Biomarkers for the diagnosis of thyroid cancer

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Thyroid tumor contributes 1% of the total tumor but 90% of the endocrine related tumors. Majority of the thyroid cancers are being diagnosed by Fine needle aspiration cytology (FNAC) and histology. Although histology is considered as gold standard, it has some limitations, like variants of papillary and follicular cancer creates confusion among pathologists, where the morphological features are indistinguishable. Conventional histology and FNAC fails to provide any prognostic and therapeutic information. To address this problem, several immunohistochemical markers are proposed and their efficiency in thyroid cancer diagnosis, treatment and prognosis are being evaluated. Among the discussed immunohistochemical markers, few have potential in accurate diagnosis and prognosis of thyroid carcinoma. Hector battifora mesothelial antigen-1 (HBME-1) and Galectin-3 (GAL-3) shows highest specificity and sensitivity in the diagnosis of thyroid cancer respectively. Overexpression of EGFR in thyroid cancer is in proportionate with the severity of the advanced thyroid carcinoma, which required further evaluation and validation. Surgery and radio-iodine therapy is the main treatment modality, however; combined targeted therapeutic approach against different thyroid cancer receptor and biomarkers can reduce the side effect, and improve therapeutic efficiency. This review is oriented towards the finding of the potent thyroid cancer receptor having enhanced sensitivity and specificity, with diagnostic, prognostic and therapeutic efficiency.

Key words: Biomarkers, Thyroid carcinoma, Immunohistochemical markers, HBME-1, GAL-3, EGFR, and FNAC

Abbreviations: Fine needle aspiration cytology (FNAC) and histology, Hector battifora mesothelial antigen-1, HBME1; Galectin-3, (GAL-3); epidermal growth factor receptor, EGFR.

INTRODUCTION

Thyroid gland is the major endocrine gland which secretes thyroid hormone. Though thyroid cancer contributes 1% of total cancer cases, but it accounts 90% of total endocrinial tumor and 60% of all death due to endocrine cancer death (1-3). The annual incidence of thyroid cancer ranges from 0.5 to 13.6 per thousand cases, and an increase in incidence from 3.2 per 100000 population in 1973 to 8.7 per 100000 population in 2002 was observed (4). This increased incidence in thyroid cancer needs attention for cancer diagnosis and its treatment. Most of the thyroid tumor is expressed as thyroid nodules, and among them 90% are benign, raises the difficulty in cancer diagnosis (5).

Thyroid tumor arises from the epithelium of the thyroid gland and divided into benign and malignant tumor. The malignant thyroid carcinoma is broadly classified into differentiated thyroid cancer (DTC), Medullary Thyroid Cancer (MTC) and undifferentiated thyroid cancer based on histological characteristic. Differentiated thyroid cancer is further subdivided into Papillary thyroid cancer (PTC) and Follicular thyroid cancer (FTC), whereas undifferentiated thyroid tumor includes Anaplastic thyroid cancer (ATC). PTC is the most common thyroid tumor accounts 85% of total thyroid tumor followed by Follicular (15%), Medullary (5%) and ATC (1%) tumor (6-7). Morphology of PTC (Figure 1-A) has characteristic architectural and nuclear features such as ground glass appearance and nuclear grooving as shown in Figure 1B, which is inconsistent with previous findings (8-9). Different variants of PTC are classified based upon the architectural and nuclear characteristic (10), whereas follicular variant of papillary cancer (FVPTC) creates diagnostic confusion due to lack of distinguished morphology.
Histopathology of FTC varies from well-differentiated follicles to a solid growth pattern; whereas the malignant behavior of FTC depends upon the pattern of tumor cell growth and morphology of the tumor cells. The more frequent dark nucleus and eosinophilic cytoplasm are less malignant than the less frequent dark nucleus and oncocytic basophilic cytoplasm observed in FTC (11). Vascular and capsular invasion is the important criteria in histopathological diagnosis of the malignant nature of FTC, raising the confusion and diagnostic difficulties in pathologist as it is not easily detected in early stages of FTC (10). MTC is an uncommon tumor originating from neuroendocrine parafollicular C-cells, which secretes calcitonin, an important cancer marker (12-13). MTC are composed of both polygonal and spindle cells, surrounded by C-cell hyperplasia and cellular amyloid deposits (13-15). ATC is divided into two variants (spindle cells and giant cells) by histopathological classification on the basis of morphology. However, the prognosis is poor due to rapid aggressive course of the disease and similar pattern of malignancy is observed in both variants (16). Though diagnosis of thyroid cancer can be done by studying the architectural characteristics, cytoplasmic pattern and nuclear morphology, but in early stage the morphological changes is indistinguishable in different thyroid cancer and creates confusion. It shows the requirement of diagnosis of thyroid cancer independent of morphology and architectural pattern with highest sensitivity and specificity.

Thyroid cancer, like other cancers is aggressive in nature, where complete remission can be achieved by early diagnosis and proper treatment. The overall 5-year survival rate of thyroid cancer is nearly 90%, and varies according to the type and stage of the cancer. In early stage differentiated thyroid cancer (PTC and FTC) shows better prognosis with 5-year survival rate varies from 85-95%, but in later stage the prognosis is very poor (17-18), shown in the Figure 2. Anaplastic thyroid cancer is the most aggressive of all cancer with 9% 5-year survival rate in all the stages with 100% mortality, needs more attention for its early detection (19). Females suffered more compared to males in thyroid cancer with ratio 4:1, but the overall prognosis is worst in males (18). Thyroid cancer occurs more frequently in the age group 20-50 year, with comparatively good outcome in younger patients than elder. Along with age and sex, other prognostic indicators like tumor size, volume, depth of invasion, lymph node involvement and extra thyroidal spread are also good prognostic indicators. Different tumor staging system like TNM, AGES, AMES and MACIS have been done based upon these criteria’s, but none of them clearly predict the thyroid cancer outcome (7). However, TNM system is most commonly preferred because it precisely provides prognostic information and this staging system is also being commonly adapted in other cancers (20). Thyroid cancer death can be reduced if diagnosed early, requiring a diagnostic method with highest sensitivity and specificity.

IMMUNOHISTOCHEMISTRY A NOBLE APPROACH TOWARDS THE DIAGNOSIS OF THYROID CANCER

Diagnosis of thyroid cancer being commonly done by histology, immunohistochemistry (IHC) and
Better prognosis of Thyroid Cancer

imaging modalities like X-ray, Ultrasonography and Computed tomography (CT), but aspiration Cytology (AC) and histology are more commonly performed and more informative (21). Though histology is considered as the standard diagnostic method for thyroid cancer but it shows some limitations where the morphological features are ambiguous. Between benign and malignant lesions morphologic similarities are frequent, and follicular and papillary architectures may be seen in both benign and malignant lesions (22), which creates difficulties in proper diagnosis. Histological diagnosis of PTC being done based on architectural (papilla, follicle, tall cells) study along with nuclear clearing, overlapping, grooving and pseudo inclusions. However, in the absence of papillary architecture, follicular variant of papillary thyroid carcinoma (FVPTC) is difficult to distinguish from nodular thyroid adenoma (22). FVPTC is characterized by follicular growth pattern and tumor cells with characteristic nuclear features of papillary carcinoma. Occasionally FVPTC may show focal or multifocal instead of diffuse distribution of nuclear features, and misdiagnosed as follicular nodule (23). Though Fine needle aspiration (FNA) biopsy is preferable used as pre-operative diagnostic tool for thyroid nodules, but it is not useful in certain histological variant where morphological architecture is atypical. In these cases, histology or IHC is required for the proper diagnosis (24). Moreover, Inter-observer discrimination among pathologists further raises error of diagnosis by histopathology (25). Though the proper diagnosis of thyroid cancer can be done based on mutation detection and gene expression profiles, but can’t be used as routine procedure due to time and expensive nature of diagnosis (26-27). However, the diagnosis of thyroid cancer may be done accurately by detecting expression of different biomarkers by IHC with highest sensitivity and specificity. Therefore, our study is focused on thyroid cancer biomarkers and their diagnostic and prognostic importance in thyroid cancer.

MOLECULAR BASIS OF THYROID CANCER AND CANCER BIOMARKERS

Though thyroid cancer occurs through multiple cell signaling pathways, but RET-RAS-BRAF and PI3K pathway are most actively involved (28). In thyroid cancer, mutation in different oncogenes leads to inhibition of apoptosis, cell proliferation, and migration and over expression of certain receptors (29). Growth factors e.g., epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) bind to their respective receptors and stimulate corresponding signaling pathways as shown in the Figure 3. The uncontrolled activation of signaling pathway due to mutation results in gene over-expression and truncated protein production. The autocrine and paracrine action of these growth factors on cell signaling pathways further enhance cell proliferation, vascular invasion and metastasis, causing further rapid growth of the cancer. Several molecular markers have been detected in thyroid cancer actively involved in cancer development and metastasis (Table 1). These biomarkers can be used in IHC for the diagnosis of thyroid cancer (30-31). Diagnostic and prognostic potential of all proposed markers are not same which varies according to the type of thyroid tumor. Therefore, more study should be conducted for the proper evaluation of these markers.

Figure 2. Stage oriented five year survival rate of different thyroid cancer. PTC has highest survival rate (100-84%) and ATC has lowest survival rate only (9%). Survival rate of PTC, FTC and MTC in stage I and II is nearly 100%.
Figure 3. Thyroid cancer cell signaling pathway and targeted therapy. Growth factors (EGF, VEGF) bind to the receptor (Growth factor receptor). The signal travels through two pathways, RAS pathway and PI3K pathway. RAS signal flows through BRAF, MEK and ERK and activates transcription and translation. In PI3K pathway signal flows through AKT and mTOR and stimulates transcription and multiplication. There are various drugs that act at different stage of cell signaling pathway.

Table 1. Thyroid cancer Biomarkers and Gene mutation

<table>
<thead>
<tr>
<th>Thyroid Cancer</th>
<th>Biomarkers Expression</th>
<th>Molecular alterations, Rearrangement/mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>GAL-3, HBME-1, CK-19, TPO, VEGFR, EGF, CITED-1, HGF</td>
<td>RET/PTC, RAS, BRAF, MET, E2F-1</td>
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<tr>
<td>Follicular</td>
<td>TPO, GAL-3, VEGFR, EGFR</td>
<td>RAS, PAX8/PPAR, PI3K-AKT-PTEN</td>
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<td>RET, C-met</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>EGFR, VEGFR,</td>
<td>P53, RAS, β-CAT, C-met</td>
</tr>
</tbody>
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Thyroid Peroxidase

Thyroid peroxidase (TPO) is the enzyme which catalyses iodination of thyroglobulin and also helps in coupling of iodotyrosine to thyroxin. The intensity of TPO expression in the serum is proportionate with the severity of thyroid cancer, and is a suitable marker for extra thyroidal tumor mass assessment after surgery. Though TPO is commonly expressed in DTC at the early stages, but its sensitivity and specificity in differentiating benign from malignant thyroid cancer is poor, as it is expressed both in inflammatory and hyperplastic thyroid nodules (32). So, TPO is not frequently used as diagnostic marker.

Calcitonin

Calcitonin is secreted from the C-cell of parafollicular cells, specifically expressed in MTC. The level of calcitonin increases with the extra thyroidal
tumor spread, hence, calcitonin level is commonly accessed for the post therapeutic follow up (33-34).

**Cytokeratin-19**

Cytokeratin-19 (CK-19) is the smallest of 20 member keratin family (48-60 KDa, IpH 4.9-7.8) expressed in the periderm, the transiently superficial layer that envelops the developing epidermis. CK-19 expression pattern is often used for distinction of different types of epithelial malignancies (35), which is also expressed in endometrial cancer, bladder cancer and breast cancers, showing marked sensitivity, but poor specificity (36). Wide expression of CK-19 occurs in thyroid cancer, but most commonly noticed in 80% of PTC than other thyroid tumors. Its high reactivity may help in diagnosis of different thyroid tumors in IHC study (37). There is no variation in the intensity of the expression of the CK-19 in metastatic and non metastatic tumor, but its usefulness as a prognostic marker needs more attention. Earlier studies of CK-19 vary from one another in terms of sensitivity and specificity for diagnosis of thyroid cancer. Study shows that CK-19 was expressed in 96.8% of thyroid cancer and 4.5% in benign thyroid nodules. The average sensitivity and specificity of CK-19 is calculated after analyzing the recent data on thyroid cancer (25,38-41) as shown in Figure 4-A. The average sensitivity and specificity of CK-19 in differentiating benign and malignant thyroid tumor is 80.4% and 72% respectively. The low specificity of CK-19 is due its expression in some benign and inflammatory thyroid nodules, limiting its usefulness as a sole biomarker for the thyroid cancer diagnosis (41). However, CK-19 can be useful as an important biomarker along with the panel of other markers because of its high sensitivity in expression in thyroid cancer cells.

**Hector Battifora Mesothelial Antigen**

Hector Battifora Mesothelial-1 (HBME-1) is an antimesothelial monoclonal antibody reacts against unknown antigen on mesothelial cell surface, commonly used in differential diagnosis of mesothelioma and adenocarcinoma (42). HBME-1 is highly expressed in both PTC and FTC with little expression in MTC and ATC, stimulates cancer cell proliferation and migration. De Micco et al. noticed that HBME-1 is not expressed

![Figure 4.](image-url)

**Figure 4.** Sensitivity and specificity of HBME-1, CK-19 and GAL-3. A, B, C showing the average sensitivity and specificity of HBME-1, CK-1 9 and GAL-3 respectively, calculated from the immunohistochemistry results of five different studies. GAL-3 is highly sensitive (93.65%) and HBME-1 is highly specific (84.64%).
in benign thyroid lesion but expressed in malignant thyroid cancer, indicating HBME-1 is the most specific marker for thyroid cancer and may be useful in differentiating malignant thyroid cancer from benign tumor (24). HBME-1 is a preferred marker for the diagnosis of PTC. Strong and generalized expression of HBME-1 suggests FTC but negative staining in poorly differentiated cancer doesn’t rule out malignancy. According to De Matos et al., HBME-1 is the most sensitive marker for thyroid cancer (43), and also recent study conducted by Nga et al. found that specificity, sensitivity and positive predictive value (PPT) of HBME-1 was 100%, 92.9% and 90% respectively (44). However, after analyzing data from different studies (25,38,40-41,44), the average sensitivity and specificity of HBME-1 was found to be 81% and 84.7% respectively, showing HBME-1 is most specific in diagnosing thyroid cancer (Figure 4-A). Therefore HBME-1 may be useful as a suitable marker for the IHC due to its high sensitivity and specificity, but its prognostic importance needs to be addressed.

**Galectin-3**

Galectin-3 (GAL-3) is a member of β-galactosyl binding lectin family and expressed in both nucleus and cytoplasm which interacts with carbohydrate and protein ligand to form pentamers therefore helping initiation and regulation of cell growth, cell differentiation and malignant transformation. Like Bcl-2, GAL-3 inhibits apoptosis by suppressing the apoptotic stimulation (45). Over expression of GAL-3 is found in various cancers, including thyroid cancer (46). It is highly sensitive in differentiating benign from malignant thyroid tumor (47). After analyzing the recent IHC data, on thyroid cancer (39-41), the average sensitivity and specificity of GAL-3 is found to be 93.7% and 83% respectively (Figure 4). The reduced specificity is due to its expression in some cases of thyroid adenoma and goiter. Though several studies have questioned the usefulness of GAL-3, in thyroid cancer diagnosis, but from Figure 4-D, it can be clearly marked that GAL-3 is the most important marker for the thyroid cancer diagnosis.

**Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1 (CITED-1)**

The *CITED1* gene was reported to be highly up-regulated in PTC relative to normal thyroid. The CITED-1 protein is a 27 KDa transcriptional transactivator nuclear protein, expressed in melanocytes, breast epithelial cells, PTC, and several embryonic tissues (48). Prasad et al. have noticed that the accuracy of CITED-1 in differentiating PTC from benign thyroid nodules, other thyroid carcinomas, and non thyroid carcinomas was 93%, 89%, and 94%, respectively (48). IHC conducted by Huang et al. detected expression of CITED-1 in 96% of PTC but not in FTC and normal thyroid tissue (49). CITED-1 can be a potential thyroid cancer marker with highest specificity in the detection of PTC. Since very few studies have been conducted on CITED-1, further studies are needed to realize the full potential of this marker in thyroid cancer diagnosis.

**Hepatocyte Growth Factor**

Hepatocyte Growth Factor (HGF) is a cytokine which acts through c-met receptor and stimulates cancer growth. Study conducted recently noticed the existence of significant correlation between HGF, c-met and thyroid cancer, where activation of c-met in response to HGF favors tumor growth, migration and morphogenesis (50-51). It has been demonstrated that the whole morphogenetic pathway HGF/c-met/STAT3 is over-expressed in PTC and is highly specific for this type of thyroid malignancy, suggesting that such autocrine signaling pathway may be relevant for the establishment of the papillary cancer (52). Trovato et al. have noticed that a subset of follicular adenomas expressing the c-met/HGF/STAT3 pathway evolves finally into PTC (52). The expression of HGF in thyroid tumor can be detected by IHC and Western blot to establish its role in cancer diagnosis (53). It can be interpreted that HGF can be a potential marker for early diagnosis of PTC.

**Epidermal Growth Factor**

Epidermal growth factor (EGF) receptor (EGFR) is a transdermal receptor, consists of an extracellular transmembrane and intracellular domain with intrinsic kinase activity after binding with appropriate ligand. EGFR promotes cell proliferation and cell growth through mitogen activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI-3K) signaling pathways (54-55). EGF stimulates thyroid cancer cell proliferation, invasion and metastasis. Though the intensity of the expression of EGFR is high in ATC and PTC, some normal and inflammatory tissue has shown positive results. Over expression of EGFR is a poor prognostic indicator in breast and lung cancer (19). However, its correlation with the severity of the thyroid cancer has yet to be established (56). A recent study established a significant correlation between the staining intensity of EGFR and recurrence of PTC.
(57), indicating its active involvement in advanced cancer and distant metastasis. Thus, molecular therapy targeting EGFR may be suitable candidate for thyroid cancer, expressing EGFR (19).

**Gene mutation and Rearrangement**

RET/PTC rearrangement, BRAF, PAX-8/PPARγ, RAS and LOH of 3p-3q are important genes involved in thyroid cancer. (30) BRAF mutation is the most sensitive papillary thyroid cancer marker, followed by RET/PTC rearrangement. BRAF is a member of Raf family, involves in activation of Raf-Ras-MAPK pathway. The point mutation of BRAF at 600 location resulting in BRAFV600E is seen in 60% of the classic variant of PTC and less frequently seen in FTC and ATC. (58-60). BRAF point mutation has a poor prognostic factor, which indicates the aggressive and progressive nature of the cancer and targeted therapy against it can be a very effective approach for thyroid cancer treatment (61). RET/PTC rearrangement results in activation of RET, which acts through Ras-Raf-MAPK signaling pathway. It is the second common genetic alteration seen in PTC and used as diagnostic tool in FNA samples. (63). Out of several variants of RET/PTC rearrangement, RET/PTC1, RET/PTC2 and RET/PTC3 are most commonly occurs in PTC. Reports suggested that these isoforms are also found in some benign thyroid nodules. (64). Though earlier it was considered to be an important prognostic marker, but recent studies proposed that there is no correlation between RET/PTC rearrangement and aggressive nature of the thyroid cancer. It was proposed that the expression of the two markers (BRAF and RET) cannot be overlapped (65), but combined expression of these two markers in PTC has been noticed in a recent study (66). This demands more study on BRAF-RET/PTC-Ras-Raf-MAPK pathway in thyroid cancer development, so that targeted therapy against this pathway may improve the therapeutic outcome in PTC. (67-68). RET somatic and germline mutations are seen in sporadic and familial MTC respectively and used as an important marker for the diagnosis and prognosis of thyroid cancer. (69-70). PAX8/PPARγ fusion genes and the loss of heterozigos-ity (LOH) on 3p and 7q loci may represent potentially useful molecular biomarkers of FTC. (31). PPARγ is a member of the nuclear hormone receptor super family that includes thyroid hormone, retinoic acid and androgen and estrogen receptors, is more sensitive in diagnosis of the FTC. This type of mutation is involved in progression of Follicular adenoma (FA) to FTC. Hence, this PAX-8/PPARγ fusion mutation can be a important marker for early diagnosis and treatment of FTC. (71). In FTC tumor progression is also associated with the LOH of 3p and 7q, which correlate with the thyroid cancer volume and presence of multiple lesions. Thus, the 3p and 7q LOH has been proposed as a diagnostic marker to assist pathologists in the task of distinguishing FTC from benign thyroid lesions. (72). Gene mutation and activation have greater importance in the thyroid cancer diagnosis, prognosis and targeted therapy. However, these are time consuming and expensive and only suitable for research and evaluation of prolonged treatment and cancer recurrence.

**COMBINED MARKER STUDY MAY IMPROVE THE ACCURACY OF THYROID CANCER DIAGNOSIS**

Individual study of biomarker shows that some markers are more specific and some are more sensitive and of course, all these markers may not be expressed in a single tumor. So with combined study, the accuracy of diagnosis of thyroid cancer increases, as single tumor may not express all the molecular markers that are specific and sensitive for detection. Therefore, the diagnosis of thyroid cancer by using a panel of markers may enhance the accuracy of diagnosis (41). It has been noticed that HBME-1 is most specific marker with poor sensitivity, whereas GAL-3 and CK-19 are most sensitive with poor specificity after calculating the sensitivity and specificity of HBME-1, CK-19 and GAL-3 as shown in Figure 4. A recent study proposed that nearly 100% sensitivity and specificity can be reached by combining a panel of markers for diagnosis of thyroid cancer (73). More studies are required to find the best combination of marker to improve the sensitivity and specificity with having both diagnostic and prognostic importance.

**THYROID CANCER TREATMENT AND TARGETED CANCER THERAPY**

Total thyroidectomy and radioactive iodine ablation of remnant thyroid tissue is being done in DTC (PTC and FTC) with excellent treatment outcome, whereas in advanced thyroid tumor with extra thyroid involvement, additional treatment required for the complete remission of the disease. (74-75). Advanced tumor with local invasion and lymph node involvement, extensive surgery may have curative or palliative effects, but morbidity should be consider before debulking operations, requiring alternative therapeutic approach. (76). Molecular understanding in the pathogenesis of DTC and development of targeted therapy have dramatically transformed the field of clinical research in thyroid can-
Therefore advanced therapy using molecular targets and anti-neoplastic agents should be involved in the treatment of advanced thyroid malignancies (19,78). As shown in Figure 3, VEGFR, EGFR, RET, BRAF and their downstream effectors are main component in the thyroid cancer signaling pathway and may be the suitable candidates for the targeted therapy. There are several reports which suggest that the targeted therapy against EGFR and/or VEGFR potentiates the antitumor potential of cytotoxic drugs (19). Cell proliferation, angiogenesis, inhibition of apoptosis are major cellular mechanisms, responsible for cancer development and progression (79). Therefore targeted therapy using growth factor inhibitor, angiogenesis inhibitor and apoptosis sensitizer along with the conventional treatment improves the survival rate in thyroid cancer (80-81). EGFR inhibitors like Cetuximab, AEE 788, Sorafenib, Somatedin A and Axitinib have shown potential results against lung, ovarian and hepatic cancer along with inspiring results in animal thyroid cancer model (82-88). There are also other inhibitors as shown in Table 2, VEGFR neutralizing antibody (Bevacizumab), VEGFR blocker (Emaxanib), TNF related apoptosis–induced ligand (TNF-α), heat-shock protein, and retinoid receptor agonist are successfully adapted with standard chemotherapeutic drugs or radiation in the treatment of PTC and ATC with significant improvement in long term patient survival rate. This shows the therapeutic importance of combined treatment in potentiating the cytotoxicity of standard treatment regimens (89-91). Along with inhibitors of VEGFR and EGFR, drugs like CL-1040, VX-680 and LY-294002 (Table 2) are targeted against other signaling molecules e.g. Ras, MEK, and PI-3K for the thyroid cancer therapy and are in different stages of clinical trial (66,78,92-93). Previous studies have shown that chemotherapeutic agents lead to activation of EGFR and activated EGFR-ERK pathway is responsible for inhibition of apoptosis induced by the cytotoxic drugs (94). Moreover cytotoxic agents are toxic to normal cells, which might limit its use in clinical practice in advanced thyroid cancer. Thus, the targeted therapy has substantial clinical relevance for thyroid cancer where clinical studies of dose-intensive radio iodine therapy are in progress.

### CONCLUSION

The outcome of cancer depends on the proper diagnosis, evaluation and treatment. Though histopathology and FNAC are routinely used, but IHC can play an important role in proper diagnosis of thyroid cancer. Extensive studies of thyroid cancer biomarkers and implementation of panel of markers along with the traditional thyroid cancer diagnostic modalities will improve the specificity and sensitivity of the thyroid cancer diagnosis. These will also help in elucidation of the molecular basis of thyroid cancer development and hence, improve the treatment outcome by the molecular targeted therapy combined with prevalent thyroid cancer therapy. Radio-iodine therapy is commonly used in post-operative advanced metastatic thyroid cancer, but the complication due to higher dose and prolonged period of therapy overweight’s overall survival rate. This lead to the search of alternative targeted therapy in combination with standard therapeutic regimens. It was found that the combined targeted therapy along with this standard radiotherapy can reduce the drug dose, duration, complication, morbidity and improve the sur-

### Table 2. Drugs used for the targeted thyroid cancer therapy and corresponding targeted gene. Drugs marked (*) are used for thyroid treatment and marked (#) are under different phases of clinical trial

<table>
<thead>
<tr>
<th>Compound</th>
<th>Receptor</th>
<th>Cancer</th>
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<td>Sorafenib*</td>
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vival rate (95). This targeted therapy can also minimize the adverse effect. Though there are several potential markers like HBME-1, CK-19, HGF and GAL-3, but controversy exist regarding the correct combination of markers for the excellent thyroid cancer diagnosis. In the current scenario IHC is not used in clinical application. There are several reports of treatment failures associated with acquired drug resistance in thyroid cancer cases. Further attention and extensive studies are needed to understand the molecular mechanism of drug resistance and treatment failures to these cytotoxic drugs may be helpful for targeted thyroid cancer therapy.

REFERENCES


