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EDITORIAL – ENDOCRINE TUMORS

Chasing Calcitonin: Reoperations for Medullary Thyroid Carcinoma

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In their article, "Biochemical Cure Following Reoperations for Medullary Thyroid Carcinoma: A Meta-Analysis," Rowland et al.[1] provide a very insightful review of the optimal surgical approach for recurrent medullary thyroid cancer. Because no randomized studies exist to guide practicing thyroid surgeons, these authors conducted a thorough meta-analysis of existing studies to determine whether patients with persistently elevated calcitonin after their initial surgery should undergo a targeted procedure removing gross disease or a more extensive compartment-oriented approach. The overall success rate in their study, defined as normalization of calcitonin, was 16.2 %. When classified by surgical technique, a selective approach yielded a biochemical cure rate of 10.5 % (95 % confidence interval [CI], 6.4–14.7), whereas a compartment-oriented approach led to a biochemical cure for 18.6 % (95 % CI, 15.9–21.3). The higher rate of calcitonin normalization with a compartment-oriented surgery was balanced, however, by a higher complication rate that included recurrent laryngeal nerve injury in 5.7 % compared with 1.9 % in the selective surgery group. The compartment-oriented group also experienced an increased incidence of thoracic duct injury, Horner's syndrome, spinal accessory nerve injury, wound infection, and seromas, but the rate of permanent hypoparathyroidism actually appeared to be higher in the targeted surgery group. The authors note that their data on complications should be interpreted cautiously because their study was not designed to assess this end point. However, it does seem reasonable that more extensive surgery leads to an overall higher complication rate.

The current study continues a long tradition by Dr. Moley's group of important contributions to our understanding of medullary thyroid cancer, especially regarding the surgical management of recurrent or persistent disease.[2,3] The philosophy of compartment-orientated neck dissection represents the preferred approach for both medullary thyroid cancer and the more common papillary thyroid cancer. However, several questions must be considered when this approach is applied to clinical practice, and some of the most important issues focus on timing and duration.

Should we chase calcitonin levels? When is the right time to reoperate? Will this operation prolong survival or palliate symptoms? Will the normalization of calcitonin be durable?

The authors were not able to provide data on the duration of biochemical cure, so long-term benefits of compartment-oriented surgery are unclear. They also were unable to determine whether survival or quality of life was improved by a compartment-oriented operation because the included studies focused on biochemical cure as the primary end point. Although they correctly note that biochemical cure correlates with prolonged survival, the argument for a particular surgical approach would have been strengthened by estimating more definitive end points. An aggressive compartment-oriented surgery with a higher complication rate is reasonable if it leads to prolonged survival or palliation of symptoms but becomes less palatable when it is only the first of many reoperations.

Identifying patients who derive the most benefit from a compartment-oriented resection is clearly not an easy task because more than 80 % of the patients in this study still had persistent disease after reoperation. Before adopting a more aggressive surgical approach it will be important for future work to better identify patients likely to obtain a

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long-term benefit from reoperation. This information is particularly important because patients with recurrent or persistent medullary thyroid cancer often have a reasonably long life expectancy, so they have ample time to relapse.

The best opportunity to cure a patient with medullary thyroid cancer is at the initial operation, whether it be prophylactic thyroidectomy in the case of hereditary disease or a more aggressive neck dissection in sporadic cases.[4,5] We know from previous studies that failure to obtain a biochemical cure at the initial surgery is associated with almost a 30 % decrease in 10-year survival.[6] This difference in survival has led some to advocate for a more aggressive lymph node dissection at the first surgery, with others maintaining that a more selective approach is still justified.[7,8] When the initial operation is unsuccessful, there may be a subset of patients who can still be cured by surgery, but clearly, the majority will continue to have disease. For those individuals, a strategy of selective intervention targeting focal and clinically evident disease recurrence is not unreasonable and may prevent subsequent development of symptoms that could impair quality of life.

Overall, the current study demonstrates that a compartment-oriented approach to recurrent medullary thyroid cancer may be of benefit for carefully chosen patients. However, because the complication rate appears to be higher even in experienced hands, we really need to know the long-term consequence of such interventions. Consequently, it is important to evaluate patients carefully on an individualized basis instead of broadly applying a compartment-oriented approach to everyone. A careful assessment of patient expectations and tolerance for surgical risks will help guide decision making for clinicians determining the optimal treatment strategy for "chasing' the calcitonin levels.

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