Lymph Node Positive Rate: An Ignored Factor Affecting the Prognosis of Medullary Thyroid Cancer

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Research Article

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Abstract

Purpose

To investigate the relationship between the positive rate of examined lymph nodes and the prognosis of patients with medullary thyroid cancer (MTC).

Method

Information on demographic and clinicopathological characteristics of patients with medullary thyroid cancer was extracted from Surveillance, Epidemiology and End Results (SEER) database of the National Institutes of Health (NIH) between 1998 and 2015. Lymph Node Positive Rate (LNPR) is defined as the number of positive lymph nodes divided by the total number of lymph nodes removed. Eligible MTC patients were divided into four LNPR groups (0-0.25, 0.26-0.50, 0.51-0.75 and 0.76 -1.00). Compare the overall survival rate (OS) and cancer-specific survival rate (CSS) calculated by the Kaplan-Meier method between the four MTC patient groups and Perform univariate and multivariate analyzes to assess the relationship between Lymph Node Positive Rate and prognosis of the MTC patients.

Result

After screening, there were 623 eligible patients with medullary thyroid cancer, of which the number of patients in four groups was 245 (LNPR: 0-0.25), 199 (LNPR: 0.26-0.50), 105 (LNPR: 0.51-0.75) and 99 (LNPR: 0.76-1.00). Compared to the group (LNPR: 0-0.25), the CSS and OS rates in the two groups were (LNPR: 0.51-0.75 and LNPR: 0.76-1.00) (both p <0.001) significantly lower, and the multivariable Cox regression analysis showed that the group (LNPR: 0.51-0.75) correlated significantly with poorer CSS and OS rates [(CSS: HR 1.77, 95% CI 0.99 3.19, P = 0.045); (OS: HR 1.69, 95% CI 1.03-2.79, P = 0.038)] and group (LNPR: 0.76-1.00) correlated significantly with poorer CSS and OS rates [(CSS: HR 2.09 95% CI 1.12-3.92, P = 0.021); (OS: HR 2.23, 95% CI 1.32 -3.76, P = 0.003)].

Conclusion

The LNPR can serve as a prognostic marker for patients, and the higher the LNPR, the worse the prognosis for patients with medullary thyroid cancer.

Introduction

Medullary thyroid cancer (MTC) is a rare and aggressive kind of thyroid cancer that is derived from parafollicular C cells of the thyroid, accounting for 2-4% of the total frequency of thyroid cancer [1, 2]. In recent years, the prevalence of MTC has gradually increased. According to reports, the average annual rate of change in the incidence of MTC is as high as 1.87% in the United States[3, 4]. Almost 25% of the cases are familial and 75% are considered sporadic. Familial cases are relevant for germline RET mutations; 43% -65% of sporadic cases relate to somatic events in the gene[5]. In general, the early detection of MTC is extremely difficult. Although ultrasound examinations, tumor markers, fine needle aspiration, and genetic testing are currently used clinically for early detection, Lymph node metastases or even distant metastases have occurred when most patients with MTC are initially diagnosed[6, 7]. Therefore, in addition to the poor prognosis of most patients with thyroid cancer due to the aggressive tumor, the untimely detection is also an important motivation for the poor prognosis [8]. A retrospective analysis of the data collected demonstrated that age, tumor size, tumor invasion and lymph node metastasis are all independent factors affecting the prognosis of MTC[9]. In the prognostic evaluation of patients with MTC, however, the lymph node-positive rate is ignored. The lymph node positive rate is described as the number of positive regional nodes divided by the number of Regional nodes examined. Previous studies focused on the patterns of cervical lymph node metastasis of medullary thyroid carcinoma and believed that the occurrence of cervical lymph node metastasis is higher in patients with MTC[10]. So far, few studies have described the influence of a positive lymph node rate on the prognosis of patients with MTC. The important clinical value of the lymph node positive rate has been ignored. The aim of this study is to investigate the influence of the positive lymph node rate on the prognosis of patients with MTC after the operation and the guiding importance of the positive lymph node rate for further
treatment in the later period using the information gathered from the SEER database, which is a popular database in the United States that collects basic clinical information from a large number of patients and information and some rare cases[11].

Methods

1. Data collection

This is a clinical retrospective investigation using information from the SEER database. The inclusion criteria for the study cohort are as follows:

The histological type only needs to be determined MTC; The histological type should correspond to the International Classification of Disease for Oncology, Third Edition (ICD-O-3; coded as 8510/3); Year of diagnosis is from 1998 to 2015. The exclusion criteria for the study cohort are as follows:

- tumor size unclear, not assessable and not documented in the patient file; The extent of the tumor is not specified and cannot be assessed; reginal lymph node is not involved in the operation; number of examined lymph node less than five in order to avoid calculation bias; dead reason is unknown or missing; and MTC is not the first tumor. SEER*Stat (version 8.3.5) software is used for data collection.

2. Data variables

In the current retrospective research, we studied the following independent variable: age(<=50y ,>50y), sex(male, female), race[white ,black, others (American Indian/AK Native, Asian/Pacific Islander)], marital status[married(including common law, other(divorced, separated, single(never married),widowed)unknown], size(0-10mm,10-20mm,20-40mm and >40mm); extension(into the thyroid capsule, invasion to adjacent tissues and distant metastases); regional lymph nodes examined; regional lymph nodes positive; surgery method of primary site(lobectomy, subtotal or near total thyroidectomy and total thyroidectomy); radiation[radiotherapy(Beam radiation, Combination of beam with implants or isotopes, None/Unknown ,Radioactive implants (includes brachytherapy), Radioisotopes),un/unknown(Recommended, unknown if administered and Refused)]; chemotherapy(yes, No/Unknown); Survival months, cause-specific death classification [(alive or dead of other cause, Dead (attributable to this cancer dx)], Vital status (alive or dead). The lymph nodes positive rate (LNPR) is calculated by dividing the number of positive lymph nodes by the total number of examined lymph nodes.

The dependent variables were overall survival (OS), which is described as the time from diagnosis to death from all causes, and cancer-specific survival (CSS), which is described as the time from diagnosis to MTC-related death.

3. Data analysis

According to the positive lymph node rate, the total patients are in the first group with LNPR (0-0.25), the second group with LNPR (0.26-0.50), and the third group with LNPR (0.51-0.75) and the fourth group with LNPR (0.76-1.00). The chi-square test is used to evaluate the significance of the difference in variables between the above 4 groups of patients. All tests with P values of 0.05 were considered significant. The Kaplan-Meier (KM) method was used for the univariate analysis, followed by a log-rank test to identify the differences. Variables with P <0.05 in the univariate analysis were included in the multivariate Cox proportional hazard analysis. In the end, a stratified analysis according to age, gender, tumor size, chemotherapy status and radiotherapy were carried out on the patients using the log-rank test. R software 3.8.9(https://www.r-project.org/) is utilized for data analysis and made of survival curves.
Results

From 1998 to 2015, a total of 632 patients with MTC (ICD-0-3 coded as: 8510/3) were eligible. The mean ± SD number of lymph nodes examined in LNPR 0-0.25 is 39.10±24.40, which is much larger than that in LNPR 0.76-1.00. However, the mean ± SD number of positive lymph nodes in LNPR 0-0.25 is 5.09±4.30, which is much smaller than that in LNPR 0.76-1.00. The detailed screening process is depicted in figure 1.

There are up to 225 MTC patients with LNPR 0-0.25, The following is MTC patients with LLPR (0.26-0.5) up to 199 cases, and the number of MTC patients with LNPR (0.51-0.75) is 105, and there are only 99 MTC patients with LNPR (0.76-1.00).

The difference in sex, tumor invasion, chemotherapy, radiotherapy and mean±SD of lymph node examined and positive lymph node between the four techniques was statistically significant. Detail clinical characteristic of MTC patients in shown in Table1.

Table 1 the clinicopathological characteristics of patients with MTC grouped by LNPR
| LNPR | 0-0.25[n (%)] | 0.26-0.50[n (%)] | 0.51-0.75[n (%)] | 0.75-1.00[n (%)] | p value |
|------|---------------|------------------|------------------|------------------|---------|
| n    | 245(39.3)     | 199(31.9)        | 105(16.9)        | 74(11.9)         |         |

Race. 0.729

|       | Black | others | White       |         |
|-------|-------|-------|-------------|---------|
|       | 13(5.3) | 16 ( 6.5) | 216 (88.2) |         |
|       | 14(7.0) | 16 ( 8.0) | 169 (84.9) |         |
|       | 11(10.5) | 7 ( 6.7) | 87 (82.9) | 63 ( 85.1) |

Sex. 0.005

|       | Male     | Female |         |
|-------|----------|--------|---------|
|       | 113 (46.1) | 132 (53.9) |         |
|       | 111 (55.8) | 88 (44.2) |         |
|       | 68 (64.8) | 37 (35.2) | 29 (39.2) |
|       | 45 (60.8) |         |         |

Age 0.104

|       | <50y | >=50y |       |
|-------|------|-------|-------|
|       | 115 (46.9) | 130 (53.1) |         |
|       | 99 (49.7) | 100 (50.3) |         |
|       | 64 (61) | 41 (39.0) | 39 (52.7) |

Marital status 0.422

|       | Married | others | Unknown |         |
|-------|---------|--------|---------|---------|
|       | 160 (65.3) | 79 (32.2) | 6 ( 2.4) |         |
|       | 132 (66.3) | 57 (28.6) | 10 ( 5.0) |         |
|       | 60 (57.1) | 42 (40.0) | 3 ( 2.9) | 3 ( 4.1) |
|       | 47 (63.5) | 24 (32.4) |         |         |

Tumor size (mm) 0.010

|       | (0,10] | (10,20] | (20,40] | >40 |         |
|-------|-------|--------|--------|-----|---------|
|       | 37 (15.1) | 56 (22.9) | 96 (39.2) | 56 (22.9) |         |
|       | 15 (7.7) | 48 (24.5) | 78 (39.8) | 55 (28.1) |         |
|       | 13 (12.4) | 22 (21.0) | 31 (29.5) | 39 (37.1) |         |
|       | 4 (5.4) | 12 (16.2) | 27 (36.5) | 31 (41.9) |         |

Tumor extension <0.001

|       | Extension to adjacent structures | Confined into capsule |         |
|-------|---------------------------------|-----------------------|---------|
|       | 52 (21.2) | 168 |         |
|       | 92 (46.2) | 96 (48.2) |         |
|       | 64 (61.0) | 32 (30.5) |         |
|       | 39 (52.7) | 31 (41.9) |         |
Distant metastasis

|                | 25 (10.2) | 11 (5.5) | 9 (8.6) | 4 (5.4) |
|----------------|-----------|----------|---------|---------|

Surgery

| Surgical Procedure         | 0.293     |
|---------------------------|-----------|
| Lobectomy                 | 3 (1.2)   |
|                           | 4 (2.0)   |
|                           | 0 (0.0)   |
|                           | 2 (2.7)   |
| Near total thyroidectomy  | 4 (1.6)   |
|                           | 1 (0.5)   |
|                           | 2 (1.9)   |
|                           | 3 (4.1)   |
| Total thyroidectomy       | 238 (97.1)|
|                           | 194 (97.5)|
|                           | 103 (98.1)|
|                           | 69 (93.2) |

Radiation

|                | <0.001    |
|----------------|-----------|
| YES            | 37 (15.1) |
|                | 54 (27.1) |
|                | 39 (37.1) |
|                | 24 (32.4) |
| NO             | 208 (84.9)|
|                | 145 (72.9)|
|                | 66 (62.9) |
|                | 50 (67.7) |

Chemotherapy

|                | 0.003     |
|----------------|-----------|
| YES            | 8 (3.3)   |
|                | 8 (4.0)   |
|                | 9 (8.6)   |
|                | 10 (13.5) |
| NO             | 237 (96.7)|
|                | 191 (96.0)|
|                | 96 (91.4) |
|                | 64 (86.5) |

*examined lymph nodes

|                | <0.001    |
|----------------|-----------|
| *positive lymph nodes | 5.09 (4.30) | 14.10 (9.43) | 20.18 (13.30) | 20.81 (16.58) | <0.001 |

abbreviation: LNPR lymph node positive rate, MTC MTC, * mean±SD

Compared to MTC patients with LLPR (0-0.25), the OS rates at 3 years, 5 years and 10 years in patients with LNPR (0.76-1.00) were significantly lower (0.918, 0.873, 0.739 vs. 0.718, 0.6, 0.415); p <0.001; Similarly, CSS rates at 3 years, 5 years and 10 years in patients with LNPR were significantly lower (0.76-1.00) (0.939, 0.908, 0.807 vs. 0.817, 0.683, 0.501; p <0.001). Survival curves is illustrated in Fig2.

On the univariate analysis, the OS and CSS correlated significantly with tumor size, age, sex, tumor extension, radiation therapy, chemotherapy and LNPR (both p<0.05).

On the multivariate analysis, the group with LNPR 0.76-1.00 show some significant correlation with the worse OS rates and CSS rates (HR=2.32,95%CI=1.32-3.76, p=0.003; HR=2.09,95%CI=1.12-3.92, P=0.021). In addition, the risk factor tumor size>40mm (HR=2.12,95%CI=1.10-4.09, P=0.025;HR=2.48,95%CI=1.04-5.89,P=0.040;respectively), age>50years (HR=3.58, 95%CI=2.45-5.24, P<0.001; HR=3.24, 95%CI=2.09-5.00, P<0.001), tumor distant metastases (HR=1.81,95%CI=1.04-3.16, P=0.036; HR=1.93, 95%CI=1.06-3.53, P=0.032), chemotherapy (HR=2.43,95%CI=1.32-4.47, P=0.004; HR=3.48, 95%CI=1.85-6.54, P<0.001) and LLNR 0.51-0.75 were related to worse OS rates and CSS rates. Moreover, MTC tumor into the capsule was the protective factor for the OS rates and CSS rates (HR=0.64,95%CI=0.42-0.96, P=0.031; HR=0.48, 95%CI=0.29-0.79, P=0.004). Detailed information about the Hazard ratios for prognosis of MTC patients is shown in table 2.
Characteristic
| Factors              | overall survival (OS) | cancer special survival (CSS) |
|---------------------|-----------------------|-----------------------------|
|                     | univariate            | Multivariate                | univariate            | Multivariate                |
|                     | P value               | P value | HR (95%CI) | P value | P value | HR (95%CI) |
| Age                 | <0.001                | <0.001 |            | <0.001  | <0.001  |            |
| <50y                | Reference             |         |            | Reference |         |            |
| >=50y               | 3.58 (2.45-5.24)      |         |            | 3.24 (2.09-5.00) |         |            |
| Sex                 | <0.001                | 0.08    | 0          | 0.14    |
| Female              | Reference             |         |            | Reference |         |            |
| Male                | 1.38 (0.96-1.98)      |         |            | 1.38 (0.90-2.10) |         |            |
| Race                | 0.2                   |         |            | 0.15    |
| white               | Reference             |         |            | Reference |         |            |
| black               |                       |         |            |         |
| others              |                       |         |            |         |
| Marital status      | 0.18                  |         | 0.17       |
| married             | Reference             |         |            | Reference |         |            |
| unmarried           |                       |         |            |         |
| others              |                       |         |            |         |
| Tumor size (mm)     | <0.001                |         | <0.001     |
| (0,10]              | Reference             |         | Reference  |         |
| (10,20]             | 0.45                  | 0.74 (0.34-1.60) | 0.95 | 0.97 (0.36-2.61) |
| (20,40]             | 0.67                  | 1.16 (0.59-2.27) | 0.31 | 1.58 (0.66-3.82) |
| >40                 | 0.03                  | 2.12 (1.10-4.09) | 0.04 | 2.48 (1.04-5.89) |
| Extent of disease   | <0.001                |         | <0.001     |
| Extension to adjacent structures | Reference |         | Reference |
| Confined into capsule | 0.03                | 0.64 (0.42-0.96) | 0      | 0.48 (0.29-0.79) |
Distant metastasis | 0.04 | 1.81(1.04 – 3.16) | 0.03 | 1.93(1.06 – 3.53) |
|-------------------|-----|----------------|-----|----------------|

Surgery at primary site | 0.59 | 0.54 |

Lobectomy
Near total thyroidectomy
Total thyroidectomy

| LNPR | <0.001 | <0.001 |
|------|--------|--------|
| 0-0.25 | Reference | Reference |
| 0.26-0.50 | 0.2 | 1.35(0.85 – 2.16) | 0.29 | 1.36(0.77 – 2.40) |
| 0.51-0.75 | 0.04 | 1.69(1.03 – 2.79) | 0.06 | 1.77(0.99 – 3.19) |
| 0.75-1.00 | 0 | 2.23(1.32 – 3.76) | 0.02 | 2.09(1.12 – 3.92) |

Radiotherapy | <0.001 | 0.13 | 0.01 | 0.09 |
| yes | 1.32(0.92 – 1.91) | 1.44(0.94 – 2.19) |
| no | Reference | Reference |

Chemotherapy | <0.001 | 0 | <0.001 | <0.001 |
| yes | 2.43(1.32 – 4.47) | 3.48(1.85 – 6.54) |
| no | Reference | Reference |

Discussion

Medullary thyroid carcinoma is a rare and highly aggressive thyroid tumor of the endocrine system that originates from parafollicular C cells of the thyroid[1]. Mutations in the RET proto-oncogene are implicated in the pathogenesis of MTC, but several other alternative patterns exist[12]. One of the major reasons for the poor prognosis for patients with MTC is that near half patients have tumor metastases in the cervical lymph nodes when they are first diagnosed. Roman, Sanziana et al. reported that in the group of 594 patients, 48% of MTC patients are available for lymph node metastasis[13]. Surgical treatment is the primary treatment for MTC. Because of cervical lymph node metastases, resection of the cervical lateral lymph nodes was required in most patients. Al-Qurayshi, Zaid et al. reported that the 5-year survival rate of MTC patients with TV-TNM stage with the surgical methods of the combination of thyroidectomy, neck dissection and resection of regional sites is up to 80.4% [14]. However, the scope of lymph node resection in MTC patients is still uncertain. We hypothesized that that the wider extent of lymph node removal in patients with MTC might suggests that the greater the number of positive lymph nodes removed, the lower the likelihood of recurrence and the better the prognosis of patients. The lymph node positive rate is defined as the number of positive lymph nodes divided by the total number of lymph nodes removed. Assuming the same number of positive lymph
nodes, the following applies: the lower the positive lymph node rate, the greater the scope of the lymph node resection. Therefore, the current investigation is primarily to explore the impact of the LNPR on the prognosis of patients with MTC by extracting information of MTC patients from the SEER database. Compared to previous studies, we divided the lymph node positive rates into four groups and compared the groups to analyze their impact on the prognosis of patients with MTC. We found that the positive lymph node rate is not only an important characteristic of clinical patients, it is also closely related to the overall survival rate and the disease-specific survival rate of the MTC patients. Our studies have shown that the higher the positive lymph node rate, the lower the number of patients with MTC.

Our study found that 39.3% of patients with MTC with a lymph node positive rate of less than 25%, while only 11.9% of patients with medullary thyroid death with a lymph node positive rate of greater than 75% state which indicates that higher the positive lymph node rate, the lower the number of patients with MTC. Moreover, the number lymph nodes removed in more patients with MTC by far exceeds the number of positive lymph nodes, which shows that the scope of the surgical resection is relatively sufficient. In addition, we found that in the MTC patients with a positive lymph node rate of less than 25%, the tumor size larger than 40 mm was only 22.9%, while in the MTC patients with a positive lymph node rate of more than 75%, the tumor size greater than 40mm accounts for 41.9%, suggesting that the larger the tumor size, the more likely it is to have lymph node metastasis and the extent of the lymph node resection is larger. Many researchers have explored the relationship between tumor size and lymph node metastasis. Carr, John Alfred et al. comment that as the tumor size increases, so does the risk of positive lymph nodes in appendiceal carcinoid tumors[15]. Yamaoka, Yusuke et al reported that More than 2% of patients with ≥ T2 tumor had metastases in main lymph nodes, and none patients with T1 tumor had metastases in main lymph nodes in colon cancer[16].And Sopik, Victoria et al thought that the correlation between tumor size, lymph node status and distant metastasis is not linear in patients with invasive breast cancer[17]. Bae, Soo Y. et al. showed that the extent of individual surgery should be based on tumor size and lymph node status, which is consistent with our study[18]. As expected, patients with a higher positive lymph node rate have a poorer prognosis. Our study not only showed that the prognosis of the group with LNPR 0-0.25 was better than that of the group with LNPR 0.75-1.00, but also that the risk of death for the group with LNPR 0.75-1.00 was 2.23 times higher than the group with LNPR 0-0.25 on OS and 2.09 times higher on CSS. We believe that the reason for the poor prognosis of patients with a higher positive rate of lymph nodes is that although patients have undergone neck lymph node resection, the scope of surgical lymph node resection is not enough, and some metastases lymph nodes have not been completely removed, which accelerates distant metastasis and leads to poor prognosis. Because in our study, we found that the average number of lymph nodes removed in MTC patients with high lymph node positive rates is 23.96, which is much lower than that of MTC patients with low lymph node positive rate. But the average number of positive lymph nodes is 20.81 with high positive lymph rate, which is much higher than that of MTC patients with low positive lymph nodes.

On the contrary, patients with a low positive lymph node rate underwent extensive scope resections of lymph node and most metastases lymph nodes are completely removed, which will slow down the spread of cancer cells and the possibility of distant metastasis. Mao, Weipu, et al. have shown that the number of lymph node dissection is the independent element in the prognosis of patients with lymph node positive penile cancer, and that more lymph node dissection enhances overall survival in patients with penile cancer[19].

Although, most patients with MTC undergo other treatments such as chemotherapy and radiotherapy after thyroidectomy, neck lymph node dissection and distant site dissection[20]. However, surgery method is still a more effective treatment plan for MTC[21]. Therefore, we believe that the scope of lymph node resection should be expanded and the positive rate of lymph nodes should be reduced to improve the prognosis of patients. In addition, the positive lymph node rate can also be used as a reference indicator for the further treatment of patients with MTC after surgery. The comprehensive treatment concept for MTC today mainly includes surgery, chemotherapy, radiation therapy and targeted molecular therapies[2]. In patients with MTC with a different lymph node positive rate, the different therapeutic optional for radiation or chemotherapy should be considered, which indicates that in addition to calcitonin, lymph node positive rate also is an important guide for further treatment for improving the patient's prognosis[2, 22–25]. For the MTC patients with high LNPR, the doses of chemotherapy and targeted therapy drugs may need more, and the specific doses need to be further studied.

Limitation
In this article, the SEER database is used to examine the influence of the lymph node positive rate on the prognosis of patients with MTC. But there are still many shortcomings. First, the receipt is from the SEER database, which does not include some factors that have an important impact on the prognosis of patients with MTC, such as calcitonin. Then there will be fewer patient samples in this article and in the later period more multicenter prospective or retrospective studies are needed to further confirm the theory. Finally, the specific diagnostic and treatment measures for patients in the later phase are not clear, such as the type of chemotherapy drugs used.

**Conclusion**

This article uses the information on clinicopathologic features of MTC in the SEER database to confirm that the lymph node positive rate is closely related to patient prognosis. Patients with a high positive lymph node rate have a poor prognosis. In addition, chemotherapy and radiation therapy in patients with a higher positive lymph node rate must be further reconsidered and optimized. However, the study requires further clinical confirmation.

**Declarations**

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**Conflicts of interest**

The authors report no declarations of interest.

**Availability of data and material**

The data that support the findings of this study are openly available in the Surveillance, Epidemiology, and End Results Program at https://seer.cancer.gov.

**Code availability**

Not applicable

**Authors’ contributions**

WF L, SF W conceived of and designed the study. XT X performed literature search. WF L generated the figures and Tables. SF W analyzed the data. WF L wrote the manuscript and XT X critically reviewed the manuscript. XT X supervised the research. All authors have read and approved the manuscript.

**Ethics approval**

The study was considered exempt from local ethics committee approval because all data are de-identified for public use.

**Consent to participate**

Not applicable

**Consent for publication**

Not applicable
References

1. Cabanillas ME, McFadden DG, Durante C (2016) Thyroid cancer. Lancet 388:2783–2795
2. Viola D, Elisei R (2019) Management of Medullary Thyroid Cancer. Endocrinol. Metab. Clin. North Am. 48:285–301
3. Kitahara CM, Sosa JA (2016) The changing incidence of thyroid cancer. Nat. Rev. Endocrinol. 12:646–653
4. Veiga LHS, Neta G, Aschebrook-Kilfoy B, et al (2013) Thyroid cancer incidence patterns in Sao Paulo, Brazil, and the U.S. SEER program, 1977-2008. Thyroid 23:748–757. https://doi.org/10.1089/thy.2012.0532
5. Larouche V, Akirov A, Thomas CM, et al (2019) A primer on the genetics of medullary thyroid cancer. Curr. Oncol. 26:389–394
6. Roman S, Mehta P, Sosa JA (2009) Medullary thyroid cancer: Early detection and novel treatments. Curr. Opin. Oncol. 21:5–10
7. Links TP, Verbeek HHG, Hofstra RMW, Plukker JTM (2015) Progressive metastatic medullary thyroid carcinoma: First-And second-line strategies. Eur. J. Endocrinol. 172:R241–R251
8. Roman S, Lin R, Sosa JA (2006) Prognosis of medullary thyroid carcinoma: Demographic, clinical, and pathologic predictors of survival in 1252 cases. Cancer 107:2134–2142. https://doi.org/10.1002/cncr.22244
9. Kebebew E, Ituarte PHG, Siperstein AE, et al (2000) Medullary thyroid carcinoma: Clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. Cancer 88:1139–1148. https://doi.org/10.1002/(SICI)1097-0142(20000301)88:5<1139::AID-CNCR26>3.0.CO;2-Z
10. Yan D, Zhang B, Li Z, et al (2015) Cervical lymph node metastasis in medullary thyroid carcinoma. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 50:290–294
11. Park HS, Lloyd S, Decker RH, et al (2012) Overview of the Surveillance, Epidemiology, and End Results Database: Evolution, Data Variables, and Quality Assurance. Curr Probl Cancer 36:183–190. https://doi.org/10.1016/j.currprobcancer.2012.03.007
12. Accardo G, Conzo G, Esposito D, et al (2017) Genetics of medullary thyroid cancer: An overview. Int J Surg 41:S2–S6. https://doi.org/10.1016/j.ijsu.2017.02.064
13. Roman S, Lin R, Sosa JA (2006) Prognosis of medullary thyroid carcinoma: Demographic, clinical, and pathologic predictors of survival in 1252 cases. Cancer 107:2134–2142. https://doi.org/10.1002/cncr.22244
14. Al-Qurayshi Z, Khadra H, Chang K, et al (2018) Risk and survival of patients with medullary thyroid cancer: National perspective. Oral Oncol 83:59–63. https://doi.org/10.1016/j.oraloncology.2018.06.002
15. Carr JA (2019) Tumor Size and Lymph Node Metastasis of Appendiceal Carcinoid Tumors. J. Am. Coll. Surg. 229:516
16. Yamaoka Y, Kinugasa Y, Shiomi A, et al (2017) The distribution of lymph node metastases and their size in colon cancer. Langenbeck's Arch Surg 402:1213–1221. https://doi.org/10.1007/s00423-017-1628-z
17. Sopik V, Narod SA (2018) The relationship between tumour size, nodal status and distant metastases: on the origins of breast cancer. Breast Cancer Res Treat 170:647–656. https://doi.org/10.1007/s10549-018-4796-9
18. Bae SY, Jung SP, Choe JH, et al (2019) Prediction of lateral neck lymph node metastasis according to preoperative calcitonin level and tumor size for medullary thyroid carcinoma. Kaohsiung J Med Sci 35:772–777. https://doi.org/10.1002/kjm2.12122
19. Mao W, Huang X, Kong M, et al (2019) More lymph node dissection improves survival in patients with newly diagnosed lymph node-positive penile cancer. Int Urol Nephrol 51:641–654. https://doi.org/10.1007/s11255-019-02084-7

20. Wells SA, Asa SL, Dralle H, et al (2015) Revised American thyroid association guidelines for the management of medullary thyroid carcinoma. Thyroid 25:567–610. https://doi.org/10.1089/thy.2014.0335

21. Jin LX, Moley JF (2016) Surgery for lymph node metastases of medullary thyroid carcinoma: A review. Cancer 122:358–366

22. Yip DT, Hassan M, Pazaitou-Panayiotou K, et al (2011) Preoperative basal calcitonin and tumor stage correlate with postoperative calcitonin normalization in patients undergoing initial surgical management of medullary thyroid carcinoma. Surgery 150:1168–1177. https://doi.org/10.1016/j.surg.2011.09.043

23. Machens A, Dralle H (2010) Biomarker-based risk stratification for previously untreated medullary thyroid cancer. J Clin Endocrinol Metab 95:2655–2663. https://doi.org/10.1210/jc.2009-2368

24. Machens A, Gimm O, Ukkat J, et al (2000) Improved prediction of calcitonin normalization in medullary thyroid carcinoma patients by quantitative lymph node analysis. Cancer 88:1909–1915. https://doi.org/10.1002/(SICI)1097-0142(20000415)88:8<1909::AID-CNCR21>3.0.CO;2-A

25. Cohen R, Campos J-M, Salaün C, et al (2000) Preoperative Calcitonin Levels Are Predictive of Tumor Size and Postoperative Calcitonin Normalization in Medullary Thyroid Carcinoma. J Clin Endocrinol Metab 85:919–919. https://doi.org/10.1210/jcem.85.2.6556

Figures

**Figure 1**

The number of examined lymph node (A) and positive lymph node (B) grouped by LNPR.
The number of mostly diagnosed medullary thyroid cancer cases between 2010 and 2015 comes from the SEER database (n=20667).

Figure 2

The detailed screening process for eligible patients with MTC
Figure 3

The Kaplan–Meier curves for overall survival (A) and disease-specific survival (B) in MTC patients grouped by LNPR.
Figure 4

Overall survival of (A) age<=50y, (B) age>50y, (C) no radiation (D) radiation, no chemotherapy (E), chemotherapy (F), female (G) and male (H) are shown, stratified by LNPR group.
Figure 5
Cancer-specific survival rate of (A) age<=50y, (B) age>50y, (C) no radiation (D) radiation, no chemotherapy (E), chemotherapy (F), female (G) and male (H) are shown, stratified by LNPR group.
**Figure 6**

Cancer-specific survival rate of tumor size <=10mm(A), 10mm < tumor size <= 20mm(B), 20mm < tumor size <= 40mm(C), 40 < tumor size(D); overall survival rate of tumor size <=10mm(E), 10mm < tumor size <= 20mm(F), 20mm < tumor size <= 40mm(G), 40 < tumor size(H);