REVIEW
Written by: Prof. Dr. Irena Dimitrova Kostadinov, DMSc

Clinic of Nuclear Medicine, Acibadem City Clinic-Mladost University Hospital, member of the Scientific Jury on the basis of Order No. P 109-473 / 5/11/2021, issued by the Rector of the Medical University of Varna, for the defense of a 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 the educational and scientific degree of *Doctor* by Assistant Dr. Tsvetelina Yordanova Petrova-Georgieva at the Department of Imaging, Interventional Radiology, and Radiation Therapy with the Medical University of Varna, the Clinic of Nuclear Medicine and Metabolic

Head and neck cancers represent 4% of all cancers worldwide. The most common locations are the oral cavity (41%), followed by the pharynx (22%) and larynx (24%).

In Europe, the risk in men is about 3 times higher than in women and, histologically, in almost all cases it is squamous cell carcinoma with major risk factors being smoking, alcohol, and the human papillomavirus. The diagnosis of malignant epithelial head and neck cancers (HNCs) is made on the basis of clinical, laparoscopic, and endoscopic evidence and biopsy. The role of the most commonly used imaging methods - CT and/or MRI with contrast matter is in the local staging to illustrate, determine the size and morphological details of cancer with the possible coverage of neighboring or more distant structures. Their disadvantages are that they are based mainly on morphological criteria, which are not always specific, and limitations in the need for whole-body imaging in the staging of locally advanced cancer and restaging.

Since the HNCs are mainly squamous, they are hypermetabolic and their precise localization, staging, restaging, radiotherapy planning, and monitoring of the therapeutic effect at the molecular level is possible through the highly sensitive functional and morphological hybrid imaging technique - PET/CT with 18F-FDG which is a very reliable alternative of conventional imaging methods.

In our country, there is no systematic prospective study on the role of PET-CT in patients with HNCs and its potential compared to physical examination and CT scan, which would quickly and effectively support the administration of timely therapy to improve survival and prognosis.

In this sense, the topic of the dissertation is very up-to-date and of great importance for all clinicians related to the diagnosis and treatment of patients with HNCs, as the goal and objectives accurately reflect the nature of development, namely to assess the role of hybrid PET-CT imaging method in:

- primary diagnosis of cancer of unknown primary (NPO) in patients with proven metastatic cervical lymph nodes of squamous cell carcinoma

- staging and proving local recurrences

- monitoring and evaluation of the therapeutic response

- detection of synchronous/metachronous primary cancer and distant metastases in patients with HNCs.

The dissertation is properly structured. It contains 121 pages, illustrated with 28 indicative tables, 22 graphs, 8 diagrams, and 13 indicative color figures, some of which include PET-CT scans to monitor the dynamics of the disease to assess the therapeutic response, and enclosed Kaplan Meier curves — for the survival of patients depending on their metabolic response. The extremely detailed tables make a big impression, most of which reflect comparative information about the methods used in patients - specialized clinical methods and CT scans, and others - detailed information about the staging of patients depending on the location of cancer. 125 literary sources have been cited, 2 of which are in Bulgarian and 123 in Latin, and most of them originating after 2000.

The author reviewed systematically, in summary, and with very good knowledge, all problems, and addressed all issues related to HNCs: epidemiology with a characterization of two prognostic groups and the factors that determine them, depending on the organ location of metastases as the modern laboratory, histopathological and imaging methods for diagnosis - CT, ultrasound, MRI - are professionally examined and their advantages and disadvantages are pointed out. The role of the hybrid imaging method PET-CT scan in these patients was considered in detail, and it was clear that this was the most sensitive method compared to other imaging methods, but there was no one-sidedness of the results for its clinical value. The review ended with a very accurate summary of the existing data, and the unsolved problems were set, which the author developed and discussed further in her dissertation.

A large number of patients were studied - a total of 205 with HNCs, in whom 308 18F-FDG PET/CT scans were made, with histological verification and the following main indications - staging - in 120 patients (58.5%), restaging and monitoring the effect of therapy - in 59 patients (28.8%) and localization of the primary cancer focus - in 26 patients (13%). A total of 105 patients underwent a follow-up second and tertiary scan to monitor the effect of relapse treatment/diagnosis. The obtained results for data analysis and objectification were processed with the most up-to-date statistical program from the IBM SPSS package for Windows, v. 20.0.

The author's introduction and the qualitative assessment of the findings for the degree of accumulation of the radiomark to reference anatomical areas and the probability of cancer presence, using a 5-point scale (similar to the Deauville scale in lymphomas) and 3-point Likert scale, to the commonly used semiquantitative assessment with Tmax is impressive. More and more researchers are introducing this qualitative assessment in some other cancer localizations to achieve objectivity and accuracy of the result, both for visualization and detection of active cancer and to assess the effect of treatment.

It has been found that 18F-FDG PET/CT scan has a high sensitivity of 91.7% for the detection of primary cancer focus in patients with CUPs and histologically proven metastatic cervical lymph nodes of squamous cell carcinoma, but a relatively low negative predictive value (NPV) – i.e. with a negative result for the presence of primary cancer, it cannot be completely ruled out due to the inability to visualize minimal cancers, as well as some histological variants

with a low degree of fixation of the radiomark. It was established that it mainly affects men over 60 years of age, with primary localization in the nasopharynx - in 25% and oropharynx - 41.7 % % by visualizing priority cancers in stage T1-2.

The results show that the application of the hybrid method after the physical and conventional imaging methods increases the T stage to a more advanced one in 7.8% of patients and so personalized therapy can be undertaken in the patient. In the staging of lymph nodes with CT scan, the sensitivity is 95%, the specificity is 66.7%, and the physical method, respectively 93.9% and 83.3%, which determines the PET-CT scan as a method of choice for visualization of metastatic lymph nodes.

The maximum sensitivity and NPV of 100% of the 18F-FDG PET/CT method for detection of locoregional residual cancer in HNCs after the end of treatment was established, compared to those of the physical method, 42% and 65.5%, respectively, which determines the PET/CT scan as a reliable non-invasive method for detection of persistent cancers or still active lymph nodes.

In patients with laryngeal cancer, local recurrence can be most reliably established with 18F-FDG PET/CT scan and in those with a negative result of physical/ endoscopic examination and CT scan, with sensitivity 100%, specificity 80%, accuracy 95 % - to exclude it reliably - NPV 100%, compared to CT scan - 62.5% and 50%, respectively, as well as the physical examination - which is 62% accurate. Due to the possibility of a false positive result following persistent inflammatory changes after radiotherapy, according to the author, it is necessary to conduct a follow-up PET-CT scan with a recommended interval of 5.4 months and another one in the 12 months to seek a late metabolic response before deciding on the therapeutic approach in the patient.

It has been found that 18F-FDG PET/CT is the most reliable non-invasive imaging method for the detection of distant metastases in HNCs, including in patients without clinical symptoms with sensitivity and NPV of 100%.

Based on the quantitative assessment of the therapeutic response with SUVmax, with the introduction of a threshold value of 2.45 by Dr. Yordanova, as well as the qualitative assessment using a five-point visual (Deauville) scale and a three-point (Likert) scale, it becomes possible not only to consider a therapeutic response, but to distinguish the group of patients with good therapeutic response and better prognosis from those with no therapeutic response/progression and to initiate more aggressive treatment in them.

Dr. Yordanova found that the majority of patients had a complete metabolic response locoregionally - 62.9% - (after radiation therapy with or without systemic chemotherapy/targeted therapy), mainly with oropharyngeal cancer with 75% response followed by nasopharyngeal cancer 66.7%, laryngeal cancer 63.2%, hypopharyngeal cancer 55.6% and cancer in the oral cavity 42.9. Patients with a complete metabolic response to the primary cancer were recommended to have a first follow-up PET/CT scan in 22 months on average, while patients with an incomplete metabolic response to primary cancer in 16 months on average if no additional indications had occurred by then.

The author found that with the application of the method, an occult second primary cancer (SPC), was reliably detected in 6.7% of patients, with high accuracy of 99%, located primarily in the gastrointestinal tract and detected most often in laryngeal cancer.

The discussion of the results and the conclusions show that the author is an experienced professional who knows and correctly interprets the results of the most modern and reliable hybrid imaging method – the PET-CT scan.

I agree with the contributions indicated by the author, which are not only of scientific importance but also of high value for the clinical practice, which I present summarized, following my previous recommendations, namely:

1. **For the first time in Bulgaria,** the role of the 18F-FDG PET/CT scan for determining the location of unknown primary focus in patients with HNCs and histologically proven metastatic cervical lymph nodes, in determining the stage of the disease, early diagnosis of recurrences, local or systemic, monitoring the effect of therapy and visualization of synchronous/metachronous cancer, was studied.

2. **For the first time**, the quantitative and qualitative assessment of the metabolic and morphological response after radiation therapy with or without systemic chemotherapy/targeted therapy is applied, using the following three methods: visual with three- and five-point scales, and determination of SUVmax with a minimum threshold value, indicated by the author. This makes it possible to select patients with a complete or incomplete response or those with progression and to predetermine the subsequent therapeutic approach.

3. In her thesis development, the author gave **plenty of valuable advice for the clinical practice**, which she put in a separate chapter, namely:

- The18F-FDG PET/CT scan should be performed during the staging of patients with HNCs, as it can accurately detect metastases in clinically and image-negative lymph nodes, which not only helps with the choice of therapeutic approach but also with the radiotherapy planning and its effectiveness.

- In the follow-up of patients with HNCs, not only the high-risk patients should be directed to undergo 18F-FDG PET/CT scan, but also low-risk patients who meet the following characteristics: with a primary cancer in the larynx, oral cavity (gingiva) or oropharynx), male, over 60 years of age and with early T stages (T1), without metastatic lymph nodes (N0) from other examinations, as their early follow-up would lead to early visualization of recurrence and successful treatment.

- The average time to report the effect of treatment with a third follow-up 18F-FDG PET/CT scan is 12 months after the end of the radiation therapy (with or without chemotherapy).

onnection with the dissertation, I made several recommendations, including some summaries of the conclusions and contributions that were adopted and corrected by the author in the final version of the dissertation and abstract.

For further publications, I suggest summarizing the data from the large number of studied patients included in the dissertation in terms of stage change and therapy after undergoing a PET/CT scan in patients with HNCs, which will further establish the method as an integral part of the diagnostic and therapeutic algorithm of these patients, leading to the most effective personalized treatment.

In connection with the topic of the dissertation, there are a sufficient number of publications, of which 3 are in our country and 4 are scientific reports, including 3 presented at the European Congresses of Nuclear Medicine, with a total IF of 19.529.

Dr. Yordanova was born in Silistra, and in 2008 she graduated Medicine from the Medical University of Pleven. In 2008-2009, she worked as a hospital physician in the Department of Nuclear Medicine at the Complex Oncological Center of Burgas, and subsequently specialized [and currently works] in the Clinic of Nuclear Medicine and Metabolic Therapy at Sveta Marina University Hospital of Varna. In 2013, she became a nuclear medicine specialist. In the period from 2017 to 2019, she worked as a part-time assistant in the Department of Imaging Diagnostics, Interventional Radiology, and Radiation Therapy, and in 2020, she became a full-time assistant. In May 2018, she was enrolled as a doctoral student with the topic of dissertation *The Role of 18F-FDG PET/CT Scan in the Diagnostic Algorithm of Malignant Epithelial Head and Neck Cancers [MEHNCs]*

Dr. Yordanova took part in training courses conducted by the IAEA and ESOR in Cyprus and Bulgaria and is a member of a total of 3 scientific and professional organizations.

Dr. Yordanova is a very responsible and hard-working specialist who is a great team player. She professionally seeks and manages to find the right way to diagnose a patient.

IN CONCLUSION, I believe that the presented dissertation of Assistant 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]* considers for the first time in Bulgaria this issue on a large number of patients. She has important theoretical and practical contributions in the field of nuclear medicine, otorhinolaryngology, and oncology, which are of great importance to our medical community.

She is already an established professional, physician and lecturer, with a number of scientific contributions. She is highly respected by her colleagues and patients.

Having in mind the above, I recommend that the members of the Scientific Jury vote positively for the acquisition of the educational and scientific degree of *Doctor* by Assistant Dr. Tsvetelina Yordanova Petrova-Georgieva.

06/12/2021г. **Reviewer:** I Kostadinov

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