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The significance of imaging examinations during follow-up for malignant melanoma

Background: Currently, there is a general lack of consensus regarding optimal strategy and imaging during follow-up for patients suffering from melanoma. *Objectives:* Our aim was to analyse the utility of various imaging procedures, in particular CT scans, during the follow-up of patients with different stages of melanoma. *Materials & Methods:* A retrospective analysis of the medical records of patients suffering from melanoma diagnosed between 2001 and 2011 was carried out at the Department of Dermatology, University of Pécs. Patients with *in situ* (Stage 0) and metastatic (Stage IV) melanoma were excluded from the analysis, as well as patients who succumbed during the first three years of follow-up. *Results:* In total, 649 melanoma patients met the inclusion criteria. During the entire follow-up period, 90 recurrences were detected. The vast majority (n = 71; 79%) of the total metastatic cases (n = 90) were diagnosed within the first three years. In 35% of the cases, metastases were detected by CT. Although more than 66% of the CT scans were performed for Stage I patients, only three cases were positive (0.1%) within this population. *Conclusion:* On the basis of our results, intensive radiological work-up is not deemed necessary during the surveillance of patients in the early stages (IA-IIA) of melanoma. Initial and regular follow-up imaging examinations (preferably CT scans) may be recommended from Stage IIB of the disease.

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Key words: computed tomography scan, follow-up, melanoma

According to the World Health Organization (WHO), more than 132,000 new occurrences of melanoma skin cancer emerge annually, worldwide [1]. The revised American Joint Committee on Cancer (AJCC) staging system categorizes malignant melanoma into three groups: localized disease with no evidence of metastases (Stage I-II), regional disease (Stage III), and distant metastatic disease (Stage IV) [2, 3]. The majority of melanoma cases are diagnosed at the localized stage, which is associated with a higher five-year survival rate (98.3%) compared to those with regional (62.4%) or distant metastases (16%) [4, 5]. The staging of melanoma is not only of prognostic value, but dictates the recommendation regarding treatment and is also used as a guide in follow-up examinations.

Despite the increasing incidence of melanoma and recent developments in treatment, melanoma follow-up care has remained an area of debate and challenge. While guidelines, national and/or institutional directives, offer straightforward recommendations on therapeutic questions, they provide limited information regarding follow-up procedures.

Recently, an increasing number of studies have been published on follow-up schedules, especially concerning the necessity regarding imaging examinations. However, up to date, no international consensus has been reached regarding the optimal follow-up strategy. Consequently, melanoma follow-up shows considerable heterogeneity from country to country, and from department to department. The recommendations may differ regarding the duration and frequency of follow-up, the type of medical history and physical examinations, and the utilization of imaging and laboratory studies to detect recurrence or metastases [6-8]. Based on our institutional recommendations, extensive diagnostic procedures were carried out as part of our melanoma surveillance program from 2001 up to 2013. All (even Stage IA) melanoma patients were offered annual chest and abdominal CT plus head CT or MRI, including semi-annual chest X-ray and abdominal and regional ultrasound examinations over a total of 10 years. Additionally, patients underwent physical examinations every three months. Since the optimal use of imaging modalities during melanoma follow-up has not been thoroughly investigated, we retrospectively analysed the value of intensive imaging work-up in our melanoma patient population focusing on the first three years of follow-up [9].

Materials and methods

A retrospective analysis of the records of patients diagnosed with malignant melanoma was carried out from December 2014 at the Department of Dermatology,

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Venerology and Oncodermatology, University of Pécs. Data was extracted from our institutional melanoma database, in which information on pathological characteristics of the patient's primary melanoma, tumour stage, melanoma specific treatments, tumour recurrence, physical examinations and imaging procedures performed at initial diagnosis and during the follow-up have been recorded. Data of all patients with a histologically confirmed malignant melanoma, between January 2001 and December 2011, were screened for this study. Patients with *in situ* melanoma (Stage 0) or clinically apparent metastatic melanoma (Stage IV) at diagnosis were excluded from the analysis, including patients with an unknown stage or with less than three years of follow-up data available. Regarding our institutional melanoma protocol, all patients included in this study with melanoma thicker than >0.75 mm, or ulceration, or with mitotic index higher than 1/mm^2 underwent sentinel lymph node biopsy. Stages were determined according to the 7th edition AJCC staging system [10]. According to the ESMO melanoma guideline (2015), high-risk melanoma is considered as a tumour of AJCC Stage IIB or higher [11].
During the data collection period (2001-2011), our institutional protocol for standard melanoma staging consisted of chest and abdominal CTs, head CT or MRI, and physical examinations. The choice between head CT or MRI was determined by the availability of the MR examination.
The regular follow-up imaging protocol for all melanoma patients from Stage I disease comprised annual chest and abdominal CTs plus head CT or MRI, and chest X-ray with abdominal and regional ultrasound, every other six months, over a total of 10 years. A physical examination was performed every three months up to three years, thereafter, every six months, up to 10 years. Patients were educated regarding self-skin examination during the follow-up visits.
CT findings were analysed in detail. Each radiological finding was classified as either i) true-positive (a positive radiological finding supported by subsequent radiological, histological or clinical evaluation), ii) false-positive (a positive radiological finding not supported by subsequent evaluations) or iii) true-negative (a negative radiological finding supported by subsequent negative evaluations). The number of metastatic and non-metastatic cases in each stage were calculated based on the true-positive and true-negative findings, respectively. The average number of imaging examinations (mainly CT scans) which led to the detection of metastatic disease was calculated for each stage. Metastases were registered as self-detected only if the suspicion of recurrence was noted initially by the patient, and were otherwise considered as physician-detected.
During the regular follow-up schedule, the first imaging modality or the patient/physician observation which had revealed the metastases was considered the method of detection. There was no overlap between the different imaging modalities primarily detecting the metastases.
Tumours other than melanoma, accidentally detected during follow-up, were also recorded. Statistical analyses including recurrence speed and survival rate analysis were performed to determine whether there were differences in the incidence rate of metastases detected by radiological imaging or physical examination during the follow-up, comparing the duration of time between primary diagnosis and the detection of the first metastases and further substages.
Trends in metastasis detection for each diagnostic modality were calculated according to the Kaplan-Meier method, using asymmetric confidence intervals. The first detection of metastases was considered as a positive event, and patients who were lost to follow-up were excluded. In order to compare the effectiveness regarding different follow-up modalities, CT, US, physician inspection, and patient self-examination results were plotted separately (*figure 3*). Metastases detected by different methods were mutually excluded [12].
The significance of trend difference between substages was calculated using the Mantel-Cox (logrank) test. A p value of less than 0.05 was considered statistically significant. Statistical analyses were carried out using Graphpad Prism software.

Results

Between 2001 and 2011, a total of 831 patients were diagnosed with melanoma at our department. Of the 831 patients, 182 were excluded from the subsequent analysis: 107 were diagnosed with *in situ* melanoma (Stage 0), 19 patients had Stage IV disease (distant metastases) at presentation, in 18 cases the histopathology report was incomplete or insufficient to establish a definite stage, and 38 patients were lost to follow-up within the first three years (mainly not responding to inquiry). Thus, the data of 649 patients were analysed. The total analysed cohort contained 339 (52%) women and 310 (48%) men, and the mean age was 56.7 years (16-95). More than half of the patients suffered from Stage I disease (IA: 297/46%; IB: 101/16%), while Stage IIA, IIB, IIC and III disease was detected in 72 (11%), 54 (8%), 47 (7%) and 78 (12%) patients, respectively (*figure 1*). The median follow-up time was 5.3 years (range: 3-13).
During the follow-up period, recurrences were detected in a total of 90 (14%) patients: 12/398 (3%) in Stage I, 47/173 (27%) in Stage II, and 31/78 (40%) in Stage III patients. The distribution of all patients and cases with metastases among the various stages are presented in *figure 1*.
Out of the 90 metastatic cases, 71 were diagnosed within the first three years of follow-up: 40, 23, and eight during the first, second and third year, respectively. Of these 71 early metastatic cases, 51 were regional (21 nodal and 30 *in transit*) recurrences, and 20 were distant metastases. The most common distant site of metastasis during the first three years of follow-up was the lung (six cases), followed by distant lymph nodes (four cases), the brain (three cases) and the liver (two cases). In five cases, multiple (at least two) organs were simultaneously affected. During the first three years of follow-up, 24 metastases were originally recognized by the patients themselves through self-examination, 12 were detected by physical examination, and 35 recurrences were discovered by imaging examinations (25 by CT scan, eight by ultrasound and two by MRI). Thus, almost half (49%) of the metastases which occurred within the first three years were detected through the use of imaging tests. In our cohort, CT was responsible for the detection of 35% (25) of all recurrences during the first three years, of which, 64% (16) were distant, and 36% (9) were regional metastases (*figure 2*). For all distant metastases, the previously used (six months prior) imaging methods (abdominal US, chest X-ray) were negative. Other imaging modalities were

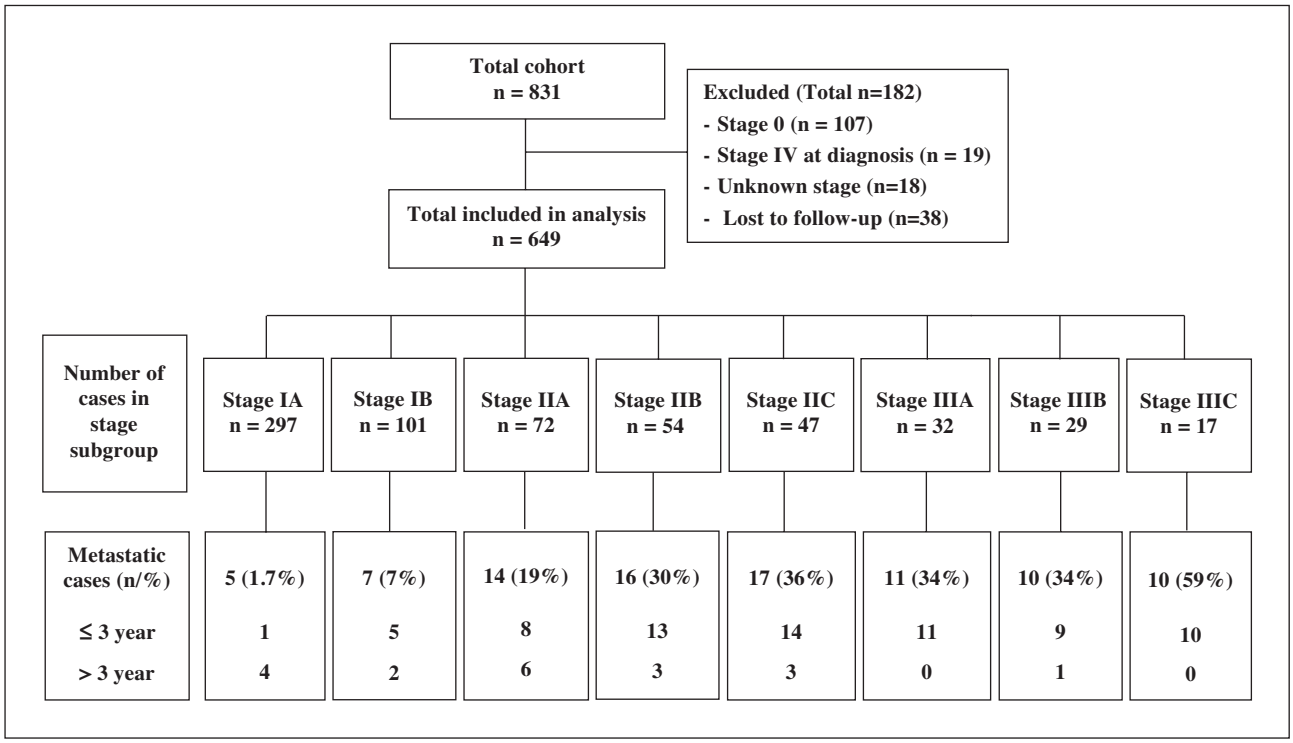

Figure 1. Study population. The figure summarizes the characteristics of the patient cohort, number of excluded and analysed cases per stage, and the number of metastatic cases per stage. Percentages in the horizontal row reflect the ratio of metastatic cases of total number of cases in the stage subgroup.

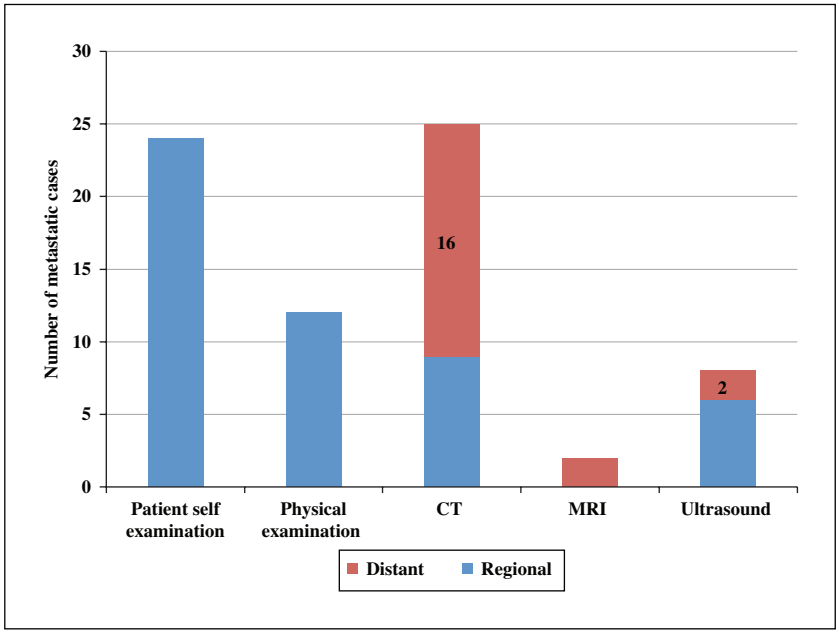

Figure 2. Number of metastatic cases during the first three years (n = 71) of follow-up according to site and method of detection. Metastases were detected using computer tomography in 25 (35%) cases, patient self-examination in 24 (34%), physical examination in 12 (17%), ultrasound in eight (11%), and MRI in two (3%). Note that this figure reflects the number of metastatic cases detected by different imaging modalities.

not performed simultaneously with the CT scans. Therefore, we were unable to predict whether any other method could have detected metastases. The sensitivity of chest CT for the detection of pulmonary metastases is proven to be high in reference to several studies. Compared with chest X-ray, CT can detect nodules smaller than 5 mm, whereas chest X-ray has a sensitivity of only 50% for nodules 6-10 mm [13-15]. Regarding the regional metastases (n = 9),

Table 1. Localization and number of metastatic cases per year.

Site of metastasis	1st year	2nd year	3rd year	4th year	5th-6th years	after 7 years	Total
Regional	30	15	6	4	3	0	58
Distant	10	8	2	5	1	6	32
Total	40 (44%)	23 (25%)	8 (9%)	9 (10%)	4 (4.4%)	6 (6.7%)	90

the first method used to detect the metastases was the CT scan, which was performed prior to the patient's follow-up visit. The patients were symptom-free, however, in five cases, enlarged regional lymph nodes were palpable during the physical examination. Half of the regional metastases were not clinically detectable. A total of 19 recurrences were detected following the third year of follow-up; nine cases in the fourth year, four cases during the fifth to sixth year, and six cases after the sixth year (*table 1*).

Next, we analysed tumour detection capacity regarding the follow-up modalities at different tumour stages and at different time points of follow-up. The distribution of CT-detected recurrences did not show significant differences per stage. Notably, while the number of CT-detected metastases was found to be constant during all follow-up years, the US was beneficial mainly in the first years of surveillance. The latest US-detected metastases were discovered in the fifth year of follow-up. For both patient and physician examination, the detection time frame was relatively short (up to five years), however, the detection rate was constant, similar to CT (*figure 3*).

Other non-cutaneous malignant tumours were found in 21 (3%) cases (including seven renal, five nervous system, three urinary bladder, three prostate, one lung, and one ovarian and one follicular lymphoma) during the follow-up period. The incidence of non-cutaneous, synchronous tumours was approximately equal in all stages (*figure 1*). There was no seasonal peak in the diagnosis of the metastases.

A total of 6,555 CT scans were performed during the entire 10 years of data collection, while during the first three years of follow-up, 3,633 (55%) CTs and 707 brain MRIs were performed. Among the 3,633 CTs, the rate of true-positive cases was 0.8 % (28), while a false-positive rate accounted for 1.07% (39). Each patient had, on average, five CTs during the first three years (1-2 annually). The quantity of CT imaging performed during the first three years and its positivity was then analysed in relation to stages. Of the total number of CT scans, 48% (1,739) were performed in patients with Stage IA, with no positivity. For Stage II, 780 scans were carried out and 14 (1.8%) were positive for metastases, and for Stage III, 449 CTs were performed and 11 (2.4%) led to the detection of metastases (*table 2*).

Discussion

Within our institutional guidelines used until 2013, CT examinations were recommended annually, while abdominal and regional ultrasound examinations, including chest X-rays, were carried out semi-annually, independently of stage (for further details, see *Materials and methods*). This offered us the opportunity to analyse the utility of intensified CT surveillance in the follow-up (focusing on the first three years) regarding melanoma.

Melanoma recurrences typically develop within the first three years following the initial diagnosis of the primary tumour, therefore, many guidelines recommend more intensive follow-up care during this period [6, 8, 16]. Our findings are consistent with these previously published data. The vast majority (n = 71; 79%) of the total metastatic cases (n = 90) were diagnosed within the first three years. Of all metastases, 44% occurred during the first year, 25% in the second year, and 9% in the third year, which also supports the recommendation of more intensive follow-up care in the first three years. The occurrence of metastases following the first three years decreased, and metastases were mainly localized in internal organs and detected by imaging techniques (CT and MR).

The probability of detecting metastases for early-stage melanomas during this period is low. In our cohort, only 3% of patients with Stage I disease developed metastases. This rate increased to 19% and 30% in Stage IIA and IIB patients, respectively. According to the few available publications, recurrence rates fall between 18-44% for Stage IB-II patients [17, 18]. Similar to recent studies, our study also confirmed the increased risk of disease relapse in patients with Stage IIB melanoma [12]. With reference to our study, it should be kept in mind that stages were determined according to the 7th edition AJCC staging system. In the current classification (8th edition AJCC), subgroup IIIA showed a slightly better five-year survival rate than Stage IIC, however, despite this, we suggest CT imaging from Stage IIB based on our results [19].

The utility of CT for the detection of clinically occult metastases has been studied by many researchers. It is known to be more sensitive compared to chest X-ray for the detection of pulmonary metastases, and optimal for examining areas unreachable by physical examination [20]. The median sensitivity and median specificity of imaging modalities (US, CT, PET and PET-CT) used for surveillance were analysed by Xing *et al.* Among the four diagnostic imaging modalities for the assessments of lymph node metastases, ultrasonography had the highest sensitivity (96%) and specificity (99%). It was superior to CT, PET, and PET-CT. For the surveillance of distant metastases, PET-CT had the highest sensitivity (86%) and specificity (91%), compared with the respective values of CT and PET alone. Positive predictive values for distant metastasis surveillance were consistently higher for PET-CT. The higher number of false-positive results (*i.e.* lower specificity) from PET-CT, however, leads to loss of precision. Furthermore, for patients at low risk of metastasis, the positive predictive value of PET-CT indicated that the use of PET-CT is not warranted without additional clinical indications [21, 22].

In the primary staging of regional metastases, CT examination was associated with 9% sensitivity and 92% specificity.

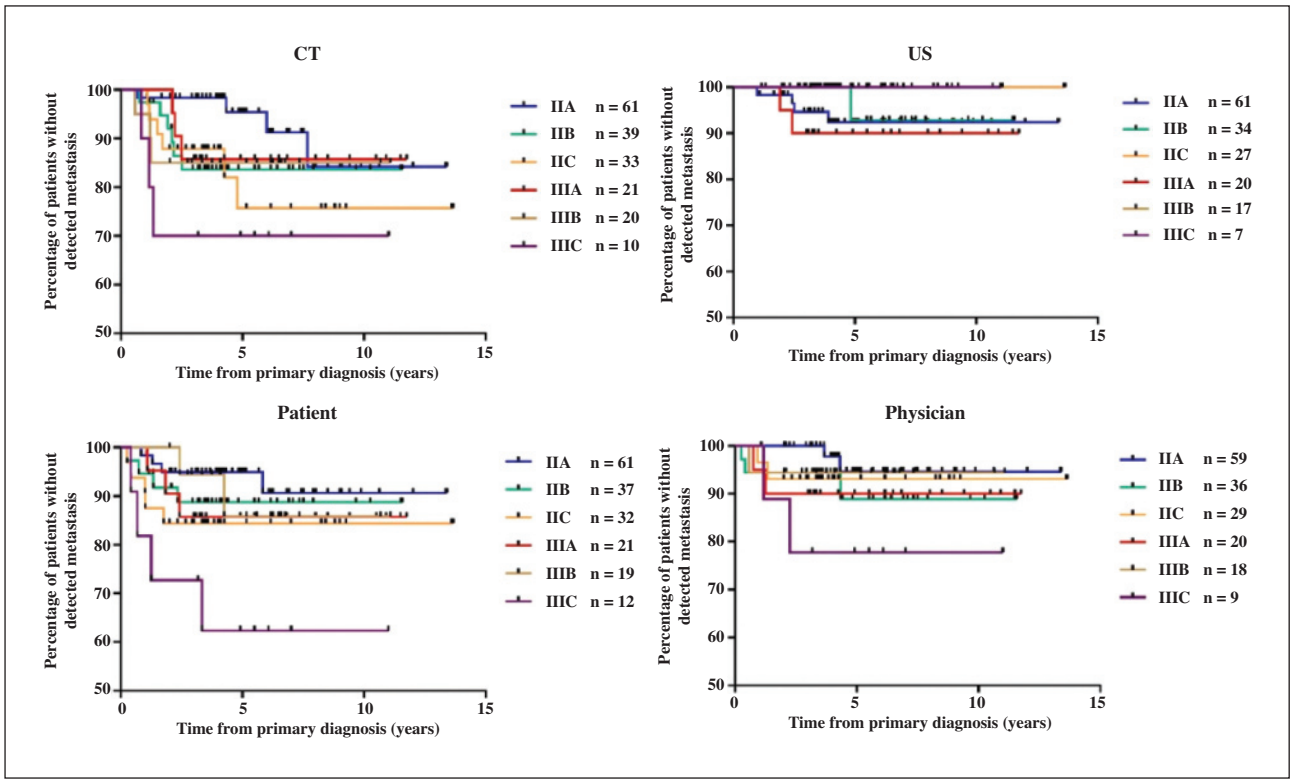

Figure 3. Survival curves comparing time from primary diagnosis to first metastases according to diagnostic methods and substages. The first detection of metastasis was considered as a positive event. There was no overlap between the different imaging modalities. Comparable numbers of metastases were detected using each of the four imaging methods. With the exception of Stage IIIC, CT exhibited the highest constant detection rate during the follow-up period. Regarding both patient and physician examination, the detection time frame was considerably shorter (up to five years), while the detection rate was constant, similar to CT. US was beneficial mainly in the first years of follow-up, and therefore showed the longest plateau phase. Notably, Stage IIIC cases exhibited the steepest decline in survival curves during the first two years, in contrast to Stage IIA, which showed the smallest decline with positive events detected over up to seven years of follow-up.

Table 2. Number of CT scans performed with respect to stage and percentage of positive cases during the first three years of follow-up.

CT	1st year		2nd year		3 rd year		Total	
	total	positive (n)	total	positive (n)	total	positive (n)	total	positive (n/%)
IA	885	0	466	0	388	0	1739	0 (0%)
IB	358	0	174	2	133	1	665	3 (0.5%)
IIA	136	1	80	0	67	0	283	1 (0.4%)
IIB	175	1	64	3	71	1	310	5 (1.6%)
IIC	97	7	54	1	36	0	187	8 (4.3%)
IIIA	82	0	51	3	52	0	185	3 (1.6%)
IIIB	90	3	44	1	37	0	171	4 (2.3%)
IIIC	49	3	31	1	13	0	93	4 (4.3%)
Total	1872	15	964	11	797	2	3633	28 (0.8%)

Note that this table shows the number of CT scans, not the number of positive cases.

Whereas for surveillance, the sensitivity was 61% while the specificity was 97%. In regard to distant metastases, the sensitivity of CT imaging was found to be much higher (51%) and the specificity was 69%. Similar trends were observed regarding the surveillance of distant metastases; 63% and 78%, respectively [21]. Park *et al*. showed that CT scanning is one of the most appropriate modalities for screening occult metastases in high-risk melanoma patients [23].

In our cohort, 35% of all recurrences during the first three years could be detected by CT. Recurrences were detected by patient self-examination in 24 (34%) cases, by physical

examination in 12 (17%) cases, by ultrasound in eight (11%) cases, and by magnetic resonance imaging in two (3%) cases (*figure 2*). When we analysed tumour detection capacity, the distribution of CT-detected recurrences did not show significant differences over all follow-up years, while the US was beneficial mainly in the first years of surveillance. The most recent US-detected metastases were discovered in the fifth year of follow-up (*figure 3*). In conclusion, CT scans showed the highest rates of recurrence detection of all imaging modalities used in this study (*figure 2*). Similar results were published by Podlipnik *et al*., and in their cohort, 48% of metastases were diagnosed by CT scanning [12]. During the first three years of follow-up, 1,739 (48%) of the total number of CTs were performed in Stage IA patients with no positivity. In Stage II patients, of the 780 CTs, 14 (1.8%) were positive for metastases, while in Stage III patients, 449 CTs led to the detection of 11 (2.4%) metastases. In this study, the false positive CT scan rate was 1.07%, which led to further examinations. Similar results were reported by Leiter *et al.*, with a total 1.25% false positivity rate for the examined radiological methods [24]. Thus, in our study, CT was an appropriate test for the detection of recurrence in patients with high-risk melanomas. MRI provides detailed anatomical localization of brain metastases, and shows higher sensitivity for the detection of small (< 2 cm) brain metastases than CT or even PET-CT. In a recent study, the sensitivity of MRI (contrast-enhanced T1-weighted) for the detection of melanoma brain metastases was 99.7% [25, 26]. During our data collection period, the availability of MRI in our region was limited, therefore minimal conclusions could be drawn from MRI data. PET-CT was even less available, therefore no conclusions were made.

Radiation used during medical imaging is known to be associated with an increased risk of cancer [27-29]. An analysis by Wen *et al.* was performed to estimate the lifetime attributable risk (LAR) of cancer in patients receiving annual or biannual PET/CT or CT of the chest, abdomen, and pelvis for 5 or 10 years, as a part of choroideal melanoma surveillance imaging. The LAR of cancer following a single chest and abdominopelvic CT among the younger population (20 years of age) was found to be 0.17% (1 in 588) for males and 0.30% (1 in 333) for females, respectively, compared with 0.06% (1 in 1667) and 0.08% (1 in 1250) for males and females, who were 70 years of age, respectively. It is estimated, that an annual chest and abdominopelvic CT for 10 years carries a potential LAR of cancer, for a 50-year-old patient, of 0.9% for males and 1.3% for females. Lifetime risk was found to be higher in younger, female patients. This risk increases to 1.8% and 2.5% if the frequency of imaging is increased to every six months. The most aggressive surveillance protocol (a PET/CT scan biannually for 10 years) has a LAR of cancer of 5.0% for a 20-year-old male compared with 1.6% for a 70-year-old male. The LAR of cancer related to PET/CT protocols was found to be higher than when related to chest and abdominopelvic CT [30]. This risk should be taken into consideration when designing the optimal imaging follow-up strategy. Intense imaging follow-up resulting in earlier detection of metastases may outweigh the radiation risks for patients at high risk of metastatic disease.

Previous studies reported different rates of metastases based on self-examination. According to Garbe *et al*., 17% of 233 recurrent cases were self-discovered metastases [8]. However, several other studies reported that 50% or more symptomatic recurrences are found by patients rather than doctors at routine follow-up visits [31-33]. In our study, 34% of all cases with metastases were primarily discerned by the patients themselves during the first three years. Hence, effective education of patients is likely to be one of the most important aspects of follow-up and should be completely integrated in the follow-up program.

There is a lack of adequate differentiation of melanoma stages in several current guidelines regarding melanoma management, although the risk of recurrence significantly changes according to the disease stage. National Comprehensive Cancer Network (NCCN) melanoma follow-up recommendations are based on tumour stages. In general, lifelong annual clinical examinations and regular self-skin examinations are advised for all patients. From Stage IIB, CT, MRI, and/or PET is recommended every 3-12 months over the ensuing 3-5 years [34]. On the contrary, the European Society for Medical Oncology (ESMO) follow-up guidance is based on the pathological staging of the primary tumour. The frequency of imaging is not specified, leaving the physician to set up an individual diagnostic regimen according to the patient's needs, hence making the guideline rather subjective. Similar to the NCCN, ESMO also recommends patient self-skin examinations [11]. Thus, the available recommendations on the frequency and duration of imaging techniques performed during follow-up are diverse, with intervals ranging from 3 to 12 months [6, 11, 34]. A current clinical trial, MELFO, examined whether a reduced follow-up schedule affects the detection of recurrences and follow-up costs in Stage IB-II melanoma patients. The results of the trial show that the frequency of follow-up visits among low-risk melanoma patients can be reduced, since neither anxiety, worry over cancer, nor detection of recurrences and second primaries were negatively affected by a reduced follow-up surveillance schedule. Additionally, this is accompanied by a 45% cost reduction of overall melanoma care and outpatient clinic visits [35]. Based on the results of our study and the MELFO trial, the utility of routine CT imaging for early-stage melanomas (Stage I-IIA) could not be confirmed. Detection of metastases in this population was rare; and likely does not justify the radiation risks and cost associated with frequent screening of this population [27-30, 35].

Since CT scans showed the highest rates for detection of recurrence of all applied imaging techniques, its use should be emphasized in patients with suspected metastases.

In summary, based on the results of this retrospective study, CT scans could be considered as part of the regular melanoma follow-up protocol from Stage IIB or higher (IIC-IIIC), and performed at least annually, preferably semi-annually over up to three years of follow-up. For Stage IA-IIA, routine CT imaging is not recommended. However CT imaging should be considered at any time during the follow-up period if clinically indicated. Our study also confirms the importance of education regarding self-examination, as seen in other studies previously [31-33]. The early detection of metastases in the era of new available therapies (targeted and immune checkpoint blockade) for unresectable melanoma is important, since these drugs are more likely to be effective if the tumour volume is low [36]. ■

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References

1. World Health Organization. *Ultraviolet radiation and the INTERSUN Programme*. (accessed 11 Dec 2016).

2. Balch CM, Gershenwald JE, Soong SJ, *et al*. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 2009; 27: 6199-206.

3. Dickson PV, Gershenwald JE. Staging and prognosis of cutaneous melanoma. *Surg Oncol Clin N Am* 2011; 20: 1-17.

4. Howlader N, Noone AM, Krapcho M, *et al*. *Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review, 1975-2014*. National Cancer Institute. Bethesda, MD. Available at: https://seer.cancer.gov/archive/csr/1975_2014/ (accessed 2 Apr 2018).

5. Mrazek AA, Chao C. Surviving Cutaneous Melanoma: A Clinical Review of Follow-up Practices, Surveillance, and Management of Recurrence. *Surg Clin North Am* 2014; 94: 989-1002.

6. Trotter SC, Sroa N, Winkelmann RR, Olencki T, Bechtel M. A Global Review of Melanoma Follow-up Guidelines. *J Clin Aesthet Dermatol* 2013; 6: 18-26.

7. Francken AB, Hoekstra HJ. Follow-Up of Melanoma Patients: The Need for Evidence-Based Protocols. *Ann Surg Oncol* 2009; 16: 804-5.

8. Garbe C, Paul A, Kohler-Späth H, *et al*. Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: recommendations for an effective follow-up strategy. *J Clin Oncol* 2003; 21: 520-9.

9. De Angelis R, Sant M, Coleman MP, *et al*. EUROCARE-5 Working Group. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5–a population-based study. *Lancet Oncol* 2014; 15: 23-34.

10. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; 17: 1471-4.

11. Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U. Cutaneous Melanoma: ESMO Clinical Practice Guidelines. *Ann Oncol* 2015; 26: 126-32.

12. Podlipnik S, Carrera C, Sánchez M, *et al*. Performance of diagnostic tests in an intensive follow-up protocol for patients with American Joint Committee on Cancer (AJCC) stage IIB, IIC, and III localized primary melanoma: A prospective cohort study. *J Am Acad Dermatol* 2016; 75: 516-24.

13. Davis SD. CT evaluation for pulmonary metastases in patients with extrathoracic malignancy. *Radiology* 1991; 180: 1-12.

14. Henschke CI, McCauley DI, Yankelevitz DF, *et al*. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999; 354: 99-105.

15. Diederich S, Das M. Solitary pulmonary nodule: detection and management. *Cancer Imaging* 2006; 6: S42-6.

16. Salama AK, de Rosa N, Scheri RP, *et al*. Hazard-Rate Analysis and Patterns of Recurrence in Early Stage Melanoma: Moving towards a Rationally Designed Surveillance Strategy. *PLoS One* 2013; 8: e57665.

17. Francken AB, Accortt NA, Shaw HM, *et al*. Follow-up schedules after treatment for malignant melanoma. *Br J Surg* 2008; 95: 1401-7.

18. Svedman FC, Pillas D, Taylor A, Kaur M, Linder R, Hansson J. Stage-specific survival and recurrence in patients with cutaneous malignant melanoma in Europe–a systematic review of the literature. *Clin Epidemiol* 2016; 8: 109-22.

19. Gershenwald JE, Scolyer RA. Melanoma Staging: American Joint Committee on Cancer (AJCC) 8th Edition and Beyond. *Ann Surg Oncol* 2018; 8: 2105-10.

20. Berman C, Reintgen D. Radiologic imaging in malignant melanoma: a review. *Semin Surg Oncol* 1993; 9: 232-8.

21. Xing Y, Bronstein Y, Ross MI, *et al*. Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. *J Natl Cancer Inst* 2011; 103: 129-42.

22. Gellén E, Sántha O, Janka E, *et al*. Diagnostic accuracy of (18) F-FDG-PET/CT in early and late stages of high-risk cutaneous malignant melanoma. *J Eur Acad Dermatol Venereol* 2015; 29: 1938-44.

23. Park TS, Phan GQ, Yang JC, *et al*. Routine Computer Tomography Imaging for the Detection of Recurrences in High-Risk Melanoma Patients. *Ann Surg Oncol* 2017; 24: 947-51.

24. Leiter U, Marghoob AA, Lasithiotakis K, *et al*. Costs of the detection of metastases and follow-up examinations in cutaneous melanoma. *Melanoma Res* 2009; 19: 50-7.

25. Pope WB. Brain metastases: neuroimaging. *Handb Clin Neurol* 2018; 149: 89-112.

26. Deike-Hofmann K, Thünemann D, Breckwoldt MO, *et al*. Sensitivity of different MRI sequences in the early detection of melanoma brain metastases. *PLoS One* 2018; 13: e0193946.

27. Pearce MS, Salotti JA, Little MP, *et al*. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumors: A retrospective cohort study. *Lancet* 2012; 380: 499-505.

28. Berrington de Gonzalez A, Mahesh M, *et al*. Projected cancer risks from computed tomography scans performed in the United States in 2007. *Arch Intern Med* 2009; 169: 2071-7.

29. Brenner DJ, Hall EJ. Computed tomography: an increasing source of radiation exposure. *N Engl J Med* 2007; 357: 2277-84.

30. Wen JC, Sai V, Straatsma BR, McCannel TA. Radiation-related cancer risk associated with surveillance imaging for metastatis from choroideal melanoma. *JAMA Ophthalmol* 2013; 131: 56-61.

31. Francken AB, Shaw HM, Accortt NA, Soong SJ, Hoekstra HJ, Thompson JF. Detection of first relapse in cutaneous melanoma patients: implications for the formulation of evidence-based follow-up guidelines. *Ann Surg Oncol* 2007; 14: 1924-33.

32. Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localised primary cutaneous melanoma. *Lancet Oncol* 2005; 6: 608-21.

33. Weiss M, Loprinzi CL, Creagan ET, Dalton RJ, Novotny P, O'Fallon JR. Utility of follow-up tests for detecting recurrent disease in patients with malignant melanomas. *JAMA* 1995; 274: 1703-5.

34. National Comprehensive Cancer Network Inc. *NCCN Clinical Practice Guidelines in oncology*. Available at: www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf (accessed 19 Dec 2019).

35. Damude S, Hoekstra-Weebers JE, Francken AB, Ter Meulen S, Bastiaannet E, Hoekstra HJ. MELFO-Study: Prospective, Randomized, Clinical Trial for the Evaluation of a Stage-adjusted Reduced Follow-up Schedule in Cutaneous Melanoma Patients-Results after 1 Year. *Ann Surg Oncol* 2016; 23: 2762-71.

36. Nakamura Y, Kitano S, Takahashi A, *et al*. Nivolumab for advanced melanoma: pretreatment prognostic factors and early outcome markers during therapy. *Oncotarget* 2016; 7: 77404-15.