Medullary thyroid cancer (MTC): Risk Factors for Recurrence and Prognostic Variables that Influence Outcome

Ayman A. Amin[a*], Hamdy Mohamed Hussein[b], Ahmed K. Fekry[c*], Mohamed Mubark[c]
[a]Surgical Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt
[b]General Surgery Department, Faculty of Medicine, Luxor University, Luxor, Egypt.
[c]General Surgery Department, Faculty of Medicine, South Valley University, Qena, Egypt.

Abstract

Background: Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor from thyroid C cells that can cause thyroid lumps or metastases. MTC accounts for 10.5% of metastasized thyroid tumors and is linked to RET proto-oncogene mutations. Surgery is the major therapy, although it's invasive and hard to cure.

Objectives: to review a contemporary institutional experience with medullary thyroid carcinoma treatment with two goals: to study the risk factors for recurrence and to identify prognostic factors that affect survival

Patients and methods: The National Cancer Institute (NCI) and Shefaa El Orman Oncology Hospital in Egypt studied 78 medullary thyroid cancer (MTC) patients during 2015-2022. It excluded unsuitable or missing pathology findings from retrospective and prospective studies. Imaging, blood testing, and fine-needle aspiration cytology were done. Total thyroidectomy and neck dissection were given depending on the diagnosis. Pathology and serum indicators were evaluated for recurrence after surgery. Inherited RET mutation patients had prophylactic thyroidectomy.

Results: The research comprised 78 patients (mean age: 43.13 ± 16.35 years; 41.03% male, 58.97% female). Diabetes (14.1%), hypertension (12.82%), and heart diseases (11.54%) were comorbidities. Left-sided tumors (50.88% vs. 28.57%) and bigger tumors (3.72 cm vs. 2.36 cm) were more common in recurrence instances Recurrence patient lymphovascular invasion (68.42% vs. 23.81%), serum calcitonin (1424.61 vs. 204.48 pg./mL), and CEA levels (263.82 vs. 23.54 ng/mL) were substantially greater. Advanced tumor stages and severe disease characteristics were connected to recurrence.

Conclusion: Medullary thyroid cancer (MTC) recurrence risk variables included bigger tumor size, advanced TMN staging, extrathyroid extension, and increased preoperative calcitonin and CEA values. Improving patient outcomes requires extensive initial surgery and postoperative monitoring.

Keywords: Medullary thyroid cancer; Recurrence risk factors; Tumor size; Calcitonin; CEA
DOI: 10.21608/SVUIJM.2024.325670.1991
***Correspondence:** aymanamin@hotmail.com
Received: 12 October,2024.
Revised: 3 November, 2024.
Accepted: 5 November, 2024.
Published: 3 February, 2025
Cite this article as Ayman A. Amin, Hamdy Mohamed Hussein, Ahmed K. Fekry, Mohamed Mubark.(2025). Medullary thyroid cancer (MTC): Risk Factors for Recurrence and Prognostic Variables that Influence Outcome. *SVU-International Journal of Medical Sciences*. Vol.8, Issue 1, pp: 249-261.

Introduction

Medullary thyroid carcinoma (MTC) originates from the Para follicular C cells of the thyroid, which derive from the neural crest, classifying MTC as a neuroendocrine tumor. It can occur either sporadically or inherited. The most common presentation is a thyroid lump, occurring in 74% of sporadic cases, but it may also be presented as mass from metastatic disease, particularly in cervical lymph nodes or distant metastases. Other presentations include symptoms from elevated calcitonin levels, such as diarrhea and flushing (seen in 10% of sporadic cases), ectopic Cushing syndrome (0.7% of cases), or it may be detected through familial screening (**Gild et al., 2023).**

MTC is responsible for 10.5% of all thyroid cancers that present with distant metastases, which mainly spread to the liver and bone (**Vuong et al., 2022).** The tumor is known for producing calcitonin, and if distant metastases are present at diagnosis, the prognosis is generally poor. Early detection and diagnosis are challenging due to atypical ultrasonographic or cytological patterns, and metastases are often microscopic, making them difficult to detect with current imaging technologies. The clinical course of MTC is also unpredictable, with metastatic disease potentially remaining stable for years before suddenly progressing (**Fugazzola, 2023).**

Approximately 15-20% of MTC cases are familial, linked to a germline mutation in the RET proto-oncogene, usually associated with multiple endocrine neoplasia type 2 (MEN2). Cure for MTC is difficult due to its tendency for vascular invasion, lymph node involvement, and distant metastasis **(Papachristos et al., 2023**). Surgical intervention is the primary treatment method, with total thyroidectomy (TT) and central lymph node dissection (CND) with or without selective lymph node dissection (SND) being the most widely recommended techniques for initial management **(Kaliszewski et al., 2022).**

Patients and methods

Study Design and Setting: This study is a combination of retrospective and prospective analyses. It was conducted at the Head and Neck Oncology Unit of the National Cancer Institute (NCI), Cairo University, Egypt, and the Shefaa El Orman Oncology Hospital (SOH), Luxor, Egypt. Both institutions function as tertiary referral centers for thyroid malignancies and maintain tumor registries based on confirmed pathological reports. Patients referred to these centers often require radical repeat surgery after inadequate primary surgery at local hospitals. Patients without detailed pathology reports from their initial surgeries were excluded from the study.

Study Duration: The study spanned from January 2015 to December 2022.

Study Subjects: The study included patients diagnosed with medullary thyroid carcinoma confirmed by pathological examination. Exclusion criteria comprised patients who were either unfit for surgery, refused surgery, or lacked detailed pathology reports from their primary surgeries.

Sample Size: A total of 78 patients were included in the study. Of these, 67 were part of a retrospective analysis from the institutional registry at NCI and SOH, having undergone surgery between January 2015 and December 2021. Additionally, 11 patients were part of a prospective study conducted between December 2021 and December 2022.

Patient Data and Medical History: All patients' records were reviewed to gather comprehensive medical histories and examination details. This included vital signs and body mass index, along with a detailed neck examination focusing on cervical lymph nodes.

Clinical Examinations and Investigations: Patients underwent thorough evaluations, including neck ultrasound, CT scans of the neck, and positron emission tomography (PET) scans. Fine needle aspiration cytology (FNAC) results were included when available. Pre-operative investigations assessed serum calcitonin, carcinoembryonic antigen (CEA), and thyroid function tests (free T3, T4, and TSH). Routine laboratory tests included complete blood count (CBC), coagulation profile (prothrombin time and INR), kidney function tests (serum urea and creatinine), and random blood sugar levels. Additional tests like chest X-rays and ECGs were also part of the evaluations.

Prophylactic Thyroidectomy in Inherited MTC: Prophylactic thyroidectomy was performed on nine patients who had inherited germline mutations in the RET proto-oncogene but showed no clinical signs of medullary thyroid carcinoma (MTC). The procedure aimed to reduce the long-term risks of morbidity and mortality associated with MTC.

Operative data: In our institution we used an 'apron' flap as incision design during study, the incision was marked using surgical marker pen **(Fig.1).** upper and lower flabs through subplatysmal plane were raised superiorly to the edge of the mandible and inferiorly to the level of the clavicle. lateral neck dissection was done (based on the likely nodal drainage for a medullary thyroid carcinoma) through removal of Level II, Level III and Level IV lymph nodes at the lateral side of the neck with preservation of spinal accessory nerve (SAN), internal jugular vein (IJV) and sternocleidomastoid muscle (SCM) **(Fig.2).** Opening of strap muscles at midline, total thyroidectomy was done with central neck dissection (CND) through removal of Level VI lymph node aiming in preservation of recurrent laryngeal nerve and parathyroid gland **(Fig.3).**

Postoperative Complications: Postoperative complications were defined as any deviation from the normal recovery process. These included issues such as hypocalcemia, vocal cord impairment, tracheostomy, chyle leakage, and hypoparathyroidism. Complications were tracked both during the hospital stay and follow-up period.

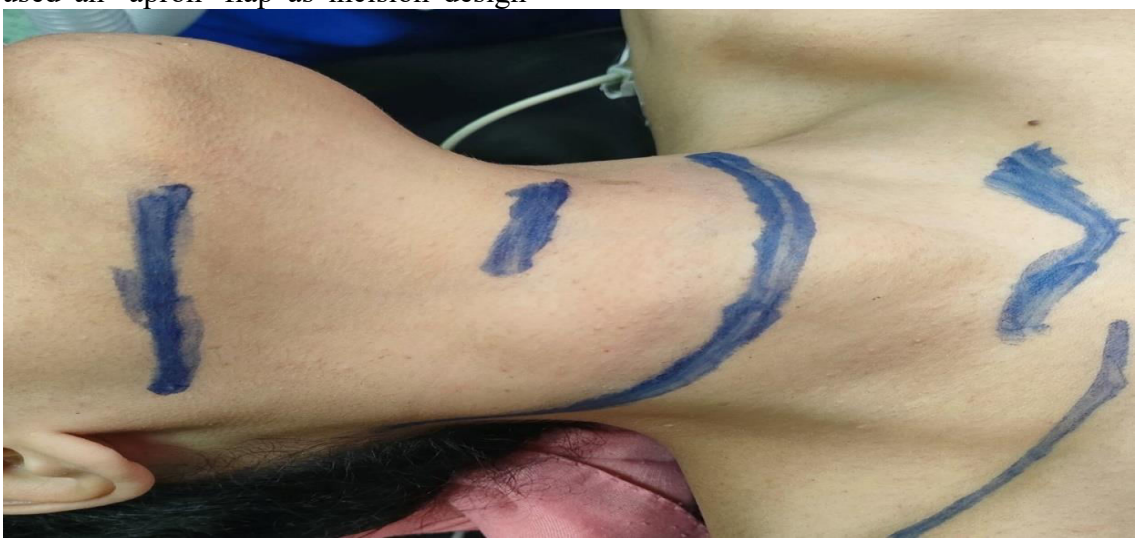

Fig .1. Intraoperative image for design of incsion for pateint underwent total thyroidectomy with centeral and lateral neck dissection

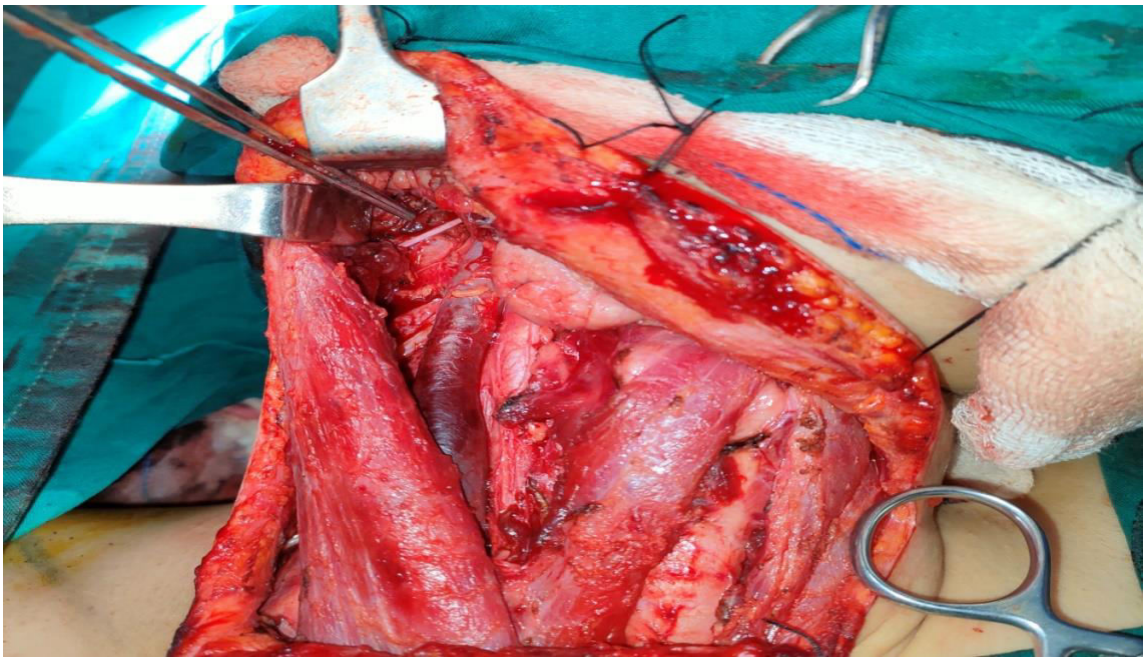

Fig 2. Intraoperative image for patient underwent lateral neck dissection for MTC

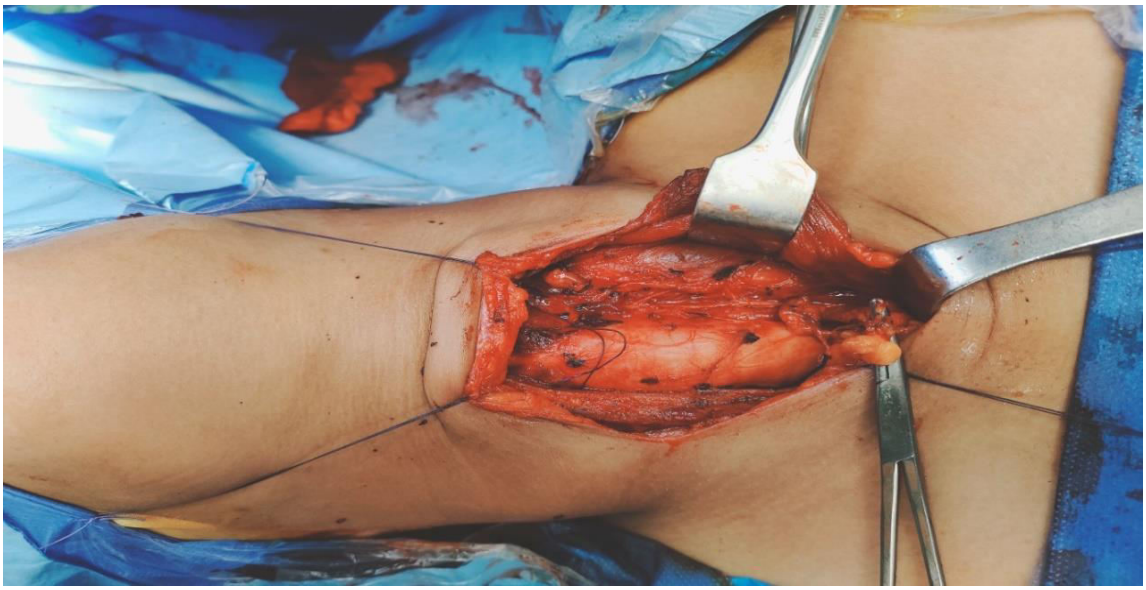

Fig 3. Intraoperative image for patient underwent total thyroidectomy+ central neck dissection

Pathological Confirmation and Follow-Up: Postoperative diagnoses were confirmed by two pathologists. All patients received oral thyroxine for thyroid hormone replacement, though no suppressive therapy was given. Follow-up was conducted through outpatient visits and phone calls. Patients were first assessed one month after surgery, then every three months for a year. Routine ultrasonography and blood tests were performed, with computed tomography (CT) scans done annually or if abnormalities were detected. For patients without lateral neck dissection, follow-up ultrasonography at 3- and 6-months post-surgery ensured no occult metastasis. Recurrences were defined as local or distant recurrence which was detected more than six months duration after surgery to exclude early inflammatory process in post operative period. In cases of

recurrence, local recurrence was diagnosed by sonographic fine-needle aspiration cytology. Distant metastasis was confirmed by chest, abdominal, or pelvis computerized tomography (CT) scans with contrast or by PET CT.

Pathology Report Review: Pathology reports were examined for tumor size, lymph node metastasis, extra-thyroidal invasion, and lymphatic or vascular invasion. Additionally, the number and location of lymph nodes removed were analyzed, with attention to whether positive lymph nodes were ipsilateral, contralateral, or bilateral, and whether they were central or lateral. If key details were missing, the patient was excluded from that specific analysis.

Monitoring of Serum Markers and Imaging: For patients diagnosed with medullary thyroid carcinoma (MTC) preoperatively, calcitonin levels were measured before surgery and one month afterward. Reference levels for calcitonin were set at <10 pg./mL in females and <15 pg./mL in males, for carcinoembryonic antigen (CEA) at ≤2.5 ng/mL in females and ≤2.5 ng/mL in males (**Machen et al., 2024).**

Follow-Up Investigations

- **Neck Ultrasound**: Used for detecting suspected local recurrence, confirmed by image-guided biopsy.
- **CT scans (Neck and Chest)**: Conducted to assess for recurrence and metastases.
- **PET-CT scans**: Combined positron emission tomography (PET) and CT were used to diagnose and stage cancer, with PET assessing physiology and CT assessing anatomy.

Laboratory Investigations During Follow-Up

- **Serum Calcitonin**: Measured with ELISA kits to monitor recurrence.
- **CEA Levels**: Monitored using ELISA kits.
- **Serum Calcium**: Assessed using reagent kits.
- **Thyroid Profile**: Included TSH, free T3, and free T4 levels.

Ethical Approval: The current study has been approved by the Ethics committee of faculty of Medicine, SVU,Qena,Egypt, with Ethical approval code: SVU-MED-SUR011 -2 -21-12-300 .

Statistical analysis

Statistical analysis was conducted using SPSS version 26.0. Qualitative data were expressed as numbers and percentages, while quantitative data were presented as means and standard deviations (SD). The arithmetic mean was used to describe central tendency, and SD measured data dispersion. The student "t" test was applied for comparing means between two independent groups, and the Mann-Whitney test was used for non-normally distributed quantitative variables. The Chi-square test assessed associations between categorical variables. A significance threshold was set at $p < 0.05$, with smaller p-values indicating more significant results.

Results

The study included 78 participants with a mean age of 43.13 ± 16.35 years; 41.03% were male, and 58.97% were female. Comorbidities included diabetes mellitus in 14.1%, hypertension in 12.82%, and cardiac conditions in 11.54%. Most (73.08%) had no family history of cancer, while 3.85% had differentiated thyroid carcinoma, 12.82% had medullary thyroid carcinoma, and 10.26% had other cancers (**Table.1**).

Table 1. Basal characteristics of all included subjects

Variables	Value (N = 78)
Demographic data	
Age (Years)	43.13 ± 16.35
Sex	
Male	32 (41.03%)
Female	46 (58.97%)
Comorbidities	
DM	11 (14.1%)
HTN	10 (12.82%)
Cardiac	9 (11.54%)
Family history of cancer	
Negative	57 (73.08%)
Positive for DTC	3 (3.85%)
Positive for MTC	10 (12.82%)
Positive for other cancers	8 (10.26%)

During follow-up, the mean serum calcitonin level was 1087.47 ± 1676.12, and the mean CEA level was 197.43 ± 647.73. Ultrasound and PET CT results were positive in 66.67% of cases and negative in 32.05%, with. Recurrence occurred in 57 cases, with 33.33% having local recurrence and 39.74% distant recurrence. No recurrence was seen in 26.92% of cases. Adjuvant therapy was not given in 46.15% of cases; 44.87% received radiotherapy, 14.1% chemotherapy, and 3.85% radioactive iodine. Repeat surgery was required in 46.15% of cases (**Table.2**).

Table 2. Follow up evaluation data among all included subjects

Variables	Value (N = 78)
Follow up evaluation	
S. Calcitonin	1087.47 ± 1676.12
S. CEA	197.43 ± 647.73
u/s	
Positive	52 (66.67%)
Negative	25 (32.05%)
PET CT	
Positive	52 (66.67%)
Negative	25 (32.05%)
Died	1 (1.28%)
Recurrence	
No	21 (26.92%)
Local	26 (33.33%)
Distant	31 (39.74%)
adjuvant	
No	36 (46.15%)
Radiotherapy	35 (44.87%)

Chemotherapy	11 (14.1%)
Radioactive iodine	3 (3.85%)
Repeat surgery	36 (46.15%)

The comparison of disease characteristics between recurrence and non-recurrence cases revealed notable differences. Recurrence cases were predominantly sporadic (91.23%) compared to 61.9% in the non-recurrence group, with hereditary cases lower in the recurrence group (8.77% vs. 38.1%). Fine needle aspiration cytology (FNAC) showed similar false positive rates (22.81% in recurrence vs. 23.81% in non-recurrence) and comparable positive (24.56% vs. 33.33%) and negative results (52.63% vs. 42.86%).

Tumors in recurrence cases were larger (average length 3.72 ± 1.76 cm, width 2.77 ± 1.58 cm) compared to non-recurrence (length 2.36 ± 1.29 cm, width 1.81 ± 0.91 cm). Bilateral tumors were less common in recurrence cases (5.26% vs. 23.81%), and left-sided tumors were more prevalent (50.88% vs. 28.57%).

Preoperative calcitonin (8133.68 ± 33346.12 vs. 5908.76 ± 19221.61) and CEA levels (686.39 ± 1326.32 vs. 80.23 ± 86.32) were higher in the recurrence group, but these differences were not statistically significant (**Table.3**).

Table 3. Comparison between cases reported recurrence and those who did not regarding Disease Characteristics

Variables	Cases reported no recurrence (N = 21)	Cases reported recurrence (N = 57)	P. Value
Type			
Sporadic	13 (61.9%)	52 (91.23%)	0.0017*[X]
Hereditary	8 (38.1%)	5 (8.77%)	0.0017*[X]
FNAC			
False positive	5 (23.81%)	13 (22.81%)	0.9269[X]
Positive	7 (33.33%)	14 (24.56%)	0.4451[X]
Negative	9 (42.86%)	30 (52.63%)	0.4503[X]
Tumor side			
Left	6 (28.57%)	29 (50.88%)	0.0808[X]
Right	10 (47.62%)	25 (43.86%)	0.7707[X]
Bilateral	5 (23.81%)	3 (5.26%)	0.0163*[X]
Tumor size			
Length	2.36 ± 1.29	3.72 ± 1.76	0.0025*[MWU]
Width	1.81 ± 0.91	2.77 ± 1.58	0.0179*[MWU]
preoperative calcitonin	5908.76 ± 19221.61	8133.68 ± 33346.12	0.8618[MWU]
preoperative CEA	80.23 ± 86.32	686.39 ± 1326.32	0.1345[MWU]

The analysis of perioperative data revealed significant differences between recurrence and non-recurrence cases. The recurrence group had a higher rate of initial surgeries involving total thyroidectomy with central neck dissection (TT+CND) (14.04%) and TT+CND with selective neck dissection (TT+CND+SND) (42.11%), compared to 0% and 57.14% in the non-recurrence group, respectively.

Complications were more common in recurrence cases, with 80.7% exhibiting extra thyroid extension compared to 28.57% in non-recurrence cases. Lymphovascular

invasion was significantly higher in recurrence cases (68.42% vs. 23.81%). The average number of positive lymph nodes was also greater in recurrence cases (7.82 ± 8.46) than in non-recurrence cases (5.1 ± 7.25) (**Table.4**).

Table 4. Comparison between cases reported recurrence and those who did not regarding Perioperative data

Variables	Cases reported no recurrence (N = 21)	Cases reported recurrence (N = 57)	P. Value
Initial surgery			
No	0 (0%)	2 (3.51%)	0.3911[X]
HT	1 (4.76%)	5 (8.77%)	0.5615[X]
TT	8 (38.1%)	18 (31.58%)	0.5938[X]
TT+CND	0 (0%)	8 (14.04%)	0.0715[X]
TT+CND+SND	12 (57.14%)	24 (42.11%)	0.2429[X]
Complication			
NO	14 (66.67%)	33 (57.89%)	0.489[X]
Chlye leakage	2 (9.52%)	4 (7.02%)	0.7169[X]
Hypocalcemia	5 (23.81%)	16 (28.07%)	0.7111[X]
Hypoparathyroidism	0 (0%)	1 (1.75%)	0.5473[X]
Immobile VC	0 (0%)	5 (8.77%)	0.1648[X]
Tracheostomy	0 (0%)	4 (7.02%)	0.2178[X]
Extrathyroid extension	6 (28.57%)	46 (80.7%)	<0.0001*[X]
Lymphovascular invasion	5 (23.81%)	39 (68.42%)	0.0003*[X]

Follow-up evaluations revealed that recurrence cases had significantly higher postoperative serum calcitonin and CEA levels compared to non-recurrence cases. The recurrence group had an average calcitonin level of 1424.61 ± 1838.93 pg./mL, significantly higher than 204.48 ± 482.9 pg./mL in the non-recurrence group. Similarly, serum CEA levels were elevated in the recurrence group at 263.82 ± 749.67 ng/mL, compared to 23.54 ± 68.57 ng/mL in non-recurrence cases (**Table.5**).

Table 5. Comparison between cases reported recurrence and those who did not regarding Follow up evaluations

Variables	Cases reported no recurrence (N = 21)	Cases reported recurrence (N = 57)	P. Value
S. Calcitonin	204.48 ± 482.9	1424.61 ± 1838.93	<0.0001*[MWU]
S. CEA	23.54 ± 68.57	263.82 ± 749.67	<0.0001*[MWU]
u/s			
Positive	1 (4.76%)	51 (89.47%)	<0.0001*[X]
Negative	19 (90.48%)	6 (10.53%)	<0.0001*[X]
Died	1 (4.76%)	0 (0%)	0.0997[X]
PET CT			
Positive	0 (0%)	52 (91.23%)	<0.0001*[X]
Negative	19 (90.48%)	6 (10.53%)	<0.0001*[X]
Died	1 (4.76%)	0 (0%)	0.0997[X]

Discussion

The study involved 78 cases with a mean age of 43.13 years, comprising 32 males (41.03%) and 46 females (58.97%). Regarding family cancer history, 73.08% had none, 3.85% had differentiated thyroid carcinoma, 12.82% had medullary thyroid carcinoma, and 10.26% had other cancers. Our study findings indicate a similar demographic trend to those observed by **Gogna et al. (2020),** who found that patients aged ≥45 years with medullary thyroid carcinoma (MTC) were predominantly female and Caucasian, with 47.6% presenting with localized disease. Their findings showed that increasing age (HR 1.05, $p < 0.001$) and advanced stage at presentation (HR 3.68, $p < 0.001$) correlated with poorer survival, while female sex (HR 0.74, $p < 0.001$) and surgical resection (HR 0.36, $p < 0.001$) were associated with better survival outcomes.

Additionally, **Fallah et al. (2013)** highlighted those relatives of patients with early-onset MTC showed a heightened risk for early-onset thyroid cancer. This suggests that the age at diagnosis of thyroid cancer in individuals may be influenced by the age at which their relatives are diagnosed with MTC, which supports our study findings regarding familial patterns in thyroid cancer incidence.

Our study found a mean serum calcitonin level of 1087.47 and a CEA level of 197.43. Ultrasound and PET CT were positive in 52 cases (66.67%), negative in 25 (32.05%), and one patient had deceased (1.28%). Recurrence occurred in 57 cases, with local recurrence at 33.33% and distant recurrence at 39.74%; 26.92% had no recurrence. Adjuvant therapies included no treatment in 46.15%, radiotherapy in 44.87%, chemotherapy in 14.1%, and radioactive iodine in 3.85%. Repeat surgery was needed in 46.15% of cases. Our study findings align with **Zhao et al. (2021),** who reported a disease recurrence rate of 19.7% (14 of 71), showing that recurrence was more common in malignant MTC compared to low-suspicion MTC ($P = 0.013$). They found associations between recurrence and extrathyroid extension ($P = 0.047$), N staging ($P = 0.003$), and preoperative serum calcitonin levels ($P = 0.009$).

In our study, the recurrence group had a higher proportion of sporadic cases (91.23% vs. 61.9%) and larger tumors (3.72 cm vs. 2.36 cm in length; 2.77 cm vs. 1.81 cm in width). Bilateral tumors were less common (5.26% vs. 23.81%), while left-sided tumors were more frequent (50.88% vs. 28.57%). No significant differences were observed between sporadic and hereditary cases concerning FNAC results, tumor size, or lymph node involvement for repeat surgeries. This suggests that recurrence is more related to overall disease progression rather than tumor type **(Pacini & DeGroot, 2013; Sakr and Sakr, 2020).**

Our findings are consistent with **Kim et al. (2017),** who noted that M-MTCs had higher rates of lateral lymph node metastases and extrathyroidal extension (all $P < 0.05$). **Rozenblat et al. (2020)** also highlighted that a higher lymph node ratio (LNR) was positively correlated with tumor size ($p = 0.018$) and inversely correlated with age at diagnosis ($p = 0.024$). They found that LNR was associated with extrathyroidal extension ($p < 0.001$), multifocality ($p = 0.001$), bilateral tumors ($p = 0.002$), and recurrence (OR = 14.7, $p < 0.001$). LNR >0.1 was linked to shorter disease-specific survival in patients with tumors larger than 20 mm at diagnosis ($p = 0.013$), sporadic MTC ($p = 0.01$), and age above 40 years at diagnosis ($p = 0.004$).

Preoperative calcitonin (mean: C1) and CEA levels (mean: C2) were higher in recurrence cases, but these differences were not statistically significant. Our study findings indicate that the recurrence group's

more advanced TMN staging reflects a more aggressive disease, contributing to higher recurrence risk, while the non-recurrence group's early-stage tumors suggest earlier detection or less aggressive disease **(Kwon et al., 2016; Raue et al., 2019).**

Additionally, higher preoperative calcitonin and CEA levels in the recurrence group, though not statistically significant, may suggest a role for these biomarkers in aggressive disease. The absence of significant differences in TMN staging and other factors for repeat surgeries implies that the need for repeat surgery is more related to overall disease severity rather than specific preoperative characteristics **(Prinzi et al., 2024; Turkdogan et al., 2018; Yip et al., 2011**). **Kim et al. (2021)** highlighted that gross extrathyroidal extension, N stage, postoperative serum calcitonin, CEA levels, and lymph node ratio (LNR) were significant predictors of structural recurrence, with postoperative serum calcitonin and LNR indicating disease-free survival ($p < 0.05$).

Our study also found that recurrence cases underwent more extensive surgeries, with higher rates of total thyroidectomy, central, and selective neck dissection. Complications like extrathyroid extension (80.7% vs. 28.57%) and lymphovascular invasion (68.42% vs. 23.81%) were more common in the recurrence group. The recurrence group's extensive initial surgeries and higher complication rates indicate a more aggressive disease, necessitating broader surgical intervention **(Jayasinghe et al., 2022; Torresan et al., 2020).**

Our study found that recurrence cases had significantly higher postoperative serum calcitonin levels (1424.61 vs. 204.48 pg./mL) and CEA levels (263.82 vs. 23.54 ng/mL). Positive ultrasound findings were observed in 89.47% and PET CT findings in 91.23% of recurrence cases. Our study findings indicate that higher postoperative serum calcitonin and CEA levels in recurrence cases suggest more active disease, as these biomarkers are directly linked to tumor activity (**Costante et al., 2018; Passos et al., 2021).** The increased frequency of positive imaging findings implies that these techniques are more effective in detecting active disease in recurrent cases **(Imperiale et al., 2024; Skoura, 2013).**

Spanheimer et al. (2019) reported long-term outcomes after curative resection of familial MTC, with a median follow-up of 9.3 years, a median tumor diameter of 1.5 cm, and preoperative calcitonin levels in 41 patients (median 636). The overall survival rate was 94% at 10 years, with a cumulative incidence of loco regional recurrence at 38% and distant recurrence at 27% within the same period. They identified predictors of distant recurrence as tumor size, positive lymph nodes, and pre- and postoperative CEA levels. **Kukulska et al. (2020)** noted that local recurrence occurred in 107 out of 254 patients, with significantly higher relapse rates in advanced MTC stages ($P < 0.001$) and patients with lymph node metastases at diagnosis. Adjuvant radiotherapy was associated with a lower risk of nodal recurrence in high-risk patients.

Furthermore, **Pazaitou-Panayiotou et al. (2014)** highlighted that during a mean follow-up of 78.8 months, persistent disease was observed in 40 patients, with local recurrences in 5 and distant metastases in 32. Local and distant disease were more frequent in patients with larger tumors ($p < 0.005$) and lymph node metastases ($p < 0.01$). The presence of lymph node metastases at diagnosis was an independent predictor of recurrence and persistent disease, emphasizing the importance of early detection and treatment in improving outcomes.

Our study has limitations, including a small sample size of 78 cases, which may affect the generalizability of the findings. The retrospective design introduces potential biases and relying on preoperative and postoperative serum markers may not fully reflect disease progression. Variability in adjuvant therapies and follow-up duration could also influence observed recurrence rates and outcomes. Future research with larger, multicentric cohorts and standardized treatment protocols is needed to validate our findings.

Conclusion

Our study on medullary thyroid carcinoma (MTC) treatment identified larger tumor size, advanced TMN staging, and significant extrathyroid extension as key recurrence risk factors. Higher preoperative calcitonin and CEA levels were strongly linked to increased recurrence risk, highlighting their role in monitoring. We emphasize the need for comprehensive initial surgical management, including total thyroidectomy with central and selective neck dissection, along with rigorous postoperative surveillance. Early detection and tailored treatment strategies can enhance management and outcomes for MTC patients.

References

- **Costante G, Lalami Y, Jungels C, Awada A. (2018).** Calcitonin and carcinoembryonic antigen for the diagnosis and management of medullary thyroid carcinoma. Atlas of Thyroid and Neuroendocrine Tumor Markers, 133-150.
- **Fallah M, Sundquist K, Hemminki K. (2013).** Risk of thyroid cancer in relatives of patients with medullary thyroid carcinoma by age at diagnosis. Endocrine-Related Cancer, 20(5): 717-724.
- **Fugazzola L. (2023).** Medullary thyroid cancer-An update. Best Practice & Research Clinical Endocrinology & Metabolism, 37(1): 101655-101655.
- **Gild ML, Clifton-Bligh RJ, Wirth LJ, Robinson BG. (2023).** Medullary thyroid cancer: updates and challenges. Endocrine Reviews, 44(5): 934-946.
- **Gogna S, Goldberg M, Samson D, Gachabayov M, Felsenreich DM, Azim A, et al. (2020).** Medullary thyroid cancer in patients older than 45—Epidemiologic trends and predictors of survival. Cancers, 12(11): 3124-3137.
- **Imperiale A, Berti V, Burgy M, Cazzato RL, Piccardo A, Treglia G, et al. (2024).** Molecular imaging and related therapeutic options for medullary thyroid carcinoma: state of the art and future opportunities. Reviews in Endocrine and Metabolic Disorders, 25(1):187-202.
- **Jayasinghe R, Basnayake O, Jayarajah U, Seneviratne S. (2022).** Management of medullary carcinoma of the thyroid: a review. Journal of International Medical Research, 50(7): 1-20.
- **Kaliszewski K, Ludwig M, Ludwig B, Mikuła A, Greniuk M, Rudnicki J, et al. (2022).** Update on the diagnosis and management of medullary thyroid cancer: what has changed in recent years? Cancers, 14(15): 3643-3667.
- **Kim C, Baek JH, Ha E, Lee JH, Choi YJ, Song DE, et al. (2017).** Ultrasonography features of medullary thyroid cancer as predictors of its biological behavior. Acta Radiologica, 58(4): 414-422.
- **Kim J, Park J, Park H, Choi MS, Jang HW, Kim TH, et al. (2021).** Metastatic lymph node ratio for predicting recurrence in medullary thyroid cancer. Cancers, 13(22): 5842-5853.

- **Kukulska A, Krajewska J, Kolosza Z, Paliczka-Cieslik E, Kropinska A, Pawlaczek A, et al. (2020).** The role of postoperative adjuvant radiotherapy in local recurrence risk in medullary thyroid carcinoma. Endocrine Connections, 9(1): 1-8.
- **Kwon H, Kim WG, Sung TY, Jeon MJ, Song DE, Lee YM, et al. (2016).** Changing trends in the clinicopathological features and clinical outcomes of medullary thyroid carcinoma. Journal of Surgical Oncology, 113(2): 152-158.
- **Machens A, Lorenz K, Weber F, Dralle H. (2024**). Origin and impact of multifocal growth in sporadic vs. hereditary medullary thyroid cancer. European Journal of Surgical Oncology, 50(11), 108625.
- **Pacini F, DeGroot LJ. (2013).** Thyroid cancer. Endotext [Internet].
- **Papachristos AJ, Nicholls LE, Mechera R, Aniss AM, Robinson B, Clifton-Bligh R, et al. (2023).** Management of medullary thyroid cancer: patterns of recurrence and outcomes of reoperative surgery. The Oncologist, 28(12): 1064-1071.
- **Passos I, Stefanidou E, Meditskou-Eythymiadou S, Mironidou-Tzouveleki M, Manaki V, Magra V, et al. (2021).** A review of the significance in measuring preoperative and postoperative carcinoembryonic antigen (CEA) values in patients with medullary thyroid carcinoma (MTC). Medicina, 57(6): 609-621.
- **Pazaitou-Panayiotou K, Chrisoulidou A, Mandanas S, Tziomalos K, Doumala E, Patakiouta F, et al. (2014).** Predictive factors that influence the course of medullary thyroid carcinoma. International Journal of Clinical Oncology, 19(1): 445-451.
- **Prinzi A, Frasca F, Russo M, Pellegriti G, Piticchio T, Tumino D, et al. (2024).** Pre-operative calcitonin and CEA values may predict the extent of metastases to the lateral neck lymph nodes in patients with medullary thyroid cancer. Cancers, 16(17): 2979-2989.
- **Raue F, Bruckner T, Frank-Raue K. (2019).** Long-term outcomes and aggressiveness of hereditary medullary thyroid carcinoma: 40 years of experience at one center. The Journal of Clinical Endocrinology & Metabolism, 104(10): 4264-4272.
- **Rozenblat T, Hirsch D, Robenshtok E, Grozinsky-Glasberg S, Gross DJ, Mazeh H, et al. (2020).** The prognostic value of lymph node ratio in medullary thyroid carcinoma: a multi-center study. European Journal of Surgical Oncology, 46(11): 2023-2028.
- **Skoura E. (2013).** Depicting medullary thyroid cancer recurrence: the past and the future of nuclear medicine imaging. International Journal of Endocrinology and Metabolism, 11(4): e8156- e8164.
- **Spanheimer PM, Ganly I, Chou J, Capanu M, Ghossein RA, Tuttle RM, et al. (2019).** Long-term oncologic outcomes after curative resection of familial medullary thyroid carcinoma. Annals of Surgical Oncology, 26(1): 4423-4429.
- **Torresan F, Armellin C, Iacobone M. (2020).** Management of medullary thyroid carcinoma. Annals of Thyroid, 5(1): 16-27.
- **Turkdogan S, Forest VI, Hier MP, Tamilia M, Florea A, Payne RJ. (2018).** Carcinoembryonic antigen levels correlated with advanced disease in medullary thyroid cancer. Journal of Otolaryngology-Head & Neck Surgery, 47(1):55-62.
- **Vuong HG, Le MK, Hassell L, Kondo T, Kakudo K. (2022).** The differences

in distant metastatic patterns and their corresponding survival between thyroid cancer subtypes. Head & Neck, 44(4): 926-932.

- **Yip DT, Hassan M, Pazaitou-Panayiotou K, Ruan DT, Gawande AA, Gaz RD, 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(6):1168-1177.
- **Zhao J, Zheng X, Gao M, Zhang S, Yun X, Chi J, et al. (2021).** Ultrasound features of medullary thyroid cancer as predictors of biological behavior. Cancer Imaging, 21(1): 1-10.
- **Zhou TH, Zhao LQ, Zhang Y, Wu F, Lu KN, Mao LL, et al. (2021).** The prediction of metastases of lateral cervical lymph node in medullary thyroid carcinoma. Frontiers in Endocrinology, 12(1): 741289-741297.