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Review

Prognostic markers in well differentiated papillary and follicular thyroid cancer (WDTC)

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Abstract

Objectives: WDTC (papillary and follicular thyroid cancer) make up around 90% of all thyroid tumours. Overall, the prognosis in patients with WDTC is excellent. However, there are small cohorts of patients who experience a more aggressive form of disease which is often associated with certain poor prognostic factors. Identifying these patients at an early stage is imperative for guiding treatment decisions. With recent developments in this area we plan to discuss the current evidence surrounding prognostic markers.

Methods: The literature regarding prognostic factors in WDTC was reviewed using an electronic database Medline – Pubmed. Using the MeSH search engine specific prognostic factors including age, size, grade, lymph node involvement, distant metastasis, extension/invasion, ethnic background, radioactive iodine avidity, and thyroglobulin level and their association with WDTC were evaluated. A broader search of prognostic markers in thyroid cancer was also carried out to avoid missing other pertinent markers.

Results: Multiple clinical and pathologic variables have been shown to be poor prognostic factors in WDTC with statistical significance. Extensive extrathyroidal extension and age may be the most important factors when predicting clinical outcomes in WDTC, although the age threshold may be increased from 45 to 55 years in due course.

Conclusions: Management of WDTC has changed considerably over the last two years as reflected in evolving British and American Thyroid Guidelines. In all cases a combined multi-disciplinary approach, with consideration of the available guidelines and stratification systems should be utilised when planning an individualised treatment program to offer the best contemporary care to WDTC patients.

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Keywords: Differentiated thyroid cancer; Prognostic markers; Stratification; Age; Size; Grade; Metastasis; Lymph node metastasis; Extrathyroid extension; Invasion; Ethnic background; Radioactive iodine avidity; Thyroglobulin

Introduction

Thyroid cancer represents the most common endocrine malignancy, and its incidence has been increasing rapidly over the last 3 decades in both genders and all ethnic backgrounds.[1] Well differentiated thyroid cancer (WDTC) is a collective term encompassing a diverse array of follicular-epithelial cell derived tumours, traditionally consisting of papillary (PTC) 80–85% and follicular thyroid cancer (FTC) 10–15%. PTC and FTC make up around 90% of all thyroid tumours. Overall, the prognosis in patients with WDTC is generally excellent[2] despite a significant risk of recurrence in comparison to the overwhelming poor outcomes of anaplastic and poorly differentiated thyroid cancers. However, there are small cohorts of patients who experience a more aggressive form of disease which is often associated with certain poor prognostic factors. 80% of patients with WDTC will do well with minimal surgical treatment while 5% may die regardless of treatment offered. The remaining 15% represents a group of patients who may benefit from a more aggressive oncological resection, with adjuvant radioactive iodine treatment and, in select cases, external-beam radiation therapy.[2] For this reason, it is important for the treating physician to understand the prognostic factors to facilitate individual patient

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risk group categorisation.[3] Unfortunately, a significant degree of overtreatment still exists because of our inability to accurately identify this cohort of at risk patients.

There are a number of studies that have investigated and identified various clinicopathologic predictors and prognostic markers to create specific risk stratification systems aimed at identifying those at high risk of cancer death[4] and recurrence. This allows patients at high risk to receive more aggressive treatment while avoiding unnecessary and invasive treatments in those at low risk. Most risk stratification systems include the same core parameters of age, tumour size, grade, presence of local invasion, and regional or distant metastases. In this paper, we will discuss the evidence surrounding these common factors as well as other upcoming markers and explore the current risk stratification systems available.

Natural history and progression

Thyroid cancer has historically been thought to arise because of multi-step carcinogenesis beginning in middle age with some patients developing a more aggressive phenotype after repeated proliferation, resulting in accumulating genetic alternations.[5] However, over the last 5 years following advances in ultrasonographical techniques/availability there have been several papers which have changed our understanding of the natural history of the disease.[6,7] The discovery of self-limiting cancers, which are truly malignant but not lethal means that early diagnosis and surgery results in over diagnosis and over treatment.[5] Our understanding of WDTC continues to evolve and redefining conditions to more suitable terms may help us create more accurate prognostic classifications. For example a recent nomenclature revision has been proposed for a low risk condition "encapsulated follicular variant papillary thyroid carcinoma without capsular or vascular invasion" to be renamed as "non-invasive follicular thyroid neoplasm with papillary like nuclear features" (NIFTP) with a much less aggressive treatment plan recommended.[8]

Through analysis of current research, we are often forced to question statements that we have always understood to be true. Interestingly many prognostic markers show discrepancy in significance between different methods of analysis. While many factors have been shown to be important on univariate analysis, few remain predictive in multivariate analysis. Most likely these variables are strongly correlated to other variables used in a multivariate analysis and so are competing which each other to explain cause. This can mean both may appear to be non-significant. In general, careful interpretation of studies and methodologies are imperative for gaining accurate inferences from statistics. As our understanding of prognostic factors in WDTC grows we must continue to question and build upon previously accepted knowledge. The future of risk stratification in WDTC involves utilising all significant variables with upcoming advances in genetic profiling and targeting specific clinical scenarios to further decrease uncertainty, so we can provide the most accurate prognostic information to our patients as possible.[9]

Staging systems

There are numerous staging classifications available for predicting outcomes in thyroid cancer. Most readily available systems include the same core parameters of age, tumour size, grade, presence of local invasion, and regional or distant metastases. Some are inclusive of all thyroid cancers[10] while others discriminate between well-differentiated[11] or poorly-differentiated cancers and others more specifically restricting usage to individual types of thyroid cancer such as papillary only.[12] Staging systems also differ for outcome predicted with some predicting risk of recurrence (American thyroid association ATA risk stratification) and other predicting risk of death (TNM staging). Another important consideration is the need for dynamic risk stratification. While initial risk stratification systems are useful in guiding initial diagnostic and therapeutic strategies it is important to remember that this may change as new information is gathered during follow-up.[13]

For all cancers, disease staging must accomplish 3 important criteria. Firstly, a system should allow for a common language to exist between physicians and institutions regardless of hospital or even country facilitating simple, clear communication of vital information. Secondly, an accurate estimate of prognosis and expected outcome will assist in decision making regarding treatment choice and patient counselling, and thirdly, to assist with the process of research including stratification for design and analysis in clinical studies and trials.[14]

To develop an ideal staging classification rigorous testing should include univariate and multivariate retrospective analysis of all potential prognostic factors with subsequent prospective validation and comparison with the existing systems.[15]

Unfortunately, within thyroid cancer no consensus has been reached regarding the optimal approach to disease staging and so multiple often overlapping classification systems have been developed. Just some of the most commonly used systems include: AGES (Age, Grade, Extent of disease, Size); AMES (Age, Metastasis, Extent of disease, Size) for differentiated thyroid carcinoma; Clinical Class for differentiated thyroid carcinoma; DAMES (DNA-Ploidy modified AMES) for papillary thyroid carcinoma; EORTC (European Organisation for Research on the Treatment of Cancer) for all thyroid carcinomas; MACIS (Metastasis, Age, Completeness of resection, Invasion and Size) for papillary thyroid carcinoma; GAMES (Memorial Sloan Kettering Cancer Centre) for differentiated thyroid carcinoma; Noguchi for papillary thyroid carcinoma; SAG (Sex, Age, Grade); NTCTCS (National Thyroid Cancer Treatment Cooperative Study group) for all thyroid carcinomas; Ohio State University for differentiated thyroid

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