stromal fibroblasts appear also to be key processes mediating local progression (Figure 2) [16]. Angiogenesis is a hallmark of many cancers, including DTC [17]. VEGF is upregulated in DTC and one of its co-receptors, NRP-2, has been implicated in metastases through enhancement of invasion and motility in thyroid cancer cells [18,19]. Several studies have shown a correlation between VEGF receptor expression and metastasis in PTC [18]. Anti-angiogenic therapies have become established as treatments for advanced DTC [11]. The fibroblast growth factor signalling pathway also drives tumourogenesis and has been successfully targeted by inhibitors (reviewed in [20]).

Mutation profiles of advanced metastatic and RAI- refractory differentiated thyroid cancers show pathogenic roles for established oncogenic mutations in *BRAF*, *RAS*, *PTEN* and *RET/PTC* rearrangements[14]. $BRAF^{V600E}$ mutation has been associated with more aggressive disease, and is clearly associated with locoregional recurrence, but not with distant metastases

or death independently from other clinicopathological risk factors [21,22]. There is significant gene expression variation between tumours with $BRAF^{V600E}$ that may explain the inconsistency of utilising it as a prognostic marker [14]. Conversely, Telomerase Reverse Transcriptase (TERT) promoter mutations specifically identify those thyroid cancers associated with disease-specific mortality and are associated with less differentiated PTCs [14,23]. The simultaneous presence of TERT and $BRAF^{V600E}$ mutations confer the highest disease-specific mortality in DTC [24,25].

There is a significantly higher prevalence of $BRAF^{V600E}$ in DTCs that have lost RAI avidity [26]. $BRAF^{V600E}$ causes constitutive activation of the MAPK pathway (Figure 3) and preclinical models and a phase II trial suggest that inhibition of MEK (downstream from BRAF) may restore RAI uptake (so called re-differentiation) in certain cases with RAIRD [27,28].

Defining radioiodine-refractory disease

RAI (I-131) emits short path length (1-2 mm) beta rays fatal to thyroid tissue. Following total thyroidectomy, RAI is used as an adjuvant treatment in selected patients to ablate residual disease. RAI is not used for thyroid cancer patients following hemi- or subtotal thyroidectomy, since residual thyroid tissue preferentially accumulates iodine and diminishes any utility for RAI in treating loco-regional disease.

In the last few decades, RAI therapy was delivered almost routinely post thyroidectomy to patients with DTC to ablate residual micrometastases. The most recent ATA guideline recommends limiting (or avoiding completely) administration of RAI to those with low risk disease to avoid non-stochastic side effects such as siloadenitis[8]. These guidelines acknowledge that even in those with intermediate risk, there is limited evidence of benefit from RAI, although it does facilitate the use of serum Tg as an accurate and sensitive tumour maker (in the absence of thyroglobulin antibodies) [29-31]. In high risk patients, postoperative RAI administration is used as adjuvant therapy, with observational data confirming an improvement in disease free survival [32]. Of note, there are no randomised controlled clinical trials demonstrating that RAI reduces the risk of mortality or recurrence these cohorts [8].

On diagnosis of distant metastases, RAI is usual first line therapy followed by long-term TSH suppression. One subgroup that does particularly well with repeated RAI therapy is those patients with pulmonary micrometastases[8]. When the thyroid tumour becomes or is intrinsically refractory to RAI, the prognosis is poor. Patients with metastatic DTC that retains RAI avidity have a 10-year survival of 60%, whereas survival falls to 10% when either RAI avidity and/or responsiveness are lost[33]. Hence restoring iodine avidity is a priority in future DTC treatments.

RAI-refractory disease occurs in less than 5% of patients with DTC. Progressive de-differentiation of DTC is accompanied by loss of the sodium iodide symporter (NIS) that is required for iodine uptake. Poorly differentiated foci with loss of iodine avidity exhibit parallel development of ^{18}F-Fludeoxyglucose (FDG)-PET positivity so that FDG-PET positive disease is more likely to be refractory [34]. Radioiodine refractory disease is far more common in older patients; those with large tumour burden and those with poorly differentiated subtypes such as tumours with Hurthle cell histology [35].

RAI-refractory disease is established when, in patients with appropriate TSH stimulation: (1) the iodine has never concentrated in the metastatic tissue so there is no uptake outside the thyroid bed; (2) the tumour tissue has lost the ability to take up iodine despite being previously RAI avid; (3) iodine can be concentrated in some metastases but not others; or (4) metastatic disease progresses despite significant uptake of RAI. There is no demonstrated role for further RAI therapy in these patients unless their iodine refractory status can be reversed.

At times, the definition of refractory disease is ambiguous. In patient cohorts who have: (1) had a total of 600 mCi cumulative RAI dose; (2) high FDG uptake on FDG-PET scan; (3) aggressive DTC histology (insular or Hurthle Cell), the presence of refractory disease is suggestive rather than definitive. Some consensus statements have suggested that those patients who have an unresectable primary DTC tumour should also be included in this classification [36]. In these cases, when the definition is unclear, features including Tg doubling time [37] and radiological progression can be indicators of whether patients should be considered for disease modulating therapy.

Local treatment targeting radioiodine-refractory disease

Local therapies are employed when the disease recurrence is localised, causing symptoms and/or posing risk to critical structures, and include surgery, external beam radiotherapy (EBRT), radiofrequency ablation, cryoablation and chemo-embolisation. The chief concerns in DTC are airway obstruction and spinal cord compression. Targeted local therapy to organs affected by metastatic disease can improve patient prognosis and quality of life. Lymph node metastases should, where possible be treated primarily with surgery. However, recent data has shown that recurrence may be indolent in some patients. In this cohort, cautious monitoring and a conservative approach is safe and recommended [38]. Criteria for identification of appropriate patients to be observed are not clear, but usually nodal metastases greater than 8mm in the central compartment or 10mm in the lateral neck are surgically removed [8]. Percutaneous radiofrequency ablation and ultrasound guided ethanol injection of local metastases are also safe and effective alternatives [39]. Despite no survival benefit, the precarious complication of local invasion into the aerodigestive region has led to the use of these palliative therapies to reduce morbidity. The American Head and Neck Society have provided an expert opinion statement specifying that older patients (>45 years) with unresectable locoregional disease would likely benefit from EBRT and that patients less than 45 years, as their disease is likely to be RAI avid, should therefore should be treated with radioiodine first line [40]. EBRT should also be considered for bone metastasis particularly in the context of pain, increased fracture risk and potential spinal cord compression [41]. Periodic bisphosphonate therapy, usually intravenous zoledronic acid infusion, may reduce pathological fracture risk [42], although high quality evidence is lacking.

Systemic therapies for radioiodine-refractory disease

Traditional systemic chemotherapies have poor response rates in DTC. The ratio of toxicity to benefit is low in these patients. Doxorubicin is the only systemic chemotherapy approved by the US Food and Drug Administration (FDA) for metastatic DTC and provides little, if any benefit [43]. More encouragingly however, several orally available multi-tyrosine kinase inhibitors (TKI) have been studied in phase I and II trials (Table 1), and two (lenvatinib and sorafenib) have now been studied in completed randomised Phase III trials. Lenvatinib which inhibits VEGFR1–3, fibroblast growth factor receptors 1–4, RET, c-KIT, and PDGFRβ (Figure 3) [44]; and sorafenib which inhibits RAF, VEGF receptors (VEGFR)1–3, PDGF receptor (PDGFR), and RET[45], has been registered with the Therapeutic Goods Administration (TGA) but is not PBS-subsidised for treatment of RAIRD. Notably, neither of

these studies has yet conclusively demonstrated a significant overall survival (OS) benefit of TKI treatment, likely due to a large proportion of the patients in the placebo arm who crossed over to receive active treatment after disease progression. Statistical adjustment of OS Kaplan-Meier curves by rank preserving structural failure time analysis suggests some improvement in OS with both sorafenib [46] and lenvatinib therapy [47].

Lenvatinib

A major phase III study compared lenvatinib (initiated at 24 mg daily) with placebo in patients with RAI- refractory thyroid cancer (the SELECT study). This study included patients with and without prior TKI exposure, and patients in the placebo group were allowed to receive open-label lenvatinib after protocol-defined progression. Progression-free survival (PFS) was 18.3 months in the treatment group compared with 3.6 months in those receiving placebo [11]. In this study of 392 patients, an unprecedented response rate of 64.8% was observed with lenvatinib compared to only 1.5% in the placebo group (odds ratio, 28.87; 95% CI, 12.46 to 66.86). The median time to response in patients treated with lenvatinib was two months, correlating with the first restaging imaging time point, suggesting that most responses occurred early during treatment. A separate analysis demonstrated that after an initial rapid decline in growth velocity (and serum thyroglobulin levels) induced by lenvatinib, tumour shrinkage continues at a reduced pace [48]. Tumour size reduction was correlated with area under the curve for lenvatinib exposure and treatment duration. Those who had a greater initial reduction in size had a better PFS. The speed of the decline in tumour bulk could potentially make surgical intervention for compression or distortion of neck structures less urgent. This alternative could be considered in precarious aerodigestive infiltration where surgical resection would be high risk. The median PFS and response rate for patients who entered the open-label phase of the study, i.e. those who received delayed lenvatinib treatment, was 10.1 months and 52.3%, suggesting that patients will still derive benefit from delayed treatment with this agent albeit to a smaller extent compared to those who started treatment earlier. The anti-tumour effect of lenvatinib is due to predominantly anti-angiogenic effects but secondary effects of inhibiting kinases including RET and FGFR may have added benefits [49].

Sorafenib

The DECISION trial was a phase III trial that used sorafenib in 417 patients with radioiodine refractory disease. Results showed a 41% improvement in progression free survival (10.8 vs 5.8 months) [50].

Selumetinib

A novel approach to treat RAIRD disease is to facilitate I-131 therapy by increasing sodium-iodide symporter expression on thyroid cancer cells. The MEK inhibitor, selumetanib, showed clinically meaningful increases in radioiodine uptake in patients with refractory thyroid cancer in a small pilot study [28]. This interesting approach may become a novel mechanism to enhance MEK inhibitor usage.

Dabrafenib

A phase II study of 14 patients with $BRAF^{V600E}$ mutant thyroid carcinoma treated with the BRAF inhibitor dabrafenib showed a durable response with median progression free survival of 11.3 months [51]. Dabrafenib has also shown an increase in RAI uptake following administration to DTC patients via a similar mechanism to selumetinib. 60% of patients with $BRAF^{V600E}$ mutant radioiodine refractory DTC showed increased radioiodine uptake following a 42 days course of dabrafenib [52]. This study shows that a short treatment course may be effective. There are however limits on the amount of radioiodine patients can receive, even if avidity can be restored. Haematological cell line toxicities are often dose limiting.

Other systemic therapies

Lenvatinib and sorafenib, following their pivotal phase III trials, are the only two TKIs approved for the treatment of radioiodine refractory thyroid cancer by the FDA, EMA and the TGA. Several other kinases have been tested in clinical trials. In a phase II trial, 145 patients with DTC unresponsive to RAI were treated with vandetanib or placebo. After 19 months follow up there was less disease progression in the treatment group with an improvement on median progression free survival [53]. Pazopanib was studied in a phase II trial in RAI refractory DTC and showed a response rate of 49% [54]. Sunitinib shares a similar TKI inhibitory profile to lenvatinib and has also shown promise in improving the median time to progression in these cohorts [55]. Other trials and results are summarised in Table 1 below.

Adverse effects of kinase therapies

The therapeutic ceiling for TKI therapies is reached quickly due to toxicities. Drug-related toxicities and dose adjustments (dose interruption or reduction) were frequent in both the DECISION and SELECT trials. Most of the side effects are common to other TKIs, such as diarrhoea, fatigue, anorexia, hand-foot skin reaction and hypertension. The majority of the adverse events are mild to moderate, with severe or life-threatening toxicities occurring in <10% of cases, except for severe hand-foot skin reaction (20.3% of sorafenib-treated patients) and severe hypertension (41.8% of lenvatinib-treated patients). These symptoms often improve with a brief treatment break and dose reduction. However, discontinuation of treatment occurred in 14.2% of lenvatinib treated patients. Deaths resulting from drug-related toxicities were rare (0.5% for sorafenib and 2.3% for lenvatinib). Nonetheless, approximately 65% of patients required at least one dose reduction in both trials, highlighting the poor tolerability of these TKIs at the approved starting dose. In light of this, a post-approval FDA-mandated open-label, randomized trial with lenvatinib at starting doses of 24mg or 18mg is currently underway to evaluate the tolerability and efficacy of lower doses of drug (NCT02702388).

The optimal management of side effects arising from TKI treatment is essential to prevent premature or avoidable dose reduction or drug cessation. Critical to this are patient education and frequent clinical reviews, especially during the first 2 months of treatment when fortnightly clinical reviews should be considered to detect and manage early side effects. Patients should be encouraged to report any side effects as early as possible so that appropriate supportive care management can be instituted. Whenever possible, side effects should be managed with supportive management or dose interruption, before consideration is given to dose reduction.

On-target adverse effects of TKIs have also been used as surrogates to predict efficacy of treatment in other cancers. On-treatment neutropenia and hypertension are independent biomarkers of sunitinib efficacy in renal cell carcinoma [56]. It is unknown if this same characteristic is seen with lenvatinib and whether adverse events could assist with prognostication.

Financial toxicity is a non-negligible consideration in particular for the use of non Australian PBS subsidised therapies such as sorafenib for DTC or vandetanib for medullary thyroid cancer.

Can TKIs be used serially?

In the SELECT study, all pre-specified sub-groups (defined according to age, sex, race or ethnic group, prior treatment or no prior treatment with a tyrosine kinase inhibitor, geographic region, histologic subtypes, BRAF or RAS mutation status, and baseline thyrotropin levels) derived benefit from lenvatinib treatment. Therefore prior use of TKI is not a contraindication to commencement of lenvatinib.

To watch or to treat?

Inclusion in the major TKI clinical trials required patients to have RECIST (Response Evaluation Criteria in Solid Tumours) radiologically measurable RAIR disease progression within the last 12 to 14 months. Although these criteria are helpful to guide patient selection for systemic TKI treatment in routine practice, they are likely not sufficient to determine if an individual patient is a good candidate for treatment. The biggest clinical challenge in these patients is risk stratification. Evidence in determining who should receive systematic TKI therapy, who should be referred for local excision/EBRT and who should be closely monitored with watchful waiting is still evolving (see Table 2). In Australia, lenvatinib is now available on the PBS for treatment of radioiodine refractory disease. In the UK, lenvatinib is not yet available commercially but access is through a compassionate program on a case by case basis. Targeted therapies for RAIRD such as sorafenib is available from the Cancer Drug Fund.

No biomarkers have been validated to successfully determine who will respond best to lenvatinib or sorafenib. There was no predictive outcome when stratifying by *BRAF* or *RAS* mutation status in the phase III trials [11,50]. There are some data looking at predictive response to TKIs based on changes in levels of soluble VEGFR-2 or angiopoietin-2 [57,58]. Lower baseline levels of VEGF have been associated with longer PFS but this is yet to be shown with the currently available TKIs.

When to stop?

Oncology doctrine is that therapy should cease when progression has occurred whilst on active treatment. However, a surge in tumour growth can occur once inhibitors of these proliferating pathways are ceased [59]. Best practice is not clear and we recommend an individualised approach, with wariness of abrupt cessation if there is radiological disease progression, especially in the setting of minimal toxicity.

The Australian PBS approval for continuation of levantinib is contingent on non-progression on the drug. Patients must have stable or responding disease according to the RECIST criteria. We recommend re-scanning at 3-monthly intervals.

Future directions

Other opportunities for re-differentiation of follicular cells and re-induction of RAI are being explored on a molecular level. Vitamin A, thiazolidinediones, lithium and phosphorylation of pituitary tumour-transforming gene-binding factor[60] have been trialled with mixed results (reviewed in [61]). Other approaches might include histone deacetylase inhibitors[62] or modulation of microRNAs[63].

There are no studies with adjuvant TKI use in DTC, and very few with neoadjuvant chemotherapy [64]. As we begin to understand more about rapid tumour inhibition, this may become an option in selected populations when emerging data become available.

Conclusions

Metastatic DTC should be carefully assessed for tumour burden and rate of progression. RAI will usually be the first-line therapy for these patients, and/or targeted local therapies. Once DTC becomes refractory to RAI, options are limited. Multi-targeted TKIs are systemic therapies that show an increase in progression free survival in patients with RAIRD. TKI therapy should thus be integrated into multimodal individualised patient care. The classification of refractory disease is nuanced and will often require input from a tertiary referral centre for marginal cases. Multidisciplinary management for these complex cases should be standard practice for endocrinologists and oncologists to ensure favourable patient

outcomes. Promising early phase studies suggest a future role for agents targeting the MAPK pathway to re-differentate thyroid cancers by re-establishing RAI avidity.

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Table 1: Examples of RAI-refractory TKI trials

Drug	Phase	Number patients	PFS (months)	Response Rate*	Evidence of RAI reinduction
Lenvatinib [11]	III	392	18	64.8%	
Sorafenib [50]	III	417	11	12%	NO
Vandetanib [53]	II	145	11	<5%	
Sunitinib [55]	II	28	13	31%	
Axitinib [65]	II	45	18	30%	
Carbozantinib [66]	I	15	-	53%	
Pazopanib [54]	II	37	12	49%	
Motesanib [67]	II	93	9	14%	
Dabrafenib [51]	II	14	11	29%	YES [52]
Selumetinib [28]	II	32	-	60%	YES

Vemurafenib [68]	I	3	-	33%

*****Response rate is overall response rate (ORR) if published or if not, then partial response rate

Table 2: Guidelines on referral

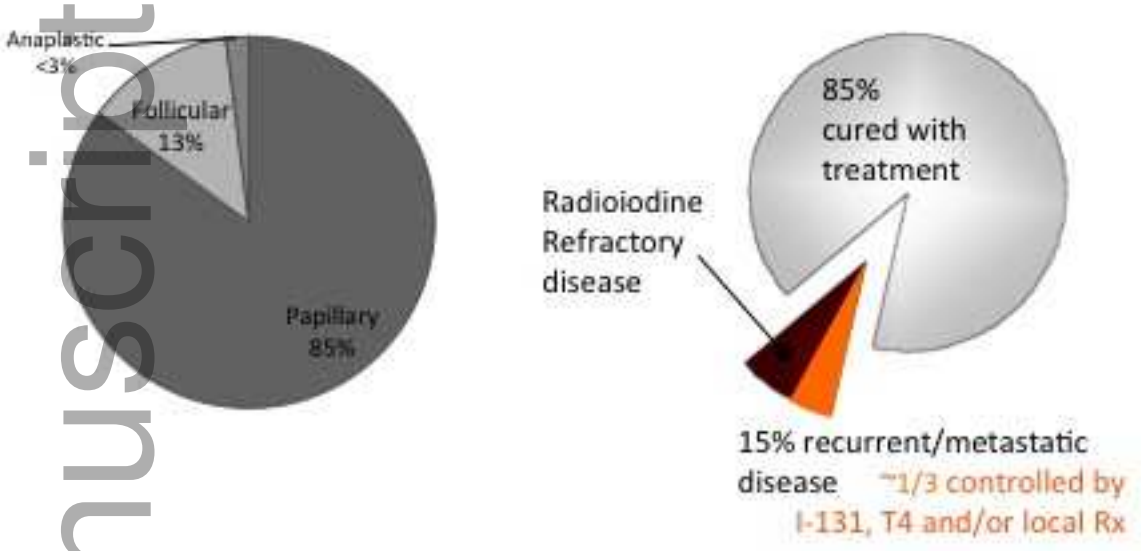
Refer for TKI	**Active Surveillance**	**Relative Contraindication**
Patients with rapidly progressive disease shown by radiological and biochemical markers: (1) 10 - 20mm increase in metastasis size in 3 months and/or (2) High doubling time of thyroglobulin Presence of large tumour bulk, metastases that are symptomatic or obstructive, eg, causing vertebral pain, haemoptysis, recurrent pleural effusions	Patients with minimally progressive disease and are asymptomatic Patients with locoregional disease that could be satisfactorily controlled with evidence-based local therapies without the side effects of systemic therapies	Large volume, uncontrollable brain metastasis or organs/locations where risk of haemorrhage would be unacceptable or life threatening, such as carotid artery extension

Patients who are not candidates for palliation with surgery or locoregional therapies

Figure 1 Differentiated thyroid cancer subtypes and prognosis[69]

Figure 2 Protumourogenic actions of VEGF. VEGF mediates actions between the tumour cell and host endothelial cell promoting angiogenesis and facilitating tumour proliferation.

Figure 3 Signalling pathway demonstrating inhibition of RET, VEGF and FGFR by the TKI lenvatinib (adapted from [70])



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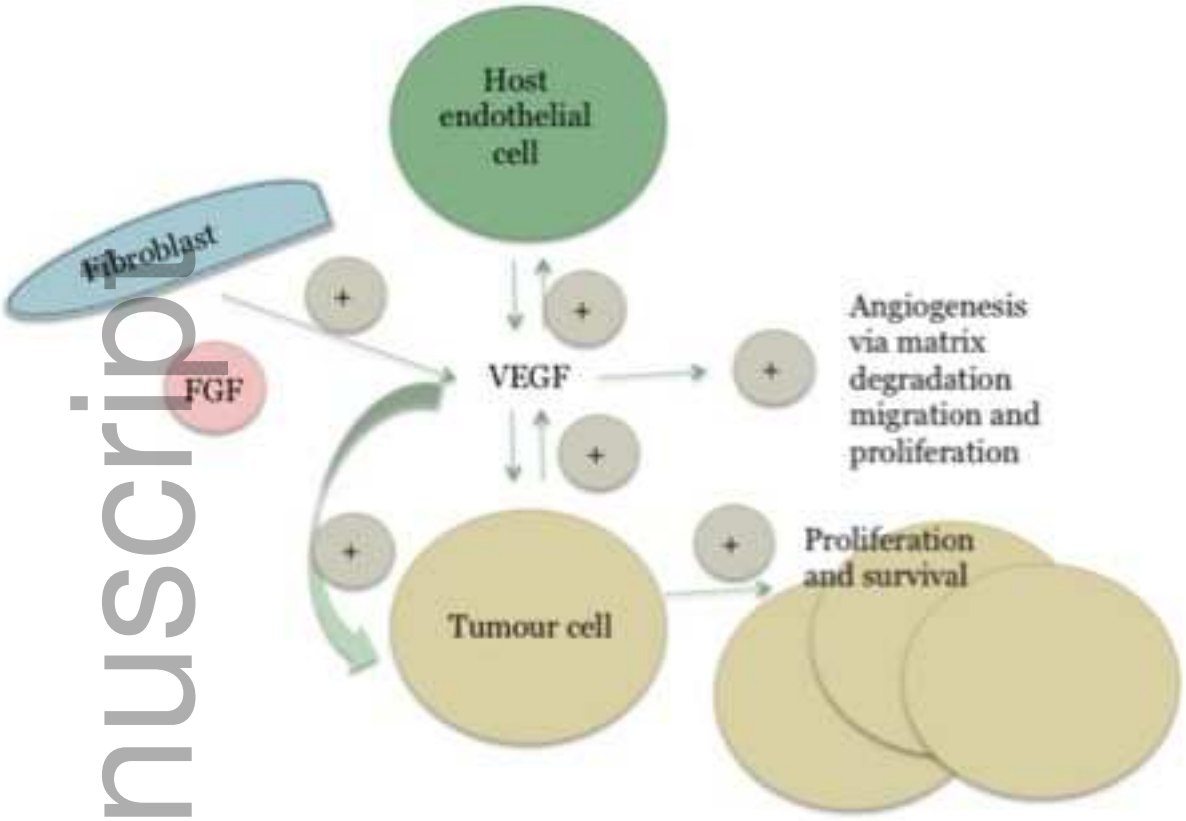

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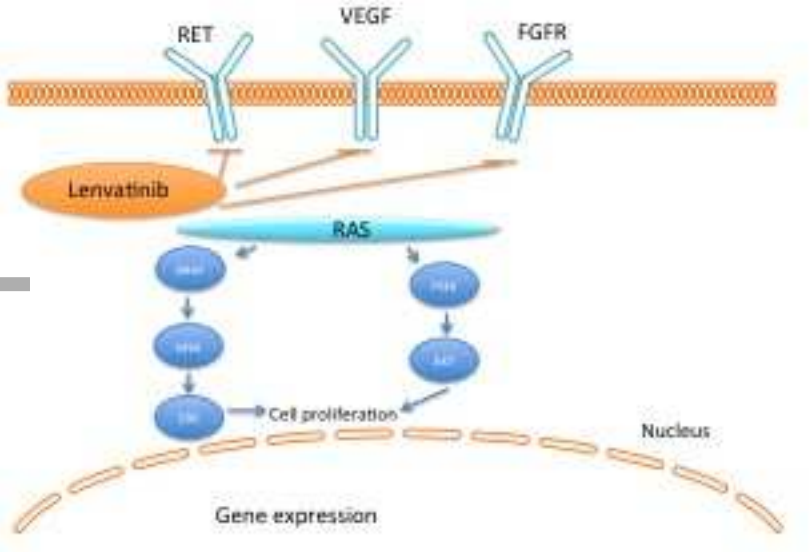

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