www.journalofcancerology.com PERMANYER J Cancerol. 2018;5:65-73

JOURNAL OF CANCEROLOGY ORIGINAL ARTICLE

Extensive medullary thyroid cancer: Aggressive surgery with mediastinal dissection is worthwhile?

Martín Granados-García[1]*, José Antonio Posada-Torres[1], Antonio Gómez-Pedraza[1], Kuauhyama Luna-Ortiz[1], Erika Ruiz-García[2], Silvia Vidal-Millán[3,4], Katia Picazo-Ferrera[5] and Imelda González-Ramírez[3]

[1]Department of Head and Neck Cancer; [2]Translational Medicine Laboratory; [3]Subdirection of Investigation; [4]Molecular Diagnostic Laboratory. Instituto Nacional de Cancerología; [5]Servicio de Cirugía Oncológica, ABC Medical Center. Mexico City, Mexico

ABSTRACT

The purpose of this study is to analyze the treatment results of patients with medullary thyroid cancer, focusing on surgical complications, biochemical cures, and survival. It is a retrospective analysis of 18 patients with advanced disease treated in a tertiary, teaching referral hospital in a developing country. Ten patients underwent only a initial surgery, of them, 7 developed surgical complications, 2 of them major. Five patients required a second procedure after the first surgery elsewhere, 2 of them developed complications, one major. Three denied further treatment after diagnosis was made. After a median follow-up of 35.5 months (1-108), 7 (39%) patients are alive without disease, 4 (22%) are alive with disease, and 7 (39%) died. From fifteen patients after surgery with curative puposes, 4 reached normal calcitonin levels and are still without evidence of recurrence after a mean follow-up of 47 months (3-86 months); 11 persisted with disease, of them, five patients needed a second surgery, two of them reached normal calcitonin levels, one of them is still under remission after 36 months, and one died 60 months later. Three patients denied more treatment. Nine patients did not reach normal calcitonin levels after first surgery or reoperation, but on postoperative images there were not evidence of residual disease and 6 of them are alive after a mean follow up of 55 (12-108) months. In conclusion, a biochemical cure for the advanced disease is rare after surgery, however, long term survival is possible when judicious surgery produces no evidence of residual disease by imaging.

Key words: Thyroid cancer. Medullary thyroid cancer. Surgical morbidity. Calcitonin. Reoperation. Head and neck cancer.

Corresponding author:
*Martín Granados-García
E-mail: martingranadosmx@gmail.com

Received for publication: 12-05-2018
Accepted for publication: 17-05-2018

RESUMEN

El objetivo de este estudio es analizar los resultados del tratamiento de pacientes con cáncer medular de tiroides con enfoque en las complicaciones, curas bioquímicas y supervivencia. Es un análisis retrospectivo de 18 pacierntes con enfermedad avanzada en un hospital oncológico de enseñanza y referencia en un país en vías de desarrollo. Diez se sometieron solo a cirugía inicial, de ellos, siete desarrollaron complicaciones, dos de ellas mayores. Cinco pacientes requirieron un segundo procedimiento después de la primera cirugía en otro lugar, dos desarrollaron complicaciones, una de ellas mayor. Tres rechazaron más tratamiento después del diagnóstico. Después de una mediana de seguimiento de 35.5 meses (1-108), siete (39%) pacientes están vivos y sin enfermedad, cuatro (22%) están vivos con enfermedad y siete (39%) murieron. De 15 pacientes después de la primera cirugía con propósitos curativos, cuatro alcanzaron niveles normales de calcitonina y permanecen aún sin evidencia de recurrencia después de un seguimiento medio de 47 meses (3-86 meses). De quince, cinco pacientes necesitaron una segunda cirugía, y dos de ellos alcanzaron niveles normales de calcitonina, uno de ellos todavía está en remisión después de 36 meses y otro murió 60 meses después. Nueve pacientes no alcanzaron los niveles normales de calcitonina después de la primera cirugía o reoperación, pero en las imágenes postoperatorias no hubo evidencia de enfermedad residual y seis de ellos están vivos después de un seguimiento medio de 55 (12-108) meses. En conclusión, la cura bioquímica de la enfermedad avanzada es rara después de cirugía, sin embargo, la supervivencia a largo plazo es posible cuando la intervención quirúrgica produce ausencia de enfermedad residual en los estudios de imagen.

(J CANCEROL. 2018;5:65-73)
Corresponding author: Martín Granados-García, martingranadosmx@gmail.com

Palabras clave: Cáncer de tiroides. Cáncer medular de tiroides. Morbilidad quirúrgica. Calcitonina. Reoperación. Cáncer de cabeza y cuello.

INTRODUCTION

Thyroid cancer represents 2.5% of malignant neoplasms in Mexico[1,2]. Medullary thyroid cancer (MTC) (3-5%) is the second one after differentiated carcinomas (80-90%) and has a less favorable outcome. Sporadic disease represents 75% of the cases, whereas hereditary accounts for the remaining.

Age and stage are major prognostic factors. Stage III and IV patients have worse prognoses than those at early stages[3]. In addition, every year of age at diagnosis increases the risk of death by 5.2%. Patients with the regional disease have 2.69 times more risk of death than those with local disease, but the distant disease has a relative risk that reaches 4.47. MTC cells do not concentrate radioactive iodine and are not sensitive to hormonal manipulation; therefore, surgery is the most effective option for curative therapy, reduction in tumor burden, or effective palliation. Prognosis of MTC is related to the stage of disease, as well as the extent of initial surgery. Extensive surgery is related to better survival[4]; however, its precise extension is controversial[5], especially in patients with initial extensive disease, or with persistent/recurrent disease since tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor receptors and RET has emerged as alternative[6] and because reoperation is associated with morbidity and uncertain oncologic results. In our country, unfortunately, most of the patients present

with advanced disease, with poor prognoses, but they requiere treatment. Our aim was to assess the results of surgical treatment in patients with advanced disease, with a special focus on surgical complications, biochemical cures, and survival.

PATIENTS AND METHODS

Patients diagnosed with MTC between July 1, 2006, and December 31, 2012, were selected. Patients were analyzed for clinical features, treatment, and outcome. Survival was calculated from diagnoses to death. Major morbidity required reoperation, extended hospitalization or resulted in death. IRB dispensed approval of this retrospective analysis because no intervention was introduced and personal data cannot be tracked to specific patients.

Pre-operative evaluation

Patients with thyroid nodules underwent neck ultrasonography and fine needle aspiration biopsy of suspicious thyroid and neck nodes. Patients with palpable neck nodes underwent a computed tomography scan of the neck, thorax, and upper abdomen. Serum carcinoembryonic antigen and calcitonin measurements were taken in all patients. Vocal cord mobility evaluation was mandatory. Patients with persistently high levels of calcitonin after surgery underwent a new complete evaluation; if complete resection seemed possible, reoperation was considered.

Statistics and definitions

We analyzed the demographic data and the outcome of patients. Pathologic material was revised to corroborate the diagnosis. Descriptive statistics were used to show results. Overall survival was defined as the time interval between medullary cancer diagnosis and the last follow-up visit to the hospital or death of the patient. Survival curves were estimated using the Kaplan–Meier Method. The Log-rank test was used to compare survival curves.

RESULTS

A total of 381 cases of thyroid cancer were identified, 24 corresponded to medullary carcinomas (6.3%). Six patients with incomplete files were excluded, 18 patients remained: 12 women and 6 men (ratio 2:1), with a mean age of 40 years (15-70). Mean age of women was 44.5 years (23-70) and 32 years for men (15-50). There were two cases of MEN 2B corroborated by molecular diagnoses, and 2 with MEN 2B and 2 with MEN 2A by clinical characteristics. All patients were index cases and no detected by molecular screening. 17 of 18 had advanced disease (corresponding to T1-T4 with N1a or N1b, or M1 disease according to AJCC, 2010). All patients were treated 2 months within diagnoses or referral (Table 1).

Table 1. Patient characteristics

	N 18	(%)
Age	40.4 (15-70)	
Sex		
Male	6	(33.3)
Female	12	
Type		
Sporadic	12	(66)
Familiar	6	(33)
Reoperation pathologic staging*		
I	1	(5.5)
II	0	(0)
III	1	(5.5)
IVa	12	(66.6)
IVb	1	(5.5)
IVc	3	(16.6)

*We show "pathologic staging" even for reoperations after incomplete surgery only for informative purposes

Table 2. Surgical morbidity

Patient/group	Surgery > additional surgery	Morbidity	Status
Primary surgery only			
1	TT + CRBND + CND	None	AWOD 54 m
5	TT + MRBND + CND + MD	Transient hypocalcemia	AWOD 3 m
7	TT + CND	Dysphonia and aspiration	AWOD 86 m
10	TT + MRBND + CND + MD	Death by hemorrhage	DOD 2 m
11	TT + MRBND + CND	Chylous fistula	AWOD 48 m
13	TT + MRBND + CND + MD	Transient hypocalcemia	DOD 21 m
14	TT + MRBND +CND + MD	Permanent hypoparathyroidism	AWOD 51 m
15	TT + MRBND + CND	Dysphonia + Dysphagia	AWD 12 m
17	TT + MRBND +CND + MD	None	AWD 36 m
18	TT	None	DOD 1 m
Patients submitted to reoperation			
2 A	TT + CRBND+ CND > SBND + MD	None	AWD 108 m
3 A	TT + CRBND+ CND > SBND + MD	Chylous fistula, vocal cord paralysis, dysphagia	DOD 60 m
4 B	HT > cTT + SBND + CND	None	AWOD 36 m
8 B	TT > SBND + CND + MD	Vocal cord paralysis	AWD 87 m
16 B	TT > MRBND + CND + MD	None	AWOD 36m
Patients treated without curative intent			
6	Node biopsy	None	DOD 7 m
9	HT + Tracheotomy	None	DOD 6 m
12	TT + Total Laryngectomy + MRBND	Pharyngocutaneous fistula	DOD 3 m

HT: hemithyroidectomy; TT: total thyroidectomy; cTT: completion total thyroidectomy; CND: central neck dissection; MD: mediastinal dissection; SBND: selective bilateral neck dissection; MBRND: modified radical bilateral neck dissection; CRBND: classical radical bilateral neck dissection; AWD: alive with disease; DOD: death of disease; AWOD: alive without disease.

Treatment

A total of 10 patients were submitted to initial surgery for therapeutic purposes. All had palpable disease in thyroid, neck or both. After imaging, 5 had a thyroid-confined tumor, 4 thyroid tumor with enlarged neck nodes and 1 a thyroid tumor with bilateral enlarged neck and mediastinal nodes. Extent of surgery is shown in table 2.

Six aditional patients were previously treated elsewhere with persistent disease, then referred. We reoperated four of them. Two declined surgical treatment after total thyroidectomy and another one after hemithyroidectomy and tracheotomy.

In our institution, 1 additional patient was previously submitted to hemithyroidectomy due to a "Follicular neoplasia," but an MTC resulted after the definitive report. Thus, five additional patients were reoperated.

Among reoperated patients, two had already undergone a total thyroidectomy, bilateral neck and central neck dissections (A GROUP) and 3 patients had undergone a form of thyroidectomy (B GROUP). 8 and 9 months after initial treatment elsewhere, both patients of A GROUP underwent a mediastinal and a selective neck dissection due to high calcitonin levels, metastatic neck nodes, and suspicious mediastinal nodes without the distant disease. Three patients of B GROUP underwent bilateral neck and central neck dissections with or without a complementary thyroidectomy; two of them also underwent mediastinal dissection. Information about surgical morbidity was scant in previously treated patients (Table 2).

Finally, three patients were amenable only to palliative treatment. One patient was diagnosed by biopsy of a neck node; further study showed distant metastasis and the patient declined further treatment. Another patient underwent elsewhere a hemithyroidectomy and tracheotomy with the unresectable residual macroscopic disease in the neck; he died 6 months later due to disease progression, the last patient underwent a total thyroidectomy with an en block laringectomy and bilateral neck disection for airway obstruction and distant metastases; he died due to progression and pharingocutaneous fistula (Table 2).

All patients submitted to surgery in our institution showed metastatic nodes in dissected neck and mediastinal nodes. Six patients showed extranodal disease, extrathyroidal extension, or both. Five of them received post-operative radiotherapy.

Surgical morbidity

From 10 patients with primary surgery, 7 (70%) developed complications. Two of 3 patients with a central neck dissection without mediastinal dissection developed morbidity: 1 dysphonia, dysphagia, and aspiration that improved with rehabilitation and 1 developed a chylous fistula that required a muscle flap for closure. From 5 patients with mediastinal dissection, 4 developed complications: 2 transient hypocalcemia; 1 permanent hypoparathyroidism, and 1 died in the post-operative period due to a neck hemorrhage.

Complications

Complications were attributable to the cervical component of surgery. Morbidity was significant, 2 of 10 patients initially operated by us developed major complications: a chylous fistula, which required reoperation, and one died from a hemorrhage at the beginning of the period under review. From 5 reoperated patients, 2 (40%) developed surgical complications; one a chylous fistula that healed spontaneously; this patient had previous dysphonia and dysphagia due to recurrent laryngeal nerve paralysis; the other patient developed dysphonia due to vocal cord paralysis; both underwent a bilateral neck and mediastinal dissection, one of them with additional central neck dissection (Table 2).

Additional treatment

Five patients received post-operative radiotherapy as a result of extrathyroidal, extranodal extension, or macroscopic residual disease, 2 are alive with disease after 108 and 36 months. In addition, 1 received radiotherapy to spine after relapse; the patient is alive with elevated but stable calcitonin levels after 87 months. One case required tracheotomy 4 years after initial treatment because of bilateral vocal cord paralysis secondary to local recurrence. The patient additionally required bronchial dilatation due to compressive mediastinal nodes.

Survival

Overall, after a median follow-up of 35.5 months (1-108), 7 (39%) patients are alive without disease, 4 (22%) are alive with disease, and 7 (39%) died with disease. Survival was higher in previously treated and reoperated patients than those with only initial surgery (Log Rank Test: $p = 0.011$; Fig. 1).

Calcitonin levels

Preoperatory calcitonin was recorded in 15 patients. Mean pre-operative level was 5996 pg/ml (26-50,000). Postoperatory calcitonin was

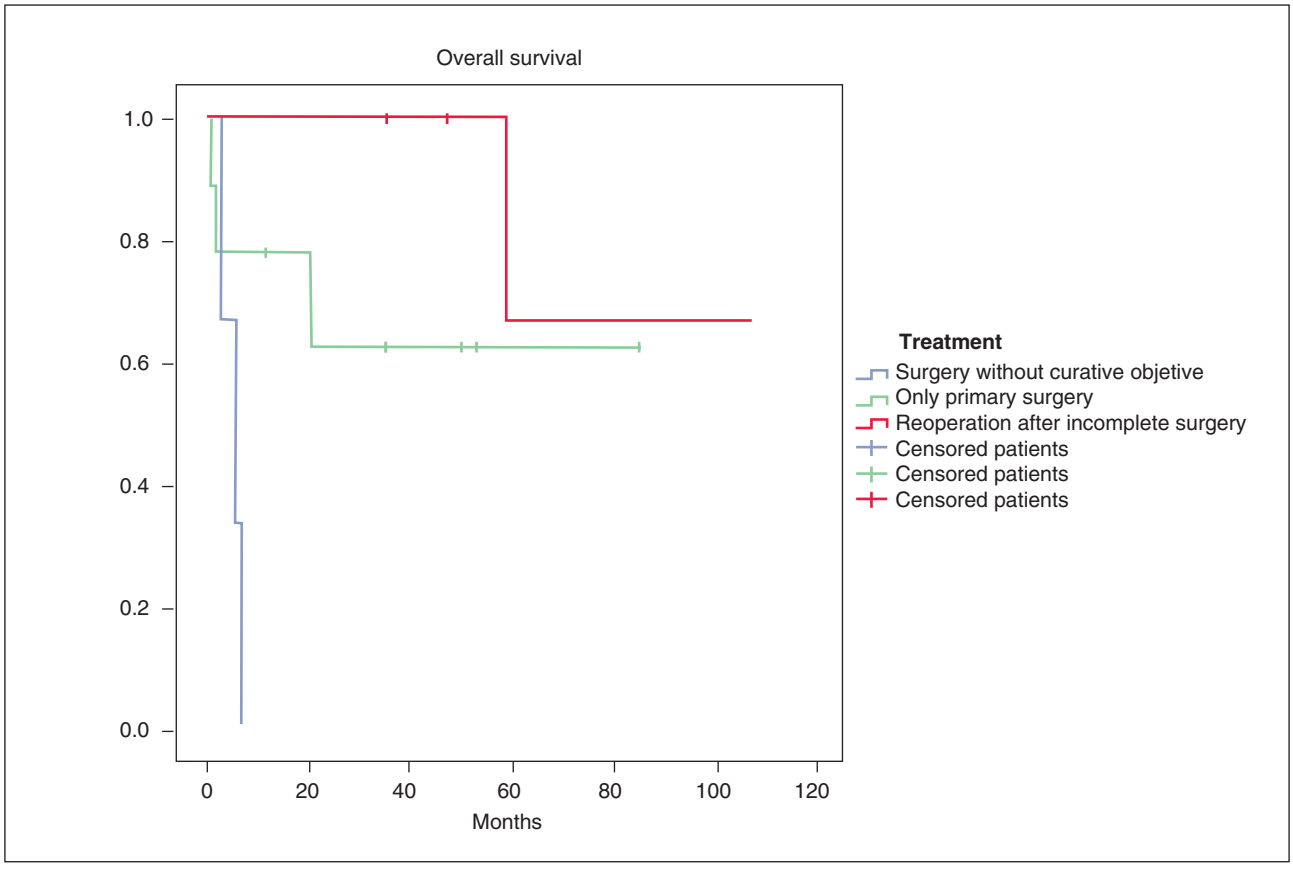

Figure 1. Overall survival of patients with medullary thyroid cancer according treatment.

measured 2 months after the surgery in 14 patients, with a mean of 685 pg/ml (0.3-4990).

Only 4 patients reached normal values (<10 pg/ml) after initial surgery and are alive without disease, with a mean follow-up time of 47 (3-86) months. All of them had lower pre-operative calcitonin levels (315, 42, 30, and 200 pg/ ml) when compared with the remaining patients. Two additional patients reached normal levels after reoperation, but 1 died after 60 months due to local and distant recurrence. However, 6 (42%) patients with elevated calcitonin after surgery without measurable disease by imaging after definitive surgery are also alive after a mean follow-up of 55 (12-108) months, even with preoperatory calcitonin levels as high as 3550, 4990, and 10364 pg/ml (mean 4077, range 182-10, 364) (Table 3). Finally, 7 of 18 (39%) patients died after a mean follow-up of 14.2 months (0-60). One of them was a surgical death, and the death of the remaining patients was due to disease progression.

DISCUSSION

Surgery is a keystone in the treatment of MTC; however, surgery extent remains controversial in patients with primary local and regionally advanced disease and even more with recurrent disease[7]. Current ATA guidelines do not recommend routine bilateral lymph node dissection in primary disease, even with the clinical evident disease in the thyroid gland and ipsilateral neck, but states that a contralateral neck dissection should be considered if basal calcitonin is >200 pg/ml[8]. Whereas, Chen advocates aggressive surgery even with

Table 3. Pre-operative and post-operative calcitonin levels, treatment and outcome

Case	Pre-operative calcitonin	Post-operative calcitonin	Initial procedure	Re operation	Status
1	315	6	TT + CRBND + CND	No	AWOD 54 m
2	460	415	TT+ CRBND + CND	SBND + MD	AWD 108 m
3	82	10	TT + CRBND + CND	SBND + MD	DOD 60 m
4	26	10	HT	CTT + SBND + CND	AWOD 36 m
5	42	2	TT+ MRBND + CND + MD	No	AWOD 3 m
6	50,000	No	Node biopsy	No	DOD 7 m
7	30	0.55	TT + CND	No	AWOD 86 m
8	3,550	4,990	TT	SBND +CND + MD	AWD 87 m
9	No	No	HT + Tracheotomy	No	DOD 6 m
10	2,775	No	Node biopsy	TT + MRBND + CND + MD	DOD 2 m
11	200	0.33	TT + CRBND + CND	No	AWOD 48 m
12	7,020	1,260	TT + Total laryngectomy + MRBND	No	DOD 3 m
13	No	1,506	TT + MRLND +CND + MD	No	DOD 21 m
14	422	196	TT+ MRBND + CND + MD	No	AWOD 51 m
15	9,485	589	TT + MRBND + CND		AWD 12 m
16	182	121	TT	MRBND + CND + MD	AWOD 36 m
17	10,364	489	Node biopsy	TT + MRBND + CND + MD	AWD 36 m
18	No	No	TT	Declined treatment	DOD 1 m

HT: hemithyroidectomy; TT: total thyroidectomy; cTT: completion total thyroidectomy; CND: central neck dissection; MRBND: modified radical bilateral neck dissection; MRLND: modified radical left dissection; CRBND: classic radical bilateral neck dissection; SBND: selective bilateral neck dissection; MD: mediastinal dissection; AWD: alive with disease; AWOD: alive without disease; DOD: death of disease.
Calcitonin in pg/ml. Calcitonin levels shown are pre definitive and post definitive treatment.

recurrent disease when cure is less probable but adds: "neck reoperations are associated with significant risks and reoperation should only be pursued if there is a significant likelihood of benefiting the patients. Such benefits include achieving locoregional control or alleviating symptoms such as tracheal or esophageal compression and pain. Therefore, if patients develop symptomatic locoregional recurrence, even in the setting of metastatic disease, then they should be offered surgical resection when feasible"[9].

Although with controversies, when primary tumor without metastatic neck nodes is present, total thyroidectomy and central neck dissection are performed[10]. When thyroid tumor is larger than 2 cm, an ipsilateral selective neck dissection (II-V) is added due to the risk of node metastasis. When nodal metastases in neck or mediastinum are demonstrated, the best local control is obtained with bilateral neck dissection, but mediastinal dissection remains controversial[11].

Two months after surgery calcitonin is measured, if undetectable, the patient is observed but with increased values reoperation is considered when previous surgery was incomplete. However, reoperation rarely produces normal values of calcitonin[12], and it is unknown its impact on survival. Clinical relapse is unusual when post-operative calcitonin values normalized, but patients who undergo surgical resection, even with distant metastasis, have better survival[13], and patients with high post-operative calcitonin values without noticeable disease by imaging may reach significant survival[14,15].

Thus, reoperation seems justifiable when calcitonin remains elevated after incomplete surgery, especially in the absence of distant disease, but this must be tailored with potential morbidity. Central

neck dissection is associated with recurrent laryngeal nerve injury and permanent hypoparathyroidism; meanwhile, superior mediastinal dissection can produce hemorrhage, chylous leak, nerve injury, and sternotomy dehiscence. Mediastinal dissection involves thymus resection along with adipose and lymphatic tissue up to the bifurcation of the trachea (metastatic low paratracheal nodes reaches 21%)[16], but it has been stated that <10% of patients with metastatic mediastinal nodes are cured.

In our experience, nine of 15 patients submitted to surgery with curative intent developed complications, 3 with major ones, and one died. Two of 10 (20%) complications in the group of initial surgery only extended the hospitalization, and one of them required reoperation, while one patient died from neck hemorrhage 3 days after surgery. From previously treated group one of 5 (20%) patients developed a chylous fistula that prolonged hospitalization. This suggests that reoperation is not significantly more morbid than the novo surgery. In addition, in our series, 9 patients underwent a mediastinal dissection; all of them with proven disease and 6 are alive after a median of 53.5 (3-108) months. It is remarkable that mediastinal dissection was not associated with significant morbidity; thus, mediastinal dissection must be performed if the patient has obvious nodal disease and a complete resection with low morbidity can be done[17]. In addition, we propose that it should be strongly considered when there is an obvious nodal disease in the neck. Elective mediastinal dissection is supported because: (1) the superior mediastinal metastasis rate is 2.6% in cN0 patients but 46.2% in cN+ patients[18], (2) in our series all patients had pathologic nodal disease at all dissected levels, including mediastinum, (3) specific morbidity of mediastinal dissection was low, and (4) of the outstanding survival of dissected patients.

It has been emphasized that patients with proven nodal disease at presentation or serum calcitonin levels are higher than 1000 pg/ml before reoperation are rarely cured[11,19,20], but survival can be long with complete macroscopic resection. After a median follow-up of 35.5 months, 7 (39%) patients are alive without disease, 4 (22%) are alive with disease, and 7 (39%) died from the disease, including 3 with metastatic disease at diagnosis.

In our experience, only 6 of 15 patients reached biochemical cure, 4 of 10 after initial surgery, and 2 of 5 after reoperation, but the mean survival after reoperation is 61 months (12-108), even better than the survival of patients with biochemical cure after initial surgery: 47 (3-86 months).

In our experience, all biochemical cures had initial low calcitonin levels (<400 pg/ml), but some with higher levels achieved prolonged survival after surgery; therefore, high isolated calcitonin levels must not preclude operation. Among patients with the clinical and voluminous disease, only 33% reached the biochemical cure, but we think surgery must be considered if it can be performed with low morbidity and can benefit the patient postponing progression or alleviating symptoms such as tracheal or esophageal compression.

Recently, two TKIs, vandetanib and cabozantinib, were approved for use in patients with advanced, metastatic, or progressive MTC, but its efficacy is questioned because of toxicity and costs. Both drugs do not prolong survival or improve symptoms, despite a favorable effect on tumor imaging and certain laboratory parameters[21].

Preoperatory diagnosis of MTC is mandatory. Reoperations resulted in incomplete surgeries because of missed pre-operative diagnoses. It is mandatory the pre-operative determination of calcitonin in any patient with a suspicious thyroid nodule, since calcitonin is a sensitive and specific test[22], even more sensitive than standard cytology, and represents a cost-effective strategy[23] that promotes complete surgeries and better survival[24].

Our study has obvious limitations. It is retrospective with a limited number of patients and a relative

short follow-up; however, surgical morbidity is assessed shortly after surgery, and biochemical cure is a valid subrogate of the final outcome. Finally, the mean follow-up is 36 months, but deaths occurred a long time before our overall mean follow-up. We think our results and conclusions can be useful in countries or similar institutions where patients are diagnosed with advanced diseases.

CONCLUSION

The biochemical cure is infrequent in patients with the obvious nodal disease. However, long survival is feasible after extensive surgery, if surgery results in non-measurable disease by imaging studies. Reoperation must be strongly considered, including mediastinal dissection, especially when surgery can be performed with low morbidity.

CONFLICTS OF INTEREST STATEMENT

Nothing to declare.

REFERENCES

1. Ferly J, Soerjomataram I, Ervik M, et al. Cancer Incidence and Mortality Worldwide: IARC Cancer Base Lyon. France: International Agency for Research on Cancer; 2012.
2. Bray F, Ren JS, Masuyer E, et al. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2008;132:1133-45.
3. Pelizzo MR, Boschin IM, Bernante P, et al. Natural history, diagnosis, treatment and outcome of medullary thyroid cancer: 37 years experience on 157 patients. Eur J Surg Oncol. 2007;33:493-7.
4. Roman S, Lin R, Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. Cancer. 2006;107:2134-42.
5. Siironen P, Hagström J, Mäenpää HO, et al. Lymph node metastases and elevated postoperative calcitonin: predictors of poor survival in medullary thyroid carcinoma. Acta Oncol. 2016;55:357-64.
6. Hadoux J, Pacini F, Tuttle RM, Schlumberger M. Management of advanced medullary thyroid cancer. Lancet Diabetes Endocrinol. 2016;4:64-71.
7. Maze H, Sippel RS. Surgical management of medullary thyroid cancer. Minerva Endocrinol. 2012;37:329-34.
8. American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the american thyroid association. Thyroid. 2009;19:565-612.
9. Chen H, Roberts JR, Ball DW, et al. Effective longterm palliation of symptomatic, incurable metastatic medullary thyroid cancer by operative resection. Ann Surg. 1998;227:887-95.
10. Lupone G, Antonino A, Rosato A, et al. Surgical strategy for the treatment of sporadic medullary thyroid carcinoma: our experience. G Chir. 2012; 33:395-9.
11. de Groot JW, Links TP, Sluiter WJ, et al. Locoregional control in patients with palpable medullary thyroid cancer: results of standardized compartment-oriented surgery. Head Neck. 2007;29:857-63.
12. Wierzbicka M, Gurgu E, Okupniak EW, et al. The feasibility and efficacy of secondary neck dissections in thyroid cancer metastases. Eur Arch Otorhinolaryngol. 2014;271:795-9.
13. Esfandiari NH, Hughes DT, Yin H, et al. The effect of extent of surgery and number of lymph node metastases on overall survival in patients with medullary thyroid cancer. J Clin Endocrinol Metab. 2014;99:448-54.
14. van Heerden JA, Grant CS, Gharib H, et al. Longterm course of patients with persistent hypercalcitoninemia after apparent curative primary surgery for medullary thyroid carcinoma. Ann Surg. 1990;212:395-400.
15. Pilaete K, Delaere P, Decallonne B, et al. Medullary thyroid cancer: prognostic factors for survival and recurrence, recommendations for the extent of lymph node dissection and for surgical therapy in recurrent disease. B-ENT. 2012;8:113-21.
16. Liu J, Xu ZG, Wang XL, et al. Surgical treatment of thyroid carcinoma with the upper mediastinal metastasis. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2007;42:277-80.
17. Machens A, Gimm O, Ukkat J, et al. Repeat mediastinal lymph-node dissection for palliation in advanced medullary thyroid carcinoma. Langenbecks Arch Surg. 1999;384:271-6.
18. Yan D, Zhang B, Li Z, et al. Cervical lymph node metastasis in medullary thyroid carcinoma. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2015;50:290-4.
19. Larin OS, Cheren'ko SM, Nechai OP, et al. Efficacy of surgical treatment of medullary thyroid carcinoma in patients with regional and distant metastases. Klin Khir. 2012;7:5-8.
20. Machens A, Dralle H. Benefit-risk balance of reoperation for persistent medullary thyroid cancer. Ann Surg. 2013;257:751-7.
21. Cabozantinib (COMETRIQ0). In medullary thyroid cancer: more harmful than beneficial, as is vandetanib. Prescrire Int. 2016;25:11-3.
22. Hasselgren M, Hegedus L, Godballe C, et al. Benefit of measuring basal serum calcitonin to detect medullary thyroid carcinoma in a Danish population with a high prevalence of thyroid nodules. Head Neck. 2010;32: 612-8.
23. Cheung K, Roman SA, Wang TS, et al. Calcitonin measurement in the evaluation of thyroid nodules in the United States: a cost-effectiveness and decision analysis. J Clin Endocrinol Metab. 2008;93:2173-80.
24. Elisei R. Routine serum calcitonin measurement in the evaluation of thyroid nodules. Best Pract Res Clin Endocrinol Metab. 2008;22:941-53.