

The Papillary Microcarcinoma Epidemic: Ignore, Observe, or Treat?

M9

Saturday, June 15

3:00–3:45 PM & 5:45–6:30 PM

Douglas Ross, MS, MD

Massachusetts General Hospital

Boston, MA

dross@partners.org

SIGNIFICANCE OF THE CLINICAL PROBLEM

Micropapillary cancers are defined as papillary cancers 10 mm or less. They represent an increasing percentage of all patients with thyroid cancer. A full understanding of their natural history is essential to prevent overzealous treatment and associated complications.

Autopsy studies:

Up to a 13% prevalence in the United States (average 6%)

Up to a 36% prevalence in Europe (Finland)

Not significantly dependent on age

7% under age 50 or over age 80 in Sweden

3% in young adults in Wisconsin

Incidental finding at time of thyroid surgery
2-24%

Increasing papillary cancer incidence in the United States (all sizes), especially women
4.85 / 100,000 in 1975

11.99 / 100,000 in 2007

Percentage of micropapillary cancers among all papillary cancers excised

5 % 1960-1980 Queen Elizabeth Hospital, Hong Kong

22 % 1991-2000 Queen Elizabeth Hospital, Hong Kong

40 % 2006 University Ferrara, Italy

43 % 2006 University Wisconsin, US

50 % 2008 Jewish General, Montreal, Canada

BARRIERS TO OPTIMAL PRACTICE

- Cancer phobia
- Overzealous treatments
- Case reports that demonstrate the exception, rather than the rule

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

1. Appreciate the natural history of papillary microcarcinoma
2. Formulate a rational approach for surgery and adjunctive radioiodine

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Scope of the Problem

- US population is over 300 million
- 6 % prevalence of micropapillary cancer in the US = 18 million people
- Prevalence of all sizes of papillary cancer in 2007 = 434,256 (SEER database)
- Therefore only 2.5 % of micropapillary cancers have come to clinical attention!
- Improved imaging and diagnostics will allow us to find the rest of them?
- Observational Trial (Ito et al, Japan)
340 of 1395 patients with biopsy-proven micropapillary cancer agreed to observation
- Exclusion criteria: tumors adjacent to trachea or possibly adjacent to the nerve (posterior), tumors associated with lateral nodes, high grade histology 28 % were multifocal and 9 % had suspicious central nodes on ultrasound
- With up to 10 years of follow-up (mean 74 months), over 60 % did not grow, and over 10 % regressed. 9% grew to >10 mm, 9% grew by 3 mm, and 2% developed lateral nodes.
- No difference in outcomes among those patients having surgery at diagnosis, and those in whom surgery was delayed.

- Data support concept of avoiding FNA in subcentimetric nodules (even suspicious nodules) under 10 mm.

Clinical Series

Mayo Clinic: average follow-up 17 years (6 to 89 years)

- Multifocal 23 %
- Bilateral 17 %
- Extrathyroidal 2 %
- Nodal involvement 30 %
- Distant metastases 0.3 %
- 40-year disease specific mortality 0.7 %
- all three patients who died had lymphadenopathy, massive in one
- one had pulmonary metastases on presentation
- recurrence rate: 8 %
 - 1.5 % in thyroid bed, the rest in nodes
 - 0.8 % if no nodes at presentation and 16 % of patients with nodes at presentation
 - 11 % in patients with multifocal disease, 4% in those with unifocal tumors

Noguchi Thyroid Clinic: average follow-up 15 years

- 0.2 % distant metastases
- 3.5 % recurrent disease
- recurrence more likely if tumor >5mm, nodal disease, or extrathyroidal invasion

Queen Elizabeth Hospital, Hong Kong

- 1 % pulmonary metastases and death
- 5 % nodal recurrences
- 1 % recurrence in the bed
- recurrence risk increased 6.2 times if nodes present initially and 5.6 times when multifocal

Asan Medical Center, Seoul, Korea

- 4.8 % recurrence
- no deaths reported, but one patient (0.3 %) with progressive disease

Yonsei University, Seoul, Korea

- 24 % central nodes
- 4 % lateral nodes

Initial Surgery

National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG)

- 6.2 % recurrence, 38 % multifocal
- patients who had less than a total thyroidectomy
- recurrence rates
 - multifocal disease 18 %, unifocal disease 4 %
 - patients with multifocal disease
 - total thyroidectomy 6 %, less than a total thyroidectomy 18 %

SEER database 1988 to 2005

- 99.9 % 15-year disease-free survival regardless of total versus lobectomy

Completion Thyroidectomy

No data. Assess contra-lateral lobe with ultrasound.

Node Dissection

Therapeutic—if nodes detected on pre-op imaging

Prophylactic?

One study (Wada et al) compared three groups for recurrence:

- Therapeutic n=24 recurrence rate 21 %
- Prophylactic n=235 recurrence rate 0.4 %
- None (incidental) n=155 recurrence rate 0.7 %

Argument A

If you do a central node dissection and nodal disease is detected the patient will benefit from radioiodine (but see below)

Argument B

If you do a central node dissection, you have removed potentially persistent disease and the patient does not need radioiodine.

- Ito et al: stage I papillary thyroid cancer
- 96 % had central node dissection
- 57 % positive nodes
- 0.1 % had radioiodine
- recurrence rates 2 % after a mean 91 months (range 6 to 240 months)
- Benefit: recurrence rate falls from 6 to 2 %
- Risks: increased hypoparathyroidism and recurrent laryngeal nerve injury
- Reserve central node dissection for those with central node recurrences
- Radioiodine

NTCTCSG

- Recurrence was higher in multifocal (7 %) versus unifocal (2 %) disease
- Radioiodine did not reduce recurrence rates in multifocal disease
- Radioiodine did not reduce recurrence rates in patients with positive nodes

Mayo Clinic

- Radioiodine did not alter recurrence in patients with node-negative disease
- Recurrence was increased in patients with node-positive disease who received radioiodine

SEER Database (1998 to 2005)

- 99.9 % 15-year disease-free survival regardless of the use of radioiodine

MAIN CONCLUSIONS

Since observed micropapillary cancers demonstrate indolent growth over many years, routine biopsy of subcentimetric thyroid nodules should be discouraged.

Where high-volume thyroid surgeons are available, a total thyroidectomy is the surgical treatment of choice for micropapillary cancer due to the high incidence of multifocality, and a reduction in recurrence rates with more extensive surgery.

The complications associated with prophylactic central node dissection may exceed the benefit of this procedure.

Radioiodine is rarely indicated for treatment of micropapillary cancer.

CASES WITH QUESTIONS**Case 1**

28 year-old woman felt something in her throat. Ultrasound—8 mm hypoechoic nodule with microcalcifications.

Questions

1. *Should she have an FNA?*
2. *FNA was suspicious for papillary cancer. Should she have BRAF?*
3. *There were no nodes seen on her ultrasound. What surgery should she have?*
4. *Pathology shows an 8 mm papillary cancer, classic variant*
5. *There was a 1 mm metastatic focus in a*

perithyroidal node. Would you give her radioiodine? How much?

Case 2

42 year-old woman with a 2 cm thyroid nodule, biopsy was FLUS and she had a hemithyroidectomy. Pathology was a benign 2 cm adenoma, and a 3, 2, 2, and < 1 mm papillary cancer. No nodes were dissected. Pre-operative ultrasound shows a 1.5 mm nodule in the contralateral lobe.

Questions

1. *Should she have a completion thyroidectomy?*
2. *If one were done, would you then give her radioiodine?*

DISCUSSION OF CASES AND ANSWERS**Case 1**

FNA should be discouraged in patients with subcentimetric nodules in the absence of nodal metastases. Data on the use of BRAF are controversial, but even if one could convincingly demonstrate that BRAF patients are more likely to have nodal metastases, the overall excellent prognosis in these patients suggests that it is premature to use BRAF as an excuse to treat patients more aggressively. If a high-volume thyroid surgeon is available, the patient should have a total thyroidectomy. There is no data to suggest a benefit of radioiodine for this patient, especially for such a trivial metastatic focus. Over half of these patients will have minimal nodal involvement.

Case 2

There are no data regarding the use of a completion thyroidectomy in this setting. While one could argue for it, based on data demonstrating reduced recurrences in patients who have had a total versus less than a total thyroidectomy (see above), the issue is whether the benefit justifies the potential cost and complications. It may be more rational to monitor and repeat surgery only when a recurrence is documented. There is no evidence that radioiodine improves outcome in multifocal disease.

REFERENCES

1. Harach HR, Franssila KO, Wasenius VM: Occult papillary cancer of the thyroid. A "normal" finding in Finland. A systematic autopsy study, *Cancer* 56:531-538, 1985.
2. Ito Y, Miyauchi A, Inoue H, et al: An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg* 34:28-35, 2010.
3. Hay ID, Hutchinson ME, Gonzalez-Losada T, et al: Papillary thyroid microcarcinoma: A study of 900 cases observed in a 60-year period, *Surgery* 144:980-988, 2008.
4. Noguchi S, Yamashita H, Uchino S et al. Papillary microcarcinoma. *World J Surg* 32:747-753, 2008.
5. Kim TY, Hong SJ, Kim JM, et al: Prognostic parameters for recurrence of papillary thyroid microcarcinoma. *BMC Cancer* 8:296, 2008.
6. Kwak JY, Kim E-K, Kim MJ, et al: Papillary microcarcinoma of the thyroid: Predicting factors of lateral neck node metastasis. *Ann Surg Oncol* 16:1348-1355, 2009.
7. Ross DS, Litofsky D, Ain KB, et al: Recurrence after treatment of micropapillary thyroid cancer. *Thyroid* 19:1043-1048, 2009.
8. Wada N, Duh Q-Y, Sugino K, et al: Lymph node metastasis from 259 papillary thyroid microcarcinomas. Frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg* 237:399-407, 2003.
9. Ito Y, Masuoka H, Fukushima M, et al: Excellent prognosis of patients with solitary T1N0M0 papillary thyroid carcinoma who underwent thyroidectomy and elective lymph node dissection without radioiodine therapy. *World J Surg* 34:1285-90, 2010.