

Approach to lymph node metastases in sporadic medullary thyroid carcinoma

An istituzionale experience.



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Approach to lymph node metastases in sporadic medullary thyroid carcinoma. An istituzionale experience.

AIM: Analyse the impact of aggressive surgical treatment with accurate lymphadenectomy in medullary thyroid carcinoma.
MATERIALS AND METHODS: We retrospectively analysed 152 patients affected by medullary thyroid carcinoma, divided in two groups, considering outcome and surgical complications.

RESULTS: Primary surgical treatment with thyroidectomy plus central and lateral neck dissection, offers significant reduction in post-operative calcitonin levels, reduced recurrences and limited complications.

DISCUSSION: Accurate lymphadenectomy, according to the international guidelines and the main results of clinical studies, is the only treatment combined to total thyroidectomy which offers improved outcome in medullary thyroid carcinoma since inefficacy of chemotherapy and radiotherapy.

CONCLUSIONS: Surgery is the unique and fundamental therapy for patients affected by medullary thyroid carcinoma. Extended neck dissection combined to precocious diagnosis and strict follow-up might be considered the standard of treatment of medullary thyroid carcinoma.

KEY WORDS: Complications, Lymphadenectomy, Medullary carcinoma, Prognosis

Introduction

Medullary thyroid carcinoma (MTC) arises from the calcitonin (CT)-producing parafollicular C cells and accounts for 5-8% of all thyroid cancers, showing significantly higher mortality rate compared to differenti-

ated thyroid cancer (DTC). MTC is mainly sporadic, but in 20-30% of cases an hereditary autosomal dominant transmission is present¹. Furthermore some authors reported mixed forms of MTC and DTC²⁻³.

The hereditary form defined also in the "multiple endocrine neoplasia type 2" (MEN 2) is characterised by MTC in combination with pheochromocytoma and hyperparathyroidism (MEN 2A), or when associated either to multiple mucosal neuroinomas and marfanoid habitus is defined (MEN 2B). A familial MTC which is not associated to other neoplasms, is also described. Treatment of DTC is based on multidisciplinary approach in which surgery has a primary role but it is also significantly supported by radioiodine treatment (RAI), particularly in spread lymph node metastases (LNM) after lymphadenectomy⁴⁻⁵.

Differently surgery is the unique and fundamental therapy for patients affected by MTC.

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In sporadic MTC, LNM are very frequent being detected up to 75% of cases and even in microcarcinomas smaller than 1 cm, they are observed in about 30% of patients, presenting central and lateral compartment equally affected⁶⁻⁸.

This invasive behaviour justifies aggressive surgical approach to MTC. Age, size of primary tumor, CT levels, positive nodes in the central compartment must be considered as prognostic factors related to LNM⁹⁻¹⁰. Extensive lymphadenectomy in adults is furthermore recommended because LNM are associated to worse prognosis but the related surgical morbidity is significant. Aim of this study is the analysis of the personal experience in the treatment of medullary carcinoma focusing on the surgical issue of cervical lymphadenectomy.

Materials and Methods

We retrospectively analyzed 152 MTC in a population of 1.765 patients underwent surgery for thyroid cancers over a period of 25 years, since 1986 to 2011, in the Unit of Endocrine Surgery, S. Maria University Hospital, Terni, University of Perugia, Italy, by the same surgical team, with standard surgical technique.

Data available in the observational period were collected from our database and analysed. Preoperative work-out included blood text with CT dosage, ECG, chest x-ray and neck ultrasound with preoperative fine needle aspiration cytology (FNAC), neck ultrasound and when indicated neck computed tomography.

Patients were divided into two groups. Group A, included 127 patients underwent primary surgery in our Department. Other 25 patients, who had been previously treated elsewhere by total thyroidectomy (TT) alone in case of unknown, occult MTC or plus limited lymphadenectomy, were, for this reason, referred for completion of lymphadenectomy to our institution and were included in group B. In group B there was no evidence of recurrent nerve palsy or hypoparathyroidism when enrolled in the study, but there was still high serum CT levels.

We performed TT with central compartment dissection (CND) and ipsilateral modified radical neck dissection (MRND) in group A. Group B underwent CND or re-excision of the central neck compartment and MRND if it had not been previously performed or if it resulted incomplete.

We considered the different complications observed in relation to the procedures performed in the two groups. As standard of treatment when approaching the central compartment, although parathyroids are identified and preserved in the standard technique, if vascular damage or accidental excision of the glands was observed, their direct autoimplantation in the sternocleidomastoideus muscle was carried out. In all patients plasmatic calcium level was tested twice in post-operative day 1 and

once in post-operative day 2, while in hypocalcemic patients daily, until normalization. Hypoparathyroidism was defined as a concentration of parathormone (PTH) under 10 ng/L (normal range 10-65 ng/L) strictly correlated to hypocalcemia defined as an ionized calcium level (iCa) under 1.0 mmol/L (normal range 1.12-1.32 mmol/L). Treatment included promptly intravenous calcium gluconate for severe hypocalcemia and oral calcium plus calcitriol as previously described¹¹.

Indirect laryngoscopy was operated preoperatively and postoperatively in all patients, eventually supported by flexible device, for evaluation of cordal motility, to assess laryngeal nerve function, although inferior laryngeal nerves are identified and preserved in the standard procedure of TT and when performing CND. We considered transient palsy if recovered up to 12 months after surgery, permanent if unmodified 12 months after surgery.

In all patients Jackson Pratt drainages were used, one in the central compartment and one along the carotid artery. The medial one is usually removed in first post-operative day, the lateral one according to the volume of drainage collected. On the left side caution with precocious removal was always considered to identify late chylous fistula from an unrecognised lesion of the thoracic duct.

When a chyle fistula is suspected postoperatively after macroscopic changes of drained fluids, diagnosis was confirmed by laboratory assessment with triglycerides dosage over 100 mg/dL.

Nervous lesions were considered with their specific clinical signs and when applicable by electromyography or for the phrenic nerve by chest x-ray. They were considered permanent if persistent 12 months after surgery. In the 98% of cases, patients were discharged in forth post-operative day. Patients were regularly followed up for a mean of 36 months in the outpatient clinic for CT levels monitoring and to evaluate eventual complications observed.

Statistical analysis

We used Student's t test for analysis of variance between groups when indicated. A *p*-value <0.05 was considered statistically significant. All of the data were analyzed using XLSTAT (Addinsoft, New York, NY, USA).

Results

The cases included 78 female (61.4%) and 49 males (38.6%), with a mean age of 42.3±11.3 years (range 20-72 years) in group A, 16 female (64%) and 9 male (36%), with a mean age of 46.3±9.4 years (range 27-68 years) in group B. In group A all 127 patients underwent TT plus CND plus ipsilateral MRND. In group

B we performed 10 CND plus MRND, 12 re-excision of the central compartment plus MRND and 3 re-excision of the central compartment plus re-excision of the lateral compartment (Table I).

An average volume of 60 ml was collected in the drainages which were removed, according to the different procedure necessity, between the 1st and the 4th post-operative day. In the 98% of cases, patients were discharged in 4th post-operative day.

Nodal metastases were detected in the central compartment in 73 (59.1%) and 14 (56%) patients respectively of group A and B and association with positive lymph node metastases in the lateral compartment was present

respectively in 61 (48%) and 13 (52%) patients, in both cases with no significant differences ($p > 0.05$). Patients not presenting lymph node metastases were respectively 52 (40.9%) and 11 (44%) ($p > 0.05$) (Table II).

Preoperative median plasma CT was 600 pg/ml (range 86-2054 pg/ml) in group A and 470 pg/ml in group B (range 148-2130 pg/ml). After a mean follow up period of 12 months, CT serum dosage showed that 95 patients (74.8%) out of 127 from group A and 7 patients (28%) out of 25 from group B, presented normal basal and stimulated CT levels ($p < 0.05$). The remnant 32 patients from group A and 18 patients from group B had still high CT plasma levels even though they showed an overall decrease of more than 50% when compared to the pre-operative levels. During the follow-up, local recurrence and distant metastases were documented in 22 patients from group A and 13 patients from group B ($p < 0.05$).

Systemic chemotherapy and local regional radiotherapy were tempted in 7 patients from group A and in 5 from group B but resulted ineffective as demonstrated by the rapidly increasing plasma CT levels and the clinical evidence of recurrent disease.

The following post-operative complications were registered in the examined groups (Table III).

TABLE I - Surgical procedures performed in the two groups.

Procedure	Group A	Group B
TT+CND+MRND	127	/
CND+MRND	/	10
re-excision CND + MRND	/	12
re-excision CND + re-excision MRND	/	3
Total	127	25

TABLE II - Lymph node metastases distribution.

	Group A	Group B	<i>p</i>
Negative node metastases (central and lateral)	52 (40.9%)	11 (44%)	>0.05
Positive central lymph nodes (n)	73 (59.1%)	14 (56%)	>0.05
Positive lateral lymph nodes (n)	61 (48%)	13 (52%)	>0.05
Positive central and lateral lymph nodes (n)	61 (48%)	13 (52%)	>0.05
Total patients (n)	127	25	

TABLE III - Incidence of post-operative complications. n.c. corresponds to not comparable.

Complication	Incidence (n)	Group	<i>p</i>	Treatment
Transient hypoparathyroidism	19	15 group A (11.8%) 4 group B (16%)	<0.05	3 parathyroid autoimplatation, substitutive therapy
Permanent hypoparathyroidism	1	1 group B	n.c.	substitutive therapy
Transient recurrent laryngeal nerve unilateral palsy	3	1 group A (0.7%) 2 group B (8%)	<0.05	corticosteroids therapy, rehabilitation
Intraoperative haemorrhage	3 (jugular vein)	2 group A 1 group B	>0.05	3 vein suture
Transient accessory nerve lesion	1	1 group B	n.c.	corticosteroids therapy, rehabilitation
Chylous fistula	1	1 group B	n.c.	conservative treatment

We observed 3 cases of unilateral temporary laryngeal recurrent nerve palsy respectively 1 in group A (0.7%) and 2 in group B (8%) ($p < 0.05$), 19 cases of temporary hypoparathyroidism (12.5%) respectively 15 in group A (11.8%) and 4 in group B (16%) ($p < 0.05$), 1 case of permanent hypoparathyroidism in group B (4%). All cases of hypoparathyroidism in group B corresponded to re-excision of the central compartment. Intra-operative haemorrhage was observed in 3 cases, 2 in group A and 1 in group B ($p > 0.05$), in all bleeding originated from the jugular vein which was directly sutured. A transient accessory nerve lesion was observed in 1 patient of group B. A chylous fistula was observed in 1 patient of group B and it was conservatively treated.

Discussion

High CT serum levels represent a strong marker of residual tumour disease and a postoperative normalization predicts a survival rate of 97.7% at 10 years¹².

The microscopic residual disease, local-regional lymph node infiltration or metastases to distant organs can be suspected in presence of elevated serum levels of CT even in the absence of clinical or radiographic evidence of disease¹³.

After inadequate surgery or late diagnosis, MTC may be fatal or remain stable for decades. In the latter case the persistence of high serum CT levels is frequently associated with high rates of local and distant recurrence with increased mortality¹²⁻¹³.

Surgery is the only curative treatment for MTC and it should remove all neoplastic foci present in the neck with an acceptable morbidity¹⁴⁻¹⁶.

In case of occult MTC, when diagnosis comes after total thyroidectomy, complete surgical treatment including lymphadenectomy, at least in the central compartment at first operation, is omitted. If CND and MRND are not correctly carried out, it can result in residual tumor with rapidly progressing disease. After surgery, persisting elevated CT levels are found in more than half of MTC patients who present high recurrence rates in neck lymph nodes^{9,17}.

Meticulous lymph node dissection has been reported to result in a higher biochemical cure rate¹⁷.

Some authors suggest the use of sentinel node even in the surgical treatment of MTC which is proposed as a new method to guide the indication and the extension of cervical lymphadenectomy¹⁸.

Several studies have suggested that recurrence and survival rates depend upon the adequacy of initial surgery¹⁹.

We experienced a significant increase in the rate of post-operative CT serum level normalization in patients underwent CND plus MRND associated to thyroidectomy at primary surgery.

Some authors reported that further surgery eventually permits CT normalization in only 8-35% of cases^{18,20-23}.

Similar results were evident in our series, having only 28% of patients, underwent redo surgery, with post-operative normalization of CT serum level.

According to the guidelines of the American Thyroid Association patients with suspected lymph node metastases limited to the central compartment and normal ultrasound examination of the lateral neck compartments should only be submitted to level VI compartment dissection. Nevertheless some investigators favour prophylactic lateral neck dissection in this group of patients. Patients with positive pre-operative imaging in the central and lateral neck compartments should be submitted to central (level VI) and lateral neck dissection (levels IIA, III, IV and V)²⁴.

In our institution TT plus CND plus MRND is the protocol in use for the treatment of MC, based on the evidence of an high rate of positive lymph nodes detected in the central compartment (in the present series up to 59%) which is associated with a very high rate of simultaneous involvement of both central and lateral compartment (in the present series up to 48% of cases).

According to this aggressive management we could offer to our patients a reduced rate of recurrence, which was significant in those patients receiving primary surgery with complete lymphadenectomy.

The extension of local-regional lymphadenectomy may improve biochemical cure and survival, although in some cases a more extensive initial surgical resection increases the rate of complications such as hypoparathyroidism, recurrent laryngeal nerve injury and rarely vagus and accessory nerve damage and thoracic duct injury²⁴⁻²⁵.

Nevertheless in the present series we registered acceptable rate of post-operative complications and we either observed that the rate of complications was significantly higher in terms of transient recurrent laryngeal nerve unilateral palsy and transient hypoparathyroidism for those patients not completely treated at first operation, thus attesting the importance of precocious and correct diagnosis and that a more radical primary approach is always recommended. Elevated CT levels after primary surgical therapy are most likely due to residual pathological tissue.

Surgery is also the main treatment for local and regional recurrences whenever feasible. The extent of surgery will depend on the type of surgical procedures undertaken previously and on the nature of the relapse: if initial surgery was complete, recurrent disease must be resected; if initial surgery was incomplete, the primary surgery protocol must be completed as in our series.

This is furthermore supported by the complete inefficacy of chemotherapy and radiotherapy in MTC as we observed in all the treated patients.

In fact systemic chemotherapy with dacarbazine, 5-fluorouracil and doxorubicin (alone or in combination) has shown very limited efficacy, achieving only partial responses of short duration. Nowadays, the use of stan-

dard chemotherapeutic agents should not be considered as first-line therapy for patients with persistent or recurrent MTC given the low response rate²⁴.

This balance between oncologic benefit and limited comorbidity is only related to the surgical expertise therefore general surgeons without specific experience in endocrine surgery should be very careful in treating a rare and complex pathologic entity such as MTC.

Conclusions

Limited extent of surgery and LNM predict worse overall survival in MTC patients. Adequate lymph node assessment can provide valuable prognostic information, reduce recurrence rate and need for further surgery which is always associated to increased morbidity otherwise limited in experienced hands.

Our findings suggest that early identification of MTC and margin-free TT with appropriate lymph node clearance must be always considered in sporadic MTC patients.

Riassunto

SCOPO: analizzare l'impatto del trattamento chirurgico aggressivo con accurata linfadenectomia nel carcinoma midollare della tiroide.

MATERIALI E METODI: sono stati confrontati 152 pazienti affetti da carcinoma midollare della tiroide divisi in due gruppi, considerandone gli esiti e le complicanze chirurgiche.

RISULTATI: il trattamento chirurgico con tiroidectomia associata a linfadenectomia centrale e laterale determina una significativa riduzione della calcitonina post-operatoria e delle recidive con limitate complicanze.

DISCUSSIONE: la linfadenectomia estesa in accordo con le linee guida internazionali e i risultati dei principali studi clinici, è l'unico trattamento combinato alla tiroidectomia totale, che offre un miglioramento degli esiti nel carcinoma midollare della tiroide in considerazione dell'inefficacia della chemioterapia e della radioterapia.

CONCLUSIONI: la chirurgia è l'unica e fondamentale terapia per i pazienti affetti da carcinoma midollare della tiroide. La linfadenectomia cervicale estesa combinata alla diagnosi precoce e al follow-up, può essere considerato il trattamento standard del carcinoma midollare della tiroide.

References

1. Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH: *Medullary thyroid carcinoma: Clinical characteristics, treatment, prognostic factors, and a comparison of staging systems*. Cancer, 2000; 88(5):1139-48.
2. Giove E, Renzulli G, Lorusso C, Merlicco D, Iacobone D: *Mixed medullary and follicular carcinoma of the thyroid: Report of one case*. Ann Ital Chir, 2004; 75(2):251-6; discussion 257.
3. Costanzo M, Marziani A, Papa V, Arcerito MC, Cannizzaro MA: *Simultaneous medullary carcinoma and differentiated thyroid cancer. Case report*. Ann Ital Chir, 2010; 81(5):357-60.
4. Monacelli M, Lucchini R, Polistena A, Triola R, Conti C, Avenia S, Di Patrizi MS, Barillaro I, Boccolini A, Sanguinetti A, Avenia N: *Total thyroidectomy and central lymph node dissection. Experience of a referral centre for endocrine surgery*. G Chir, 2014; 35(5-6):117-21.
5. Conzo G, Avenia N, Bellastella G, Candela G, de Bellis A, Esposito K, Pasquali D, Polistena A, Santini L, Sinisi AA: *The role of surgery in the current management of differentiated thyroid cancer*. Endocrine, 2014; 47:380-88.
6. Scollo C, Baudin E, Travagli JP, Cailou B, Bellon N, Leboulleux S, Schlumberger M: *Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer*. J Clin Endocrinol Metab, 2003; 88(5):2070-75.
7. Moley JF, DeBenedetti MK: *Patterns of nodal metastases in palpable medullary thyroid carcinoma: Recommendations for extent of node dissection*. Ann Surg, 1999; 229(6):880-87.
8. Beressi N, Campos JM, Beressi JP, Franc B, Niccoli-Sire P, Conte-Devolx B, Murat A, Caron P, Baldet L, Kraimps JL, Cohen R, Bigorgne JC, Chabre O, Lecomte P, Modigliani E: *Sporadic medullary microcarcinoma of the thyroid: A retrospective analysis of eighty cases*. Thyroid, 1998; 8(11):1039-44.
9. Fleming JB, Lee JE, Bouvet M, Schultz PN, Sherman SI, Sellin RV, Friend KE, Burgess MA, Cote GJ, Gagel RF, Evans DB: *Surgical strategy for the treatment of medullary thyroid carcinoma*. Ann Surg, 1999; 230(5):697-707.
10. Yen TW, Shapiro SE, Gagel RF, Sherman SI, Lee JE, Evans DB: *Medullary thyroid carcinoma: Results of a standardized surgical approach in a contemporary series of 80 consecutive patients*. Surgery, 2003; 134(6):890-99.
11. Puzziello A, Rosato L, Innaro N, Orlando G, Avenia N, Perigli G, Calò PG, De Palma M: *Hypocalcemia following thyroid surgery: incidence and risk factors. A longitudinal multicenter study comprising 2,631 patients*. Endocrine, 2014; 47:537-42.
12. Modigliani E, Cohen R, Campos JM, Conte-Devolx B, Maes B, Boneu A, Schlumberger M, Bigorgne JC, Dumontier P, Leclerc L, Corcuff B, Guilhem I: *Prognostic factors for biochemical cure in medullary thyroid carcinoma: results in 899 patients*. Clin Endocrinol, 1998; 48:265-73.
13. Machens A, Schneyer U, Holzhausen H-J, Dralle H: *Prospects of remission in medullary thyroid carcinoma according to basal calcitonin level*. J Clin Endocrinol Metab, 2005; 90(4): 2029-34.
14. Tuttle RM, Ball DW, Byrd D, Daniels GH, Dilawari RA, Doherty GM, Duh QY, Ehya H, Farrar WB, Haddad RI, Kandeel F, Kloos RT, Kopp P, Lamonica DM, Loree TR, Lydiatt WM, McCaffrey J, Olson JA Jr, Parks L, Ridge JA, Shah JP, Sherman SI, Sturgeon C, Waguespack SG, Wang TN, Wirth LJ: *National Comprehensive Cancer Network: Medullary carcinoma*. J Natl Compr Canc Netw. 2010;8(5):512-30.
15. Roman S, Lin R, Sosa JA: *Prognosis of medullary thyroid carcinoma*. American Cancer Society. Cancer, 2006; 107(9):2134-42.

16. Antonelli AR(1), Piazza C, Lombardi D, Casigli F: *Management of lymph node metastases in well-differentiated and medullary thyroid cancer: Retrospective study on 52 cases.* Ann Ital Chir, 2004; 75(3):305-14.
17. van Heerden JA, Grant CS, Gharib H, Hay ID, Ilstrup DM: *Long-term course of patients with persistent hypercalcitoninemia after apparent curative primary surgery for medullary thyroid carcinoma.* Ann Surg, 1990; 212:395-400.
18. Boni G, Mazzarri S, Grosso M, Manca G, Biricotti M, Ambrosini CE, Fregoli L, Puccini M, Caldarelli C, Spisni R: *Sentinel node radioguided biopsy in surgical management of the medullary thyroid carcinoma. A case report.* Ann Ital Chir, 2014; 21;85(ePub).
19. Dralle H, Damm I, Scheumann GF, Kotzerke J, Kupsch E, Geerlings H, Pichlmayr R: *Compartment-oriented microdissection of regional lymph nodes in medullary thyroid carcinoma.* Surg Today, 1994; 24:112-21.
20. Ellenhorn JD, Shah JP, Brennan MF: *Impact of therapeutic regional lymph node dissection for medullary carcinoma of the thyroid gland.* Surgery, 1993; 114:1078-81.
21. Gimm O, Dralle H: *Reoperation in metastasizing medullary thyroid carcinoma: Is a tumor stage-oriented approach justified?* Surgery 1997; 122:1124-30.
22. Moley JF, Dilley WG, DeBenedetti MK: *Improved results of cervical reoperation for medullary thyroid carcinoma.* Ann Surg 1997; 225:734-40.
23. Misso C, Calzolari F, Puxeddu E, Lucchini R, Monacelli M, D'Ajello F, Giammartino C, D'Ajello M, Ragusa M, Avenia N: *Surgical treatment of sporadic medullary thyroid carcinoma: Strategy and outcome.* G Chir, 2008; 29(11-12):475-78.
24. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JF, Pacini F, Ringel MD, Schlumberger M, Wells SA Jr: *Medullary thyroid cancer: Management guidelines of the American Thyroid Association.* Thyroid, 2009; 19(6):565-612.
25. Giove E, Merlicco D, Nacchiero E, Marzaioli R: *Conservative treatment of chyle fistula of the neck following a reintervention of cervical bilateral lymphectomy for medullary carcinoma of the thyroid. Case report.* Ann Ital Chir, 2010; 81(5):361-64.

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