

Peer Review File

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Comment 1: To consider this manuscript for publication, I suggest the authors to discuss:

- Other treatment options: for instance, chemotherapy, immunotherapy, target agents, radiotherapy, radiofrequency thermoablation, etc. Please look at the literature, if available. I suggest to add a paragraph (after “surgical treatment”): “non-surgical treatment”, clarifying in which settings these treatments may be considered. In patients with synchronous metastases in multiple organs and a big burden of disease, after considering the PS, comorbidities and prognosis, a systemic approach (chemo, immunotherapy, targeted agents,...based on the primary histology) may be a valid option. In which context the authors may consider other local approach other than surgery? Please comment this point at the best of literature evidences.

Response 1: The paragraph have been modified and added.

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 in resistant tumors - capecitabine, 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.

Zhou L.,Chen L.,Xu D. et al.: Breast cancer metastasis to thyroid: a retrospective analysis. *African Health Sciences*, 2017, 17(4):1035-1043.

Cardoso F., Senkus E., Costa a. et al: 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Annals of Oncology* 2018,0: 1–24.

Pensabene M., Stanzione B., Cerillo I. et al: It is no longer the time to disregard thyroid metastases from breast cancer: a case report and review of the literature. *BMC Cancer*. 2018; 18: 146-154.

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 capecitabine in monotherapy or combined with a surgical procedure and/or radiotherapy in selected patients with metastases to the thyroid gland. 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.

Cheung W., Brierley J, Mackay H. :Treatment of rectal cancer metastases to the thyroid gland: report of two cases. *Clinical Colorectal Cancer*, 2008, 7(4):280-282

Mennet A., De Blasi V., Simoné G. et al: Thyroid Metastasis from Colorectal Cancer: A Case Report and Review of Literature. *Clin Med Rev Case Rep* 2016, 3(11):141-144.

Froylich D., Shiloni E., Hazzan D. Metachronous colon metastasis to the thyroid: a case report and literature review. *Case Rep. Surg.* 2013;2013:1–5

Comment 2: The role of molecular markers in the differential diagnosis between primary thyroid cancer and metastases. (lines 92-97): the sentence about immunohistochemical tests and molecular markers (for example BRAF V600E) is confusing. The analysis of multiple markers may be helpful in differential diagnosis. Some of these markers are positive both in thyroid cancer and lung cancer and/or

melanoma (BRAF) and/or kidney cancer. Please, try to make this point clear.

Response 2: The sentences have been modified as requested

Of immunohistochemical tests employed in the 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-); the next step are separate specific markers:

- Renal cancer (renal cell carcinoma): CD10+, PAX8+, Vimentin+, pVHL+, RCCMa+, Inhibin-, TTF1-, CEA-;
- Colon cancer: SATB2+, CDH17+, TFF3+/-, Calretinin+/-, CDX2-/+ (CDX2 : positive in 90–100% of colon adenocarcinoma cancers,
 - ✓ 80% small intestine cancers: CDX2+, CDH17+, Villin+/-, MUC5AC+/-
 - ✓ 70% of gastric cancer: CEA+, CDX2-/+ , MUC1-/+ , MUC5AC-/+ , CDH17+/-, TTF1-;
- Breast cancer: ER+/PgR+, GATA3+, GCDFP15-/+ , MGB+/-, TFF1- ;
- Lung cancer (mucinous): TTF1-/+ , CK7-/+ , CDX2-/+ , CK19 (subtype CYFRA21.1);
- Pancreatic cancer: Maspin A+, S100P+, IMP-3+, pVHL-, SMAD4-/+ , MUC5AC+, CDX2-/+;
- Esophagus cancer : CEA+, MUC5AC+/-, CDH17+, MUC1-/+ , CDX2-/+;
- Adrenocortical cancer: Melan A+, Calretinin+, Inhibin A+, Synaptophysin+, Chromograni-, CEA-.

Specific markers for thyroid cancers: PTC/FTC (papillary/follicular thyroid cancer): Thyroglobulin+, TTF1+(and Napsin A for undifferentiated thyroid carcinomas); PAX8+, and for medullary thyroid cancer: Calcitonin+, TTF1+; CEA+.

The BRAF V600E oncogene is an integral component of the kinase pathway and is present in leukemia (58.33%); papillary thyroid carcinoma (56.55%), cutaneous melanoma and other locations of melanoma (20.38%), colorectal adenocarcinoma (7.32%) and lung adenocarcinoma.

Selves J., Long-Mira E., Mathieu M.C. et al: Immunohistochemistry for Diagnosis of Metastatic Carcinomas of Unknown Primary Site. *Cancers* , 2018;10(4): 108-131.

The AACR Project GENIE Consortium. AACR Project GENIE: powering precision medicine through an international consortium. *Cancer Discovery*. 2017;7(8):818-831.

Nakano K, Yamamoto H, Fujiwara M et al.: Clinicopathologic and Molecular Characteristics of Synchronous Colorectal Carcinoma With Mismatch Repair

Deficiency. Am J Surg Pathol. 2018; 42(2):172-182.

Comment 3: Other remarks:

- Abstract, lines 18-19: the author write clinical grade, histological structures and profiles of metastases...Do the authors refer to the overall burden of metastatic disease? I would suggest to modify the last line of the abstract with: "are important factors influencing individualized survival rate".

Response 3: The sentences have been modified as requested.

Comment 4: Across the manuscript, the authors use several times the expression "local tumor grade". Please clarify the meaning.

Response 4: In our paper, the expression refers to the diameter of the primary tumor, infiltration of locoregional tissues, vessels, nerves etc.

Comment 5: Lines 35-37: the authors write "metastases to the thyroid gland account for 1.5-3% of all malignancies". Do the author mean that 1.5-3% of thyroid malignancies ultimately prove to be metastases from other primary tumors?

Response 5: Yes, we do. Some papers suggest a much higher incidence of thyroid metastases in patients with a history of cancer ranging from 1.25% to 24% and the value depends on the methods of investigations. Generally, the majority of publications present in clinical and surgical databases the incidence of thyroid metastases equal to approximately 3%.

Comment 6: Line 62: my suggestion is to modify the title "preoperative diagnosis" with "diagnosis"

Response 6: The sentences have been modified as requested.

Comment 7: Line 68: is breast vessels US examination a routine diagnostic procedure? I agree with the authors that thyroid lesions are often detect during diagnostic US of cervical vessels but breast vessels is something uncommon. Please clarify.

Response 7: Yes, I admit the sentence is not quite clear.

The sentences have been modified to read: ... happening in the course of routine ultrasonography in diagnostic examinations of the cervical vessels or ultrasound breast examinations.

Comment 8: Please explain the role of PET/CT in the diagnosis of metastatic lesions to the thyroid and the comparison of metabolic uptake of the lesion within the

thyroid gland with lesions in other organs.

Response 8: There have been several studies trying to clarify the role of PET/CT scans in diagnostic management of thyroid cancers and the relationship between benign and malignant lesions. The purpose of the afore-mentioned imaging method is to detect an increased uptake and determine the role of maximal standardized uptake value (SUVmax) in the high metabolic regions. According to one of publications, the use of 18F-FDG PET/CT scan revealed an increased focal FDG uptake in multiple thyroid masses (SUV max:9.7) and multiple cervical lymph nodes metastases (SUV max: 7.8). Thus, PET/CT fusion imaging indicates that determining the exact location of hypermetabolic lesions leads to a better reliability of results and a higher diagnostic confidence as compared to each imaging modality alone.

Sundram F.: Clinical use of PET/CT in thyroid cancer diagnosis and management. Biomed Imaging Interv J. 2006,2(4): 56.

Comment 9: Line 99: please add a “,” after autoimmune inflammatory processes

Response 9: The sentences have been modified as requested.

Comment 10: Line 107-108: please clarify the sentence.

Response 10: In my opinion, that is the role of high-experience and high-volume centers because patients highly suspected of malignancies should be always referred for urgent treatment to allow for making the best diagnosis and choosing the best method of further therapy. The basis of treatment should be the suspicion of metastatic lesions as compared to their genuine occurrence. Nevertheless, if the sentences you mention are not clear enough to be used in the publication, We agree for them to be deleted.

Comment 11: Line 117: do the authors mean “prevention of relapse”, don’t they?

Response 11: The sentences have been modified as requested.

Comment 12: Line 197-198: the authors write “cancer of the colon (gastric...)”: it is likely the authors mean “gastro-intestinal cancer (colon, gastric pancreas)”. Same consideration for “laryngeal cancer (....)”. Please modify with: laryngeal, pharyngeal, lung cancer, and melanoma.

Response 12: The sentences have been modified as requested.

Comment 13: Line 203-204: Please clarify the sentence because local grade is not clear.

Response 13: This is the same line as discussed above:

In our paper, the expression refers to the diameter of the primary tumor, infiltration of locoregional tissues, vessels, nerves etc.

Comment 14: In summary, the authors are invited to add a sentence explaining that a careful balancing of mentioned factors (lines 209-211) and multidisciplinary discussion should determine individualized treatment approach.

Response 14: The sentences have been modified and added.