BRAF Mutation Flags Aggressive Thyroid Cancer

BY BRUCE JANCIN
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COLORADO SPRINGS — Papillary thyroid cancers positive for the BRAF V600E mutation behave markedly more aggressively than those that aren't, Dr. Electron Kebebew said at the annual meeting of the American Surgical Association.

"Future testing for this mutation could help us select how extensive our initial surgery should be, an appropriate adjuvant therapy, and how closely we monitor these patients in follow-up," added Dr. Kebebew of the University of California, San Francisco.

The incidence of thyroid cancer has nearly doubled during the past 3 decades. Most of this increase involves small papillary thyroid cancers, many of which are occult and detected only incidentally. Today papillary thyroid cancer accounts for roughly 85% of all thyroid cancers. Some series of occult papillary thyroid cancers less than 1.5 cm in size show a recurrence rate of less than 6% and near-normal life expectancy. But buried within the large group of generally favorable-prognosis papillary thyroid cancers is a subset that behaves aggressively.

The V600E missense mutation located on exon 15 of the BRAF gene—the most potent mitogen-activating gene—might have a valuable role in sorting out this higher-risk subset. The mutation occurs commonly in patients with anaplastic thyroid cancer, which is almost uniformly lethal.

To determine whether the BRAF mutation predicts tumor aggressiveness, Dr. Kebebew reported on 347 tumor samples obtained from 314 patients with thyroid cancer. A total of 212 had classic or usual papillary thyroid cancer histologically, 29 had the follicular variant of papillary thyroid cancer, and 73 had follicular thyroid cancer. Most of the patients were in their fifties. Their tumors averaged slightly less than 3 cm in size. Most were well differentiated. Roughly one-third of the tumors were multicentric, one-quarter entailed extrathyroidal invasion, and one-third involved lymph node metastases. However, just four patients had distant metastases. More than 80% had stage I or II disease. Thirteen percent of subjects had high-risk thyroid cancer by the AMES (age, distant metastases, extent, and size of tumor) criteria.

The prevalence of the BRAF V600E mutation was 51% in those with classic papillary thyroid cancer, 24% in patients with the follicular variant, and just 1% in those with follicular thyroid cancer.

In a multivariate analysis, there were only two independent predictors of recurrent or persistent disease at a mean follow-up of 6 years: lymph node metastases, which conferred a 7.7-fold increased risk; and BRAF V600E–positive status of the primary tumor, which was associated with a 4.2-fold increased risk. Even when the analysis was restricted to the subgroup of patients with stage I localized disease and low-risk status by the AMES criteria, the BRAF mutation was associated with a highly significant nearly 2.5-fold increased risk of persistent or recurrent disease.

An intriguing finding was that 5 of 32 patients with lymph node metastases had discordance with regard to BRAF mutation status. That is, while 13 patients had the BRAF V600E mutation in both their primary tumor and nodal metastases and 14 didn't have the mutation at either site, there were 3 patients who were primary tumor mutation positive but lymph node negative and 2 others who were primary tumor negative but lymph node positive. A possible explanation for this, said Dr. Kebebew, lies in the observation by other researchers that about one-third of multicentric papillary thyroid cancers are heterogenous with regard to BRAF V600E; that is, one portion of the primary tumor is mutation positive while the other is negative.

Discussant Dr. Richard A. Prinz, professor and chairman of surgery at Rush University Medical Center, Chicago, asked if BRAF mutation testing is likely to make any real difference to clinical practice given that many surgeons are moving toward more liberal use of total thyroidectomy and some endocrinologists already are using adjuvant radioiodine in almost all patients.

Dr. Kebebew replied that although this approach may be gaining some popularity, that's not necessarily the case elsewhere. Indeed, some surgeons have suggested observation might be an appropriate approach to small papillary thyroid cancers. BRAF mutation testing could be extremely useful in refining such a strategy. It could be argued that mutation-positive patients are candidates not for watchful waiting, but for total thyroidectomy and prophylactic central lymph node dissection, followed by adjuvant radioiodine and more frequent follow-up. ■

POINT/COUNTERPOINT

Can the course of low-risk thyroid cancer be accurately predicted?

Scoring schemes can be used to predict the course.

Papillary thyroid cancers represent around 80% of all thyroid cancers seen in doctors' offices, and most present when they are small (a median 1.7 cm in diameter) and unlikely to have gross extrathyroid invasion (less than 1.5%).

Forty percent of patients will have positive regional lymph nodes, whereas only 2% will have distant metastasis. This is in contrast to follicular thyroid cancer, the next most common type, which is found in older patients who often have larger tumors (average of 3.5 cm), and that has a 25-year mortality rate that is six times higher.


IAN D. HAY, M.D.

At the Mayo Clinic, we have used our database of 2,512 papillary thyroid cancer patients treated since 1940 to evaluate the different thyroid cancer scoring schemes and have found that all perform fairly similarly and do fairly well at predicting prognosis.

Since 1994, we have used the MACIS [metastasis, age, completeness, invasive, size] score we developed, where a score of 6 is the cutoff between high and low risk. We have reported that 84% of the 2,512 patients were low risk according to the MACIS score, and their mortality rate at 20 years was less than 1%. In contrast, patients with a score higher than 6 had a 32% mortality rate.

So I think we can predict who can be treated conservatively with surgery and thyroid hormone suppression, and who needs more advanced treatment.

Most papillary thyroid cancers are bilateral and many have positive regional nodes, so at Mayo, normal treatment is bilateral lobar resection with evaluation of the nodes. We have reported that, compared with lobectomy, this procedure decreases the recurrence rate in low-risk patients from 25% to 5%, though mortality stays the same. In high-risk patients, this procedure reduces recurrence by two-thirds and halves mortality.

We do not believe in using indiscriminate radioiodine remnant ablation. In 1,163 of our low-risk patients, of whom 43% had remnant ablation, we found a mortality of 0.6% at 20 years out with ablation and of 0.4% without ablation. And we still found no difference in recurrence or mortality when we stratified the patients according to nodal status.

At Mayo, we ablate only patients with a MACIS score of 6 or above and those with follicular cell–derived cancers. We follow low-risk patients with ultrasound surveillance, and when we find a nodal metastasis, we use ultrasound-guided alcohol injection to ablate the specific node. We are concerned about the use of radioiodine ablation when it is not necessary, and we think it shouldn't be used in low-risk patients. ■

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It's difficult to predict the course of low-risk disease.

A review of almost 54,000 cases of thyroid cancer treated between 1985 and 1995, showed the 10-year survival rate for cases of papillary thyroid cancer is 93%. But because papillary thyroid cancer makes up such a preponderance of thyroid cancer cases, that 7% mortality rate made up 53% of all the thyroid cancer deaths.

The 7% mortality reported in that review represents the experience across the nation. It is more than twice the 2% rate noted by the Mayo Clinic investigators, and therein lies part of the rub. There are institutional differences, probably for many reasons, and the experience of one place may not be reflectively translatable to all institutions.


ERNEST L. MAZZAFERRI, M.D.

Since 1973, there has been a 2.4-fold rise in thyroid cancer, and almost all of that increase has been in small papillary cancers. For women, mortality has been falling significantly over this period. For men, it has been rising by 2% a year between 1992 and 2000.

The 7% mortality rate, and the fact that mortality is increasing in men, suggests that low-risk is not zero risk. And we cannot reliably predict who is low risk.

Most importantly, no staging scheme has been able to show that it accurately predicts low-risk cancers or survival. Investigators such as Dr. James Brierley of the University of Toronto have taken the various staging schemes, including the AMES (age, metastasis, extent, and size) system, the AGES (age, grade, extent, and size) system, and the MACIS system, and tried to determine how prognostic they are. Dr. Brierley found that for any of the six schemes he examined, about 80% of deaths are not predicted by staging. Others have found staging systems even less predictive of prognosis.

The staging systems are imperfect partly because thyroid cancer is unpredictable. In a Mayo study by Dr. Hay, of 535 patients with thyroid papillary microcarcinoma, median tumor size was 8 mm in diameter. But 32% of the patients had nodal metastasis, 20% had multifocal disease, and two patients died from their thyroid cancer. In those with positive lymph nodes, the recurrence rate at 30 years was 18%.

There may be low-risk thyroid cancers, but low-risk is not synonymous with no risk. Thus, the only papillary thyroid cancers that might require less therapy are those in patients with no family history, no other thyroid cancer–related diseases, and no history of radiation treatment. In addition, the patient should be younger than 45 years old, have only one primary tumor less than 1 cm with classic histology, and have no invasion or metastasis beyond the thyroid capsule. ■

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