73.2. Thyroid: Anaplastic

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Emerging Prognostic Factors for Clinical Care

Impact of Molecular Profiling on Risk Stratification

Tumors harboring *BRAF*, *TERT*, and/or *P53* mutations have the potential to be aggressive, with increased rates of recurrence and disease-specific mortality.[1-6] Furthermore, *BRAF* V600E mutation appears to increase the risk of disease-specific mortality if identified in conjunction with lymph node metastases, distant metastases, AJCC Stage IV disease, and age ≥45 years at diagnosis.[4] More recent data suggest that tumors harboring multiple oncogenic mutations, although uncommon, may have a more aggressive phenotype.[5,7] Because many of these mutations are tightly linked to aggressive histologic features, it is difficult to estimate the proportion of risk attributable to the actual mutation versus that attributable to the other clinicopathologic features. Although the 2015 ATA guidelines recognize the potential for improvement in risk stratification with regard to molecular profiling, they do not recommend molecular testing for initial staging because it is not yet clear how much incremental improvement in risk stratification would be gained.[8]

The increased use of more complete, in-depth genomic analyses has led to the discovery of targetable mutations in a small percentage of patients with aggressive thyroid cancers. Recently, promising results were seen with inhibitors of *ALK* fusion genes in medullary[9] and anaplastic thyroid cancer[10] and with a *BRAF* inhibitor in anaplastic thyroid cancer.[11,12]

Risk Assessment Models

The AJCC recently established guidelines that will be used to evaluate published statistical prediction models for the purpose of granting endorsement for clinical use.[13] Although this is a monumental step toward the goal of precision medicine, this work was published only very recently. Therefore, the existing models that have been published or may be in clinical use have not yet been evaluated for this cancer site by the Precision Medicine Core of the AJCC. In the future, the statistical prediction models for this cancer site will be evaluated, and those that meet all AJCC criteria will be endorsed.

Recommendations for Clinical Trial Stratification

The following stratification criteria stem from the prognostic factor analyses suggested for use in thyroid cancer trials, depending on the specific objectives of the study, the cancer stage(s), and the population under study, including sample size:

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- Tumor histology
    - Perineural invasion
    - Multifocality
    - High mitotic index
- AJCC stage
- Age
- Biomarker analysis

The primary stratification for thyroid cancer clinical trials focused primarily on structurally progressive RAI-refractory patient populations will be based on tumor histology, AJCC stage, and age. However, as many of the clinical trial agents are molecularly targeted therapies, risk stratification and data analysis based on biomarker analysis of the tumor may also yield important insights.

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