

## Surgical Treatment of Intrathyroid Metastases: Preliminary Results of a Multicentric Study

FILIPPO CALZOLARI<sup>1</sup>, PAOLA VINCENZA SARTORI<sup>2</sup>, CARLO TALARICO<sup>3</sup>, DOMENICO PARMEGGIANI<sup>4</sup>,  
EDOARDO BERETTA<sup>5</sup>, LUCIANO PEZZULLO<sup>6</sup>, GIORGIO BOVO<sup>2</sup>, PASQUALE SPERLONGANO<sup>4</sup>,  
MASSIMO MONACELLI<sup>1</sup>, ROBERTA LUCCHINI<sup>1</sup>, CLAUDIA MISSO<sup>1</sup>, ANGELA GURRADO<sup>7</sup>,  
MICHELE D'AJELLO<sup>1</sup>, FRANCO UGGERI<sup>2</sup>, EFISIO PUXEDDU<sup>1</sup>, PIERGIORGIO NASI<sup>8</sup>,  
MARIO TESTINI<sup>7</sup>, LODOVICO ROSATO<sup>9</sup>, ALFONSO BARBARISI<sup>10</sup> and NICOLA AVENIA<sup>1</sup>

<sup>1</sup>Inter-Hospital Functional Area of Endocrine Surgery, Umbria Region, Perugia;

<sup>2</sup>Surgical Department and Pathology Service, San Gerardo Hospital, University of Milan-Bicocca;

<sup>3</sup>General Surgery Department, San Biagio Hospital, Chiaravalle C.le, Catanzaro;

<sup>4</sup>Anesthesiological, Surgical and Emergency Sciences Department,  
V Surgical Unit, University Federico 2nd, Naples;

<sup>5</sup>Endocrine Surgery Unit, Surgical Department, San Raffaele Hospital, Vita-Salute San Raffaele University, Milan;

<sup>6</sup>Thyroid and Parathyroid Surgery Unit, National Cancer Institute "G. Pascale", Naples;

<sup>7</sup>Section of General, Vascular, and Clinical Oncology,

Department of Application in Surgery of Innovative Technologies, University Medical School, Bari;

<sup>8</sup>Department of Surgery, Endocrine Surgical Unit, "Mauriziano" Hospital, Turin;

<sup>9</sup>Department of Surgery, Endocrine Surgical Unit, Ivrea Hospital, Ivrea;

<sup>10</sup>Department of Anaesthesiological, IX Division of General Surgery and Applied Biotechnology,  
Surgical and Emergency Sciences, Second University of Naples, Naples, Italy

**Abstract.** Background: Intrathyroid metastases (ITM) are rare and usually have a dismal prognosis. The aim of this study was to detect which neoplasms metastasize most often to the thyroid gland, their clinical features and treatment options. Materials and Methods: Retrospective analysis of clinical files of 17,122 patients submitted to surgery for thyroid disease between 1995 and 2005. Twenty-five patients (median age 61 years) were affected by ITM. Results: The site of the primary tumor was: kidney (15), lung (4), colon (3), breast (1), melanoma (1), and unknown in 1 patient. Ten patients (40%) complained of preoperative symptoms, in the others, thyroid involvement was incidentally discovered during the follow-up for the primary cancer. Twenty patients (80%) underwent total thyroidectomy, 3 received thyroid lobectomy and 2 palliative procedures. Morbidity was 16%, mortality was nil. The median follow-up was 24 months. Conclusion: ITM should always be suspected in any patient with a previous history of malignancy. Fine-needle agobiopsy (FNAB) with immunohistochemical stains may help in

preoperative workup. A long delay between the primary tumor and the recurrence warrants surgery and total thyroidectomy seems to be the treatment of choice because of the multifocality of metastasis to the thyroid gland.

Metastatic lesions account for 1.4% -3% of thyroid neoplasms and between 0.05 and 0.1% of all thyroid diseases. The incidence of intrathyroid metastases (ITM) in autopsic series varies between 1.25% and 24.4% when considering patients dying of primary or metastatic malignancies, indicating that it is a rather frequent event in the general population (1-3).

Primary neoplasms most often responsible for thyroid metastases are clear cell renal carcinoma, lung carcinoma, breast cancer and, less frequently, colonic carcinoma (4-7).

Preoperative diagnosis may be troublesome since at fine-needle agobiopsy (FNAB), ITM may mimic a poorly differentiated thyroid cancer. The aim of this study was to detect which neoplasms metastasize most often to the thyroid gland, their clinical features and treatment options (8-11).

### Materials and Methods

A retrospective review was carried out of the clinical files of 17,122 patients operated for thyroid pathology at 10 Italian surgical departments over a 10-year period; among these patients, 25 were identified as having ITM. Patients with known multiple metastases were not considered.

Correspondence to: Filippo Calzolari, MD, Castel Rinaldi 66, 06056 Massa Martana (PG), Italy. Tel: +39 348 6095388, Fax: +39 06-62276134, e-mail: calzolari@chirurgia.it

Key Words: Thyroid, metastases, surgery, carcinoma, neoplasm.

Table I. Onset of symptoms of intrathyroid metastasis.

Symptom	No. of cases
Incidental finding	15 (60%)
Palpable thyroid nodule	7 (28%)
Cough	2 (8%)
Haemoptysis	1 (4%)

Table II. Patient characteristics.

Patient	Primary tumor	S/M	Treatment	Resection	Metastasis	Follow-up (months)	Status
1	RCC	M	TT + LN	R2	Mu	8	DOD
2	RCC	M	TT + MRND	R0	Si	88	NED
3	COLON	M	TT	R0	Si	51	WD
4	COLON	M	TT	R0	Mu	30	DOD
5	COLON	S	LI	R0	Si	38	NED
6	MEL	M	LI	R1	Si	23	DOD
7	LUNG	S	TT + LN	R2	Mu	6	DOD
8	LUNG	S	STENT	NA	-	3	DOD
9	RCC	M	TCT	NA	-	13	DOD
10	RCC	M	TT	R0	Mu	2	NED
11	RCC	M	TT+ MRND	R0	Si	78	DOD
12	ADC	M	TT	R1	-	NA	LFU
13	RCC	M	TT + LN	R0	Si	17	DOD
14	RCC	M	TT	R0	Mu	4	NED
15	RCC	M	TT	R0	Si	72	DOD
16	RCC	M	TT	R0	Mu	24	NED
17	BREAST	M	TT	R0	Si	60	DOD
18	LUNG	M	TT	R0	Mu	26	LFU
19	RCC	M	TT	R0	Si	56	DOD
20	RCC	M	LI + CND	R0	Mu	24	DOD
21	LUNG	M	TT	R0	Si	11	DOD
22	RCC	M	TT + TCT	R2	Mu	6	DOD
23	RCC	M	TT	R0	Mu	48	DOD
24	RCC	M	TT	R0	Mu	18	NED
25	RCC	M	TT	R0	Si	132	DOD

RCC: Renal cell cancer; COLON: Colonic adenocarcinoma; MEL: skin melanoma; LUNG: non-small cell lung cancer; ADC: adenocarcinoma of unknown origin; BREAST: Breast adenocarcinoma; S: synchronous; M: metachronous; TT: total thyroidectomy; LN: lymphadenectomy; MRND: modified radical neck dissection; STENT: tracheal stent; TCT: tracheotomy; CND: central neck dissection; R0: complete macroscopic resection; R1: microscopically incomplete resection; R2: macroscopically incomplete resection; Si: single metastasis in the thyroid gland; Mu: multiple metastases in the thyroid gland; DOD: dead of disease; NED: alive with no evidence of disease; WD: alive with disease; LFU: lost to follow-up; NA: not available.

There were 14 males and 11 females with a median age of 61 years (range 42-77 years). Ten patients (40%) complained of preoperative symptoms, in the others, thyroid involvement was incidentally discovered during the follow-

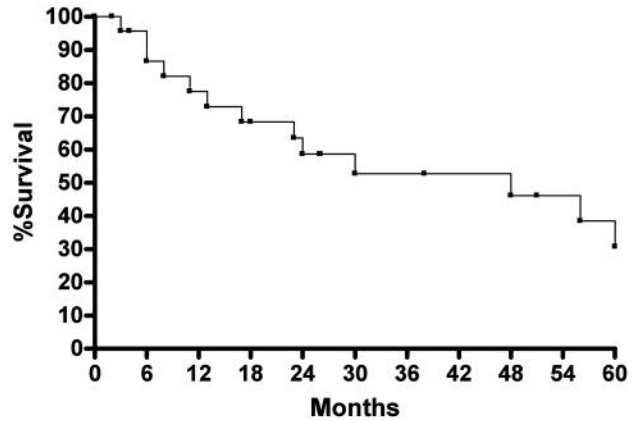


Figure 1. Five-year overall survival of 25 patients affected by metastases to the thyroid.

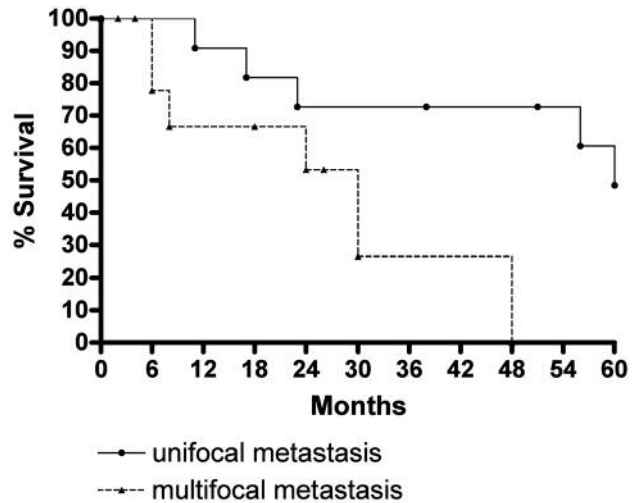


Figure 2. Comparison between 5-year survival of patients with unifocal metastasis and those with multifocal metastasis.

up for the primary cancer. Onset symptoms are detailed in Table I. Symptomatic patients were investigated with neck ultrasound and thyroid hormone measurements. After having been diagnosed with a thyroid nodule, 17 patients (68%) were submitted to preoperative FNAB. Preoperative investigations were carried out on an outpatient basis. Patient characteristics are detailed in Table II.

Survival curves were calculated by Kaplan-Meier method and the difference between groups was analyzed by the log-rank test.

Follow-up was carried out every six months by visits, neck ultrasound, and, depending on the site of the primary tumor, either by abdominal or thoracic computed tomography (CT) scan. In more recent years, positron-emission computed

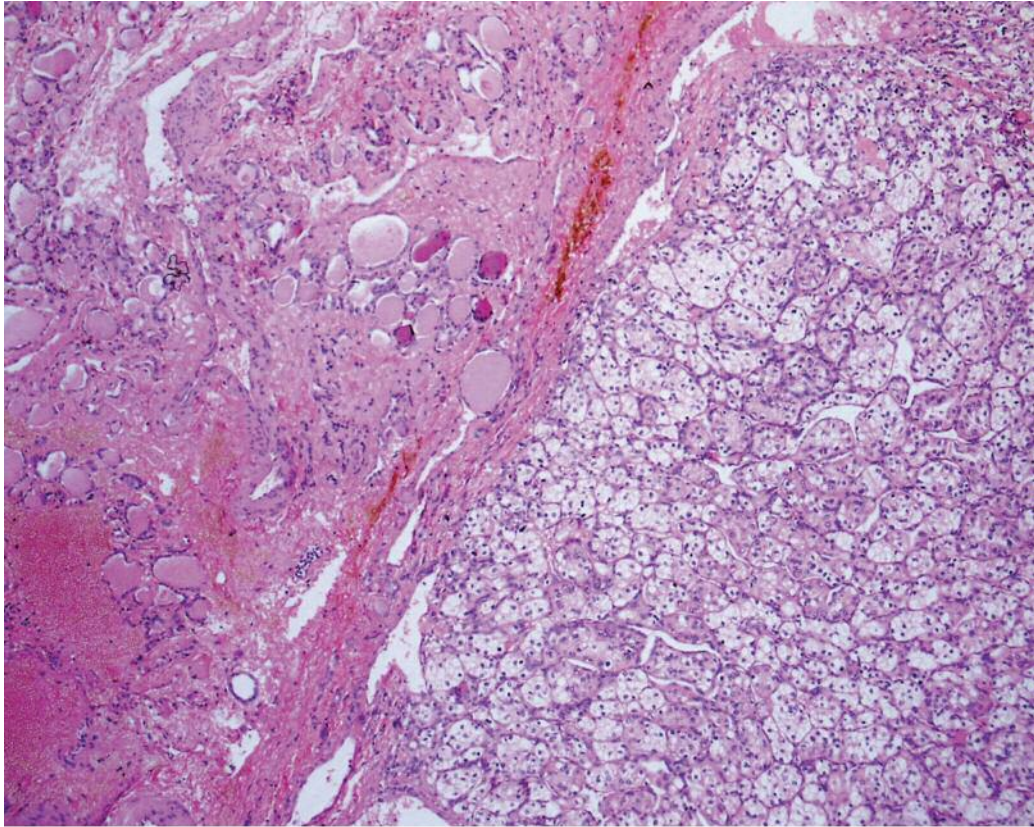


Figure 3. Thyroid metastasis from clear cell renal cancer (hematoxylin–eosin  $\times 200$ ) with infiltrative growth pattern (upper right).

tomography (PET) was employed. The median follow-up was 24 months (range 2-132 months). Statistical significance was set at a threshold of  $p < 0.05$ . Statistical analysis was performed by SPSS® 14th edition, Chicago, USA.

## Results

The prevalence of ITM in our series was 0.15%. Preoperative FNAB in 8 patients (32%) diagnosed with a neoplastic lesion (3 metastases and 5 poorly differentiated thyroid cancers), showed in 3 patients a follicular nodule and in the remaining 6 patients no tumoral cells. Twenty patients (80%) underwent total thyroidectomy and 3 received thyroid lobectomy. In 2 patients with massive tracheal involvement, only palliative procedures (1 tracheotomy and 1 tracheal stent) were carried out. Neck dissection was performed in 3 patients with metastasis from renal cell cancer and preoperative evidence of nodal involvement (2 modified radical neck dissections and 1 central neck dissection), while in 3 others, only macroscopically involved nodes were removed. All the patients submitted to neck dissection had positive lymph nodes (N+). In 3 patients, the thyroid lesion was

synchronous with the primary tumor, while in 22, the metastasis appeared after a median delay of 40.5 months (range 7-215 months). Fifteen patients (60%) were affected by clear cell renal cancer metastasis, 4 by lung carcinoma, 3 by colonic cancer, breast cancer and melanoma accounted for 1 patient each, and in another patient the primary remained unknown; histology revealed plurifocal thyroid metastasis in 44% of the patients.

Morbidity was 16% (1 permanent recurrent nerve palsy, 1 permanent and 2 transient hypoparathyroidisms), mortality was nil. Actuarial 5-year overall survival was 31%, with a median survival of 48 months (Figure 1), and 5-year disease-free survival of the 18 patients submitted to R0 surgery was 18%, with a median disease-free survival of 25 months (Figure 2). Patients affected by renal cancer metastasis had a 5-year survival of 40% with a median survival time of 56 months, while those affected by other malignancies had a median survival time of 30 months and none was alive at 60 months ( $p = \text{not significant}$ ). Patients submitted to total thyroidectomy had a median survival of 56 months and those who underwent other operations survived for a median of 24 months ( $p = \text{not significant}$ ). The median survival time of patients with multicentric lesions was 30 months and that of

patients with only one metastatic focus within the thyroid gland was of 60 months. While 5-year survival in cases of a single lesion was 48% , none of the patients with multifocal cancer was alive ( $p=0.03$ ) at the time of writing.

## Discussion

The thyroid is at very high risk of metastatic localization due to its very large blood supply. The reported prevalence of distant metastasis to the thyroid in autopsy series ranges from 1.2 to 24% ; on the contrary, clinical thyroid metastases are rather uncommon (1-3). In our series, as reported by other authors, clear cell renal cancer was the most common primary tumor responsible for ITM, and patients with metastases from this neoplasm seem to survive longer than those affected by other malignancies, although the difference is not significant (12). Metastases, especially those from clear cell kidney cancer, may have the macroscopic appearance of a single lesion (60% of the cases) or be multicentric (40% of the cases). When multicentric, they usually infiltrate and replace the thyroid tissue and may extend beyond the thyroid capsule (10) (Figure 3).

In our series, 44% of the patients had more than one metastatic focus and multifocal metastases adversely affected the prognosis: patients with a single metastatic lesion within the gland had a significantly better survival than those with multiple foci.

ITM may appear many years, even decades, after the primary lesion, thus the differential diagnosis between a metastasis and a primary thyroid cancer may be very difficult. Fine-needle agobiopsy (FNAB) is crucial in the diagnostic workup of these patients but it has a low specificity and it is often difficult to distinguish between a metastasis and a primary poorly differentiated thyroid cancer (1): among our patients only 3 were properly diagnosed in the preoperative setting. In patients with a previous clinical history of neoplasm, immunohistochemical staining of FNAB specimens may greatly help in distinguishing between a primary thyroid cancer, which stains positively for thyroglobulin, and a metastatic lesion that does not (8, 13-14).

The extension of surgical resection does not seem to have a significant impact on survival, in fact the difference in survival between patients submitted to total thyroidectomy and those who underwent less radical operation was not statistically significant, however our data are limited.

## Conclusion

A clinical history of malignancy prone to thyroid metastatization should raise suspicion of ITM in every patient with a thyroid nodule. FNAB may be helpful in ruling out a poorly differentiated thyroid cancer provided

specific immunohistochemical stains are performed. Metastatic lesions are very often multifocal and this significantly impairs survival, therefore total thyroidectomy seems to be the best treatment option to avoid leaving behind residual thyroid tissue that may harbour neoplastic foci.

## References

- Mirallie E, Rigaud J, Mathonnet M, Gibelin H, Regenet N, Hamy A, Bretagnol F, de Calan L, Le Neel JC and Kraimps JL: Management and prognosis of metastases to the thyroid gland. *J Am Coll Surg* 200: 203-207, 2005.
- Piazza C, Bolzoni A, Peretti G and Antonelli AR: Thyroid metastasis from rectal adenocarcinoma involving the airway treated by crico-tracheal resection and anastomosis: the role of palliative surgery. *Eur Arch Otorhinolaryngol* 261: 469-472, 2004.
- Wood K, Vini L and Harmer C: Metastases to the thyroid gland: the Royal Marsden experience. *EJSO* 30: 583-588, 2004.
- Menegaux F and Chigot JP: Thyroid metastases. *Ann Chir* 126: 981-984, 2001.
- Lin JD, Weng HF and Ho YS: Clinical and pathological characteristics of secondary thyroid cancer. *Thyroid* 8: 149-153, 1998.
- Benoit L, Favoulet P, Arnould L, Margat A, Franceschini C, Collin F, Fraisse J, Cuisenier J and Cougard P: Metastatic renal cell carcinoma to the thyroid gland: report of seven cases and review of the literature. *Ann Chir* 129: 218-223, 2004.
- Chen H, Nicol TL and Udelsman R: Clinically significant, isolated metastatic disease to the thyroid gland. *World J Surg* 23: 177-180, 1999.
- Heffess CS, Wenig BM and Thompson LD: Metastatic renal cell carcinoma to the thyroid gland: a clinicopathologic study of 36 cases. *Cancer* 95: 1869-1878, 2002.
- De Ridder M, Sermeus AB, Urbain D and Storme GA: Metastases to the thyroid gland a report of six cases. *Eur J Intern Med* 14: 377-379, 2003.
- Rosai J: Thyroid. *In: Rosai and Ackermann's Surgical Pathology* 9th ed. Rosai J (ed.): London, Mosby, pp. 515-594.
- Bellantone R, Lombardi CP, Boscherini M and Alesina P: Metastasi della tiroide e alla tiroide; *In: La Patologia Chirurgica della Tiroide e delle Paratiroidi*. Rosato L (ed.): Santhià (VC), Grafica Santhiatese Editrice, pp. 186-187, 2000.
- May M, Marusch F, Kaufmann O, Seehafer M, Helke C, Hoschke B and Gastinger I: Die solitäre Niedertzellkarzinom-metastase in der Schilddrüse. *Chirurg* 74: 768-774, 2003.
- Kumamoto K, Yasufumi U, Kouju S, Masami H, Shinichi S and Seiichi T: Colon carcinoma metastasis to the thyroid gland: report of a case with review of the literature. *Tumori* 92: 252-256, 2006.
- Mattavelli F, Colli P, Geravasoni C, Pizzi N, Pallotti F and Pastorino U: Double, metachronous thyroid metastasis of colon cancer. *Tumori* 92: 249-251, 2006.

Received February 13, 2008

Revised July 15, 2008

Accepted August 5, 2008