OPPONENT ASSESSMENT OF THE DISSERTATION

Author: Olena Koshyk, MD
Šikl's Department of Pathology, Faculty of Medicine in Pilsen, Charles University

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

Statement on the chosen topic of the dissertation:

This dissertation presents and discusses the morphological, immunohistochemical and molecular genetic profile of some newly defined tumours of the salivary glands and sinonasal tract. It also presents new and interesting findings on several well-established neoplasms.

Surgical excision is the main treatment option for tumours at both sites, and is likely to remain so for the foreseeable future. In addition, neck lymph node dissection is advised in selected cases in some cancers, as well as adjuvant chemoradiation. All are significant procedures with adverse effects in some instances.

The role of histopathology is therefore to make as accurate a diagnosis as possible, and to give as much prognostic information as can be gleaned from any biopsy or excision specimen. Whereas much can be identified from traditional morphological assessment, newer techniques can identify new entities and refine our understanding of existing ones. A particular issue is that the morphological spectrum of several tumours often overlaps with others, so studies on the immunohistochemical and molecular-genetic profiles in such cases can often help in a decisive manner. Thus, by improving knowledge of the nature and likely behaviour of a tumour in any particular patient, this will guide the clinical oncologist and surgeon as to the optimum therapy.

Furthermore, by identifying various molecular genetic abnormalities, this opens the way to drug therapies (such as specific targeted agents) to be used instead of, or in combination with other treatments.

Therefore, the topic of this dissertation is on the evolving forefront of our knowledge of this group of interesting tumours.

Form and content of the dissertation:

The first part of this dissertation outlines current knowledge of the pathology of tumours of the salivary glands and sinonasal tract, as set out in the most recent WHO International Classification. It adds a list of known molecular genetic abnormalities often found in some of the entities. The introduction sets out five main goals of the study.

The work is composed of six studies, all published in leading international pathology journals. The doctoral candidate is the first author in one of them, and a co-author in five. Each publication is preceded by a commentary summarising the tumour type studied, the main results, and pointing out principal issues arising.

One point is that the title of the dissertation undersells the extent of the work itself, as apart from studying four interesting salivary tumours, it also looks at two rare and ill-defined sinonasal neoplasms.

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

The methods used in this dissertation principally include histopathological, immunohistochemical and molecular-genetic techniques applied to various types of tumour specimens from the pathology archives. These techniques, some of which are available in

only a few centres worldwide, are the most up to date ways of analysing the nature of the particular types of neoplasm.

Five objectives of the work are set out in the introduction, and it is reasonable to conclude that all have been more than achieved. The findings have been published in leading international pathology journals, and it is not an exaggeration to state that it is likely that the results identified here will alter diagnostic practice worldwide.

Statement on the orderliness, clarity, formal arrangement and language level of the dissertation:

The introduction and the comments on the individual publications are well set out, and thus very easy to follow.

The command of scientific English is generally very good, although there are a very small number of what to a native English-speaker seem slightly odd usage of grammar. The one error I note is on page 51, paragraph 2: - "germ centers"; it would be better to use "germinal center".

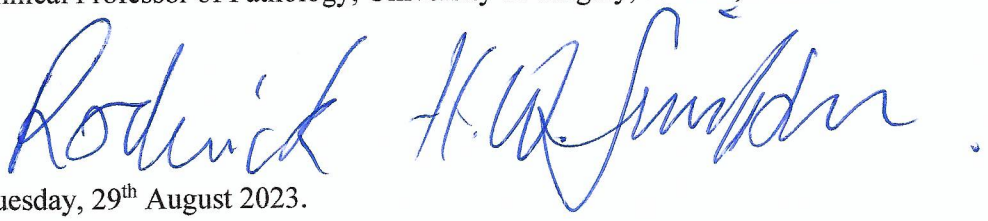
Advocacy recommendation:

Overall, my opinion is that Dr Koshyk has produced an excellent doctoral dissertation..

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

Date, name, surname, titles, affiliation….signature of the reviewer

Roderick H. W. Simpson, BSc, MB ChB, MMed (Anat Path), FRCPath.
Clinical Professor of Pathology, University of Calgary, Alberta, Canada.



Tuesday, 29th August 2023.

Questions for the candidate:

1. In oncocytic mucoepidermoid carcinoma, you found that 5 of 22 cases lacked mucous cells, which is interesting as we normally consider them essential to the diagnosis. Did you find squamoid cells? Were there any other morphological pointers in those five cases?

2. 23% of your oncocytic mucoepidermoid carcinomas were fusion negative, but FISH positive – was this a technical issue or could FISH be identifying some false positives?

3. Do you think any of the 103 other oncocytic lesions could also be mucoepidermoid carcinomas that FISH failed to identify?

4. In myoepithelial carcinoma, you postulate that EWSR1 mutations could be associated with clear cell morphology. Have you any thoughts on why this may be so, as EWSR1 mutations are found in many other non-clear cell neoplasms, such as Ewing/PNET and various other sarcomas?

5. In acinic cell carcinoma, you looked at a large series of 128 cases, of which 36 showed high grade transformation, which seems quite a lot. How did you subdivide the others into high and low grade? Also, we are all familiar with apparently low grade acinic cell carcinomas that recur and metastasise after many years – looking at such a large series, did you find any new prognostic indicators? In particular, did the NR4A2 cases behave any differently?

6. In sclerosing polycystic adenoma, the most striking and distinctive feature is the presence of the large intracytoplasmic granules. Have you any comment on their nature and, other than in aiding diagnosis, their significance, if any.

7. In polyphenotypic sinonasal sarcoma, you note that low and high grade histological features have no impact on prognosis. I note that in your series, some patients have survived without disease for 3 to 4 years, and some are alive with disease at longer follow up intervals. Did you find any histopathological or other prognostic indicators?