Ann Surg Oncol (2012) 19:1–2
DOI 10.1245/s10434-011-2098-0

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL

Bilaterality in Papillary Thyroid Carcinoma: Does It Influence Prognosis?

Jason D. Prescott, MD, PhD and Sareh Parangi, MD

Thyroid Cancer Research Lab., Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Papillary carcinoma is the most prevalent thyroid tumor subtype, and the incidence of this variant is rising in developed countries.[1] The majority of papillary thyroid cancers (PTC) are indolent, and 5-year survival among those patients receiving appropriate surgical and medical therapy is greater than 95%. Nonetheless, a subgroup of PTCs will behave aggressively, and these tumors are associated with poorer overall and disease-free survival. Identification of specific disease characteristics correlating with prognosis has therefore become an important goal, both in understanding PTC biology and in directing therapeutic intervention. Historically, prognostic variables have included age, histopathological subtype, larger tumor size, and presence of extrathyroidal extension/metastasis.[1,2] Multifocality is also an important feature of PTC. Multifocal disease is common, being identified in 38% of micropapillary carcinoma cases, and is associated with tumor recurrence. The American Thyroid Association recommends using "clinical judgment" when considering whether radioactive iodine ablation (RAI) should be used to treat multifocal PTC, especially in light of recent studies showing that, for microscopic multifocal PTC, RAI does not improve recurrence rates.[2,3] In addition, significant interest has recently developed in ascertaining the relationship between PTC prognosis and the presence of mutations in *BRAF*, a tyrosine kinase-encoding protooncogene commonly mutated in PTC cells.[4–6]

In this edition of *The Annals of Surgical Oncology*, Wang and colleagues consider whether bilaterality should be considered a new, potentially important prognostic feature of PTC. Interestingly, though both multifocality and bilaterality in PTC are traditionally considered indications for total or near-total thyroidectomy, few data specifically examining the prognostic implications of bilateral disease have been reported.[7,8] In their manuscript "Poorer prognosis and higher prevalence of $BRAF^{V600E}$ mutation in synchronous bilateral papillary thyroid cancer," Wang and colleagues detail the first formal evaluation of the relationship between bilaterality and prognosis in 891 PTC patients treated with total or near-total thyroidectomy over a 9-year period who were retrospectively identified. Bilateral synchronous PTC was defined as cancer diagnosed in both thyroid lobes at the same time or within a period of 3 months following removal of the first tumor. The authors found that bilateral PTC is common, occurring in 19.9% of their cohort, and that bilaterality is associated with poorer prognosis. Increased rates of extrathyroidal extension, nodal metastasis, as well as an overall higher stage at presentation were associated with bilateral disease. Further, these findings correlated with disease-free and overall survival, both of which decreased in the context of bilateral disease. Taken together, Wang and colleagues' findings suggest that bilaterality is an important feature of PTC biology that may improve the clinician's ability to predict the behavior of these tumors.

Because mutation of the *BRAF* protooncogene is now recognized as a common genetic aberrancy contributing to the pathophysiology of PTC, evaluation for *BRAF* mutation may also be important in assessing the prognostic relevance of disease bilaterality. As such, the authors were able to assay *BRAF* gene sequences obtained from 208 consecutive patients, identifying a statistically significant increase in the prevalence of *BRAF* protooncogene mutations in bilateral versus unilateral cases (65.7 vs. 50.4%, $P = 0.038$). Nonetheless, these data must be interpreted

Published Online: 29 September 2011

S. Parangi, MD
e-mail: sparangi@partners.org

carefully, as mutation of the *BRAF* protooncogene in the bilateral disease cohort did not correlate with other known prognostic features of PTC, including tumor size and extrathyroidal extension.

The identification of tumor features associated with poor prognosis plays an important role in defining the pathophysiology of cancer and provides insight into the clinical management of malignancy. Here, Wang and colleagues provide initial data suggesting that disease bilaterality confers poor prognosis among patients diagnosed with PTC. Although data describing the prognostic relevance of multifocal PTC have been previously reported, this study represents the first published report to examine the prognostic relevance of bilateral disease. Potentially important correlations between disease bilaterality and tumor size, *BRAF* protooncogene mutation, extrathyroidal extension, and metastasis are supported by the authors' findings. Future studies should be done prospectively, should detail tumor sizes in each lobe, and should normalize the performance and extent of neck dissection, as well as the use of postoperative ^{131}I therapy. Analysis of histopathological subtypes among PTC patients having bilateral disease, relative to unilateral cases, may also provide insight into the prognostic value of bilaterality. Although Wang and colleagues provide an interesting initial study of the significance of bilateral disease in cases of papillary thyroid carcinoma, additional data will be required to validate bilaterality as an independent predictor of disease prognosis.

REFERENCES

1. Cramer JD, Fu P, Harth KC, Margevicius S, Wilhelm SM. Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results national cancer data registry. *Surgery.* 2010;148:1147–52; discussion 1152–43.
2. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2009;19:1167–214.
3. Ross DS, Litofsky D, Ain KB, Bigos T, Brierley JD, Cooper DS, et al. Recurrence after treatment of micropapillary thyroid cancer. *Thyroid.* 2009;19:1043–8.
4. Xing M. Prognostic utility of BRAF mutation in papillary thyroid cancer. *Mol Cell Endocrinol.* 2010;321:86–93.
5. Kebebew E, Weng J, Bauer J, Ranvier G, Clark OH, Duh QY, et al. The prevalence and prognostic value of BRAF mutation in thyroid cancer. *Ann Surg.* 2007;246:466–70; discussion 470–1.
6. Elisei R, Ugolini C, Viola D, Lupi C, Biagini A, Giannini R, et al. BRAF(V600E) mutation and outcome of patients with papillary thyroid carcinoma: a 15-year median follow-up study. *J Clin Endocrinol Metab.* 2008;93:3943–9.
7. Pellegriti G, Scollo C, Lumera G, Regalbuto C, Vigneri R, Belfiore A. Clinical behavior and outcome of papillary thyroid cancers smaller than 1.5 cm in diameter: study of 299 cases. *J Clin Endocrinol Metab.* 2004;89:3713–20.
8. Clark OH, Levin K, Zeng QH, Greenspan FS, Siperstein A. Thyroid cancer: the case for total thyroidectomy. *Eur J Cancer Clin Oncol.* 1988;24:305–13.