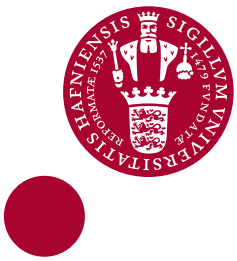

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Original Article

The value of FDG PET/CT for follow-up of patients with melanoma: a retrospective analysis

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Abstract: The incidence of melanoma (MM) is among the fastest rising cancers in the western countries. Positron Emission Tomography with Computed Tomography (PET/CT) is a valuable non-invasive tool for the diagnosis and staging of patients with MM. However, research on the value of PET/CT in follow-up of melanoma patients is limited. This study assesses the diagnostic value of PET/CT for follow-up after melanoma surgery. This retrospective study includes patients with MM who performed at least one PET/CT scan after initial surgery and staging. PET/CT findings were compared to histology, MRI or fine needle aspiration (FNA) to estimate the diagnostic accuracy. The diagnostic performance of PET/CT performed in patients with and without a clinical suspicion of relapse was compared. 238 patients (526 scans) were included. Of the 526 scans 130 (25%) scans were PET-positive, 365 (69%) PET-negative, and 28 (5%) had equivocal findings. Sensitivity was 89% [0.82-0.94], specificity 92% [0.89-0.95], positive and negative predictive values of 78% [0.70-0.84] and 97% [0.94-0.98] respectively. When stratified for reason of referral there was no statistical significant difference in the diagnostic accuracy of PET/CT between patients referred with or without a clinical suspicion of relapse. This study demonstrates that PET/CT despite a moderate sensitivity has a high negative predictive value in the follow-up of melanoma patients. Thus, a negative PET/CT-scan essentially rules out relapse. However, the frequency of false positive findings is relatively high, especially among patients undergoing a "routine" PET/CT with no clinical suspicion of relapse, potentially causing anxiety and leading to further diagnostic procedures.

Keywords: Melanoma, follow-up, surveillance, PET, PET/CT, cancer diagnostics, skin cancer, FDG, diagnostic accuracy

Introduction

Melanoma is among the most common cancers in the western world, and despite numerous preventive campaigns there is a steady increase in incidence, in particular in Australia and northern Europe [1, 2]. As many as half of all patients treated for MM will eventually relapse [3]. Of these, approximately 20% will be local, 50% in regional lymph nodes, and 30% will relapse with distant metastases [4, 5], emphasizing the importance of an efficient follow-up program, enabling early detection of relapse while it is still amendable to treatment.

A conventional follow-up program includes medical history, palpation of lymph nodes and a general clinical examination as well as an assessment of the patient's nevi. The frequency of follow-up visits and whether or not to include imaging differs according to national guidelines. For the follow-up of patients with MM, recent reviews suggest a role for PET/CT [6]. In Denmark PET and PET/CT has been widely used for follow-up of patients with higher stages of melanoma, with or without a clinical suspicion of relapse. Since 2015 PET/CT has been included in the Danish national follow up program as a routine examination at 6, 12 and 24 months after treatment for MM (> stage IIB). In the US, the most recent guidelines from the National Comprehensive Cancer Network (NCCN Guidelines Version 1, 2017) suggests to consider Chest CT, brain MRI and/or PET/CT

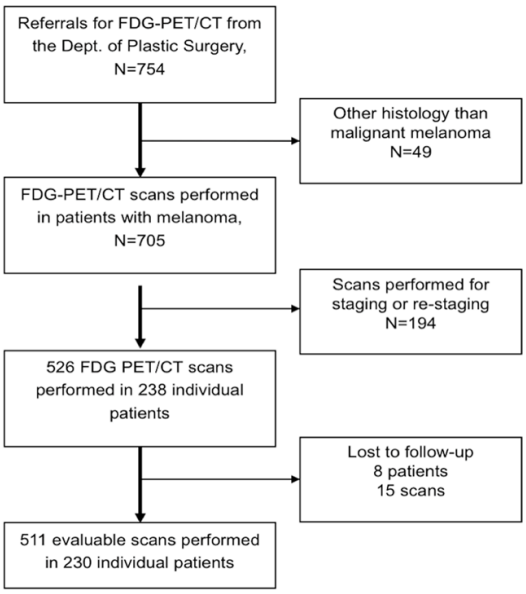

Figure 1. Flowchart for the selection of patients included in the study.

every 3 to 12 months for stage IIB-IV (evidence level 2B) [7]. There is however no international consensus [8], reflecting the scarcity of studies assessing the value of routine PET/CT to detect relapse in this group of patients.

In this study, we will examine the diagnostic value of PET/CT for surveillance of patients treated for melanoma, and assess whether the accuracy of PET/CT differs if applied as part of a routine follow-up scheme or as an examination applied after a clinical suspicion of relapse. We will also compare the diagnostic accuracy of PET when applied with a full diagnostic CT respectively low-dose CT.

Materials and methods

Patients

This single-site retrospective study includes all patients treated for MM with at least one follow-up PET or PET/CT during a 3-year period (Jan. 1st 2009 to Dec. 31st 2011) at Rigshospitalet in Copenhagen. All referrals from the Department of Plastic Surgery to the PET-department were extracted from our clinical database, returning a total of 754 referrals for a FDG-PET/CT scan. 49 patients with histology other than MM and 194 patients referred for initial staging or re-staging were excluded. This includes PET/CT scans performed earlier than three months after primary surgery which were considered as staging or re-staging. Eight patients (15 scans) were lost to follow-up leaving 230 patients and 511 scans for the final analysis (**Figure 1**). The study was approved by The Danish Health Authority (RH-2013-30-0978), and The Danish Data Protection Agency (2007-58-0015).

FDG PET/CT imaging

All patients were scanned on an integrated PET/CT scanner (Biograph TruePoint (16, 40 and 64 slice), Siemens Medical Solution, Malvern PA; Biography 64 mCT, Siemens Medical Solutions, Malvern PA or Discovery LS, 4 Slice, General Electric, Milwaukee, WI). Patients fasted for at least 6 hours before intravenous administration of FDG. A dosage of 200-555 MBq FDG (4 MBq/kg) was administered and after 60 minutes of rest the scan was performed. PET scans were combined with a low dose CT for attenuation correction or a CT of diagnostic quality acquired at 120-140 Kilo electron volts (KeV) with or without iodine based intravenous contrast agent.

As routine, the scans are performed as a whole body examination (WB, skull base to proximal thigh), but at the discretion of the referring clinician an extended WB (from apex to toes) was performed. The attenuation corrected PET data were reconstructed iteratively using a 3D ordered-subset expectation-maximization algorithm (OSEM), for scans performed on the Biography mCT this included point spread function and time of flight information. For initial reporting, all PET/CT scans were reviewed by a nuclear medicine physician and a radiologist.

Classification of FDG PET/CT scans and follow-up

Original PET/CT reports were retrieved and reviewed by a nuclear medicine specialist blinded to other examinations and clinical follow-up. For each scan location of findings were registered and each finding classified as benign, equivocal or malignant and other clinically relevant findings were registered.

The reference standard was based on pathology reports, ultrasonography (US) and magnetic resonance imaging (MRI) as well as clinical follow-up for at least 6 months after PET/CT.

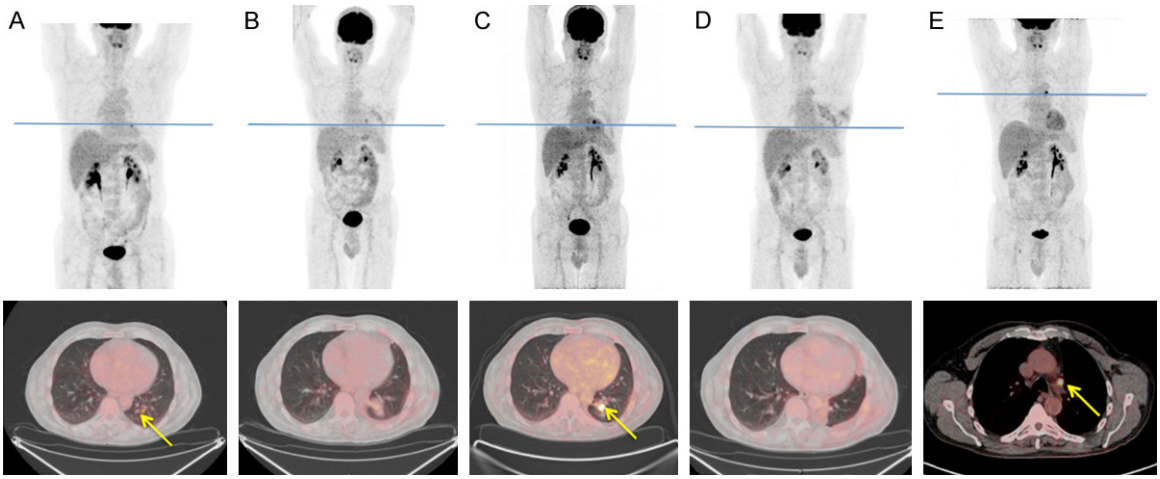

Figure 2. These images illustrate a series of surveillance PET/CT scans of a male born in 1951. He was operated for malignant melanoma on the back with micro-metastases to the left axilla and groin. The blue lines indicate the level of the inserted axial images. A: PET scan was performed as a routine control 3 years after surgery revealing a small, PET positive metastasis in the left lung (yellow arrow). This was surgically removed. Here after the patient was followed with PET-scan every 3-4 months. B: Three months after surgery PET revealed structural changes on CT and a slightly increased FDG-uptake reported as post-operative inflammation. C: After another 3 months PET revealed a highly increased focal FDG-uptake in the left lung (yellow arrow), reported as a new lung metastases. This was removed and confirmed by surgery. D: The next scan was without any suspicious findings. E: After another 3 months (a total of 12 months after surgery) a malignant lymph node in the aortic-pulmonary window was diagnosed by PET (yellow arrow). The patient is currently, more than ten years after his initial diagnosis, alive with disseminated disease receiving treatment with aldesleukin. This case illustrates how a follow-up course can repeatedly diagnose recurrence before clinical manifestations, potentially improving patient survival.

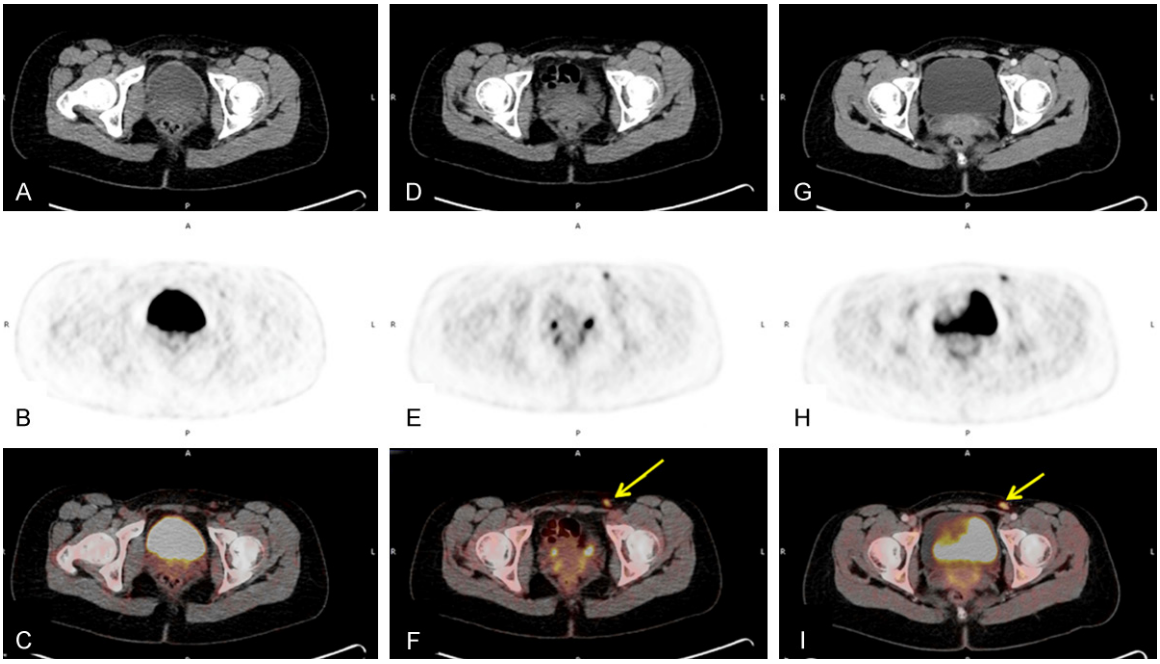

Figure 3. This case illustrates the follow up course of a female born in 1993. After being surgically treated for a malignant melanoma on the right calf, she is followed with a PET scan every 6 months. (A-C) (first column) is from the PET scan performed 3 years after surgery, reported as normal. Six months later a new scan was performed (second column, D-F) and the small, PET positive lymph node in the left groin was reported as suspicious for malignancy (yellow arrow). This was disproved by biopsy. After another 6 months, a new PET scan was performed (third column, G-I), now with increasing FDG-uptake corresponding to the same lymph node in the left groin (yellow arrow). The lymph node was surgically removed, again with benign histology. This case is a typical example of how interpretation of PET positive lymph nodes can be difficult and often result in false positive reporting. The surveillance program was concluded 10 years after surgery with no evidence of relapse.

Table 1. Patient characteristics, including information on initial AJCC* stage and reason for referral to PET scan

Age (years) median	53	
Age (years) range	11-89	
Sex (male/female)	117/121	
Stage after initial resection	Number of patients	Percentage
Ia	22	9.2
Ib	31	13
IIa	26	10.9
IIb	12	5.5
IIc	8	3.4
IIIa	54	22.7
IIIb	40	16.8
IIIc	8	3.4
IV	22	9.2
NA	15	6.3
Total	238	100
Cause of referral	Number of scans	Percentage
Relapse likely based on another modality	29	5.5
Evaluation after finding of solitary metastasis	46	8.7
Treatment evaluation	6	1.1
Clinical suspicion of relapse	92	17.5
Planned control due to initial high-risk staging	352	66.9
Patients' wish	1	0.2
Total	526	100

*American Joint Committee on Cancer.

Imaging, clinical and pathology databases were searched for relevant entries for all patients.

A true positive (TP) result was a PET/CT scan suggesting relapse, confirmed by pathology, MRI, or US within 6 months.

A false positive (FP) result was a PET/CT scan suggesting relapse, but disproved by pathology, MRI, or US within 6 months.

A true negative (TN) result was a PET/CT scan with no signs of relapse, and no relapse detected by pathology, MRI, US or at clinical follow-up for at least 6 months.

A false negative (FN) result was a PET/CT scan with no relapse, but where a relapse was later diagnosed by biopsy, MRI, US or at clinical follow-up within 6 months.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 24.0 (IBM SPSS Statistics for Mac; IBM Corporation, Armonk, NY, USA). Sensitivity was defined as: [number of true positive cases, TP]/[total number of true positive and false negative cases]). Specificity was defined as: [number of true negative cases, TN]/[total number of false positive, FP and true negative cases]. Positive predictive value (PPV) was defined as: [number of true positive cases]/[total number of true positive and false positive cases]. Negative predictive value (NPV) was defined as: [number of true negative cases]/[total number of true negative and false negative cases, FN]. Confidence intervals were estimated using Wilson score method. Comparison of the prevalence of relapse and the diagnostic accuracy of PET/CT compared to PET with low-dose CT and of PET/CT in the following sub-groups: 1) patients referred with a clinical suspicion of relapse and 2) regular follow-up due to the initial high risk staging were performed using a z-test for comparison of two independent proportions and ratios of TP, FP, TN and FN by the Pearson's Chi-squared test. Mean age was compared by a t-test for two independent samples. Applied *p*-values are two-sided and considered to be significant when $p<0.05$, no correction for multiple comparisons was performed.

Results

Baseline patient characteristic and follow-up

238 patients (526 scans) had been treated for MM in the period from Jan. 1st 2009 to Dec. 31st 2011 and been subjected to one or more PET/CT scans for follow-up (**Figure 1**). Two illustrative examples are presented in **Figures 2** and **3**. Patient characteristics are described in

Table 2. Classification of PET/CT results and diagnostic accuracy as calculated in primary as well as sensitivity analysis

Number of scans*		Relapse confirmed		Lost to follow-up	Total
		Yes	No		
PET/CT	+ Relapse	98	28	4	130
	- Relapse	12	345	8	365
	Equivocal	3	22	3	28
	Other	0	3	0	3
Total		113	398	15	526

Diagnostic Accuracy [95% CI]	Primary analysis	Sensitivity analysis†	
		Equivocals included as positive for relapse	Equivocals included as negative for relapse
Sensitivity	0.89 [0.82-0.94]	0.89 [0.82-0.94]	0.87 [0.79-0.92]
Specificity	0.92 [0.89-0.95]	0.87 [0.84-0.90]	0.93 [0.90-0.95]
Positive Predictive Value	0.78 [0.70-0.84]	0.67 [0.59-0.74]	0.78 [0.70-0.84]
Negative Predictive Value	0.97 [0.94-0.98]	0.97 [0.94-0.98]	0.96 [0.94-0.98]
Overall accuracy	0.92 [0.89-0.94]	0.88 [0.85-0.90]	0.92 [0.89-0.94]

*Numbers in red included in primary analysis. †Equivocal included as positive respectively negative for sensitivity analysis. The remaining 18 scans (lost to follow-up n=15 or with findings not related to MM n=3) not included for further analysis.

Table 1. The scans were divided into groups according to the reason for referral (**Table 1**): Relapse very likely based on another modality (n=29), evaluation after finding of solitary metastasis (n=46), treatment evaluation (n=6), clinical suspicion of relapse (n=92), planned control due to initial high-risk staging (n=352) and the patients' wish (n=1). The majority of scans were done as part of planned follow-up scheme (n=352, 67%) or due to a known or suspected relapse (n=29+92, 23%). Of the 526 scans 130 (25%) scans were PET-positive, 365 (69%) PET-negative and 28 (5%) equivocal. In 3 scans (0.6%) there were other clinical relevant findings.

Classification and diagnostic accuracy

Follow-up was complete in 230 patients (511 scans). Ninety four of 126 (75%) PET/CT scans suggesting relapse were confirmed or disproved by pathology and 8 (6%) by MRI or US. In the remaining 24 scans (19%) no other diagnostic confirmation was sought, mainly due to findings of multiple metastases clinically deemed as certain proof of relapse.

As expected the clinical follow-up after a negative PET/CT scan was less thorough: 316 of 357 negative PET/CT scans (89%) were either confirmed or disproved based on clinical follow-up for 6 months.

For all scans with a complete follow-up (n= 511) sensitivity and specificity was 89% and 92% respectively and the positive and negative predictive value was 78% and 97% respectively in the primary analysis (**Table 2**). Including equivocal scans as positive for relapse sensitivity and specificity was 89% and 87%, respectively, and the positive and negative predictive value was 67% and 97%, respectively. Including equivocal scans as negative, sensitivity and specificity was 87% and 93%, and the positive and negative predictive value was 78% respectively 96%. There was no significant difference between the two approaches.

The diagnostic values of PET/CT, when stratified for reason for referral, are reported in **Table 3**. Overall, no statistical significance between the two groups could be found: The NPV in the both groups was very high: 94% in the high risk group and 98% in low risk group. The PPV and the specificity are lower in the low risk group (NS), possibly reflecting the difference in prevalence of relapse in the two groups (33% respectively 15%, p<0.0001).

Comparing the diagnostic accuracy of PET performed with diagnostic CT respectively low-dose CT (**Table 3**) the overall accuracy of PET with low-dose CT appears higher than that of PET/CT (96% respectively 90%, p<0.0001). No difference between WB (skull-base to mid-thigh)

Table 3. Comparison of diagnostic accuracy between high vs. low risk patients and diagnostic accuracy between PET with diagnostic CT vs. PET with low dose CT

Diagnostic Accuracy [95% CI]	High Risk*	Low Risk†	PET with low dose CT	PET/CT (diagnostic CT)
Sensitivity	0.89 [0.75-0.96]	0.92 [0.80-0.97]	0.93 [0.78-0.98]	0.89 [0.80-0.94]
Specificity	0.88 [0.78-0.93]	0.94 [0.90-0.96]	0.97 [0.93-0.99]	0.90 [0.85-0.93]
Positive Predictive Value	0.79 [0.64-0.88]	0.71 [0.59-0.81]	0.87 [0.71-0.95]	0.75 [0.65-0.82]
Negative Predictive Value	0.94 [0.86-0.98]	0.98 [0.96-0.99]	0.99 [0.95-0.99]	0.96 [0.93-0.98]
Overall accuracy	0.88 [0.81-0.93]	0.93 [0.90-0.96]	0.96 [0.92-0.98]	0.90 [0.86-0.92]
Prevalence of relapse	0.34 [0.25-0.43]	0.15 [0.11-0.19]	0.18 [0.13-0.24]	0.25 [0.21-0.30]
Mean age			44.8 [SD 20.8]	54.8 [SD 17.7]

*High risk = patients with a clinical suspicion of relapse or relapse likely based on other modality. †Low risk = Planned control due to initial high-risk staging.

Table 4. Description of patients with a diagnosed relapse who had a negative PET or PET/CT scan less than 6 months before the relapse

Patient	Indication	Scan	Findings
1	Planned control	PET/CT, wb	Cutaneous relapse in close proximity to surgical scar, found by inspection and verified by histology (app. 1 week after PET/CT)
2	Planned control	PET/CT, wb	Subcutaneous relapse in the occipital region, found by inspection and verified by histology (app. 3 months after PET/CT)
3	Clinical suspicion	PET/CT, wb	Bilateral lung metastases found and confirmed by cytology app. 3 months after PET/CT
4	Clinical suspicion	PET/CT, extended wb	Multiple cutaneous metastases on crus, found by inspection and verified by histology (app. 1 week after PET/CT)
5	Clinical suspicion	PET/CT, extended wb	Metastases from MM found in 8/9 iliac lymph nodes removed during HRP 3 weeks after PET/CT
6	Planned control	PET/CT, wb	Cutaneous relapse, found by inspection and verified by histology (app. 1 week after PET/CT)
7	Clinical suspicion	PET/CT, wb	Cutaneous relapse, found by inspection and verified by histology (app. 1 week after PET/CT)

compared to extended WB (including legs) was found.

In 7 (3%) patients a relapse was diagnosed less than 6 months after a negative PET/CT (false negative, listed in **Table 4**): In 5 patients a cutaneous relapse was found, in one metastases to iliac lymph nodes was found during HILP (hyperthermic isolated limb perfusion) 3 weeks after PET and one patient was diagnosed with bilateral lung metastases 3 months after PET/CT. A false positive PET/CT scan was seen at some point in 21 patients (9%). Of all the false positive findings (28 scans) 17 were in lymph nodes (refer to **Figure 3** for an example), 3 were in the lungs, 3 were located at the trunk or extremities, 1 in the gastro intestinal canal, 1 in the urinary tract and 3 in other locations.

Discussion

The purpose of this study was to assess the value of PET/CT for surveillance of patients treated for MM with curative intend. It was analyzed through a retrospective, cross-sectional design, which demonstrated that PET/CT has a moderate sensitivity and specificity (89% and 92%) but a high NPV (97%) for detection of relapse. The amount of data on surveillance of MM patients with PET/CT is scarce and very few original studies have been published on this topic [9-11]. Nonetheless, PET/CT for surveillance has gained widespread acceptance and has been a part of e.g. Danish guidelines since 2015. To the best of our knowledge, the current study is the largest focusing strictly on surveillance published to date.

The main rationale behind close follow-up of patients with MM is the hypothesis that early detection of relapse renders salvage therapy possible and prolongs survival. This seems intuitively correct, but nonetheless, remains to be proven in a prospective, randomized trial. A recent analysis based on the National Comprehensive Cancer Network guidelines for melanoma surveillance, confirms that routine imaging surveillance effectively predicted absence of disease, but only resulted in minimal gains in life expectancy [12]. A recent retrospective study including 110 patients found that PET/CT

detected a recurrence in 1 of 4 asymptomatic melanoma patients, but without any impact on survival [11].

Other studies examining the ability of PET/CT to detect distant metastases after a MM-diagnosis, shows a relatively higher sensitivity and specificity compared to our findings [13]. Akcali [13] investigated patients with stage III and IV finding the sensitivity of PET/CT to be 91% and NPV 96%. Wider [14] found the sensitivity and NPV of PET/CT in the follow-up of malignant melanoma to be 87% respectively 93%. Based on 7 original studies Danielsen et al. [9] investigated PET in follow-up of cutaneous malignant melanoma in a systematic review and found a pooled sensitivity and NPV of 96% and 95%.

The relatively high sensitivity in this meta-analysis may be explained as the included studies are based mostly on high stage (III&IV) patients, and some studies have a positive PET/CT as an inclusion criteria resulting in a sensitivity at 100%.

Overall, the NPV in our study was high, confirming that PET/CT can effectively rule out relapse. In total we observed 113 relapses in 74 patients. 98 of these were diagnosed by PET/CT. Thus 15 of 365 (4%) negative scans were false negative for relapse at any time, but only 7 (2%) patients experienced a relapse within 6 months of a negative PET/CT. The majority of the false negative findings in this study were located to the skin, underlining the importance of clinical inspection, also in the era of PET.

On the downside, this study found a relatively low positive predictive value (PPV), particularly in the group of patients with no clinical suspicion of recurrence (71%). Thus, in this group almost 30% of the PET/CT scans with a suspicion of relapse were later proved to be false alarm. This may cause anxiety and can potentially lead to further invasive diagnostic procedures and draws on hospital resources.

The reason for the substantial number of false positive results in this, as well as in previous studies, is the well-known increased FDG-uptake by inflammatory cells. This corresponds well to the fact that the majority of false positive findings in our study were located to lymph nodes. Our sensitivity analysis also indicates that a conservative approach (equivocal scans interpreted as negative) may result in a higher accuracy, but this will be dependent on local settings and needs confirmation in larger studies.

When using PET/CT for routine follow-up of MM patients, many of them being young and potentially cured for their MM, it is preferable to reduce the amount of radiation to a minimum. We investigated the performance of PET/CT with a low-dose CT versus PET/CT with a whole body diagnostic CT and found no statistical significant difference in sensitivity, specificity, NPV or PPV. Surprisingly PET with low-dose CT appeared to have a higher overall accuracy than PET/CT, primarily reflecting the difference in the number of false positive scans (3% respectively 8%, p=0.04). This may be attributed to the fact that it is two different groups of patients assigned to each investigation: typically younger patients will be referred for PET with low-dose CT (mean age in this study: 44.8 yrs.), whereas older patients or patients with a higher risk of malignancy will be referred to PET with diagnostic CT (mean age 54.0 yrs., p<0.0001). In the older patient population, more inflammatory findings can be expected. Similarly, Pfluger [15] found that PET with contrast-enhanced CT versus plain low-dose CT had similar specificity. These findings make it reasonable to believe that diagnostic PET/CT and PET with low-dose CT performs equally well in ruling out relapses, especially in younger patients.

Conclusion

This study demonstrated that PET/CT has a moderate specificity and sensitivity but a high negative predictive value (97%) for follow-up of patients treated for MM. Approximately 1/10 patients experienced a false positive result, most frequent among patients undergoing a routine PET/CT without a clinical suspicion of relapse. Whether the high accuracy in ruling out relapse translates into a clinical benefit remains to be proven.

Disclosure of conflict of interest

None.

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References

[1] Little EG and Eide MJ. Update on the current state of melanoma incidence. Dermatol Clin 2012; 30: 355-361.

[2] Cancer stat facts: melanoma of the skin. Retrieved May 2, 2017, from https://seer.cancer.gov/statfacts/html/melan.html.

[3] Leiter U, Meier F, Schittek B and Garbe C. The natural course of cutaneous melanoma. J Surg Oncol 2004; 86: 172-178.

[4] Soong SJ, Harrison RA, McCarthy WH, Urist MM and Balch CM. Factors affecting survival following local, regional, or distant recurrence from localized melanoma. J Surg Oncol 1998; 67: 228-233.

[5] Dicker TJ, Kavanagh GM, Herd RM, Ahmad T, McLaren KM, Chetty U and Hunter JA. A rational approach to melanoma follow-up in patients with primary cutaneous melanoma. Scottish melanoma group. Br J Dermatol 1999; 140: 249-254.

[6] Xing Y, Bronstein Y, Ross MI, Askew RL, Lee JE, Gershenwald JE, Royal R and Cormier JN. Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. J Natl Cancer Inst 2011; 103: 129-142.

[7] Network NCC. NCCN guidelines version 1.2017 melanoma: national comprehensive cancer network; 2017 [cited 2017 May 02]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf.

[8] Trotter SC, Sroa N, Winkelmann RR, Olencki T and Bechtel M. A global review of melanoma follow-up guidelines. J Clin Aesthet Dermatol 2013; 6: 18-26.

[9] Danielsen M, Hojgaard L, Kjaer A and Fischer BM. Positron emission tomography in the follow-up of cutaneous malignant melanoma patients: a systematic review. Am J Nucl Med Mol Imaging 2013; 4: 17-28.

[10] Baker JJ, Meyers MO, Frank J, Amos KD, Stitzenberg KB and Ollila DW. Routine restaging PET/CT and detection of initial recurrence in sentinel lymph node positive stage III melanoma. Am J Surg 2014; 207: 549-554.

[11] Koskivuo I, Kemppainen J, Giordano S, Seppanen M, Verajankorva E, Vihinen P and Minn H. Whole body PET/CT in the follow-up of asymptomatic patients with stage IIB-IIIB cutaneous melanoma. Acta Oncol 2016; 55: 1355-1359.

[12] Rueth NM, Xing Y, Chiang YJ, Cromwell KD, Ross MI, Lee JE, Gershenwald JE, Royal RE and Cormier JN. Is surveillance imaging effective for detecting surgically treatable recurrences in patients with melanoma? A comparative analysis of stage-specific surveillance strategies. Ann Surg 2014; 259: 1215-1222.

[13] Akcali C, Zincirkeser S, Erbagcy Z, Akcali A, Halac M, Durak G, Sager S and Sahin E. Detection of metastases in patients with cutaneous melanoma using FDG-PET/CT. J Int Med Res 2007; 35: 547-553.

[14] Wieder HA, Tekin G, Rosenbaum-Krumme S, Klode J, Altenbernd J, Bockisch A and Nagarajah J. 18FDG-PET to assess recurrence and long term survival in patients with malignant melanoma. Nuklearmedizin 2013; 52: 198-203.

[15] Pfluger T, Melzer HI, Schneider V, La Fougere C, Coppenrath E, Berking C, Bartenstein P and Weiss M. PET/CT in malignant melanoma: contrast-enhanced CT versus plain low-dose CT. Eur J Nucl Med Mol Imaging 2011; 38: 822-831.