



Original Research

Timing and extension of lymphadenectomy in medullary thyroid carcinoma: A case series from a single institution



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HIGHLIGHTS

- Medullary thyroid carcinoma presents with more aggressive behaviour than differentiated tumor.
- Cervical lymphadenectomy has a key role in the treatment of medullary thyroid carcinoma.
- Total thyroidectomy and central dissection is the standard treatment for medullary carcinoma.
- Lateral neck dissection is recommended for US suspicion of lateral neck metastases.
- Central and lateral neck dissection is characterized by potential severe complications.
- Complications can be reduced by correct indications and expertise in specialized centre.

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ABSTRACT

Background: Medullary thyroid carcinoma is an aggressive tumor and presents with significant morbidity and mortality and a high rate of lymph node metastases. The combination of total thyroidectomy and cervical lymphadenectomy is the essential treatment for those patients presenting with cervical lymph node metastases.

Materials and methods: A retrospective analysis of 117 patients operated for medullary thyroid carcinoma over a period of 15 years at a single institution. Surgical complications and calcitonin levels were noted.

Results: Nodal metastases were detected in the central compartment in 72.6% patients. Positive lymph nodes were detected in the lateral compartment of 34 patients who had undergone ipsilateral dissection and in all 10 patients of those with bilateral surgery. We found 3 cases of unilateral transient recurrent laryngeal nerve palsy, 15 cases of temporary hypoparathyroidism, a permanent accessory nerve lesion and a case of chylous fistula. Normalization of post-operative calcitonin was found in 82.6% and of patients who underwent total thyroidectomy and central neck dissection alone compared to 35.4% in those with ipsilateral and bilateral neck dissection.

Conclusions: Total thyroidectomy and cervical lymphadenectomy planned on the ultrasound preoperative study and on the calcitonin level represent the standard of treatment for medullary thyroid carcinoma.

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1. Introduction

Medullary thyroid carcinoma (MTC) presents with significant higher mortality compared to differentiated thyroid carcinoma (DTC) and it is characterized by difficult management due to its aggressive behaviour and to apparently ineffective application of radioiodine ablation (RAI) treatment. MTC in its sporadic presentation accounts for only 5–8% of all thyroid cancers and in about 20% of cases it shows an hereditary autosomal dominant transmission [1]. Rare mixed forms of MTC and DTC represent a favourable clinical condition even in metastatic cases where the differentiated compound is present in the lymph nodes the use of post-operative RAI is found to increase therapeutic response [2,3]. Surgery is the fundamental therapy for patients affected by MTC including those presenting with cervical lymph node metastases (LNM) [4]. In MTC, LNM are very frequent, being detected in up to 75% of cases and significantly correlated to tumor size with involved lymph nodes in 20–30% of tumors less than 1 cm large, up to 90% of those larger than 4 cm. The presence of metastases in the central compartment is strictly related to a synchronous involvement of the lateral nodes [5–8]. Level II is involved in up to 20% of patients presenting as N0 in levels III and IV and 20% of patients with unilateral tumors, even less than 1 cm, both in sporadic and hereditary forms, present contralateral cervical metastases [5]. This aggressive presentation justifies a more aggressive surgical approach to MTC, compared to what is usually adopted in DTC, where the application of RAI may complement non radical surgery. Extensive lymphadenectomy is often associated with severe complications but these are often balanced by the prognostic advantage on the overall survival after radical primary surgery [9]. High pre-operative calcitonin (CT) levels and detection of positive nodes in the central compartment are strictly related to LNM in the latero-cervical compartment and even to distant metastases with relevant impact on the overall survival [10,11].

Aim of this study is to assess the results of treatment of medullary carcinoma at our institution in correlation to current available guidelines of treatment provided by the American Thyroid Association (ATA) in 2015 [12].

2. Materials and methods

We retrospectively analyzed a case series of 117 resectable MTC consecutively operated by specialists in endocrine surgery, over a period of 15 years (2000–2015) at the Unit of Endocrine Surgery at our institute. This case series is fully compliant with the PROCESS Guidelines [13]. The study was registered in a publicly accessible database (ResearchRegistry.com, registration number: 1942). No ethical approval was required.

Data available in the observational period were collected from our records and analyzed. Preoperative work-out included blood tests, CT-dosage, ECG, chest x-ray, neck ultrasound (US) with pre-operative fine needle aspiration cytology (FNAC) and when indicated neck computed tomography and positron emission tomography. The extension of surgical resection was planned pre-operatively according to the US detection of suspected lymph nodes and to the preoperative CT levels. In all patients, standard treatment included total thyroidectomy (TT) and central neck dissection (CND) whereas unilateral or bilateral lateral modified radical neck dissection (MRND) were added when involvement of lateral compartment was suspected. Specific indication for ipsilateral MRND synchronous with TT + CND was based on US suspicion of lateral lymph node involvement and on high preoperative CT levels (above 100 pg/ml).

Indication to eventually postpone MRND was based on negative US of the lateral compartments before first surgery and

postoperatively on positive lymph nodes in the central compartment and on post-operative persistent high levels of CT after TT + CND. Indication for bilateral MRND was primarily considered for US suspicion of lymph nodes metastases in the lateral compartments and for preoperative CT levels above 200 pg/ml.

The post-operative CT value was analyzed to assess the quality and consistency in the delivery of the intervention. In order to minimize surgical complications, thyroidectomy and lymphadenectomy were carried out as previously reported with preservation of nerves, parathyroids and thoracic duct [14].

The preservation of recurrent laryngeal nerves and of accessory nerves was maintained by direct visualization aided by standard use of intra-operative nerve monitoring (IONM) as previously described [14,15]. To evaluate patient outcome, incidence of surgical complications and post-operative CT levels were considered. Follow up was carried out up to at least one year after surgery in the outpatient department.

2.1. 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).

3. Results

The present case series included 70 female (59.8%) and 47 males (40.2%), with a mean age of 43.7 ± 9.2 years. TT plus CND was the standard treatment for all 117 patients. TT and CND were carried out as unique treatment in 69 (59%) patients with CT level < 30 pg/ml and with no evidence of lateral nodal involvement. Ipsilateral MRND was added in 38 (32.5%) patients, where in 15 (39.5%) and in 23 (60.5%) cases it was respectively synchronous to TT + CND and postponed after histology of the central compartment and detection of post-operative CT. In all 15 patients receiving MRND at first surgery, US was positive in the ipsilateral and negative in the contralateral compartment and CT was above 100 pg/ml. In all 23 patients receiving MRND at a second surgery, US was negative in both lateral compartments but a central compartment involvement after TT + CND and post-operative persistent high levels of CT above 30 pg/ml were observed. In 10 (8.5%) other cases bilateral neck dissection was primarily indicated due to positive US of the ipsilateral and contralateral compartments, respectively in 100% and 80% of cases and with CT levels above 200 pg/ml in all patients. In these 10 cases contralateral MRND was postponed at least 30 days after ipsilateral surgery.

In 98% of cases, patients were discharged in 2nd post-operative day after TT + CND and in the 5th post-operative day following MRND. Nodal metastases were detected in the central compartment in 85 (72.6%) patients. Central metastases were found in 37 (53.6%) out of 69 patients who had undergone TT + CND and in all 38 who had undergone unilateral and in 10 patients bilateral MRND respectively. Positive lymph nodes were detected in the lateral compartment in all 15 patients undergoing synchronous MRND and in 19 (82.6%) out of 23 patients undergoing postponed lateral lymphadenectomy. Positive lymph nodes were detected in both lateral compartments in all 10 patients undergoing bilateral MRND. In the 4 cases with negative lateral lymph nodes after ipsilateral postponed MRND, distant metastases were detected after surgery. Data concerning the correlation between surgical procedure, pathology, US evaluation and CT levels are presented in Table 1. In terms of post-operative complications we observed 3 (2.5%) cases of unilateral temporary laryngeal recurrent nerve palsy and 15 (12.8%) cases of temporary hypoparathyroidism. Intra-operative

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