Searching for genetic determinants of follicular thyroid malignancy employing genomic screening

Thyroid nodules are detected in ultrasound examination (US) more and more frequently. The progress of ultrasound diagnosis - steadily increasing quality of the equipment and, above all, high experience of investigators – enables assessing of the nodules already stage of US examination. However, sometimes to determine whether the nodule may be malignant, it is necessary to collect the cells specimen by fine needle aspiration (FNA) biopsy. Among particular types of nodular lesions there are such that cannot be distinguished with these methods. In such cases surgical treatment is undertaken, even though it is known that 80% of the qualified patients will receive the ultimate diagnosis of a benign lesion.

We live in the era of immense progress in genetic research techniques. We want to put these achievements to use. Employing the newest method of next-generation sequencing (NGS) and whole genome microarray – which enable precise analysis of multiple genes simultaneously – we want to search for such new genetic changes that are characteristic for follicular thyroid carcinomas and do not appear in follicular thyroid adenomas – so that that the subsequent progress will enable differentiating between malignant and benign nodules to enhance clinical decision making in the context of potential operative treatment.

We intend to carry out the research on material from formalin-fixed, paraffin-embedded (FFPE) follicular thyroid adenoma and carcinoma specimens, which were collected after the surgery to remove the cancer or follicular thyroid adenoma. Histopathological diagnosis will first be verified independently by two pathologists cooperating with us. Then, using the latest techniques of microdissection, we will acquire the genetic material of tumor tissues for research. We will use tools that will make the genetic material, which may be partially damaged by paraffin embedding, viable for further testing. Parallel to this, we will gather clinical data of patients, whose removed tissues we will explore. We will search for clinical, laboratory and imaging data (such as the results of their preoperative thyroid ultrasound or the results of a novel imaging technique – shear wave elastography). Then we will perform the appropriate experiments. We will examine hundreds of thousands of genes using NGS. Among the genetic alterations we will look for those, which are present in carcinomas but not in adenomas, and were not described before, and those which are present in the thyroid cancers, as well as in cancers of other organs. Although the concept of NGS is brilliant, it does not allow to study the occurrence of all genetic alterations. To complement this "genetic landscape," we will use the method of whole genome microarray and molecular inversion probe (MIP) (for the first time in this context), through which we will be able to look for particular loci in the genome where certain genes are repeated or conversed. We will thoughtfully post-process and analyze the complete data yielded by the NGS and MIP analyses (which we expect to be particularly abundant). We will compare data from two sources: the genetic study and retrospectively accessed clinical records.

Thanks to the project we will be able to answer the questions whether:

- follicular thyroid cancers and adenomas different with detectable genetic alterations,
- among these alterations we may find those which have the potential to differentiate between malignant and benign nodules already before surgery,
- thyroid cancers share common genetic background with other cancers (perhaps in the future we will not be talking about cancer classification according to localization in specific organs, but according to specific genetic mutations).

The study will increase our knowledge about appearance of cancer – cancerogenesis. If, thanks to our study, we find different genetic alterations for follicular thyroid carcinomas and follicular thyroid adenomas, it will mean that these diseases are distinct entities and not their simple continuum (that carcinoma does not arise on the basis of adenoma). Thanks to our research based on FFPE specimens we may stimulate next studies on this material. In our research we will also correlate genetic data obtained after simultaneous study of many genetic alterations with clinical data (for the first time so comprehensively in this context). The results of our study may contribute in the future to find such a set of genetic changes and clinical characteristics, the presence of which will enable the accurate determination of the type of thyroid nodule - its benign or malignant nature without having to undergo surgery. The results of our research could also be used to make the best surgical treatment planning or control strategy (frequency of control visits and the scope of activities performed on their occasion). The results of our study will contribute to understanding of: tumor growth in general, gene involvement in this process, and targeted drug development in the future.