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Sentinel lymph node (SLN) – SPECT/CT imaging and ^{18}F-FDG-PET/CT follow-up – a contemporary diagnostic algorithm in early stage malignant melanoma for individual treatment tailoring

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Изобразяване на сентинелни лимфни възли чрез SPECT/CT и проследяване чрез ^{18}F-FDG-PET/CT – съвременен диагностичен алгоритъм при ранен малигнен меланом за индивидуализиране на терапията

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Abstract. In the setting of available and very successful adjuvant immune and target-therapy regimens of stage III disease, early stage malignant melanoma (ESMM) requires contemporary diagnostic algorithm for correct staging and follow-up. According to international clinical trials more than 60% of the patients, 5 years after adjuvant treatment in stage III are alive and free of disease recurrence. SLN biopsy (SLNB) is the only opportunity for early restaging from stage I-II to III. While hybrid SPECT/CT is established for precise mapping of SLNB, the role of ^{18}F-FDG-PET/CT in ESMM is still questionable.

The aim of this pilot study is to assess the additional input of SPECT/CT-lymphoscintigraphy prior to SLNB and check for the possibilities of full-digital (fd) ^{18}FDG-PET/CT in the follow-up of ESMM pts.

Резюме. Наличието и достъпността на съвременните адювантни терапевтични протоколи за имуно- и таргетна терапия при трети клиничен стадий (КС) на малигнен меланом, изискват също адекватен и стандартизиран алгоритъм за стадиране на ранните стадии и проследяване на болните. Според международните клинични проучвания, над 60% от пациентите в III КС са в ремисия 5 години след проведено адювантно лечение. Биопсията на сентинелни лимфни възли (БСЛВ) е единствената възможност за най-ранно рестадиране на пациентите от стадий I-II в стадий III. Докато хибридната SPECT/CT е установен метод за прецизно картиране на лимфния дренаж, то ролята на ^{18}F-FDG-PET/CT при ранния малигнен меланом (РММ) все още е дискутабилна.
Целта на това пилотно проучване е да установи добавъчната стойност на SPECT/CT-лимфосцинтиграфията преди БСЛВ и да оцени възможностите на напълно дигиталната ^{18}F-FDG-PET/CT за проследяването на пациентите с РММ.

Material and methods: 77 ESMM patients (36 male, 41 female; 28-83 years; stage IA-IIC) underwent 99mTc-Nanocoll planar and hybrid SPECT/CT imaging. After SLNB, 22 pts were followed up by FDG-PET/CT with overall 28 PET-studies: 17 pts had one scan only, 4 pts – 2, 1 patient – 3. PET/CT was indicated in high risk patients stage IIB/IIC /T3b,T4a,T4bN0M0/ and also in those with more than one lymph drainage zone but only one zone resected for SLN (because of weak intraoperative signal of the second or unwillingness of patient).

Results: SPECT/CT found the SLN(s) in all 77 pts, with successful intraoperative detection of 141 SLN. In 26% of pts patients more than one drainage zone was detected. Micrometastases were found in 17 pts, with respective stage III upstaging. SPECT/CT detected one unexpected intransit subcutaneous focus, proven metastatic; in 5 pts – distinguished lymph "depots". Additionally SPECT/CT found a solid lung lesion in 1 and micronodules in 7pts. In 7.8% of pts preoperative PET/CT was performed based on risk factors – all negative for metastases. In 32.5% of pts postoperative follow-up PET/CT was done, in 20pts free of metastases, in 5 pts – showing progressive disease, in 1 patient - suspicious finding.

SPECT/CT-SLN mapping improves lymphoscintigraphic sensitivity, increasing intraoperative detection rate of SLN, distinguishing possible lymph depots, intransit lesions and unexpected additional pathology from low-dose CT (e.g. lung nodules). fdPET/CT in the follow-up of ESMM could help finding initial /small-sized/ metastases in high-risk patients and in the presence of SPECT/CT-multidirectional lymph drainage. After collection of additional data we intend to assess the dissemination rate of ESMM via fdPET/CT depending on SLN-histologic status. Further studies are needed.

Key words: MALIGNANT MELANOMA. SLN. SPECT/CT. FDPET/CT

Материал и методи: При 77 пациенти с РММ (36 мъже, 41 жени, възраст 28-83г; стадий IA-IIC) се проведе планарно и хибридно SPECT/CT сканиране след апликация на 99mTc-Nanocoll. След БСЛВ, 22 пациенти бяха проследени с общо 28 PET-изследвания: 17 пациенти с 1 скен, 4 с 2, 1 пациент с 3. PET/CT беше показана при високо-рискови пациенти с КС IIB/IIC /T3b,T4a,T4bN0M0/, както и при тези с повече от една лимфно-дренажна област, но само с един резециран регион (заради слаб интраоперативен гама-фотонен сигнал или нежелание от страна на пациента).

Резултати: SPECT/CT детектира общо 141 СЛВ при всички 77 пациенти. При 26% от пациентите се намери повече от една дренажна зона. Микрометастази се намериха при 17 пациенти с последващо рестадиране към по-висок стадий – III. SPECT/CT установи 1 неочакван ин-транзитен подкожен ЛВ, хистологично метастатичен; при 5 пациенти се отграничиха лимфни депа. В допълнение, SPECT/CT намери солидна белодробна лезия при 1 и микронодули при 7 пациенти. При 7,8% от пациентите предоперативната PET/CT се проведе въз основа на налични рискови фактори – всички изследвания бяха негативни за метастатична болест. При 32,5% от пациентите постоперативната PET/CT за проследяване установи ремисия при 20 пациенти, прогресия при 5 пациенти и суспектна находка при 1 пациент.

SPECT/CT-лимфното картиране подобрява лимфосцинтиграфската чувствителност и интраоперативна детекция на СЛВ, отграничава транзиторни лимфни депа, ин-транзитни лезии и неочаквани патологични находки от ндКТ (напр. белодробни нодули). Напълно дигиталната /full digital – fd/ PET/CT в проследяването на РММ подпомага откриването на начални /дребни/ метастази при високо-рискови пациенти и при наличие на разнопосочен лимфен дренаж на SPECT/CT. След оценяване на по-голям обем данни, възнамеряваме да оценим параметрите на дисеминация на РММ с fdPET/CT в зависимост от статуса на СЛВ. Необходими са допълнителни проучвания.

Ключови думи: МАЛИГНЕН МЕЛАНОМ. СЛВ. SPECT/CT. FDPET/CT

Introduction

Contemporary nuclear medicine (NM) hybrid methods SPECT/CT and PET/CT enabled the exact topographic and structural assessment of functional-metabolic images and turned to be extremely helpful in diagnosis, prognosis and treatment tailoring of different malignancies

Malignant melanoma (MM) is well known for its biologic aggressiveness, metastatic potential, worldwide increasing incidence and mortality, complex and expensive treatment in advanced stages. However, contemporary treatment regimens with immune and targeted therapies show highly promising results in the adjuvant setting of stage III melanoma. An adequate diagnostic algorithm for early restaging of stage I-II into stage III is therefore required and of highest importance for individual treatment tailoring and improving the prognosis of the patients.

Sentinel lymphoscintigraphy (SLSc) in combination with hybrid SPECT/CT imaging of the sentinel lymph node and ^{18}F-FDG-PET/CT for whole-body imaging in high-risk patients are the main NM methods suitable for personalized therapy approaches in early-stage melanoma. So far, SLSc is an established method for precise mapping of SLN worldwide, gaining even more significance in the setting of newly appeared adjuvant therapies. In Bulgaria, SLSc with following biopsy of the SLN was introduced in clinical Nuclear medicine at the National University Oncology Centre with the team work of E. Piperkova and K. Kirov in 1993, almost simultaneously with the rest of the world. The procedure was developed in the following years and achieved both clinical routine and scientific success [1, 2]. The implementation of the gamma probe in surgery also took its time and experience curve. However, SLNB after radionuclide mapping is still somewhat feared of (radioactivity), not popular enough in surgical routine in Bulgaria and often passed by. Preoperative patient selection by oncodermatologists is essential and needs to be emphasized on. And last but not least – the role of ^{18}F-FDG-PET/CT in ESMM is still questionable, needing verification.

The need for setting up a standardized diagnostic algorithm for ESMM patients in Bulgaria led to the dedicated collection and analysis of data from SPECT/CT sentinel lymph node scintigraphies with consequent BSLN and follow up ^{18}F-FDG-PET/CT studies in this patient group.

The aim of the pilot study is to define the role and standardize the protocols of NM methods SPECT/CT and PET/CT in ESMM patients with respect to their potential for patients' early restaging, prognostic potential and individualized therapy management. In addition, the principles for interdisciplinary team work between nuclear medicine, oncodermatology, surgical oncology and pathology are discussed.

We collected data from 77 ESMM patients, eligible for sentinel lymphoscintigraphy in the period 02.2020г – 07.2022г. All studies were conducted in the setting of preoperative lymphatic mapping at time point of wide local excision (WLE) of primary lesion with SLNB. 41 women and 36 men were studied, aged 28-83y. The distribution of patients according to histology, localization of primary and preoperative (pre-SLNB) stage is presented in Fig. 1.

Sentinel lymphoscintigraphy was conducted according to European and national guidelines (3). The used radiopharmaceutical was 99mTc-Nanocoll/ Nanotop, applied intradermally at 4 injection sites (x0,1ml) around the scar after diagnostic excision of primary lesion. The used activity was 37 MBq/pt for a 1-day protocol (surgery in the same day), 74-111MBq for 2-days protocol, respectively (surgery 24h p.i.). All patients received planar scans of injection site and registered lymph drainage direction in AP/PA and, if needed, oblique (LPO/LRO) projections with following SPECT/CT of the region with detected „hot" SLNs.

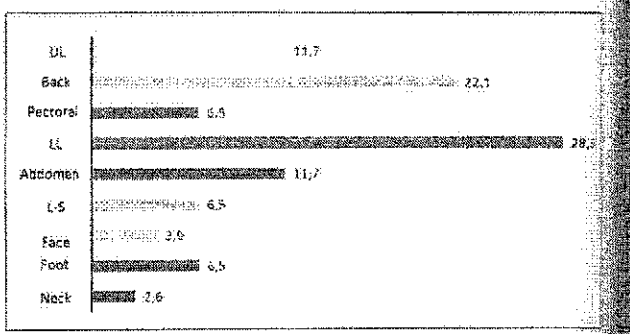

Fig. 1. B. *Localisation of primary MM lesion: UL – upper limb; LL – lower limb; L-S – lumbosacral region*

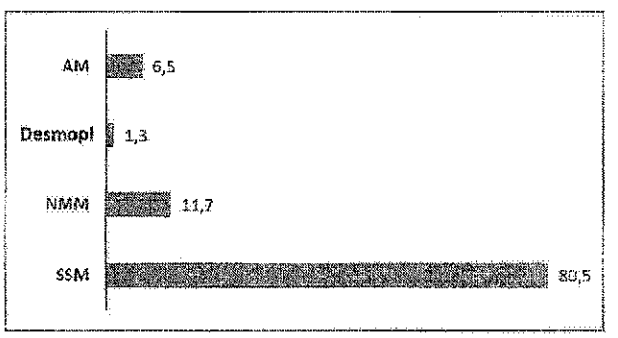

Fig. 1. A. *Malignant melanoma histologic subtype (%): AM – acral; NMM – nodular; SMM – superficial spreading; Desmoplastic MM*

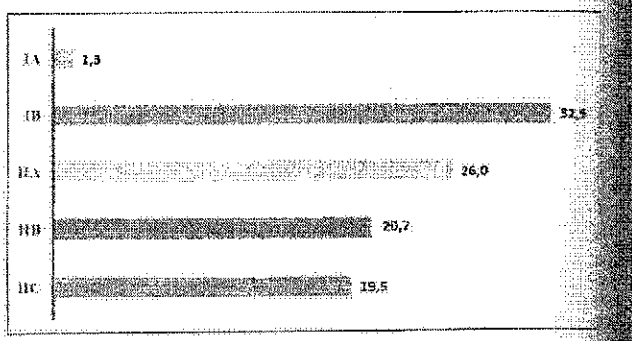

Fig. 1. C. *Preoperative (pre-SLNB) staging of patients (%)*

Results

Lymphoscintigraphy detected at least one SLN in all patients, with 100% discovery rate during surgery. Expectedly, planar imaging revealed less SLNs – 117, whereas hybrid SPECT/CT detected 11,3% more sentinels – 132. Planar imaging failed to detect a SLN in only one patient due to proximity to injection site and "masking" from it. SPECT/CT managed to "unmask" the sentinel in this patient.

The number of visualized SLNs varied between 1 and 4, the most patients with 2 (33) and 1 [29] SLNs. In a few patients false-positive findings were detected – e.g. focal transitory tracer activity without intraoperative correlate, or false negative – e.g. 2 SLNs reported scintigraphically as one because of very close position next to one another.

In 74% of patients we observed lymphatic flow to one drainage basin only, the rest 26% showed more than one. The most common SLN region was the axillary (96 pts) followed by the inguinal (32 pts) (Fig. 2).

During SLNB 141 LN were removed, reported as sentinel on the base of the radioactivity level available and detected with the gamma probe. The difference in the number of scintigraphically detected and intraoperatively removed SLNs is due mainly to some "second-tier" according to NM criteria LN, defined as sentinels in surgery because of the amount of activity and their close proximity.

Pathology revealed micrometastasis in the SLN in 22% of studied patients which led to their restaging from stadium I and II into stage III (Fig. 3). The logical expectation, that higher preoperative stadium would be connected with a larger number of micrometastases in the SLN was confirmed – with a 2,4-fold probability.

All patients that got a stage III after SLNB, were appointed to adjuvant immune or target therapy according to clinical and mutation status, with regular clinical and imaging follow-up.

Expectedly, all primaries on upper limb drained into ipsilateral axilla and all lower limb lesions drained

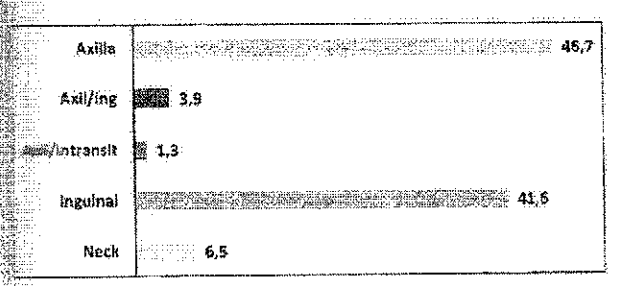

Fig. 2. Patient distribution according to lymph drainage region (%). Axil/ing – drainage both to axillary and inguinal region; Axil/intransit – drainage both to axillary and and an intransit SLN

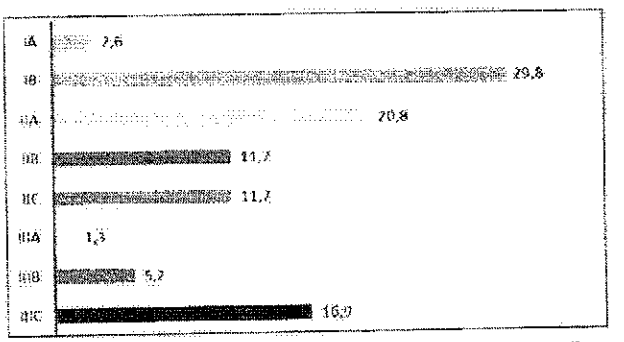

Fig. 3. Distribution of patients according to post-SLNB stadium

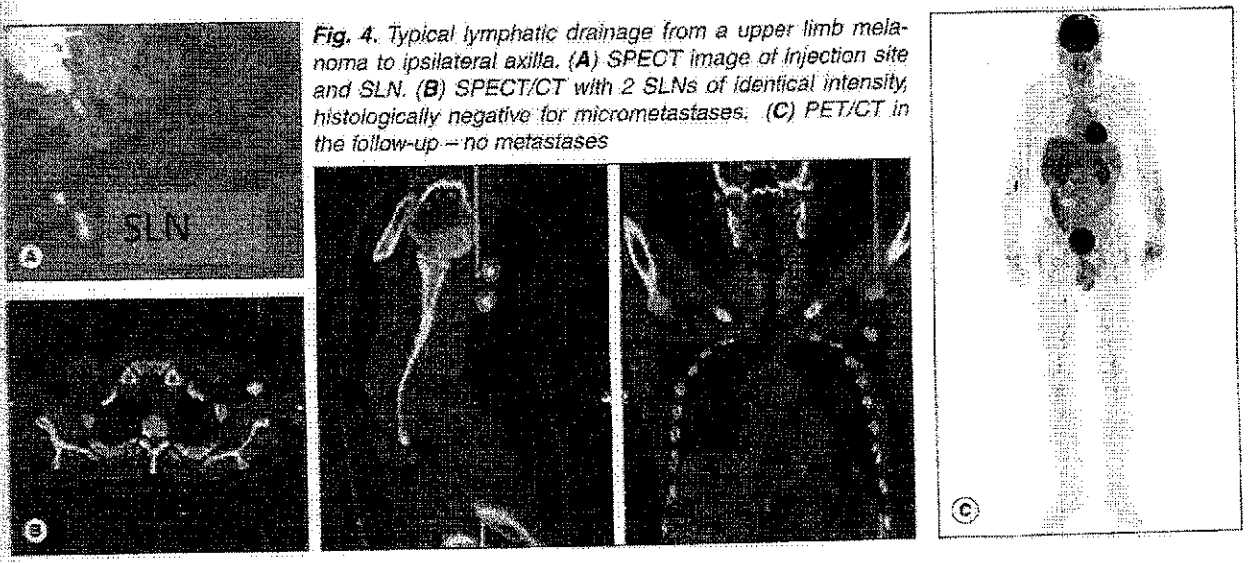

*Fig. 4. Typical lymphatic drainage from a upper limb melanoma to ipsilateral axilla. (**A**) SPECT image of injection site and SLN. (**B**) SPECT/CT with 2 SLNs of identical intensity, histologically negative for micrometastases. (**C**) PET/CT in the follow-up – no metastases*

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Fig. 5. Typical lymphatic drainage from a right thigh melanoma to ipsilateral inguinal region (NMM, pT3b, IIB). (A) Planar image. (B) Injection site - hybrid. (C) SPECT/CT: 1 SLN and 1 second-tier neighbour LN right inguinal. Histologically: pN(sl)0. (D, E) – PET/CT in follow-up – no dissemination

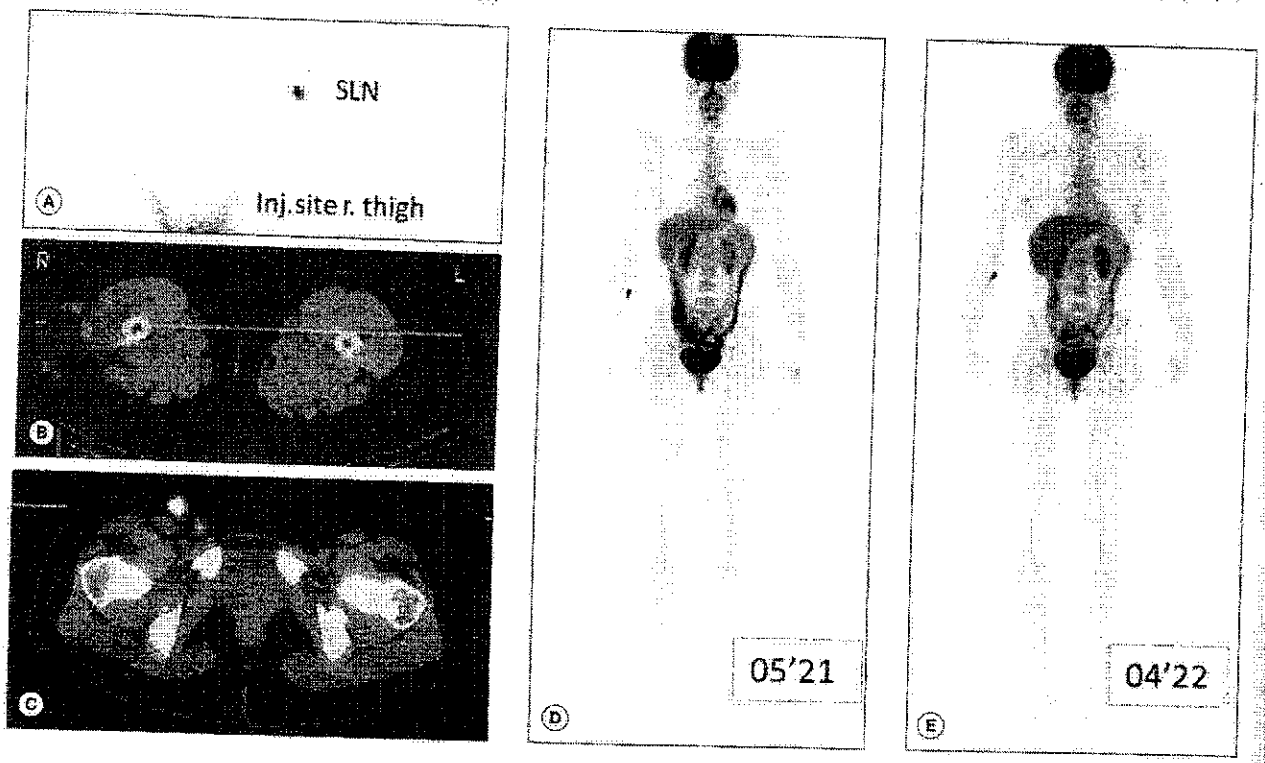
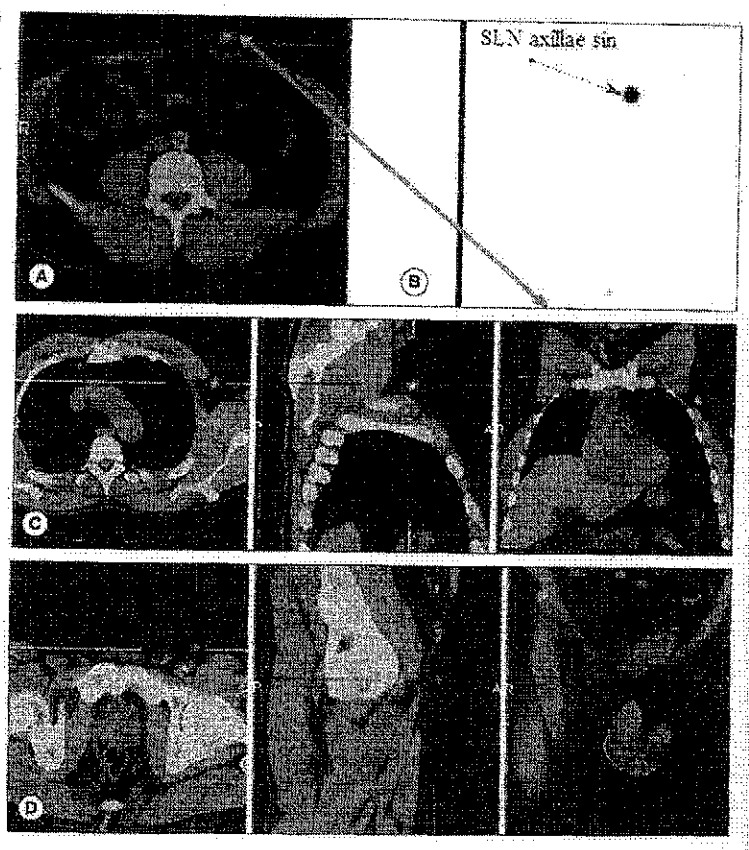


Fig. 6. EIA, 50y. SSM on abdominal skin, left from midline (A - injection site, red arrow), pT2a, IB. Lymph flow to left axilla (B – planar, C – hybrid) and left inguinal (D) regions. Histologically micrometastatic SLN in axilla. Postoperative stage IIIA, appointed for adjuvant target therapy.



into ipsilateral inguinal region (Fig. 4 and 5). No SLN in cubital and popliteal areas were found in our study.

In 20 pts we observed lymph flow to more than one basin, in 3 pts simultaneously to axilla and inguinal region – both biopsied (Fig. 6). As reported in literature, more than one drainage basin was more often to be found if the primary is on the skin of torso – back, abdomen and lumbosacral regions.

Some patients with simultaneous drainage to more than one region but with different intensity of radiotracer uptake, there should be a discussion between the nuclear medicine physician and the surgeon. After gamma-probe measurements and having in mind patient's informed consent, the surgeon could decide to take bi-

...apsy of one (more intense) region only, and leave the other on clinical observation, using ultrasound and/or PET/CT. In our study group, there's still no evidence of relapse in a "left over" drainage region, without SLN-biopsy.

In 7,8% of studied patients, preoperative (pre-SLNB) PET/CT was performed, all of them being negative for residual tumour tissue of the primary (after diagnostic excision) and no dissemination. In 26 (32,5%) patients (9 of them with a positive SLN), postoperative PET/CT was done, in 20 of them with no sign of metastases, in 5 patients progressive disease, in one patient – suspicious finding. Pathologic findings were as follows – an intransit LN in one patient (Fig. 7), metastatic regional LN in two and systemic disease in two patients, appointed for immune therapy.

In the post-SLNB follow-up of a patient with two drainage zones – axilla and inguinal, with both regions positive SLNs, follow-up PET/CT found a highly suspicious LN in ipsilateral axilla, proven metastatic histologically. Patient continued on immune therapy (Fig. 8).

Assessing therapeutic response to adjuvant and target therapies in the follow-up PET/CT also has some distinctive pitfalls, as are the distinction of immune-related phenomena like pseudo- and hyperprogression, as well as treatment side-effects – e.g. sarcoid-like lymph node reaction or pulmonitis (Fig. 9) and their discrimination from metastatic lesions. Using semiquantitative parameters adds diagnostic information to visual PET/CT assessment and is used routinely in our work to distinguish response to therapy. Specialized software allows calculation of standard SUVmax, as well as total-lesion glycolysis (TLG) and metabolic tumor volume (MTV). The relation between SUVmax of a lesion and the mean uptake in the blood pool and the liver as reference

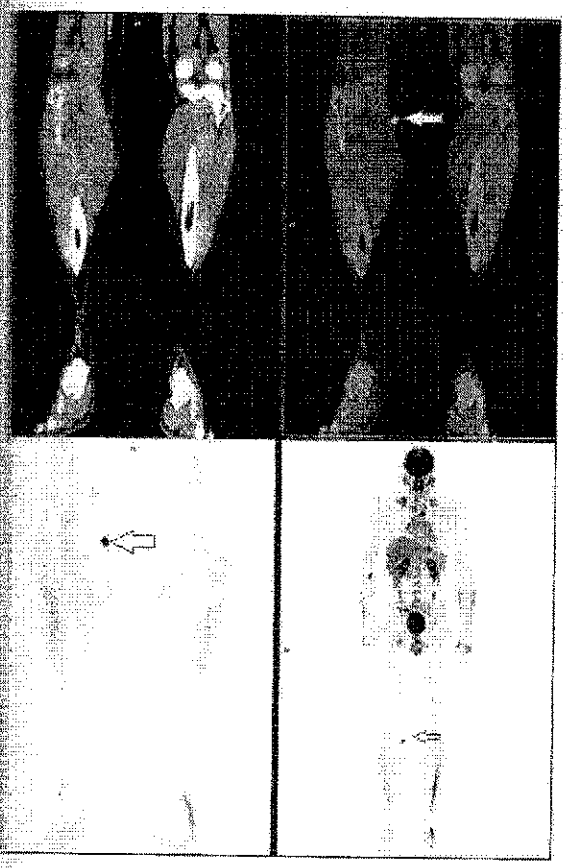


Fig. 7. GDV, 38y. SSM on the right leg, pT3aNsl(0), IIA. PET/CT in the follow-up: 06'21 – single hypermetabolic subcutaneous lesion of <1cm on right shank, cranial from primary (arrow). Restaged in stage IIIB, target therapy started.

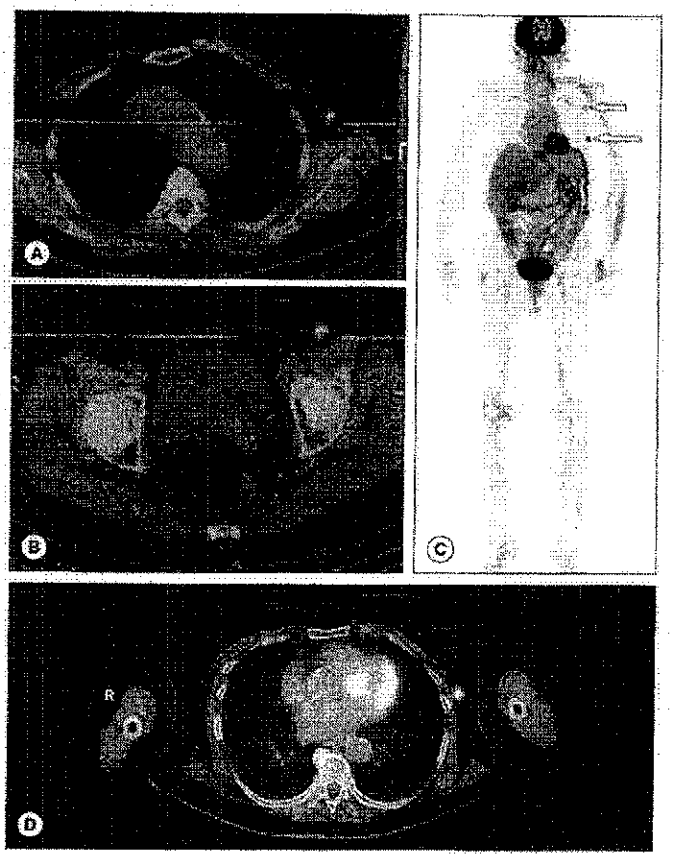


***Fig. 8.** STD, 75y. SSM left lumbar region, pT3b L0 V0 Pn0 R0, IIB. (**A**, **B**) – SPECT/CT with SLN in left axilla and left inguinal region, both positive for micrometastases with IIIC upstaging and adjuvant immune therapy started. (**C**, **D**) Follow-up PET/CT with metastatic appearing LN in left axilla – histologically verified.*

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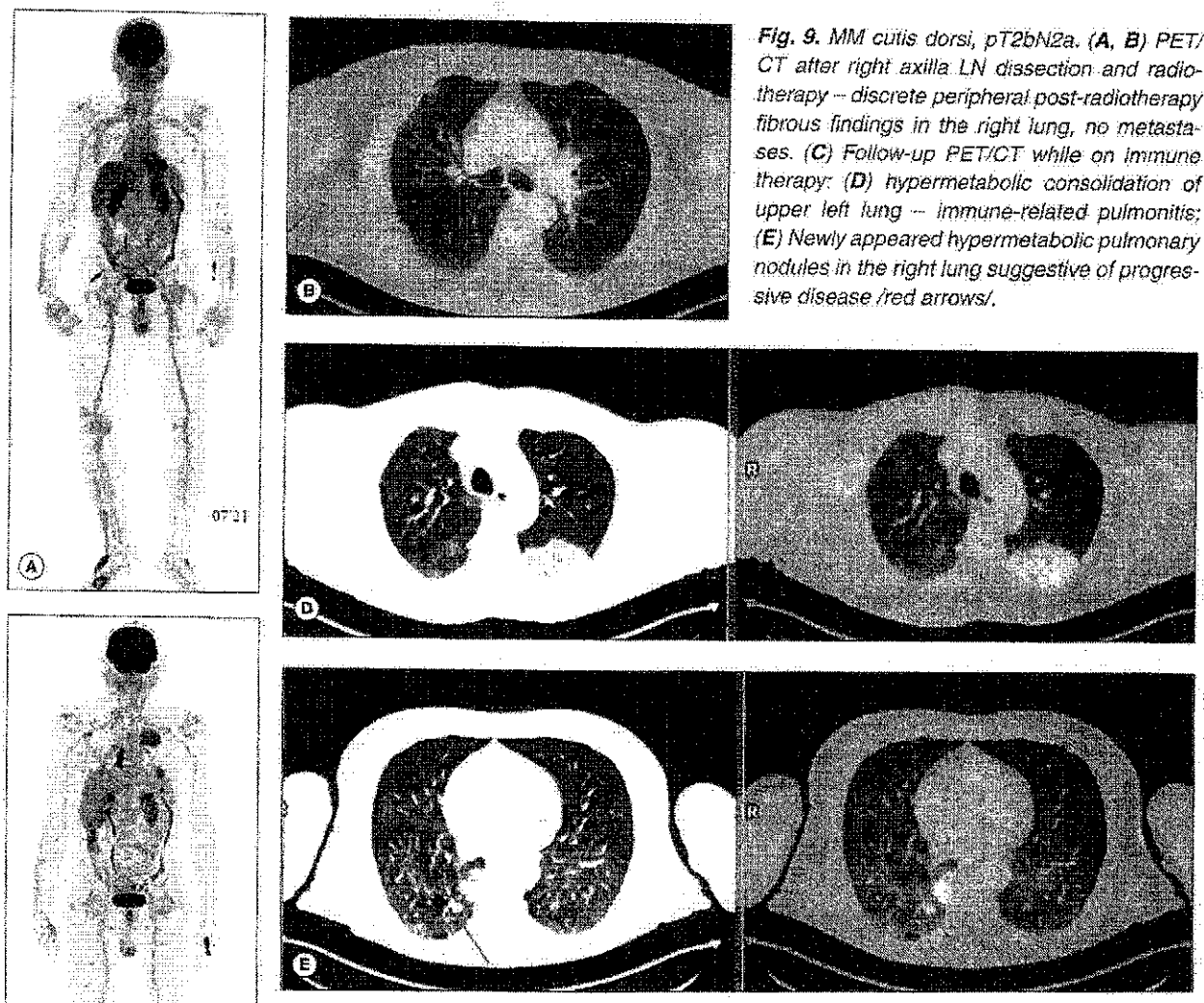

*Fig. 9. MM cutis dorsi, pT2bN2a. (**A**, **B**) PET/CT after right axilla LN dissection and radiotherapy – discrete peripheral post-radiotherapy fibrous findings in the right lung, no metastases. (**C**) Follow-up PET/CT while on immune therapy: (**D**) hypermetabolic consolidation of upper left lung – immune-related pulmonitis; (**E**) Newly appeared hypermetabolic pulmonary nodules in the right lung suggestive of progressive disease /red arrows/.*

sites is another parameter /score/ used in our practice with solid tumors, including melanoma, similarly to the well-known Deauville score in malignant lymphomas. Gathering prospective data from our pilot study would give the chance to assess the potential of these metabolic parameter for prognostic stratification.

Discussion

SLNB used to be the method mostly connected to answer the question if regional lymph node dissection is to be done – in the case of micrometastasis in the SLN, in order to improve patient's prognosis [4]. Later studies proved however, that complete LN dissection doesn't bring a lot to survival [5] and the "paradigm" was changed with the help of new adjuvant immune and target therapies [6]. They are proving more effective after early melanoma restaging with BSLN, including overall long-term survival benefit [7, 8].

The concept of the most exact "mapping" of the sentinel lymph node also underwent decades of studies, using different protocols and strategies, most of them combining radiopharmaceuticals with dyes. Technological development facing hybrid SPECT/CT, came as an additional breakthrough for precise lymphatic mapping, helping the surgeon with exact topography during intraoperative gamma probe search. Metaanalyses show high detection rate of the SLN in preoperative SLNSc with following gamma probe search – 98,1% in planar and 99-100% in additional target SPECT/CT [9]. False negative findings could be decreased and overcome with correct check of indication (stage and age of the patient, exclusion of morphologically and

clinically suspicious lymph nodes in preoperative ultrasound) [10] and experienced staff.

Our study confirms the possibility of SPECT/CT to detect more SLNs and to change the surgical approach, with overcoming the "shine through" phenomena of the neighboring to injection site lymph nodes and detecting unexpected in-transit lymph nodes [11-13].

As for now, international guidelines don't recommend the routine use of 18F-FDG-PET/CT for initial staging of early melanoma, since BSLN has proven more exact for unvealing micrometastasis in lymph nodes. The official indications for the use of PET/CT are advanced melanomas and suspicious findings from conventional imaging [14]. According to NCCN, PET/CT could be taken into in high-risk patients with palpable or ultrasound-suspicious lymph nodes or those with a positive SLN and/or in transit metastatic lymph nodes [15]. In cases where SLN proved metastatic and adjuvant therapy is to be initiated, PET/CT has the advantage of being a single-study whole-body diagnostic follow-up, checking not only for signs of progression but also for treatment side-effects, which is also to be observed in our pilot results. The results from international studies on this setting are however still non-conclusive enough [16-18].

Conclusion

Increasing the use of the established diagnostic algorithm for early stage melanoma and the additional experience from our ongoing study would hopefully also "change some paradigms" in our country, help spread the use of hybrid NM technologies, bring additional clarity and certainty on the use of PET/CT in the still non-advanced melanoma scenario and improve patient survival and quality of life.

The authors declare no conflict of interest!

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