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ORIGINAL ARTICLE

Interest of sentinel node biopsy in apparently intrathyroidal medullary thyroid cancer: a pilot study

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Abstract
Purpose Initial surgery for medullary thyroid cancer (MTC) with no evidence of lymph node involvement in neck compartments consists of total thyroidectomy and prophylactic central neck dissection. This study evaluated the reliability of a radiotracer technique for the intraoperative detection of sentinel lymph nodes (SLNs) in lateral compartments in patients with early MTC.
Methods Patients with limited (cT1 N0) MTC entered the study (2009–2012). A 0.1–0.3 ml suspension of macrocolloidal technetium-99-labeled human albumin was injected (under echo-guide) in the tumor 5 h before surgery. Preoperative lymphoscintigraphy confirmed the identification of SLNs in the lateral neck. The operation consisted of total thyroidectomy and central neck dissection, and a hand-held gamma-probe (Neoprobe) guide was used to remove the SLNs from the lateral neck.
Results Four patients were recruited. The tracer always indicated a SLN. Pathology reports indicated micrometastases from MTC in SLN in three patients. At a mean follow-up of 30.5 months, all patients were biochemically cured. The technique we describe to detect and remove neck SLN from MTC seemed to be very accurate. It always showed the SLNs (usually two) in the lateral compartments. Micrometastases were detected in three of four patients, allowing their correct staging.
Conclusions The method described here for the detection of SLNs in early MTC seems effective and reliable and can be used for a more precise N staging of the patients. It could play a role, alone or combined with other techniques, in driving the extent of prophylactic neck dissection or other potential applications.

Keywords Thyroid surgery · Medullary thyroid carcinoma · Sentinel lymph node biopsy · Radio guided surgery · Technetium-99-labeled human albumin

Introduction

Medullary thyroid cancer (MTC) is an uncommon tumor with four distinctive features: the secretion of a specific tumor marker, calcitonin, the tendency to spread relatively early into the lymphatic system, a sporadic (about 75 % of cases) and a hereditary form, and the lack of effective treatments other than radical surgery. Hence, to obtain high cure rates and a low incidence of locoregional relapses, total thyroidectomy and dissection of central and both lateral compartments of the neck has been suggested, even for those tumors with no clinical or instrumental evidence of regional or distant metastases.

The prophylactic removal of apparently uninvolved lateral compartments has been questioned in recent years, and current guidelines for apparently intrathyroidal MTC recommend total thyroidectomy and central neck dissection alone. The measurement of postoperative calcitonin levels is widely used as a surrogate marker of cure, even

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though the normalization of calcitonin levels (basal and stimulated) cannot exclude the presence of residual micrometastases that would result in a later recurrence of the disease.

To test whether the technique for sentinel lymph node (SLN) mapping and biopsy is capable of identifying eventual micrometastases in nodes outside the central neck, and potentially to drive the extent of lymph node dissection in apparently intrathyroidal MTC, we initiated a pilot study to adjunct the method to the recommended treatment plan. The concept is to offer patients the best chance of a cure while avoiding unnecessary prophylactic lateral neck dissections.

Materials and methods

We proposed to a consecutive series of patients, referred to us from 2009 to 2012 for surgical treatment of an early-stage (T1 cN0) MTC, to enter the study in which they would receive the treatment recommended by 2009 American Thyroid Association guidelines (total thyroidectomy and central neck dissection) integrated by the biopsy of SLN in extracentral neck compartments.

Selection of patients: patients with small MTC at the first neck surgery, no clinical or echographic evidence of suspicious lymph nodes in the neck; clinical, biochemical and morphologic screening were used to exclude pheochromocytoma and hyperparathyroidism.

To identify the SLN, a 0.1- to 0.3-ml suspension of macrocolloidal technetium-99-labeled human albumin was injected into the primary tumor under echographic guidance 5 h before surgery. We obtained a preoperative lymphoscintigram that confirmed the identification of at least one SLN (usually two) in the lateral neck. In the operative room, the surgeon performed a total thyroidectomy en block with a central neck dissection. After this he used an hand-held gamma-probe (Neoprobe) to localize and remove the SLN in the lateral neck (Fig. 1). The specimen consisted in a block of gamma-emitting soft tissue of about 15/20 mm diameter. The presence of the SLN in the specimen was tested ex vivo, and the operative field too was checked again after the removal of the SLN to verify the absence of residual emissions. A standard lateral neck dissection was not performed after the biopsy since we agreed with our pathologists (in the protocol of the study) not to perform a frozen section of SLNs in order not to miss small clusters of cells for definitive histology.

All SLNs were fixed in formalin, sampled in toto, and embedded in paraffin. The bivalve technique of sampling was used whenever possible. The pathologic examination consisted of standard hematoxylin and eosin staining, and slices were immunostained for calcitonin (Benchmark instrument) and for antibody (Roche-Ventana Medical System, Tucson, AZ, USA). Sections were made every 20 μm. All of the embedded material was examined.

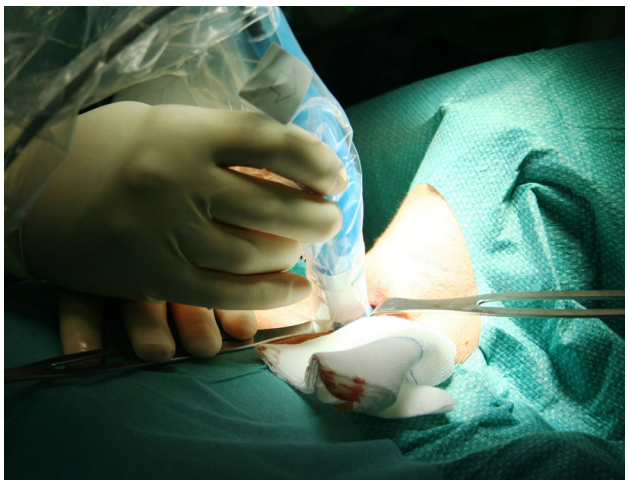

Fig. 1 Localization of the SLN by hand-held gamma probe

Follow-up consisted of measurement of basal calcitonin levels at 6 months, then a yearly measurement of basal and pentagastrin-stimulated calcitonin (0.5 μg/kg body weight). Patients with apparently sporadic MTC underwent postoperative genetic testing to formally exclude the presence of a hereditary form.

Results

Four patients were recruited, and their demographic and preoperative details are listed in Table 1. At lymphoscintigram, the tracer always indicated the SLN (usually two foci, homolateral). One patient showed an uptake behind the jugular vein, on the lower edge between the central and right lateral compartment, which created some uncertainty in attributing it to the central compartment.

The patients' perioperative course was uneventful. We registered a transient asymptomatic hypocalcemia and a self-limiting chylous leak that ceased spontaneously on the second postoperative day. All patients left the hospital 2 days after the operation.

Histologic report (see Figs. 2, 3) revealed micrometastasis in the SLN in three of four patients, two of whom also had micrometastases in the central neck. The mean diameter of micrometastases was 30 μm. The details of pathology reports are listed in Table 2.

At a mean follow-up of 30.5 months, all patients were biochemically cured as determined by basal and stimulated calcitonin in three patients. A completion lateral compartment dissection was proposed to patients with

Table 1 Sample details at diagnosis

Patient	Sex	Age (years)	Form of MTC	Initial diagnostic tool	Tumor size (mm)	Side	Basal calcitonin (pg/ml)
1	F	70	Apparently sporadic	FNAC	10	Right	139
2	M	70	Apparently sporadic	Calcitonin + FNAC	6	Right	40
3	M	68	Hereditary	Genetic screening	12	Left	142
4	F	23	Apparently sporadic	Calcitonin screening	8	Right	100

MTC medullary thyroid cancer, *F* female, *M* male, *FNAC* fine needle aspiration cytology

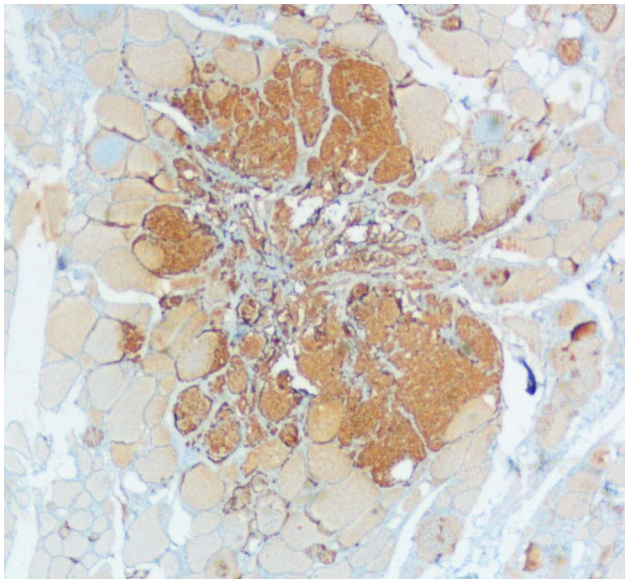

Fig. 2 Medullary thyroid cancer: CT immuno-staining (×2)

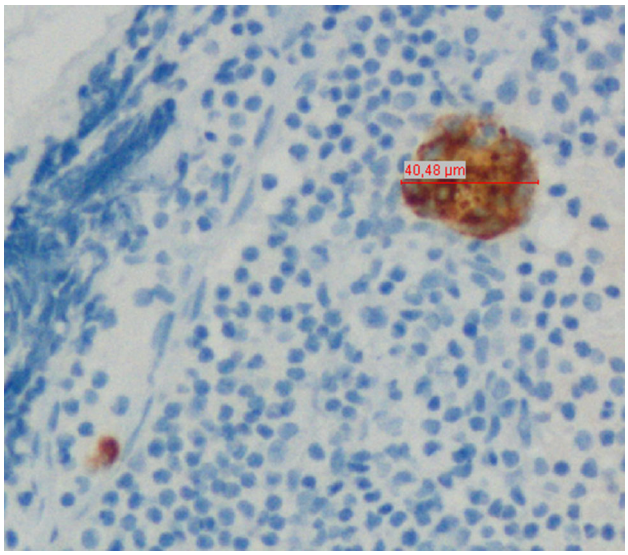

Fig. 3 Micrometastasis in a SLN (×20)

micrometastases in the SLN, but they declined the redo operation due to the absence of biochemical and instrumental evidence of disease persistence or relapse.

Table 2 Pathological data

Patient	Thyroid	Central compartment	SLN (lateral compartment)
1	10 mm R MTC	7 reactive nodes	(1) R: 3 reactive nodes
	3 mm L papillary TC		(2) R: 1 reactive node
2	6 mm R MTC	9 reactive nodes, 1 parathyroid gland	(1) R: 1 micromet/ 23 nodes
	5 mm L papillary TC, thyroiditis		(2) R: 7 reactive nodes
3	12 mm L MTC	2 micrometastases + 1 reactive node	(1) L: 1 reactive node
			(2) L: 1 micromet/5 nodes
			(3) R: 1 reactive node
			(4) R: 11 reactive nodes
4	8 mm R MTC	1 micrometastasis + thymic tissue + fragment of a parathyroid gland	(1) R: 3 reactive nodes
	3 mm L MTC		(2) R: 1 micromet

MTC medullary thyroid cancer, *papillary TC* papillary thyroid cancer, *micromet* micrometastasis, *(1)* SLN nr 1, *(2)* SLN nr 2, etc., *R* right side, *L* left side

Discussion

Medullary thyroid cancer has been characterized by a tendency to colonize lymph nodes superior to those of differentiated thyroid cancers [1–5]. Other distinguishing features of MTC are the availability of a specific and sensitive tumor marker, calcitonin, whose circulating levels grossly reflect the tumor burden, and the lack of effective

curative treatments other than surgery, the only cure of the disease consisting in radical removal of the thyroid and of the regional lymph nodes.

A controversial issue is how to determine the extent of lymphadenectomy when there is no gross, macroscopic node involvement. Modulating the extent of the dissection according to the stage of the disease is controversial because many factors have been related to the stage of the disease, including the dimension of the primary tumor and its side [6, 7], the presurgical basal and stimulated calcitonin levels [8], the presence and the number of metastatic lymphnodes [9, 10], the number of involved neck compartments [11], and the histologic features of the primary tumor (such as capsular invasion) [10] among others. Nonetheless, not a single preoperative factor is exactly predictive of the presence of occult metastases and, hence, of cure.

Many efforts have been made to obtain an early diagnosis of MTC for the control of this tumor, because its treatment at early stages is obviously associated with the best chance of a biochemical cure. Currently, the genetic screening test for hereditary MTC [12–15] and basal calcitonin screening for the sporadic variety [16–18] represent a unique opportunity to intercept MTC at a preclinical stage. Thanks to the diffusion of these tests, the scenario of an apparently intrathyroidal MTC with no clinical or echographic evidence of regional node involvement is no longer a rare one, and the prophylactic dissection of lateral compartments of the neck for all patients could be an unnecessary and time- and energy-consuming procedure that adds to complications without substantial benefits for the patient compared with central neck dissection alone. As a consequence, updated guidelines from several authoritative organizations recommend total thyroidectomy and central dissection, generally excluding prophylactic lateral lymphadenectomy [19–21].

We adhered to those guidelines in our pilot study but borrowed the concept of SLN from other solid-tumor treatment strategies (i.e., breast cancer and melanoma) to spot micrometastases in undissected lateral compartments that would otherwise be left behind, free to grow with time and potentially able to cause persistence or recurrence of the disease. Our aim was to verify the efficacy of the method we chose to identify SLN from a thyroid cancer, its practicability, and finally, to verify whether it could be used to drive lateral neck dissections on the ground of histologically proven metastases and thus offer the best chance of cure to this selected group of patients. Other authors have applied the SLN concept to the neck region, but not for medullary thyroid cancer [22–27].

Our preliminary results witness in favor of the efficacy of this radionuclide-based method for the identification of SLN from a thyroid tumor in the lateral neck: we found SLN micrometastases in three of four patients, with no evidence of persisting disease. All patients are apparently cured, even if a formal completion lateral lymphadenectomy has not been performed, with a follow-up length for three patients approaching 4 years. An interpretation of these results is that there was just a single micrometastasis in the lateral compartment on the side of the main tumor and that the SLN biopsy, a diagnostic procedure, became a therapeutic one, attaining the definitive cure of the patient. Alternatively, the SLN showed one tumor microdeposit, and others that could be present at a distance from the biopsied SLN were not large enough to produce a detectable basal/stimulated elevation of serum calcitonin or that the residual metastatic cells might have lost the property to secrete calcitonin.

As far as the costs of the procedure regards we can easily have a precise idea of it since the methodology is widely used for the current treatment of clinically N0 breast cancer, melanoma and other solid tumors; the gamma probe can be shared with the other colleagues, so the costs are those of any sentinel node biopsy.

The low power of gamma-emissions delivered with this procedure is such that neither special protective measures nor special waste material discharge is necessary, thus creating no inconvenience to the standard routine activity of the surgical room.

The presence of lateral neck micrometastases in 75 % of the patients in this sample seems to be in contrast with the high cure rates reported for the total thyroidectomy and central neck dissection without prophylactic lateral neck dissection for apparently intrathyroidal MTC [5, 28–34]. The discordance could simply be due to chance, given the small number of observations. Another possible speculation is that the effective destiny of micrometastases of MTC is not ineluctably the progression to macrodeposits but rather their disappearance because of effective host immune reaction or apoptosis.

We found the results of this pilot study are undoubtedly intriguing, and we hope they will stimulate further investigations to better define the management of neck compartments in apparently intrathyroidal MTC.

Conclusion

To our knowledge, this is the first report about the use of SLN in MTC. Radiocolloid-based SLN sampling in the lateral neck by a hand-held gamma probe in early-stage MTC seems extremely precise in detecting the first node encountered by micrometastases. The results of this small sample indicate that there is no residual tumor in any subject. Given our results, we think this method deserves further evaluation in a larger number of patients. The

optimal evaluation would consist of a multicenter, prospective, randomized study comparing the SLN biopsy with total thyroidectomy and central compartment dissection alone and/or total thyroidectomy and central and lateral prophylactic dissection, to compare the cure rate, disease-free survival, complications rate, operative time, costs, and all other pertinent issues.

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Conflict of interest The authors declare no conflict of interest.

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