

# Prophylactic central neck dissection with total thyroidectomy in familial medullary thyroid cancer with codon 634 mutations is safe and results in high cure rates

Schellhaas E, König C, Frank-Raue K, Buhr H, Hotz H. Long-term outcome of “prophylactic therapy” for familial medullary thyroid cancer. *Surgery* 2009;146-906-12.

## SUMMARY

### BACKGROUND

Patients with medullary thyroid carcinoma (MTC) should be tested for genetic mutations in the RET proto-oncogene. Such testing provides information about the clinical behavior of the tumor and at the same time determines the risk of genetic susceptibility in first-degree relatives. Identification of gene carriers can prevent the development of invasive MTC at a premalignant stage by leading surgeons to perform prophylactic total thyroidectomy, the timing of which is dependent upon the type of mutation. The most common mutation at codon 634 is associated with progression from C-cell hyperplasia to MTC at an early age. Total thyroidectomy by 5 years of age is therefore recommended by the American Thyroid Association guidelines to reduce the likelihood of invasive MTC developing. However, the role and timing of prophylactic central neck dissection in patients with codon 634 mutations is less clear. The present study thus seeks to ascertain whether central neck dissection is beneficial for asymptomatic patients with codon 634 mutations.

### METHODS

The study subjects were 17 patients with codon 634 mutations who underwent total thyroidectomy with central neck dissection from 1992 through 1999. All patients were asymptomatic genetic carriers undergoing prophylactic surgery. Fourteen had multiple endocrine neoplasia 2A (MEN2A) and 3 had familial MTC. The

median age of the patients under study was 13 years (range, 4 to 36). Prior to surgery, ultrasonography (US) was performed on all patients, and basal serum calcitonin levels were obtained on all patients. Follow-up phone calls were made to the patients and their physicians to determine the subsequent course of the patient’s disease. Inquiries were made about additional treatments as well as basal and stimulated calcitonin levels. The median follow-up was 147 months (range, 90 to 181).

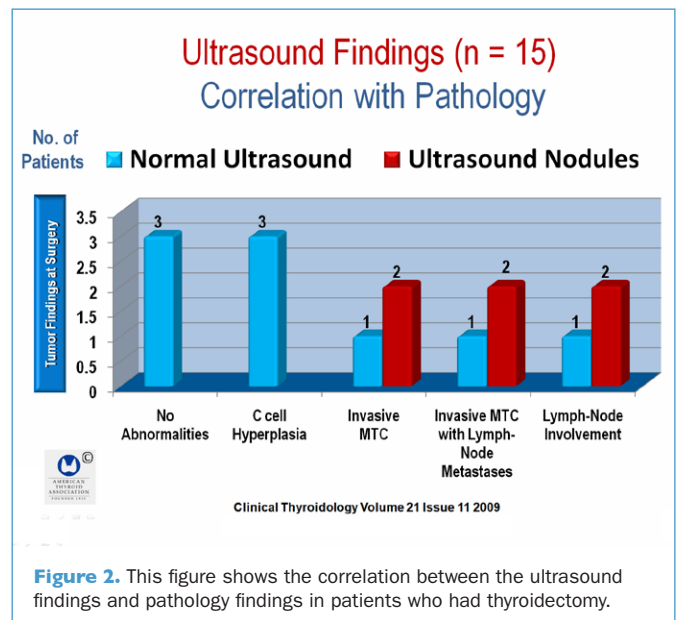
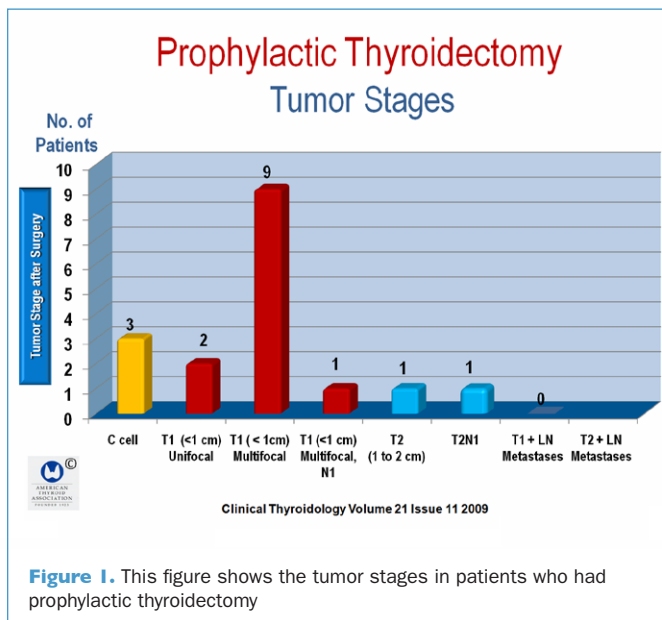
### RESULTS

#### Tumor Stages in Patients Who Underwent Prophylactic Thyroidectomy (Figure 1)

Surgical pathology revealed C-cell hyperplasia in 3 patients, invasive MTC (T1 tumor) <1 cm in 12 patients, and MTC from 1 to 2 cm (T2 tumor) in 2 patients. A mean of 10 lymph nodes were removed. Only two patients, ages 9 and 36 years, had lymph-node involvement, with T1 and T2 tumors, respectively. The preoperative serum calcitonin levels correlated with tumor size (P = 0.012) but not the presence of lymph-node metastases. Preoperative stimulated calcitonin levels did not correlate with tumor size or the extent of lymph-node metastases.

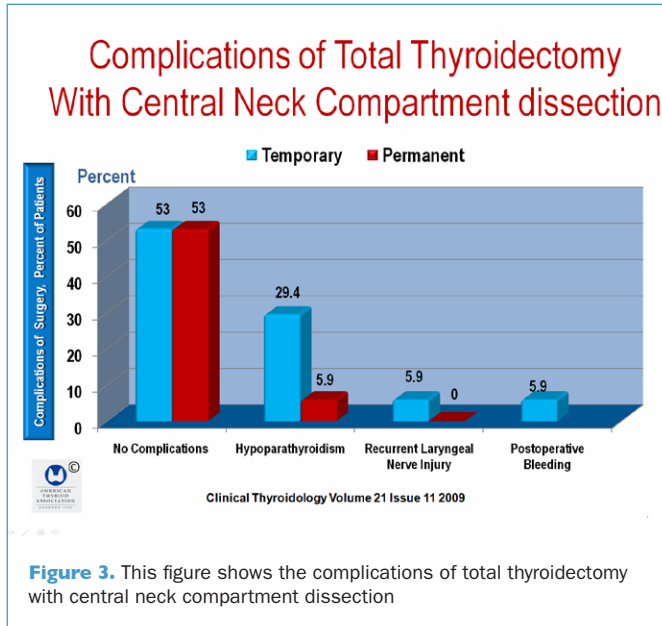
#### Pathology in 15 Patients with Ultrasound Findings (Figure 2)

Fifteen patients underwent preoperative US; nine did not reveal abnormalities. Six of these patients had invasive MTC, and one had lymph-node involvement. The remaining three patients had C-cell hyperplasia. Six patients were found to have thyroid nodules on US, all of whom had invasive MTCs.



**Postoperative Morbidity (Figure 3)**

The incidence of permanent postoperative morbidity was low; only one patient (5.9%) had permanent hypoparathyroidism,



**Figure 3.** This figure shows the complications of total thyroidectomy with central neck compartment dissection

requiring oral calcium supplementation. Five patients experienced transient hypoparathyroidism that resolved with long-term follow up. One patient had temporary recurrent laryngeal nerve injury, but repeat examination after the initial surgery revealed bilateral normally functioning nerves.

Recurrent disease was found in the two patients with lymph-node metastases at initial surgery. In the 36-year-old, calcitonin levels failed to normalize after initial surgery and 3 months later, he underwent a lateral neck dissection. Repeat calcitonin levels normalized after surgery and the patient remains free of disease. The 9-year-old patient, who had a T1 tumor, had malignant nodes removed 2 and 5 years after initial surgery as a result of persistently elevated calcitonin levels. At present, the patient's calcitonin remains elevated but there is no clinical evidence of disease.

**CONCLUSION** In the hands of experienced surgeons, prophylactic central neck dissection in conjunction with total thyroidectomy may be safely performed with minimal morbidity and results in high cure rates. However, the incidence of lymph-node metastases in patients with asymptomatic MTC was low in this patient population with codon 634 mutations; therefore, no general conclusion can be made about whether prophylactic central neck dissection is beneficial.

**COMMENTARY**

Medullary thyroid cancer, although difficult to treat once it becomes clinically evident, is unique in that it can be prevented with prophylactic thyroidectomy in patients with genetic mutations of the RET proto-oncogene. It has become the standard of care to perform genetic testing of all individuals diagnosed with MTC (1). A positive test becomes important for evaluation of the MEN syndromes in the patient, but also is significant for first-degree relatives who should determine their genetic susceptibility to the disease. Once clinically evident disease develops, the cure rate declines significantly (2, 3). Therefore, it is generally accepted that prophylactic thyroidectomy should be performed in patients testing positive for a RET mutation and may be recommended as early as the first year of life, depending on the specific codon involved (1).

However, the question of whether prophylactic lymph-node dissection should accompany the total thyroidectomy is more controversial. Lymph-node metastases are rare before the age of 11 years; in one large study of 50 children with MEN2A undergoing prophylactic total thyroidectomy and central-compartment dissection, only one patient was found to have lymph-node metastases before this age (4). Once present, however, these lymph-node metastases reduced the rate of biochemical cure to approximately 33% (4).

None of the patients in this study by Schellhaas et al. had clinical evidence of MTC before thyroidectomy. Only 3 of 17 patients had C-cell hyperplasia; the remaining 14 already had invasive MTC. The authors rightly contend that these 14 patients underwent therapeutic rather than prophylactic thyroidectomies. All but 2 patients had preoperative US to determine the extent

of disease, and neither of the patients with metastatic disease at surgery were found to have abnormalities on US exam. The authors thus argue that because the majority of patients with codon 634 mutations already have invasive disease, which cannot readily be detected preoperatively, central cervical lymphadenectomy should be performed at the time of the initial thyroidectomy. This decision is justified by the fact that there were very few complications in their patients; only one patient had permanent hypoparathyroidism. The authors also maintain that such extensive surgery provides a more accurate method of staging and that removal of involved nodes decreases tumor mass, thereby improving outcome.

Schellhaas et al. measured serum calcitonin levels in addition to performing cervical US for preoperative staging. As expected, there was a direct correlation between serum calcitonin levels and tumor size. However, the calcitonin levels did not correlate with the presence of lymph-node metastases. Nevertheless, conclusions about the futility of measuring calcitonin for preoperative detection of lymph-node metastases should not be made from this study because of the small number of patients with metastatic disease. In fact, several studies have shown that a basal calcitonin of <40 pg/ml is only rarely associated with lymph-node metastases (5-7). A basal calcitonin of <40 pg/ml thus provides a reasonable cutoff below which prophylactic central-neck dissection may not be necessary (1). When prophylactic central-neck dissection is deemed necessary, it is critical that it be performed at a facility with experienced and highly skilled surgeons such as those in the study by Schellhaas et al.

This study provides valuable insight into the frequency of lymph-node metastases in patients with the codon 634 mutation.

Although it tends to be a more aggressive phenotype requiring thyroidectomy by age 5, it is reassuring that only 2 patients with codon 634 mutations had metastatic disease at the time of their initial surgery. Further, both of these patients had surpassed the recommended timeframe for thyroidectomy (ages 9 and 36 years). Because lymph-node metastases are uncommon before the age of 11 years, it may be beneficial to

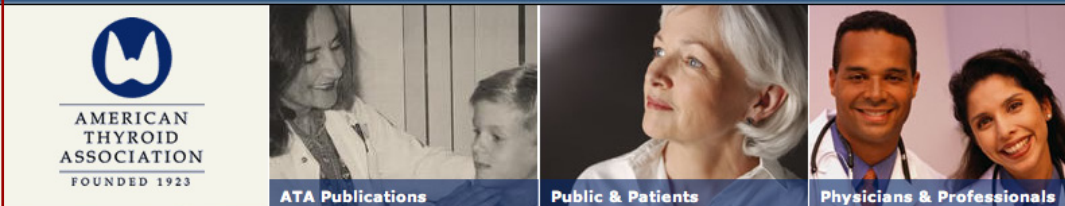
consider the patient's age in addition to the preoperative basal serum calcitonin levels and cervical US in order to decide on the extent of surgery needed for an individual patient rather than recommend prophylactic central-neck dissection for all patients with codon 634 mutations (1).

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References

1. Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009;19:565-612.
2. Telander RL, Zimmerman D, Sizemore GW, et al. Medullary carcinoma in children: results of early detection and surgery. *Arch Surg* 1989;124:841-3.
3. Wells SA Jr, Baylin SB, Gann DS, et al. Medullary thyroid carcinoma: relationship of method of diagnosis to pathologic staging. *Ann Surg* 1978;188:377-83.
4. Skinner MA, Moley JA, Dilley WG, et al. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. *N Engl J Med* 2005;353:1105-13.
5. Machens A, Schneyer U, Holzhausen HJ, et al. Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level. *J Clin Endocrinol Metab* 2005;90:2029-34.
6. Niccoli-Sire P, Murat A, Rohmer V, et al. When should thyroidectomy be performed in familial medullary thyroid carcinoma gene carriers with non-cysteine RET mutations? *Surgery* 2003;134:1029-36.
7. Scheuba C, Kaserer K, Bieglmayer C, et al. Medullary thyroid microcarcinoma recommendations for treatment—a single-center experience. *Surgery* 2007;142:1003-10.

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