WWW.BULRAD.BG

РЕНТГЕНОЛОГИЯ И РАДИОЛОГИЯ

ПРАВОПРИЕМНИК НА "ИЗВЕСТИЯ НА БЪЛГАРСКОТО РЕНТГЕНОЛОГИЧНО ДРУЖЕСТВО"

ROENTGENOLOGIA RADIOLOGIA

1`22

Том/Volume LXI, ISSN 0486-400X

РЕНТГЕНОЛОГИЯ И РАДИОЛОГИЯ
ROENTGENOLOGIA RADIOLOGIA

ADDRESS FOR CORRESPONDENCE:

Lidia Chavdarova, MD
Clinic of Nuclear Medicine,
University Hospital on Oncology,
Sofia
e-mai: dr.lidia.chavdarova@gmail.com

Added Value of Nuclear Medicine Methods in Staging, Restaging and Follow-up of Merkel-cell Carcinoma – review and own clinical experience

L. Chavdarova[1], I. Gavrilova[2], E. Piperkova[1]

[1]Clinic of Nuclear medicine, University Hospital on Oncology – Sofia, Bulgaria
[2]Clinic of Oncodermatology, University Hospital on Oncology – Sofia, Bulgaria

АДРЕС ЗА КОРЕСПОНДЕНЦИЯ:

Д-р Лидия Чавдарова
Клиника по нуклеарна медицина
УСБАЛО София
e-mai: dr.lidia.chavdarova@gmail.com

Принос на нуклеарно-медицинските методи в стадирането, рестадиранетои проследяване на Меркел-клетъчния карцином – литературен обзор със собствен клиничен опит

Л. Чавдарова[1], И. Гаврилова[2], Е. Пиперкова[1]

[1]Клиника по нуклеарна медицина, УСБАЛО – София
[2]Клиника по онкодерматология, УСБАЛО – София

Abstract. Merkel-cell carcinoma (MCC) is a rare cutaneous malignancy with a complex etiology, histopathology and aggressive behavior with high mortality. The necessity for correct staging to define adequate on-time treatment in oncology is undoubtedly influenced by contemporary imaging diagnostics. For MCC however, an established diagnostic algorithm is still missing. Modern hybrid SPECT/CT and PET/CT nuclear medicine (NM) methods play an essential role for accurate definition of loco-regional lymph node status and whole-body TNM staging and restaging to individualize the therapeutic algorithm.

Key words: MERKEL-CELL CARCINOMA. SPECT/CT. PET/CT

Резюме. Меркел-клетъчният карцином (МКК) е рядък кожен тумор с комплексна етиология, хистопатология и агресивен характер с висока смъртност. Необходимостта от коректно стадиране за определяне на адекватно навременно лечение в онкологията е неизменно свързана със съвременните образно-диагностични подходи. За МКК обаче все още липсва утвърден диагностичен протокол. Модерните хибридни SPECT/CT и PET/CT нуклеарно-медицински (НМ) методи имат съществена роля за точно определяне на регионалния лимфонодален статус и целотелесното TNM-стадиране и рестадиране за насочване на индивидуализирания терапевтичен алгоритъм.

Ключови думи: МЕРКЕЛ-КЛЕТЪЧЕН КАРЦИНОМ. SPECT/CT, PET/CT

Introduction

Etiology and pathogenesis: *Neuroendocrine carcinoma of the skin (NCS)*, also known as Merkel cell carcinoma (MCC), is a rare malignant disease of the skin. Though assigned to the group of neuroendocrine tumors (NET), the origin of the tumor cells is arguable. After 1980, with the introduction of anti-citokeratin 20 (CK20) antibodies, which makes its diagnostics easier, the incidence of MCC increases, surely connected with the more precise histological verification.

The tumor is known for its aggressive behavior and high mortality rates – 33-46%, it takes the second place among cancers of the skin as a reason for fatality after malignant melanoma. More than 37%

Roentgenology & Radiology, 2022, LXI: 29-36

of cases in the world have metastatic lymph nodes (LN) at time of diagnosis, in 6-12% the disease presents itself with distant metastases [1]. NCS affects predominantly adults over 70 years.

Ultraviolet rays are considered as main etiologic factor. People with fair skin are mostly affected, males predominate (1). Most frequent sites of MCC appearance are the exposed to sunlight body parts – the skin of the head, face mostly, neckline, upper limbs, especially the back of the hands. Other associated etiologic factors are immune-suppression (e.g. the risk of MCC appearance is 13 times higher in HIV-positive patients and 30-50 times higher in patients with chronic lymphocytic leukaemia), as well as the presence of **Merkel-cell human polyoma virus (MCPyV) –** in ~ 80% of studied patients with NCS, though the virus could not be the only cause of the disease. Some **genetic anomalies** also range among the risk factors – most common is (1p36), trisomy 1, trisomy 6, trisomy 18 and deletion of chromosome 7 [1].

NCS is often associated with oncohematologic disorders and rises the risk for their development. It is combined with another type of skin cancer in more than 30% of cases – e.g. squamous cell carcinoma, basal cell carcinoma, skin melanoma, carcinoma or sarcoma of skin adnexa.

Clinics and diagnostics

MCC arises as a fast growing, usually asymptomatic, hard and well-defined tumor lesion. Its color could vary from violet-black, pink, livid up to identical to surrounding skin. In 15% the disease presents itself directly with metastatic LN and/or visceral metastases and the primary could not be found.

Schematically the clinics of NCS lesions could be summarized with the acronym **AEIOU** [2]:

Asymptomatic
Expanding rapidly
Immune suppressed
Older than 50years
UV- exposed fair skin

The diagnosis is mainly histologically and especially immunohistochemically (ICC) based. Any clinical suspicion for MCC should be directed to excisional biopsy.

All NCS are cytokeratin-20 positive and cytokeratin-7 negative (CK20+/CK7-). Doubtful for MCC skin lesions should be examined with ICC for specific markers and to make differential diagnosis – chromogranin A, synaptophysin and CK-20 [3].

Staging. Exact tumor staging at time point of diagnosis is of extreme importance in determining therapy and prognosis.

The primary tumor (T) is staged based on its extensive growth as in skin cancer, but its biologic behavior is closer to the one of malignant melanoma, so N- and M-staging is identical to that of melanoma. In 32% of cases regional LN are negative at clinical examination but positive for micrometastases. That's why exact staging requires performing *a sentinel lymph node biopsy* (SLNB). In histologically proven negative SLN, 5-year-survival rate reaches 76%, while in patients with clinically negative LN with no staging SLNB it is only 59%. The tumor spreads mainly in the first 3 years, involving regional LN, followed by distant skin metastases, engagement of the lungs, CNS, bones and liver.

Therapy. Aggressive behavior and disease specifics require precise choice of therapeutic strategy, multidisciplinary consult, based on disease stage, status of regional LN and patient's performance status.

There are established models for therapeutic behavior in loco-regional disease. In the advanced form of MCC, however, there is still no consensus for the most effective therapeutic algorithm.

The main curative method in loco-regional NCS is surgery – a wide excision of primary with 1-2 cm defence zone, depending on its thickness, on assumption *Mohs-technique* for the delicate face zones if feasible.

According to stage, following therapeutic procedures include radiotherapy and medicinal (mainly immune-) therapy. In patients with clinically positive regional LN radical LN dissection is performed with obligatory adjuvant radiotherapy [4], as MCC is radiosensitive. In microscopically verified metastatic regional LN, again radical LN dissection follows with recommended aduvant radiotherapy in the zone. Standard chemotherapy regimen is recommended only for stage IV, mainly for palliative care.

Only virus-positive NSC express PD-L1 so plenty of clinical studies using immune therapy with monoclonal anti-PD-1 (Pembrolizumab) and anti-CTLA-4 (Ipilimumab) have started. Since 2020, the most effective up to date anti-PD-L1 monoclonal antibody Avelumab is being reimbursed in our country as first and second-line treatment.

Follow-up. The course of the disease is extremely aggressive, with tendency for relapses and fast progression. This implicates the need for adequate and precise follow-up and monitoring of patients

Thorough physical examination including LN should be done every 3-6 months in the first 2 years and every 6-12 months afterwards. In our country in the first 2 years the patients are examined monthly. Imaging is required in any clinical suspicion for regional LN, as a routine screening procedure it should be done in high-risk patients. In the case of subjective complaints or present clinical suspicion, a whole-body PET/CT is recommended.

Role of NM methods in the diagnostic algorithm and monitoring of MCC patients SPECT/CT – hybrid lymphoscintigraphy and biopsy of sentinel lymph nodes

The concept of SLN is introduced in 1977 by Cabanas in penile carcinoma [5] and developed afterwards for different localisations. Fee et al. define lymphoscintigraphy as pointing the route of lymph drainage from the primary in 1978 [6] and in 1990, at the annual meeting of surgical Society, Morton et al introduce lymphatic mapping of the first tumor-draining LN – the "guard", the sentinel (7, 8). Afterwards this technique is introduced for different solid tumors, among which predominantly in breast cancer and tumors of head and neck.

Scintigraphic mapping of individual lymph drainage from the tumor region has proven its significance in long-term world praxis, with or without additional intraoperative dye-labelling. The experience in malignant melanoma has shown that primary lesions of torso, as well as those of head and neck, often have unpredictable lymph drainage. In head and neck tumors additional problem is the anatomic complexity with following technical difficulties for intraoperative detection and excision of SLN. In MCC an unpredictable lymph drainage has been reported in 37-85% of cases [9]. To overcome these problems, nuclear medicine introduced an appropriate apprentice in the last decade – hybrid SPECT/CT. In modern NM clinics, sentinel lymphoscintigraphy is performed nowadays with exact combined anatomical, structural and functional imaging, which helps the surgeon immensely.

In the Clinic of Nuclear medicine in the University Hospital on Oncology in Sofia, lymphoscintigraphy was introduced in clinical practice by Prof. E. Piperkova in 1993, as a routine procedure in malignant melanoma and breast cancer, in fewer cases in gynecological and head and neck malignancies. Our team work with the Clinic of Oncodermatology in the University Hospital on Oncology in particular helped gathering rich clinical and organizational experience [10, 11]. Up to date successful collaboration with surgical clinics allows labelling SLN and following biopsy to be performed both as a one-day (lymphoscintigraphy and biopsy in the same day) as well as a two-day (SLN mapping on day 1, biopsy on day 2) procedure. The 2-day protocol allows performing the scintigraphic imaging as an ambulatory procedure, preceding hospitalization. This enables SLN-mapping also for patients who would get their biopsy in hospitals without a nuclear medicine department. In these cases, labelled SLN on day 1 can be detected via gamma-probe and excised on day 2 in a different hospital and even in a different town.

Staging sentinel biopsy in patients with clinically negative regional LN is performed together with the definitive /wide/ excision in the region of the primary, after previous diagnostic excision of the tumor itself and histologic verification. This algorithm is established in world's practical guidelines also for MCC [12] and is routinely applied when indicated. SLNB is a procedure for early restaging of patients from stage I and II into stage III. In MCC clinically invisible LN metastases in different studies rate between 26-32%, and the clinical presentation could take up to 8 months [13]. Patients with a positive SLN have higher risk of in-transit metastases and would profit from adjuvant radiotherapy including the in-transit field. In the case of positive SLN and adjuvant target therapy of the lymph region, overall survival (OS) and disease specific survival (DSS) are similar to those in patients with a negative SLN [14]. The lack of metastases in SLN has a high negative predictive value (NPV) as the cases of "skip" metastases surpassing the sentinel node are quite rare *(<2%)*. A metaanalysis with 136 patients with head and neck MCC (stage I-II) found that in 19,2% of cases a lymph node relapse in the regional nodal basin appears even if the SLN was negative (false-negative SLN), which, though statistically non-significant, is observed more often in primaries along the middle line of head and neck [15]. In addition, Liu et al. define SLNB as a more sensitive staging method ^{18}F-FDG PET/CT in stage I and II patients [16].

Protocol

The procedure of SLN labelling includes the application of a specific radiopharmaceutical (RPh), containing colloid particles of a certain size, labelled with the routinely used and readily available radionuclide - 99mTc. The application of the RPh is done intra-

Roentgenology & Radiology, 2022, LXI: 29-36

dermally in 4 spots around the cicatrix of the primary lesion, in total volume of 0,4ml and total acitivity 37 MBq (in 1-day protocol) – 72MBq (in 2-day protocol) (Fig. 1a).

Hybrid SPECT/CT is performed as an obligatory stage of the nuclear medicine imaging, right after the application of the tracer and the standard dynamic and/or static planar projections, visualizing the direction of the lymph/radiotracer flow (Fig. 1b).

In the Clinic of Nuclear medicine in the University Hospital on Oncology this technique has been applied since 2013, after the installation of the two-headed 16-slice-SPECT/CT gamma camera - Symbia T16 (Siemens). Using the low-dose CT-information, the exact anatomic localization of the "hot" SLN on SPECT-images becomes possible, its size and structure can be recorded, closely situated LN could be differentiated form one another or defined as "second-tier" lymph nodes. Additional structural information about the nearby lying organs could also be obtained from the low-dose CT-images of the scanned region.

After detecting the SLN its projection site on the skin of the patient is marked with paint. The nuclear-medicine physician writes the report which goes to the surgeon together with the imaging material. In the OR the surgeon holding the gamma probe searches for the "hottest" LN in the region labelled by SPECT/CT, using sound signal and measuring counts of radioactivity (Fig. 2).

Carrying the highest risk for (micro) metastatic spread, the SLN defines the status of the whole lymphatic region, the following therapeutic algorithm and patient's prognosis. The need of a radical lymph node dissection is herewith eliminated, reducing patient's morbidity (lymphedema, neuralgia etc.) and costs. The work load for the pathologist is also reduced - he could examine only 1-3 SLN in detail instead 10-20 lymph nodes in the case of a regional dissection. Obligatory conditions for performing SLNB are the early clinical stage of the disease, predominant lymphatic spread, lack of clinically suspicious regional LN. The patient should have signed an informed consent about the application of minimal activity radioactive material, with no significant risk of side-effects – allergic or radiation-induced. The nuclear medicine physician informs the patient about the sense and meaning of the procedure, and that "hot" does not mean "carrying metastasis". Thus the psychological pressure on the patient is reduced.

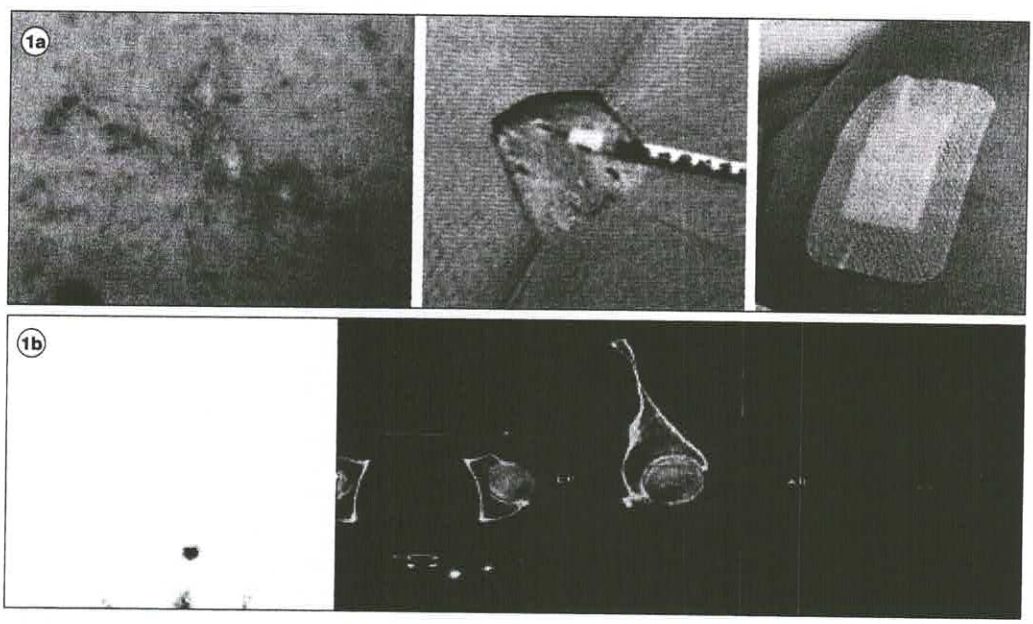

Fig. 1.

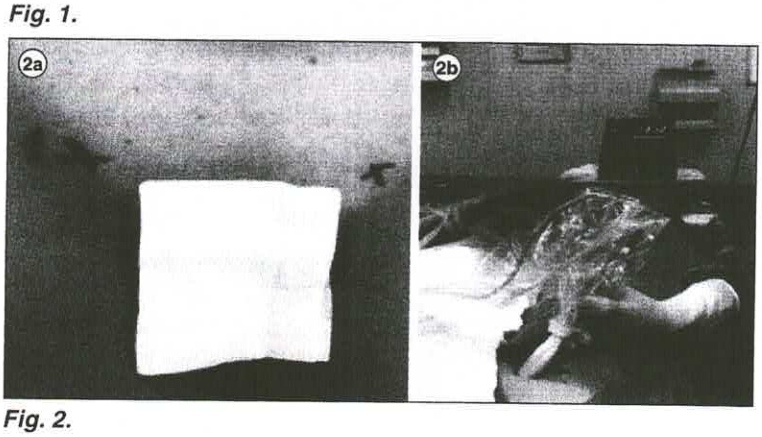

Fig. 2.

Basic prerequisite for performing sentinel lymphoscintigraphy and SLNB is the good collaboration and communication between the departments of nuclear medicine, surgery and pathology, their team work. The correct selection of appropriate for the procedure patients is in the hands of the surgeon-oncologist. Patient's history is of great importance – e.g. if there have been previous surgeries in the region of the primary that could possibly derive the lymph flow into the wrong direction. Checking regional lymph nodes before scintigraphy via ultra-

sound is crucial. The final indication check, knowing the whole clinical data, is done by the nuclear medicine physician, responsible for the use of radioactive pharmaceutical.

^{18}F-FDG-PET/CT in staging and follow-up of MCC

Having in mind the similar biologic behavior with melanoma and the considerable metastatic potential, PET/CT can be recommended for use as a staging method even in the early I-II stages of NSC, especially if the SLN is possible for micrometastases. In addition, PET/CT could be of significance to better define the fields for future radiotherapy-planning.

MCC is typically FDG-avid, with SUVmax range for distant metastases 7.2–11.5 [17]. The method is more sensitive for detection of low-differentiated NET with Ki-67 >20%, as it gives indirect but important prognostic information. In different studies sensitivity of PET/CT reaches 90%, specificity – 98%. Concerning brain metastases MRI stays the gold standard, also because of the intensive physiologic uptake of FDG in brain parenchyma. Nevertheless, in our full-digital PET/CT practice using different contrast-levels, we happen to observe well-defined brain lesions with greater uptake than normal parenchyma in patients with melanoma [18], which made us perform the PET/CT scan head-to-feet – both in melanoma and in MCC. Initial ^{18}F-FDG PET/CT changes therapy in ~ 40% of patients, mostly upstaging [19]. (Fig. 3).

Not only the surgeon-oncologist, but also the nuclear medicine physician should pay special attention to the skin in the region of the primary as MCC tends to engage normal-looking surrounding skin with appearance of in-transit and satellite lesions [20, 21].

Another important possibility of PET/CT is its role in the establishment of newer immunotherapeutic drugs and the assessment of their effectivity [22, 23] (Fig. 4).

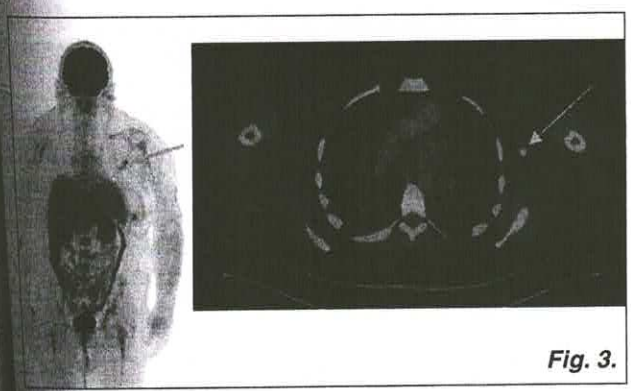

Fig. 3.

Having in mind the complex metabolic whole-body influence of immune therapy, PET/CT is the most suitable method for assessment of treatment effect, considering both glucose metabolism and structural tumor volume. Very important for adequate image interpretation is considering the immune-therapy modified criteria for treatment effect assessment

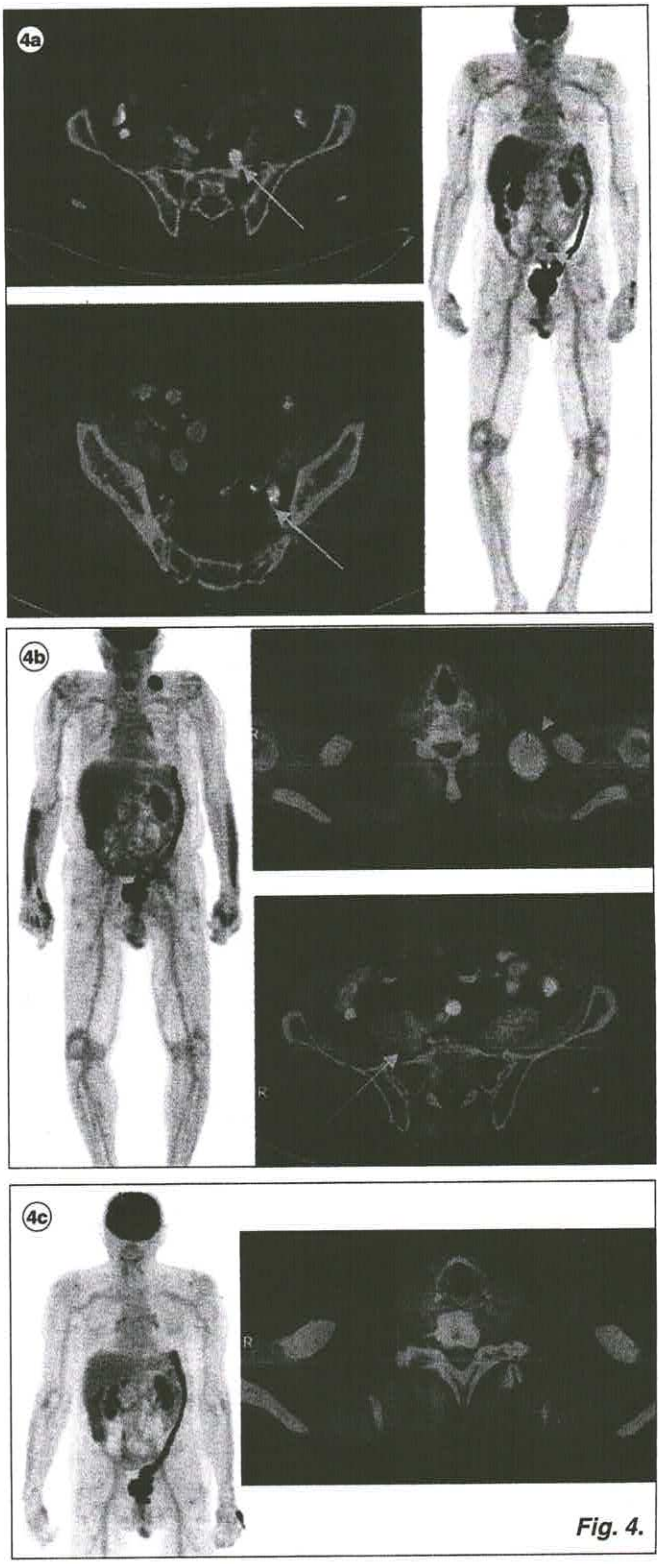

Fig. 4.

(imRECIST) [24] and the correct use of the terms "pseudoprogression" and "hyperprogression". In addition, induction of therapeutic side-effects could be detected functionally as soon as possible in order to deescalate therapeutic protocol and avoid toxicity. Inflammatory side effects of immune therapy are typically FDG-avid and should be kept in mind during interpretation.

During follow-up PET/CT keeps its importance in the case of suspicion of relapse and metastases [12]. In advanced stages of disease also routine intermittent imaging control could be done.

Bone scintigraphy. Being the classic "gold standard" for early diagnostics of bone-metastatic disease, the nuclear medicine physician should be aware of possible immune therapy-induced "flare phenomenon" in the whole-body bone. Enhanced bone density due to therapy on CT should be well discriminated from new lesions. Most metaanalyses show however higher sensitivity for detection of bone metastases for PET/CT than for bone scan in different solid tumors [25-27].

Specific somatostatin-receptor imaging in staging and follow-up of MCC

Somatostatin-receptor analogues for SPECT/CT

Similarly to other neuroendocrine tumors, MCC shows high expression of SSTR types 2A and 5.

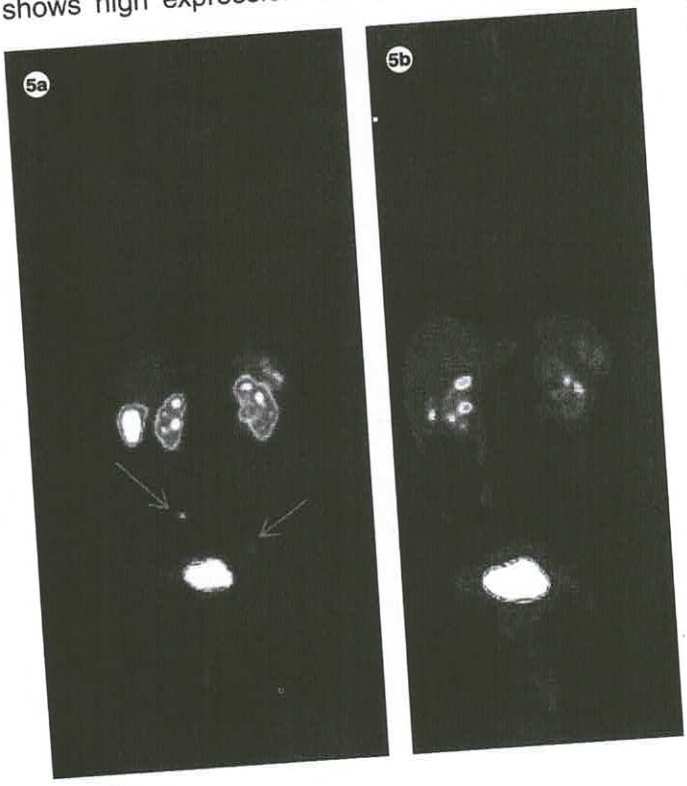

Fig. 5.

[28]. This allows the use of radiolabeled somatos
tin-receptor analogues for SPECT and PET both
diagnostics and for therapy – theranostic agents [

Used in the past, „OctreoScan" with Indium
(^{111}In)–pentetreotide was blown away by ^{99m}Tc-
DA/HYNIC-Tyr3-Octreotide, better known as ^{99}
Tektrotyd, with its lower radiation burden and b
image quality, using the cheaper and much ea
to deal with ^{99m}Tc. Though NET and especially
are rare oncologic entities, since the initiatio
this RPH in our Clinic in 2019 we managed to
some experience and achieve good results tail
therapy in NET patients. In a 1-year time (09
– 09.2020) diagnostic-staging and restaging st
have been performed on 15 patients with dif
NET (small bowel, pancreas, small-cell lung c
and others) in our Clinic (Fig. 5 a-b).

The accessibility of ^{99}mTc-Tektrotyd in da
clear medicine practice makes it possible to
diagnostics and follow-up also in MCC patien
SSR-expression, especially when 68Ga-(
PET/CT is not available.

Somatostatin-receptor analogues (SSRA) PET/CT

Labelled with ^{68}Ga-SSRA, ^{68}Ga DOTA (tetr
clododecane tetraacetic acid)–Tyr3-octreota
TATATE), ^{68}Ga DOTA–Nal3-octreotide (DOT
and ^{68}Ga DOTA–Tyl3-octreotide (DOTATO
PET tracers with high affinity for SSR, that tu
a substantive part of routine diagnostic algo
NET. The basic advantages of these radio
ceuticals in comparison to those for SPEC
ability to detect smaller tumor lesions in liv
and normal-sized LN. ^{68}Ga-DOTA-analogu
ported to have up to 97% sensitivity for de
primary and metastatic NET lesions in co
with CT – 61% and somatostatin-recepto
imaging – 52%. On the other hand, the rad
SSR-avidity of target lesions on PET is a p
for possible peptide-radioreceptor therapy
the therapeutic algorithm for some NET.

^{18}F-FDG and ^{68}Ga-DOTATOC/DOTAT
basically different sides of NSC biology.
only 18F-FDG-PET/CT in included in NC
lines but ^{68}Ga-DOTA-RPhs may be used
selected cases with high SSR-express
sonalized" algorithm with a theranostic g
ing PRRT (Fig. 6).

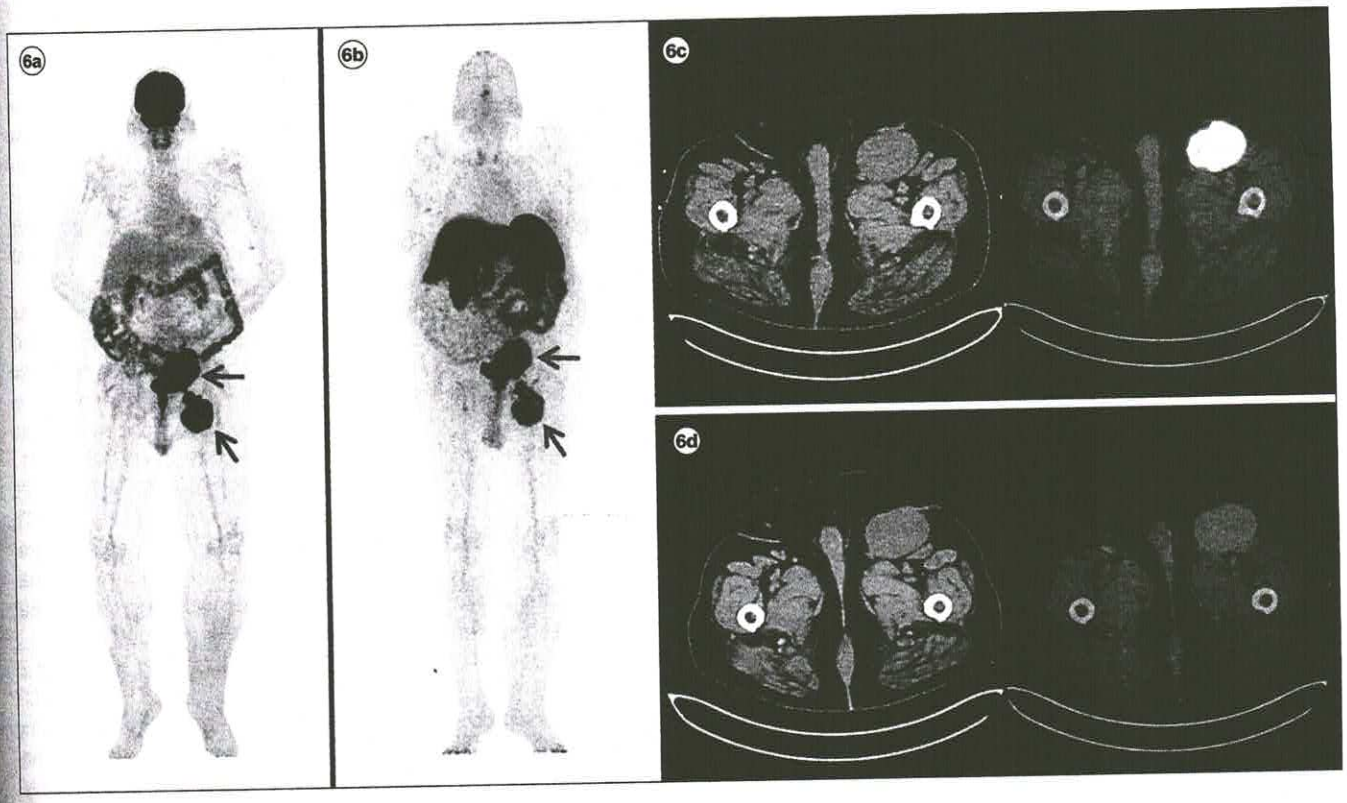

Fig. 6.

Conclusion

Contemporary diagnostic protocols in staging and follow-up of oncologic diseases include early functional-molecular and hybrid imaging with the possibility of theranostics – all domain of clinical nuclear medicine. In aggressive though relatively rare Merkel-cell carcinoma, SPECT/CT detection of the SLN and ^{18}F-FDG-PET/CT are important parts of diagnostic algorithm, according to the stage of disease. Team work of the clinics of nuclear medicine, oncologic surgery and pathology is obligatory for setting up the correct therapeutic behavior in MCC patients.

The authors declare no conflict of interest!

References

1. *Schadendorf D, Lebbe C, Hausen A et al.* Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer. 2017 Jan; 71:53-69. doi: 10.1016/j.ejca.2016.10.022.
2. *Heath M, Jaimes N, Lemos B, et al.* Clinical characteristics of Merkel cell carcinoma. Dermatol 2008 Mar;58(3):375e81.
3. NCCN Guidelines, Melanoma , Merkel cell carcinoma Version 1.2019, NCCN.org.
4. *Hughes MP, Hardee ME, Cornelius LA, Hutchins LF,Becker JC, Gao L.* Merkel cell carcinoma: epidemiology, target,and therapy. Curr Dermatol Rep 2014 Jan 22;3:46e53.
5. *Cabanas RM.* An approach for the treatment of penile carcinoma. Cancer. 1977; 39 (2): 456-66.
6. *Fee HJ, Robinson DS, Sample WF, Graham LS, Holmes EC, Morton DL Surgery.* The determination of lymph shed by colloidal gold scanning in patients with malignant melanoma: a preliminary study. 1978 Nov; 84(5):626-32.
7. *Morton D, Cagle L, Wong J, et al.* Intraoperative lymphatic mapping and selective lymphadenectomy: technical details of a new procedure for clinical stage I melanoma. Presented at the Annual Meeting of the Society of Surgical Oncology; Washington, DC. 1990.
8. *Morton DL, Wen DR, Wong JH, et al.* Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg. 1992;127:392–399.
9. *Kritikos N, Priftakis D, Stavrinides S et al.* Nuclear medicine techniques in Merkel cell carcinoma: A case report and review of the literature. Oncol Lett. 2015 Sep; 10(3): 1610–1616.
10. *Киров К, Пиперкова Е, Цоневска А, Чавдарова Л, Гаврилова И.* Сравнение на резултатите от предоперативната лимфосцинтиграфия и биопсията на стражевите лимфни възли при пациенти с малигнен меланом. Онкология. 2008; 36:38-49.
11. *Киров К.* Биопсия на стражевите лимфни възли при пациенти

с малигнен меланом. Дисертационен труд за научната и образователна степен „Доктор". УСБАЛО-ЕАД. София. 2009. 182 стр.

12. *Bichakjian CK, Olencki T, Aasi SZ et al.* Merkel Cell Carcinoma, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2018;16(6):742–774.
13. *Messina JL, Reintgen DS, Cruse CW et al.*Selective lymphadenectomy in patients with Merkel cell (cutaneous neuroendocrine) carcinoma. Ann Surg Oncol. 1997;4(5):389-95).
14. *Sims JR, Grotz TE, Pockaj BA et al.* Sentinel lymph node biopsy in Merkel cell carcinoma: The Mayo Clinic experience of 150 patients. Surg Oncol. 2018; 27(1):11-17.
15. *Karunaratne YJ, Gunaratne DA, Veness MJ.* Systematic review of sentinel lymph node biopsy in Merkel cell carcinoma of the head and neck. Head Neck. 2018 Dec;40(12):2704-2713. doi: 10.1002/hed.25345.
16. *Liu J, Larcos G, Howle J, Veness M.* Lack of clinical impact of 18 F-fluorodeoxyglucose positron emission tomography with simultaneous computed tomography for stage I and II Merkel cell carcinoma with concurrent sentinel lymph node biopsy staging: a single institutional experience from Westmead Hospital, Sydney. Australas J Dermatol 2017;58(2):99–105.
17. *Hawryluk EB, O'Regan K, Sheehy N et al.* Positron emission tomography/computed tomography imaging in Merkel cell carcinoma: a study of 270 scans in 97 patients at the Dana-Farber/Brigham and Women's Cancer Center. 2013. J Am Acad Dermatol. 2013 Apr;68(4):592-599.
18. *Chavdarova L., I. Gavrilova, E. Piperkova.* ^{18}F-FDG-PET/CT in the staging, follow-up and treatment tailoring of malignant melanoma – first "full-digital" experience in a single institution. 34-th Congress of EANM – Virtual – 20-23.10.2021. Clinical Oncology Track – TROP Session: Gynaecological and Melanoma. Eur J Nuc Med Mol Imaging (2021). 48 (Suppl 1): OP-1078. S 378-S379.
19. *George A, Girault S, Testard A, et al.* The impact of (18)F-FDG-PET/CT on Merkel cell carcinoma management: a retrospective study of 66 scans from a single institution. Nucl Med Commun. 2014 Mar;35(3):282-90. doi: 10.1097/MNM.0000000000000039.
20. *Akaike G, Akaike T, Fadl S et al.* Imaging of Merkel Cell Carcinoma: What Imaging Experts Should Know. RadioGraphics 2019; 39 (7).
21. *Lewis KG, Weinstock MA, Weaver AL, Otley CC.* Adjuvant local irradiation for Merkel cell carcinoma. Arch Dermatol 2006;142(6):693–700.
22. *Eshghi N, Lundeen TF, MacKinnon L, Avery R, Kuo PH.* ^{18}F-FDG PET/CT for Monitoring Response of Merkel Cell Carcinoma to the Novel Programmed Cell Death Ligand 1 Inhibitor Avelumab. Clin Nucl Med 2018;43(5):e142–e144.
23. *Vellani C, D'Ambrosio D, Licata L, Vacchieri I, Bernardo A, Trifirò G.* Monitoring response of advanced Merkel cell carcinoma to avelumab with ^{18}F-FDG PET/CT. Eur J Nucl Med Mol Imaging 2019;46(5):1197–1198.
24. *Hodi FS, Ballinger M, Lyons B, et al.* Immune-Modified Response Evaluation Criteria In Solid Tumors (imRECIST): Refining Guidelines to Assess the Clinical Benefit of Cancer Immunotherapy. J Clin Oncol 2018;36(9):850–858.
25. *Rong J, Wang S, Ding Q, Yun M, Zheng Z, Ye S.* Comparison of ^{18}FDG PET-CT and bone scintigraphy for detection of bone metastases in breast cancer patients: a meta-analysis. Surg Oncol 2013;22(2):86–91.
26. *Qu X, Huang X, Yan W, Wu L, Dai K.* A meta-analysis of ^{18}FDG-PET-CT, ^{18}FDG-PET, MRI and bone scintigraphy for diagnosis of bone metastases in patients with lung cancer. Eur J Radiol 2012;81(5):1007–1015.
27. *Xu C, Zhang R, Zhang H, Zhang Z.* Comparison of ^{18FDG} PET/PET-CT and bone scintigraphy for detecting bone metastases in patients with nasopharyngeal cancer: a metaanalysis. Oncotarget 2017;8(35):59740–59747.
28. *Gardair C, Samimi M, Touzé A, et al.* Somatostatin Receptors 2A and 5 are expressed in Merkel Cell carcinoma with no association with disease severity. Neuroendocrinology 2015;101(3):223–235.
29. *Taralli, S., Sollini, M., Milella, M. et al.* ^{18}F-FDG and ^{68}Ga-somatostatin analogs PET/CT in patients with Merkel cell carcinoma: a comparison study. EJNMMI Res 8, 64 (2018). https://doi.org/10.1186/s13550-018-0423-3.