Predicting Outcome and Directing Therapy for Papillary Thyroid Carcinoma

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Hypothesis: The prognosis of papillary thyroid carcinoma has been stratified into low- and high-risk groups. Patients in the high-risk group can be substratified on the basis of increasing age, with implications for prognosis and treatment.

Design: Retrospective study.

Setting: Tertiary care center.

Patients: A total of 727 patients with papillary thyroid cancer treated at Lahey Clinic, Burlington, Mass, from 1940 to 1998.

Interventions: Stratification into low- and high-risk groups based on age, metastases, extent, and size. High-risk patients were substratified into “younger” and “older” high-risk groups by age younger than 60 years or 60 years and older, respectively. Effects of surgery, lymph node dissection, and radiation therapy were examined.

Main Outcome Measure: Survival.

Results: Of the 727 patients, 585 (80.5%) were classified as low risk and 142 (19.5%) as high risk. The 20-year survival was 97.8% in low-risk patients and 61.3% in high-risk patients ($P<.001$); it was 72.3% in the younger high-risk group and 45.1% in the older high-risk group ($P<.001$). Older high-risk patients had a survival advantage with bilateral thyroidectomy: 54.7% 20-year survival for those undergoing bilateral thyroidectomy and 25.0% for unilateral thyroidectomy ($P=.004$). In the older high-risk group, patients with lymph node dissection ($n=22$) had a 20-year survival of 72.4% vs 30.2% in patients who did not undergo lymph node dissection ($n=38$) ($P=.03$). Twenty-year survival in low-risk, younger high-risk, and older high-risk patients receiving radioactive iodine vs no radiation was 100% vs 97.6% ($P=.24$), 64.2% vs 73.2% ($P=.53$), and 44.7% vs 44.4% ($P=.53$).

Conclusions: Papillary thyroid carcinoma in low-risk patients had a favorable prognosis regardless of treatment. Older high-risk patients had a survival benefit with total thyroidectomy and lymph node dissection. Radioactive iodine did not affect 20-year survival in any of the risk groups.

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Although most patients with papillary thyroid carcinoma have a favorable prognosis, ideal surgical management of this well-differentiated thyroid cancer remains controversial. Scoring systems have been developed to distinguish patients with favorable outcomes (low-risk patients) from those with poor outcomes (high-risk patients). Application of these prognostic criteria allows optimal surgical treatment to be planned according to risk classification. The Lahey Clinic, Burlington, Mass, previously published reports on treatment outcomes of well-differentiated thyroid carcinoma, but papillary thyroid carcinoma has not been examined independently with the application of a system of prognostic criteria: age and sex, presence of metastases, extent of disease, and size of tumor (AMES). In this study, the prognosis of patients with papillary thyroid carcinoma was examined and a further substratification of high-risk patients based on age was developed, with implications for treatment.

METHODS

In 1990 the Lahey Clinic thyroid cancer registry was transformed into a formal database. Additional information gathered by medical record review and direct patient contact was entered into the database. Patients were categorized according to age and sex, pathology of tumor, presence of metastases, extent of tumor, size, and nodal involvement. Nine hundred sixty-three cases of thyroid carcinoma...
were registered from 1940 to 1998. Of these cases, 727 patients were diagnosed as having papillary thyroid carcinoma.

The AMES prognostic criteria were used to stratify patients with papillary thyroid carcinoma into high- and low-risk groups. The low-risk group included women younger than 51 years and men younger than 41 years with no distant metastasis. Also included in this group were older patients with favorable tumors smaller than 5 cm and no extrathyroidal extension of tumor. The high-risk patient group included all patients with metastatic disease, women aged 51 years or older, and men aged 41 years and older with tumors greater than or equal to 5 cm or with extrathyroidal extension. High-risk patients were further categorized into 2 groups based on age: younger than 60 years, or 60 years and older.

Because many surgeons were involved in the care of these patients, treatment varied during the 58-year period. The operation performed was not based on a treatment protocol, but rather on the preference of the individual surgeon. The effect of surgery, lymph node dissection, and radioactive iodine on survival was examined. The extent of surgical treatment was divided into 2 main groups: ipsilateral lobectomy and bilateral lobectomy. This latter bilateral group included patients with both ipsilateral total and contralateral subtotal thyroidectomy, patients with bilateral subtotal thyroidectomy, and patients with total thyroidectomy.

Kaplan-Meier analysis was used to develop survival curves based on death as a result of disease. Comparisons between cohorts were made by log-rank analysis. P < .05 was considered statistically significant.

## RESULTS

Between 1940 and 1998, 727 patients were treated for papillary thyroid carcinoma. Of these patients, 546 (75%) were female and 181 (25%) were male. The median age was 41.8 years. For patients treated between 1940 and 1960, 1960 and 1980, and 1980 and later, the median follow-up was 19.96, 14.72, and 7.56 years, respectively. Median aggregate follow-up was 14.5 years.

With the use of the AMES prognostic criteria, 585 patients (80.5%) were defined as low-risk patients and 142 (19.5%) as high-risk patients. Overall 20-year survival for the low-risk group was 97.8%, and that of the entire high-risk group was 61.3% (P < .001) (Figure 1A). Of these high-risk patients, 60 (42.3%, or 8.3% of total) were subcategorized into the older high-risk group and 82 (57.7%, or 11.3% of the total) into the younger high-risk group. Further analysis of the high-risk group showed that patients younger than 60 years had a 20-year survival of 72.3% vs only 45.1% in the older high-risk group (P < .001) (Figure 1B).

### EXTENT OF SURGERY

Extent of surgery was defined as unilateral thyroidectomy or bilateral thyroidectomy. Of the low-risk group, 126 patients (21.5%) had a unilateral thyroidectomy and 452 patients (77.3%) underwent bilateral thyroidectomy. The remaining 7 patients had excision of tumor alone and were excluded from this study. There was no significant difference in 20-year survival in low-risk patients undergoing unilateral vs bilateral thyroidectomy: 97.2% vs 100%, respectively (P = .20) (Figure 2A).

There was no significant survival difference between unilateral (n = 39) vs bilateral (n = 103) thyroidectomy in the total high-risk group (P = .93). When the younger high-risk group was examined (age < 60 years) (n = 82), there was no significant 20-year survival difference between unilateral (n = 21) and bilateral (n = 61) thyroidectomy: 70.2% vs 79.9%, respectively (P = .70) (Figure 2B). In the older high-risk group, patients 60 years old or older (n = 60), 42 patients underwent bilateral thyroidectomy. The 20-year survival was 54.7%. For patients who underwent a unilateral thyroidectomy (n = 18), the 20-year survival was only 25.0% (Figure 2C). This was statistically significant (P = .004).

### LYMPH NODE DISSECTION

In the low-risk group, 212 patients (36.0%) had a lymph node dissection and 369 (64.0%) did not. In 4 patients, data were not available on whether lymph node dissection was performed. The 20-year survival for patients who had a lymph node dissection and those who did not was 96.9% and 98.6%, respectively. Lymph node dissection did not have a statistically significant effect on 20-year survival in the low-risk group (P = .47). Forty-eight patients in the younger high-risk group did not have a lymph node dissection and 33 did have a lymph node dissection. Data were not available on whether lymph node dissection was performed for 1 patient. Twenty-year sur-

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survival was 72.0% and 74.0%, respectively. This was not statistically significant \( (P = .64) \). In the older high-risk group, patients who underwent lymph node dissection \( (n=22) \) had a 20-year survival of 72.4%. Patients who did not undergo lymph node dissection \( (n=38) \) had a 20-year survival of 30.2%. This was found to be statistically significant \( (P = .03) \) (Figure 3).

**Radioactive Iodine**

Radioactive iodine did not appear to have a clear effect on patients in any risk group. Within the low-risk group, 20-year survival was 100% and 97.6% for patients who received \( (n=112) \) and did not receive \( (n=468) \) radioactive iodine, respectively \( (P = .24) \). Adjuvant use of radioactive iodine was not specified in records of 5 patients. In the younger high-risk group, 20-year survival was 64.2% for those who received \( (n=13) \) and 73.2% for those who did not receive \( (n=69) \) radioactive iodine \( (P = .53) \). In the older high-risk group, results were almost identical, with a 20-year survival of 44.7% in those who received \( (n=10) \) vs 44.4% in those who did not receive \( (n=50) \) radioactive iodine \( (P = .53) \).

**Comment**

Although thyroid nodules are commonly seen in clinical practice, thyroid carcinoma is a relatively rare entity, accounting for less than 1% of all cancers. Eighty percent of all differentiated carcinomas of the thyroid are papillary carcinoma. Several retrospective studies have reported excellent 5-, 10-, and 30-year mortality rates of 3%, 6%, and 8%, respectively. \(^3\)\(^-\)\(^5\).

In 1988, Cady and Rossi\(^1\) reported on a clinical categorization of patients with differentiated thyroid cancers. Patients were retrospectively stratified into high- and low-risk groups by means of the AMES criteria. Their results have been reproduced in numerous studies with modifications in classifications based on tumor grade and residual tumor after resection. The AMES, AGES (age, grade, extent of tumor, size), and MACIS (distant metastasis, patient age, completeness of resection, local invasion, tumor size) were consistent in predicting outcomes for high- and low-risk patients with thyroid carcinoma.\(^6\)

This study used the AMES criteria to stratify patients with papillary thyroid carcinoma into low- and high-risk groups. Patients in the high-risk group were stratified by age into a younger high-risk group (aged younger than 60 years) and an older high-risk group (aged...
60 years and older). This allowed for critical examination of high-risk patients who might benefit from a more aggressive treatment.

Bilateral thyroidectomy has not been shown to improve survival in “low-risk” patients with well-differentiated thyroid carcinoma. Published therapeutic guidelines state that unilateral thyroidectomy may be appropriate in minimal papillary carcinomas (less than 1-1.5 cm, intralobar, unifocal). Ultimately, however, total or subtotal thyroidectomy is performed for the following reasons: the multifocality of papillary thyroid carcinoma, the ability to use postoperative iodine 131 for ablation and identification of residual tumor, and the ability to use thyroglobulin as a postoperative tumor marker.

Low-risk patients had an excellent prognosis, with a 20-year adjusted survival of 97.8%. Survival for these patients did not appear to be affected by extent of surgery, performance of a lymph node dissection, or the use of radioactive iodine. Previous studies support the finding that extent of surgery and radioactive iodine do not affect outcomes in patients with an already minimal risk of death from papillary thyroid carcinoma.

A definitive survival benefit was identified when the high-risk group was substratified into younger and older high-risk groups. Our study demonstrates that survival rates for the younger high-risk group were almost double those of the older high-risk group. In the younger high-risk group, extent of surgery and lymph node dissection did not affect adjusted 20-year survival rates. Radioactive iodine did not appear to have an effect on either high-risk group; however, the significance of this is unclear, as the number of patients undergoing treatment with radioactive iodine was small.

Bilateral thyroidectomy, however, dramatically improved outcomes in the older high-risk patient group. Age is a well-defined risk factor for papillary thyroid carcinoma, and in this study we demonstrated that older high-risk patients have a worse prognosis than younger high-risk patients. Furthermore, older high-risk patients who underwent lymph node dissection had better outcomes than those who did not.

**CONCLUSIONS**

Our findings support those of earlier studies that examined the outcomes of low-risk patients: these patients did extremely well regardless of treatment modality. Extent of surgery, lymph node dissection, and radioactive iodine for ablation had no effect on survival for this group. There was also no improvement seen in the younger high-risk group.

In this study we identified one group of patients who showed definite improved survival advantage with bilateral thyroidectomy and lymph node dissection. High-risk patients aged 60 years and older with tumors 5 cm or more or with extrathyroidal extension demonstrated improved survival with total thyroidectomy and lymph node dissection.

**REFERENCES**


**DISCUSSION**

Blake Cady, MD, Providence, RI: I obviously have a conflict of interest. The original AMES group applied to both papillary and follicular, and I guess one of the questions I have is, have you looked at the follicular lesions?

A critical feature of surgical oncology is separating risk groups so that therapy can be modified and low-risk groups that can receive minimal therapy. The authors reaffirm this in thyroid cancer. It seems to me the future in oncology management is sophisticated separation by multiple gene analysis. This has recently been demonstrated in the New England Journal by a 70-gene array in breast cancer that separated low-risk from high-risk patients regardless of standard classification such as size, lymph node analysis, and so on. It seems to me this is the kind of thing that is going to make a difference in not only breast cancer but other cancers as we get more sophisticated in genetic analysis.

The issue is, can we find this genetic difference in thyroid cancer, and there is some early work that has been published over the past decade that shows some independent gene analyses that do relate to various features that are partly defined by the low-risk group here? The most notable example of this is p53, which is uniformly found in anaplastic thyroid cancer arising from the same follicular cell as papillary cancer and follicular cancer. That’s a hint that genetic analysis, sophisticated

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They did, how you dealt with those patients. Patients had substernal goiters or tumors, and I am wondering if there weren’t some other things that may have played a role in their survival. Are going to be 80 by the end of that 20 years and I am wondering if there were things that I wondered about. First of all, in a group of people who are 60 for the cutoff point, for them to live 20 years, they probably the more favorable patients were picked for a node dissection and therefore that would lead to your results.

One last comment would be that I have always said over a number of years that any high-risk patient ought to have a total thyroidectomy since the disease seems to always require radioactive iodine use. Your data seem to support that there is no justification for doing a routine total thyroidectomy in the lower high-risk group. I think this is a wonderful paper because it supports all my biases and of course that is the greatest accomplishment of all.

Francis D. Moore, MD, Boston, Mass: I congratulate you for bringing your data back into conformity with this longstanding series that we have been seeing on and off for years, and just to reiterate the great service this series really did, which was pointing out that patients did not necessarily need total thyroidectomy, massive lymph node dissections, deforming and morbidity surgery for papillary cancer.

My concern with the series is actually when you start to show differences between the curves, because this series at this point extends back some 60 years through different surgeons. To make any statistical comparison of these curves, you have to make the assumption that these surgeries were being randomly picked for each patient. However, it is actually possible that your surgeons were absolutely superb in picking out the patients who needed more surgery and more treatment and were able to bring up higher-risk patients to the same survival. So, I’m concerned that when you go back retrospectively without knowing how the patients were chosen for surgery, can you actually make any statistical comparison? Thank you.

William A. Cook, MD, North Andover, Mass: There are 2 things that I wondered about. First of all, in a group of people who are 60 for the cutoff point, for them to live 20 years, they are going to be 80 by the end of that 20 years and I am wondering if there weren’t some other things that may have played a role in their survival.

Secondly, you did allude to the fact that many of these patients had substernal goiters or tumors, and I am wondering if they did, how you dealt with those patients.

Harold Wanebo, MD, Providence: This is a very nice presentation and it is interesting that you recapitulated previous criteria. One of the simplest questions is, what does age have to do with this? Why is it when you get to be older, and I guess that age 60 looks like a benchmark, why do things seem to go so bad with that group? I guess you could look at this because you actually have the data. In the patients who had the bilateral thyroidectomies compared to the unilateral group, as you increase in age, is there an increase in the amount of disease in the contralateral gland? I don’t know what the incidence is, but I guess it must be around 20%. If you do a unilateral thyroid, remove that tumor and that’s the main site of the tumor, about 20% of the opposite gland I presume has disease, not 100%, and so the question is, in older patients, do they just have a larger amount of disease in the contralateral gland?

The second thing is, in your data set, what is the reason for lymph node dissection? I would presume that most of these patients actually had palpable nodes and so the ones that had no palpable nodes had no dissection. We had a much smaller data set, which obviously is nothing like what you have, but it seemed that the patients with node dissection did just as well—I mean with nodal disease—did just as well as those without nodal disease, and I think others have shown this. Is it just an indicator?

Lastly, I think your data is very good in that the question about the use of radioactive iodine, especially in the good-risk patients, may be a waste of time. Maybe we should stop doing this in the good-risk or low-risk patients.

Dr Kim: Starting off with Dr Cady’s question: First, we did not look at follicular cancer separately. This study certainly confirms what Dr Cady has said regarding dividing patients with papillary thyroid cancer into high-risk and low-risk categories. This study confirms that an extensive procedure is not needed in those low-risk patients who will do well regardless of whether they have a unilateral vs bilateral thyroidectomy. The benefit of total thyroidectomy is mainly seen in older high-risk patients with papillary thyroid cancer.

What does age have to do with it? Age is definitely a marker for a worse prognosis. It has been hypothesized that perhaps patients who present at an older age have an entirely different disease process. A genetic analysis of their tumors might demonstrate different mutations producing thyroid malignancies with different prognoses in younger vs older patients.

The prognosis of patients with papillary carcinoma arising in substernal goiters was not examined separately.

In terms of lymph node dissection, most of these lymph node dissections were performed for palpable nodal disease. I think that the lymph node dissection may have helped in those high-risk patients in whom local disease was controlled by removing all of the lymph nodes.