Introduction

Metastasis to the thyroid gland (MTG) is rarely diagnosed clinically but the incidence of MTG at autopsy is not rare [1-8] (Table 1). Although the incidence of MTG at autopsy in unselected populations is low (0.5~2.8%), the incidence in populations with known primary cancers is reported to be much higher (3.9~24.2%). The most frequent primary sites are breast and lung.

The number of clinical cases with MTG has been gradually increasing [9-12], probably because of the development of various diagnostic techniques, including computed tomography (CT), F-18-fluorodeoxyglucose positron emission tomography (FDG-PET), [13] and fine needle aspiration biopsy (FNAB). [12]

The treatment of MTG is controversial because the prognosis of these cases is basically poor, depending on the primary sites. Thyroidectomy for these patients is relatively invasive, and may not be effective in prolonging of survival time: however it may help preserve quality of life (QOL) in some circumstances because extension of MTG to surrounding tissues such as the trachea, esophagus, recurrent laryngeal nerve, or the larynx tends to worsen QOL. The decision to perform thyroidectomy may depend on the condition and needs of the individual

patient. The aims of this current report are to assess the clinical characteristics of MTG, and the role of thyroidectomy. We reviewed the charts of our patients with MTG who previously underwent thyroidectomy, and performed a literature review.

Methods

Patients who underwent thyroidectomy between 1988 and 2008 for MTG at the Kyoto University Hospital Department of Otolaryngology-Head and Neck Surgery were chart-reviewed. Patients with lymphoma or with tumors that directly invaded the thyroid from adjacent organs were excluded. Ultrasonography (US), CT, and FDG-PET were the preoperative imaging studies used for diagnosis. Cytological and histological diagnostic examinations were performed on biopsies from every patient. Metastatic cancer in the thyroid gland was confirmed by histological comparison of the thyroid specimen with the primary tumor. Immunohistochemistry of both primary and thyroid tumors was also performed if required. This study was approved by ethic committee of Kyoto University.

Results

Patient Demographics

Thyroidectomy was performed in 970 patients with malignant tumors of the thyroid.

Four patients (1 male and 3 female) were diagnosed with MTG. Their ages ranged from 48 to 69

years (median, 60 years) (Table 2). The incidence of MTG in thyroid malignancies was 0.4%.

Each of the 4 patients had a different primary tumor, which included lung, liver, breast,

and colon cancers, and each patient had undergone surgical resection and/or chemotherapy for

the primary tumor before detection of MTG.

Clinical presentation of metastasis to the thyroid gland

Three of 4 patients were asymptomatic, and their MTGs were incidentally detected by

follow-up FDG-PET or CT. None of the patients had thyroid tumor calcifications detected by US.

One patient (case 3) presented with rapidly-growing thyroid nodules and skin redness involving

the neck to the left precordial region because of invasive breast cancer in the left breast. The

patient received steroid therapy for 1 week to prevent edema of the larynx but she gradually

complained of dysphagia and dyspnea.

The time to detection of MTG after primary tumor diagnosis ranged from 1 to 3 years.

All patients had concurrent nodal and distant metastases (lung or brain).

Fine needle aspiration biopsies (FNABs) were used for diagnoses, which indicated adenocarcinoma in all cases: however it was difficult to definitively differentiate metastatic cancers from primary thyroid cancers. In 3 cases the diagnoses were further confirmed by postoperative immunohistochemistry.

Treatment and prognosis

Three patients underwent total thyroidectomy, and 1 patient (case 4) underwent subtotal thyroidectomy. There were no major postoperative complications observed, such as recurrent laryngeal nerve paralysis, hematoma, or respiratory distress.

Three patients died from their primary disease 3 to 23 months after thyroidectomy, with a median survival time of 10 months. No patient developed cervical recurrences or respiratory symptoms. One patient (case 1 with lung cancer) has survived tumor-free for 1 year after thryoidectomy. She was treated with chemotherapy after thyroidectomy for intrapulmonary metastasis with complete resolution of the lung metastasis.

Representative case presentation (case 1)

A 67-year-old woman underwent left upper lobectomy by video-assisted thoracoscopic surgery (VATS) for lung carcinoma. The pathologic diagnosis was adenocarcinoma with mixed subtypes (acinar and papillary), and was staged pT2N0M0. Two years later, a follow-up FDG-PET scan detected hypermetabolic lesions in the right lobe of the thyroid gland, as well as in the right upper lobe of the lung (Figure 1). The patient had no symptoms caused by the thyroid tumor. Physical examination revealed a hard 1 × 1 cm in the right lobe of the thyroid gland. Her regional cervical lymph nodes were not palpable. US and CT revealed a tumor without calcification in the right lobe of the thyroid gland (Figure 2A), and chest CT revealed 1 nodule in the right upper lobe of the lung without apparent lymphadenopathy, which corresponded to the same region of the FDG-PET findings (Figure 2B). Laboratory data revealed a serum carcinoembryonic antigen (CEA) of 1.3 ng/ml (normal range, 0-5.0). Free triiodothyronine (FT3) was 2.8 pg/ml (normal range, 2.3-4.0), and free thyroxine (FT4) was 1.04 ng/dl (normal range, 0.8-1.6). Thyroid stimulating hormone (TSH) was 10.8 IU/ml (normal range, 0.5-5.0) and thyroglobulin was 42.4 ng/ml (normal range, 0-45). FNAB cytology of the thyroid tumor revealed adenocarcinoma with papillary structure, which was suspicious for primary

thyroid tumor or lung cancer metastasis.

After consultation with the thoracic surgeon, a total thyroidectomy was performed.

Histology of the thyroid tumor showed papillary structures (Figure 3A). Immunohistochemically,

the tumor cells were negative for thyroglobulin (Figure 3B) and positive for cytokeratin 19 (CK19)

(Figure 3C), and the thyroid tumor was diagnosed as a lung cancer metastasis.

Postoperatively, the patient was treated with gefitinib with good response. The lung

nodule disappeared on follow-up CT, and the patient is alive without disease for one year after

thyroidectomy.

Discussion

The incidence of MTG has been thought to be very low. According to the report of

Wychulis et al., [9] there were 10 cases with MTG out of 20,262 patients (0.05%) who underwent

operation on the thyroid. The current case series also demonstrates a 0.4% incidence of MTG

among patients undergoing thyroidectomy in our department over 20 years for a diagnosis of

malignant thyroid tumor. According to the reports from Mayo clinic [9-12], however, the number of

MTG cases has been gradually increasing. It is suggested that the recent development of

diagnostic techniques such as CT, FDG-PET, [13] or FNAB [12] may improve the ability to detect

MTG.

The most frequent sites of primary malignancies metastatic to the thyroid are reported

to be kidney, followed by breast and lung (Table 3). [9-12,14-18] Nakhjavani et al. [15] reported the

frequency of kidney, lung, and breast primaries as 33%, 16%, and 16%, respectively. Our study

also detected lung and breast cancers as the origin of metastasis in 1 patient each in addition to

colon and liver cancer metastases.

Metastasis to the thyroid gland is a clinical diagnostic problem. The reasons for this

are thought to be as follows [8]: (1) most patients are asymptomatic: (2) the sizes of the lesions are

small in most cases: (3) a small sample size by FNAB makes a definitive pathologic diagnosis

difficult: (4) the time to detection is long in some cases: and (5) the metastatic lesion is solitary in

most cases. These reasons make differentiation from the primary thyroid tumor difficult.

A malignant thyroid tumor is thought to be much more likely to be metastatic than

primary in patients with a history of cancer. [5] It has been reported that an interval of 15 years

elapsed from the diagnosis renal cell carcinoma to the detection of thyroid metastasis. [17] In our

series, the time to detection ranged from 1 to 3 years. Therefore, it is important to include

metastasis to the thyroid gland in the differential diagnosis when a thyroid tumor is found in a

patient with a history of cancer.

It has been reported that a palpable thyroid nodule was found in 72% of patients with

MTG. [18] The other 28% of patients were asymptomatic and a thyroid mass was incidentally

detected by various imaging studies. However, as seen in case 3 in our series, there are some

patients who complain of a rapidly-growing mass in the neck, dysphagia, or hoarseness. In these

patients it is necessary to distinguish MTG from anaplastic thyroid tumors.

US, CT, FDG-PET, and tumor markers specific to the primary tumor are useful

diagnostic tools for early detection of MTG. Clinically FDG-PET has been frequently used for

detection of recurrent cancer. In some cases, MTG is occult, and FDG-PET should be a useful

imaging modality for these patients. Indeed, in case 1 we incidentally detected a thyroid tumor by

FDG-PET.

FNAB is also useful for the diagnosis. [12] We suspected MTG from the findings of

FNAB in all the patients of this present series, but the diagnosis was not definitive. It is relatively

difficult to accurately diagnose MTG by FNAB only, and it has been reported that the accuracy

rate of FNAB for MTG was only 50%, although the percent of cases positive for malignancy was

90%. [14] Immunohistochemistry is a useful method for improving the accuracy of diagnosis,

because metastasis to the thyroid gland can be distinguished from primary thyroid tumor by

immunohistochemical demonstration of thyroglobulin. [19] However, 70~80% of anaplastic thyroid

tumors are negative for thyroglobulin. [20]

Although thyroidectomy for MTG is recommended by some authors, [14-16] there is no

clear consensus for therapy. One reason for this may be because the recommendations were

based on case reports or uncontrolled studies. In a controlled study, [18] thyroidectomy was useful

in preventing further dissemination of the primary tumor in patients whose metastases were

limited only to the thyroid, although it did not contribute to prolonged survival. In addition,

metastasis to the thyroid gland does not always mean poor prognosis, which depends on the

dissemination and advanced stage of the primary tumor. In our series, thyroidectomy was

performed for all of the MTG patients in order to prevent difficulty in respiration and/or swallowing.

Although survival after thyroidectomy was poor in 3 of 4 cases, thyroidectomy was thought to

contribute to maintaining QOL in respect to respiratory and swallowing functions. In addition one

patient with lung cancer MTG remains alive without disease after thyroidectomy followed by

chemotherapy.

In conclusion, it is still difficult to determine which patient with MTG is a good candidate for thyroidectomy, but we suggest that patients complaining of dysphagia or dyspnea, or those at high risk for developing respiratory distress in the near future, should undergo thyroidectomy.

Acknowledgement

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Figure legends

Figure 1. Case 1. F-18-fluorodexoxyglucose positron emission tomography scan.

Hypermetabolic lesions are seen in the neck (black arrow), and in the right lung (white arrow).

Figure 2. Case1. Computed tomography scan showing tumor lesion in the right lobe of the

thyroid (A, black arrow), as well as a tumor in the right upper lobe of the lung (B, black arrow).
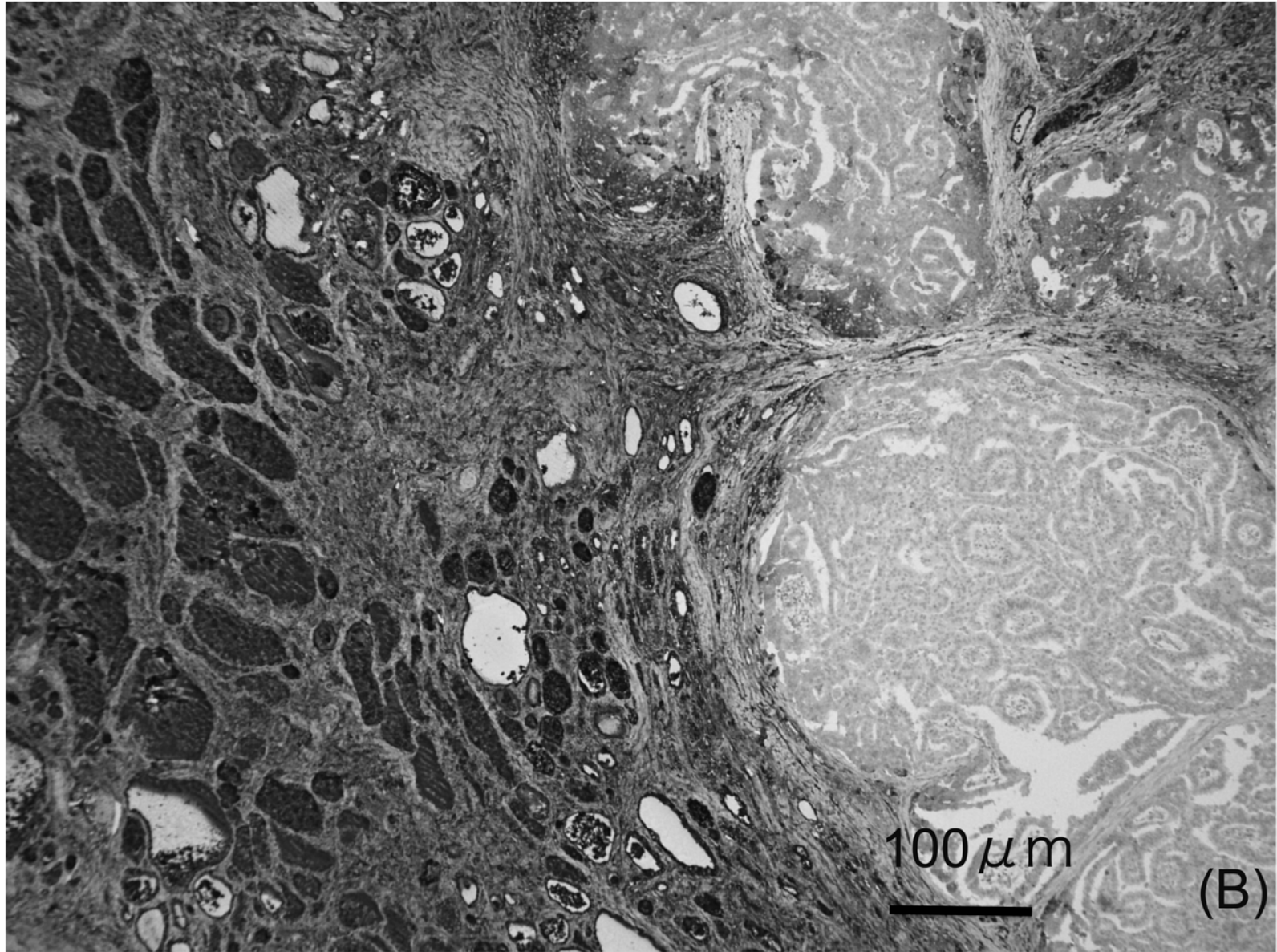
Figure 3. Histological findings of the thyroid tumor show (A) carcinoma with papillary structures

(hematoxylin and eosin staining, ×40). (B) Immunohistochemistry shows negative for

thyroglobulin in tumor cells while positive for normal thyroid tissue (×40). (C) Tumor cells are

positive for cytokeratin 19 (×40) (black arrow).

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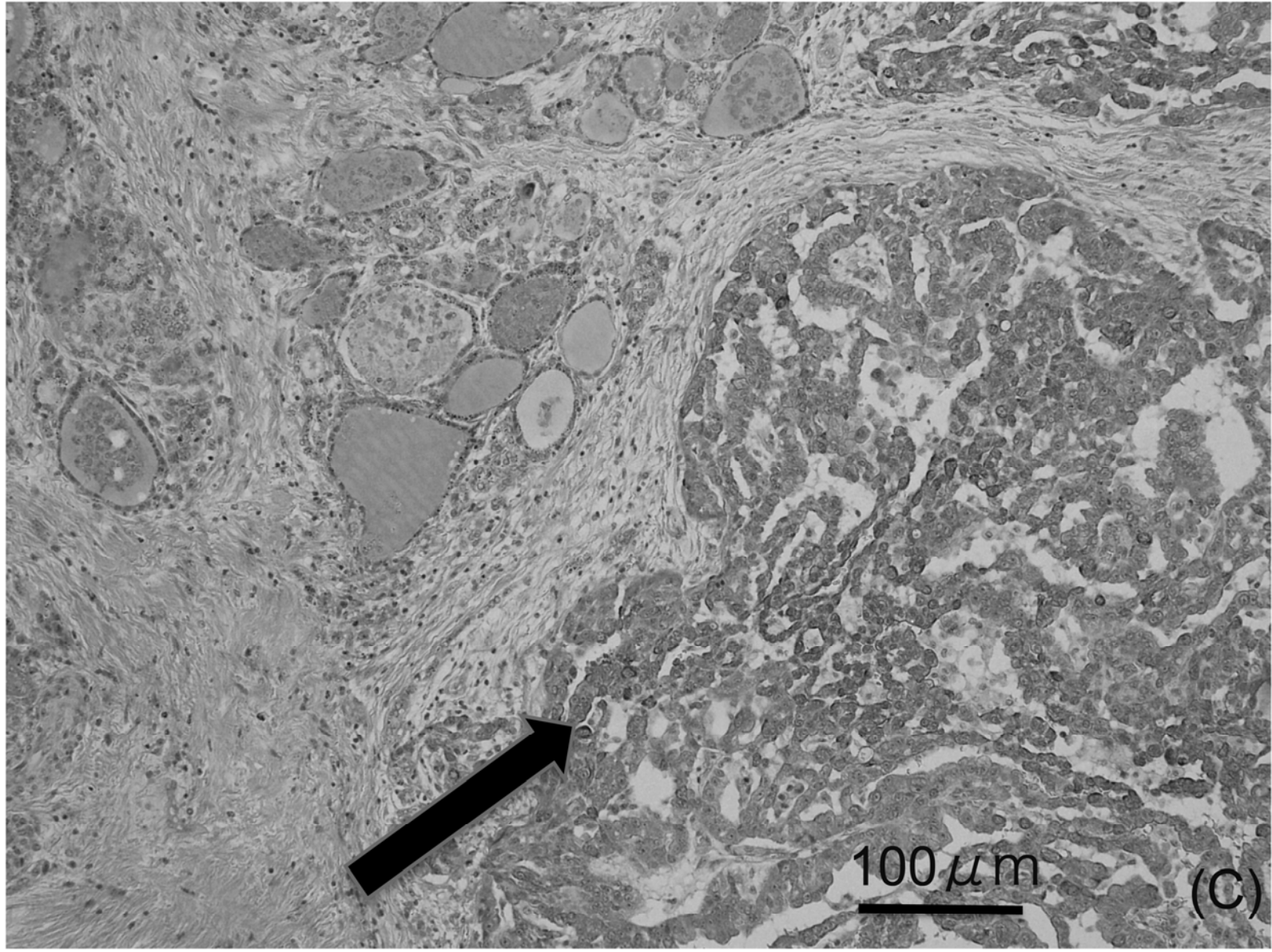
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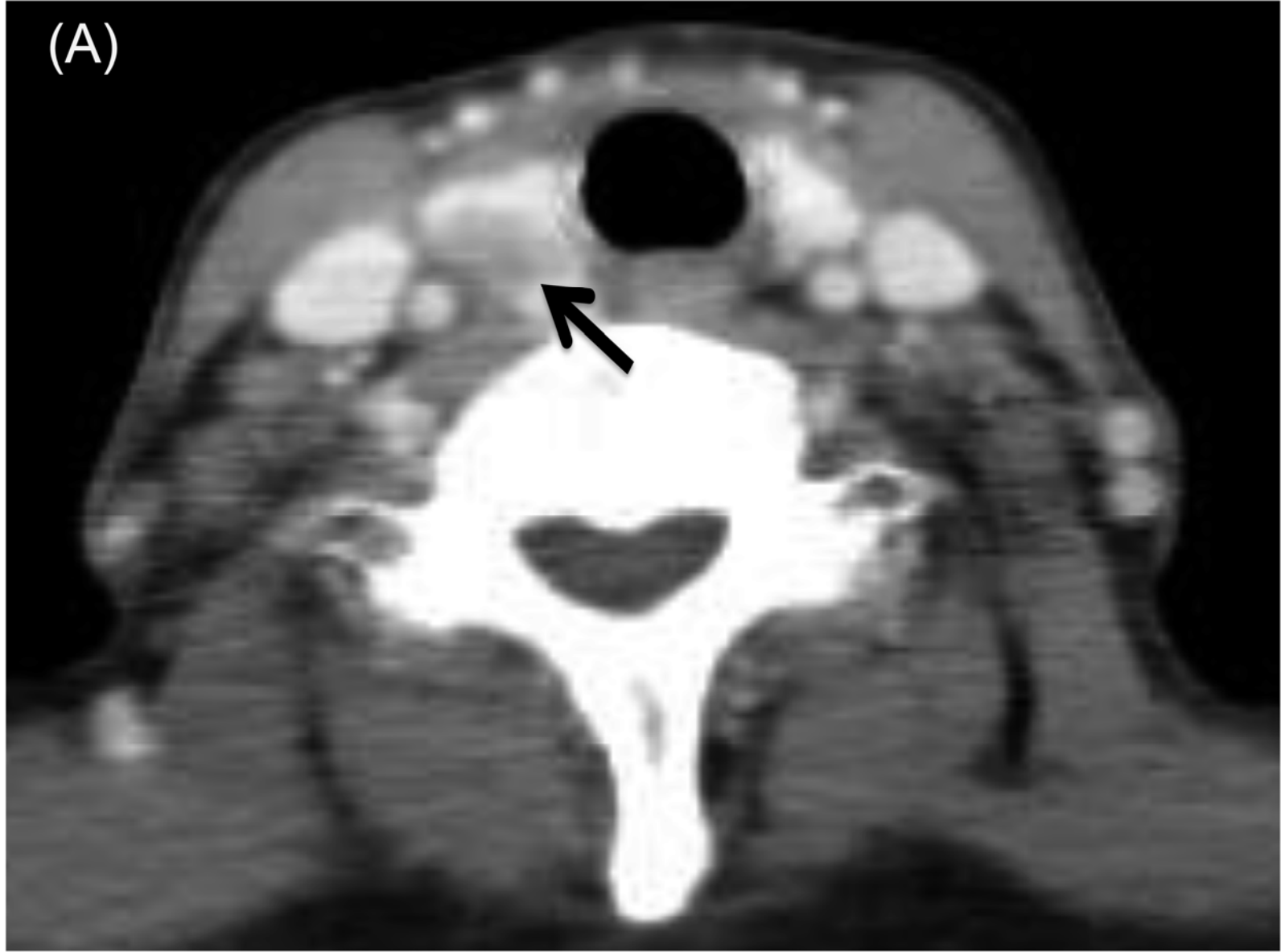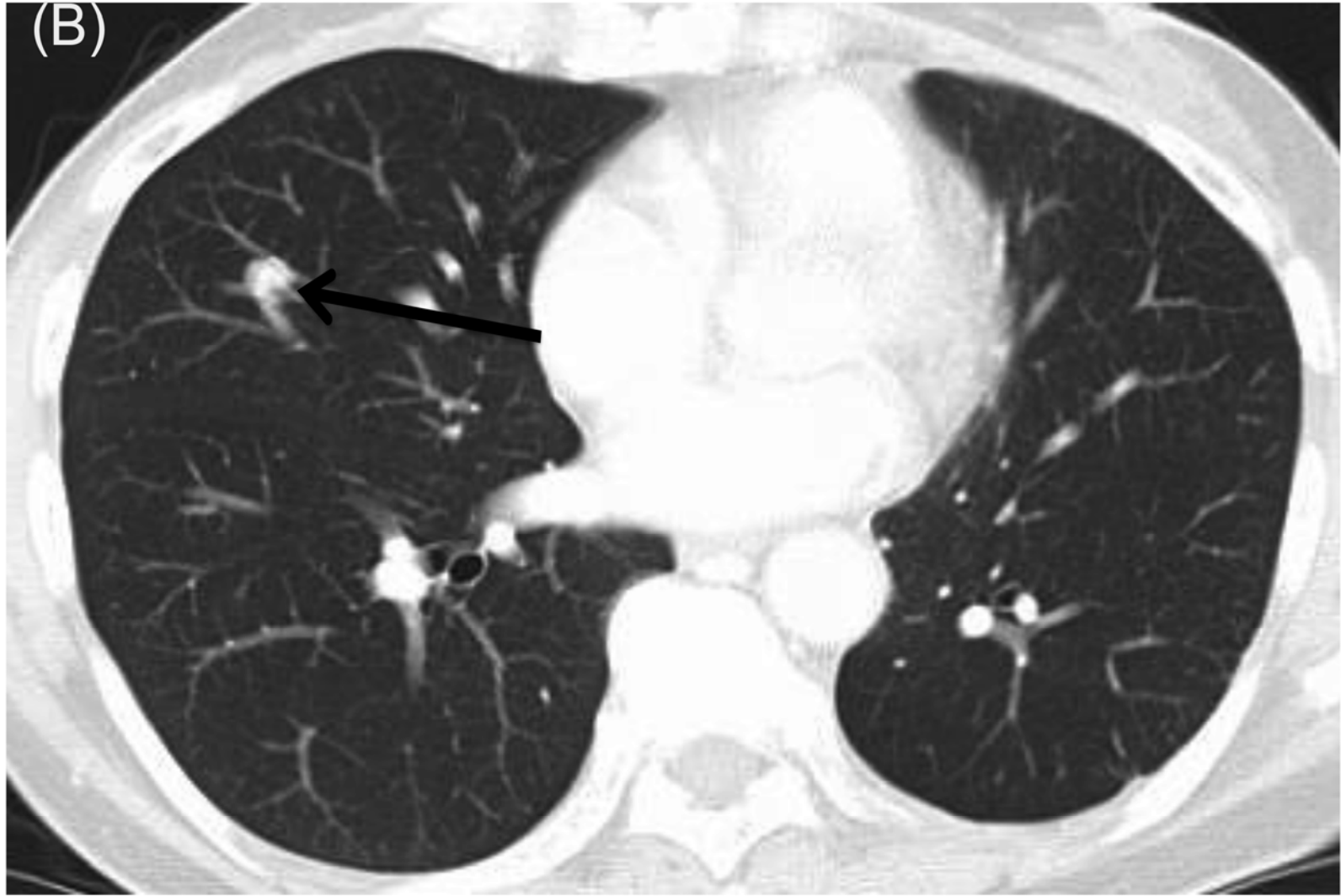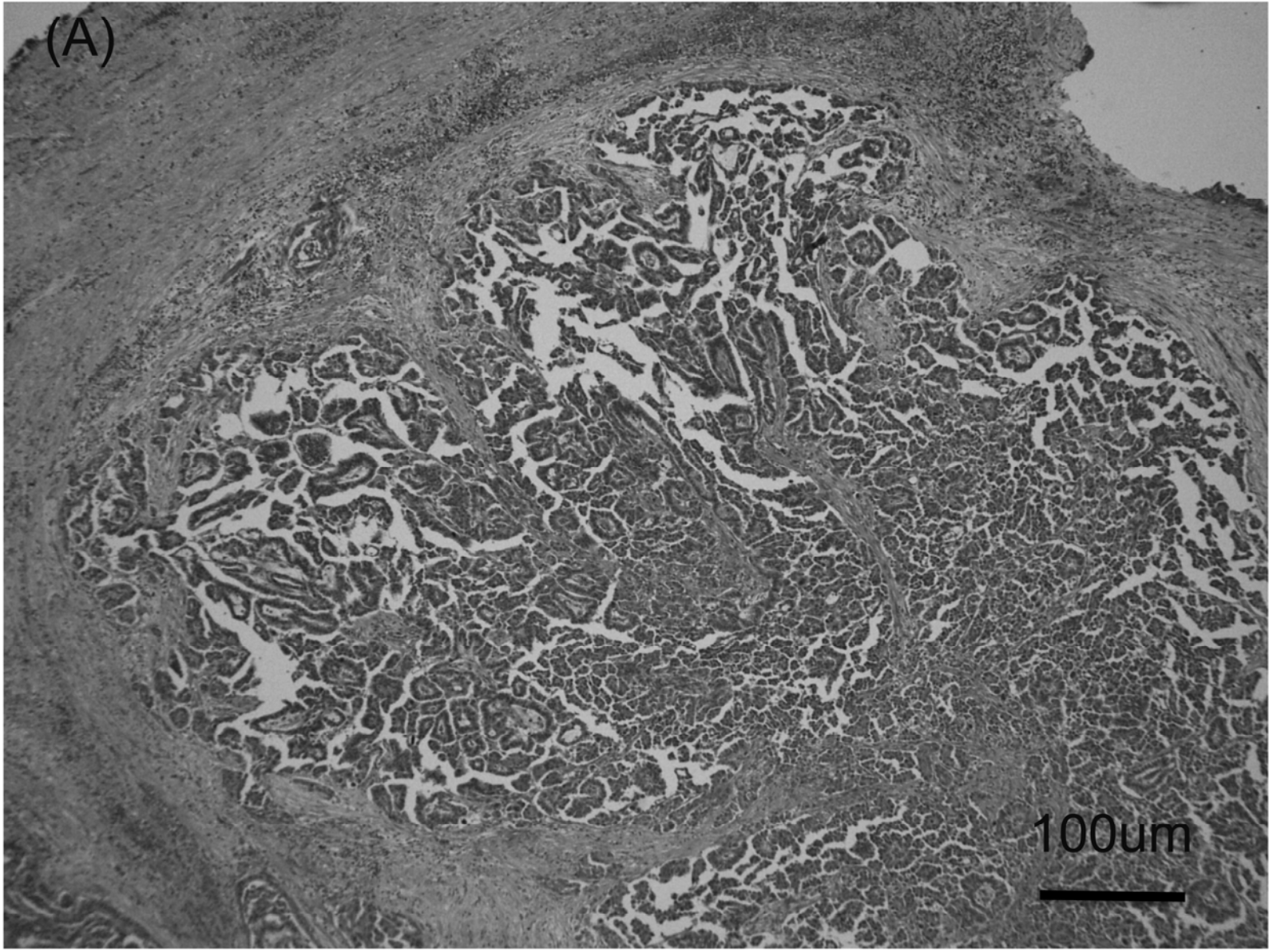
Table 1. Incidence of metastases to thyroid gland in autopsy series

Authors	Study years	No. of cases	Thyroid metastasis (%)	Common primary sites of metastasis	Comments
Rice[1]	1933	89	10.1	Uncertain	Known primary cancer
Abrams et al.[2]	1943~1947	1000	1.9	Breast, lung	Unselected case
Hull[3]	1952~1953	59	16.9	Lymphoid tissue	Known primary cancer
Mortensen et al.[4]	1951~1953	467	3.9	Lymphoid tissue, lung, breast	Known primary cancer
Shimaoka et al.[5]	1955~1960	1980	9.5	Breast, Lymphoid tisse, lung	Known primary cancer
Silverman and Vidone[6]	1964~1965	62	24.2	Lung, breast, lymphoid tissue	Widespread malignancy
Berge and Lundberg[7]	1958~1969	7732	2.8	Breast, lung, kidney	Unselected case
Lam and Lo[8]	1971~1995	12955	0.5	Lung, stomach, breast,	Unselected case

Table 2. Characteristic of patients with metastasis to the thyroid gland in current series

Case	Age	Gender	Primary tumor site	Clinical presentation of thyroid metastasis	Time to detection of thyroid metastasis (years)	Metastases elsewhere	cytological findings	Immunohistochemistry	Treatment	Prognosis (months)
1	69	Female	Lung	FDG-PET	1	Lung	Adenocaricinoma with papillary structure	thyroglobulin (−) CK19 (+)	Total thyroidectomy	12 Alive
2	63	Male	Liver	Neck CT	1	Lymph node	Adenocarcinoma	TTF-1 (−) AFP (2+) thyroglobulin (−) HepPar1 (focally 2+)	Total thyroidectomy	23
3	48	Female	Breast	dysphagia dyspnea	1	Lymph node Lt precordial skin	Adenocarcinoma	Estrogen-Receptor（−） Progesterone-Receptor（−） HER-2（3+）	Total thyroidectomy	6
4	60	Female	Colon	Neck CT	3	Brain Lung	Adenocarcinoma	no use	Subtotal thyroidectomy	3

Table 3. Incidence of metastases to thyroid gland in clinical series.

Authors	Study years	No. of cases	Common primary sites of metastasis	Comments
Wychulis et al.[9]	1907~1962	14	Kidney, breast	Surgical cases
Czech et al.[10]	1960~1980	12	Kidney, breast, lung	Surgical cases
Ivy[11]	1946~1982	30	Kidney, breast, lung	Surgical cases
Smith et al.[12]	1980~1985	15	Breast, lung, kidney	Diagnosed by FNAB
Rosen et al.[14]	1978~1993	11	Various origin	Surgical cases
Nakhjavani et al.[15]	1985~1994	39	Breast, kidney, lung	Majority diagnosed by FNAB
Chen et al.[16]	1986~1994	10	Kidney	Surgical cases
Kim et al.[17]	1997~2003	22	Breast, lung, colon, kidney	Diagnosed by FNAB
Papi et al.[18]	1993~2003	36	Lung, kidney, oesophagus	Surgical cases and diagnosed by FNAB