Thyroid Gland as a Target of Secondary Malignancies - an Autopsy Study and Review Data

Antigony Mistelou, Stamatis S. Papadatos, Chrysavgi Kousi, Evangelí Lampri, Michael Mitsis, Theodoros Vougiouklakis, Vasiliki Galani

1 Department of Forensic Medicine and Toxicology, University of Ioannina, Ioannina, Greece
2 Third Department of Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece
3 Department of Pathology, University of Ioannina, Ioannina, Greece
4 Department of Surgery, University Hospital of Ioannina, Ioannina, Greece
5 Department of Anatomy, Histology, and Embryology, University of Ioannina, Ioannina, Greece

Correspondence:
Vasiliki Galani, Department of Anatomy, Histology and Embryology, University of Ioannina, Ioannina, 45110, Greece.
E-mail: vgalani@uoi.gr; Tel:+302651007587

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Aim: Secondary malignancies of the thyroid gland are rarely diagnosed but their incidence at autopsy is not uncommon.

Materials and methods: To investigate the clinicopathological features of patients with metastatic tumours of the thyroid gland, we reviewed autopsy records and pathological features of 36 cases with thyroidal secondary tumours from 266 cases of malignant neoplasias (excluding cases of primary thyroid cancer), over a 16-year period.

Results: There were 19 men and 17 women in the study, ranging in age from 37 to 95 years (mean 70.4 years). The incidence of metastasis in thyroid gland was 0.9% in all autopsy cases, and 13.53% of the malignant tumours. The majority were carcinomas of epithelial origin. The lung was the most common primary tumour site (33.3%), followed by the breast (8.33%) and the kidney (8.33%). The most common non-epithelial malignancy was lymphoma, followed by leukaemia (total of both 25%). As for the microscopic morphological observations, diffuse infiltration pattern of tumour cells was noted in 63.89% of the cases, the formation of nodules in 33.33% of the cases and contiguous invasion in 2.79% of the cases. There were 35.71% cases of metastases associated with multinodular goitre and 28.57% cases associated with papillary microcarcinoma.

Conclusion: Our study indicates that thyroid secondary malignancies are not infrequent and may constitute a diagnostic problem. Lung cancer is the most common neoplasm that metastasizes to the thyroid gland in north-western Greek population.

INTRODUCTION

Although solitary benign nodules, multinodular goitre, follicular adenomas and primary thyroid malignancies are the most common diagnoses concerning thyroid pathology, metastases to the thyroid should also be considered.1-4 Despite the abundant arterial supply, the thyroid gland receives few metastatic deposits. In 1931, Willis proposed that fast arterial flow through the thyroid depresses adhesion of malignant cells, while the high oxygen satiety and iodine content of the thyroid gland inhibit the growth of malignant cells.5 In the ensuing 80 years, after Willis hypothesized why metastases to the thyroid gland were rare, their prevalence in various reports has been variable.

Metastatic disease of the thyroid gland is rarely detected in clinical practice; yet it is more common in autopsies due to widespread participation or direct invasion from a primary neck or mediastinal neoplasm.6,7 However, the number of clinical cases with metastasis to the thyroid gland has been progressively increasing, probably because of the development of various diagnostic techniques, such as fine needle aspiration biopsy (FNAB), computed tomography (CT) and F-18-fluorodeoxyglucose positron emission tomography (FDG-PET). Although the possibility of detection of thyroid tumour increases, differential diagnosis of metastatic tumours to the thyroid from primary thyroid cancer is still intricate.8-10
In effect, all organs may be the source of primary tumours metastasizing to the thyroid gland. Its involvement by non-thyroid malignancies may occur with direct dispersion from adjacent structures, retrograde lymphatic propagation and haematogenous propagation. Many studies have shown that the frequency of thyroid metastases from a given primary tumour histotype varies broadly, proportionately of ethnic/demographic and epidemiological differences in major cancer types in the different populations.

Although the autopsy rate is actually diminishing in many countries, post-mortem examination preserves in full its importance for verifying clinical diagnosis and cause of death, even nowadays with the current precision of diagnostic techniques. The malignant neoplasm is a notably interesting being and we believe that a major part of the problem, regarding the differences in frequency of thyroid metastases and their origin, is lack of uniform analysis of autopsy material. One reason for this is the frequently insufficient examination of thyroid at routine post-mortem conditions. Even when thyroid is examined grossly, often no section or perhaps a single section is submitted for microscopic examination.

Starting from our personal experience in the thyroid pathology and from studies on thyroid metastases reported in the literature, the purpose of the present investigation was to carry out a retrospective study to determine the clinicopathological features of secondary tumors of the thyroid gland, including their incidence, primary site, gross findings, microscopic findings and the application of immunohistochemical (IHC) method as a useful technique to the identification and affirmation of the primary tumour. This is the first time that this retrospective study was conducted in the northwestern region of Greece.

MATERIALS AND METHODS

Epirus is a mountainous area that is located in North West Greece. The urban and semi-urban population of the region is 33% of the total population, while the remaining 67% is rural. The total population of Epirus in 2011 was 336,856 inhabitants as given by the National Statistical Service Bureau, constituting almost 3.1% of the total population of Greece. The Department of Forensic Medicine and Toxicology is authorized to perform all medico-legal autopsies, in the four prefectures of the region, including deaths that are unexpected; death unnatural or violent or resulting directly or indirectly from accident or injury, death in persons whose identity is unknown; those for which a death certificate has not been completed, and deaths of people held in care. This report focuses on individuals with malignant tumours who died from diseases (metastatic disease and others), accidental injury, homicides, suicide or unexpected death.

We reviewed autopsy records and clinicopathological findings of 3969 autopsies done at the Department of Forensic Pathology, Ioannina Medical School, Greece, from 1998 to 2013. At post-mortem investigation each organ involved with neoplasm were removed and sectioned. In the case of tumour, including all four stages (TNM classification of tumours), many sections were routinely taken for histological examination. The organs with malignant involvement were noted. The number of metastases to the specific organ was not recorded, but the particular organ involved, e.g. liver, thyroid, pancreas, etc. was regarded as one site and the size of the metastases (minimum and maximum diameter) was measured in each case.

At autopsy, the thyroid gland was removed entirely along with loco-regional lymph nodes and examined. The thyroid gland of each patient was sectioned at 2-to-3-mm-thick slices. All lesions observed on inspection for each slice were subjected to scrupulous microscopic examination to detect any pathology of the gland, as well as all deposits of carcinoma cells. All sections of primary tumours, metastases and thyroid lesions were stained with hematoxylin-eosin. In all instances which neoplastic metastasis to the thyroid gland was identified, but either generated misgivings or the diagnosis needed further confirmation, we used immunohistochemical methods to verify or clarify its origin. Immunohistochemistry was performed on formalin-fixed paraffin-embedded tissues using the streptavidin-biotin method (KSAB Kit, Dako). The antibodies used were thyroglobulin (Tg), thyroid transcription factor-1 (TTF-1), calcitonin (Ca), cytokeratins (K7, K8, K19, K19-9, K20, K5/6), carcinoembryonic antigen (CEA), neuron specific enolase (NSE), p63, chromogranin (Chr), Her-2, Wilms tumour product-1 (WT-1), α-fetoprotein, (AFP), epithelial membrane antigen (EMA), HMB45, CD1, CD3, CD5, CD15, CD30, CD38, CD40, CD23, CD43, and CD99. We recorded the age, gender, primary site, gross findings, microscopic findings (including histological type) and the mode of spread.
RESULTS

PATIENT’S CHARACTERISTICS

We identified 36 cases with secondary tumours of the thyroid gland. The incidence of secondary thyroidal tumours at autopsy was 0.9% (36 out of 3969 cases), and the incidence among malignant tumours was 13.53% (out of 266 cases). The cases with thyroidal secondary tumours were 19 males (52.78%) and 17 females (47.22%), with age ranging from 37 to 95 years (mean 70.4 years). Thirty-two of these were in the sixth, seventh, and eight decades, and 4 were younger than 50 years. **Table 1** shows

**Table 1.** Characteristics of patients with metastasis in the thyroid gland in current series

| Case | Sex | Age | Primary site | Morphology | Metastases elsewhere |
|------|-----|-----|--------------|------------|----------------------|
| 1    | F   | 62  | Breast Ca (Fig. 1) | Infiltration | LN, pleura, chest wall, lung, heart, diaphragm, liver |
| 2    | M   | 68  | Larynx Ca | Contiguity | Regional and Pa-Ln, regional muscles and soft tissue |
| 3    | F   | 87  | CRC        | Nodule     | LN regional and Pa-Ln, liver, peritoneum, liver |
| 4    | F   | 81  | Ovary Ca   | Nodule     | Pa-Ln, peritoneum, uterus, liver, lung |
| 5    | M   | 48  | HCC        | Nodule     | Diaphragm, liver, adrenal, LN regional and Pa-Ln |
| 6    | F   | 90  | Lung Ca    | Infiltration | Pleura, chest wall, diaphragm, LN, liver, ipsilateral lung |
| 7    | M   | 70  | Lung Ca    | Infiltration | LN regional and Pa-Ln, ipsilateral lung, pleura |
| 8    | M   | 68  | Lung Ca    | Infiltration | Pleura, mediastinum, heart, CNS, liver, LN, Pa-Ln |
| 9    | M   | 68  | Lung Ca    | Infiltration | Pleura, mediastinum, LN, liver, adrenal gland |
| 10   | F   | 76  | Breast Ca  | Infiltration | LN, pleura, skeleton (ribs), chest wall, lung, adrenal |
| 11   | M   | 64  | Leukaemia  | Infiltration | LN, liver, spleen |
| 12   | M   | 91  | Lung Ca    | Infiltration | LN, pleura, mediastinum, liver, CNS |
| 13   | F   | 45  | Lung Ca    | Infiltration | LN regional, pleura, mediastinum, ipsilateral lung |
| 14   | M   | 82  | Lung Ca    | Nodule     | LN, pleura, mediastinum, diaphragm |
| 15   | M   | 37  | Lymphoma   | Infiltration | LN regional, Pa-Ln, liver, adrenal gland, lung |
| 16   | M   | 76  | Lymphoma (Fig. 2) | Infiltration | LN regional, Pa-Ln, mediastinum, liver, spleen |
| 17   | M   | 73  | Lymphoma   | Infiltration | LN regional, Pa-Ln, mediastinum, liver, spleen |
| 18   | M   | 71  | Lymphoma   | Infiltration | LN regional, Pa-Ln, mediastinum, spleen |
| 19   | M   | 57  | Lung Ca    | Infiltration | LN, pleura, chest wall, mediastinum, liver, CNS |
| 20   | M   | 72  | Lymphoma   | Infiltration | LN regional, Pa-Ln, mediastinum, liver, spleen |
| 21   | F   | 81  | Lung Ca    | Infiltration | LN, liver, lung, pericardium, chest wall |
| 22   | F   | 76  | Breast Ca  | Nodule     | LN, chest wall, pleura, lung, ribs, liver |
| 23   | F   | 78  | Kidney Ca  | Nodule     | Perinephrotic fat, LN regional and Pa-Ln, liver |
| 24   | F   | 68  | Pancreas Ca| Nodule     | LN, peritoneum, liver, gastrointestinal tract, lung, Pa-Ln |
| 25   | F   | 65  | Hodgkin L  | Infiltration | LN, lung, liver, spleen, Pa-Ln |
| 26   | M   | 72  | Unknown Primary | Infiltration | LN, lung, liver, adrenal, heart |
| 27   | M   | 81  | Lung Ca    | Infiltration | LN, pleura, lung, mediastinum, liver, Pa-Ln |
| 28   | F   | 95  | Lung Ca    | Infiltration | LN, pleura, lung, mediastinum, liver, Pa-Ln |
| 29   | M   | 84  | Lung Ca    | Nodule     | LN, Lung, pleura, Pa-Ln, liver |
| 30   | F   | 81  | Chol Ca    | Nodule     | LN, liver, peritoneum, diaphragm, pancreas, lung |
| 31   | M   | 67  | Kidney Ca  | Nodule     | Perinephrotic fat, LN regional and Pa-Ln, liver, adrenal |
| 32   | F   | 73  | Kidney Ca  | Nodule     | Perinephrotic fat, LN regional and Pa-Ln, liver |
| 33   | F   | 71  | Endometrial Ca (Fig. 3) | Nodule | LN, ovaries, peritoneum, liver, lung, Pa-Ln, CNS |
| 34   | F   | 83  | Melanoma   | Infiltration | Liver, lung, heart, CNS, gastrointestinal tract, adrenal, LN |
| 35   | M   | 56  | Leukaemia  | Infiltration | LN, liver, spleen |
| 36   | F   | 49  | Leukaemia  | Infiltration | LN, liver, spleen |

Ca: cancer, CRC: colorectal cancer, HCC: hepatocellular carcinoma, Chol Ca: cholangiocarcinoma, LN: lymph node, Pa-Ln: para-aortic lymph node, CNS: central nervous system
Figure 1. Metastasis of breast carcinoma in thyroid gland. Multifocal nests or sheets of tumor cells are distributed surrounded and between the follicles (as diffuse infiltration fashion), (H-E×200).

Figure 2. Intravascular B-cell lymphoma (angiotropic lymphoma): medium to large size atypical lymphoid cells in the vascular lumen within the parenchyma of the thyroid gland, (H-E×200).

Figure 3. Metastasis of high grade (undifferentiated) endometrioid endometrial adenocarcinoma, in thyroid gland in nodular fashion (upper right), (H-E×100). Inset microscopic characteristics of the tumor, with areas of high grade endometrioid endometrial carcinoma showing predominantly solid growth, with nuclear atypia. The nuclei are pleomorphic and hyperchromatic, (H-E×400).
the characteristics of patients in the present study.

**Pathological Features**

The lung was the most common primary site (n=12, 33.3%), followed by breast (n=3, 8.3%), kidney (n=3, 8.3%), and one case each of colon (2.78%), liver (2.78%), extrabiliary carcinoma (cholangiocarcinoma, 2.78%), pancreas (2.78%), endometrium (2.78%), and unknown origin (2.78%). The most common non-epithelial malignancy was lymphomas/leukemias (total of both 9 cases, 25%), and one skin melanoma (2.78%), as shown in Table 1.

Of the 36 metastatic tumours, there were 26 (72.2%) cases of primary carcinomas of epithelial origin, 18 (50%) were adenocarcinomas and 6 (16.7%) were squamous cell carcinomas, 1 (5.6%) was small cell carcinoma and 1 (5.6%) was large cell carcinoma. For adenocarcinomas, 1 (5.6%) was well-differentiated, 13 (72.2%) cases were moderately differentiated and 4 (22.2%) were poorly differentiated. On the other hand, squamous cell carcinoma consisted of 2 (33.3%) well differentiated, 3 (50%) moderately differentiated and 1 (16.7%) poorly differentiated (Table 2).

Metastases in both lobes and isthmus were noted in the majority of the patients, (n=29 cases, 80.6%); of the remained 7 cases (19.4%) unilateral involvement was more often in the right (n=5), compared with the left lobe (n=2). Morphological observation showed the formation of nodules in 12 (33.3%) cases, diffuse infiltration in 23 (68.89%), and one (2.78%) contiguous extension. The mean size of the metastatic nodular lesion was 2.2 cm. The mean weight of the thyroid gland was 60.17 g. In three cases the thyroid gland weighed more than 150 g.

### Table 2. Histological and immunohistochemical characteristics of secondary tumors of the thyroid gland

| Primaries | Number of cases (n) | % | Subtypes cases (n) | Immunohistochemistry |
|-----------|---------------------|---|-------------------|----------------------|
| Lung      | 12                  | 33.3 | Adenocarcinoma (6) | Tg (-), Ck7(+), CEA (+), TTF (+) |
|           |                     |     | Squamous cell (4)  | Tg (-), Ck 5/6 (+), p63 (+), TTF-1 (-) |
|           |                     |     | Large cell (1)     | Tg (-), CEA (-), NSE (+) |
|           |                     |     | Small cell (1)     | Tg (-), Chr (+), Ck20 (-), CEA (-) |
| Larynx    | 1                   | 2.78 | Squamous cell (1)  | Tg (-), Ck 18 (+) |
| Breast    | 3                   | 8.33 | Ductal (2)         | Tg (-), Her2 (+) |
|           |                     |     | Lobular (1)        | Tg (-), Her2 (+) |
| Kidney    | 3                   | 8.33 | Clear cell carcinoma (3) | Tg (-), CEA (+), WT1 (+) |
| Colorectal | 1                  | 2.78 | Adenocarcinoma (1) | Tg (-), CEA (+), Ck20 (+) |
| Pancreas  | 1                   | 2.78 | Acinar cell carcinoma (1) | Tg (-), CEA (+), CA19-9 (+) |
| Liver     | 1                   | 2.78 | Hepatocellular carcinoma (1) | Tg (-), AFP (+), TTF1 (-) |
| Bile duct Ca | 1                | 2.78 | Cholangiocarcinoma(1) | Tg (-), AFP (+), TTF1 (-), EMA (+), CEA (+) |
| Endometrium | 1              | 2.78 | Endometrial adenocarcinoma (1) | Tg (-), Ck18 (+), Ck19 (+), Ck8 (+) |
| Ovary     | 1                   | 2.78 | Mucinous adenocarcinoma (1) | Tg (-), CEA (+), Ck7 (+), Ck20 (-) |
| Unknown  | 1                   | 2.78 | Squamous cell (1)  | Tg (-), CEA (+), Ck5/6 (+) |
| Melanoma  | 1                   | 2.78 | Melanoma (1)       | Tg (-), HMB45 (+) |
| Lymphoma  | 6                   | 16.67 | Hodgkin (1)        | Tg (-), CD15 (+), CD30(+), CD40 (+) |
|           |                     |     | Small lymphocytic lymphoma (1) | Tg (-), CD5(+), CD23 (+), CD43(+) |
|           |                     |     | Diffuse large B-cell lymphoma (1) | Tg (-), CD23 (+), CD43(+) |
|           |                     |     | Peripheral T-cell lymphoma (1) | Tg (-), CD3(+) , CD45(+) |
|           |                     |     | Lymphoblastic lymphoma (1) | Tg (-), CD1 (+), CD3(+) , CD99(+) |
|           |                     |     | Angiotropic large cell lymphoma (1) | Tg (-), CD20 (+), CD45 (+) |
| Leukemia  | 3                   | 8.33 | Chronic lymphocytic leukaemia (B-cell) (2) | Tg (-), CD38(+)|
|           |                     |     | Chronic lymphocytic leukaemia (T-cell) (1) | Tg (-), CD3(+) , CD43(+) |

Tg: thyroglobulin mAb, Ck: cytokeratin, CEA: carcinoembryonic antigen, TTF-1: thyroid transcription factor 1, NSE: neuron specific enolase, Chr: chromogranin, EMA: epithelial membrane antigen, WT1: Wilms’ tumor gene, AFP: alpha feto-protein, (+): positive immunostaining, (-): no immunostaining
There were 14 (38.89%) cases in which thyroid metastases occurred in glands that were also otherwise abnormal. These pathologies included primary thyroid neoplasms and benign thyroid conditions (Table 3). We found 5 cases (35.71%) of metastases associated with multinodular goitre, 4 cases (28.57%) associated with papillary microcarcinomas and one case each with toxic multinodular goitre (7.14%), non-toxic benign nodule (7.14%), follicular adenoma (7.14%), Hashimoto’s thyroiditis (7.14%), and lymphocytic thyroiditis (7.14%).

The underlying cause of death in 47.22% (17 cases) of these 36 patients was directly related to malignancy. In the remaining 52.78% of the cases, the most common immediate cause of death was cardiovascular disease (24.99%). Deaths attributed to cardiovascular disease included such diagnoses as myocardial ischemia (11.11%), myocardial infarction (8.33%), and coronary thrombosis (5.55%). The second leading cause of death other than malignancy was pulmonary disease, including diagnoses of pulmonary embolism (8.33%), pneumonia (8.33%), diffuse alveolar damage / acute respiratory distress

### Table 3. Types of co-existing pathology in thyroid glands with metastases

| Coexisting thyroid disease | Number of cases | %      |
|---------------------------|-----------------|--------|
| Multinodular goitre       | 5               | 35.71  |
| Toxic goitre              | 1               | 7.14   |
| Simple thyroid nodule     | 1               | 7.14   |
| Hashimoto’s thyroiditis   | 1               | 7.14   |
| Lymphocytic thyroiditis   | 1               | 7.14   |
| Adenoma                   | 1               | 7.14   |
| Papillary microcarcinoma  | 4               | 28.57  |
| Total cases with metastasis | 14          | 38.89  |
| Total cases without metastasis | 22      | 61.11  |

### Table 4. Frequencies of metastases to thyroid gland in autopsy series

| Authors                        | Study years | Cases number | Thyroid metastasis (%) | Comments          |
|--------------------------------|-------------|--------------|-------------------------|-------------------|
| Willis5                        | 1923-1930   | 500          | 4.4                     | Cancer cases      |
| Kitain15                       | 1930        | 452          | 3.1                     | Cancer cases      |
| Muller15                       | 1930        | 623          | 1.8                     | Cancer cases      |
| Symmers15                      | 1932        | 298          | 2.3                     | Cancer cases      |
| Rice4                          | 1933        | 89           | 10.1                    | Cancer cases      |
| Abrams, et al16               | 1943-1947   | 1000         | 1.9                     | Unselected cases  |
| Hull12                         | 1952-1953   | 59           | 16.9                    | Cancer cases      |
| Mortensen, et al13            | 1951-1953   | 467          | 3.9                     | Cancer cases      |
| Thorpe31                       | 1953        | 200          | 2.0                     | Unselected cases  |
| Shimaoka, et al10             | 1955-1960   | 1980         | 9.5                     | Cancer cases      |
| Silverberg & Vidone15         | 1964-1965   | 62           | 24.2                    | Widespread malignancy |
| Berge & Lundberg17            | 1958-1969   | 7732         | 2.8                     | Unselected cases  |
| Briere & Dickinson29          | 1964        | 53           | 26.4                    | Cancer cases      |
| Fukunaga & Yatani24           | 1975        | 187          | 12.8                    | Unselected cases  |
| Watanabe & Tsuchiya6          | 1980        | 309          | 1.3                     | Cancer cases      |
| Takashima, et al18            | 1983        | 621          | 8.1                     | Unselected cases  |
| Ottino, et al22               | 1985-1986   | -            | 6                       | Unselected cases  |
| Komorowski, et al19           | 1988        | 138          | 1.4                     | Unselected cases  |
| Lang et al21                  | 1988        | 1020         | 3.4                     | Unselected cases  |
| Bisi, et al26                 | 1931-1989   | 145043       | 0.07                    | Unselected cases  |
| Furmanchuk, et al20           | 1990-1991   | 215          | 3.3                     | Unselected cases  |
| Pusel, et al11                | 1992        | 100          | 10                      | Unselected cases  |
| Autelitano, et al3            | 1992        | 507          | 26                      | Unselected cases  |
| Tiszlavicz & Varga23          | 1992        | 385          | 22.7                    | Unselected cases  |
| Lam and Lo30                  | 1951-1995   | 12955        | 0.5                     | Unselected cases  |
| Present study                 | 1998-2013   | 266          | 13.5                    | Cancer cases      |
syndrome (DAD/ARDS) (2.78%). Other causes of death included peritonitis (2.78%), cerebral stroke (2.78%), and injuries of car crash accident (2.78%).

DISCUSSION

The first document case of metastatic disease to the thyroid was reported by Willis and described by Foester in 1858. Willis suggested that the low incidence of the reported thyroid metastases was due to inadequate examination of the gland, and he found thyroid involvement in 9 out of 170 consecutive autopsies corresponding to an incidence of 5.2%. During the ensuing 80 years, many institutions evaluated their own patients; the reported incidences of thyroid metastases have revealed a wide range of findings and a lack of a clear unanimity (Table 4). Silverberg and Vidone approached the indefinable figure in perhaps the most scrupulous autopsy study on the subject, wherein they microscopically examined at least on slice of thyroid for every 5 g of tissue, and established thyroid involvement in 15 of 62 (24.2%) autopsy patients with metastatic neoplasms. More recent reports, Autelitano et al., Furmanchuk et al., Pusel et al., showed an incidence of 26%, 3.3%, and 10%, respectively. Because of the significant variance in the incidences of thyroid metastasis reported in these studies (0.5% to 24.2%), it is impossible at this time to establish the true incidence of metastasis to the thyroid. In our study, we identified 36 cases with secondary tumours of the thyroid gland out of the 266 cases of malignant tumours investigated. The incidence of metastasis at autopsy was 0.9% and the incidence among malignant tumours was 13.5%, in accordance with other studies. Possible explanations for the high percentage of metastasis to the thyroid in our study include the scrupulous examination of the thyroid gland (the examined gland was sectioned at 2-3 mm intervals), the study population, the geophysical characteristics of the region and the epidemiology of cancer. Our hospital serves mainly rural and indigent population and, on presentation, malignancies may be cloaked by other more acute problems. The majority of the cases in our study had extensive disease at autopsy. In clinical and surgical cases thyroid metastasis incidence varies from 0.05% to 3.1% and the most common primary cancer sites are the kidney, gastrointestinal cancer, breast, and lung (Table 5). An explanation of the different results obtained in autopsy and clinical-surgical series may be due to the fact that most lesions seen at autopsy were clinically untraceable and were found only because the examined gland was sectioned at 2-3 mm intervals, as in our cases.

Primary tumours that most frequently metastasize to the thyroid gland are the ones that most often give rise to bloodborne metastases, such as malignant melanoma, lung, breast, renal cancer, and less frequently, secondary lesions from pancreatic and gastrointestinal malignancies. Breast and lung carcinoma have been reported as the most frequently identified secondary thyroid carcinomas at autopsy, and in some clinical studies, while renal cell carcinoma as comprising over 50% of secondary malignancies discovered clinically. However, renal cell carcinoma was diagnosed in our series in 8.3% of the cases. In our study a high percentage of cancer metastasizes to the thyroid were from lung primary tumours (33.3%) and adenocarcinoma and squamous cell carcinoma are the main histological types, followed by breast cancer (8.3%), in agreement with other reports. The reason for these diverse results may be the different racial, geographic nature of the cohort, epidemiological prevalence of the primary cancer, and clinical behaviour and aggressiveness of primary cancer. The finding of the prevalence of lung cancer metastases to the thyroid in our study may be explained by the fact that the incidence of this tumour is increasing among women and men in Greece as compared to incidence rates in many other countries. Because of the aggressive nature of lung malignancies, patients are often treated with soothing intention from an early stage and therefore investigation for additional metastases is limited. In contrast, renal cell carcinoma is less aggressive, and patients are more likely to be further investigated and treated for metastatic disease. The insertion of lymphoma and leukaemia appears unsuitable in view of its multicentric nature, but it has been included in previous reviews and reports. In our series, we found 9 (25%) cases of thyroid infiltration by lymphoma and leukaemia, including angiotropic lymphoma, lymphoblastic lymphoma, Hodgkin lymphoma, small lymphocytic lymphoma, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, and chronic lymphocytic leukaemia, in agreement with other reports.

There has always been a strong female predominance in cases of differentiated thyroid cancer. A recent study using the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) database reported a clear difference in prevalence between men and women for differentiated thyroid...
Table 5. Frequencies of metastases to the thyroid gland in clinical series

| Authors          | Study years | Number of cases | Primary sites                          | Comments                  |
|------------------|-------------|-----------------|----------------------------------------|---------------------------|
| Elliot and Frantz | 1949-1958   | 14              | Breast, lung, kidney                   | Surgical cases            |
| Shimaoka, et al  | 1955-1960   | 10              | Melanoma, lung, breast                 | Surgical cases            |
| Wychulis, et al  | 1907-1962   | 14              | Kidney, breast                         | Surgical cases            |
| Harcourt-Webster | -           | 11              | Kidney, breast, melanoma               | Surgical cases            |
| Brady, et al     | 1960-1975   | 14              | Lung, lymphoid tissue                  | -                         |
| Pillay et al     | 1976-1976   | 7               | Esophagus, kidney, breast              | Needle core biopsy        |
| Shimaoka, et al  | 1955-1960   | 10              | Melanoma, lung, breast                 | Surgical cases            |
| Wychulis, et al  | 1907-1962   | 14              | Kidney, breast                         | Surgical cases            |
| Harcourt-Webster | -           | 11              | Kidney, breast, melanoma               | Surgical cases            |
| Shimaoka, et al  | 1955-1960   | 10              | Melanoma, lung, breast                 | Surgical cases            |
| Wychulis, et al  | 1907-1962   | 14              | Kidney, breast                         | Surgical cases            |
| Harcourt-Webster | -           | 11              | Kidney, breast, melanoma               | Surgical cases            |
| Brady, et al     | 1960-1975   | 14              | Lung, lymphoid tissue                  | -                         |
| Pillay et al     | 1976-1976   | 7               | Esophagus, kidney, breast              | Needle core biopsy        |
| Ericson, et al   | 1970-1979   | 10              | Kidney melanoma                        | Surgical cases            |
| Czech, et al     | 1960-1980   | 12              | Kidney, breast, lung                   | Surgical cases            |
| Ivy              | 1966-1982   | 30              | Kidney, breast, lung                   | Surgical cases            |
| McCabe, et al    | 1962-1985   | 9               | Lung                                   | Surgical cases            |
| Chacho, et al    | 1978-1985   | 8               | Various                                | Diagnosed by FNA biopsy   |
| Smith, et al     | 1980-1985   | 15              | Breast, lung, kidney                   | Diagnosed by FNA biopsy   |
| Watts            | 1983-1984   | 4               | Various                                | Diagnosed by FNA biopsy   |
| Michelow & Leiman| 1986-1992   | 21              | Lung, stomach                          | Diagnosed by FNA biopsy   |
| Rosen, et al     | 1978-1993   | 11              | Various                                | Surgical cases            |
| Nakhjavani, et al| 1985-1994   | 43              | Breast, kidney, lung                   | Diagnosed by FNA biopsy   |
| Giardini, et al  | 1993        | 40              | Various                                | Surgical cases            |
| Chen, et al      | 1986-1994   | 10              | Kidney                                 | Diagnosed by FNA biopsy   |
| Lin, et al       | 1977-1995   | 14              | Various                                | Diagnosed by FNA biopsy   |
| Lam & Lo         | 1971-1996   | 18              | Various                                | Surgical or biopsy proven cases |
| De Ridder, et al | 1982-2002   | 6               | Kidney                                 | Diagnosed by FNA biopsy   |
| Miralieu, et al  | 1982-2002   | 29              | Kidney, lung colon                     | Surgical cases            |
| Wood, et al      | 1985-2002   | 15              | Kidney                                 | Diagnosed by FNA biopsy   |
| Cichon, et al    | 1984-2003   | 17              | Kidney, breast, uterine               | Surgical cases            |
| Papi, et al      | 1993-2003   | 36              | Lung, esophagus, breast                | Diagnosed by FNA biopsy   |
| Kim, et al       | 1997-2004   | 22              | Breast, lung, colon                    | Diagnosed by FNA biopsy   |
| Lee, et al       | 1993-2013   | 5               | Kidney, lung, melanoma                 | Diagnosed by FNA biopsy   |
| Gerges, et al    | 1989-2004   | 7               | Various                                | Surgical cases            |
| Calzolari, et al | 1995-2005   | 25              | Kidney, lung, colon                    | Surgical cases            |
| Hegerova, et al  | 1980-2010   | 97              | Kidney, lung, head& neck               | Diagnosed by FNA biopsy   |
| Moghaddam, et al | 1993-2013   | 6               | Various                                | Diagnosed by FNA biopsy   |

FNA: fine needle aspiration

However, it remains unclear whether or not there is any sex predominance for metastases to the thyroid gland.\(^{42}\) One study found no female predominance and postulated that this depicts the pathogenic role of equivalence and estrogen on primary thyroid malignancy, whereas for secondary malignancy this is not the case.\(^{9}\) In contrast, another study in fact observed a male predominance of 3.6:1.\(^{7}\) Others have noted female predominance of metastasis to the thyroid, some reporting ratios of 1.4:1.\(^{42}\) In our report, we noted a slightly higher percentage of male cases (52.78%) compared to...
female (47.22%) cases of metastases to the thyroid gland, a ratio 1:1:1, in accordance with a previous report.30 One possible explanation for the slight increased incidence in men in our study may be related to the high frequency of thyroid secondaries from lung primaries and lymphoproliferative diseases in males.

Metastatic disease involving the thyroid is observed in the elderly individuals, in their sixth and seventh decades of life. In the present analyzed group of patients the mean age was 70.4 years, being thus analogous reported in the literature.3,13,29 The youngest male individual of our series was 37 years old, with lymphoblastic lymphoma (Table 1).

As mentioned before, the thyroid gland is an infrequent site of secondary malignancies, even though the gland has a rich vascular supply (560 mL/100 g tissue/min).5 Willis described 10 case-reports in the literature of metastatic cancer to a diseased gland and found that 9/21 of his own autopsy cases presented thyroid pathology including adenomatous goitre and chronic lymphocytic thyroiditis.5 In our study 14 (38.89%) cases of metastases to the thyroid gland occurred in glands with other pathologies such as primary thyroid neoplasms (papillary microcarcinoma 28.57% of cases) and benign thyroid conditions (multinodular goitre 35.71% of the cases) (Table 1). The frequent association of the metastatic deposits, both in this and other reports5,13,15,43 with benign and malignant conditions of the thyroid in which the oxygen tension and iodine content are probably reduced and the gland is probably enlarged, supports this conviction. This fact could additionally justify that the mean thyroid weight in the study group of the present study is twice as much as the mean weight of a healthy thyroid gland. In contrast with this theory, others have suggested that vascular deterioration by itself would not be sufficient to explain the metastatic disease, that the filtering system of the lungs would possibly remove most tumour emboli, and that there was no difference in frequency of metastasis in altered thyroid glands versus normal thyroid glands.43 Thus, there is no explanation for the long latent period between the identification of the primary tumour and the development of clinical thyroid metastases.44-46

The appearance of a nodule or goitre in the thyroid of a patient with extensive cancer presents a difficult diagnostic problem even at autopsy. Such lesions could be benign, could represent a metastasis from an original neoplasm and comprise evidence of dispersed disease, or could be a new primary cancer.13-15 In our series the presence of metastatic nodules was found in 12 (33.33%) cases (Table 1). A predominantly interstitial pattern of infiltration with metastasis was noted in 23 (63.89%) cases, resulting in folliculi being surrounded and misshapen by tumour but rarely infiltrated by it, unlike primary thyroid neoplasms. Most tumours involving the thyroid by direct extension are squamous cell carcinoma, e.g. larynx. In our study we found one of such tumours.

Although metastatic tumours generally retain the histological features of the primary tumours but are frequently less differentiated, the pathological diagnosis of metastases may be difficult. The most useful data in making the diagnosis of metastasis to the thyroid is the morphological assessment of hematoxylin and eosin-stained sections, particularly if sections of the primary tumour are available for comparison, as in our study. Primary thyroid neoplasms that can be misinterpreted as metastases are tumours with clear cell, mucinous or squamous cell changes. On the other hand columnar carcinoma of the lung, tubule-papillary adenocarcinoma of the lung, small cell carcinoma of the lung, clear cell carcinoma of the kidney, adenocarcinoma of the breast, and lymphoproliferative processes may be similar to thyroid gland neoplasm. In such occasions immunohistochemistry analysis will help to discriminate between primary and metastatic malignancies; primary thyroid follicular tumours will usually present with thyroglobulin immunoreactivity, CK7, and TTF-1 (Table 2).47,48 Using an immunohistochemical stain for anti-thyroglobulin marker to demonstrate if the tumour is primary or secondary may not be wholly definitive. This marker is usually positive in primary thyroid neoplasms and negative in metastases, however entrap of normal thyroid follicles by secondary tumour cells, which may then stain positively (false positive immunoreaction). As shown in Table 2, specific immunopanels could be helpful in cases of misgivings.

Metastatic thyroid cancer may be more common than primary thyroid malignancy especially in patients who have medical history of cancer.26 The most common primary sites, as mentioned, was the lung, kidney, breast, gastrointestinal and ovary/endometrial cancer. However, a wide variety of rare neoplasms may metastasize to the thyroid including choriocarcinoma49, nasopharyngeal carcinoma50, leiomyosarcoma51, liposarcoma52, malignant fibrous
histiocytoma\textsuperscript{53}, malignant adenomyoepithelioma of the breast\textsuperscript{44}, adrenocortical carcinoma\textsuperscript{46}, esophagus adenocarcinoma\textsuperscript{44}, alveolar rhabdomyosarcoma\textsuperscript{55}, neuroendocrine tumors\textsuperscript{56}, and mesenchymal chondrosarcoma\textsuperscript{57}.

Metastatic disease of the thyroid is overall regarded an ominous finding. Most authors concur that surgical treatment is warranted in the absence of extensive metastatic disease or for moderation of local symptoms. Survival after surgical treatment has been variable with some patients succumbing to metastatic disease in just a few months, while others have had long-term survival. Patients with secondary carcinoma of the thyroid from a lung primary have a particularly poor prognosis with most patients dying within months of metastatic disease\textsuperscript{27-30,58,59}.

**CONCLUSION**

In conclusion, thyroid secondary malignancies are not infrequent, and may constitute a diagnostic problem, even at post-mortem examination. Immunohistochemistry is a useful method for improving the precision of diagnosis. Lung cancer constitutes the most common neoplasm that metastasizes to the thyroid gland following by breast carcinoma and renal carcinoma in north-western Greek population. The clinicians must keep in mind that in patients with a known or unknown history of malignant disease, the finding of a new thyroid mass should be rapidly evaluated, in search for metastatic disease.

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Цель: Вторичные злокачественные новообразования щитовидной железы редко диагностируются, но их обнаружение при вскрытии не является редкостью.

Материалы и методы: Для изучения клинико-патологических характеристик пациентов с метастатическими опухолями щитовидной железы мы рассмотрели протоколы вскрытий и патологические особенности 36 случаев метастазов щитовидной железы из 266 случаев злокачественных новообразований (исключая случаи первичного рака щитовидной железы) в течение на 16 лет.

Результаты: В исследовании приняли участие 19 мужчин и 17 женщин в возрасте от 37 до 95 лет (в среднем 70.4 года). Метастазирование щитовидной железы составило 0.9% всех случаев вскрытия и 13.53% злокачественных опухолей. Подавляющее большинство были эпителиальные карциномы. Лёгкие были наиболее распространённым местом первичной опухоли (33.3%), затем следовали молочная железа (8.33%) и почки (8.33%). Наиболее распространённой неэпителиальной злокачественной опухолью была лимфома, за которой следовала лейкемия (в общей сложности 25%). Что касается микроскопических морфологических наблюдений, характер рассеянной инфильтрации наблюдался в 63.89% случаев, узловое образование - в 33.33% случаях и инвазия в соседние ткани - в 2.79% случаев. 35.71% случаев метастазирования были связаны с многоузловым зобом и 28.57% случаев с папillary микрокарциномой.

Заключение: Наше исследование показывает, что вторичные злокачественные опухоли щитовидной железы не являются редкостью и могут быть диагностической проблемой. Рак лёгких является наиболее распространённым новообразованием, которое метастазирует в щитовидную железу среди населения северо-западной Греции.