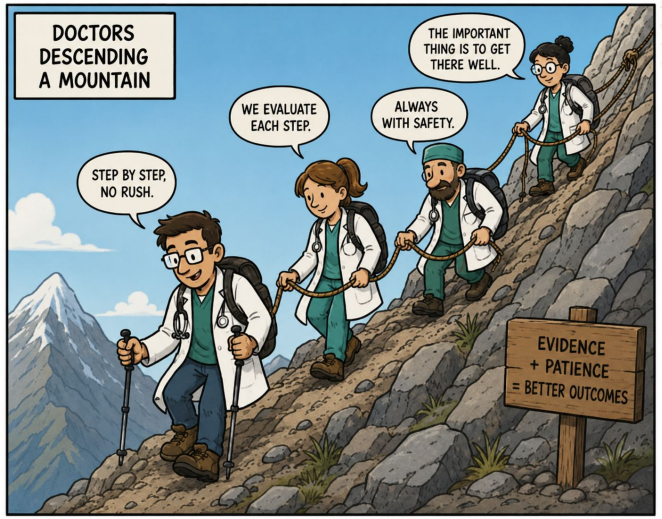


De-escalation in the surgical management of medullary thyroid cancer

How did we get here, and where are we going?

Joaquín Gómez Ramírez

Endocrine Surgery Unit

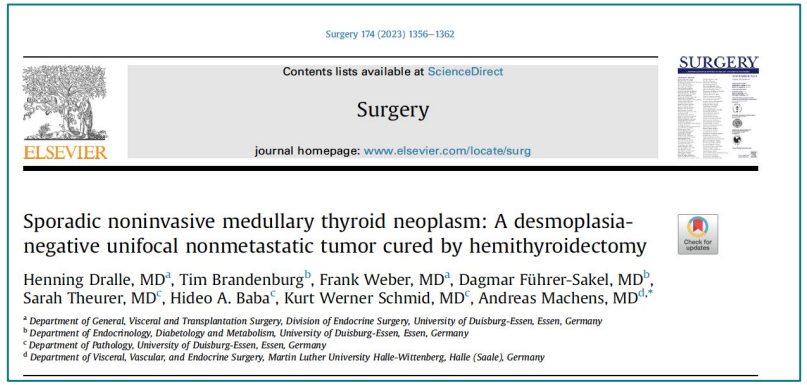
University Hospital La Paz



De-escalation in medullary thyroid carcinoma

How did we get here?

2020-



Surgery 174 (2023) 1356–1362

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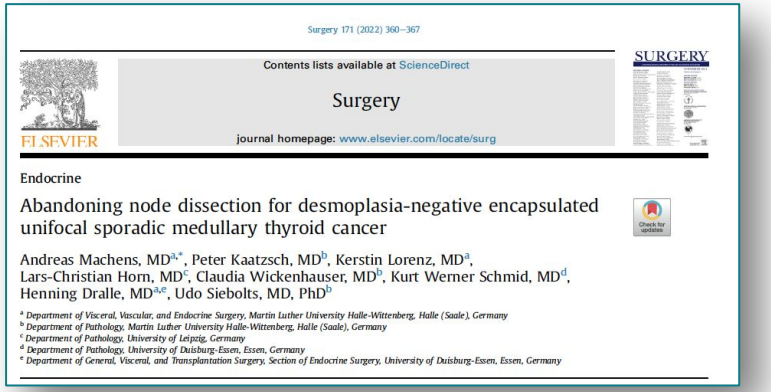
Surgery

journal homepage: www.elsevier.com/locate/surg

Sporadic noninvasive medullary thyroid neoplasm: A desmoplasia-negative unifocal nonmetastatic tumor cured by hemithyroidectomy

Henning Dralle, MD[a], Tim Brandenburg[b], Frank Weber, MD[a], Dagmar Führer-Sakel, MD[b], Sarah Theurer, MD[c], Hideo A. Baba[c], Kurt Werner Schmid, MD[c], Andreas Machens, MD[d,*]

[a] Department of General, Visceral and Transplantation Surgery, Division of Endocrine Surgery, University of Duisburg-Essen, Essen, Germany
[b] Department of Endocrinology, Diabetology and Metabolism, University of Duisburg-Essen, Essen, Germany
[c] Department of Pathology, University of Duisburg-Essen, Essen, Germany
[d] Department of Visceral, Vascular, and Endocrine Surgery, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany



Surgery 171 (2022) 360–367

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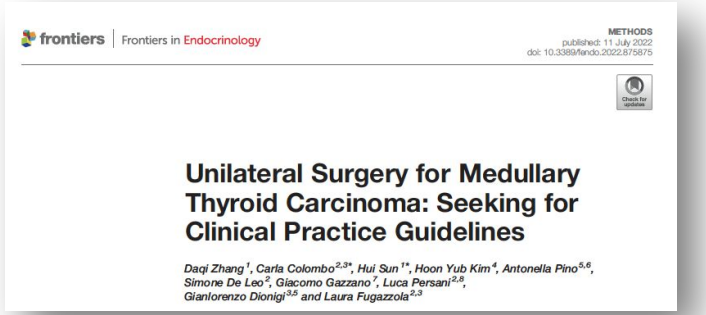
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Endocrine

Abandoning node dissection for desmoplasia-negative encapsulated unifocal sporadic medullary thyroid cancer

Andreas Machens, MD[a,*], Peter Kaatzsch, MD[b], Kerstin Lorenz, MD[a], Lars-Christian Horn, MD[c], Claudia Wickenhauser, MD[b], Kurt Werner Schmid, MD[d], Henning Dralle, MD[a,e], Udo Siebolts, MD, PhD[b]

[a] Department of Visceral, Vascular, and Endocrine Surgery, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany
[b] Department of Pathology, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany
[c] Department of Pathology, University of Leipzig, Germany
[d] Department of Pathology, University of Duisburg-Essen, Essen, Germany
[e] Department of General, Visceral, and Transplantation Surgery, Section of Endocrine Surgery, University of Duisburg-Essen, Essen, Germany



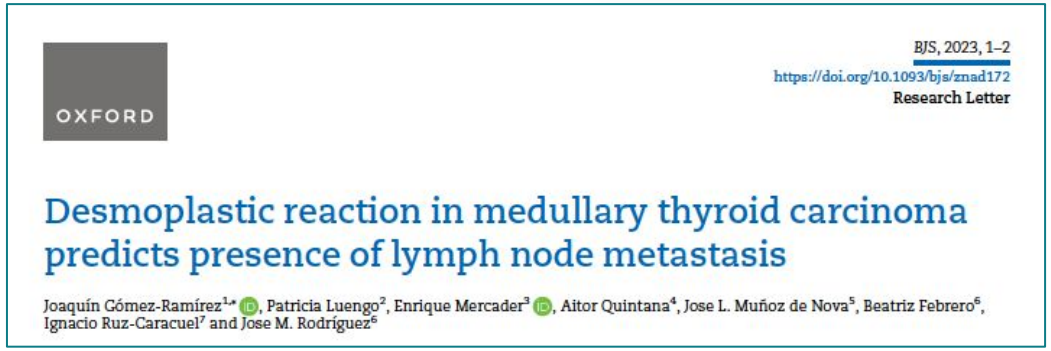
frontiers | Frontiers in Endocrinology

METHODS

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doi: 10.3389/fendo.2022.875875

Unilateral Surgery for Medullary Thyroid Carcinoma: Seeking for Clinical Practice Guidelines

Daqi Zhang[1], Carla Colombo[2,3]*, Hui Sun[1]*, Hoon Yub Kim[4], Antonella Pino[5,6], Simone De Leo[2], Giacomo Gazzano[7], Luca Persani[2,8], Gianlorenzo Dionigi[3,5] and Laura Fugazzola[2,3]

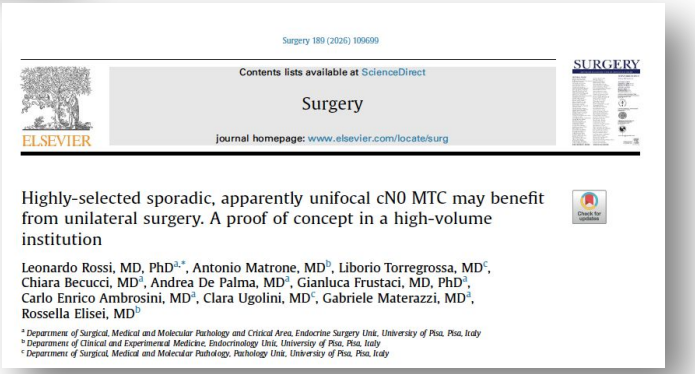


OXFORD

BJS, 2023, 1–2
https://doi.org/10.1093/bjs/znad172
Research Letter

Desmoplastic reaction in medullary thyroid carcinoma predicts presence of lymph node metastasis

Joaquín Gómez-Ramírez[1,*], Patricia Luengo[2], Enrique Mercader[3], Aitor Quintana[4], Jose L. Muñoz de Nova[5], Beatriz Febrero[6], Ignacio Ruz-Caracuel[7] and Jose M. Rodríguez[6]



Surgery 189 (2026) 109699

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Surgery

journal homepage: www.elsevier.com/locate/surg

Highly-selected sporadic, apparently unifocal cN0 MTC may benefit from unilateral surgery. A proof of concept in a high-volume institution

Leonardo Rossi, MD, PhD[a,*], Antonio Matrone, MD[b], Liborio Torregrossa, MD[c], Chiara Becucci, MD[a], Andrea De Palma, MD[a], Gianluca Frustaci, MD, PhD[a], Carlo Enrico Ambrosini, MD[a], Clara Ugolini, MD[c], Gabriele Materazzi, MD[a], Rossella Elisei, MD[b]

[a] Department of Surgical, Medical and Molecular Pathology and Critical Area, Endocrine Surgery Unit, University of Pisa, Pisa, Italy
[b] Department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Pisa, Italy
[c] Department of Surgical, Medical and Molecular Pathology, Pathology Unit, University of Pisa, Pisa, Italy

De-escalation in medullary thyroid carcinoma

1950-60



1951

CARCINOMA OF THE THYROID

Description of a Distinctive Morphological Variant and Report of Seven Cases

ROBERT C. HORN, JR., M.D.

ALTHOUGH carcinoma of the thyroid gland has been given increasing attention in the medical literature in recent years, little has been written regarding morphology, save as it pertains to radioactive-iodine utilization.[2] The variations of the morphological guise that thyroid cancer may assume have long been recognized and are familiar to all pathologists. It is the purpose of the present report to describe a distinctive morphological pattern, which has been encountered seven times in the material of the Laboratory of Surgical Pathology of the Hospital of the University of Pennsylvania. This pattern has undoubtedly been seen and properly labeled as carcinoma of the thyroid by other observers, but its significance has not always been appreciated when it is noted in metastatic lesions and even, at times, in the thyroid gland itself. In case 1, this histological picture was observed in a supraclavicular–lymph-node metastasis, but the correct diagnosis of thyroid carcinoma was not made until years later, after cases 2, 3, and 5 had been encountered. In case 3, the carcinoma, studied only in the metastatic lesions, was recognized as of thyroid origin only after a year's observation and study of additional pathological material; in case 5, the tumor was misdiagnosed in another hospital, on the basis of study of a lymph-node metastasis, as a hemangioendothelioma, two years before the patient was admitted to the Hospital of the University of Pennsylvania. For these reasons, it seems worth while to record a description of this morphological variant of thyroid cancer. Inasmuch as all of the tumors of this type studied were basically similar, a single microscopic description will be made for the group, noting individual variations rather than detailing the appearance of each tumor.

From the Laboratory of Surgical Pathology, Hospital of the University of Pennsylvania, and the Penn Mutual Life Insurance Company Foundation for the Study of Neoplastic Disease, Philadelphia, Pennsylvania.
Received for publication, November 30, 1950.

HISTOLOGICAL APPEARANCE

The basic pattern of the thyroid carcinomas of this group is one of sharply defined, rounded or ovoid, compact cell groups of moderate, although variable, size (see Fig. 1). The stroma separating these cell masses varies from delicate trabeculae, consisting largely of blood vessels with a few reticulin or collagen fibers, to broad bands of dense, sometimes hyaline, fibrous tissue. The cells vary from cuboidal or polyhedral to oval, frequently becoming elongated and even spindle shaped (see Fig. 12). Occasional clusters are composed of elongated cells arranged in a concentric fashion suggesting the formation of rudimentary epithelial "pearls" (see Fig. 5). For the most part, the cells have moderate amounts of cytoplasm, although the outlines are usually indistinct.

The cells are of fairly uniform size in any given tumor, although there is some variation between different tumors. Their average diameters are estimated to be about three times that of the erythrocyte, ranging from two to four times. The nuclei tend to follow the contour of the cells and are generally vesicular, the chromatin occurring in scattered small clumps. Small, usually single, but occasionally double, nucleoli are numerous in the tumor of case 3. Nucleoli are seen in fewer numbers in case 4 and only infrequently in the remaining tumors. Gigantic and bizarre nuclei are observed occasionally, being conspicuous only in case 3 (see Fig. 6). Mitotic figures are generally infrequent.

Adenomatous differentiation, with the formation of colloid-containing follicles, is readily apparent only in case 5 (see Fig. 9), but similar areas may be detected after prolonged search in cases 2, 3, and 7 (see Figs. 4, 13). A distinct papillary structure is present in portions of the tumor in case 6 (see Fig. 11) and a vague semblance in case 2.

In five cases, we have been able to study histologically the tumor in the thyroid gland

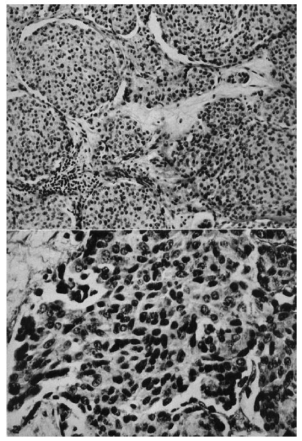


FIG. 1. Case 1. General pattern characterizing the thyroid carcinomas of this group. (×195.)
FIG. 2. Case 1. Higher magnification of Fig. 1, showing cell detail. (Masson's trichrome. ×440.)

SUMMARY

Seven cases of thyroid carcinoma presenting a distinctive histological appearance are reported. Recognition of this pattern as characteristic for thyroid origin should permit identification of certain metastatic carcinomas in the absence of a clinically definite tumor in the thyroid gland proper and in the absence of the familiar pictures of papillary growth or colloid-containing follicles. The finding of small, differentiated areas in five of these cases re-emphasizes the necessity of studying multiple microscopic sections, not only of thyroid cancers, but of all metastatic carcinomas of obscure origin. The tumor type described appears to rank among the more malignant thyroid carcinomas, although it may pursue its course remarkably slowly.

- ✔ *Seven cases of thyroid carcinoma with a distinct histological pattern*
- ✔ *Undifferentiated thyroid tumours*
- ✔ *High rate of cervical lymph node metastases*
- ✔ *Better prognosis than anaplastic carcinoma*

De-escalation in medullary thyroid carcinoma

1950-60

1959

MEDULLARY (SOLID) CARCINOMA OF THE THYROID—A CLINICOPATHOLOGIC ENTITY*

JOHN B. HAZARD, M.D., WILLIAM A. HAWK, M.D. AND GEORGE CRILE, JR., M.D.

The Department of Anatomic Pathol... and the Department of General Surgery, The Cleveland Clinic Foundati... e Frank E. Bunts Educational Institute, ... Ohio

...CT

M... ...y a solid nonfollicular histologic ..., and a high incidence of lymph ... intermediate rather than a high gr... ...entiated character. It is important to dis... ...alignant solid form of anaplastic carcinoma, and ... ...ma, which is of a lower grade of malignancy.

Tw... ...are reported. Fourteen patients were women and 7 were men; t... ...anged from 33 to 66 years with a median of 50 years. The regional cervical lymph nodes contained metastases at the time of initial surgery in 10 of 21 cases (48 per cent). Distant metastases occurred in 8 patients and were principally evident in the lungs, liver and bone. Amyloid, though of variable amount, was present in the stroma of all tumors of this series. The course of the disease was usually chronic; 12 patients survived six to twenty-seven years after the initial thyroid operation. Eleven patients died (6 because of neoplasm) four months to twenty-seven years after definitive surgical treatment.

THE multitude of histologic variants of carcinoma of the thyroid has resulted in the development of a highly complicated terminology; therefore, the addition of a new diagnostic term should be recommended only upon established necessity. In an appraisal of thyroid carcinoma several years ago, it became evident that a type of tumor existed which apparently had not received previous special recognition, although it had specific clinical and pathologic features. This tumor was basically of solid histologic structure and of nonpapillary configuration, yet had a high potentiality for metastasizing to lymph nodes. At first, because of a suggestive papillary arrangement of cells associated with artifacts in the old formalin-fixed material, it was thought that certain of these neoplasms might be a form of papillary carcinoma; but recent and freshly fixed tissue has yielded

* Presented at the Annual Meeting of the American Goiter Association, San Francisco, California, June 17–19, 1958.

- ✔ *Solid tumour not derived from follicular cells*
- ✔ *Amyloid deposition*
- ✔ *"Medullary or solid carcinoma"*
- ✔ *Intermediate aggressiveness*



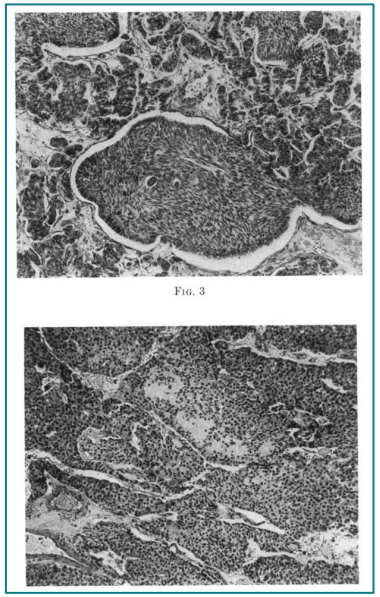


FIG. 3

De-escalation in medullary thyroid carcinoma

1960-80

Familial Endocrine Tumors*

Report of Two Unrelated Kindred Affected with Pheochromocytomas, One also with Multiple Thyroid Carcinomas

PAUL CUSHMAN, JR., M.D.†
Rochester, New York

IN recent years ten separate families, each with multiple involvement by pheochromocytoma, have been described [1–9]. From detailed study of the available family pedigrees Carman and Brashear [9] have concluded that inheritance of this anomaly is best explained by simple Mendelian dominance with varying but usually high penetrance. This paper will review the literature, present in detail two additional unrelated families, and comment on the genetics involved.

MATERIALS AND METHODS

Estimation of urinary catecholamines was carried out in the Special Determinations Laboratory, Department of Biochemistry, using a method developed by Dr. W. B. Mason and associates.

Catecholamines in a twenty-four-hour specimen collected with hydrochloric acid as preservative are concentrated by adsorption onto alumina and eluted with acetic acid. Following condensation with ethylenediamine, catecholamine derivatives are extracted into n-butanol. Butanol is removed by evaporation, and that portion of the residue which is soluble in methanol is transferred to Whatman No. 1 paper and chromatographed on the same paper to provide reference standards.

The principal epinephrine condensation products separate clearly from those formed with norepinephrine. Visual evaluation of R_f, color and intensity of the principal fluorescent spots was deemed sufficient for identification of active tumors, since the spots corresponding to epinephrine and norepinephrine were grossly increased in urine from our patients with pheochromocytoma. Many urines give strongly fluorescent spots which do not match those from epinephrine or norepinephrine with regard to R_f and/or color. These urines are easily distinguished from those containing increased catecholamines. A preliminary discussion of this procedure was presented in 1956 [10]. The results are reported as "grossly elevated" or "within normal limits."

Phentolamine (Regitine®) testing was carried out according to the method of Roth [11].

In Dr. Albert Sjoerdsma's laboratory, National Heart Institute, were performed: (1) Measurements of free urinary catecholamines, consisting of norepinephrine plus epinephrine, expressed as norepinephrine equivalents. Normal values are <100 μg. per day as norepinephrine, and differentially 10 to 70 μg. as norepinephrine and 0 to 20 μg. per day as epinephrine. (2) 3-methoxy-4-hydroxymandelic acid (VMA) with normal range 2 to 6 mg. per twenty-four hours. (3) Metanephrines (metanephrines plus normetanephrine, free and conjugated) with normal range of <1.3 mg. per day.

The members of the families investigated were in most instances studied personally. Occasionally, correspondence with the family physician or contact was made solely by letter or telephone. Autopsy protocols and hospital records were reviewed.

CASE REPORTS

Family 1

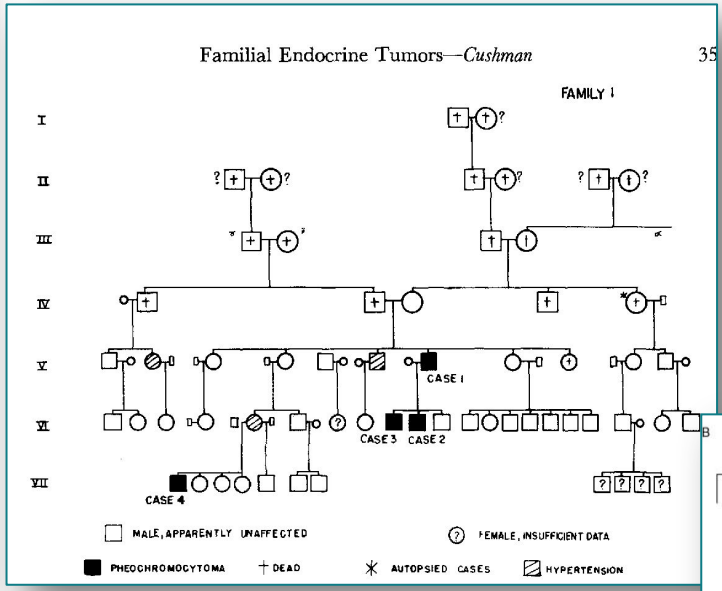
CASE 1. R. J. S. (*S.M.H. No. 33-47-75*). A thirty-four year old accountant was admitted to Strong Memorial Hospital in November 1953 because of hypertension of eight years' duration, at first intermittent, later sustained. A history was obtained of paroxysms of diaphoresis and anxiety accompanied by bilateral severe frontal headaches in increasing frequency of two years' duration. The history was otherwise non-contributory.

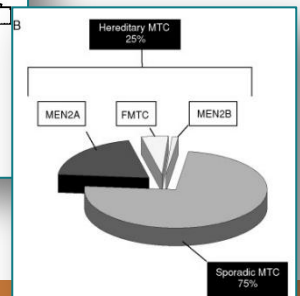
On examination the blood pressure range was 180–200/110–120 mm. Hg. The pulse rate was 82. The patient was a well developed, well nourished

* From the Department of Medicine, The University of Rochester School of Medicine and Dentistry, Rochester, New York. This study was supported by Grants CY 1003 and 2A-5022 of the National Institutes of Health, Bethesda, Maryland. Manuscript received March 28, 1961.

† Trainee, National Institute of Arthritis and Metabolic Diseases. Present address: Department of Medicine, St. Lukes Hospital, New York, New York.

- ✔ *Familial occurrence of MTC and pheo*
- ✔ *MTC as sporadic tumor or familial syndroms*





De-escalation in medullary thyroid carcinoma

1960-80

SINCE the recognition of medullary carcinoma of the thyroid as a histologic entity, its distinctive biological and clinical features have also become apparent.[1,2] Adequate surgical treatment requires an awareness of its tendency to simulate certain behavioral characteristics of both papillary and poorly differentiated carcinoma, to involve both lobes of the thyroid, to metastasize to cervical nodes, to metastasize to distant sites, to resist therapeutic measures other than surgery, to be associated with other endocrine lesions, and to occur as an autosomal dominant characteristic in some families. For these reasons, an early, aggressive surgical approach, including total thyroidectomy and neck dissection, modified in accordance with operative findings, is indicated.



Western Surgical Association

Medullary Carcinoma of the Thyroid: Surgical Implications

Melvin A. Block, MD; J. Martin Miller, MD; and Robert C. Horn, Jr., MD, Detroit

SINCE the recognition of medullary carcinoma of the thyroid as a histologic entity, its distinctive biological and clinical features have also become apparent.[1,2] Adequate surgical treatment requires an awareness of its tendency to simulate certain behavioral characteristics of both papillary and poorly differentiated carcinoma, to involve both lobes of the thyroid, to metastasize to cervical nodes, to metastasize to distant sites, to resist therapeutic measures other than surgery, to be associated with other endocrine lesions, and to occur as an autosomal dominant characteristic in some families. For these reasons, an early, aggressive surgical approach, including total thyroidectomy and neck dissection, modified in accordance with operative findings, is indicated.

Clinical Material

Our experience with medullary carcinoma of the thyroid includes 18 patients seen during the past 12 years. It is biased to some extent in that ten of the 18 patients are members of two families with an inherited trait for this disease. During the past 12 years, a total of 204 patients with primary thyroid carcinoma have been treated in our institution. Medullary carcinoma has comprised 6% to 10% of thyroid carcinomas in other reports.[3-5]

Diagnostic Features

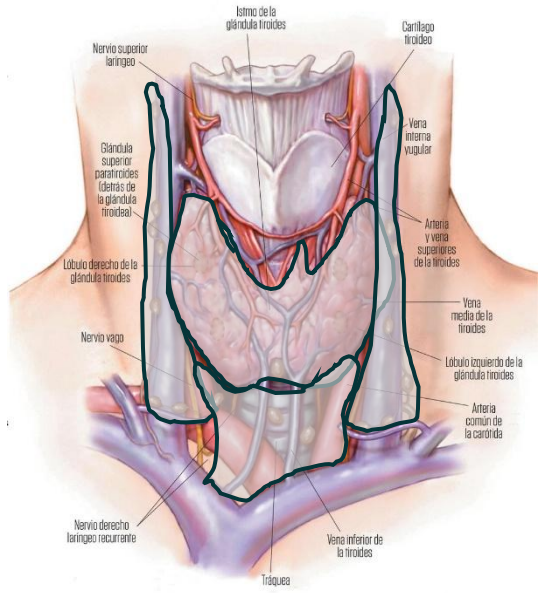
The diagnosis of medullary carcinoma of the thyroid is based on specific microscopic features. The basic pattern is aggregates of cells, the individual cells varying considerably in shape from small and round to large and ovoid to spindle forms, the latter often showing considerable pleomorphism. Occasionally colloid-containing follicles are present within the tumor which appear to be neoplastic rather than trapped elements of the invaded gland. In a few instances, portions of the tumor have a distinct follicular pattern (Fig 1). The stroma separating cell groups contains varying amounts of amyloid, inconspicuous in some tumors or regions of tumors, but striking in others (Fig 2). Amyloid has been identified in the cytoplasm of some neoplastic cells. It seems likely to one of us (R.C.H.) that tumors of this type occasionally occur without demonstrable amyloid, but most authors have considered the presence of amyloid necessary for the diagnosis of medullary carcinoma of the thyroid. Amyloid can usually be identified in hematoxylin-eosin-stained sections, but sometimes special stains are required for confirmation.[6]

In the past, medullary carcinomas of the thyroid have been designated both as follicular carcinomas and as poorly differentiated or spindle-cell carcinomas. Since medullary thyroid carcinoma is potentially more lethal than the papillary or follicular carcinoma, but less formidable than poorly differentiated tumors, proper histologic identification is important for management and expression of prognosis.

Medullary thyroid carcinoma should be considered in the study of cervical lymph nodes removed for diagnosis, since cervical lymphadenopathy due to metastasis was the first clinical evidence of disease in three of our patients. In one of these patients, a cer-

Submitted for publication Dec 29, 1967.
From the Departments of General Surgery and Pathology and the Division of Endocrinology, Henry Ford Hospital, Detroit.
Read before the 75th annual meeting of the Western Surgical Association, Los Angeles, Nov 16, 1967.
Reprint requests to the Department of General Surgery, Henry Ford Hospital, 2799 W Grand Blvd, Detroit 48202 (Dr. Block).

- ✔ *Should be considered as an aggressive tumour*
- ✔ *Aggressive surgery*
- ✔ *Total thyroidectomy and neck dissection*



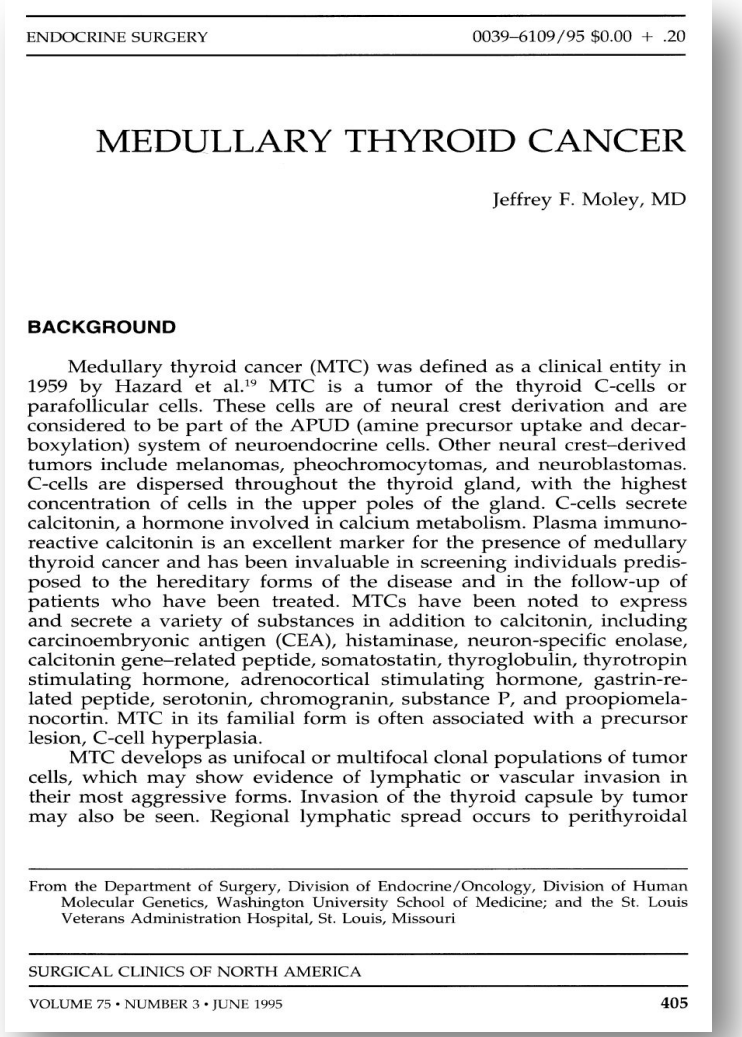
De-escalation in medullary thyroid carcinoma

1980-2000

- ✔ *Aggressive tumour*
- ✔ *Aggressive surgery*
- ✔ *Total thyroidectomy and neck dissection*
- ✔ *Lateral neck dissection if involvement suspected*

SURGICAL TREATMENT

The primary treatment of MTC in all its clinical presentations is total thyroidectomy with central node dissection. This entails removal of all thyroid tissue and of all nodal tissue from the level of the hyoid bone superiorly to the innominate vessels inferiorly. Laterally, the nodes should be cleared from the paratracheal region, where the recurrent nerve courses, to the carotid sheaths. In patients who have palpable adenopathy in the jugular or paratracheal nodes and in patients with a large (>2 cm) palpable mass in the thyroid, an ipsilateral functional neck dissection should be performed. This entails removal of the jugular



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MEDULLARY THYROID CANCER

Jeffrey F. Moley, MD

BACKGROUND

Medullary thyroid cancer (MTC) was defined as a clinical entity in 1959 by Hazard et al.[19] MTC is a tumor of the thyroid C-cells or parafollicular cells. These cells are of neural crest derivation and are considered to be part of the APUD (amine precursor uptake and decarboxylation) system of neuroendocrine cells. Other neural crest–derived tumors include melanomas, pheochromocytomas, and neuroblastomas. C-cells are dispersed throughout the thyroid gland, with the highest concentration of cells in the upper poles of the gland. C-cells secrete calcitonin, a hormone involved in calcium metabolism. Plasma immunoreactive calcitonin is an excellent marker for the presence of medullary thyroid cancer and has been invaluable in screening individuals predisposed to the hereditary forms of the disease and in the follow-up of patients who have been treated. MTCs have been noted to express and secrete a variety of substances in addition to calcitonin, including carcinoembryonic antigen (CEA), histaminase, neuron-specific enolase, calcitonin gene–related peptide, somatostatin, thyroglobulin, thyrotropin stimulating hormone, adrenocortical stimulating hormone, gastrin-related peptide, serotonin, chromogranin, substance P, and proopiomelanocortin. MTC in its familial form is often associated with a precursor lesion, C-cell hyperplasia.

MTC develops as unifocal or multifocal clonal populations of tumor cells, which may show evidence of lymphatic or vascular invasion in their most aggressive forms. Invasion of the thyroid capsule by tumor may also be seen. Regional lymphatic spread occurs to perithyroidal

From the Department of Surgery, Division of Endocrine/Oncology, Division of Human Molecular Genetics, Washington University School of Medicine; and the St. Louis Veterans Administration Hospital, St. Louis, Missouri

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De-escalation in medullary thyroid carcinoma

1980-2000



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Activation of a Novel Human Transforming Gene, *ret*, by DNA Rearrangement

Masahide Takahashi,*‡ Jerome Ritz,†§ and Geoffrey M. Cooper*‡
* Laboratory of Molecular Carcinogenesis
† Division of Tumor Immunology
Dana-Farber Cancer Institute
‡ Department of Pathology
§ Department of Medicine
Harvard Medical School
Boston, Massachusetts 02115

Summary

A novel transforming gene was detected by transfection of NIH 3T3 cells with human lymphoma DNA. The tumor DNA induced a single focus in primary transfections, whereas DNAs of transformed NIH cells induced transformation with high efficiencies in secondary and tertiary assays. Molecular clones spanning about 37 kb of human sequence were isolated from tertiary transformant DNA. Blot hybridization indicated that the transforming gene consisted of two segments that were unlinked in both normal human and primary lymphoma DNAs. The two segments of human DNA were cotranscribed in transformed NIH cells but not in any human cells examined. The transforming gene thus appeared to be activated by recombination between two unlinked human DNA segments, possibly by cointegration during transfection.

Introduction

Cellular genes that may contribute to tumor development have been identified by several criteria, including the biological activity of avian, rodent, and human DNAs in transfection assays. DNAs of a variety of neoplasms have been found to induce transformation of NIH 3T3 cells with high efficiencies (reviewed in G. M. Cooper, 1982). At least 12 transforming genes have been identified by this approach (Der et al., 1982; Parada et al., 1982; Santos et al., 1982; Lane et al., 1981, 1982; Hall et al., 1983; C. S. Cooper et al., 1984a; Padua et al., 1984; Schechter et al., 1984). Some of them—*ras*^{H}, *ras*^{K}, *ras*^{N}, *Blym-1*, *Tlym-1*, and *met*—have been isolated by molecular cloning (Goldfarb et al., 1982; Shih and Weinberg, 1982; Pulciani et al., 1982; Shimizu et al., 1983a, 1983b; Diamond et al., 1983; Lane et al., 1984; C. S. Cooper et al., 1984b). Evidence for additional transforming genes, which are not detected by focus formation on NIH 3T3 cells, has been obtained recently by transfection of primary human foreskin fibroblasts and other transforming genes have not been established, blot hybridization analyses indicate that activation of *Blym-1*, *Tlym-1*, and *met* does not involve gene amplification or gross DNA rearrangements (Diamond et al., 1983; Lane et al., 1984; C. S. Cooper et al., 1984b).

Transfection of NIH 3T3 cells has also been used to investigate the potential transforming activity of genes of normal cells. Sonicated fragments (0.5-5 kb) of DNAs of normal chicken fibroblasts, nontransformed mouse fibroblasts (G. M. Cooper et al., 1980), and normal human lymphocytes (Schafer et al., 1984) induced transformation of NIH 3T3 cells with low efficiencies (approximately 0.001-0.003 transformants/μg DNA). In contrast, high efficiencies (0.1-1 transformants/μg DNA) of transformation were observed in secondary transfection assays of high molecular weight DNAs from NIH cells transformed by normal cell DNAs (G. M. Cooper et al., 1980; Schafer et al., 1984). Normal mouse DNAs were also reported to induce transformation of both NIH 3T3 and BALB/c 3T3 cells infected with murine leukemia viruses (Krump-Konvalinkova and van den Berg, 1980). Furthermore, cotransfection with normal NIH 3T3 DNA and retroviral LTR sequences was found to activate cellular transforming genes, one of which was the cellular homolog of the retroviral *raf* gene (Muller and Muller, 1984). Similarly, ligation of molecular clones of the normal cellular homologs of the retroviral oncogenes *mos* (Blair et al., 1981) and *ras*^{H} (DeFeo et al., 1981) to retroviral LTRs activated their transforming potential. These results indicate that potential transforming genes of normal cells can be activated as a consequence of DNA rearrangements during transfection.

We report the identification and molecular cloning of a novel transforming gene detected by transfection of NIH 3T3 cells with high molecular weight DNA of a human T cell lymphoma. Characterization of this gene indicated that it was activated by a DNA rearrangement in which two unlinked segments of human DNA recombined to generate a new transcriptional unit. In addition, the results suggest that this transforming gene was activated by rearrangement of normal human DNAs during the transfection process.

Results

Transformation of NIH 3T3 Cells by 3215 Lymphoma DNA

High molecular weight DNA of a T cell lymphoma patient-isolate (designated 3215) was assayed for transforming activity by transfection of NIH 3T3 cells. DNA of this lymphoma induced a single, morphologically distinct focus in

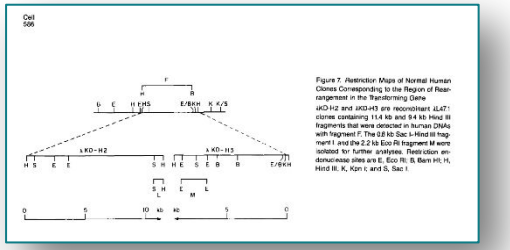


Figure 7. Restriction Maps of Normal Human Clones Corresponding to the Region of Rearrangement in the Transforming Gene

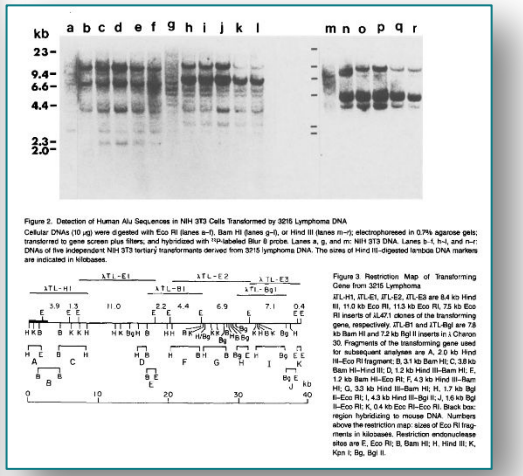


Figure 2. Detection of Human Alu Sequences in NIH 3T3 Cells Transformed by 3215 Lymphoma DNA

Figure 3. Restriction Map of Transforming Gene from 3215 Lymphoma

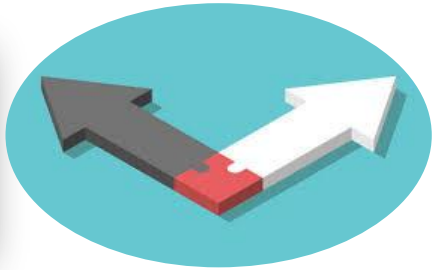
- ✔ *Molecular genetics (1985)*
- ✔ *All patients with MEN2A, MEN2B, and FMTC have RET germline mutations*
- ✔ *Approximately 50% of sporadic*
- ✔ *The prevalence of somatic RET codon mutations is different depending on tumor size*
- ✔ *Over 100 mutations, duplications, insertions, or deletions involving RET have been identified*
- ✔ *Surgical management according to the type of mutation*

De-escalation in medullary thyroid carcinoma

2000-2020

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German Association of Endocrine Surgeons practice guideline for the surgical management of malignant thyroid tumors

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Management of Medullary Thyroid Cancer

David Viola, MD, Rossella Elisei, MD*

Surgical Treatment of Medullary Thyroid Cancer

Andreas Machens and Henning Dralle

De-escalation in medullary thyroid carcinoma

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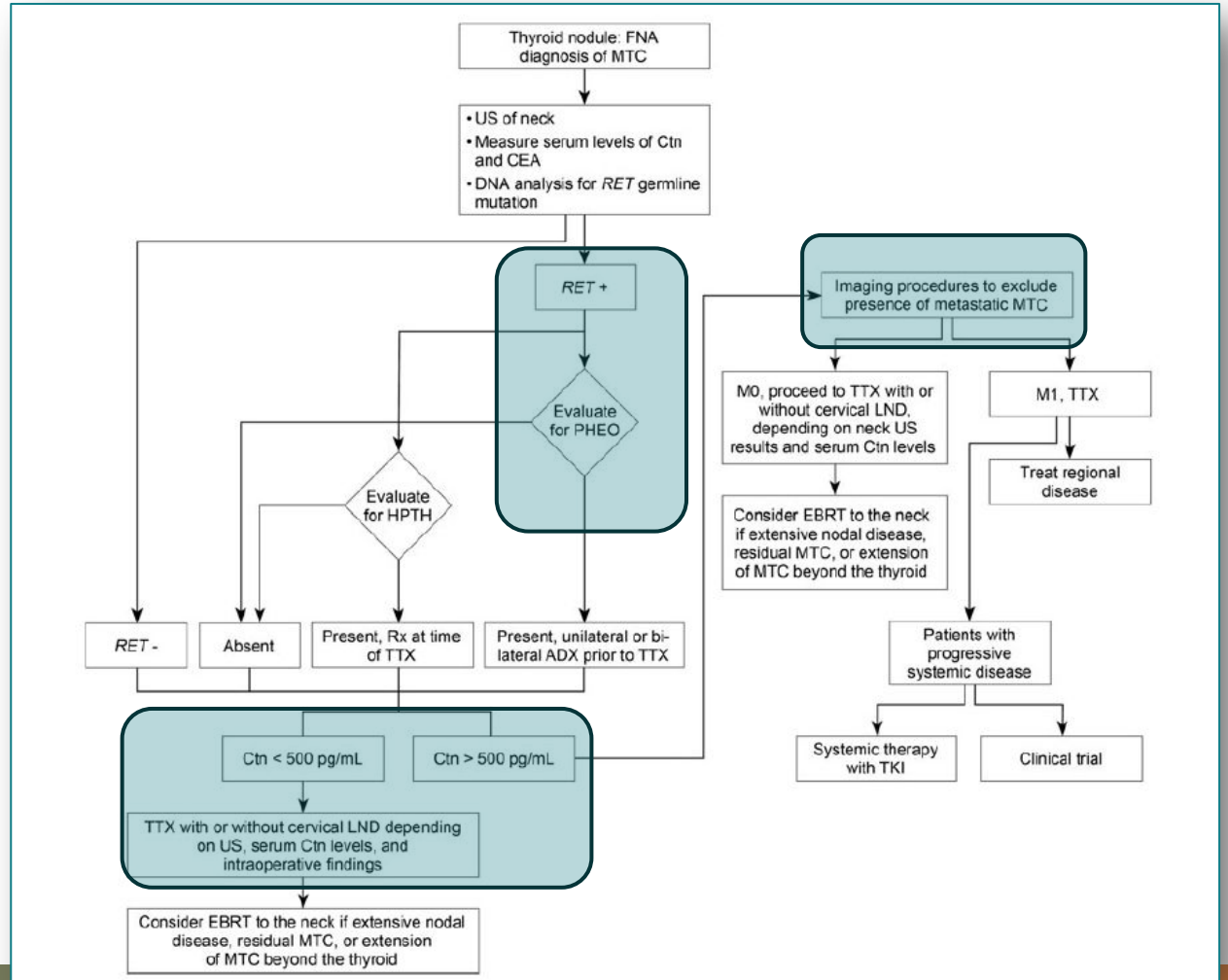
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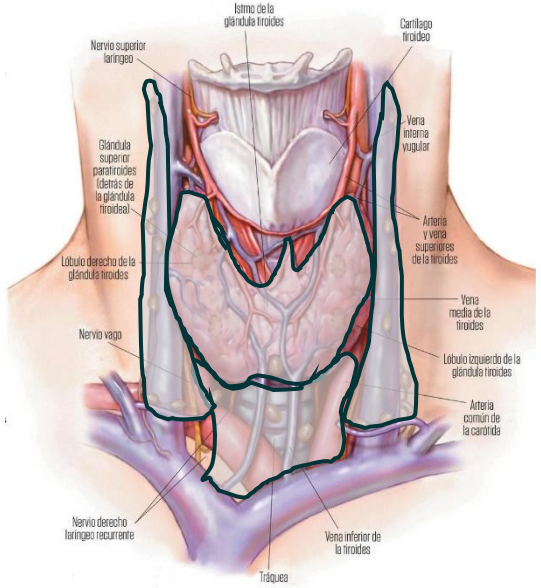
■ **RECOMMENDATION 25**

In patients with MTC and no evidence of
US, and no distant metastases, dissection o
lateral compartments (levels II–V) may b
on serum Ctn levels. The Task Force di
sensus on this recommendation. Grade I Recommendation

■ **RECOMMENDATION 26**

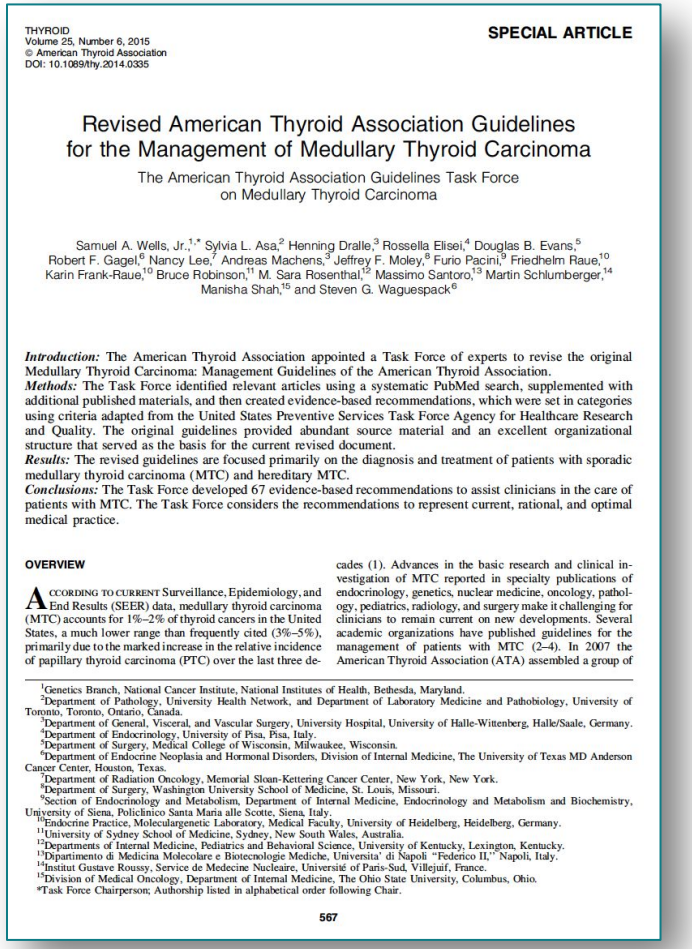
Patients with MTC confined to the neck and cervical lymph nodes should have a total thyroidectomy, dissection of the central lymph node compartment (level VI), and dissection of the involved lateral neck compartments (levels II–V). When preoperative imaging is positive in the ipsilateral lateral neck compartment but negative in the contralateral neck compartment, contralateral neck dissection should be considered if the basal serum calcitonin level is greater than 200 pg/mL. Grade C Recommendation

✔ ***Conservative management of the lateral compartment.***
✔ ***Surgery only if there is evidence of disease.***



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■ **RECOMMENDATION 28**
Following unilateral thyroidectomy for presumed sporadic MTC completion thyroidectomy is recommended in patients with a *RET* germline mutation, an elevated postoperative serum Ctn level, or imaging studies indicating residual MTC. The presence of an enlarged lymph node in association with a normal serum Ctn level is not an indication for repeat surgery. Grade B Recommendation

✔ ***Completion surgery not recommended for incidental medullary carcinoma with normal calcitonin levels.***

De-escalation in medullary thyroid carcinoma

2000-2020

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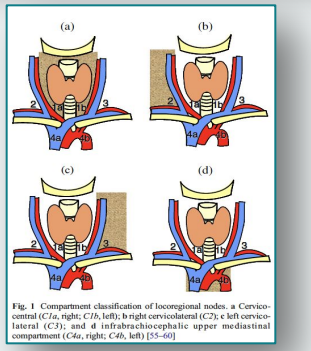


Fig. 1 Compartment classification of locoregional nodes. a Cervicocentral (*C1a*, right; *C1b*, left); b right cervicolateral (*C2*); c left cervicolateral (*C3*); and d infrabrachiocephalic upper mediastinal compartment (*C4a*, right; *C4b*, left) [55–60]

Recommendation 6:

Basal calcitonin serum levels should be determined for early diagnosis of medullary thyroid cancer before thyroid surgery. If calcitonin levels are elevated, a calcitonin stimulation test with pentagastrin or calcium is recommended.

✔ ***Routine calcitonin in all suspicious thyroid nodules (avoiding FNA)***

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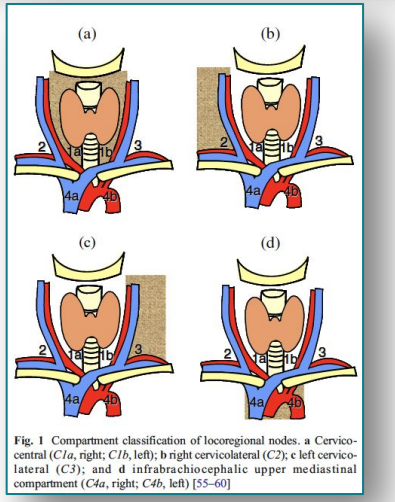
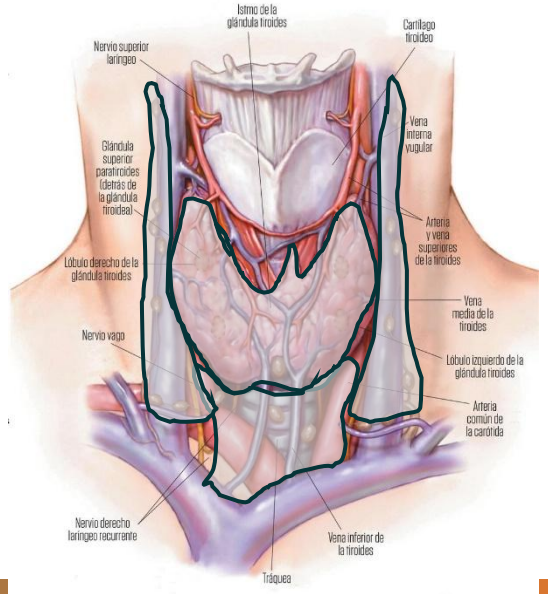


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Recommendation 40:
Sporadic MTC spreads to the central and ipilateral lateral neck compartment early on. With basal calcitonin levels ranging between >20 and 200 pg/mL (upper normal limit >10 pg/mL), prophylactic dissection of the central and ipsilateral lateral neck compartments with curative intent is recommended even in the absence of enlarged lymph nodes. Above that threshold (>200 pg/mL), reflecting primary tumor growth, the risk of contralateral lateral neck involvement and distant metastases continues to rise gradually. The inherent benefits and risks of a one-stage versus a possible two-stage procedure, with or without initial inclusion of the contrala-teral lateral neck compartment, need to be discussed with the patient during the informed consent process.

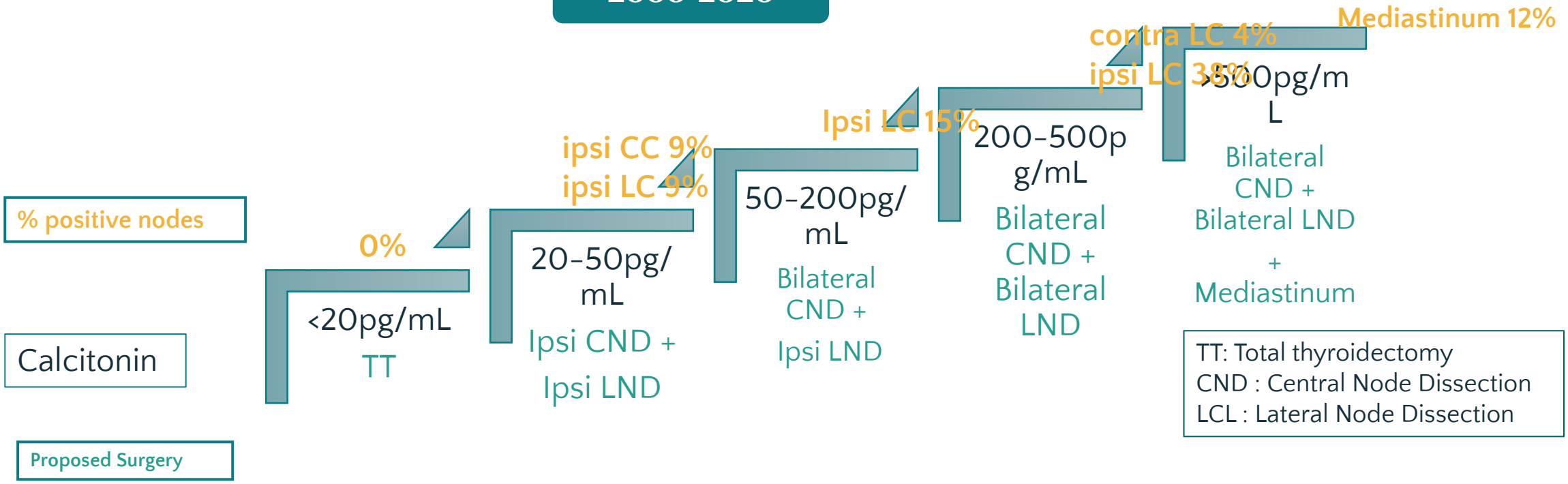
- ✔ *Aggressive management*
- ✔ *Lateral neck dissection with calcitonin above 20 pg/mL*
- ✔ *Contralateral dissection if above 200 pg/mL*



De-escalation in medullary thyroid carcinoma

- ✔ *Correlation between calcitonin levels and nodal involvement*
- ✔ *Imaging less accurate than previously assumed*
- ✔ *Concern for achieving cure at the initial* **operation**

2000-2020



TT: Total thyroidectomy
CND : Central Node Dissection
LCL : Lateral Node Dissection

Surgical Treatment of Medullary Thyroid Cancer

Andreas Machens and Henning Dralle

Management of Medullary Thyroid Cancer

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Node dissection?

Total thyroidectomy?



De-escalation in medullary thyroid carcinoma

Node dissection?



De-escalation in medullary thyroid carcinoma

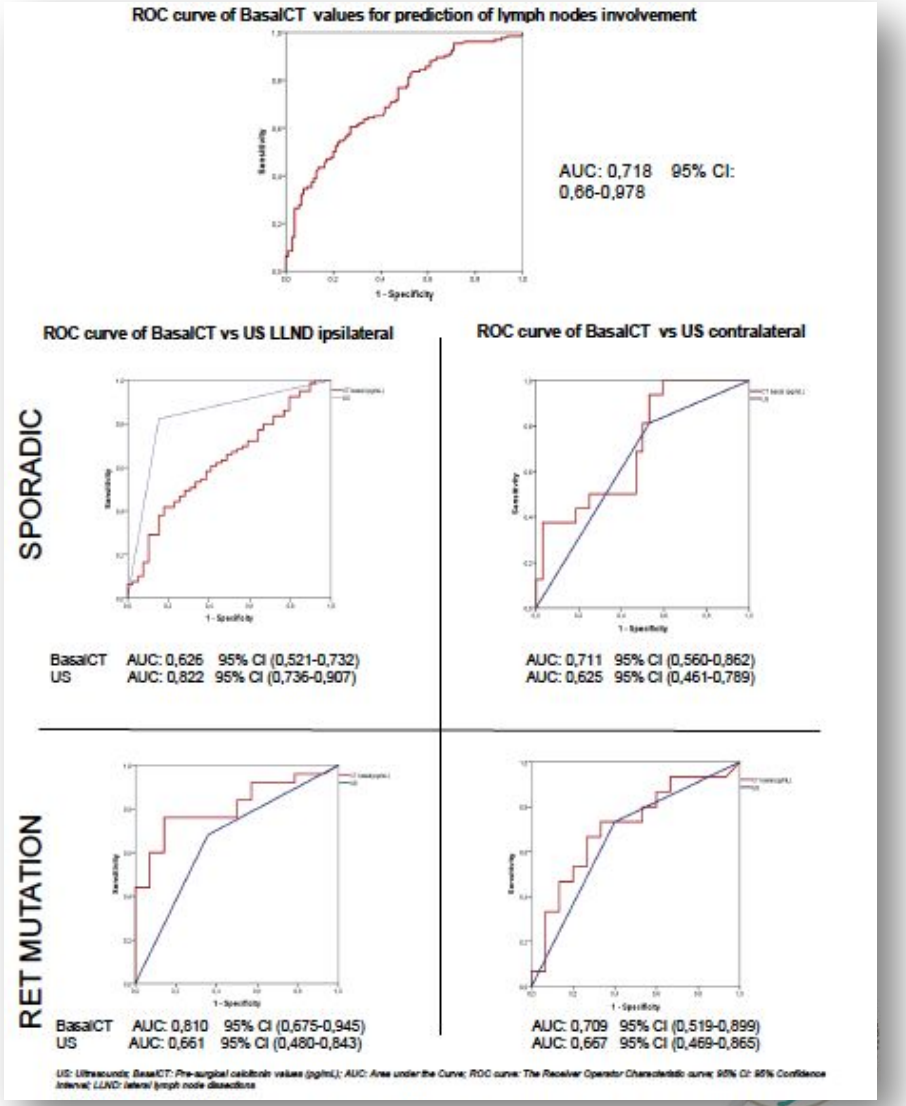
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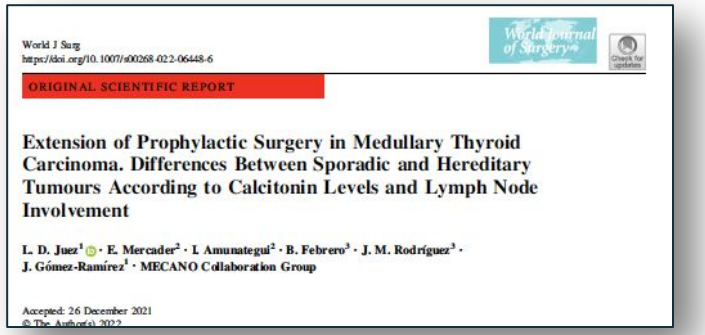
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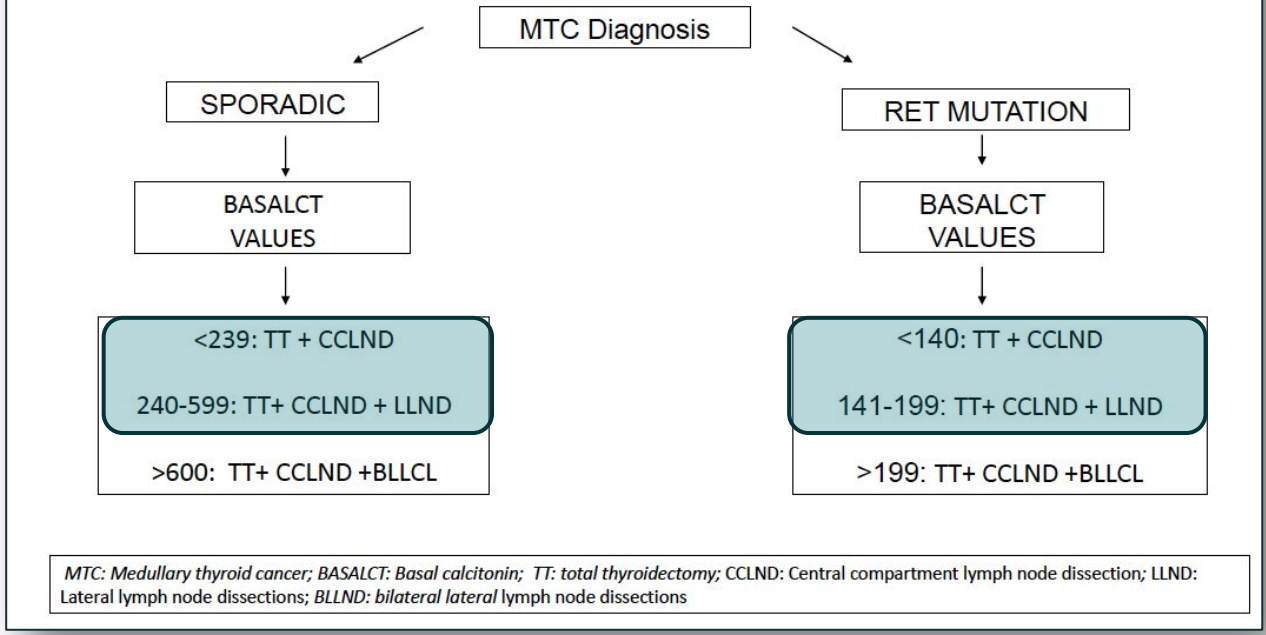
Accepted: 26 December 2021

2000-2020

	Correlation coefficient	p
Age (years)	0.071	0.267
Gender	0.106	0.100
RET gen mutation	**-0.248**	**0.000**

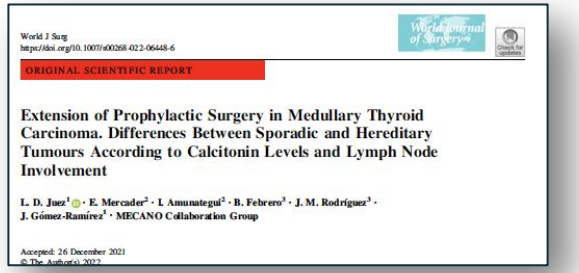
- ✔ *Cut-offs for lateral neck involvement could be higher*
- ✔ *Less aggressive management in RET-negative patients*

Figure 3. A new proposal algorithm for managing MTC based on its sporadic or hereditary nature according to basalCT levels



MTC: Medullary thyroid cancer; BASALCT: Basal calcitonin; TT: total thyroidectomy; CCLND: Central compartment lymph node dissection; LLND: Lateral lymph node dissections; *BLLND: bilateral lateral* lymph node dissections

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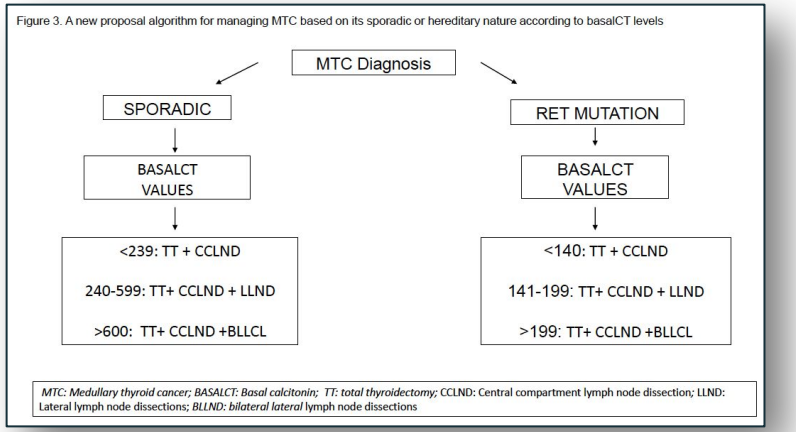


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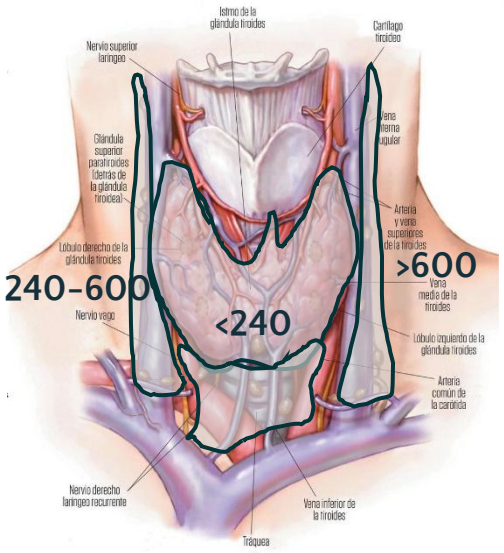
MTC Diagnosis

SPORADIC → BASALCT VALUES → <239: TT + CCLND; 240-599: TT+ CCLND + LLND; >600: TT+ CCLND +BLLCL

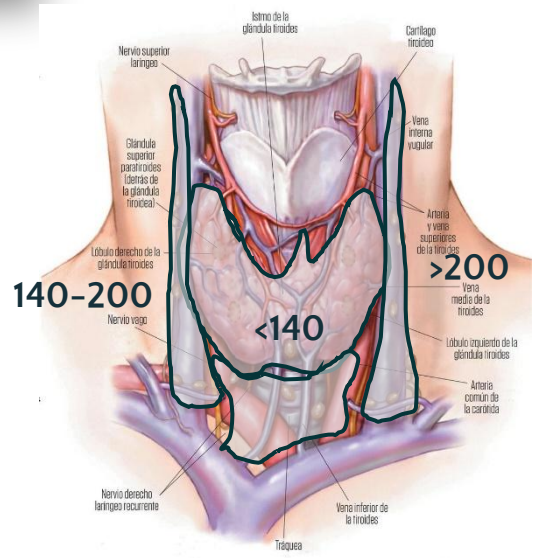
RET MUTATION → BASALCT VALUES → <140: TT + CCLND; 141-199: TT+ CCLND + LLND; >199: TT+ CCLND +BLLCL

MTC: Medullary thyroid cancer; BASALCT: Basal calcitonin; TT: total thyroidectomy; CCLND: Central compartment lymph node dissection; LLND: Lateral lymph node dissections; *BLLND: bilateral lateral* lymph node dissections

SPORADIC



HEREDITARY



De-escalation in medullary thyroid carcinoma



What next?

OXFORD

BJS, 2023, 1–2
https://doi.org/10.1093/bjs/znad172
Research Letter

Desmoplastic reaction in medullary thyroid carcinoma predicts presence of lymph node metastasis

Joaquín Gómez-Ramírez[1,*], Patricia Luengo[2], Enrique Mercader[3], Aitor Quintana[4], Jose L. Muñoz de Nova[5], Beatriz Febrero[6], Ignacio Ruz-Caracuel[7] and Jose M. Rodríguez[6]

[1]Endocrine and Breast Surgery Unit, Department of General and Digestive Surgery, Instituto de Investigación, Hospital Universitario La Paz (IdiPAZ), Madrid, Spain
[2]Endocrine and Breast Surgery Unit, Department of Surgery, Hospital Universitario Ramón y Cajal, Madrid, Spain
[3]Endocrine Surgery Unit, Department of Surgery, Hospital Universitario Gregorio Marañón, Madrid, Spain
[4]Endocrine Surgery Unit, Department of Surgery, Hospital Universitario Cruces, Bilbao, Spain
[5]Endocrine and Breast Surgery Unit, Department of Surgery, Hospital Universitario La Princesa, Madrid, Spain
[6]Endocrine and Breast Surgery Unit, Department of Surgery, Hospital Universitario Virgen de la Arreixaca, Murcia, Spain
[7]Pathology department, Hospital Universitario Ramon y Cajal, IRYCIS, Madrid, Spain. CIBERONC.

OXFORD

BJS, 2021, 108, 174–181
DOI: 10.1093/bjs/znaa047
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Original Article

Omission of lateral lymph node dissection in medullary thyroid cancer without a desmoplastic stromal reaction

M. B. Niederle[1,2,*], P. Riss[1], A. Selberherr[1], O. Koperek[3,4], K. Kaserer[3,4], B. Niederle[1,5] and C. Scheuba[1]

[1]Division of General Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria
[2]Department of General Anaesthesia, General Intensive Care and Pain Management, Medical University of Vienna, Vienna, Austria
[3]Labor Kaserer, Koperek & Beer, Pathology, Medical University of Vienna, Vienna, Austria
[4]Clinical Institute of Pathology, Medical University of Vienna, Vienna, Austria
[5]Former Head of Endocrine Surgery Section, Department of Surgery, Medical University of Vienna, Vienna, Austria

*Correspondence to: Department of General Anesthesia and Intensive Care Medicine, Medical University of Vienna, Waehringer Guertel 18-20, Vienna, A-1090, Austria. (e-mail: martin.niederle@meduniwien.ac.at)

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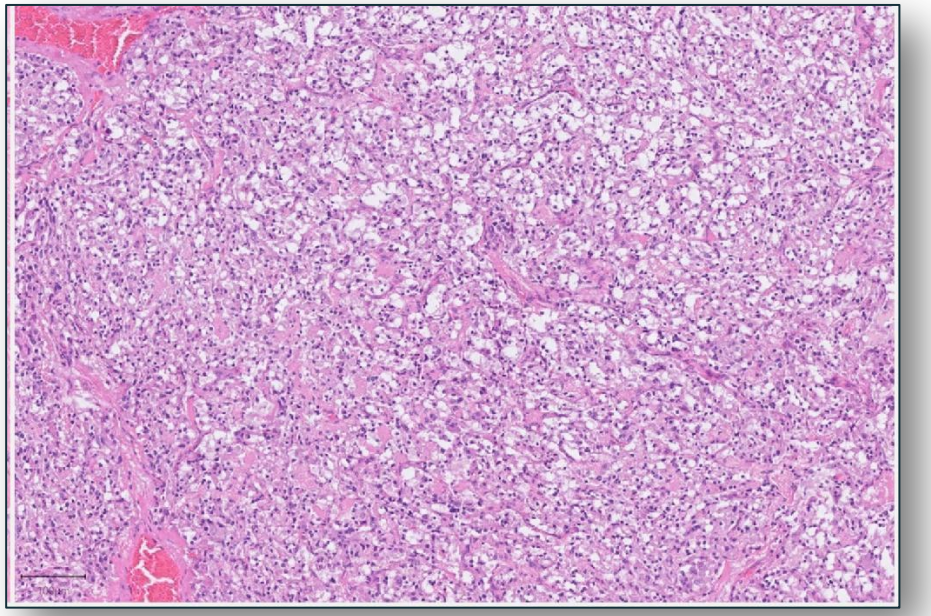
Endocrine

Abandoning node dissection for desmoplasia-negative encapsulated unifocal sporadic medullary thyroid cancer

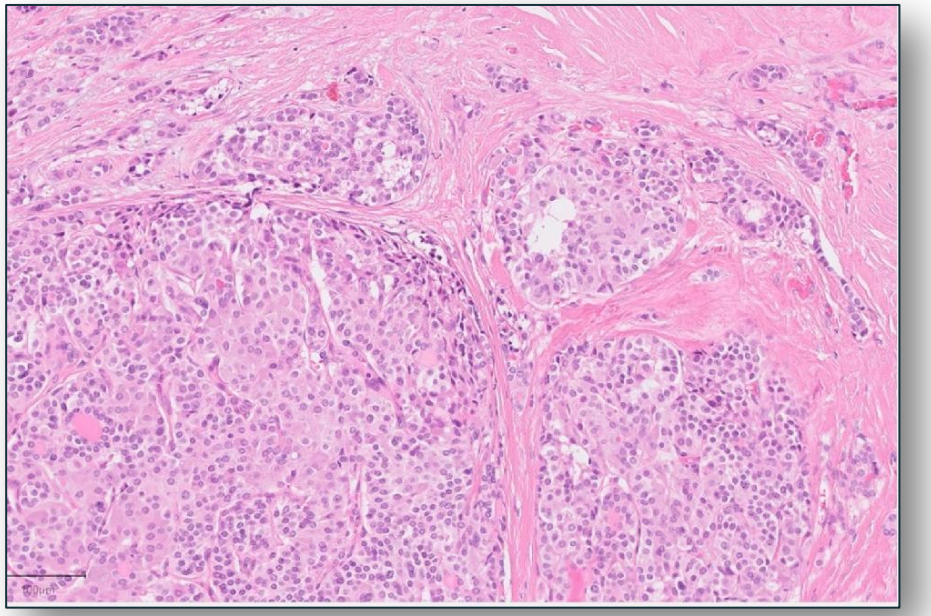
Andreas Machens, MD[a,*], Peter Kaatzsch, MD[b], Kerstin Lorenz, MD[a], Lars-Christian Horn, MD[c], Claudia Wickenhauser, MD[b], Kurt Werner Schmid, MD[d], Henning Dralle, MD[a,e], Udo Siebolts, MD, PhD[b]

[a] Department of Visceral, Vascular, and Endocrine Surgery, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany
[b] Department of Pathology, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany
[c] Department of Pathology, University of Leipzig, Germany
[d] Department of Pathology, University of Duisburg-Essen, Essen, Germany
[e] Department of General, Visceral, and Transplantation Surgery, Section of Endocrine Surgery, University of Duisburg-Essen, Essen, Germany

De-escalation in medullary thyroid carcinoma



Desmoplastic stromal reaction negative



Desmoplastic stromal reaction positive

- ***Can be assessed intraoperatively***
- ***Qualitative/semi-quantitative***
- ***Interference from prior FNA***

De-escalation in medullary thyroid carcinoma

OXFORD

BJS, 2023, 1–2
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Research Letter

Desmoplastic reaction in medullary thyroid carcinoma predicts presence of lymph node metastasis

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[7]Pathology department, Hospital Universitario Ramon y Cajal, IRYCIS, Madrid, Spain. CIBERONC.

Sensitivity	**100%**
Specificity	**30%**
Positive Predictive Value	**54%**
Negative Predictive Value	**100%**

Table 1 Clinical and pathological features according to desmoplastic reaction

Desmoplastic reaction	NO = 11 (16%)	YES = 57 (84%)	P
Sporadic	10 (91%)	42 (74%)	0.21
Tumour diameter measured by ultrasound (mm)	16 (6–44)	19 (3–62)	0.58
Calcitonin (pg/ml)	359 (18–9741)	708 (1–34149)	0.51
CEA (ng/ml)	27 (0–124)	213.2 (0–1158)	0.54
Pre-operative suspicious nodes (patiens)	0	22 (39%)	0.01
Extra-thyroidal extension (patients)	0	6 (10%)	0.2
Multifocality	2 (18%)	25 (44%)	0.1
Affected nodes CND (patients)	0	31 (54%)	0.001
Affected nodes LND (patients)	0	20 (67%)	0.001
Persistence	0	21 (37%)	0.01

Based on these results, analysis of the desmoplastic reaction can predict lymph node involvement with a sensitivity and specificity of 100 per cent, a positive predictive value of 84 per cent, and a negative predictive value of 100 per cent. This means that no patient with a NDR had lymph node involvement at final pathology or signs of persistent disease.

De-escalation in medullary thyroid carcinoma

OXFORD

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[5]Former Head of Endocrine Surgery Section, Department of Surgery, Medical University of Vienna, Vienna, Austria

*Correspondence to: Department of General Anesthesia and Intensive Care Medicine, Medical University of Vienna, Waehringer Guertel 18-20, Vienna, A-1090, Austria. (e-mail: martin.niederle@meduniwien.ac.at)

Table 1 Demographic details, preoperative parameters, and follow-up

	MTC		$P^{\P}$
	DSR-negative ($n = 64$)	DSR-positive ($n = 296$)	
Age (years)*	58 (49–65)	58 (47–68)	0.677#
Sex ratio (M:F)	30:34	139:157	0.990
Basal calcitonin (pg/ml)*‡	24 (12–66)	87 (21–707)	< 0.001#
CEA (μg/l)*§	3.0 (2.0–8.0)	6.3 (2.4–29.3)	0.020#
Genetics of MTC			< 0.001
Sporadic	60 (94)	207 (69.9)	
Hereditary	4 (6)	89 (30.1)	
Hereditary index	1	39	
Hereditary screening	3	50	
Initial postoperative follow-up			< 0.001
Persisting	0 (0)	71 (24.5)	
Disease-free	64 (100)	219 (75.5)	
Lost to follow-up	0	6	0.596
Duration of follow-up (months)†	114 (76)	92 (69)	0.026**
Long-term follow-up			< 0.001
Alive and disease-free	58 (91)	190 (65.5)	
Alive with disease	0 (0)	49 (16.9)	
Persisting	0	49	
Recurrent	0	0	
Died from MTC	0 (0)	11 (3.8)	0.112
Died from other causes	6 (9)	40 (13.8)	0.369
Cured of MTC	6	29	
Persisting MTC	0	11	

Values in parentheses are percentages unless indicated otherwise; values are *median (i.q.r.) and †mean(s.d.). ‡Older assay results were converted to facilitate comparability with Diagnostic Products Corporation Immulite® 2000 assay results. §Carcinoembryonic antigen (CEA) measurement available for 217 patients: 38 desmoplastic stromal reaction (DSR)-negative and 179 DSR-positive; normal range 0–3.8 μg/l. MTC, medullary thyroid cancer. ¶χ^2 or Fisher's exact test, except #Wilcoxon signed-rank test and **independent-samples *t* test.

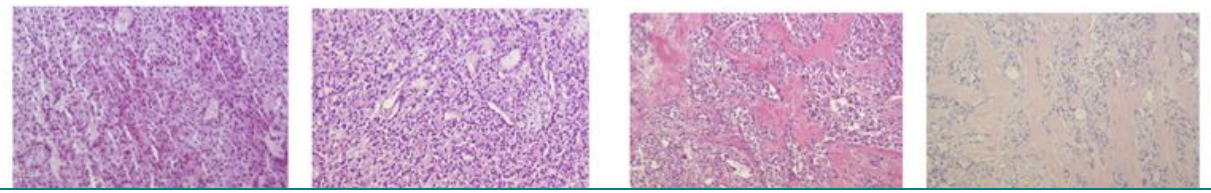
Table 2 Histopathological characteristics and classification

	MTC		$P^{\ddagger}$
	DSR-negative ($n = 64$)	DSR-positive ($n = 296$)	
Pathological tumour category			
pT1a	54 (84)	192 (64.9)	0.001
pT1b	5 (8)	47 (15.9)	0.096
pT2	5 (8)	43 (14.5)	0.152
pT3a	0 (0)	7 (2.4)	0.361
pT3b	0 (0)	2 (0.7)	1.000
pT4a	0 (0)	5 (1.7)	0.591
Pathological node category			< 0.001
pN0	64 (100)	203 (68.6)	
pN1	0 (0)	93 (31.4)	
Radiological metastasis category			0.031
rM0	64 (100)	277 (93.6)	
rM1	0 (0)	19 (6.4)	
Tumour stage			
I	59 (92)	182 (61.5)	< 0.001
II	5 (8)	21 (7.1)	0.841
III	0 (0)	16 (5.4)	0.087
IVA	0 (0)	57 (19.3)	
		1 (0.3)	
IVB	0 (0)	0 (0)	
IVC	0 (0)	19 (6.4)	
Tumour size (mm)*	3 (2–7; 1–39)	7 (2–16; 1–90)	0.001‡
Multifocal			< 0.001
No	56 (88)	179 (60.5)	
Yes	8 (12)	117 (39.5)	
Unilateral	2	15	
Bilateral	6	102	
C-cell hyperplasia			0.955
No	25 (39)	116 (39.2)	
Yes	39 (61)	180 (60.8)	
Linear	1	0	
Diffuse	3	20	
Focal	5	23	
Nodular	3	21	
Neoplastic	27	116	
Well differentiated thyroid cancer			0.572
No	49 (77)	236 (79.7)	
Yes	15 (23)	60 (20.3)	
PTC	15	54	
FTC	0	5	
FTC + PTC	0	1	

($P = 0.001$). The difference in median tumour size was 4 mm between the DSR groups.

Minimal extrathyroidal extension[39] was not found in any of the DSR-negative tumours. In contrast, 19 DSR-positive tumours (6.4 per cent) showed perithyroidal adipose tissue invasion (pT1a, 4 of 192; pT1b, 4 of 47; pT2, 8 of 43; pT3a, 3 of 7). Another two patients (0.7 per cent) presented with gross extrathyroidal exten-

De-escalation in medullary thyroid carcinoma



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Table II
Study cohort grouped by increasing intensity of desmoplasia

Desmoplasia Intensity of fibrosis	
No. of patients[†]	
Age at thyroidectomy, y, median [IQR] (range)	
Gender, no. of male patients	
Preoperative basal calcitonin level, pg/ml,[‖] median [IQR] (range)	
Preoperative CEA level, ng/ml,[#] median [IQR] (range)	
Primary tumor diameter, mm[**] median [IQR] (range)	
No. of patients with extrathyroid exte	
No. of patients with nodal disease[§,¶]	
No. of node metastases removed,[§,††] median [IQR] (range)	
No. of nodes removed,[§] median [IQR]	
No. of patients with distant metastasis	
No. of patients with biochemical cure[¶]	

Table III
Study cohort grouped by decreasing tumor capsule integrity

Tumor capsule	Evenly demarcated	Irregular but intact	≤3 extensions ≤3 mm wide	>3 extensions, or one >3 mm wide	diffuse growth, no capsule	
No. of patients[†]	6	28	13	34	58	*P*
Age at thyroidectomy, y, median [IQR] (range)	52.5 [43.5;66.3] (39–79)	60.5 [51.8;65.8] (36–71)	58 [55.5;68.5] (35–72)	61.5 [52.3;66] (34–85)	53.5 [46.8;62] (24–79)	0.163
Gender, no. of male patients	1 (17)	6 (21)	4 (31)	11 (32)	27 (47)	0.165
Preoperative basal calcitonin level, pg/ml,[‖] median [IQR] (range)	219 [40;322] (36–431)	107 [84;210] (7.5–773)	192 [96;723] (58–1834)	283 [76;801] (16–1738) *(n = 33)*	258 [77;1516] (14–32 232) *(n=57)*	0.068
Preoperative CEA level, ng/ml,[#] median [IQR] (range)	5.7 [1.5;14.4] (1.2–15.9)	5.1 [3.7;6.8] (0.8–51.2) *(n = 23)*	9.5 [6.1;27.3] (1.0–445.7) *(n = 12)*	7.3 [2.7;15.0] (1.2–383.3) *(n = 32)*	11.2 [3.7;33.2] (0.9–186.1) *(n=48)*	0.085
Primary tumor diameter, mm[**] median [IQR] (range)	7 [6;10.3] (6–11)	8.3 [6;10.8] (1.8–23)	12 [8;16] (8–25)	13 [7.8;18] (4–25)	12 [7;18.3] (2–25)	0.022
No. of patients with extrathyroid extension	0	0	0	1 (3)	12 (21)	0.007
No. of patients with nodal disease[§,¶]	0	0	0	6 (18)	36 (62)	<0.001*
No. of node metastases removed,[§,††] median [IQR] (range)	0 [0;0] (0–0)	0 [0;0] (0–0)	0 [0;0] (0–0)	0 [0;0] (0–9)	2 [0;8] (0–29)	<0.001*
No. of nodes removed,[§] median [IQR] (range)	60 [39.3;78.8] (10–93)	44 [18.3;71.3] (10–128)	37 [22.5;61.5] (14–87)	54 [35.5;66.5] (11–97)	52 [31;68.8] (12–137)	0.676
No. of patients with distant metastasis[¶]	0	0	0	0	5 (9)	0.253
No. of patients with biochemical cure[¶,‡]	6 (100)	27 (100) *(n = 27)*	12 (92)	31 (94) *(n = 33)*	30 (58) *(n=52)*	<0.001*

De-escalation in medullary thyroid carcinoma

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Table IV
Prediction of nodal disease by desmoplasia

		Nodal disease		Total
		Present	Absent	
Desmoplasia	Present	42	42	84
	Absent	0	55*	55
	Total	42	97	139
				$P < .001$
	Sensitivity			100%
	Specificity			57%
	PPV			50%
	NPV			100%
	Accuracy			70%

Presence defined as low–moderate to high desmoplasia; fibrosis >10%.
PPV, positive predictive value; *NPV*, negative predictive value.
* 55 (57%) of 97 patients underwent unnecessary neck dissection for node-negative medullary thyroid cancer in retrospect (no desmoplasia in the thyroid specimen).

Table V
Prediction of nodal disease by breach of the tumor capsule

		Nodal disease		Total
		Present	Absent	
Breach of the tumor capsule	Present	42	50	92
	Absent	0	47*	47
	Total	42	97	139
				$P < .001$
	Sensitivity			100%
	Specificity			48%
	PPV			46%
	NPV			100%
	Accuracy			64%

Presence defined as >3 extensions, 1 extension >3 mm in width, or diffuse growth without tumor capsule.
* 47 (48%) of 97 patients underwent unnecessary neck dissection for node-negative medullary thyroid cancer in retrospect (intact tumor capsule in the thyroid specimen).

De-escalation in medullary thyroid carcinoma

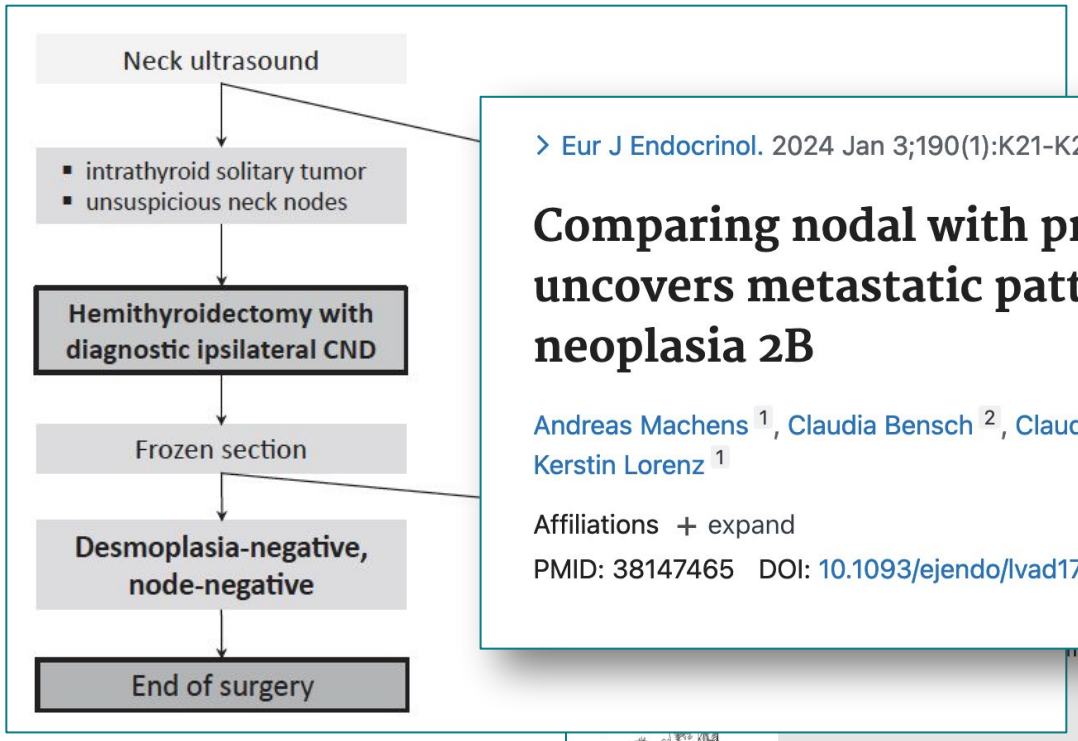


Table II
Study population grouped by frozen section of primary thyroid tumor

	No clinical evidence of		P value
	plasia positive		
		–72; 27–79)	.985
			.175
		94–1327; 79.8–1406)	.975
		21; 0.5–22.6)	.140
			.350
			.335
			.002
			>.999
		20) (6–21)	.427
			.430
			.050
			>.999
			<.001
		11; 1–14)	<.001
		43; 20–53)	<.001
No. of patients with biochemical cure (%)	19 (100)	5 (83)	.240
Follow-up, mo, median (IQR; range)	19.5 (4.8–26.8; 3–47) (n = 18)	20.5 (9.3 31.3; 4–50)	.733

> Eur J Endocrinol. 2024 Jan 3;190(1):K21-K25. doi: 10.1093/ejendo/lvad177.

Comparing nodal with primary tumor desmoplasia uncovers metastatic patterns in multiple endocrine neoplasia 2B

Andreas Machens [1], Claudia Bensch [2], Claudia Wickenhauser [2], Henning Dralle [1 3], Kerstin Lorenz [1]

Affiliations + expand

PMID: 38147465 DOI: 10.1093/ejendo/lvad177

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Sporadic noninvasive medullary thyroid neoplasm: A desmoplasia-negative unifocal nonmetastatic tumor cured by hemithyroidectomy

Henning Dralle, MD[a], Tim Brandenburg[b], Frank Weber, MD[a], Dagmar Führer-Sakel, MD[b], Sarah Theurer, MD[c], Hideo A. Baba[c], Kurt Werner Schmid, MD[c], Andreas Machens, MD[d,*]

[a] Department of General, Visceral and Transplantation Surgery, Division of Endocrine Surgery, University of Duisburg-Essen, Essen, Germany
[b] Department of Endocrinology, Diabetology and Metabolism, University of Duisburg-Essen, Essen, Germany
[c] Department of Pathology, University of Duisburg-Essen, Essen, Germany
[d] Department of Visceral, Vascular, and Endocrine Surgery, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany

De-escalation in medullary thyroid carcinoma

BJS *Prize Session*

DESMOPLASIA AND OTHER PROGNOSTIC FACTORS FOR NODAL INVOLVEMENT IN MEDULLARY THYROID CANCER.

PRELIMINARY RESULTS OF A PROSPECTIVE MULTICENTRE NATIONAL STUDY (MECANO)

Joaquín Gómez Ramírez, MD, PhD, FEBS
University Hospital La Paz, Madrid, SPAIN





De-escalation in medullary thyroid carcinoma

Risk factors of central node involvement in non-RET mutation tumour



	No Central node involvement (N=12)	Central node involvement (N=15)	P
Preoperative tumour size (mean ± SD) (mm)	18.1± 9	27.8 ± 16	.06
Preoperative Calcitonin (median (range)) (pg/mL)	229 (18-5629)	3325 (243-13808)	**.01**
DRS negative	9 (75%)	1 (6.6%)	**.001**
No capsular invasion	11 (91.7%)	5 (35.7%)	**.003**
Ki-67% <5%	10* (90.9%)	8 (57.1%)	.06

De-escalation in medullary thyroid carcinoma



RET negative tumours				
	Sensitivity	Specificity	PPV	NPV
DSR	93%	75%	82%	90%
Ki-67% >5%	43%	91%	86%	55%
Capsular invasion	64%	92%	90%	69%

De-escalation in medullary thyroid carcinoma

Total thyroidectomy?



De-escalation in medullary thyroid carcinoma

Surgery 172 (2022) 1385–1391

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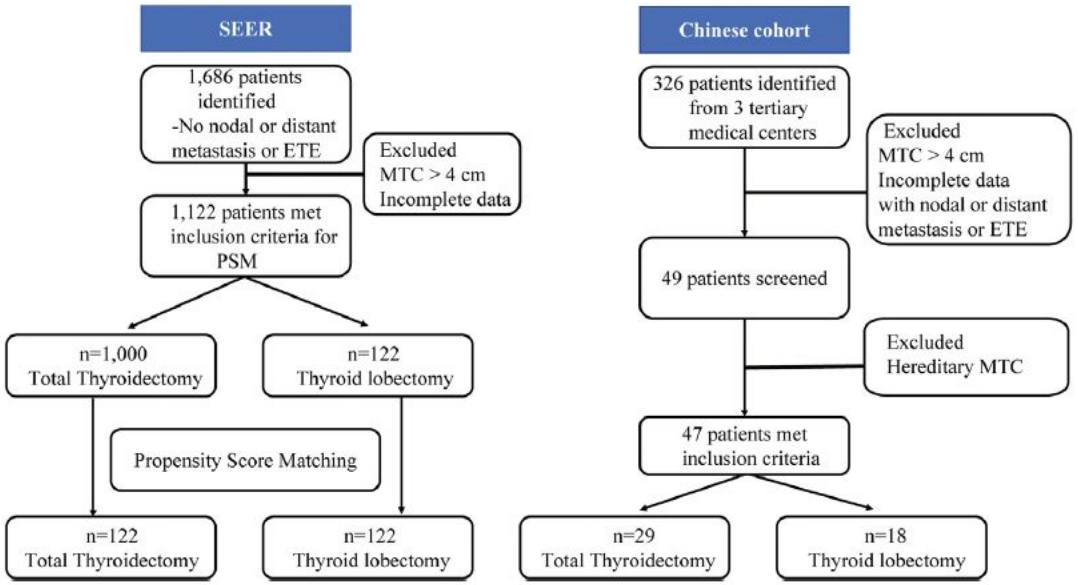
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Total thyroidectomy vs thyroid lobectomy for localized medullary thyroid cancer in adults: A propensity-matched survival analysis

Weili Liang, PhD[a], Jinyuan Shi, MD[a,b], Hui Zhang, MD[c], Guixu Lv, MD[a], Tiantian Wang, PhD[d], Yong Wang, PhD[d], Bin Lv, PhD[a], Luchuan Li, MD[a], Qingdong Zeng, MD[a], Lei Sheng, PhD[a,*]

[a] Department of Thyroid Surgery, General Surgery, Qilu Hospital of Shandong University, Jinan, China
[b] Department of Thyroid Surgery, the First Hospital of China Medical University, Shenyang, China
[c] Department of Thyroid Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China
[d] Department of Thyroid Surgery, The Second Affiliated Hospital of Zhejiang University College of Medicine, Hangzhou, Zhejiang, China



De-escalation in medullary thyroid carcinoma

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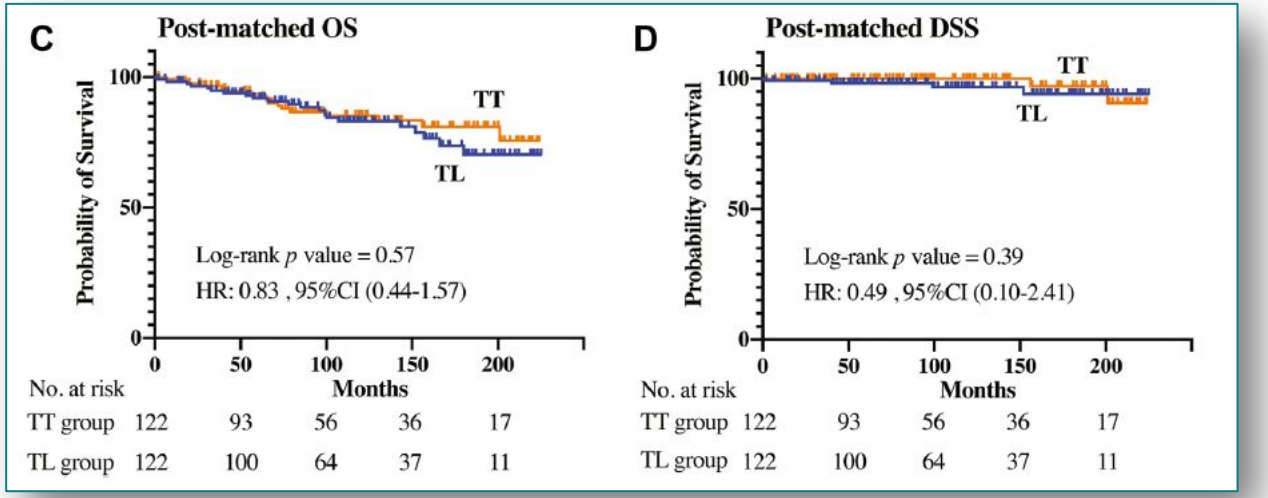
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[d] Department of Thyroid Surgery, The Second Affiliated Hospital of Zhejiang University College of Medicine, Hangzhou, Zhejiang, China



De-escalation in medullary thyroid carcinoma

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https://doi.org/10.1007/s00405-025-09929-1

HEAD AND NECK

Is hemithyroidectomy enough? Low risk of occult contralateral disease in sporadic medullary thyroid cancer

Andreas Spörlein[1] · Christoph Becker[1] · Joseph Berthelot[1] · Valentin Burkhardt[1] · Katharina Laubner[2] · Mira Fink[3] · Bernd Jänigen[3]

Risk of occult contralateral disease

Out of 48 patients, 44 (91.7%) were treated with TT. Five of those patients who received TT (11.4%) had bilateral disease. All patients with bilateral disease were diagnosed on preoperative ultrasound; thus, no occult disease was detected incidentally by resection of the contralateral lobe. Two

Table 1 Cohort characteristics

Total (*n*, %)	48 (100)
Gender (n, %)	
Female	32 (66.7)
Male	16 (33.3)
Age at surgery (median, IQR), years	60.5 (45.3–65.8)
Follow up (median, IQR), years	3.4 (1.5–7.7)
T stage (n, %)	
T1	31 (64.6)
T2	10 (20.8)
T3	6 (12.5)
T4	1 (2.1)
N (n, %)	
N0	36 (75.0)
N1a	3 (6.3)
N1b	9 (18.8)
M (n, %)	
M0	44 (91.7)
M1	4 (8.3)
Primary tumor size (median, IQR), mm	14.0 (8.3–27.5)
≤ 20	30 (62.5)
>20≤40	12 (25.0)
>40	6 (12.5)
Extent of thyroidectomy (n, %)	
Hemithyroidectomy	2 (4.2)
Completion hemithyroidectomy	2 (4.2)
Total thyroidectomy	44 (91.7)
Extent of neck dissection (n, %)	
No neck dissection	3 (6.3)
Central	16 (33.3)
Central and ipsilateral lateral	1 (2.1)
Central and bilateral lateral	24 (50.0)
Central, bilateral lateral and mediastinal	1 (2.1)
Preoperative calcitonin (median, IQR), pg/mL	582.5 (191.3–1362.3)
≤ 500	18 (40.0)
>500	27 (60.0)
Disease recurrence (n, %)	
No	41 (85.4)
Yes	7 (14.6)

De-escalation in medullary thyroid carcinoma

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HEAD AND NECK

Is hemithyroidectomy enough? Low risk of occult contralateral disease in sporadic medullary thyroid cancer

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node-negative T1 tumors without clinically suspect lymph nodes and without histopathological adverse markers, when rigorous calcitonin surveillance is ensured—HT may be oncologically equivalent to TT and associated with lower morbidity. Our data therefore support a paradigm shift

De-escalation in medullary thyroid carcinoma

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Highly-selected sporadic, apparently unifocal cN0 MTC may benefit from unilateral surgery. A proof of concept in a high-volume institution

Leonardo Rossi, MD, PhD[a,*], Antonio Matrone, MD[b], Liborio Torregrossa, MD[c], Chiara Becucci, MD[a], Andrea De Palma, MD[a], Gianluca Frustaci, MD, PhD[a], Carlo Enrico Ambrosini, MD[a], Clara Ugolini, MD[c], Gabriele Materazzi, MD[a], Rossella Elisei, MD[b]

[a] Department of Surgical, Medical and Molecular Pathology and Critical Area, Endocrine Surgery Unit, University of Pisa, Pisa, Italy
[b] Department of Clinical and Experimental Medicine, Endocrinology Unit, University of Pisa, Pisa, Italy
[c] Department of Surgical, Medical and Molecular Pathology, Pathology Unit, University of Pisa, Pisa, Italy

Table II
MTC histologic details

Variables	
Tumor size, mm, median (IQR); range	11 (8–18); 4–40
No. of patients with tumor <10 mm, *n* (%)	26 (48.1)
No. of patients with tumor >10 and ≤20 mm, *n* (%)	18 (33.3)
No of patients with tumor >20 mm, *n* (%)	10 (18.5)
Extrathyroidal extension, *n* (%)	
Microscopic	4 (7.4)
Macroscopic	0
Vascular invasion, *n* (%)	7 (13)
Tumor necrosis, *n* (%)	0
Ki-67 proliferative index , %, median (IQR)	2 (1.5)
Mitotic index per 2 mm^2 , *n*, mean (SD)	1.2 (0.9)
MTC grading, *n* (%)	
High	3 (5.6)
Low	51 (94.4)
Multifocality, *n* (%)	3 (5.6)
Bilaterality, *n* (%)	1 (1.9)
Primary tumor desmoplasia, *n* (%)	43 (79.6)
Primary tumor desmoplasia grading, *n* (%)	

Table III
Histologic details of central compartment lymph nodes

Variables	
No. of nodes removed, median (IQR); range	10 (5–12); 4–28
No. of patients pN1, *n* (%)	12 (22.2)
No. of node metastasis in pN1 patients, median (IQR); range	2 (1–5); 1–7
Maximum diameter of node metastasis, median (IQR); range	1 (1–4); 1–5
No. of pN1 patients with mMTS, *n* (%)	7 (58.3)
No. of iCC nodes removed, median (IQR); range	4 (3–7); 2–28
No. of cCCs removed, median (IQR); range	4 (2–7); 2–11
No. of iCC node metastasis, median (IQR); range	2 (1–4); 1–7
No. of cCC node metastasis, median (IQR); range	0 (0); 0–1
Maximum diameter of iCC node metastasis, mm, median (IQR); range	1 (1–3); 1–5
No. of iCC nodes with extranodal invasion, *n* (%)	3 (25)
Maximum diameter of cCC node metastasis, mm, median (IQR)	0 (0)*
No. of cCC node with extranodal invasion	0
with pN1 iCC nodes, *n* (%)	12 (22.2)
with pN1 cCC nodes, *n* (%)	2 (3.7)

central compartment; *iCC*, ipsilateral central compartment; *IQR*, ge; *mMTS*, micrometastasis.
ly 2 patients presented with cCC node metastasis, the calculation considered unnecessary.

In conclusion, unilateral surgery (hemithyroidectomy + prophylactic ipsilateral central compartment lymph node dissection) may be a safe and appropriate option in patients with suspicious unifocal sMTC without extrathyroidal spread. Over

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Research

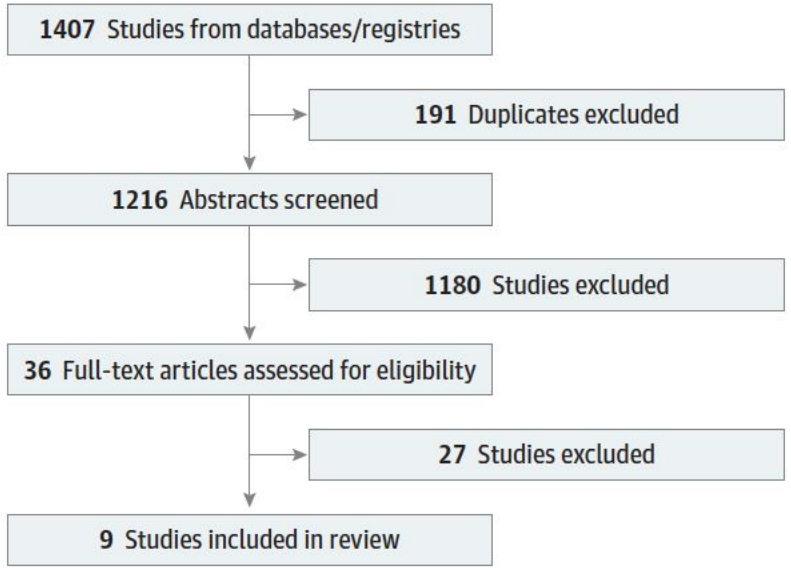
JAMA Otolaryngol Head Neck Surg. 2026;152(4):400-408. doi:10.1001/jamaoto.2025.5599

JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Total Thyroidectomy vs Lobectomy for Sporadic Medullary Thyroid Cancer
A Systematic Review and Meta-Analysis

Eddy P. Lincango, MD, MSc; Luis Vilatuna-Andrango, MD; Andrea Arce-Camposano, MD; Cristina Mena-García, MD; Luis Figueroa, MD; Sarah Herold, BS; Matias Zaldumbide, MD; Fernanda Pacheco, MD; Jennifer Cayambe, MD; Paola Solis-Pazmino, MD; Tamarah J. Westmoreland, MD; John I. Lew, MD; Frederick Drake, MD; Gustavo Romero-Velez, MD; Julie A. Sosa, MD; Juan P. Brito, MD

Figure 1. PRISMA Flow Diagram



De-escalation in medullary thyroid carcinoma

Research

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Figure 2. Forest Plots of Mortality, Survival, and Structural Recurrence Among Patients With Sporadic Medullary Thyroid Cancer Following Thyroidectomy or Thyroid Lobectomy

A Mortality

Source	Total thyroidectomy, No./total No.	Lobectomy, No./total No.	RR (95% CI)	Weight, %
≤5 y				
Wang et al,[32] 2025	0/60	0/13	0.23 (0.00-11.08)	15.2
Zhang et al,[26] 2022	1/49	7/80	0.23 (0.03-1.84)	53.6
Pillarisetty et al,[27] 2009	0/14	0/4	0.33 (0.01-14.71)	15.9
Ni et al,[25] 2024	0/20	0/16	0.81 (0.02-38.71)	15.3
Overall RR	1/143	7/113	0.30 (0.07-1.35)	
Heterogeneity: $\tau_3^2 = 0$; $P = .95$; $I^2 = 0\%$				
>5 y				
Shi et al,[28] 2025	9/230	9/230	1.00 (0.40-2.47)	100

Lower risk | Higher risk

0.03 | 0.25 | 1 | 3.50

RR (95% CI)

B Survival

Source	Total thyroidectomy, No./total No.	Lobectomy, No./total No.	RR (95% CI)	Weight, %
≤5 y				
Shi et al,[28] 2025	155/156	165/166	1.00 (0.98-1.02)	59.4
Zhang et al,[26] 2022	48/49	74/80	1.06 (0.98-1.14)	40.6
Overall RR	203/205	239/246	1.02 (0.94-1.11)	
Heterogeneity: $\tau_1^2 = 0$; $P = .14$; $I^2 = 79.1\%$				

Lower risk | Higher risk

0.90 | 0.95 | 1 | 1.05 | 1.10 | 1.15

RR (95% CI)

C Structural recurrence

Source	Total thyroidectomy, No./total No.	Lobectomy, No./total No.	OR (95% CI)	Weight, %
≤5 y				
Gülben et al,[24] 2006	4/22	7/10	0.10 (0.02-0.54)	30.1
Ni et al,[25] 2024	0/20	1/16	0.25 (0.01-6.62)	11.5
Zhang et al,[26] 2022	5/49	11/80	0.71 (0.23-2.19)	47.5
Pillarisetty et al,[27] 2009	1/14	0/4	1.00 (0.03-29.19)	10.9
Overall OR	10/105	19/110	0.45 (0.14-1.49)	
Heterogeneity: $\tau_3^2 = 0.46$; $P = .26$; $I^2 = 29.9\%$				
>5 y				
Shi et al,[28] 2025	28/230	33/230	0.83 (0.48-1.42)	46.7
Ito et al,[29] 2009	0/31	0/40	1.29 (0.02-66.61)	15.8
Ma et al,[30] 2011	9/12	9/58	16.33 (3.69-72.29)	37.5
Overall OR	37/273	42/328	7.26 (1.07-49.21)	
Heterogeneity: $\tau_3^2 = 1.97$; $P = .001$; $I^2 = 77.5\%$				

Lower odds | Higher odds

0.1 | 1 | 10 | 100

OR (95% CI)

OR indicates odds ratio; RR, relative risk.

Figure 3. Forest Plots of Biochemical Cure and Distant Metastasis Among Patients With Sporadic Medullary Thyroid Cancer Following Thyroidectomy or Thyroid Lobectomy

A Biochemical cure

Source	Total thyroidectomy, No./total No.	Lobectomy, No./total No.	OR (95% CI)	Weight, %
≤5 y				
Pillarisetty et al,[27] 2009	10/14	4/4	0.26 (0.01-5.89)	3.7
Wang et al,[32] 2025	49/60	12/13	0.37 (0.04-3.16)	7.9
Zhang et al,[26] 2022	30/49	50/80	0.95 (0.46-1.97)	67.7
Ni et al,[25] 2024	9/20	7/16	1.05 (0.28-3.95)	20.7
Overall OR	98/143	73/113	0.86 (0.47-1.56)	
Heterogeneity: $\tau_3^2 = 0$; $P = .73$; $I^2 = 0\%$				
>5 y				
Ma et al,[30] 2011	3/12	49/58	0.06 (0.01-0.27)	20.1
Ito et al,[29] 2009	19/31	31/40	0.46 (0.16-1.30)	24.0
Shi et al,[28] 2025	144/215	139/203	0.93 (062-1.41)	28.3
Semenov et al,[31] 2023	335/464	58/80	0.99 (0.58-1.68)	27.6
Overall OR	501/722	277/381	0.87 (0.26-2.89)	
Heterogeneity: $\tau_2^2 = 1.28$; $P = .003$; $I^2 = 91.2\%$				

Lower odds | Higher odds

0.01 | 0.1 | 10

OR (95% CI)

B Distant metastasis

Source	Total thyroidectomy, No./total No.	Lobectomy, No./total No.	OR (95% CI)	Weight, %
≤5 y				
Gülben et al,[24] 2006	3/22	6/10	0.11 (0.02-0.61)	60.4
Ni et al,[25] 2025	1/20	0/16	2.54 (0.10-66.59)	
Overall OR	4/42	6/26	1.64 (0.09-31.52)	
Heterogeneity: $\tau_1^2 = 2.97$; $P = .09$; $I^2 = 62.4\%$				

Lower odds | Higher odds

0.01 | 0.1 | 1 | 10 | 50

OR (95% CI)

De-escalation in medullary thyroid carcinoma

Research

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Conclusions

In this systematic review and meta-analysis, evidence from retrospective studies suggested that, in patients with small and unilateral sMTC without nodal involvement or local invasion who underwent curative surgery, oncologic outcomes were broadly comparable between total thyroidectomy and lobectomy. Lobectomy plus central neck dissection showed a low

De-escalation in medullary thyroid carcinoma

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REVIEW ARTICLE ENDOCRINE TUMORS

The Management of Medullary Thyroid Cancer: A Review

Amblessed E. Onuma, MD, MS[1] · Saba Kurtom, MD[2] · Lauren N. Krumeich, MD[3] · Sarah B. Fisher, MD[4] · Paxton Dickson, MD[5] · Yinin Hu, MD[6]

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Abstract
Medullary thyroid cancer (MTC) is a rare neuroendocrine malignancy arising from parafollicular C cells. Diagnosis is based on cytologic and histologic features, supported by biochemical testing for calcitonin and carcinoembryonic antigen, *RET* germline testing, and appropriate imaging. This educational review, developed by the Society of Surgical Oncology's Endocrine and Head and Neck Disease Site Working Group, provides an updated overview of the diagnosis and management of MTC, emphasizing evolving surgical principles and the integration of targeted therapies. Ongoing multidisciplinary collaboration and participation in clinical trials remain essential to further refine progn
improve patient outcomes in MTC.

Keywords Medullary thyroid cancer · Thyroidectomy · Targeted therapy · I

For sporadic MTC, the risk of occult contralateral disease is low. Therefore, index lobectomy could be considered when hereditary disease has been ruled out, there is no clinical evidence of contralateral disease, and calcitonin is undetectable after resection.[36] In a retrospective study by

De-escalation in medullary thyroid carcinoma

If it's written here, it must be important

In **sporadic, unifocal** medullary carcinoma without nodal disease,

unilateral surgery may be considered

De-escalation in medullary thyroid carcinoma

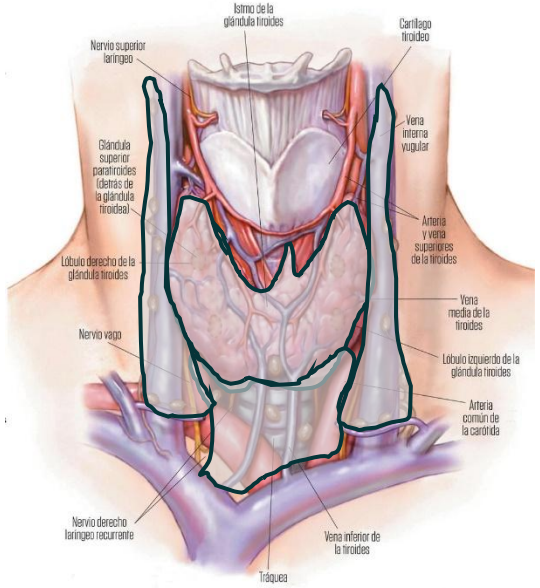
1950-60

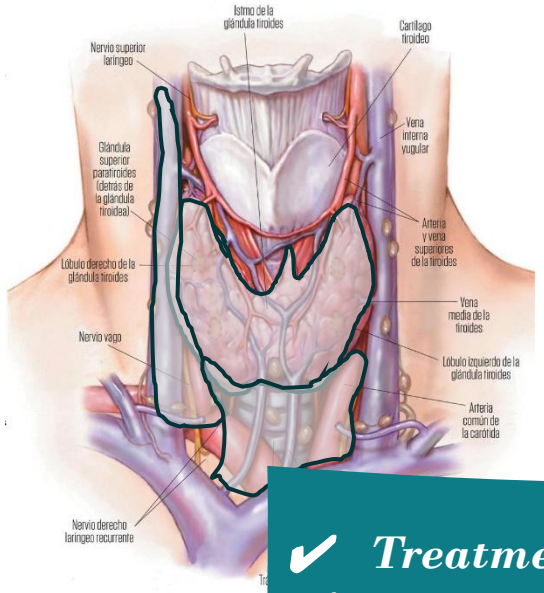
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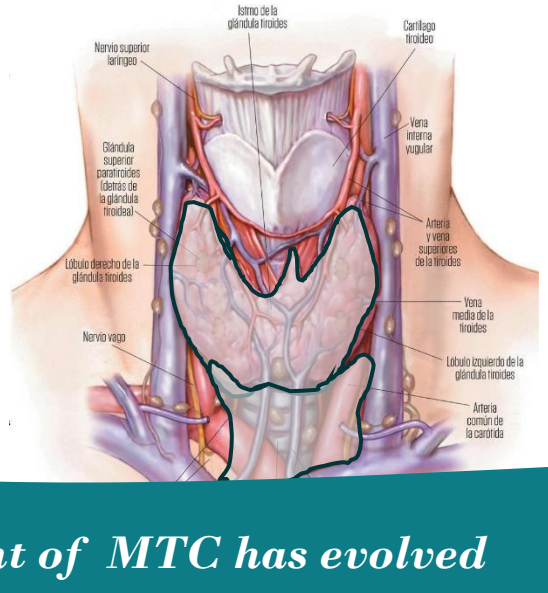
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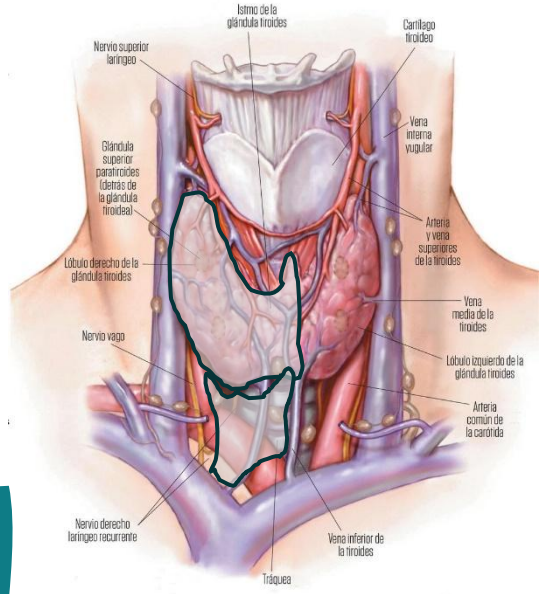
2000-2020

2020-



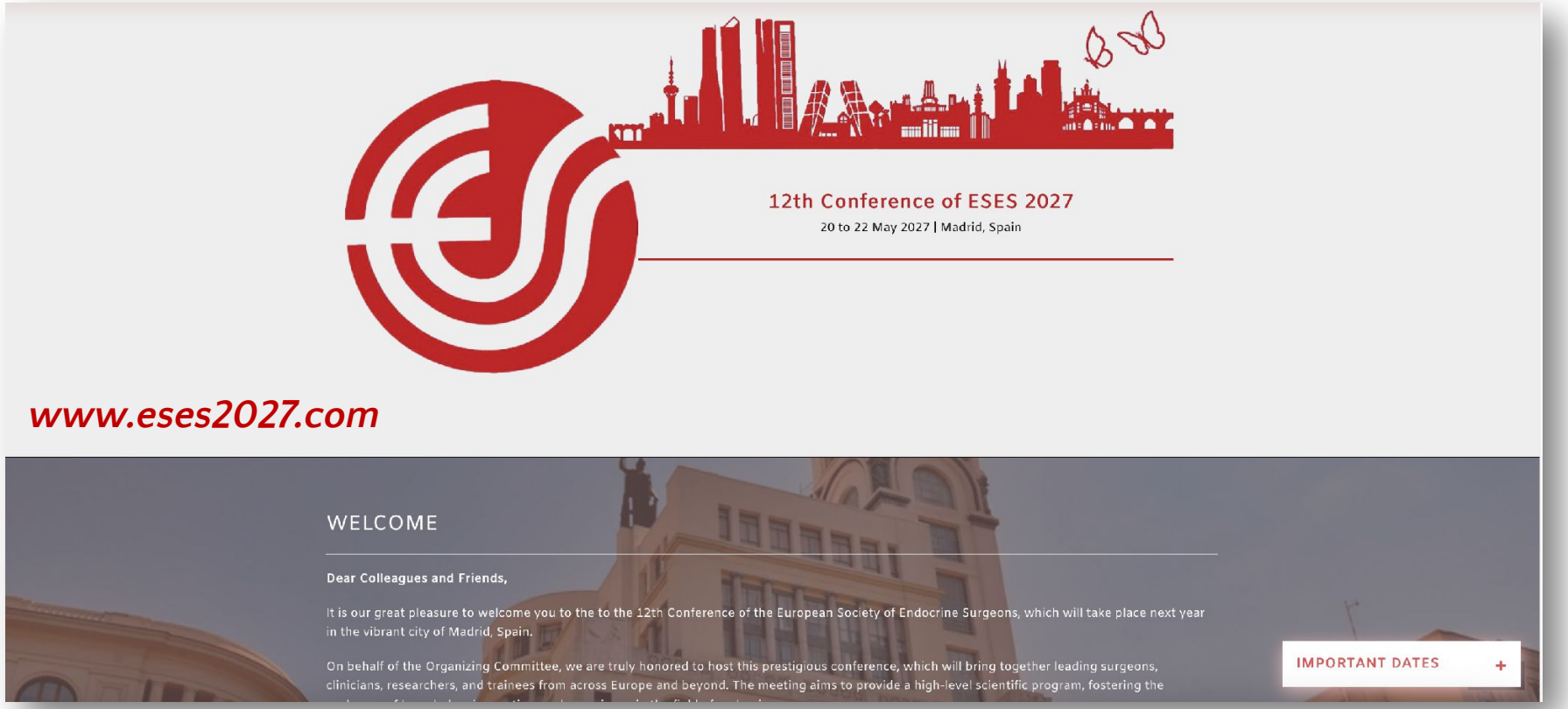






- ✔ *Treatment of MTC has evolved*
- ✔ *Prognostic factors*
- ✔ *Tailored surgery*

Thank you


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WELCOME
Dear Colleagues and Friends,
It is our great pleasure to welcome you to the to the 12th Conference of the European Society of Endocrine Surgeons, which will take place next year in the vibrant city of Madrid, Spain.
On behalf of the Organizing Committee, we are truly honored to host this prestigious conference, which will bring together leading surgeons, clinicians, researchers, and trainees from across Europe and beyond. The meeting aims to provide a high-level scientific program, fostering the
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