



## Review

## Management of lymph nodes in medullary thyroid carcinoma: A review

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## A B S T R A C T

**Introduction:** Medullary Thyroid Carcinoma (MTC) as a neuroendocrine tumor that arises from the parafollicular C-cells and shows a potentially aggressive behavior with early lymph node metastasis. MTC cells do not absorb radioactive iodine and are not sensitive to Thyroid Stimulating Hormone (TSH) suppression, and therefore surgery is the most effective option for curative therapy.

**Results:** Medical imaging and biomarkers (calcitonin & CEA) assessment are necessary to determine the appropriate approach to lymph nodes surgery in MTC. Prophylactic central, lateral or contralateral neck dissections are recommended based on calcitonin level and volume of tumor. In general, guidelines are in agreement with prophylactic central dissection in most cases. Central and lateral dissections are recommended in all guidelines and review articles if lymphadenopathy is confirmed in preoperative examinations. Because lymph node dissection in most cases of locally advanced or metastatic MTC has no prognostic effect, dissection is done with palliative goal with maximum attention to maintaining function in these cases. In patients with an incomplete lymph node dissection, decision for reoperation can be based on calcitonin levels and the number of metastatic lymph nodes removed in previous surgery. Symptoms as well as speed of disease progression are also important in adopting the type of surgery. Consensus is in favor of reoperation in patients with recurrent regional MTC without distant metastasis.

**Conclusion:** Thyroidectomy is mandatory in patients with MTC but the type and extension of lymph node dissection are depending on the calcitonin level and tumor burden.

## 1. Introduction

Medullary Thyroid Cancer (MTC) accounts for 4% of all thyroid cancers. MTC is a neuroendocrine tumor that arises from the parafollicular C-cells. C-cells secrete calcitonin, and therefore calcitonin is the most sensitive and specific marker for the diagnosis and follow-up of MTC [1,2]. 75% of MTC are sporadic [3]. The ten-year survival of MTC is reported between 69% and 89% [4]. MTC has a high cost of care including surgery, lifetime follow-up with ultrasound, and medical treatment. Also, psychological services for survivors have own economic burden. The study from the U.S showed that economic hardship between thyroid cancer survivors and other cancers (colon, lung, breast, prostate) weren't different [5].

In one study with high volume of MTC patients that was performed by "French calcitonin tumors study group", the ten-year survival with lymph nodes metastasis was over 70% [6]. This tumor does not absorb

and concentrate iodine. MTC is not sensitive to TSH suppression and has no response to conventional cytotoxic chemotherapy [7]. For this reason, the only cytoreductive treatment in these patients with locoregional disease is surgery [8]. In MTC, lymph nodes metastasis occurs as soon as the tumor develops, behavior that not seen in other differentiated thyroid cancers [9,10]. Due to the effect of lymph node involvement, on the prognosis of patients, based on American Joint Committee on Cancer (AJCC) system, the presence or absence of lymph nodes metastasis is significant in staging [11]. There is a lot of controversy about surgical approach to cervical lymph nodes in MTC [12–14]. The purpose of this review article is to summarize the authoritative articles and guidelines on MTC and help surgeons to decide on surgical approach to MTC.

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## 2. Preoperative evaluation

Medical imaging and biomarkers assessments are necessary to determine the appropriate approach to lymph nodes surgery in MTC:

### 1 biomarkers assessment:

evaluation of serum calcitonin level is essential. The baseline level has two main applications:

- determining the extent and type of lymph nodes surgery (palliative vs therapeutic).
- as a baseline for comparison with the biomarkers obtained in post-operative follow-up [15,16]

The risk of central lymph nodes metastasis increases substantially when the carcinoembryonic antigen (CEA) concentration is greater than 30 ng/ml (60.0% vs 34.3%) [17].

- Medical imaging: Ultrasound is very helpful in determining the extent of central and lateral lymph nodes involvement. Imaging to evaluate systemic metastasis in patients with regional lymph nodes involvement during the first surgery and recurrence, in the presence of serum calcitonin greater than 500 pg/ml and 150 pg/ml, respectively, is of great importance and very significant in deciding the extent of lymphatic dissection [3].

## 3. Lymphatic drainage of thyroid gland

Lymph node metastasis in thyroid cancer occurs in the following order:

- Central (zone 6)
- Lower jugular chain (zone 4)
- Superior mediastinum (zone 7).

At the central level, prelaryngeal (delphian node), pretracheal, right and left paratracheal lymph nodes are involved, respectively.

In cases of tumor in the upper thyroid lobe, metastasis can occur to the lateral zones without central zone involvement [18].

Of course, there is also disagreement about the route of lymph node involvement. In an article published by Fialkowski EA and colleagues the route of lymph node involvement is described as follows: zones 6 and 7 are the most common lymphatic zones to be attacked and next, zones 2 to 5 are involved on the same side of the tumor. Finally, the lymph nodes of zones 2 to 5 on the opposite side become involved [19].

## 4. Surgical approach

### 4.1. MTC limited to the neck

The extent of neck dissection in these cases depends on the ultrasound findings, the results of biochemical tests (calcitonin and CEA levels), the surgeon's judgment and the findings during the operation [8, 20] (Table 1).

- No ultrasound evidence of cervical lymph node involvement (prophylactic neck dissection):** MTC often spreads to the central lymph nodes of the neck. In one study of 101 patients with MTC, approximately 50% of patients had central lymph node involvement [21]. In these cases, the preferred surgical treatment is bilateral prophylactic central neck dissection. It should be noted that the rate of occult metastasis to the lymph nodes is high and lymph nodes involvement is an accurate predictor of outcome. Surgeons must dissect lymph nodes in the area from the hyoid bone to the innominate veins and medial to the jugular veins [3].

**Table 1**

Characteristics of the included studies.

	Authors	Year	Type of study	
MTC limited to neck	Jin & Moley [8]	2016	Review	
	Polistena et al. [20]	2017	Retrospective	
	Scollo et al. [21]	2003	Retrospective	
	ATA [3]	2015	Guideline	
	NCCN [22]	2021	Guideline	
	ATA, AAES, AHNS, AAO-HNS [23]	2009	Review	
	Machens & Dralle [25]	2010	Retrospective	
	Machens et al. [32]	2008	Retrospective	
	ESMO [33]	2019	Guideline	
	UpToDate [12]	2021	Guideline	
Locally advanced or metastatic MTC	Asimakopoulos et al. [39]	2017	Review	
	ATA [3]	2015	Guideline	
	UpToDate [12]	2021	Guideline	
	Persistent disease (Incomplete lymph node dissection)	Machens & Dralle [40]	2013	Retrospective
		ATA [3]	2015	Guideline
		UpToDate [12]	2021	Guideline
		NCCN [22]	2021	Guideline
	ESMO [33]	2019	Guideline	
	Recurrent regional MTC	ATA [3]	2015	Guideline
		NCCN [22]	2021	Guideline

MTC: medullary thyroid carcinoma, ATA: American Thyroid Association, NCCN: National Comprehensive Cancer Network, AAES: American Association of Endocrine Surgeons, AHNS: American Head and Neck Society, AAO-HNS: American Academy of Otolaryngology—Head and Neck Surgery, ESMO: European Society for Medical Oncology.

American Thyroid Association (ATA) recommendation in MTC, without lymph node involvement (according to ultrasonographic study) and without systemic metastasis, is prophylactic central (zone 6) lymph node dissection (grade B Recommendation\*) [3].

Based on current recommendation of National Comprehensive Cancer Network (NCCN) [22]: In addition to total thyroidectomy, bilateral central neck dissection (level 6) are indicated in all patients with MTC whose tumor is 1 cm or larger or who have bilateral disease. Neck dissection can be considered for those whose tumor is less than 1 cm and for unilateral thyroid disease [23,24].

If the calcitonin level is lower than 20 pg/ml, the risk of central lymph node metastasis is very low. Therefore, in an article published in 2010 in Journal of Clinical Endocrinology Metabolism, it is mentioned that in the case of small MTC and calcitonin level lower than 20 pg/ml, central prophylactic lymph node dissection can be omitted [25]. However, the need for reoperation was less likely if total thyroidectomy and central lymph node dissection was performed previously [26–28].

There is a lot of controversy about prophylactic lateral lymph nodes dissection [14,29–31]. According to a 2008 report by Machens A et al.; with increasing the number of lymph nodes involved in the central zone, the likelihood of lateral involvement increases. He explained the relationship between central lymph nodes involvement and ipsilateral and contralateral lymph nodes involvement as follows: if the central lymph nodes are not involved, 1 to 3 lymph nodes are involved, and 4, or more lymph nodes are involved, the chances of ipsilateral lymph node involvement are 10%, 77%, and 98%, respectively. In addition, these authors state, if there is no involvement of the central lymph nodes, involvement of 1–9 lymph nodes and involvement of more than 9, the probability of involvement of the contralateral lymph nodes are 4.9%, 38%, and 77%, respectively [32]. Biochemical results can help determine the extent of lymphatic dissection. According to a 2010 study by Machens and Dralle, lymph nodes metastases were present in the ipsilateral (central and lateral) neck, contralateral central neck, contralateral lateral neck, and upper mediastinum if basal calcitonin thresholds were higher than 20, 50, 200, and 500 pg/ml, respectively [25]. According to ATA, they have not been able to reach a consensus on prophylactic lateral neck dissection in MTC (Grade I Recommendation\*\*\*) [3]. ATA recommendation is prophylactic lateral neck dissection (zone

2–5) “may be considered based on serum calcitonin levels”. In other words, some members oppose prophylactic lateral dissection, while others agree with prophylactic lateral dissection based on calcitonin levels. Thus, if the level of calcitonin is higher than 20 pg/ml, a prophylactic ipsilateral central and ipsilateral lateral dissection is recommended and if it is higher than 200 pg/ml, a prophylactic dissection in uninvolved contralateral lateral neck compartments is recommended [3].

The latest version of NCCN guideline considers prophylactic ipsilateral dissection if there is a high volume or gross disease in the adjacent central neck [22].

The authors of European Society for Medical Oncology (ESMO) have minor disagreement with ATA, as they recommend bilateral central neck dissection if calcitonin is 20–50 pg/ml, ipsilateral lateral neck dissection if calcitonin is 50–200 pg/ml, and contralateral lateral neck dissection if the calcitonin level is 200–500 pg/ml [33].

Most experienced thyroid surgeons believe that sternotomy is not useful for prophylactic neck dissection in MTC [8].

Another difference between the ESMO guideline and the American guidelines (ATA & NCCN) is the extent of the lateral dissection.

In the American guidelines, dissection of zones 2 to 5 is recommended, whereas according to the ESMO guideline dissection of zones 2A, 3, and 4 is sufficient [3,22,33].

The authors of UpToDate, in addition to considering the amount of preoperative calcitonin, advise examining the lateral zones of the neck and mediastinum during surgery to perform dissection based on these findings [12].

However, Moley JF and his colleagues believe that intraoperative surgeon’s assessment of nodal status by palpation and inspection has low sensitivity (64%) and specificity (71%), and reliance on intraoperative assessment in more than one third of cases leads to misdiagnosis of positive lymph nodes [34].

It should be noted that the above approaches have many pros and cons: Proponents believe that 50% of patients with serum calcitonin level  $\leq 1000$  pg/ml, are cured biochemically after prophylactic lateral neck dissection (calcitonin  $< 10$  pg/ml) [25]. Because biochemical cure is associated with a 98% survival rate over 10 years and there is only 3–4% chance of recurrence, proponents believe that the benefits of prophylactic lateral dissection outweigh the complications of surgery, when performed by an experienced surgeon [6,35,36]. Opponents believe that the long-term survival rate is excellent in patients who have an incomplete biochemical response but no signs of disease in imaging studies. This survival rate is between 90 and 100% over 10 years. It should be noted that if MTC is limited to the thyroid before surgery, survival rate will be maximal [35,37,38]. So perhaps biology of the disease in different people is the cause of the difference in survival rate, not aggressive prophylactic surgery [12].

#### b) Ultrasound evidence of cervical lymph node involvement (therapeutic neck dissection):

All guidelines and review articles recommend central and lateral dissection if lymphadenopathy is confirmed in preoperative examinations. The main controversy is over the need for prophylactic contralateral compartments dissection when we are facing with central and/or unilateral involvement. Many guidelines based on the high percentage of occult metastasis in the contralateral lymph nodes believe that prophylactic contralateral dissection is necessary, even in the presence of normal preoperative sonography, if basal calcitonin level is greater than 200 pg/ml [12].

Although this approach is recommended by many authors, it should be noted that in the presence of bilateral neck involvement, the chance of biochemical cure is low. For this reason, the therapeutic team must carefully balance the increased risk of complications associated with bilateral neck dissection with the probability for potential clinical cure [39].

#### 4.2. Locally advanced or metastatic MTC

In patients with locally advanced or metastatic MTC, in addition to thyroidectomy, dissection of compartments with involved lymph nodes is often recommended. It should be borne in mind that the goal in these settings is palliative surgery. For this reason, during dissection of the central and lateral zones of the neck, proceedings that cause damage to speech, swallowing, shoulder movements and parathyroid glands should be avoided. In cases of invasive gross disease, extensive surgery of involved structures of the neck can be performed exceptionally. However, it should be noted that these measures have no prognostic effect. Finally, it can be said that many of these decisions must be based on the patient’s desires and longevity [3,12].

#### 4.3. Persistent disease (Patients with an incomplete lymph node dissection)

A 2013 study was performed on 334 patients with high serum calcitonin levels who were candidates for reoperation. In this study, biochemical cure rate was only 5% after a previous clearance of more than 5 metastatic lymph nodes. Also, when serum calcitonin levels exceeded 1000 pg/ml (reference rang  $< 10$  pg/ml) before reoperation, a biochemical cure was exceptional (1 of 76 patients) [40].

ATA recommendation is “compartment oriented lymph node dissection, should be considered in patients having an inadequate lymphadenectomy at the initial thyroidectomy”, if the preoperative calcitonin level is lower than 1000 pg/ml and five or fewer metastatic lymph nodes are removed initially (Grade C Recommendation\*\*) [3].

Because of the high probability of surgical complication, in patients with asymptomatic small-volume locoregional disease (sub-centimeter lymph node metastases), the authors of “UpToDate” suggest active surveillance. In addition, observation of asymptomatic stable lymph node metastases is nearly always recommended if the basal serum calcitonin is above 1000 pg/ml or if more than five metastatic lymph nodes were removed in previous surgery as reoperation is almost never curative in these settings [12]. Also, these authors consider cautious observation or systemic therapies for asymptomatic large-volume lymph node metastases, if the basal serum calcitonin is  $> 1000$  pg/ml or if more than five metastatic lymph nodes were removed with a previous surgery. They believe resection of symptomatic or large-volume locoregional lymph node disease, is only allowed to prevent invasion into surrounding major structures or for pain control [12].

The NCCN guideline recommends palliative surgery in symptomatic or progressive cases as treatment options, although in asymptomatic cases it considers resection if possible, however it also suggests disease monitoring [22].

ESMO guideline recommends resection, if there is a single symptomatic and progressive disease [33].

#### 4.4. Patients with recurrent regional MTC

In about one third of patients treated with repeat operation for persistent or recurrent MTC, the postoperative basal or stimulated serum calcitonin levels reach the normal range; however, they are rarely undetectable [41–44].

ATA recommendation is surgical resection of recurrent loco-regional MTC in patients without distant metastases, including compartmental dissection in the central (level 6) or lateral (level 2–5) neck compartments. Limited operative procedures, such as resection of only grossly metastatic lymph nodes, should be avoided unless there has been prior extensive and classic surgery. (Grade C Recommendation\*\*) [3]. NCCN guideline also recommends surgical resection of recurrent loco-regional disease in patients without distant metastases [22].

The main limitation and our challenge in this study was different patients’ categorization in different guidelines. For solving this problem, we decided to classified patients in a way that is needed by clinician.

## 5. Conclusion

There is a lot of controversy about the type (prophylactic vs therapeutic) and extent of lymph node dissection in the central and lateral zones of the neck in MTC. guidelines and thyroid surgery centers make decisions about prophylactic neck surgery based on the amount of calcitonin and the extent of tumoral involvement in thyroid gland and central compartment. In Locally Advanced or Metastatic MTC dissection is done with maximum attention to maintaining function. In cases with an incomplete lymph node dissection, decisions for dissection can be based on calcitonin levels, the number of metastatic lymph nodes in the first surgery and symptoms and speed of disease progression. In recurrent regional MTC without distant metastasis, consensus is in favor of reoperation.

\*Grade B: “**Recommends**. The recommendation is based on fair evidence that the service or intervention can improve important health outcomes. The evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.”

\*\*Grade C: “**Recommends**. The recommendation is based on expert opinion.”

\*\*\*Grade I: “**Recommends neither for nor against**. The panel concludes that the evidence is insufficient to recommend for or against providing the service or intervention because evidence is lacking that the service or intervention improves important health outcomes, the evidence is of poor quality, or the evidence is conflicting. As a result, the balance of benefits and harms cannot be determined.”

Adapted from American Thyroid Association [3].

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## Authors contribution

Ali Shaghghi: Study design, writing the manuscript  
Abolfazl Salari & Amirmohsen Jalaeefar: writing the manuscript  
Mohammad Shirkhoda: Study design, supervisor, and editing the manuscript

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## Declaration of competing interest

The authors declare that they have no conflicts of interests related to this study

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## References

- [1] F. Torresan, C. Armellini, M. Iacobone, Management of medullary thyroid carcinoma, *Annals of Thyroid* 5 (16) (2020) 1–11.
- [2] S.A. Hundahl, I.D. Fleming, A.M. Fremgen, H.R. Menck, A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the US, 1985–1995. *Cancer, Interdisciplinary International Journal of the American Cancer Society* 83 (12) (1998) 2638–2648.
- [3] S. Wells Jr., S. Asa, H. Dralle, R. Elisei, D. Evans, R. Gagel, et al., American Thyroid Association guidelines task force on medullary thyroid carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma, *Thyroid* 25 (6) (2015) 567–610.
- [4] U. Bergholm, H. Adami, R. Bergström, M. Bäckdahl, G. Akerström, Long-term survival in sporadic and familial medullary thyroid carcinoma with special reference to clinical characteristics as prognostic factors. *The Swedish MTC Study Group, Acta chirurgica scandinavica* 156 (1) (1990) 37–46.
- [5] C.E. Barrows, J.M. Belle, A. Fleishman, C.C. Lubitz, B.C. James, Financial burden of thyroid cancer in the United States: an estimate of economic and psychological hardship among thyroid cancer survivors, *Surgery* 167 (2) (2020) 378–384.
- [6] E. Modigliani, R. Cohen, J.M. Campos, B. Conte-Devolx, B. Maes, A. Boneu, et al., Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients, *Clinical endocrinology* 48 (3) (1998) 265–273.
- [7] R.W. Tsang, J.D. Brierley, W.J. Simpson, T. Panzarella, M.K. Gospodarowicz, S. B. Sutcliffe, The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma, *Cancer: Interdisciplinary International Journal of the American Cancer Society* 82 (2) (1998) 375–388.
- [8] L.X. Jin, J.F. Moley, Surgery for lymph node metastases of medullary thyroid carcinoma: a review, *Cancer* 122 (3) (2016) 358–366.
- [9] A. Machens, S. Hauptmann, H. Dralle, Increased risk of lymph node metastasis in multifocal hereditary and sporadic medullary thyroid cancer, *World journal of surgery* 31 (10) (2007) 1960–1965.
- [10] T. Weber, Medullary thyroid carcinoma: why is specialization mandatory? *Visceral medicine* 34 (6) (2018) 419–421.
- [11] S. Edition, S. Edge, D. Byrd, *AJCC Cancer Staging Manual*, AJCC cancer staging manual, 2017.
- [12] Tuttle RM, Ross DS. *Medullary Thyroid Cancer: Surgical Treatment and Prognosis*.
- [13] S. Momin, D. Chute, B. Burkey, J. Scharpf, Prognostic variables affecting primary treatment outcome for medullary thyroid cancer, *Endocrine Practice* 23 (9) (2017) 1053–1058.
- [14] F.-J. Gan, T. Zhou, S. Wu, M.-X. Xu, S.-H. Sun, Do medullary thyroid carcinoma patients with high calcitonin require bilateral neck lymph node clearance? A case report, *World journal of clinical cases* 9 (6) (2021) 1343.
- [15] Rg Cohen, J.-M. Campos, C. Salaün, H. Massoud Heshmati, J.-L. Kraimps, C. Proye, et al., Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma, *The Journal of Clinical Endocrinology Metabolism* 85 (2) (2000) 919.
- [16] H. Park, J. Park, M.S. Choi, J. Kim, H. Kim, J.H. Shin, et al., Preoperative serum calcitonin and its correlation with extent of lymph node metastasis in medullary thyroid carcinoma, *Cancers* 12 (10) (2020) 2894.
- [17] W. Fan, C. Xiao, F. Wu, Analysis of risk factors for cervical lymph node metastases in patients with sporadic medullary thyroid carcinoma, *Journal of International Medical Research* 46 (5) (2018) 1982–1989.
- [18] J.H. Park, Y.S. Lee, B.W. Kim, H.-S. Chang, C.S. Park, Skip lateral neck node metastases in papillary thyroid carcinoma, *World journal of surgery* 36 (4) (2012) 743–747.
- [19] E.A. Fialkowski, J.F. Moley, Current approaches to medullary thyroid carcinoma, sporadic and familial, *Journal of surgical oncology* 94 (8) (2006) 737–747.
- [20] A. Polistena, A. Sanguinetti, R. Lucchini, S. Galasse, M. Monacelli, S. Avenia, et al., Timing and extension of lymphadenectomy in medullary thyroid carcinoma: a case series from a single institution, *International Journal of Surgery* 41 (2017) S70–S74.
- [21] C. Scollo, E. Baudin, J.-P. Travaglini, B. Caillou, N. Bellon, S. Lebouleux, et al., Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer, *The Journal of Clinical Endocrinology Metabolism* 88 (5) (2003) 2070–2075.
- [22] National Comprehensive Cancer Network. *Thyroid Carcinoma, 2021* [Available from: [www.nccn.org/patients](http://www.nccn.org/patients)].
- [23] S.E. Carty, D.S. Cooper, G.M. Doherty, Q.-Y. Duh, R.T. Kloos, S.J. Mandel, et al., Consensus statement on the terminology and classification of central neck dissection for thyroid cancer: the American thyroid association surgery working group with participation from the American association of endocrine surgeons, American academy of otolaryngology—head and neck surgery, and American head and neck society, *Thyroid* 19 (11) (2009) 1153–1158.

- [24] M.F. Saad, N.G. Ordonez, R.K. Rashid, J.J. Guido, C.S. Hill Jr., R.C. Hickey, et al., Medullary carcinoma of the thyroid. A study of the clinical features and prognostic factors in 161 patients, *Medicine* 63 (6) (1984) 319–342.
- [25] A. Machens, H. Dralle, Biomarker-based risk stratification for previously untreated medullary thyroid cancer, *The Journal of Clinical Endocrinology Metabolism* 95 (6) (2010) 2655–2663.
- [26] E. Kebebew, P.H. Ituarte, A.E. Siperstein, Q.Y. Duh, O.H. Clark, Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems, *Cancer: Interdisciplinary International Journal of the American Cancer Society* 88 (5) (2000) 1139–1148.
- [27] Q.-Y. Duh, J.J. Sancho, F.S. Greenspan, T.K. Hunt, M. Galante, A.A. deLorimier, et al., Medullary thyroid carcinoma: the need for early diagnosis and total thyroidectomy, *Archives of Surgery* 124 (10) (1989) 1206–1210.
- [28] J.B. Fleming, J.E. Lee, M. Bouvet, P.N. Schultz, S.I. Sherman, R.V. Sellin, et al., Surgical strategy for the treatment of medullary thyroid carcinoma, *Annals of surgery* 230 (5) (1999) 697.
- [29] X. Wu, B. Li, C. Zheng, W. Liu, T. Hong, X. He, Risk factors for lateral lymph node metastases in patients with sporadic medullary thyroid carcinoma, *Technology in Cancer Research Treatment* 19 (2020).
- [30] S.Y. Bae, S.P. Jung, J.H. Choe, J.S. Kim, J.H. Kim, Prediction of lateral neck lymph node metastasis according to preoperative calcitonin level and tumor size for medullary thyroid carcinoma, *The Kaohsiung journal of medical sciences* 35 (12) (2019) 772–777.
- [31] P.M. Spanheimer, I. Ganly, J.F. Chou, M. Capanu, A. Nigam, R.A. Ghossein, et al., Prophylactic lateral neck dissection for medullary thyroid carcinoma is not associated with improved survival, *Annals of Surgical Oncology* (2021) 1–8.
- [32] A. Machens, S. Hauptmann, H. Dralle, Prediction of lateral lymph node metastases in medullary thyroid cancer, *Journal of British Surgery* 95 (5) (2008) 586–591.
- [33] S. Filetti, C. Durante, D. Hartl, S. Leboulleux, L. Locati, K. Newbold, et al., Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, *Annals of Oncology* 30 (12) (2019) 1856–1883.
- [34] J.F. Moley, M.K. DeBenedetti, Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection, *Annals of surgery* 229 (6) (1999) 880.
- [35] S.C. Lindsey, I. Ganly, F. Palmer, R.M. Tuttle, Response to initial therapy predicts clinical outcomes in medullary thyroid cancer, *Thyroid* 25 (2) (2015) 242–249.
- [36] S. Franc, P. Niccoli-Sire, R. Cohen, S. Bardet, B. Maes, A. Murat, et al., Complete surgical lymph node resection does not prevent authentic recurrences of medullary thyroid carcinoma, *Clinical endocrinology* 55 (3) (2001) 403–409.
- [37] R.M. Tuttle, I. Ganly, Risk stratification in medullary thyroid cancer: moving beyond static anatomic staging, *Oral oncology* 49 (7) (2013) 695–701.
- [38] S.Y. Boostrom, C.S. Grant, G.B. Thompson, D.R. Farley, M.L. Richards, T.L. Hoskin, et al., Need for a revised staging consensus in medullary thyroid carcinoma, *Archives of surgery* 144 (7) (2009) 663–669.
- [39] P. Asimakopoulos, I. Nixon, A. Shaha, Differentiated and medullary thyroid cancer: surgical management of cervical lymph nodes, *Clinical Oncology* 29 (5) (2017) 283–289.
- [40] A. Machens, H. Dralle, Benefit-risk balance of reoperation for persistent medullary thyroid cancer, *Annals of surgery* 257 (4) (2013) 751–757.
- [41] E. Fialkowski, M. DeBenedetti, J. Moley, Long-term outcome of reoperations for medullary thyroid carcinoma, *World journal of surgery* 32 (5) (2008) 754–765.
- [42] E. Kebebew, S. Kikuchi, Q.-Y. Duh, O.H. Clark, Long-term results of reoperation and localizing studies in patients with persistent or recurrent medullary thyroid cancer, *Archives of Surgery* 135 (8) (2000) 895–901.
- [43] L.-E. Tisell, G. Hansson, S. Jansson, H. Salander, Reoperation in the treatment of asymptomatic metastasizing medullary thyroid carcinoma, *Surgery* 99 (1) (1986) 60–66.
- [44] L. Tisell, S. Jansson, Recent results of reoperative surgery in medullary carcinoma of the thyroid, *Wiener klinische Wochenschrift* 100 (11) (1988) 347–348.