

Review of the Dissertation by Antonina Kalmykova entitled “The diagnostics of rare soft tissue and skin tumours using the histological, immunohistochemical, and molecular biological methods”

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At the outset, I think that it is helpful to emphasize Dr. Kalmykova’s stated goals which included:

1. To investigate rare soft tissue and skin tumors to identify specific clinical and morphological characteristics that could potentially enhance diagnostic accuracy.
2. To study genetic mutations and pathogenic molecular pathways involved in the tumorigenesis and progression of soft tissue and skin tumors to identify potential therapeutic targets and predictive markers.
3. To establish correlations between clinical presentation, histopathology, and molecular profiles to improve our understanding of the biological behavior of these rare entities.
4. To expand existing knowledge for soft tissue and skin tumors, facilitating research, data sharing, and collaborative efforts in understanding these diseases.
5. To extend and refine the current classification of soft tissue and skin tumors.

In short, I can confirm that she has more than met these objectives.

The methodology which includes clinical studies, light microscopy and molecular investigation is highly appropriate for this topic.

Cutaneous and soft tissue tumours range from the very common and biologically benign through to carcinomas and sarcomas of variable biological potential. Some of the entities in the last two categories are exceedingly rare. I think that this dissertation focuses attention on a range of the latter tumours including a wealth of new data and as such, this is an excellent choice for a dissertation topic

This dissertation comprises translational research presented as a series of publications on a variety of cutaneous and soft tissue tumors. Included for each tumor are clinical information, histology/morphology, immunohistochemistry and molecular genetic data. Each publication is preceded by the author’s concise summary.

One of the stated aims of the thesis is to “extend and/or improve” better classification and diagnostic criteria. Thus, the thesis emphasizes the limitations of morphology (and to some extent immunohistochemistry) in accurate diagnosis and discusses problems with differential diagnosis. The author shows that ultimately, fluorescent in

situ hybridization (FISH) and next generation sequencing (NGS) is often necessary to establish the correct diagnosis. She emphasizes the critical importance of the latter as treatment and prognosis are potentially variable. It underscores the point that ultimately, molecular data is often necessary to reach a final diagnosis. Prospectively, this will become of particular importance for treatment with targeted immunotherapy.

The tumors chosen are topical and of considerable importance as they are accompanied by significant implications for patient care, investigation, treatment and outcome/prognosis. In addition to the collection of patient clinical data and morphology, the study includes state of the art immunohistochemistry, FISH and NGS. The author demonstrates clearly that morphology on its own is insufficient in establishing a definitive diagnosis in certain tumors. In some examples e.g. BAP1-inactivated melanocytoma, immunohistochemistry is all that is necessary to enable the pathologist to reach the correct diagnosis. For the other tumors discussed in this thesis, all the other technologies are necessary for a definitive diagnosis. The work presented in this thesis has provided additional and very valuable diagnostic data. The clinical information collected for the various tumors has added considerably to the previously documented database. The results for each of the tumors investigated have the potential for influencing treatment.

The published work lists Dr. Kalmykova as either first author or as a co-author (with significant contribution to the study and manuscript preparation to justify such coauthorship).

The great strength of this dissertation is the presentation of a considerable wealth of new/singular data in addition to that available from prior literature. As well as morphological descriptions including novel variations, valuable new immunohistochemistry observations utilizing state-of-the-art reagents and detailed molecular data provide invaluable knowledge. Her investigations have resulted in important new information, for example 6 novel BAP-1 mutations and an absence of *TERT1* mutations are presented in the BAP1-inactivated melanocytic neoplasms (melanocytoma) paper. The addition of two additional examples of *MITF::CREM*-rearranged tumor has been particularly useful as there was only one previously documented case. The addition of nine cases of inflammatory leiomyosarcoma has contributed additional relevant clinical and diagnostic data.

A potential weakness of the study is the limited follow-up data that has (sometimes been available) which renders prognostic implication less than optimal. This is a common problem with clinicopathological projects and in no way detracts from the value of study. Similarly with the literature review, immunohistochemical and molecular data is variable. Dr. Kalmykova's presented data goes a long way in correcting this shortfall.

I emphasize that the goals outlined by Dr. Kalmykova at the start of this have been satisfactorily realized.

In conclusion, I think that this body of work has been undertaken meticulously and is extremely well presented. I recommend that Dr. Antonina Kalmykova be awarded the academic title of Doctor of Philosophy (PhD).

Signed Phillip H McKee 05/05/2025

