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Research Article

LODDS and Other Prognostic Factors in Medullary Thyroid Cancers, Single Center Experience

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Abstract

Objectives: This study analyzes patients with medullary thyroid carcinomas (MTC) to determine the factors that affect their survival rates and the value of LODDS values in predicting outcomes, due to the high recurrence and metastasis rates of MTC despite available treatments.

Methods: 39 patients who underwent surgical treatment for MTC between January 2012 and June 2022 were evaluated. The effects of clinicopathologic features and LODDS values on survival were evaluated using univariate, multivariate analyses and Kaplan-Meier method.

Results: In the study, 51.3% of patients were female, with a mean age of 50.30±15.06 years. Poor prognosis for survival was associated with male gender, tumor size, extrathyroidal extension, presence of metastasis at diagnosis, metastasis during follow-up, advanced stage, lymph node metastasis, and high LODDS value (p=0.031, 0.002, <0.001, 0.045, 0.019, 0.025, 0.025, <0.001, respectively). However, these factors did not significantly affect disease-free survival or overall survival in multivariate analyses.

Conclusion: Factors affecting survival in MTC include gender, tumor size, extension, lymph node status, metastasis at diagnosis or follow-up. LODDS values may be a reliable measure to predict survival, but more comprehensive studies are needed to confirm their effect on survival times.

Keywords: LODDS, medullary thyroid cancer, prognosis

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Medullary thyroid carcinoma (MTC) is a neuroendocrine neoplasm that originates from parafollicular C cells in the thyroid gland. These cells secrete calcitonin and carcinoembryonic antigen (CEA).[1] MTC accounts for 1-2% of all thyroid cancer incidences, but causes 8-13% of deaths due to thyroid cancer.[2] While most MTC cases are sporadic, some occur as hereditary MTC resulting from mutations in the RET proto-oncogene.[3] Hereditary MTC has three types: multiple endocrine neoplasia type 2A (MEN 2A), MEN 2B, and familial MTC.[4]

Curative treatment for MTC includes total thyroidectomy with lymph node dissection. Modified neck dissection is also performed in cases with cervical lymph node metastasis. Radiotherapy may be applied for postoperative control.[5] However, despite the available treatment options, MTC has high recurrence and metastasis rates. Epidemiological studies have shown no improvement in the survival of MTC patients in the last 30 years.[6] Therefore, prognostic factors that are used for survival and clinical evaluation of MTC are crucial for accurate selection and evaluation.[7]

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Tumor markers play an important role in the diagnosis, prognosis, and treatment of MTC. Calcitonin is an important tumor marker for MTC, and its levels should be measured in patients with a histologically confirmed MTC diagnosis.[8] In addition, the CEA level is also used as a tumor marker. A disproportionate increase in serum CEA level raises suspicion of poorly differentiated MTC.[9]

When evaluating MTC prognosis, it is important to consider not only the location of lymph node metastasis, but also the number of lymph node metastases. The number of positive lymph nodes significantly affects the survival of MTC patients.[10, 11] However, evaluating prognosis based Solely on the number of positive lymph nodes can lead to bias due to the possibility of inadequate thyroidectomy and histopathological examination.[12]

The log odds of positive lymph nodes (LODDS) is a more advanced parameter used to evaluate the prognosis of patients based on their lymph node status. LODDS is calculated by taking the logarithm of the ratio of the number of positive lymph nodes to the number of negative lymph nodes.[13, 14] LODDS values can be used in different cancers and have been proven to be more reliable than evaluating patients' lymph node status as a prognostic factor.[15, 16]

This study aims to examine the clinical characteristics of patients with MTC, prognostic factors affecting survival, and the prognostic value of LODDS values.

Methods

In this study, a retrospective analysis was conducted on 39 patients who underwent surgical treatment due to MTC in the Department of General Surgery at at Gazi University Faculty of Medicine between January 2012 and June 2022. Patients who did not receive operative treatment were excluded. The study protocol was approved by the Gazi University Faculty of Medicine Institutional Ethics Board. Medical records were reviewed for demographic, pathological and clinical Variables. The primary outcome measure was disease-free survival while the secondary outcome measures were development of recurrence and associated metastasis. The log odds of positive lymph nodes (LODDS) were calculated using the formula "log (positive nodes + 0.5)/(total nodes – positive nodes + 0.5)".

Statistical Analysis

Statistical analysis of the research was carried out using the SPSS 23.0 package program. The normal distribution of continuous variables was evaluated using the Kolmogorov-Smirnov, histogram, and Q-Q plot tests. Descriptive statistics were presented as table for frequency distribution and percentage for categorical variables, mean±standard deviation and median (IQR) for continuous Variables. Pearson and Fisher's Chi-Square tests were used for comparison of categorical Variables, and Mann Whitney U test was used for comparison of continuous variables. Univariate and multivariate Cox regression analysis were used to examine the effects of patients' demographic, clinical, and histopathological characteristics on disease-free and overall survival. Statistical significance level was set at 95% and $p<0.05$ was considered significant.

Results

Table 1 shows the distribution of demographic characteristics of the patients included in the study. The mean age was 50.30±15.06, 51.3% were female and 48.7% were male. Family history was present in 12.8% of the patients. 7.7% of patients have RET-mutations. The distribution of histopathological prognostic factors of the patients is shown in Table 2. A statistically significant difference was found between survival status and gender in Table 3 ($p=0.031$).

Table 4 provides a comparison of histopathological characteristics with survival status. It is observed that tumor sizes are higher in the exitus group ($p=0.002$). There was a statistically significant difference in survival status between patients with and without extrathyroidal extension ($p<0.001$). LODDS value was higher in the exitus group ($p<0.001$). 66.7% of patients with bilateral metastatic lymph nodes reached the exitus (p:0.004). 75.0% of patients with distant metastasis at diagnosis and 20.0% of patients without distant metastasis reached the exitus ($p=0.045$). Patients with metastasis during follow-up had a significantly higher exitus rate than those without metastasis ($p=0.019$). Exitus rates are higher in patients with lymph node metastasis at diagnosis compared to those without (0.025). Exitus rates were higher in advanced stage (Stage 3 and Stage 4) patients ($p=0.025$). The exitus rate of patients who received radiotherapy was statistically significantly higher than those who did not receive radiotherapy ($p=0.004$)

Table 1. Distribution of Demographic Characteristics of Patients

Parameters	
Age (mean±SD)	50.30±15.06
Age groups (%)	
<40	9 (23.1)
≥40	30 (76.9)
Sex, n (%)	
Male	19 (48.7)
Female	20 (51.3)
Family history, n (%)	
No	34 (87.2)
Yes	5 (12.8)

Table 2. Distribution of Clinical and Histopathological Prognostic Factors of Patients

Parameters	
Tumor size Median (IQR)	1.70 (1.70)
Tumor location n(%)	
Right	19 (48.7)
Left	13 (33.3)
Bilateral	7 (17.9)
Tumor focality n(%)	
Unifocal	25 (64.1)
Multifocal	14 (35.9)
Lymph node metastasis at diagnosis n(%)	
No	21 (53.8)
Yes	18 (46.2)
Distant metastasis at diagnosis n(%)	
No	35 (89.7)
Yes	4 (10.3)
T stage n(%)	
T1	25 (64.1)
T2	10 (25.6)
T3	4 (10.3)
Stage n(%)	
Stage1	16 (41.0)
Stage2	5 (12.8)
Stage3	4 (10.3)
Stage4	14 (35.9)
CEA Median (IQR)	15.09 (88.01)
Calcitonin Median (IQR)	427.0 (1574.40)
Extrathyroidal extension n (%)	
No	23 (59.0)
Yes	16 (41.0)
Neck dissection n(%)	
No	9 (23.1)
Central Lymph Node Disection	16 (41.0)
Lateral Lymph Node Disection	14 (35.9)
Total lymph node Median(IQR)	25.0 (52.2)
Metastatic lymph node Median(IQR)	2.0 (15.0)
LODDS Median (IQR)	-0.62 (2.53)
Site of metastatic lymph node n (%)	
No	21 (53.8)
psilateral	9 (23.1)
Bilateral	9 (23.1)
Follow-up metastasis n(%)	
No	31 (88.6)
Yes	4 (11.4)
Local recurrence n(%)	
No	32 (91.4)
Yes	3 (8.6)
Chemotherapy n(%)	
No	29 (74.4)
Yes	10 (25.6)
Radiotherapy n(%)	
No	30 (76.9)
Yes	9 (23.1)
Survival status n(%)	
Alive	29 (74.4)
Exitus	10 (25.6)

In Table 4, disease-free survival analysis is provided. It is observed that factors with significant effects in univariate analysis did not have an effect in multivariate analysis. Similarly, in the disease specific survival analysis in Table 5, it is observed that only the risk of patients receiving radiotherapy was higher than those not receiving radiotherapy (HR: 9.328, 95% CI: 1.039-83.772, p=0.046).

Discussion

Surgical intervention is the primary treatment for MTC. Although total thyroidectomy is applied to all cases of MTC, adding prophylactic central lymph node dissection can improve the cure rate and make biochemical follow-up easier. If there are clinically or radiologically detectable metastases in the neck lymph nodes lateral groups, neck dissection, including lateral groups, should be added. While postoperative radiotherapy is recommended for residual tissue, chemotherapy and radiotherapy have weak effectiveness.[17]

Although most previous studies have reported that MTC is more common in women; some studies similar to this one has also reported a similar ratio between women and men. [17-20] Male gender has been found to be a risk factor associated with poor survival in several studies.[20-22] A larger tumor size has also been found to be associated with poor survival in previous studies.[23-25]

While cervical lymph node involvement is reported in 70% of cases at diagnosis, distant metastases are reported in 10%.[26] In this study, we found these rates to be 46.2% and 10.3%, respectively. Age, gender, local invasion, angioinvasion, postoperative calcitonin, and surgical cure are the most important prognostic factors for MTC.[6, 26-30] Similarly, gender, tumor size, extrathyroidal spread, lymph node metastasis, distant metastasis, and stage were found to be important for survival in our study. The side of lymph node metastasis has also been shown to affect survival. Increasing tumor size has been reported to increase the risk of tumor recurrence.[23] In our study, tumor size was also found to be associated with poor survival. The presence of distant metastasis at diagnosis or the occurrence of surgical distant metastasis has a negative effect on survival.

This study found that the presence and location of lymph node metastasis, as well as the LODDS ratio, are associated with survival in MTC. Nodal status has been reported as the most important prognostic factor in MTC.[31] Kuo et al. reported that patients without LNM had similar survival rates to the general population.[32] The LODDS ratio reflects not only the presence of lymph node metastasis, but also the extent of lymphadenectomy. However, there are limited studies on the prognostic value of LODDS in MTC. Tang et al. reported that LODDS is a better prognostic indicator than

Table 3. Comparison of Demographic, Clinical and Histopathological Characteristics of Patients by Survival Status

Parameters	Alive	Exitus	p
Age n (%)			
<40	9 (31.0)	0 (0)	N/A
≥40	20 (69.0)	10 (100)	
Sex n(%)			
Male	11 (38.9)	8 (80.0)	0.031
Female	18 (62.1)	2 (20.0)	
Family history n(%)			
No	24 (82.8)	10 (100)	N/A
Yes	5 (17.2)	0 (0)	
Tumor size Median(IQR)	1.40 (1.50)	3.55 (4.67)	0.002
Tumor location n(%)			
Right	16 (55.2)	3 (10.0)	0.327
Left	9 (31.0)	4 (10.0)	
Bilateral	4 (13.8)	3 (80.0)	
Tumor focality n(%)			
Unifocal	19 (65.5)	6 (60.0)	>0.999
Multifokal	10 (34.5)	4 (40.0)	
Lymph node metastasis at diagnosis n(%)			
Unknown	8 (27.6)	1 (10.0)	0.049
No	11 (37.9)	1 (10.0)	
Yes	10 (34.5)	8 (80.0)	
Distant metastasis at diagnosis n(%)			
No	28 (96.5)	7 (70.0)	0.045
Yes	1 (3.5)	3 (30.0)	
T stage n(%)			
T1	21 (72.4)	4 (40.0)	N/A
T2	8 (27.6)	2 (20.0)	
T3	0 (0.0)	4 (40.0)	
Stage n(%)			
Stage 1-2	19 (65.5)	2 (20.0)	0.025
Stage 3-4	10 (34.5)	8 (80.0)	
CEA Median(IQR)	15.0 (102.2)	14.9 (40.6)	0.655
Calcitonin Median(IQR)	427.0 (1407.8)	416.2 (3515.5)	0.838
Extrathyroidal extension n(%)			
No	22 (75.9)	1 (10.0)	<0.001
Yes	7 (24.1)	9 (90.0)	
Neck dissection n(%)			
No	8 (27.6)	1 (10.0)	0.033
Central Lymph Node Disection	14 (48.3)	2 (20.0)	
Lateral Lymph Node Disection	7 (24.1)	7 (70.0)	
Total lymph node Median(IQR)	20.0 (32.5)	43.0 (63.0)	0.193
Metastatic lymph node Median(IQR)	0 (4.0)	17.0 (30.0)	N/A
LODDS Median(IQR)	-1.02 (2.18)	-0.01 (0.56)	<0.001
Site of metastatic lymph node n(%)			
No	19 (65.5)	2 (20.0)	0.004
İpsilateral	7 (24.1)	2 (20.0)	
Bilateral	3 (10.4)	6 (60.0)	
Distant metastasis at diagnosis n(%)			
No	28 (96.5)	7 (70.0)	0.045
Yes	1 (3.5)	3 (30.0)	
Follow-up metastasis n(%)			
No	27 (96.4)	4 (57.1)	0.019
Yes	1 (3.6)	3 (42.9)	
Local recurrence n(%)			
No	25 (89.3)	7 (100)	N/A
Yes	3 (10.7)	0 (0)	
Chemotherapy n(%)			
No	22 (75.9)	7 (70.0)	0.696
Yes	7 (24.1)	3 (30.0)	
Radiotherapy n(%)			
No	26 (89.65)	4 (40.0)	0.004
Yes	3 (10.35)	6 (60.0)	

N/A (Not Applicable): Not suitable for statistical analysis.

Table 4. Analysis of the Effect of Prognostic Factors of Patients on Disease-Free Survival

	UniVariate Analysis (DFS)			Multivariate Analysis (DFS)		
	HR	%95 CI	p	HR	%95 CI	p
Sex						
Female	1			-	-	-
Male	5.360	0.940-30.357	0.059	3.481	0.657-18.444	0.143
Tumor size	2.301	1.348-3.930	0.002			
Lymph node metastasis at diagnosis n(%)	1			N/A	N/A	N/A
No	7.377	1.280-42.500	0.025			
Yes						
Distant metastasis at diagnosis n(%)	N/A	N/A	N/A	-	-	-
No						
Yes						
Stage	1			N/A	N/A	N/A
Stage 1-2	7.377	1.280-42.500	0.025			
Stage 3-4						
Extrathyroidal extension	1			N/A	N/A	N/A
No	11.879	1.419-99.447	0.022			
Yes						
Neck dissection	N/A	N/A	N/A	-	-	-
No						
Central Lymph Node Disection						
Lateral Lymph Node Disection						
Total lymph node	1.019	0.998-1.041	0.075	-	-	-
LODDS	8.963	1.457-55.125	0.018	0.380	0.007-20.678	0.635
Site of metastatic lymph node	1			-	-	-
No	2.757	0.229-33.225	0.425			
İpsilateral	N/A	N/A	N/A			
Bilateral						
Follow-up metastasis	1			1		
No	16.306	2.690-98.861	0.002	0.713	0.044-11.467	0.811
Yes						
Stage	1			N/A	N/A	N/A
Stage 1-2	7.377	1.280-42.500	0.025			
Stage 3-4						
Radiotherapy	1			N/A	N/A	N/A
No	5.972	1.327-26.864	0.020			
Yes						

N/A (Not Applicable): Not suitable for statistical analysis.

N stage and the number of positive lymph nodes in their study of 1110 MTC patients.[12] Cao et al. showed that MTC patients with a LODDS ratio of >-1.004 had a poor prognosis.[33] Prassas et al. suggested that the staging based on LODDS value in the literature can be used for overall survival.[34] In this study, the effect of LODDS on survival was confirmed, but its effect on disease-free survival could not be shown due to the limited number of patients in the cohort.

This study has limitations, including a small number of patients and the fact that the study cohort was limited to surgical candidates only. The record information, variables investigated, and sample size were not pre-planned due to the retrospective nature of the study. Prospective and multicenter clinical studies should be conducted to overcome these limitations and obtain more reliable and robust data.

Table 5. Analysis of the Effect of Prognostic Factors of Patients on Disease Specific Survival

	Univariate Analysis (Dis. Spes. Surv.)			Multivariate Analysis (Dis. Spes. Surv.)		
	HR	%95 CI	p	HR	%95 CI	p
Sex						
Female	1			N/A	N/A	N/A
Male	6.410	1.322-31.072	0.021			
Tumor size	1.751	1.317-2.329	<0.001	1.683	0.954-2.970	0.072
Lymph node metastasis at diagnosis n(%)						
No	1			N/A	N/A	N/A
Yes	10.892	2.067-57.412	0.005			
Distant metastasis at diagnosis						
No	1			N/A	N/A	N/A
Yes	8.930	1.962-40.646	0.005			
Stage						
Stage 1-2	1			N/A	N/A	N/A
Stage 3-4	10.892	2.067-57.412	0.005			
Extrathyroidal extension						
No	1			N/A	N/A	N/A
Yes	15.862	2.003-95.590	0.009			
Neck dissection						
No	1			-	-	-
Central Lymph Node Disection	2.115	0.185-24.208	0.547			
Lateral Lymph Node Disection	N/A	N/A	N/A			
Total lymph node	1.018	1.001-1.036	0.035	1.005	0.980-1.031	0.691
LODDS	4.017	1.138-14.175	0.031	1.408	0.287-6.911	0.674
Site of metastatic lymph node						
No	1			-	-	-
İpsilateral	5.484	0.711-42.328	0.103			
Bilateral	N/A	N/A	N/A			
Follow-up metastasis						
No	1			1	0.044-11.467	0.811
Yes	13.490	2.206-82.478	0.005	0.713		
Radiotherapy						
No	1			1		
Yes	6.725	1.884-24.004	0.003	9.328	1.039-83.772	0.046

N/A (Not Applicable): Not suitable for statistical analysis.

Conclusion

Medullary thyroid cancer (MTC) is a rare but unique type of thyroid cancer with a different origin and specific treatment strategy. Our cohort study identified several factors associated with poor survival in MTC, including male gender, tumor size, extrathyroidal spread, lymph node status, metastatic lymph node localization, and distant metastasis at diagnosis or follow-up. Furthermore, we found that lymph node ratio (LODDS) values may be predictive of survival in MTC.

Disclosures

Ethics Committee Approval: Gazi University Faculty of Medicine Institutional Ethics Board 09.01.2023-22.

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Conflict of Interest: None declared.

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