# Stromal Desmoplastic reaction as a predictive factor for lymph node metastasis in medullary thyroid cancer

**Acronym: DESMED study**

**Type of study: Prospective multicenter international study**

**Promoter Center:**

**1st Propedeutic Department of Surgery, AHEPA University Hospital, School of Medicine, Faculty of Health Science, Aristotle University, Thessaloniki, Greece**

## Research hypothesis

Negative Desmoplastic stromal reaction is correlated to negative nodal disease in medullary thyroid cancer.

## Introduction

Medullary thyroid cancer is a rare but aggressive subtype of thyroid cancer, counting for 5-10% of thyroid cancers with a 1-2% incidence in nodular thyroid diseases. The aggressiveness of this tumor has been correlated with certain factors in the international literature. These are the tumor size, carcinoembryonic antigen (CEA) and calcitonin levels pre- and postoperatively, patient age and sex, TNM stage, type of surgery and time interval to relapse. Recently, desmoplastic stromal reaction is considered a major risk factor for nodal metastases, but is still a debatable topic in the literature(1–6). Our study aims to assess desmoplastic stromal reaction as an independent risk factor for lymph node metastasis in medullary thyroid cancer.

## Study Description

This study is designed as a **prospective multicenter cohort study**. Five centers will take part in this study:

1. 1st Propaedeutic Department of Surgery, AHEPA University Hospital, Aristotle University Hospital, Thessaloniki, Greece
2. General Surgery Unit, Cagliari University Hospital, Monserrato, Italy
3. Endocrine Surgery Unit, University Hospital of Pisa, Pisa, Italy
4. Endocrine Surgery Unit, Verona University Hospital, Verona, Italy
5. Endocrine Surgery Unit, University Hospital Agostino Gemelli IRCCS, Rome, Italy

The aim of this study is to evaluate desmoplastic stromal reaction as an independent factor of lymph node metastasis (central and lateral neck compartment) in medullary thyroid cancer.

**Sample size calculation**

Each research question—whether primary or secondary—will be evaluated individually to determine whether the null or the alternative hypothesis holds true. Theoretically, each hypothesis carries a 50% probability of being correct. To ensure a robust study design that aligns with globally accepted research standards, the statistical power was set at 80% with a margin of error (significance level) of 0.05. Based on sample size calculations conducted via G*power application, the required sample size was determined to be 74 patients.

## Materials and Methods

**Inclusion criteria:**

- Patients who underwent thyroidectomy for medullary thyroid cancer (total thyroidectomy) +/- central/lateral neck dissection
- Sporadic medullary thyroid cancer

## Exclusion criteria

- Age < 18 years
- Hereditary medullary thyroid cancer cases
- Patients that do not undergo central or lateral lymph node dissection
- Patient unwillingness to participate in this study
- Incomplete follow-up
- Patient is participating in another clinical trial which may affect this study's outcomes

## Study period

**September 2026- September 2027**

## Data collection

Data will be collected prospectively in this study, by each participating center. This data include: age, gender, tumor diameter, Body Mass Index (BMI), preoperative basal calcitonin and CEA (carcinoembryonic antigen) levels, Fine-needle Aspiration (FNA) (conduction preoperatively or not and time period before operation), type of operation underwent, presence of lymph node and distant metastasis preoperatively, TNM stage in the pathology report, presence of extrathyroidal extension, lymphovascular invasion, capsular invasion, multifocality, postoperative levels of calcitonin and CEA.

## Evaluation of stromal desmoplastic reaction

Two independent and experienced pathologists from each center will evaluate the stromal desmoplastic reaction (DSR) around tumor according to international guidelines. Stromal desmoplastic reaction is defined by the fibrotic response in the tumor microenvironment. It is evaluated under a standard **hematoxylin and eosin (H&E)** microscope review. Masson's Trichrome staining is a specialized histological stain, highlighting the architecture, density, and distribution of collagen, allowing pathologists to accurately visualize the extent of fibrosis and the structural maturity of the tumor stroma. DSR will be categorized into three distinct categories: (a) negative (<1%), (b) low-intermediate (1-10%), (c) intermediate-high (11-50%) and (d) high (>50%).

## Database

The database will be held on Microsoft Excel, where all centers included in this study will add the parameters needed.

## Outcomes

Primary outcome: Absence of Desmoplastic stromal reaction and lymph node status.

Secondary outcome: Multivariable analysis of several factors including desmoplastic reaction related to lymph node metastasis.

## Statistical analysis

Statistical analysis will be applied in Statistical Package for the Social Sciences 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables will be demonstrated as mean with standard deviation (SD) or as median with interquartile range (IQR), depending on normality having been assumed or not, respectively, while categorical variables will be presented as frequencies with percentages (%). Univariate and multivariate analysis will be applied to assess the correlation of these parameters with tumor aggressiveness**. In case of data heterogeneity, we will conduct propensity score matching analysis in order to eliminate the risk of bias (Selection bias, extrapolation bias).**

## Data monitoring plan

We are going to monitor all data accrual. Furthermore, we will review the progress of the clinical trial including safety data and ensure as possible that it is conducted, recorded and reported in accordance with the protocol, good clinical practice and the applicable regulatory requirements.

## Data confidentiality

Each patient- sample will be identified by his/her initials and a unique patient identification number. Source data will be stored with source documents. Only personnel responsible for collecting data and transcribing it into the case report forms will have access to the data. Records will remain on site in secure areas.

## Funding

No additional funding for the execution of the present protocol is necessary. The investigators are willing to execute the present study without any additional reimbursement.

## Ethics

The aim of this study is to evaluate stromal desmoplastic reaction as an independent risk factor for nodal metastasis in medullary thyroid cancer. Information regarding desmoplasia will be collected postoperatively and this will not interfere with the therapeutic decisions for the patients. Therapeutic strategy will **NOT** be altered and patients will receive the treatment of choice regarding their disease stage according to the international guidelines.
Prior to study institution review board (IRB) approval should be obtained. Any changes in the study protocol, informed consent forms, or investigator must be re-approved by the IRB. All patients enrolled in the study will provide their consent prior to entering the study. An informed consent form shall be signed and dated by the patient. The investigator will retain the forms as part of the study records.
This study will be executed in accordance with the Declaration of Helsinki, in agreement with the guidelines for conducting a clinical investigation in accordance with the principles of ICH GCP outlined in the E6 document. By signing the present protocol, participants in the study commit themselves to carry it out in accordance with local legal requirements.

**Informed consent**

All eligible patients should have the capacity to provide an informed consent. The above described inclusion and exclusion criteria were designed to ensure the entry of the appropriate population of patients to this study and will be approved by the local IRB. Screening for these criteria will be conducted by the coordinator. Eligible patients will be educated about the research proposal by a study investigator. To determine whether the patient has understood the issues, he/she will be asked to describe what the research entails and whether they have any questions. All questions will be addressed prior to enrollment. The patient can refuse participation in the study at any time. A written informed consent form will be generated. For each patient, a case report form (CRF) will be completed, providing general medical information and history.

## References

1. Machens A, Kaatzsch P, Lorenz K, Horn LC, Wickenhauser C, Schmid KW, et al. Abandoning node dissection for desmoplasia-negative encapsulated unifocal sporadic medullary thyroid cancer. Surgery. 2022 Feb;171(2):360–7. doi:10.1016/j.surg.2021.07.035
2. Koperek O, Scheuba C, Cherenko M, Neuhold N, De Micco C, Schmid KW, et al. Desmoplasia in medullary thyroid carcinoma: a reliable indicator of metastatic potential. Histopathology. 2008 Apr 26;52(5):623–30. doi:10.1111/j.1365-2559.2008.03002.x
3. Gómez-Ramírez J, Luengo P, Mercader E, Quintana A, Muñoz De Nova JL, Febrero B, et al. Desmoplastic reaction in medullary thyroid carcinoma predicts presence of lymph node metastasis. British Journal of Surgery. Oxford University Press; 2023. p. 1011–2. doi:10.1093/bjs/znad172 PubMed PMID: 37343053.

4. Machens A, Lorenz K, Bensch C, Wickenhauser C, Dralle H. Tumor desmoplasia outperforms preoperative serum calcitonin as surgical biomarker in sporadic medullary thyroid cancer. Head Neck. 2024 Nov 1. doi:10.1002/hed.27827 PubMed PMID: 38850101.
5. Dralle H, Brandenburg T, Weber F, Führer-Sakel D, Theurer S, Baba HA, et al. Sporadic noninvasive medullary thyroid neoplasm: A desmoplasia-negative unifocal nonmetastatic tumor cured by hemithyroidectomy. Surgery (United States). 2023 Dec 1;174(6):1356–62. doi:10.1016/j.surg.2023.09.003 PubMed PMID: 37821265.
6. Procopio PF, Pennestrì F, Voloudakis N, La Rocca S, Gallucci P, Rossi ED, et al. Is desmoplastic stromal reaction useful to modulate lymph node dissection in sporadic medullary thyroid carcinoma? Surgery (United States). 2024. doi:10.1016/j.surg.2024.05.063