The Prognostic Implications from Molecular Testing of Thyroid Cancer

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KEYWORDS

• Thyroid cancer • Prognosis • Molecular genetics • BRAF • RAS • RET/PTC • PAX8-PPAR • Targeted therapy

KEY POINTS

- Molecular testing offers valuable information for the management and prognosis of patients with thyroid cancer by detecting genetic alterations.
- Molecular markers may guide clinicians to assess the individual risk of recurrence and metastasis from thyroid cancer and to tailor the treatment according to that risk stratification.
- B-type RAF mutation has emerged as a possible marker for more aggressive behavior of papillary thyroid cancer; RET/PTC may be a marker of more favorable thyroid tumor behavior.
- There are currently no prospective, well-defined data supporting the use of molecular markers alone to decide on the extent of treatment or to predict the prognosis in patients with thyroid cancer.
- Molecular markers are promising targets for novel therapies and, in particular, for thyroid cancers with aggressive behavior.

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy and accounts for approximately 1% of all newly diagnosed cancers. A significant worldwide increase in the incidence of thyroid cancer has been noted over the past few decades.

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Age-standardized incidence of thyroid cancer in developed countries is estimated to be 9.1 per 100,000 women and 2.9 per 100,000 men.[1] Papillary thyroid carcinoma is almost entirely responsible for the overall increase in the incidence of thyroid cancer in the last several decades. There is also an increase in the incidence of diagnosed thyroid nodules that parallels the rapid increase in the incidence of thyroid cancer. The prevalence of thyroid nodules on physical examination is almost 10% in adults and is detected at a higher rate (up to 70%) in the elderly population if thyroid ultrasonography is used. It is crucial to distinguish cancer from benign thyroid nodules because there is an overall 5% to 10% risk of malignancy in thyroid nodules.[2]

Most of the thyroid cancers are epithelial, follicular cell derived, and the most frequent type is papillary thyroid carcinoma, which constitutes more than 80% of all thyroid malignancies. The second most frequent type of thyroid cancer is follicular thyroid carcinoma, which accounts for 10% to 15% of all thyroid malignancies.[1–4] Follicular carcinoma most likely originates either from a preexisting benign follicular adenoma or directly, bypassing the stage of adenoma.[2,3] Medullary thyroid carcinomas, which account for approximately 3% of all thyroid malignancies, develop from the parafollicular C cells of the thyroid gland. Anaplastic and poorly differentiated thyroid carcinomas are rare but represent the most aggressive types, with high mortality.[1] Papillary and follicular thyroid carcinomas, the so-called differentiated thyroid cancers, constitute more than 90% of all thyroid malignancies and they are usually associated with a good prognosis because most have an indolent course. The classic treatment of choice for thyroid cancer is total thyroidectomy with or without radioactive iodine. Despite high disease recurrence rates of up to 20% to 30% in differentiated thyroid cancers, the overall prognosis is still favorable, with a 10-year survival rate of more than 90%. However, surgically inoperable or radioiodine-resistant differentiated thyroid cancers do not yet have an effective treatment and can still cause death.[1–4]

The prognostic factors favoring recurrence, metastasis, and death from differentiated thyroid cancer include both patient and tumor factors. Among patient factors are age less than 15 years or more than 45 years, male sex, and family history of thyroid cancer.[4] Tumor factors include a primary tumor larger than 2 cm, multifocal cancer, nuclear atypia, tumor necrosis, vascular invasion, extrathyroidal extension, lymph node metastasis, distant metastasis, tall cell and columnar cell variants, and radioiodine resistance.[4] A poor prognosis is most commonly associated with neck recurrence caused by lymph node metastasis or thyroid bed remnant disease and less commonly with distant metastasis.[4]

It can be challenging to assess the individual risk for recurrence and metastasis of thyroid cancer and tailor the treatment according to that risk stratification. However, recent investigations have made progress in understanding the molecular mechanisms of thyroid cancer. These investigations have revealed that thyroid cancers frequently have genetic alterations, and current molecular studies can detect these alterations and offer valuable information for diagnosis, management, and prognosis of patients with thyroid cancer. This article discusses the current use of molecular markers for thyroid cancer from a prognostic and therapeutic perspective.

RELEVANT PATHOPHYSIOLOGY

Genetic Alteration of Mitogen-activated Protein Kinase Signaling Pathway

The mitogen-activated protein kinase (MAPK) signaling pathway is an intracellular cascade regulating division, proliferation, differentiation, adhesion, migration, and