

OPPONENT ASSESSMENT OF DISSERTATION

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Thesis title: **Clinicopathological morphological, immunohistochemical and molecular biological characteristics of rare salivary tumors.**

1. Topic of the dissertation:

The dissertation of Olena Koshyk deals with the pathomorphology, as well as the immunohistochemical and molecular genetic profiles of some rare and newly defined tumors of the head and neck. The standard treatment in this group of tumors is primary surgical removal. However, the extent of surgical removal must comply with the characteristics of biological behavior of each tumor subtype. In particular, in the head and neck excessive removal of tissues may result in serious functional and cosmetic consequences, while insufficient removal leads to local recurrences that are very difficult to treat. The problem of prognostic information is particularly relevant in tumor types where biological behavior cannot be predicted from a simple histopathological diagnosis. Furthermore, the differential diagnosis of some tumor types with overlapping morphologies can be very difficult. Studies on the immunohistochemical and molecular-genetic profiles of such tumors can often help in a decisive manner. Such studies may also open up a possibility for biological treatments in some tumor types.

Thus, the topic of this dissertation is on the cutting edge of patient stratification in a challenging group of tumors.

2. Form and content of the dissertation:

The work is composed of an annotated collection of six published studies. The doctoral candidate is the first author in one of them, and a co-author in five. Individual publications are preceded by a commentary containing a concise outline of the issue under investigation, followed by the main results, and the principal conclusions.

In my view, the title of the work should include a mention to sinonasal tumors as two publications of the six deal with them. Thus, I am proposing the title: **Clinicopathological morphological, immunohistochemical and molecular biological characteristics of rare salivary and sinonasal tumors.**

In the introduction, the author deals with the epidemiology of head and neck tumors and reports recent changes in the WHO classification with a list of newly defined and emerging histopathological entities. Subsequently, clinical aspects, immunohistochemical characteristics, histopathological differential diagnoses and molecular genetic profiles of selected tumors are discussed in more detail. Aims of the dissertation are defined in five main points.

3. Methods and results of the dissertation. New findings. Completion of set goals:

Methods of the dissertation include histopathological, immunohistochemical and molecular-genetic techniques. They represent the current state of the art highest international standards. Objectives of the work that include characterization of the chosen tumor types using the above technical arsenal have been reached gallantly. However, publications of the dissertation reach higher than that, developing differential diagnostic algorithms, describing hitherto unknown pathogenetic mechanisms, confirming the neoplastic nature of a lesion, and establishing pathways of tumor progression. Results of the studies are significant, having refined and redefined the present WHO Classification of tumors of the head and neck. Thus, high numbers of international citations can be expected for these studies.

4. Orderliness, clarity, formal arrangement and level of language of the dissertation:

The introduction and the comments relating to the individual publications of the dissertation are characterized by clarity of expression and good command of scientific English language. The excellent quality of the included publications is evidenced by the high impact factors of the journals in which they were published. The whole dissertation is very clearly written.

5. Advocacy recommendation:

The doctoral candidate has demonstrated her ability of independent scientific work. The evaluated dissertation greatly exceeds the standard requirements for a doctoral dissertation.

Therefore, I warmly recommend to the Medical Faculty of Charles University in Pilsen that the dissertation of Olena Koshek is granted permission to public defense.

Turku, Finland

27 August 2023



Ilmo Leivo, MD PhD

Professor of Pathology

University of Turku, FINLAND

Questions for the doctoral candidate:

- 1) What is the relationship of *MAML2* rearrangement and grade of mucoepidermoid carcinoma ? How do you define high-grade mucoepidermoid carcinoma ?
- 2) Which morphologic features distinguish oncocytic cells ?
- 3) Why do you conclude that *EWSR1*-FISH abnormality in myoepithelial carcinoma represents a passenger mutation with no oncologic significance, as opposed to a pathogenetic mechanism ?
- 4) Which gene rearrangements are known to be present in pleomorphic adenomas ? I wonder if *EWSR1* fusions would be found, particularly in pleomorphic adenomas with clear cell features ?
- 5) The dissertation does not mention the functions of *NR4A3* or *NR4A2* genes or proteins. What is known about them ?
- 6) Besides variations in breakpoint location, what might explain a false negative result in molecular testing for gene rearrangements ?
- 7) In polyphenotypic sarcoma, what is the strongest evidence indicating that this tumor is a single entity with a wide morphological spectrum ?