REVIEW

Written by: Prof. Dr. Marina Borisova Garcheva-Tsacheva

Clinic of Nuclear Medicine, Acibadem City Clinic-Oncology, Sofia, regarding dissertation on the topic *THE ROLE OF 18F-FDG PET/CT SCAN IN THE DIAGNOSTIC ALGORITHM OF MALIGNANT EPITHELIAL HEAD AND NECK CANCERS [MEHNCs]* for the acquisition of educational and scientific degree of *Doctor* by Dr. Tsvetelina Yordanova Petrova-Georgieva, an assistant at the Department of Imaging, *Nuclear Medicine* doctoral program, professional field 7.1. Medicine, higher education 7. Health and sports.

The topic of the dissertation is up-to-date and valuable for clinicians since head and neck cancers are not only a heterogeneous group but also very difficult to diagnose in an area with complex anatomical structure, uncertainty in distinguishing physiological and pathological phenomena, with difficulty staging patients and assessing the effectiveness of the conducted therapy. The frequency of recurrences in these diseases is high and this requires the determination of the most appropriate method of follow-up, as well as the intervals of this follow-up.

By now, the leading method in diagnosis was clinical examination combined with endoscopy, which, however, should be made together with imaging methods to assess the relationship of cancer to important neighboring structures and to achieve adequate staging of patients. Given the whole-body nature of the 18F-FDG PET/CT scan, its advantage to detect cancers and their metastases by metabolic criteria, the author focused on determining its overall use in these diseases.

Numerous histological determinations, as well as prospective follow-up of patients, have been used as reference methods for this purpose. The possibilities of the method are compared with those of physical methods and conventional imaging methods – basic contrast computed tomography.

The dissertation includes 121 pages. It contains 28 tables, 30 graphs and diagrams, and 13 high-quality color figures. The bibliography includes 125 sources of literature, most of which have recently been published, as two of them, are by Bulgarian authors, due to the lack of systematic research on the subject in the country so far.

The literature review presents the known modern diagnostic methods with emphasis on the advantages of nuclear medicine methods and especially the FDG PET/CT scan, as well as the frequency of head and neck cancers for our country and histological variants, including by individual locations, the most common stages in the presentation of patients, risk factors, including genetic ones, the possibility of combining with synchronous cancers with other localizations. The problematic moments for making clinical decisions, subject of the present study, have been highlighted.

The goal and tasks are precisely and concisely formulated in 6 directions: detection of unclear primary focus, role in staging, role in diagnosing local recurrence, role in assessing the therapeutic effect and follow-up, role in detecting synchronous cancers.

A total of 205 patients with head and neck cancers (HNCs) were studied, in which a significant number of FDG PET/CT scans were performed - a total of 308 scans, mainly between 2015 and 2017. The number of patient examinations varies between 1 and 3 depending on the tasks - 26 patients were examined for an unknown primary focus, 120 patients were scanned for staging, 29 of whom were followed up, 59 were in the restaging group, 74 were scanned for response to conducted treatment. An additional large number of physical examinations, endoscopies, excisional biopsies, CT scans with a more limited or greater scope were performed. Statistical data processing was performed with SPSS v.25 for Windows and included ROC analysis and Kaplan Meier survival analysis.

The results are presented according to the tasks set:

High detection was achieved in patients with proven metastatic cervical lymph nodes of squamous cell carcinoma (the most common histological variant in these cancers) and unknown primary focus - 61.1% - higher than in the literature, while in another 28% the result remained negative with all methods used. No correlation between the number of lymph nodes involved was found.

The confirmatory and blind biopsies performed on these patients are impressive. The author summarized the most common localization in these cases – oro- and in the second place - nasopharyngeal cancers, and further clarified the predilection concerning gender and age /naso- and oropharynx - in men and oropharynx in women, as well as the more common nasopharyngeal cancers at a young age.

The staging results were derived from a study of 120 cases (predominantly squamous cell carcinoma), 55 of which were compared with contrast-enhanced head and neck CT scans, and in 28 of them, thoracic scans were made as well. Despite the comparability of the two methods, the CT scan is better in the T-staging of patients (96.4 versus 95.7%). Nevertheless, the author points out that the PET/CT scan increased the T-stage of the disease in 7.8% of cases, which was in good agreement with the literature (5 and 8.5%) and thus changed the therapeutic approach.

The PET/CT scan has proved to be a very important method in determining nodal status, with the best sensitivity (100%) for detecting affected lymph nodes, superior to other methods, although not to be the most specific one (83.3% specificity).

To detect a local recurrence, 22 patients with clinical suspicion were studied, in 14 of them confirmed and verified histologically. The method was found to be superior to all the others in terms of laryngeal recurrence with 100% sensitivity compared to 81% for the physical method and 62.5% for the computed tomography.

Regarding the determination of the response to treatment, 62 patients were studied, and persistence of the cancer was found in 23, a relatively high percentage - 37.1% of them and an even higher percentage - 40% after the expulsion of five who developed distant metastases.

Three methods were compared for visual assessment of the local response to treatment (a 5-point scale (Deauville), and a 3-point scale (Likert) relative to reference areas), in addition to the usual determination of the standard degree of accumulation, SUV max, and determined the interval after the end of treatment in which an early follow-up scan should be performed no earlier than 3 months, in 5.4 months on average; a second follow-up PET scan in case of incomplete response and histologically negative result would be appropriate in 12 months. The author introduced a threshold value of SUV max of 2.5 which would serve as a prognostic indicator for future progression of the disease and determined the indicators for selection of patients at risk. The survival of patients up to the first follow-up PET and without locoregional recurrence was determined.

Regarding the diagnosis of synchronous cancers, common in these diseases, the PET/CT scan proved to be a valuable method with high diagnostic potential which in the material, studied by the author, diagnosed a second primary cancer in 6.7% of patients, changing their approach and prognosis. 11 conclusions were made, which summarize the achieved results and outline the role of 18F-FDG PET/CT scan in the diagnostic algorithm of malignant cancers of the head and neck.

At the end of the dissertation, advice on clinical practice was presented as a result of the author's experience:

1. The FDG PET/CT scan is mandatory in patients with head and neck cancers (especially in locally advanced cancers) to detect nodal and distant metastases, having higher sensitivity than other diagnostic methods.

In this regard, it is an extremely valuable method when planning radiation therapy. It is also important to use additional static scans of the head and neck, as well as histological verification of metabolically active foci.

2. Follow-up examinations should be performed no earlier than in 3 months, and in 5 and 12 months on average to assess the completeness of the response to treatment.

The recommendations to the author, made at an earlier stage, were taken into account by her in the presented final version of the dissertation.

In connection with the presented dissertation, there are three real publications in Bulgaria and four scientific papers in Bulgaria and abroad with a high total IF of 19.529. For the first time in Bulgaria, the dissertation summarizes the data from the studies of a large number of patients with head and neck cancers, and all areas of application of the FDG PET/CT scan were studied and

thus enriched not only diagnostic capabilities but also therapeutic planning and control, and the prognosis in these patients improved.

The discussion of the results and the conclusions showed that the author is already an experienced professional in the field of nuclear medicine with extensive clinical knowledge. The main contributions of the dissertation development are as follows:

- A comprehensive study on the role of the FDG PET/CT scan in patients with head and neck cancers for the detection of an unknown primary focus and/or disease staging has been made for the first time.

- A comprehensive study of the role of research to control the effect of treatment, timely diagnosis of recurrences (local or systemic), and detection of synchronous cancers of other organs and systems has been made for the first time.

- Methods for semi-quantitative assessment of the response to therapy have been introduced to determine the subsequent behavior and prognosis of patients. Valuable advice to clinicians has been provided.

IN CONCLUSION, I believe that the presented dissertation by Dr. Tsvetelina Yordanova Petrova-Georgieva on the topic *The Role of 18F-FDG PET/CT Scan in the Diagnostic Algorithm of Malignant Epithelial Head and Neck Cancers [MEHNCs]* is the first summarized study on this issue in Bulgaria, with important practical contributions and a precise justification for the use of this modern nuclear medical method. Given the above, I strongly recommend that the members of the Scientific Jury admit this paper to the defense for the acquisition of educational and scientific degree of *Doctor of Medicine* by Assistant Dr. Tsvetelina Yordanova Petrova-Georgieva.

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