Management of metastases to the thyroid gland

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Abstract: The thyroid gland is rarely the site of metastatic disease because the vascularization, high oxygenation and high iodine of arterial blood content in the thyroid gland inhibit the growth of cancer cells. The incidence of the metastases depends on the type of primary tumor. Metastases to the thyroid gland account for 1.5–3% (approximately 2%) of all malignancies, with their autopsy-confirmed incidence rate ranging from 1.25% to 24.2%. Clinical material predominantly demonstrates metachronous metastases of clear cell carcinoma of the kidney, autopsy results show a predominance of metastases of the lung, colon and breast cancers. Metastases to the thyroid gland are most commonly unifocal metachronous tumors. Multifocal synchronous tumors are associated with a considerably poorer prognosis. The diagnostic method of choice is ultrasound-guided fine needle aspiration biopsy (FNAB) combined with immunohistochemically tests. Total thyroidectomy allows for a thorough evaluation of local tumor grade and is an important factor in oncological radicality of the surgical procedure. The role of multidisciplinary team is essential because balancing between the features of the primary tumor, status of the health (patient's comorbidities), age of the patient, clinical grade, histological structure and profile of metastases at the time of diagnosis are important factors influencing individualized survival rate.

Keywords: Metastases to thyroid gland; surgical management; thyroidectomy

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Introduction

Documented metastases of testicular cancer and posterior pharynx wall cancer to the thyroid gland demonstrating lesions resulting from multinodular goiter were described for the first time by Rudolf Virchow in 1871 in a 53-year old male and a 65-year old female. Metastases to the thyroid gland, despite its rich vasculature, are relatively rare. Most commonly they represent distant metastases spreading along blood vessels from other organs (the lung, mammary gland, colon, stomach, pancreas or ovary). Sporadically, apart from the phenomenon of infiltration itself, they may be a consequence of metastasizing tumors involving neighboring organs, such as the pharynx, larynx, trachea or esophagus in patients with squamous cell carcinomas. Metastases from a primary tumor involving another organ to already existing lesions in the thyroid gland, e.g., to adenomas (tumor to tumor metastasis) are also highly uncommon. As it has been mentioned, in spite of rich vasculature, a metastatic focus rarely develops in the thyroid gland. As demonstrated by data from the literature on the subject, metastases to the thyroid gland account for 1.5–3% (approximately 2%) of all malignancies, with their autopsy-confirmed incidence rate ranging from 1.25% to 24.2%, being related both to blood-
associated cancer spread from a distant focus and the afore-
mentioned thyroid invasion by a neighboring neoplastic
process. It is difficult to unambiguously determine the
pathophysiological foundations of the phenomenon;
nevertheless, among the oldest hypotheses, two are stressed
in particular:

- In view of the markedly high blood flow rate within
  the thyroid (in euthyreosis, the average rate is
  approximately 8 mL/100 g of tissue/sec., thus, the
  thyroid gland is one of the human organs with the
  best blood supply), cancer cells lose their adherence
  ability and ability to be subsequently implanted in
  the parenchyma of the gland;
- High oxygenation of arterial blood and high iodine
  content in the thyroid gland additionally inhibit the
  growth of cancer cells (1-8).

Clinical material predominantly demonstrates
metachronous metastases of clear cell carcinoma of the
kidney, which constitute a considerable majority of
metastases to the thyroid gland. Only some of them are
manifested by nodular lesions detected by palpation.
Autopsy results show a predominance of metastases of the
bronchus and mammary gland carcinomas which are rarely
clinically manifested, mostly due to the rapid progress of
the primary neoplastic disease. Since the decidedly most
common route of neoplastic process spreading to the
thyroid gland is the blood vessels, concomitant thyroid
pathologies, such as multinodular lesions, isolated adenomas
and thyroid fibrosis may constitute factors predisposing
to occurrence of metastases, mostly due to a decelerated
blood flow and decreased partial oxygen pressure in the
microcirculatory system. Metastatic lesions are detected
statistically more frequently in the female population (1.4:1)
in the sixth and seventh decade of life. Metachronous
metastases are most commonly single lesions (76%), but
unfortunately they are very often concomitant with other
primary focus metastases to other locations in the organism
(79%) (9-12).

Diagnosis

Metastatic lesions to the thyroid gland may be preliminarily
diagnosed based on conscientiously taken medical history
aiming at obtaining information on past neoplastic diseases
or current anti-cancer treatment. The majority of nodular
lesions within the thyroid gland, especially when small in
size, do not produce clinical symptoms, and detecting the
focus is often incidental, happening in the course of routine
ultrasonography in diagnostic examinations of the cervical
vessels or ultrasound breast examination. Enlarged neck
circumference with signs of constriction, a fast growing
unilateral tumor, symptoms of hoarseness, problems with
swallowing and breathing represent late symptoms of
thyroid diseases, most commonly associated with a poor
prognosis. Nevertheless, such symptoms do not differ
from the basic clinical picture illustrating primary lesions
involving the gland. At times one may observe changes in
hormonal activity of the thyroid, however, they are non-
specific and may occur without concomitant alteration in
the morphology of the gland. Usually a metastatic lesion
of the thyroid is detected following the detection of a
primary focus in another organ at various time intervals
after primary surgical treatment (from 2.4 to 25 years).
According to data presented in the literature on the subject,
metachronous metastases predominate over synchronous
lesions (metachronous/synchronous =2:1) (13-16).

Development of modern diagnostic imaging methods
has decidedly affected the improvement of quality and
accuracy of preliminary diagnoses. The method of choice
is ultrasonography combined with fine needle aspiration
biopsy (FNAB). Metastatic lesions are not characterized
by their differing in ultrasonographic images from primary
lesions of the thyroid gland, hence such symptoms as
solid structure, blurred tumor outline, uneven shape,
hypoechogeticity and microcalcifications may raise
suspicions of neoplastic lesions. In case of isolated lesions
in the thyroid gland, the sensitivity and specificity of
the above imaging method are high and the positive and
negative predictive values are 89% and 93%, respectively.
The presence of nodular goiter markedly decreases
ultrasound diagnostic accuracy; in such a situation, while
selecting the biopsy site, of assistance may be evaluation
of vasculature using Power-Doppler USG as well as the
technique termed elastography. In case of metastases to
the thyroid the use of molecular and immunohistochemical
methods may be of a considerable help in differentiating
between metastatic lesions and primary thyroid tumors.
Of immunohistochemical tests employed in diagnostic
management of lesions situated in the thyroid gland, one
should emphasize: the first-line tests aiming at determining
the theoretical primary origins of carcinomas of unknown
primary sites based on staining for CK7/CK20: breast
(CK7+/CK20−), colon (CK7−/CK20+/−), renal (CK7−/
CK20−), prostate (CK7+/CK20−), hepatic (CK7−/CK20−),
adrenal gland (CK7−/CK20−) and next step are separate
specific markers:
Metastases of a primary neoplastic focus to distant organs always raise considerable fears and deteriorate the prognosis. When detected intravitaly, synchronous and metachronous metastases of other tumors to the thyroid gland necessitate undertaking specific diagnostic and therapeutic activities. In spite of their rare incidence, in view of the specific structure of the thyroid gland, they constitute a problem and a therapeutic challenge. From the viewpoint of the patient the most important objective of all therapeutic modalities, including surgical treatment, is prevention of relapse. Such a standpoint renders a surgical procedure to be a step in therapy that should take into consideration the stage of the disease, thus reflecting the balance between the local and general state of the patient, showing possibilities and extent of surgical treatment; it should also evaluate quality of life as a significant factor of probability of surgical success.

In spite of the number of reported cases of distant metastases to the thyroid gland continuously increasing, there is no fully agreed upon and unambiguous consensus as to the management strategy and surgical treatment of metastatic tumors.

While analyzing the literature on the subject, one notes that the most common metastatic focus in the thyroid gland is single focus clear cell carcinoma of the kidney. All the authors agree that the extent of the surgical procedure should ensure oncological radicality, nevertheless, some recommend unilateral lobectomy and isthmectomy only, while others are in favor of total thyroidectomy. Although there is no unambiguous direct evidence supporting the idea that resection of a metastatic focus of carcinoma of the kidney from the thyroid gland is a contributory factor in prolonging survival time, such a management modality is fully accepted by surgeons. The continuing discussion addressing the extent of the procedure favors the solution accepted by the majority of authors showing the supremacy of total thyroidectomy over hemithyroidectomy (a decreased recurrence rate in the group of patients after total thyroid resection as compared to lobectomy =13% vs. 4.8%, P<0.005). Concomitant nodular goiter, a possibility of multinodular metastasis or concomitant primary carcinoma of the thyroid gland speak for the necessity of performing total thyroid resection. This allows not only for a thorough evaluation of the local stage of the tumor, but also constitutes an important factor in oncological radicality of the procedure, especially in the case of patients with other multiple metastases of clear cell carcinoma of the kidney.
to other organs (e.g., the pancreas). Total thyroidectomy may trigger an injury of the recurrent laryngeal nerves and hypoparathyroidism, nevertheless, the incidence rate of such complications in reference centers is low and comparable to that observed in thyroid surgery performed for other indications. A simultaneous involvement of the cervical lymph nodes in case of metastases to the thyroid is rare and this is why preventive lymph node resection is not recommended. However, the presence of the nodes should be always evaluated in preoperative examinations (US, angio-CT). In case metastases are present in the lymph nodes, lymphadenectomy should be performed taking into consideration the location of lesions in particular lateral and central compartments of the neck. A local high grade of the tumor that infiltrates the neighboring structures, what indicates that the lesion is non-operative, requires ensuring patency of the respiratory tract and possible respiratory support with an attempt at decreasing the tumor mass. In such cases, planning permanent tracheostomy is warranted. In view of the absence of thyroid iodine uptake of distant metastases to the gland, this treatment modality cannot be employed. Other alternative therapeutic methods (radiotherapy, chemotherapy) are of a low applicability due to lack of proven effectiveness of such modalities.

Thus, the selection of the therapeutic method continues to depend on the experience of the center and the surgeon, while prolonged survival of patients without local carcinoma recurrence may be an argument for the advantage of surgical treatment. In case of carcinomas other than clear cell carcinoma of the kidney metastasizing to the thyroid gland, a decisive role in the therapeutic success is fulfilled by grade of primary disease. Multiorgan resections decrease the percentage of local recurrent disease without increasing the survival time (18,29-33).

**Non-surgical treatment**

As it has been repeatedly mentioned, metastases to the thyroid gland are most commonly of a metachronous character and it is the stage of the primary disease that constitutes a decisive factor in therapeutic success. Synchronous metastases reflect the generalized stage of the disease and pronouncedly worsen the prognosis. Surgical treatment of a palliative character should be always considered in view of the time of survival with respect to comorbidities, as well as location and number of metastases. Thus, chemotherapy may be the treatment of choice in the group of patients with extensive distant metastases. In case of breast cancer with numerous metastases to other organs or in the group with a very high surgical risk, positive effects have been achieved when systemic treatment has been introduced (adjuvant chemotherapy, hormonotherapy, immunotherapy, radiotherapy) in keeping with the international recommendations addressing high-stage breast cancer (taxane, anthracycline or with in resistant tumors - capcitabine, vinorelbine or eribulin are the preferred choices), while in case of HER-2 positivity, chemotherapy is based on trastuzumab and pertuzumab, and for HER-2 negative tumors—on bevacizumab. Pensabene et al. demonstrated in their report a positive effect of chemotherapy on intrathyroid metastatic foci, at the same time recommending the above therapy in cases of distant synchronous metastases, thus eliminating the need of thyroidectomy. It should be mentioned, however, that in the group of patients with multiple metastases to other organs and concomitant pressure signs, tumor cytoreduction combined with permanent tracheostomy are performed in order to eliminate total airway obstruction or prior to planned local radiotherapy (34-36).

In the course of colorectal cancer metastases to the thyroid, the customary treatment modality accepted by numerous centers is thyroidectomy that is particularly justified in the afore-mentioned airway compression. Nevertheless, when the primary disease promptly progresses, recommendations for surgical treatment are controversial and the prognosis is poor. Radioiodine therapy is not justified in view of no iodine uptake by metastases, while local radiotherapy should be considered in combination with chemotherapy. Positive effects have been noted in first-line treatment employing oxaliplatin and/or capcitabine in monotherapy or combined with a surgical procedure and/or radiotherapy in selected patients with metastases to the thyroid gland (37). No data that would recommend aggressive chemotherapy have been found in the literature on the subject, nevertheless, the average survival time of patients subjected to combination therapy was longer and the use of targeted immunotherapy (cetuximab; bevacizumab) increased the effectiveness of therapy in metastatic tumors (38,39).

**Prognostic factors and prognosis**

Negative prognostic factors in metastatic thyroid tumors:
- Age >70 years of life,
- High grade and high aggressiveness (high mitotic activity) of the primary focus,
Synchronicity of carcinomatous lesions metastasizing from a primary focus to other organs,
Multifocality of metastatic thyroid lesions,
Local grade with infiltration of surrounding structures,
Regional grade (lymph node involvement),
Non-radical surgical treatment,
Rapid development in medical history and rapid growth of metastatic focus.

**Prognosis**

Metastatic foci are accompanied by synchronous multiorgan foci in 35–80% (an unfavorable prognostic factor).

- Clear cell carcinoma of the kidney: in 20% of cases—synchronous tumors; in 80% of cases—metachronous tumors (in 30% of cases they develop within 5 initial years); general 5-year survival rate of approximately 51%, long-term remission in case of an isolated metachronous tumor long after surgical procedure performed in the primary focus (40-43).
- Non-small cell lung cancer: poor prognosis, in case of high-grade primary foci no cases of 5-year survival are noted, average survival time of 5–27 months (44,45).
- Breast cancer: in 5–10% of cases, the prognosis is generally poor (depending on the size of the primary focus and histological structure of carcinoma), especially in the course of aggressive primary focus (neoplastic emboli with thyroiditis), average survival time depends on primary focus grade: 5-year survival—single cases (34,46,47).
- Colon cancer: poor prognosis, 50% survival rate after 1 year (48-52).
- Melanoma: prognosis depends on treatment and grade of the primary focus, as well as on presence of synchronous metastases to the lymph nodes and other organs (53,54).

**Summary**

(I) The most common malignant tumor metastasizing to the thyroid gland as confirmed by autopsy is lung cancer. The most common intravitally (clinically) detected and surgically treated metastatic thyroid carcinoma is clear cell carcinoma of the kidney. Further places on the list of most frequent thyroid tumors are occupied by gastro-intestinal cancer (colon, gastric and pancreas cancers), breast cancer, laryngeal, pharyngeal, lung cancer, and melanoma.

(II) Metastases to the thyroid gland are most commonly unifocal metachronous tumors. Multifocal synchronous tumors are associated with a considerably poorer prognosis.

(III) The diagnostic method of choice is ultrasound-guided fine needle aspiration biopsy (FNAB) combined with immunohistochemical tests. Evaluation of local grade may be extended to include additional imaging examinations.

(IV) Total thyroidectomy allows for a thorough evaluation of local tumor grade and is an important factor in oncological radicality of the surgical procedure, especially in case of concomitant multinodular goiter, suspected multifocal character of metastases and suspected primary thyroid carcinoma, but it does not affect survival time.

(V) Prognosis depends on the age of the patient, clinical grade, histological structure and profile of metastases at the time of diagnosis. It also depends on time, number of metastatic foci and their location (multiorgan metastases).

(VI) A careful balancing of mentioned factors and multidisciplinary discussion should determine individualized treatment approach (55).

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