Review

by Prof. Marina Borisova Garcheva -Tsacheva

of the dissertation work of Dr. Gabriela Mateva on the topic:

The role of positron emission computed tomography (18F-FDG PET/CT) in patients with colorectal cancer

Colorectal cancer is a fairly common malignant disease, the third in the world, affecting both sexes. This necessitates the search for new diagnostic and therapeutic options. Despite improved diagnostics, the mortality curve is growing. For our country, the frequency of new cases and mortality is 13 % , respectively 14% compared to 12%, respectively 13% of those on average for European countries. The lower 5-year survival rate (5 2% compared to 60%) once again requires attention to screening programs and early diagnosis, as well as to the possibilities for new therapeutic approaches.

That is why the topic of this dissertation is relevant - its focus is precisely the possibilities of new approaches in the diagnosis and therapy of colorectal carcinoma. The application of nuclear medicine Methods and more specifically 18 F - FDG PET/CT are not well studied in this location. The only established indication is to clarify the cause of an increase in the level of carcinoembryonic antigen (CEA) .

The author has chosen a topic on which there is scarce data in the literature. Although the diagnostic method she uses, namely 18 F - FDG PET/CT, is widely used in oncological diagnostics, it is not recommended in the guidelines for colorectal carcinoma (CRC). Therefore, Dr. Mateva's dissertation work is conceived as pioneering, touching on unexplored or little-studied areas.

It includes 141 pages and is structured as follows: 35 pages of literature review, goal and resulting tasks - 1 page, 7 pages of material and methods, 76 pages of results and discussion /related to the tasks set/, and 3 pages of conclusions and contributions. The literature review includes 135 contemporary sources, 100 of which were published after 2011 (reiterating the relevance of the problem) , including 14 by Bulgarian authors.

It has separate sections that include: modern methods of diagnosis, staging , screening tests, risk groups, histological and immunohistochemical diagnostics, as well as prognostic and predictive characteristics, thoroughly studied by the author. The second section covers the pathways of metastasis , the factors determining metastasis , the importance of the primary tumor localization. For the purposes of further analysis, staging according to the 8th edition of the the classification of tumors, as well as the current recommendations for the use of tumor markers.

Material and methods: a total of 110 patients were studied over a period of 7 years, and in addition to patients with colorectal carcinoma, 16 patients with other tumors that caused liver metastases were included in task 3. This does not violate the purity of the processed data, but on the contrary - it complements them. Most patients were studied retrospectively, and a prospective part was included to assess the effect of SBRT . A huge amount of information from other imaging methods and laboratory tests was processed.

Thus, 50 patients included in the staging and restaging group during dynamic observation had 109 PET/CT scans and 144 CT and 24 MRI follow-up scans, which were interpreted with the help of an imaging specialist. To assess the response to SBRT , 26 patients with 42 liver lesions were studied, in whom a pre-procedural PET/CT scan was performed, repeated after 3 to 6 months, a total of 52 scans.

To evaluate the effect of RFA , 23 patients (28 lesions) were studied, 7 with CRC, the rest with other tumors. All underwent contrast-enhanced ultrasound (CEUS) before, after, and in some cases during the procedure.

Eighteen patients (n=18) were studied to assess the prognostic value of tumor markers, some (n=7) serially.

The total number of PET/CT scans exceeds 200.

The evaluation criteria were complete metabolic response (CMP) , partial metabolic response (PMR), stable disease (SMD), progressive disease (PMD) . The parameters SUV max, SUV mean, MTV, TLG and sum of diameters of selected lesion were calculated .

Descriptive and analytical statistical methods were used, including correlation and ROC analyses.

The results and discussion are in 4 sections as follows:

1. PET/CT for staging and restaging and its place in the diagnostic algorithm for therapy selection.

In this section, the author points out the more frequent use of PET/CT than reported in the literature, the high variability in follow-up periods, and the inadequate follow-up of tumor markers, emphasizing the need for standardized follow-up protocols.

The higher frequency of lung metastases is indicated (48% compared to literature data (10-30%) which is explained by the higher percentage of rectal carcinoma in the sample). The lack of a current tumor marker in 68% of patients is indicated, as a deviation from generally accepted practice. Patients are distributed, in addition to the localization of the primary tumor, by clinical stage (including indeterminate, designated as stage V with incomplete lymphatic dissection, usually with a poor prognosis). In the group, it is striking that 62% of patients are at risk (III and IV and indeterminate). cl. stage/. PET/CT was used within the framework of dynamic follow-up in half of

between their values above the median for non-responsive lesions, as a prognostic indicator (ROC analysis) and as a means of patient selection.
In conclusion, the author points out that there is a greater likelihood of local control in oligometastatic disease. The group of patients unsuitable for systemic therapy had an overall response rate (ORR) of 33% compared to 27% for those with combination therapy, confirming the meaningfulness of the local therapeutic approach.
The weaknesses of the study, which may affect the conclusions, are explicitly highlighted, namely - a single-center study, entirely dependent on routine practice, without research conducted solely for the purposes of the study.

3. Application for evaluating the effect of radiofrequency ablation .
23 patients with 28 lesions were studied, in parallel with contrast-enhanced ultrasound. Of these patients, 16 had a different primary localization, and in fact the effect of the method on liver lesions with different histology was evaluated. However, the majority of patients had CRC. 39% of the patients had no other dissemination , and the remaining 61% had lung, bone, skin lesions, or combined lesions in several locations. In these cases, ablation of a solitary lesion aims to reduce the tumor burden, which explains the presence of systemic therapy in all of them, as well as in some of the other patients or in total in 78% of the group.
Again, the effect is compared in one or more treated lesions.
The lesion-specific response for all patients was 50%, with progression being 36%, the PERCIST assessment performed the general course of the disease is a 43% response to 44% progression parallel to the local.
The best response was in patients with hepatocellular carcinoma - 100%, and patients with CRC had a 57% response. Comparison with CEUS showed a 70% agreement, with PET/CT appearing to be a more sensitive 100%, specific 88 % and accurate 96% method for diagnosing metabolically active residual lesion, better distinguishing it from necrosis. The determination of sizes between the two methods again showed incomparability.
The main drawback highlighted in the discussion is the lack of long-term follow-up and not so much the heterogeneity of the group as the lack of sufficient cases in the subgroups.

4. The last task examines the relationship between metabolic parameters and tumor markers, analyzing 18 patients with CRC in whom the indicators SUV max , SUV mean , MTV and TLG and the sum of the lesion diameters are correlated with the carcinoembryonic antigen CEA and Ca19-9. Patients were selected in whom the examination interval was not greater than 1 month and in the meantime there was no therapy. In 39% of the patients (n=7) serial measurements of tumor markers

conclusions have been drawn on each of the achieved tasks. In addition to being the first of its kind in Bulgaria, the study is pioneering in a broader aspect because it defines a broader role of the study in the diagnostic algorithm of colorectal carcinoma.

IN CONCLUSION, I highly appreciate the presented work of Dr. Gabriela Mateva "The role of positron emission computed tomography (18F-FDG PET/CT) in patients with colorectal carcinoma". It represents the first comprehensive study on this issue in Bulgaria, with important practical contributions and a precise justification for the application of this modern nuclear medicine method. Considering the above, I strongly recommend of the specialized scientific jury to allow this dissertation to be defended for the acquisition of the educational and scientific degree of Doctor of Medicine by Dr. Gabriela Hristova Mateva.

Respectfully:

Prof. Marina Garcheva -Tsacheva, MD .

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