Overview of Hurthle cell carcinoma of thyroid

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Abstract: The clinical behaviour of Hurthle cell carcinoma (HCC) of the thyroid is variable and there are many controversies in the literature. Here, we summarize an up-to-date review of the literature on genetics, diagnosis (ultrasound scan, fine needle aspiration, frozen section, etc.), and management. At presentation, treatment decision should be made by a multidisciplinary board. Recurrent HCCs are seldom curable despite salvage treatments, which include radioactive iodine ablation, radiofrequency ablation, ethanol ablation, external radiotherapy, and systemic therapy. Further research is needed to develop more efficacious systemic treatments. Currently, lenvatinib, sunitinib, and sorafenib are available. The completed and ongoing clinical trials for HCC are summarized.

Keywords: Hurthle cell; neoplasm; carcinoma; radiotherapy; radioactive iodine; targeted therapy


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Introduction

Hurthle cell carcinoma (HCC) is a relatively rare thyroid cancer, of which many physicians or researchers have little experience or knowledge. This review is based on PubMed and clinical trial searches. It highlights updates in HCC research in the last few years. It also concisely summarizes the overall practical management.

Updates on diagnosis and investigations

Hurthle cell neoplasms (HCNs) of the thyroid include benign adenomas or carcinomas. HCC is a variant of follicular carcinoma (FC), according to the World Health Organization⁴. HCC only represents about 5% of all differentiated thyroid carcinomas. The incidence of malignancy in HCN is variable, ranging from 13% to 67%. Pre-operative diagnosis of the benign adenoma versus carcinoma is difficult. HCC can present as minimally invasive or more invasive tumor. Minimally invasive tumors are less aggressive. Generally, HCC patients are older, and more likely to have lymphovascular invasion and nodal metastases than FC patients⁵. Distant metastases are significantly more common in patients with older age, widely invasive cancer and extra-thyroidal invasion⁶.⁷. The histological diagnosis of FC has changed in the last few decades⁸. Figure 1 illustrates a case of HCC from our institute, reviewed by our pathologist Dr. Angus Kirby in 2016 before the submission of this manuscript. Figures 2 to 6 show microscopic slides of differential diagnoses, all taken with the same magnification of 600X, of papillary carcinoma, follicular variant of papillary carcinoma, follicular neoplasm, and medullary carcinoma, with anaplastic carcinoma for comparison.

It is important for clinicians and pathologists to correlate the entire information from clinical history, laboratory (calcium, thyroglobulin (Tg), etc.), microscopy, immunostaining, imaging (ultrasound and radioactive iodine scans), and fine needle aspiration (FNA) biopsy. More research studies to improve diagnostic accuracy are needed. In the 2014 American Society for Clinical...
Pathology (ASCP) Non-Gynecologic Assessment program of thyroid HCN aspirates, respondents achieved 83% correct interpretation, 6.75% incorrect interpretation as a benign thyroid nodule, and 9.75% incorrect interpretation of malignancy[6].

In 2016, Renshaw et al. reported on all FNA specimens of 24 FCs and 35 HCCs[7]. Microfollicular component was found in all FCs, but only 75% (18/24 cases) showed cytologic atypia, which most commonly consisted of enlarged nuclei with slightly pale chromatin. Diagnosing cases without cytologic atypia as benign would significantly decrease the sensitivity for FC ($P = 0.02$). The group of 35 HCCs consisted of only scant Hurthle cells (5 cases), large cell dysplasia (15 cases), small cell dysplasia (10 cases), anisonucleosis insufficient for a diagnosis of large cell dysplasia (4 cases), and Hurthle cells in flat sheets without atypia (1 case). In conclusion, a cellular pattern without atypia is a good criterion for benign HCN in contrast to FC.

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is a very useful guide[8]. It describes several subcategories within atypia of undetermined significance (AUS), including: (a) presence of focal nuclear

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Figure 1. Typical appearance of a Hurthle cell carcinoma showing large, round nuclei with prominent nucleoli and the abundant, granular eosinophilic cytoplasm. The eosinophilic cytoplasm is due to abundant mitochondria after staining with hematoxylin and eosin stains.

Figure 2. Papillary carcinoma with papillae, and specific nuclear features (crowded overlapping, longitudinal grooves)

Figure 3. Encapsulated follicular variant of papillary carcinoma showing follicles, but typical nuclear features of papillary carcinoma. The new terminology is non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

Figure 4. Follicular neoplasm. Cuboidal cells line follicles with colloid in inferior part of the slide. There are more solid areas. Nuclear features of papillary carcinoma are absent.
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Figure 5. Medullary carcinoma with pleomorphic cells and trabecular growth pattern. The cytoplasm does not have the granular, eosinophilic quality of Hurthle cells.

Figure 6. Anaplastic carcinoma with spindle, squamoid cells, and a giant cell (marked by an arrow in the lower part of the figure).

atypia (AUS-N), (b) focal microfollicular proliferation (AUS-F), (c) focal Hurthle cell proliferation (AUS-HC), and (d) others (AUS-O)[3].

In the literature, modern series are more important than the older ones, as the diagnosis and treatment of thyroid cancer have changed over the years[9,10]. Older series may consist of lesions that look similar to HCC but are actually other types of thyroid cancers. The Johns Hopkins Hospital performed a literature meta-analysis of indeterminate ‘Suspicious for a follicular or Hurthle cell neoplasm’ (SFN/HCN) category before and after the introduction of the Bethesda System for Reporting Thyroid Cytopathology[11]. The fraction of cases called SFN/HCN or the equivalent increased from 6.1% to 7.4% (P = 0.0002), and the histological malignancy rate among cases that were resected increased from 22% to 28% (P = 0.03)[12].

Liquid-based preparation of thyroid FNA samples appears to be more helpful as compared to the conventional smear[13]. At the John Hopkins University, specimens diagnosed as containing Hurthle cells have a 19% (9/47 patients) chance of being malignant if they are classified as atypia of undetermined significance with Hurthle cells[14,15]. At Indiana University, the corresponding figure of malignancy is 24%[16]. FNA cytology can be enhanced by a rapid on-site evaluation, correlating with clinical and ultrasound data to classify subtypes of differentiated thyroid cancer, according to the Bethesda system[17,18]. Screening by cytotechnologists is another way to improve the efficiency of cytopathologists and to avoid oversights.

The American Thyroid Association (ATA) recommends pathologists to be acquainted with the local prevalence of malignancy within each indeterminate cytologic category[19,20]. Despite all the above strategies, it is still very difficult to differentiate adenomas from carcinomas.

It should be noted that HCC can occur in conjunction with other pathology entities, e.g. follicular adenoma or parathyroid carcinoma[21]. A follicular HCC harbouring the BRAF v600e mutation was reported to occur in collision with multifocal papillary carcinoma[22]. To complicate matters further, FNA cytology of parathyroid carcinoma can mimic HCC[23].

A positron emission tomography (PET) scan is not useful to predict malignancy, as all Hurthle cell adenomas and carcinomas are 18fludeoxyglucose (18FDG)-PET-positive[24]. Researchers at the University of Vienna reported that the average maximum standardized uptake values (SUV) of HCN was 5.8 (range: 2.6–16)[25]. To increase the sensitivity of PET, thyroxine withdrawal or recombinant thyroid-stimulating hormone can be used especially in the setting of suspected non-radioiodine avid recurrence with elevated Tg[26]. Newer PET radiotracers are needed, such as 124Iodine, 18F-DOPA (3,4-dihydroxy-L-phenylalanine), and 68Gallium-DOTA[27].

While HCC may not always have a high Tg value, a level >80 ng/mL in HCN predicts malignancy[28]. The median pre-operative Tg concentration in benign tumors, papillary carcinomas, FC, and HCC was 41, 87, 72, and 106 ng/mL (P = 0.05), respectively. The predictive factors for malignancy are sex, thyroid volume, and pre-operative Tg concentration, of which male sex and Tg level are
independent predictors by multivariate logistic regression. Higher body mass index ≥30 kg/m² and waist circumference ≥ 88 cm are associated with a higher risk of malignancy. The exact mechanism for RAS gene mutation to cause HCC progression is unknown. The V-raf murine sarcoma viral oncogene homolog B1 gene (BRAF) produces RAF proteins (ARAF, BRAF, and CRAF), which are essential serine/threonine protein kinases. BRAF can be targeted by vemurafenib, which is the subject of a phase II study. The mutation of the phosphatidylinositol-3-kinase catalytic alpha polypeptide (PIK3CA) gene (the product which binds specifically with RAS and activates the phosphoinositide-3-kinase/Akt (PI3K/Akt) signaling pathway) also has an important role in thyroid tumorigenesis. The AKT1 gene provides instructions for making a protein called AKT1 kinase. This protein is found in various cell types throughout the body, where it plays a critical role in many signaling pathways. For example, AKT1 kinase helps regulate cell growth and division (proliferation), the process by which cells mature to carry out specific functions (differentiation) and cell survival. AKT1 kinase also helps control apoptosis, which is the self-destruction of cells when they become damaged or are no longer needed. At the cellular level, common functional polymorphisms in antioxidant gene GPX1 have been found to be associated with occurrence of recurrent disease. A micro-ribonucleic acid (miRNA) is a small non-coding RNA molecule (containing about 22 nucleotides) found in plants, animals, and some viruses, which functions in RNA-silencing and post-transcriptional regulation of gene expression. The expression of miRNA (miR-183, miR-221, and miR-885-5p) in tumor tissue is correlated with the risk of distant metastases in patients with HCC.

**Updates on treatment and outcome**

The National Comprehensive Cancer Network (NCCN) guideline in 2017 recommends thyroid lesions with high clinical and/or radiographic suspicion of malignancy, especially with size >1 cm, to have lobectomy or total thyroidectomy for definitive diagnosis and treatment. After lobectomy, minimally invasive cancer may be observed and those with invasive cancer should undergo complete thyroidectomy. For patients with unresectable gross residual disease in the neck, thyroid-stimulating

**Updates on genetic and molecular diagnostics**

Molecular pathways that differentiate Hurthle cell adenomas from widely invasive HCCs include the PIK3CA-Akt-mTOR and Wnt/β-catenin pathways, which may provide new targets for HCC in the future. Testing for genetic alteration in HCN shows aneuploidy, H-ras mutations, allelic alterations, mitochondrial genetics, and polymerase chain reaction-based microsatellite polymorphism analysis. The latter has been shown to differentiate invasive HCC from other thyroid cancers; however, larger studies are needed to validate these findings before the tests are incorporated into routine practice. A catalogue of somatic mutations in cancer database for HCC is summarized in Table 1. Mutation or translocation of the ras oncogene is common in both follicular adenomas and follicular thyroid carcinomas (around 40%). Such ras oncogene mutations are not specific for follicular tumors and as it also occurs in papillary thyroid cancer (PTC). The ras oncogene is frequently involved in the pathogenesis of Hurthle cell tumors.

ThyroSeq v2 complete next-generation sequencing assay on thyroid cytology specimens was performed by researchers from the University of Pittsburgh. Point mutations involve the neuroblastoma rat sarcoma viral oncogene homolog (NRAS), followed by the Kirsten rat sarcoma viral oncogene homolog (KRAS), the telomerase reverse transcriptase (TERT) gene, and the thyroid-stimulating hormone receptor (TSHR) gene. The identified fusions involve the thyroid adenoma-associated (THADA) gene, the peroxisome proliferator-activated receptor γ (PPARG) gene, and the neurotrophic tyrosine kinase receptor, type 3 (NTRK3) gene.

Kasaian et al. found multiple endocrine neoplasia (MEN-1) gene mutations in 4% of HCC. Another genetic mutation, human TERT (hTERT), is detected by immunohistochemistry, and the telomere length can be determined by tissue quantitative fluorescence in-situ hybridization. The hTERT protein expression is observed in 86% of FCs and 49% of follicular adenoma. All HCNs express hTERT protein, but HCCs have significantly very shortened telomeres than Hurthle cell adenomas. The common TERT C228T promoter mutation is detected in both widely invasive and minimally invasive tumors. This promoter mutation is very common in advanced cancers, especially those with BRAF or RAS mutation.

The mutation of the phosphatidylinositol-3-kinase catalytic alpha polypeptide (PIK3CA) gene (the product which binds specifically with RAS and activates the phosphoinositide-3-kinase/Akt (PI3K/Akt) signaling pathway) also has an important role in thyroid tumorigenesis. The AKT1 gene provides instructions for making a protein called AKT1 kinase. This protein is found in various cell types throughout the body, where it plays a critical role in many signaling pathways. For example, AKT1 kinase helps regulate cell growth and division (proliferation), the process by which cells mature to carry out specific functions (differentiation) and cell survival. AKT1 kinase also helps control apoptosis, which is the self-destruction of cells when they become damaged or are no longer needed. At the cellular level, common functional polymorphisms in antioxidant gene GPX1 have been found to be associated with occurrence of recurrent disease. A micro-ribonucleic acid (miRNA) is a small non-coding RNA molecule (containing about 22 nucleotides) found in plants, animals, and some viruses, which functions in RNA-silencing and post-transcriptional regulation of gene expression. The expression of miRNA (miR-183, miR-221, and miR-885-5p) in tumor tissue is correlated with the risk of distant metastases in patients with HCC.
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Table 1. Genetic mutations in Hurthle cell carcinoma

<table>
<thead>
<tr>
<th>Gene</th>
<th>Possible mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN1[^39]</td>
<td>Loss of function to produce the tumor suppressor protein, called menin which is required for apoptosis</td>
</tr>
<tr>
<td>TERT, telomerase reverse transcriptase[^29]</td>
<td>TERT encodes the reverse transcriptase component of telomerase, which is required for cell immortalization</td>
</tr>
<tr>
<td>HRAS, Harvey rat sarcoma viral oncogene homolog (RAS)[^33]</td>
<td>Encodes transforming protein 21. Point mutations affect production of proteins that convey signals originating from tyrosine kinase membrane receptors to a cascade of mitogen-activated protein kinases (MAPK). This activates the transcription of target genes involved in cell proliferation, survival, and apoptosis.</td>
</tr>
<tr>
<td>PIK3CA, phosphatidylinositol-3-kinase catalytic alpha polypeptide[^37]</td>
<td>The product binds specifically with RAS and activates the phosphoinositide-3-kinase/Akt (PI3K/Akt) signaling pathway</td>
</tr>
<tr>
<td>NRAS, neuroblastoma RAS[^32]</td>
<td>Encodes the protein N-Ras that is involved primarily in regulating cell division</td>
</tr>
<tr>
<td>BRAF, murine sarcoma viral oncogene homolog B1</td>
<td>A potent activator of the MAPK pathway</td>
</tr>
<tr>
<td>KRAS, Kirsten RAS[^32]</td>
<td>Encodes the protein K-Ras that is involved primarily in regulating cell division</td>
</tr>
<tr>
<td>AKT1[^34]</td>
<td>Encodes a protein called AKT1 kinase, which is found in various cell types throughout the body, where it plays a critical role in many signaling pathways.</td>
</tr>
<tr>
<td>IDH1, isocitrate dehydrogenase 1[^38,39]</td>
<td>Produces 2-hydroxyglutarate (2HG), which induces histone- and DNA-hypermethylation through inhibition of epigenetic regulators</td>
</tr>
<tr>
<td>SMAD4[^37]</td>
<td>Gene promoter’s mutation. SMAD4 is a tumor suppressor.</td>
</tr>
<tr>
<td>TSHR, thyroid-stimulating hormone receptor[^40]</td>
<td>Promotes growth and progression of thyroid cancer once initiated by oncogenic alterations</td>
</tr>
<tr>
<td>SETD2[^39]</td>
<td>Required for DNA double-strand break repair and activation of the p53-mediated checkpoint</td>
</tr>
<tr>
<td>ARID1B[^37]</td>
<td>Encodes the largest subunit of the SWI/SNF chromatin re-modeling complex which has tumor suppressor activity</td>
</tr>
<tr>
<td>DAXX[^41]</td>
<td>Telomere maintenance</td>
</tr>
<tr>
<td>EWSR1 Ewing sarcoma[^42]</td>
<td>A member of the TET family of genes (detailed mechanism unknown)</td>
</tr>
<tr>
<td>DDX6[^31]</td>
<td>Increases messenger ribonucleic acid production</td>
</tr>
<tr>
<td>SEPT6, Septin 6[^46]</td>
<td>Membrane-interacting proteins with a highly conserved domain structure involved in various cellular processes, including cytoskeleton organization, cytokinesis, and membrane dynamics</td>
</tr>
<tr>
<td>CACNA1D[^47]</td>
<td>Proteins involved in calcium signaling</td>
</tr>
</tbody>
</table>

hormone and Tg, anti-thyroglobulin should be obtained at 6 to 12 weeks postoperatively. Postoperative radioactive iodine (RAI) imaging is recommended. If there is gross residual disease with inadequate RAI uptake, external radiotherapy with intensity-modulated radiotherapy can be arranged. Clinicians have to watch for complication such as venous thrombosis[^60]. Continuous surveillance and thyroid hormone suppression are necessary.

The National Cancer Database 1998–2006 was searched by Jillard et al., for patients with HCC who underwent total thyroidectomy[^61]. There were 1,099 T1 tumors with N1/M1 disease, or T2-4 tumors with any N/M disease. Of these, 1,162 (60.9%) received RAI ablation, and 747 (39.1%) did not. Patients treated with RAI ablation tended to be younger, with private insurance, and treated at an academic center. Five- and ten-year survival rates with and without RAI ablation were 88.9% vs. 83.1% and 74.4% vs. 65.0%, respectively (P < 0.001). Present guidelines are inconsistent with regard to indications for using RAI for HCC. This could explain why nearly 40% of HCC patients did not receive RAI ablation. RAI administration was associated with a 30% reduction in mortality (hazard ratio = 0.703, P = 0.001), and is advocated for tumors >2 cm or nodal/distant metastatic disease. The latter view is also shared by Ahmadi et al.[^62]

The NCCN guideline recommends RAI ablation for gross extra-thyroidal extension/primary tumor size >4 cm/ extensive vascular invasion/post-operative unstimulated Tg >5–10 ng/L[^59]. RAI ablation can be selectively recommended for primary tumor 2–4 cm/minor vascular invasion/cervical lymph node metastases/post-operative unstimulated Tg <5–10 ng/mL. RAI ablation is not indicated
for intrathyroidal tumor <2 cm without vascular invasion, or for node involvement/detectable anti-Tg antibodies/postoperative unstimulated Tg <1 ng/mL. An on-going study is looking at the question of the necessity of RAI ablation for low-risk thyroid cancer including HCC\(^{63}\).

Prognostic factors for survival include age, sex, mitotic rate, and depth of invasion. While multifocal disease, size of primary, nodal involvement, metastases, stage, microscopic residual disease, extra-glandular invasion, and degree of invasion are factors for both survival and recurrence. On follow-up, the loco-regional recurrence rates range from 3% to 50% and distant recurrence rates are 17%–27% in literature\(^{3,5,61,62}\).

It should be noted that HCC recurrence may occur without detectable serum Tg. Researchers from the University of Florida reported a patient with neck carcinoma recurrence who was successfully treated with further surgery, radiiodine ablation, external beam radiotherapy, and alive nine years later\(^{64}\). The most common site of distant metastases is lung, followed by bone\(^{65}\). On average patients with metastatic HCC have a 10-year cause-specific survival rate of 60% and live a median of 77 months after developing metastases\(^{66}\).

Salvage treatments for recurrent HCC include RAI or radiofrequency ablation, ethanol ablation, external beam radiotherapy, and systemic treatment. Currently, targeted therapy with lenvatinib, sunitinib, and sorafenib are available as systemic management for refractory metastatic disease in the NCCN guideline\(^{69}\). Studies on the addition of everolimus or temsirolimus to sorafenib are on-going (Table 2)\(^{61,62,67–71}\). Romidepsin was found to have poor response\(^{72,73}\). AMG 706 and bortezomib studies had been completed but results are not available\(^{74,75}\). The most common adverse events of immunotherapy include decreases in blood cell counts (especially leukocytes), diarrhea, fatigue, hand-foot skin reaction, nausea, musculoskeletal pain, and hypertension. They are grade 1–2 and manageable.

In the Surveillance, Epidemiology, and End Results (SEER)-9 database (1975–2009), 10-year survival rates of HCC improve dramatically over time: 75% in 1975–1979, 81% in 1995–1999, and 91% in 2000–2004\(^{66}\).

The improvement in survival occurred in both genders, age ≥45 years, local and regional disease, tumors >4 cm, and Caucasian race. It is not certain if this is related to improved diagnosis or treatment such as PET scan, more extensive surgery, and increased use of external beam radiotherapy and RAI ablation. The SEER database and also a Japanese study both found that the outcome of HCC approaches that of FC, which has a stable survival over the recent decades\(^{76}\).

### Other Research

Table 2 summarizes important clinical trials on HCC. A natural history protocol studies methods for follow-up using radiopharmaceutical tracers such as \(^{131}\)I, \(^{123}\)I, \(^{99m}\)Tc-sestamibi, \(^{111}\)In-pentetreotide, and 18-FDG PET\(^{77}\). The limitations and significance of serum Tg measurement for diagnosing tumor recurrence will be assessed. The same study evaluates the administration of lithium (a well-established, yet not widely used, adjuvant to \(^{131}\)I treatment), especially in selected cases of thyroid cancer in which high-dose (>150 mCi) \(^{131}\)I therapy is clinically indicated\(^{77}\). Tissue specimens are collected to assess new immunohistochemical markers, and other techniques are implemented to characterize tumors for correlation with response to therapy and prognosis. Blood and urine specimens will be collected for future clinical and research studies in both the hypothyroid and euthyroid state.

### Conclusion

Retrospective single or multi-centre studies, population studies, and prospective trials form the basis of modern management of this rare cancer. Knowledge of new pathologic entities and ways to differentiate benign versus malignant HCN will help clinicians. More genetic mutations for HCC will be discovered in the future. We have provided a summary table for 20 most common mutations of HCC. Radiiodine diagnostic studies should be considered in some patients following latest recommendations of NCCN and ATA guidelines. RAI ablation has a role in primary post-surgical management, while EBRT, local ablative procedures, and systemic molecular targeted therapy are available for RAI-resistant recurrent/metastatic disease.

### Conflict of interest

The authors declare no potential conflicts of interest with respect to the research authorship, and/or publication of this article.

### Author contributions

MA Korzeniowski and P Tai wrote the manuscript. Both performed literature search. A Mahmud started the project.
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<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>N</th>
<th>Eligibility criteria</th>
<th>Research question</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bikas et al., 2016[67]</td>
<td>Phase II non-randomized</td>
<td>23</td>
<td>Advanced DTC, at least one RAI</td>
<td>Sunitinib 37.5 mg oral daily</td>
<td>26% PR, 56% SD; Median PFS 241 days (interquartile limits: 114–518)</td>
</tr>
<tr>
<td>Brose et al., 2014 DECISION trial[68]</td>
<td>Phase III international multicenter, randomized</td>
<td>317</td>
<td>Locally advanced/metastatic RAI-refractory DTC (including HCC), or poorly differentiated; progression within past 14 months, at least one measurable lesion</td>
<td>Sorafenib 400 mg (2 × 200 mg tablets) twice daily vs. placebo</td>
<td>Median PFS 10.8 vs. 5.8 months AE in 98.6% vs. 87.6%, respectively. Mostly, grades 1 and 2 occurring early in treatments, and are manageable</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering Cancer Center at Suffolk[72]</td>
<td>Phase II, single-group assignment. Closed due to poor response and AE.</td>
<td>20 (11 HCC)</td>
<td>Recurrent/metastatic RAI-refractory, non-medullary thyroid cancer</td>
<td>Romidepsin 13 mg/ m² IV, days 1, 8 and 15, in cycles of 28 days</td>
<td>SD 13(65%), PD 7(35%), AE grade 5, 1 sudden death; grade 4, 1 pulmonary embolus</td>
</tr>
<tr>
<td>Mayo Clinic[73]</td>
<td>Phase II randomized, Recruiting.</td>
<td>–</td>
<td>Unresectable locally advanced or metastatic RAI-refractory HCC, progression within the past 14 months, at least one measurable lesion</td>
<td>Sorafenib +/− everolimus</td>
<td>–</td>
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<tr>
<td>Amgen[74]</td>
<td>Phase II single-group assignment, open label. Completed.</td>
<td>–</td>
<td>Locally advanced/metastatic, progression within past 6 months, measurable lesion</td>
<td>AMG 706</td>
<td>–</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering Cancer Centre[75]</td>
<td>Phase II open label, single-group assignment. On-going but not recruiting.</td>
<td>–</td>
<td>Surgically unresectable/recurrent/metastatic</td>
<td>Temsirolimus and sorafenib</td>
<td>–</td>
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<tr>
<td>Instituto Nacional de Cancerologia, Columbia[76]</td>
<td>Phase II open label, single-group assignment. Recruiting.</td>
<td>–</td>
<td>Surgically unresectable/metastatic</td>
<td>Sorafenib</td>
<td>–</td>
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<tr>
<td>National Cancer Institute, America[79]</td>
<td>Phase II open label, single-group assignment. Completed.</td>
<td>–</td>
<td>Metastatic RAI-refractory DTC</td>
<td>Bortezomib</td>
<td>–</td>
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<tr>
<td>National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)[77]</td>
<td>Observational, retrospective. Recruiting.</td>
<td>–</td>
<td>–</td>
<td>Studies on tumors of thyroid</td>
<td>–</td>
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<tr>
<td>University College, London (IoN)[96]</td>
<td>Phase II/III randomized open label. Recruiting.</td>
<td>–</td>
<td>–</td>
<td>Is ablative RAI necessary for low risk differentiated thyroid cancer patients?</td>
<td>–</td>
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</table>

and also supervised MA Korzeniowski. A Kirby critically reviewed manuscript with substantial input as a pathologist. All authors critically reviewed the manuscript and approved the final manuscript.

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