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# Lymph Node Ratio as a Predictive Factor of Persistent/Recurrent Disease in Patients With Medullary Thyroid Cancer: A Single-Center Retrospective Study

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ABSTRACT

*Objective:* Thyroidectomy with neck lymph node dissection is curative for most patients with medullary thyroid cancer (MTC). Lymph node ratio (LNR, ie, the ratio between the metastatic and the removed lymph nodes) is a reliable parameter with which to estimate both disease extent and quality of neck dissection. The aim of this study was to investigate the prognostic role of LNR to predict persistent/recurrent disease in patients with MTC.

*Methods:* A single-center, retrospective study of a consecutive cohort of 95 patients with MTC treated with total thyroidectomy and neck dissection. Receiver operating characteristics curve analysis was performed to identify the LNR cut-off.

*Results:* LNR was positively associated with tumor size, preoperative and postoperative calcitonin values, postsurgery carcinoembryonic antigen values, persistent/recurrent disease, and the occurrence of distant metastases during follow-up. At multivariate analysis, persistent/recurrent disease was independently associated with the LNR value and was accurately predicted by a cut-off value of 0.12 (area under the curve = 0.85). Indeed, patients with LNR ≥0.12 had a higher probability of developing persistent/recurrent disease (79.3% vs 10.6%, odds ratio = 32.3, 95% CI = 9.8-106.4; $P < .001$) and distant metastasis (34.5% vs 3.0%, odds ratio = 16.8, 95% CI = 3.4-83.6; $P < .001$) than patients with LNR <0.12. The median time to progression was 15 months in patients with LNR ≥0.12 whereas it was not reached in patients with LNR <0.12 (hazard ratio: 7.18, 95% CI = 3.01-17.11, $P < .001$).

*Conclusions:* LNR is a reliable prognostic factor to predict the risk of recurrence, persistence, and distant metastases in patients with MTC.



## Introduction

Medullary thyroid cancer (MTC) is a neuroendocrine tumor that arises from the calcitonin (Ctn)-producing parafollicular C-cells and represents <5% of all thyroid malignancies.[1] The majority of MTCs are sporadic, but the familial form, responsible for about 25% of cases, occurs in the context of multiple endocrine neoplasia (MEN) 2A or 2B or pure familial MTC syndrome.[2] Features of MEN 2A include medullary thyroid carcinoma, pheochromocytoma, and primary hyperparathyroidism. MEN 2B, on the other hand, is characterized by MTC, phaeochromocytoma, multiple mucosal neuromas, ganglioneuromatosis, marfanoid habitus, and corneal

*Abbreviations:* CEA, carcinoembryonic antigen; Ctn, calcitonin; HR, hazard ratio; LNM, lymph node metastases; LNR, lymph node ratio; MEN, multiple endocrine neoplasia; MTC, medullary thyroid cancer; OR, odds ratio; PFS, progression-free survival; ROC, receiver operating characteristics.

LNR is a reliable parameter that reflects the quality of the surgery and the extent of the disease; in fact, it can predict the risk of recurrence or persistence, both locally and at distance. For this reason, it should be used to predict the outcome and guide the follow-up.

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nerve thickening.[3] C-cells produce multiple products, including the polypeptide hormone Ctn and glycoprotein carcinoembryonic antigen (CEA). Both Ctn and CEA have serum concentrations that are directly related to C-cell mass, making them valuable tumor markers in patients with MTC.[4] MTC is characterized by relatively slow tumor growth but early lymphatic metastatic spread, which is present in 35% of patients at the time of initial diagnosis, with the predominance of cervical and mediastinal lymph node metastases (LNM).[5] Patients with either familial sporadic MTC should be treated by total thyroidectomy plus dissection of the lymph nodes in the central zone of the neck.[6] Dissection of the lateral neck compartments is only recommended when metastatic disease is suspected based on neck ultrasound and serum Ctn levels.[7,8] The prognosis is strongly related to various patient- and disease-related parameters including gender, age at diagnosis, local tumor invasion, LNM, distant metastases, and response to initial treatment.[9]

An additional prognostic factor in MTC could be the lymph node ratio (LNR), which reflects the degree of metastatic extent in the neck and the quality of the lymphadenectomy. LNR is a recognized prognostic factor in various tumors, including cancers of the head and neck,[10] stomach,[11] breast, pancreas,[12] neuroendocrine tumors of the small bowel,[13] colon-rectum,[14] and for papillary thyroid cancer[15] as well. The prognostic role of LNR in MTC has been poorly studied and its role remains controversial due to discrepancy of values that have been evaluated as cut-off, although the few works present in the literature agree with the utility of the LNR as a tool to predict the outcome of patients with MTC.

The aim of this study was to evaluate the potential role of LNR as a prognostic factor of the recurrence or persistence of disease in MTC patients and to find the best cut-off able to predict the outcome.

**Highlights**

- Lymph node ratio (LNR) is a factor independently associated with the recurrent/persistent disease.
- The LNR cut-off value of 0.12 can reliably predict persistent/recurrent disease.
- LNR is a reliable tool to predict progression-free survival in patients with medullary thyroid cancer.

**Clinical Relevance**

Lymph node ratio is a reliable parameter that reflects the quality of the surgery and the extent of the disease; in fact, it can predict the risk of recurrence or persistence, both locally and at distance. For this reason, it should be used to predict the outcome and guide the follow-up.

## Methods

### *Patient Selection and Treatment Modality*

We retrospectively analyzed the clinical characteristics at presentation, treatment and outcome of a continuous series of 95 patients with MTC referred to our Thyroid Clinic and followed up from 2000 to 2022. All patients were identified from our computerized medical records and selected according to the following criteria: (1) histological diagnosis of MTC; (2) total thyroidectomy with lymph node dissection; (3) available data on the number of removed and metastatic lymph nodes of the neck; (4) absence of distant metastases at diagnosis; (5) available data on postsurgical follow-up, including both biochemical tests (thyroid hormonal status, Ctn, and CEA assay) and imaging (neck ultrasound and, in case of persistent/recurrent disease, computed tomography scan, magnetic resonance imaging and bone scan); and (6) at least 12 months of postsurgical follow-up. The retrospective study was conducted following the Declaration of Helsinki and approved by the Institutional Review Board and local Ethics Committee; the signed informed consent from patients was waived because of the retrospective design of this study.

For each selected patient we collected demographic and pathological data, including the extent of surgery, the number and the site of locoregional metastatic lymph nodes, the presence of distant metastases during follow-up, as well as the mutational status of the rearranged during transfection (RET) gene. In accordance with the American Thyroid Association guidelines,[8] patients with no evidence of neck LNM on preoperative imaging underwent total thyroidectomy with dissection of the lymph nodes in the central compartment. When LNM in the lateral neck were identified before surgery, modified radical neck dissection was performed. Even if only ipsilateral involvement was confirmed, contralateral dissection was considered for patients with a preoperative Ctn level of >200 pg/mL. The extent of surgery was classified according to the type of neck dissection (central, central and ipsilateral, lateral and bilateral) performed with total thyroidectomy. Central neck dissection referred to prelaryngeal, pretracheal, and paratracheal lymph nodes (either ipsilateral or bilateral). Since guidelines on MTC provide no specific recommendations regarding the number of lymph nodes to be dissected, we included patients with at least 1 lymph node yield.

### *Follow-Up*

Patients were followed up every 6 months for the first 2 years and annually thereafter. Persistent and recurrent diseases were defined as detected within the first 12 months of diagnosis or later during follow-up, respectively.

At follow-up, biochemical and/or structural disease was defined based on serum Ctn and CEA values and radiological findings, as follows: serum Ctn and CEA values higher than the upper limit of the assay, local or distant metastases confirmed at surgery, Ctn measurement in the washout specimen from lymph node fine-needle aspiration biopsy, and computed tomography scan or magnetic resonacne imaging.

Patients with persistent/recurrent disease were discussed in a dedicated multidisciplinary board and, based on the individual patient's risk, had undergone further treatments including surgery for local recurrence, local therapies, and/or systemic treatment with tyrosine-kinase inhibitors (ie, vandetanib, cabozantinib) for distant metastases.

Response to treatments was defined according to RECIST Criteria 1.1.

### *Serum Markers and Pathological Examination*

Serum Ctn was measured by the Siemens IMMULITE 2000 automatic chemiluminescence immunoassay analyzer using a standard assay kit for in vitro diagnosis (Siemens Healthcare Diagnostics Products Limited) while CEA was measured by the Siemens Centaur XP automatic chemiluminescence immunoassay analyzer and its supporting reagents (Siemens Healthcare Diagnostics Inc). The histological samples were evaluated by an expert pathologist. The following features were recorded: size, multifocality, extrathyroidal extension, total lymph nodes removed, presence of LNM, and the number of metastatic lymph nodes. In multifocal or bilateral tumors, the largest tumor was considered.

### Statistical Analysis

Quantitative data are shown as the mean ± SD and numbers and percentages are provided for qualitative data. Percentages were compared using $\chi 2$ tests and $t$ test was used for continuous variables. LNR was defined as the number of metastatic lymph nodes divided by the number of lymph nodes removed during surgery. The linear regression analysis was used to investigate the relationship between LNR and clinicopathological and biochemical parameters. To identify the LNR cut-off value that best predicted persistent/recurrent disease, we performed receiver operating characteristics (ROC) curve analysis and calculated the area under the curve. The cut-off was the value that maximized the sum of the sensitivity and specificity deduced from the ROC curve analysis. Univariate and multivariate Cox proportional model was applied to analyze factors associated with persistent/recurrent disease. The results were reported as hazard ratio (HR) and its 95% confidential interval (95% CI). Survival curves were analyzed by the Kaplan-Meier method, and statistical significance was determined using the log-rank test. $P$ values <.05 were considered statistically significant. Statistical analyses were performed using Stata software version 17.0 (StataCorp, College Station, TX, USA).

## Results

### Patient Features at Diagnosis

The demographic and clinicopathological features at diagnosis of the 95 patients with MTC are shown in Table 1. Sixty-three (66.3%) patients were females and 32 (33.7%) were males; the mean age at diagnosis was 47.7 ± 17.6 years, with no difference between females and males (48.8 ± 17.1 vs 45.7 ± 18.7, respectively; $P = .42$). Most patients ($n = 56$, 58.9%) had sporadic cancer, while 39 (41.1%) patients showed an MTC in the context of a hereditary syndrome due to a germline RET mutation. As expected, the mean age at diagnosis was lower in patients with a germline RET mutation: 38.0 ± 18.4 vs 53.7 ± 13.8 years in patients with sporadic MTC ($P < .001$).

Mean tumor size was 13.9 ± 9.9 mm. A multifocal or bilateral MTC was detected in 24 (25.3%) and 19 (20.0%) patients, respectively. The occurrence of multifocal and bilateral tumors was not different between females and males, whereas they were significantly more frequent in patients with RET mutation (51.3% and 46.2%, respectively) than in patients with sporadic MTC (5.4% and 1.8%, respectively; $P < .001$).

**Table 1**
Baseline and Clinicopathological Characteristics of the Study Cohort

| Parameter | $N = 95$ |
|---|---|
| Age, y (mean ± SD) | 47.7 ± 17.6 |
| Gender, female *n.* (%) | 66.3 (66) |
| Sporadic type, *n.* (%) | 56 (58.9) |
| Tumor size (mm), mean ± SD | 13.9 ± 9.9 |
| Bilateral tumor, *n.* (%) | 20 (21) |
| Multifocal tumor, *n.* (%) | 24 (25.3) |
| Distant metastases during follow-up | 13 (14%) |
| Persistence disease, *n.* (%) | 18 (60) |
| Recurrent disease, *n.* (%) | 12 (40) |
| Type of surgery | *N.* (%) |
| Thyroidectomy + central neck dissection | 61 (64.21%) |
| Thyroidectomy + ipsilateral neck dissection | 18 (18.95%) |
| Thyroidectomy + bilateral neck dissection | 16 (16.84%) |
| Lymph node status | *N.* (%) |
| N0 | 58 (61.1%) |
| N1a | 18 (18.9%) |
| N1b | 19 (20.0%) |

### Surgical Treatment

Most patients ($n = 61$, 64.21%) underwent total thyroidectomy with lymph node dissection of the neck central compartment (level 6), 18 (18.95%) patients also underwent lymph node dissection of the neck ipsilateral compartment (levels 2, 3, and 4), while the remaining 16 (16.84%) patients underwent lymph node dissection of the neck bilateral compartments (Table 1). Overall, 2024 lymph nodes were removed in 95 patients, and the median number of lymph nodes removed per patient was 15 (25-75° IQR = 7-28). The median number of lymph nodes removed was 9 in patients who underwent lymph node dissection of the central neck compartment, 21 in patients who also underwent lymph node dissection of the ipsilateral neck compartment, and 54 in patients who underwent lymph node dissection of the bilateral neck compartments. In the final histopathological report, 58 patients (61.1%) showed no evidence of LNM, while 37 (39.0%) had LNM, with 18 (18.9%) involving only the central compartment and 19 (20.0%) involving both central and lateral compartments.

### Correlation of LNR with Clinicopathological and Biochemical Parameters

The median LNR was 0 (25-75° IQR = 0-0.16) in the whole population studied, while the median LNR on patients with metastatic lymph nodes (37 out of 95) was 0.24 (25-75° IQR = 0.13-0.45). Lymph node ratio was positively associated with the following parameters: tumor size ($P = .026$), presurgery and postsurgery Ctn values ($P < .001$), and postsurgery CEA values ($P = .001$) (Table 2). In contrast, we found no association between LNR and age at diagnosis ($P = .50$), sex ($P = .65$), RET mutational status ($P = .79$), multifocality ($P = .93$), bilaterality ($P = .32$), or presurgery CEA values ($P = .28$).

### Lymph Node Ratio and MTC Outcome

Median follow-up length was 67.7 months (25-75° IQR = 22.4-128.2). Persistent or recurrent disease was observed in 30 (31.6%) patients. Among these patients, 18 (60.0%) had persistent disease and the remaining 12 (40.0%) patients had recurrent disease that was diagnosed after a median time of 78.0 months (25-75° IQR = 35.5-139.3) from the diagnosis.

Lymph node ratio was positively associated with persistent or recurrent disease ($P < .001$). The median LNR was 0 (25-75° IQR = 0-0) in patients with no evidence of disease during the follow-up, and it was 0.19 (25-75° IQR = 0.12-0.45) in patients with persistent or recurrent disease ($P < .001$). We then calculated the predicted probability of persistent or recurrent disease and, as shown in Fig. 1, observed that it increased with the increasing LNR value. Distant metastases were diagnosed in 13 patients (14%) during follow-up (Table 1). A significant correlation was found between increasing LNR and the occurrence of distant metastases during follow-up ($P < .001$) (Table 2).

Median LNR was significantly higher in patients with persistent disease compared with patients with recurrent disease: 0.31 (25-75° IQR = 0.13-0.67) vs 0.11 (25-75° IQR = 0-0.22) ($P = .006$).

### Cut-Off Value of LNR

By ROC curve analysis we found that a LNR cut-off value of 0.12 (Fig. 2) has the best performance in predicting patients with persistent or recurrent disease (sensitivity 78.8%, specificity 90.9%.

**Table 2**
Histopathological Characteristics, Biochemical Markers and Outcome Variables, and Their Univariable Associations With Lymph Node Ratio

| Parameters | Median LNR (25-75° IQR) | R-squared | Coefficient | *P* value |
|---|---|---|---|---|
| Tumor size at diagnosis | | 0.058 | 0.067 | .026 |
| ≤1 cm | 0 (0-0.09) | | | |
| 1.1-2 cm | 0 (0-0.18) | | | |
| >2 cm | 0.13 (0-0.31) | | | |
| Ctn preoperative (pg/mL) | | 0.188 | 0.066 | <.001 |
| ≤200 | 0 (0-0) | | | |
| 201-500 | 0 (0-0.16) | | | |
| >500 | 0.16 (0-0.54) | | | |
| Ctn postoperative (pg/mL) | | 0.412 | 0.072 | <.001 |
| ≤10 | 0 (0-0) | | | |
| 11-100 | 0.13 (0-0.27) | | | |
| >100 | 0.45 (0.29-0.49) | | | |
| CEA postoperative (ng/mL) | | 0.123 | 0.094 | .001 |
| ≤5 | 0 (0-0.11) | | | |
| 5.1-10 | 0.19 (0.10-0.27) | | | |
| >10 | 0.29 (0.19-0.31) | | | |
| Persistence/recurrence | | 0.308 | 0.272 | <.001 |
| No | 0 (0-0) | | | |
| Yes | 0.19 (0.12-0.45) | | | |
| Distant metastases | | 0.167 | 0.280 | <.001 |
| No | 0 (0-0.11) | | | |
| Yes | 0.25 (0.15-0.60) | | | |

Abbreviations: CEA = carcinoembryonic antigen; Ctn = calcitonin.

area under the curve = 0.85). Indeed, we observed that persistent/recurrent disease occurred in only 10.6% of patients with LNR <0.12 vs 79.3% of patients with LNR ≥0.12 (odds ratio [OR] = 32.3, 95% CI = 9.8-106.4; $P < .001$). This finding was also confirmed when adjusting for both the number of metastatic and removed lymph nodes (OR = 14.3, 95% CI = 2.7-76.6; $P = .002$). Moreover, patients with LNR ≥0.12 had a higher probability of developing distant metastases than patients with LNR <0.12 (34.5% vs 3.0%, OR = 16.8, 95% CI = 3.4-83.6; $P < .001$). Interestingly, an LNR ≥0.12 was more frequent in patients with persistent disease than in patients with recurrent disease (94.1% vs 53.9%, respectively; $P = .010$).

Using the multivariate Cox proportional hazard model, factors independently associated with persistent or recurrent disease were male sex, LNR, hereditary type, postoperative Ctn, and postoperative CEA (Table 3).

As shown in Fig. 3, the median progression-free survival (PFS) was 15 months in patients with LNR ≥0.12 whereas the median PFS was not reached in patients with LNR <0.12 (HR: 7.18, 95% CI = 3.01-17.11, $P < .001$). A statistically significant different PFS was also confirmed when adjusted for the number of metastatic and removed lymph nodes (HR: 5.84, 95% CI = 2.12-16.03, $P = .001$).

## Discussion

According to the current guidelines,[8] the gold-standard treatment for MTC is thyroidectomy with central neck dissection, depending on serum Ctn levels and ultrasound (US) findings; however, there is no strong indication of the type or extent of lymphadenectomy. A more extensive lymph node dissection is thought to reduce the risk of recurrence but may also negatively affect patients' quality of life because of an increased risk of complications.[16]

The eighth edition of American Joint Committee on Cancer staging system[17] adopted tumor size, extrathyroidal invasion,

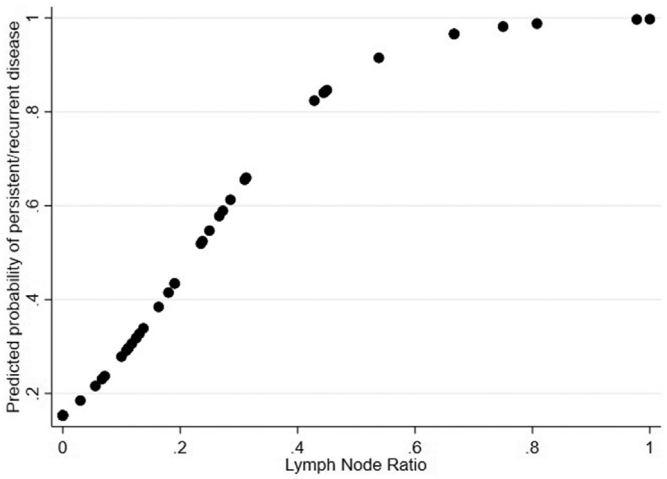


**Fig. 1.** Predicted probability of persistent or recurrent disease according to lymph node ratio values.

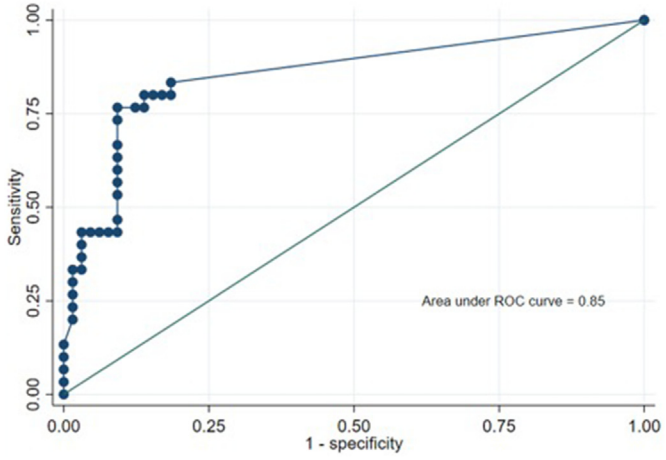


**Fig. 2.** Lymph node ratio receiver operating characteristic (ROC) curve considering patients with persistent or recurrent disease (sensitivity 78.8%, specificity 90.9%. AUC = 0.85) *AUC* = area under the curve.

**Table 3**
Multivariate Cox Proportional Hazard Model of the Risk Factors Associated with Recurrent and Persistent Disease

| Features | Hazard ratio | 95% Confidence interval | *P* value |
|---|---|---|---|
| Male sex | 10.8 | 1.6 - 71.3 | .014 |
| LNR | 0.02 | 0.0 - 0.8 | .038 |
| Hereditary type | 8.9 | 1.2 - 65.0 | .031 |
| Postoperative Ctn | 9.8 | 2.7 - 35.9 | .010 |
| Postoperative CEA | 0.14 | 0.0 - 0.7 | .017 |

Abbreviations: CEA = carcinoembryonic antigen; Ctn = calcitonin; LNR = lymph node ratio.

location of the metastatic lymph nodes within (N1a) or outside (N1b) the central neck and distant metastasis as prognostic factors in patients with MTC. Furthermore, many studies have identified additional risk factors as prognostic of recurrence risk after surgery: age at diagnosis, stage of disease, gender, extent of surgery, and postoperative Ctn and CEA.[18-21] However, none of these prognostic factors predict either the effectiveness and quality of surgery or the degree of lymph node involvement.

Herein, we evaluated the potential role of LNR as a prognostic marker immediately after initial surgery for risk stratification of patients with MTC. By analyzing a continuous series of MTC patients followed up at a single tertiary referral center we identified, through univariate linear regression analysis, a significant correlation between an elevated LNR and the following factors: larger tumor size, elevated preoperative and postoperative Ctn values, increased postoperative CEA values, as well as a greater likelihood of persistence, recurrence, and distant metastases during the follow-up period. We also found that LNR, such as for male sex, inheritance type, postoperative Ctn, and postoperative CEA was independently associated with the recurrence/persistence of disease.

LNR had been evaluated as a prognostic factor in various types of cancers, including cancers of the head and neck, stomach, breast, pancreas, neuroendocrine tumors of the small intestine, colorectal and papillary thyroid cancers[10-15] and was first proposed as a prognostic factor in MTC by Leggett et al.[22] The study highlighted differences between Cox proportional hazard models informed by the LNR and by the lymph node yield. In fact, the number of lymph nodes harvested at surgery was not correlated to overall survival as a continuous variable; the authors suggested that the benefit of performing an extensive dissection of lymph nodes is limited. These data were confirmed by the study of Qu et al which found that increasing the number of lymph nodes removed during surgery was not associated with improved survival. They concluded that the benefit to remove a high number of lymph nodes is finite and largely dominated by the effects of other factors.[23] Therefore, consensus remains lacking on the minimum number of lymph nodes necessary for reliable predictions. Elevated LNR values may result from either a low lymph node yield or a high number of metastatic lymph nodes. In the former scenario, it may indicate incomplete surgery, while in the latter it suggests a more extensive disease burden. Consequently, high LNR values could predict the risk of persistent or recurrent disease, irrespective of the number of lymph nodes harvested.

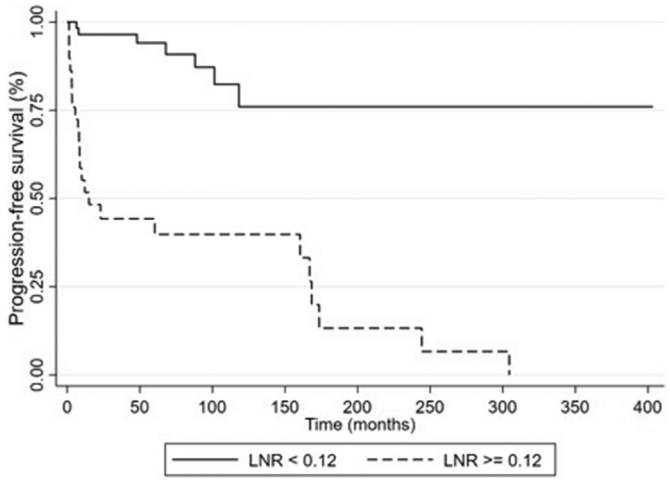


**Fig. 3.** Kaplan-Meyer analysis for progression free survival (PFS) in patients with medullary thyroid cancer (MTC) according to lymph node ratio (LNR) cut-off.

In our study, we have highlighted that LNR is able to predict the PFS in patients with MTC and LNR is a better prognostic factor than the number of metastatic lymph nodes and the number of lymph nodes removed during surgery. In agreement with our present data, Machens et al[24] demonstrated that LNR predicts the cancer-specific survival better than the number of LNM. These results are especially important because the current guidelines recommend considering the tumor-nodes-metastasis classification, the number of LNM, and postoperative serum Ctn levels in predicting outcome and planning the long-term follow-up of patients treated by thyroidectomy for MTC.[8]

We speculate that LNR rather than the number of LNM could suggest the most appropriate follow-up strategy and predict the outcome.

Despite the undoubted and reliable prognostic role of the LNR, the best cut-off to consider as predictive of disease is much debated; in several studies, a different cut-off was proposed, ranging from 0.1 to 0.60.[9,22-26]

We found an optimal LNR cut-off of 0.12 to define high risk or low risk patients with good sensitivity and excellent specificity. An LNR $\geq$0.12 can reliably predict the risk of persistent/recurrent disease and distant metastases together with postoperative Ctn and CEA levels: below this value, only 3% of patients developed distant metastases while, above this value, 79.3% of patients had a recurrence/persistent disease.

This study has some limitations as the retrospective analysis of a series of patients recruited to a single center; however, the data appear to be potentially useful and very promising in the clinical management of MTC patients and should hopefully be further validated by prospective and multi-center studies.

## Conclusion

In patients who underwent thyroidectomy and node dissection, LNR is able to predict the risk of recurrence/persistence, either local or at a distance. LNR, together with postoperative Ctn and CEA, is an important prognostic factor in patients with MTC and should be considered to predict the outcome and guide the follow-up.

## Disclosure

The authors have no multiplicity of interest to disclose.

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