Tailored surgery according to molecular analysis in differentiated thyroid carcinomas

Paolo Miccoli[1], Gabriele Materazzi[1], Elisabetta Macerola[2], Sohail Bakkar[1,3]

[1]Division of Endocrine Surgery, [2]Division of Surgical Pathology, Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; [3]Department of Surgery, Faculty of Medicine, The Hashemite University, Zarqa, Jordan

Contributions: (I) Conception and design: P Miccoli; (II) Administrative support: All authors; (III) Provision of study materials: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Paolo Miccoli, MD, PhD. Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, via Paradisa 2, 56124 Pisa, Italy. Email: paolo.miccoli@dc.unipi.it.

Abstract: Papillary thyroid carcinoma (PTC) is an often indolent disease implying a long survival and in most of the cases an excellent prognosis, but there is still a limited percentage of cases where, in spite of their pre-operative conventional staging, these tumors could better be treated through a more selective surgical approach. Small PTC in fact are generally considered as "low risk" tumors but using simply a TNM classification might lead to a limited surgery such as unilateral hemithyroidectomy, in particular according to the most recent guidelines of the American Thyroid Association. On the other hand though, an absence of the mutation could allow simplifying the follow-up of these patients, for example avoiding unnecessary radioactivated iodine therapy after surgery or even limiting to a unilateral thyroidectomy the operative procedure for these cases. Molecular testing has a peculiar interest for surgeons in two different ways: (I) with respect to diagnosis, in order to reduce the number of indeterminate citologies; (II) with respect to prognosis after both cytology and histology, in order to improve risk stratification and help the surgeon in developing a tailored surgical therapy. The aim of this review is the second issue: how to implement the concept of a tailored surgery according to molecular analysis in differentiated thyroid carcinomas (DTC).

Keywords: Thyroid cancer; endocrine surgery; molecular markers

Submitted Oct 20, 2017. Accepted for publication Oct 23, 2017.
doi: 10.21037/gs.2017.10.07
View this article at: http://dx.doi.org/10.21037/gs.2017.10.07

Introduction

The optimal surgical strategy for papillary thyroid carcinoma (PTC) remains a hotly debated topic, and the concept of offering patients a tailored surgical approach has been gaining increasing popularity among Endocrinologists and Endocrine Surgeons. This is attributed to both the considerably increasing prevalence rate of these tumors, and their conventionally favorable prognosis (1). The potential adverse prognostic implications of the high frequency of multicentric occult disease whether within the gland itself or within loco-regional lymph nodes has placed the extent of surgical resection at the core of the debate. Recent clinical practice guidelines consider a thyroid lobectomy as sufficient therapy for low-risk disease and more extensive surgery as the optimal treatment modality for high-risk disease (2,3).

Following more than 2 decades of experience, active surveillance has been advocated by some as the standard of care for low-risk papillary microcarcinoma (4). The ongoing debate over the ideal treatment modality for low-risk disease aims to reach the optimal risk-benefit ratio; the risk being that of increased morbidity and the requirement for life-long hormone replacement therapy following aggressive therapy weighed against disease-free and overall survival rates. In an attempt to resolve this issue, some have

© Gland Surgery. All rights reserved.

turned to molecular markers. The use of molecular marker as a tool that helps in decision making regarding surgical strategy is not limited to cancerous lesions but also extends to a broad category of thyroid lesions collectively labeled as "indeterminate" which comprise Bethesda categories III, IV, and V (5). Patients with indeterminate nodules are at risk of overly radical surgery or an unnecessary two-stage surgery (6). The aim herein is to review the role of molecular markers as a prognosticator and a tool for determining surgical strategy.

Risk stratification of patients based on molecular markers

BRAF gene status is well known as an important factor influencing some parameters of tumors invasiveness, but only few of these parameters could imply a significant change in the surgical strategy: the most often involved ones seem to be the capsule invasion, the multifocality and the lymph node involvement (7,8). More recently other mutations and gene expression profiles (9,10) have been recognized as possible factors influencing the prognosis of PTC: the aim of the paper is to revise all these parameters aiming to find a correlation between their prognostic influence and the choice of a more personalized surgical strategy.

One of the most popular, commercially available tool using molecular cytology is Afirma®, a thyroid FNA analysis based on the Gene Expression Classifier (GEC) which employs a 167-gene signature.

The risk of malignancy in indeterminate thyroid nodules defined as "benign" by Afirma analysis is reported to be less than 6% (9): in other words it can be defined as a "rule-out" test. This first report was not an independent institutional study, but others followed which only partially confirmed this first report (11), since they assessed lower than expected rate of "benign" reports and lower than anticipated malignancy rate in GEC "suspicious" nodules. It is also noteworthy that cytology remains an irreplaceable tool to make both a correct pre-operative morphologic diagnosis and a correct molecular analysis. It has been assumed in fact that repeat biopsy of initial insufficient aspirates, as well as more detailed classification, proved to change in some cases the final diagnosis, thus reducing the necessity for surgical intervention (12).

When *BRAF* and other mutations or molecular profiles are known before surgery in fact the surgeon should be helped in making a decision about two crucial aspects of his surgical approach: (I) extent of primary operation (total thyroidectomy versus hemithyroidectomy) and (II) necessity of a prophylactic central compartment lymphadenectomy.

In terms of the first decision to make it seems that there is no clear evidence that *BRAF* V600E mutation is associated with higher rate of multicentricity (13) and for this reason it could be assumed that the surgeon, when operating on a small PTC, even in presence of a *BRAF* mutation, should decide for a hemithyroidectomy. On the other hand the Recommendation 35 by American Thyroid Association guidelines of 2015 (2) admits that "*however, the treatment team may choose total thyroidectomy to enable RAI therapy*" but this is highly arguable because, given the well recognized decrease of ability to take up radioiodine in these patients, it is questionable whether post op ^{131}I ablation might represent a really necessary option.

By opposite most of the authors assume that there is an increased rate of lymph node metastases in patients harboring these mutations (13,14) . Apparently if this opinion was widely shared a routine central compartment lymphadenectomy might be considered mandatory. More recently other authors (15,16) argued that this correlation between *BRAF* mutation and node metastases is not present in all the cases and by then the presence of the mutation does not help in deciding whether or not to perform a central compartment clearance.

Also the authors that always supported the prognostic value of this mutation recently admitted that the "*predictive power of BRAF for CLN metastases was high but less prominent than some of these pathological factors*", namely extrathyroidal invasion, vascular invasion, and AJCC stage (17). For these reasons a central compartment clearance only on the basis of *BRAF* mutation cannot be considered mandatory according to the most recent studies.

Another important issue to consider is the time (8) when the presence of a molecular pattern indicating a higher aggressiveness of the tumor has been registered: was it known before the surgical intervention on the basis of a cytological examination of the nodule or was it registered after the operation on a histological specimen? In the latter case if a total thyroidectomy had been performed a radioactive iodine treatment could be recommended, but should not be carried out in case of negative molecular testing. In a similar situation but after a conservative surgical approach such as a hemithyroidectomy a completion thyroidectomy is certainly to avoid in the latter case: it is debatable whether a redo surgery could improve the prognosis of the patient showing positive molecular testing

© Gland Surgery. All rights reserved.

but it must be said that, in absence of other significant risk factors a completion thyroidectomy can be avoided without any further risk.

More recently a clinical algorithm using *BRAF* and *RAS* point mutations and *RET/PTC* and *PAX8/PPARg* rearrangements, accounting for about 70% of mutations in DTC, has been proposed and its use seems to have significantly improved the stratification of risk factors leading to the following results: with molecular testing the percentage of a completion thyroidectomy after initial lobectomy was 18% of the operated patients whereas in absence of molecular testing it was 30% (18). Another important issue will be the discrimination at molecular level among all the follicular-patterned lesions in the light of the recently defined pathological entity of "noninvasive follicular neoplasms with papillary-like nuclear features", NIFTP (19).

Moreover some authors investigated molecular biomarkers able to differentiate between minimally invasive follicular carcinoma and both adenoma and widely invasive carcinoma. The attempt seemed to have sorted out a significant result since the authors were able to correctly identify the exact nature among 18 follicular adenomas, 14 minimally invasive and 6 widely invasive follicular thyroid carcinomas (20).

For a correct stratification of the risk factors though a comparison between molecular testings and morphological or clinical factors is strictly necessary. In a recent paper it was demonstrated that integrating molecular analysis with ultrasonographic features can improve significantly the diagnosis in order to select patients for surgery (6). In this series by an Italian group the absence of both mutational markers and suspicious ultrasonographic features proved extremely useful in tailoring surgical strategy, as it could have ultimately spared 143 out of 258 patients (55%) an overly radical thyroidectomy.

Conclusions

In most of the cases the clinical staging is able to determine unequivocally the extent of surgery with no regard to molecular prognostication. In fact molecular testing by itself alone is a poor prognostic factor. It must be recalled that the major limitation of mutational markers is their low occurrence in malignancy.

Several other important risk factors other than TNM should be evaluated. Molecular testing certainly could play an important role in cancers that could be conventionally considered as low risk. Ultrasonography, alone or coupled with molecular testing should always be fully evaluated.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Miccoli P, Bakkar S. Surgical management of papillary thyroid carcinoma: an overview. Updates Surg 2017;69:145-50.
2. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1-133.
3. Haddad RI, Lydiatt WM, Ball DW, et al. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines). Anaplastic Thyroid Carcinoma, Version 2.2015. JNCCN 2015;13:1140-50.
4. Miyauchi A. Clinical Trials of Active Surveillance of Papillary Microcarcinoma of the Thyroid. World J Surg 2016;40:516-22.
5. Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference. The Bethesda System For Reporting Thyroid Cytopathology. Am J Clin Pathol 2009;132:658-65.
6. De Napoli L, Bakkar S, Ambrosini CE, et al. Indeterminate Single Thyroid Nodule: Synergistic Impact of Mutational Markers and Sonographic Features in Triaging Patients to Appropriate Surgery. Thyroid 2016;26:390-4.
7. Liu C, Chen T, Liu Z. Associations between BRAF(V600E) and prognostic factors and poor outcomes in papillary thyroid carcinoma: a meta-analysis. World J Surg Oncol 2016;14:241.
8. Miccoli P, Basolo F. BRAF mutation status in papillary thyroid carcinoma: significance for surgical strategy. Langenbecks Arch Surg 2014;399:225-8.
9. Alexander EK, Schorr M, Klopper J, et al. Multicenter clinical experience with the Afirma gene expression classifier. J Clin Endocrinol Metab 2014;99:119-25.

© Gland Surgery. All rights reserved.

10. Kloos RT. Molecular Profiling of Thyroid Nodules: Current Role for the Afirma Gene Expression Classifier on Clinical Decision Making. Mol Imaging Radionucl Ther 2017;26:36-49.
11. McIver B, Castro MR, Morris JC, et al. An independent study of a gene expression classifier (Afirma) in the evaluation of cytologically indeterminate thyroid nodules. J Clin Endocrinol Metab 2014;99:4069-77.
12. Yassa L, Cibas ES, Benson CB, et al. Long-term assessment of a multidisciplinary approach to thyroid nodule diagnostic evaluation. Cancer 2007;111:508-16.
13. Elisei R, Viola D, Torregrossa L, et al. The BRAF(V600E) mutation is an independent, poor prognostic factor for the outcome of patients with low-risk intrathyroid papillary thyroid carcinoma: single-institution results from a large cohort study. J Clin Endocrinol Metab 2012;97:4390-8.
14. Xing M, Westra WH, Tufano RP, et al. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. J Clin Endocrinol Metab 2005;90:6373-9.
15. Gandolfi G, Sancisi V, Torricelli F, et al. Allele percentage of the BRAF V600E mutation in papillary thyroid carcinomas and corresponding lymph node metastases: no evidence for a role in tumor progression. J Clin Endocrinol Metab 2013;98:E934-42.
16. Dutenhefner SE, Marui S, Santos AB, et al. BRAF: a tool in the decision to perform elective neck dissection? Thyroid 2013;23:1541-6.
17. Alzahrani AS, Xing M. Impact of lymph node metastases identified on central neck dissection (CND) on the recurrence of papillary thyroid cancer: potential role of BRAFV600E mutation in defining CND. Endocr Relat Cancer 2013;20:13-22.
18. Yip L, Wharry LI, Armstrong MJ, et al. A clinical algorithm for fine-needle aspiration molecular testing effectively guides the appropriate extent of initial thyroidectomy. Ann Surg 2014;260:163-8.
19. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors. JAMA Oncol 2016;2:1023-9.
20. Poma A, Giannini R, Ugolini C, et al. Gene expression profiling of follicular thyroid adenoma, minimally invasive and widely invasive follicular thyroid carcinoma. Pathologica JotISoAPaDC, Italian Division of the International Academy of Pathology, 7th edition. Congresso Triennale di Anatomia Patologica SIAPEC-IAP, Genova: IT, Pacini, 2016:179-404.

Cite this article as: Miccoli P, Materazzi G, Macerola E, Bakkar S. Tailored surgery according to molecular analysis in differentiated thyroid carcinomas. Gland Surg 2018;7(Suppl 1):S30-S33. doi: 10.21037/gs.2017.10.07

© Gland Surgery. All rights reserved.