Do the results from Paoletti et al. (6) justify PFS as an endpoint for trials of advanced gastric cancer? The authors conclude that the answer is no, but it is not entirely clear how they reached this conclusion. They quote a number of statistics that characterize in various ways the concordance of PFS and OS results, in addition to $R^2$. However, these measures are all ultimately descriptive and do not lend themselves to a definitive criterion for determining whether the use of the surrogate endpoint is justified. There is an implicit comparison with a previous study evaluating PFS for use in advanced trials of colorectal cancer involving several of the same authors, which concluded that PFS is a valid surrogate (9). However the rank correlation of PFS and OS is actually higher in the gastric cancer study, 0.85 compared with 0.82, and the $R^2$ value of 0.61 correlating the effect sizes is only modestly lower than the 0.74 observed in the colorectal study. [Note that this latter estimate involved the exclusion of an “outlier” study.] So what is different about gastric cancer that would justify the disparate recommendations?

The style of presentation of these studies is heavily focused on the various statistical comparisons but it is light on the aspects of the clinical setting that might help to influence a conclusion that is ultimately a judgment call. In studies of this nature, there is no accepted statistical test or definitive statistical standard that a surrogate endpoint must meet to justify its use in future studies. Consequently the statistical evidence must be embellished with knowledge about the clinical context for which hard statistical evidence may be unavailable or more difficult to collect. How valuable is delay of progression to the quality of life of patients generally? How much variation exists in techniques used to measure progression, and how much confidence do we have in the available methods? To what extent might the use of PFS speed the process of evaluating new treatments without undermining the credibility of the evaluation process? Decision making in this context cannot be relegated to purely statistical comparisons without substantive judgment of this nature.

References


References


Notes

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Cowden Syndrome and the PTEN Hamartoma Tumor Syndrome: How to Define Rare Genetic Syndromes

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Cowden syndrome (OMIM No. 158350) and Bannayan-Riley-Ruvalcaba syndrome (BRRS) (OMIM No. 153480) are autosomal dominant conditions described before the genetic testing era. The early reports of Cowden syndrome were by adult physicians and dermatologists who recognized a pattern of benign and malignant tumors affecting the breast and thyroid, accompanied by characteristic acral keratosis and trichilemmomas of the skin (1,2,3). BRRS was described by pediatricians and clinical geneticists, with the principle features being macrocephaly, delayed development, lipomata, hemangiomas, and vascular malformations, along with pigmented macules of the penis (4,5). Both conditions are caused by mutations in the PTEN gene (OMIM#190880) (6,7). There is no definite association between the type or position of mutation within the PTEN gene and the clinical presentation of the patient. Both conditions have been described in different members of the same family with the same mutations, and it is clear that meticulous examination reveals features of childhood-onset BRRS in adults presenting with the features of Cowden syndrome and vice versa. It is therefore generally accepted that they are one condition, with variable expression and age-related penetrance (8,9,10,11). Genetic
heterogeneity has been reported with reports of Cowden-like patients (i.e., those who do not fulfill criteria for PTEN hamartoma syndrome [PHTS]) with mutations in SDHB, SDHD, AKT, and PIK3CA, as well as hypermethylation of the promoter of the KLLN gene (12,13,14,15).

In recent years, the conditions have been collectively referred to as PHTS (9), reflecting the underlying genetic cause rather than the clinical phenotype. Most recently the phrase PTEN-opathies has been coined (16).

Diagnostic criteria for Cowden syndrome, which were initially based on case reports and expert opinion, have evolved (17). They have been modified over time, taking into account the wider spectrum of clinical presentations published since the discovery of the PTEN gene (18). The National Comprehensive Cancer Network (NCCN) has adopted the criteria published in this issue of the Journal. The main difficulty with all previous versions of the NCCN diagnostic criteria for PHTS (19) was that the criteria were challenging to use outside of a specialist clinic setting, with complex combinations of pathognomonic major and minor criteria and family history required to reach an operational diagnosis. The age-related penetrance of some components of the condition meant that these criteria needed to be interpreted loosely in younger patients in particular.

An interesting article published by Pilarski et al. (20) in this issue of the Journal provides an excellent review of the medical literature about PHTS. The authors review the clinical problems, both commonly and rarely faced by people with mutations in the PTEN gene. They evaluate the additional features that have become associated with PHTS. The diagnostic criteria they propose, in particular those features listed as minor criteria, are very useful in guiding clinicians toward testing the PTEN gene. Moreover, autistic spectrum disorder, colon cancer, esophageal glycogenic acanthosis, testicular lipomatosis, and vascular anomalies are valuable additions. These new criteria eliminate the anomalies in the previous NCCN guidance, whereby, for example, a woman with macrocephaly and breast cancer should be considered for PTEN mutation testing (19). From their review of the literature, they do away with the pathognomonic features, leading to a much simpler format, with major and minor criteria only. Based on their literature review, they have eliminated some criteria, notably benign disease of the breast, described in the eponymous first patient, Rachel Cowden (1).

Pilarski et al. (20) find that these new criteria are more specific, leading to a high mutation detection rate (n = 44 of 48) in their own cohort of patients with PTEN mutations. They rightly highlight that children and younger adults may not have developed sufficient clinical features to meet these diagnostic criteria and demonstrate that this was the case in their own cohort. They recognize that additional clinical judgement may be necessary in these circumstances. For example, I would discuss testing of the PTEN gene with parents of a 5-year-old girl with autistic spectrum disorder, macrocephaly greater than the 97th percentile, motor delay, two lipomata, and a vascular anomaly, yet she would not meet these new NCCN criteria (or the previous set) for clinical diagnosis. Unless another family member independently met the diagnostic criteria, it would be unusual for any female patient aged less than 10 years and even aged less than 25 years to be diagnosed with this condition. A clinical scoring system with different calculators for adult and pediatric patients has been recently published and also includes many of the more recently described associations (21). This system has a different emphasis than the criteria published in this issue of the Journal because their aim was to predict the likelihood of finding a PTEN mutation. The diagnostic criteria proposed by Pilarski et al. (20) encompass the wider phenotypes associated with PTEN mutations. They have been tested on only a small group of patients, and wider assessment and application in clinical practice will be required to determine their utility.

On a more general note, the Pilarski et al. article (20) adds to the debate about the utility of diagnostic criteria in rare genetic conditions. Do we define a condition by the molecular cause or by clinical phenotype? Does a person or family still have the condition if the genetic test is normal, even though they have the appropriate clinical phenotype? These questions further raise the question: At what level of clinical suspicion should cancer surveillance advice be implemented? In the early stages of description of a new genetic condition, in particular, in a quest to discover new genes, tight diagnostic criteria are essential to ensure a consistent phenotype, or the ensuing heterogeneity of the sample will dilute the power of any study. However, if these same tight criteria are used in clinical practice to guide genetic testing, the result may be that genetic testing is offered only to those families in whom the clinical diagnosis is secure even without genetic testing. Of course, in some health systems, there may be no access to genetic testing, so the clinical criteria need to be robust. Where access to testing is limited because of financial constraints, stringent criteria can highlight which patients are most likely to have a pathogenic mutation. Where possible, when using such guidance to identify families (whether through genetic testing or the meeting of clinical criteria alone) predisposed to develop early-onset cancers, do we not want to cast the net more widely? Of course, surveillance programs and risk-reducing surgeries have disadvantages, so we do not want criteria to be so broad that we are offering these options to individuals who are not actually affected with the condition. In PHTS, the challenge is to define a set of criteria that encompass all age groups, are simple to administer by the nonspecialist, and are sensitive and specific enough that resources are targeted to those with substantial clinical risks.

Genetic testing is often adopted into clinical practice swiftly after gene discovery. The broader phenotype associated with a gene will not be elucidated if restrictive testing is the norm. It is good clinical practice to offer testing to patients who do not meet stringent criteria but in whom we suspect a diagnosis based on our own experience and knowledge of the rarer phenotypes associated with a particular condition. It is important that we continue to collect, either by submission of case reports or by more systematic, ideally international collaborations, details of these patients and families so we can better advise them in the future.

References
RASAL1 in Thyroid Cancer: Wisdom From an Old Foe

Joanne Ngeow, Charis Eng

The best way to defeat an enemy is to make him a friend.—Abraham Lincoln

True therapeutic success in oncology relies on a sound understanding of the molecular arena of the cancer in question. Thyroid cancer has rapidly increased in global incidence in recent decades (1). Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are differentiated thyroid cancers (DTCs), which account for more than 90% of all thyroid malignancies. Most DTCs are indolent tumors and are usually curable. However, in surgically inoperable, radioiodine-refractory DTCs and in poorly differentiated thyroid cancers and anaplastic thyroid cancers (ATCs), the prognosis is poor with no effective treatment available. Although much progress has been made in understanding the molecular mechanisms of thyroid cancer in the past 5 to 10 years, as demonstrated by the elucidation of the role the MAPK and PI3K–AKT pathways play in differentiated thyroid cancer (2). Mutations in these two key signaling pathways, in genes such as \( RAS \), \( BRAF \), \( PI3KCA \), and \( PTEN \), account for 65% to 70% of DTCs (2). In this issue of the Journal, Liu and colleagues add to our current understanding of thyroid tumorigenesis by providing a compelling study of how alternative RAS signaling–related genes impact on thyroid tumorigenesis (3).

Compared with normal human thyroid tissue, the RAS GTPase-activating protein (RasGAP) gene, \( RASAL1 \), was commonly silenced in the thyroid cell lines surveyed, with consistently low mRNA and protein expression. Previous studies have shown that promoter hypermethylation in tumor suppressor genes (eg, \( PTEN \), \( RASSF1A \)) is common in thyroid cancer (4–9), and again aberrant hypermethylation in the promoter region of \( RASAL1 \) was likewise associated with thyroid cancer cell lines and with primary thyroid cancers when compared with matched normal thyroid tissues here. Importantly, \( RASAL1 \) hypermethylation appears to be seen in predominantly in FTC and ATC compared with PTC and benign thyroid tumors. Sequence analysis of primary thyroid cancer samples for mutations in \( RASAL1 \) identified mutations in approximately 17% of ATCs, 5% of FTCs, and 3% of PTCs, but not in benign thyroid tumors. All of the mutations were located in the RAS GTPase-activating domain of \( RASAL1 \), with six of seven of the missense mutations located at highly conserved sites, and