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Long-term results of ultrasound guided fine needle aspiration cytology in conjunction with sentinel node biopsy support step-wise approach in melanoma

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Abstract

Background: US-FNAC is a common diagnostic tool in the work-up of many cancers. Results in melanoma were initially poor (sensitivity 20–40%). Introduction of the Berlin Morphology criteria has shown potential improvement up to 65–80% in selected patients.
Aim: This cohort study evaluates the long-term survival outcome of melanoma patients undergoing Ultrasound (US) guided Fine Needle Aspiration Cytology (FNAC) prior to sentinel node biopsy (SNB) or direct lymphadenectomy.
Methods: Between 2001 and 2010 over 1000 consecutive melanoma patients prospectively underwent targeted US-FNAC prior to SNB. The Berlin US morphology criteria: peripheral perfusion (PP), loss of central echoes (LCE) and balloon shape (BS) were registered. FNAC was performed if any factor was present. All patients underwent SNB or lymphadenectomy in case of positive FNAC.
Results: Median follow-up was 61 months (IQR 40–95). SN positivity rate was 21%. Survival analyses demonstrated that patients with positive US-FNAC had poor survival. After adjustment for SN status and other known prognostic features, patients with positive US-FNAC (hazard ratio (HR) 1.80, 95% CI 1.10–2.96) had worse survival than patients with normal US (reference). Patients with suspicious US and negative FNAC (HR 1.13, 95% CI 0.71–1.78) had survival comparable to patients with normal US.
Conclusions: The long-term US-FNAC results support this step-wise approach to melanoma patients. Patients with positive US-FNAC have a poor survival and can be spared a SNB. Patients with suspicious US and negative FNAC should undergo SNB to detect microscopic occult disease. Completely US-FNAC negative patients might only require follow-up and no SN staging at all.

Keywords: Melanoma; Ultrasound/ultrasonography; Fine needle aspiration cytology FNAC; Sentinel node biopsy; Survival; Prognosis

Introduction

Primary cutaneous melanoma used to be treated with aggressive surgery in absence of other successful treatment modalities. Elective lymphadenectomy was performed based on the hypothesis of sequential metastatic spread.[1]

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It aimed to potentially prevent metastatic spread of the disease, and to minimize the number of patients who would develop aggressive regional disease burden.[1] This prophylactic procedure came with a cost: only a minority of patients had involved lymph nodes at the time of surgery, a significant amount of patients suffered from long-term morbidity, and survival was not altered.[2] Morton et al. introduced a more sophisticated manner to identify those patients with regional nodal involvement; the sentinel node biopsy (SNB).[3]

To date, SNB remains the gold standard for adequate staging of the N-status in clinically node negative melanoma patients.[4–6] Meanwhile, its therapeutic power continues to be topic of debate. As the final trial report of the MSLT 1 did not find an overall survival benefit for melanoma patients undergoing wide local excision (WLE) + SNB vs. WLE only and nodal observation,[7] the search for less invasive diagnostic staging methods continues to be worthwhile.

Early diagnosis of regional nodal involvement is important not only for adequate staging, but also for potential participation in adjuvant therapy trials. Adjuvant therapy may be of a potential greater benefit in early stage III (SN-positive patients) compared to patients with palpable stage III disease. Stratification by stage III (N1: SN positive) vs. stage III (N2: palpable nodal disease) was performed in the two largest adjuvant IFN trials EORTC 18952 and 18991 demonstrated a significantly greater benefit in SN-positive patients.[8–12] Recently a recurrence free survival benefit for SN-positive patients was also demonstrated in the EORTC 18071 trial regarding adjuvant ipilimumab in stage III patients.[13] The ongoing EORTC 1325 trial regarding adjuvant pembrolizumab is stratified similarly.[14] Final results regarding recurrence free survival and overall survival will have to be awaited for these trials, but results of the EORTC 18071 are promising.

Ultrasound (US) guided Fine Needle Aspiration Cytology (FNAC) is a common diagnostic tool proven to be helpful in the work-up of breast cancer and thyroid cancer.[15,16] The results of diagnostic preoperative US of the regional lymph node basins in melanoma patients were poor in the past decades, with a reported sensitivity of only 5–40%.[17–21] Hence preoperative US in combination with FNAC has not yet been adopted as a standard preoperative diagnostic tool.

Previously, our group has demonstrated that is it possible to identify the sentinel node (SN) using targeted US with a good accuracy.[22] Several others have performed targeted US of the SN area directly after lymphoscintigraphy as well.[21,23,24] Correct identification of tumor positive SNs prior to surgery is the ultimate goal of targeted US; results vary but can be promising when this technique is further improved. Marone et al. correctly identified 18 out of 122 positive SNs (15%) (from 831 excised SNs in total), and Testori et al. correctly identified 16 out of 16 positive SNs (100%) with targeted US, but also had 9 false positive patients at histological analysis (false positive rate = 36% (FP/(TP + FP))).[21,24]

In a second study by our group US-FNAC of the SN could identify up to 65% of all tumor positive SNs preoperatively, and additionally the Berlin morphology criteria have been presented, describing specific US patterns related to early involvement with which a high sensitivity for US-FNAC could be achieved.[25,26]

More recently our group reported on the first 1000 prospective melanoma patients who underwent US-FNAC prior to a scheduled SNB: application of the Berlin Morphology criteria yielded a sensitivity of up to 76% in selected patients.[27] 5-year estimated Kaplan–Meier melanoma specific survival (MSS) and disease free survival (DFS) showed a significant difference in survival outcomes for each US-FNAC status,[27] indicating it's potential as a prognostic indicator.

The current study aims to evaluate the long-term survival outcomes of this now fully matured cohort of melanoma patients undergoing US-FNAC prior to SNB or direct lymphadenectomy.

Patients and methods

Patients

The current study concerns the long-term follow-up of a previously collected cohort by Voit et al. published previously[27] of over 1000 melanoma patients who underwent US-FNAC and SNB or immediate lymph node dissection (LND) in case of positive US-FNAC.

Briefly, the cohort consisted of over 1000 stage I/II consecutive melanoma patients who prospectively underwent US-FNAC prior to Sentinel Node Biopsy (SNB) between 2001 and 2010. All patients had a histopathologically proven malignant melanoma (Breslow thickness $\geq$1.00 mm, or at least one risk factor such as Clark level IV/V, ulceration or regression) and were scheduled for a SNB at the Department of Dermatology, Charité, University Medicine Berlin, Germany. The institutional ethics review board (ERB) approved the study and informed consent was obtained from all patients enrolled. For the current analysis the first 1000 consecutive patients with sufficient follow-up (July 2001–November 2010) were selected. A quality control of the database was carried out to assure maximum retrieval of any missing data from patient records at 5-year follow-up. Two duplicate cases were excluded and 6 patients with a second primary melanoma requiring a second US-FNAC and SNB were censored for survival analysis. Eight consecutive study patients were added to the cohort to restore a sample size of 1000 patients (1006 US-FNAC cases) for the current analyses.

Design

All patients underwent lymphoscintigraphy prior to US-FNAC. The Berlin US morphology criteria: Peripheral perfusion (PP), loss of central echoes (LCE) and balloon shaped (BS) were registered and FNAC was performed if any factor was present. If FNAC could not verify a clearly malignant US pattern, patients always proceeded to undergo a SNB. In the early phase of the study all patients proceeded to undergo a SNB even if FNAC was positive (n = 47). During the course of the study, a change in hospital policy allowed the surgeon to proceed to an immediate LND after a positive FNAC. The decision to change a scheduled SNB to a LND was always based on a positive FNAC.

Definitions

US was considered malignant in case of LCE or BS. US was considered suspicious in case of PP or the wandering to the rim of the central echo. US-FNAC was considered positive if LCE or BS (with or without a FNAC verification) was seen or in case of a positive FNAC.

When an echo-poor disruption of the lymph node architecture was observed this was described as Echo free island (EFI). Results of EFI have been described in detail previously.[28]

US-FNAC technique and analysis

The high-end US device MyLab 70 (ESAOTE, Genova, Italy) was used for all US examinations. An expert ultrasonographist identified the lymph node, measured it and described the morphologic pattern. The lymph node was classified as benign, suspicious or malignant according to the visualized pattern. Details of the ultrasound technique, image analysis using ultrasound morphology criteria and classification have been described previously.[25,27] For FNAC a hand-held Binder-valve was used as described in detail previously.[27] A smear had to contain at least approximately 100 cells to be considered technically sufficient.

Details of pathologic examination of the SN have been described previously.[27] SN tumor burden was measured according to the Rotterdam criteria.[29,30] Microanatomic location of SN metastases was evaluated according to the criteria by Dewar et al.[31] Final histology of the SN or LND was considered as the gold standard. The first 120 patients underwent both targeted US and FNAC of the SN regardless of the US classification, as a feasibility study.

Statistics

DFS and MSS were calculated from SN date until first recurrence or death or censored at the date of last known follow-up, if no events had taken place. 5-year DFS and MSS were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox's proportional hazard model was applied for univariable and multivariable analyses to determine the prognostic value of covariates regarding MSS. Hazard ratios (HR) were estimated for: SN status, SN tumor burden, US-FNAC result, age, gender, primary tumor location, histologic subtype, Breslow thickness, and ulceration status. SN tumor burden was left out as covariate for the multivariate Cox regression model 1 as a significant correlation with SN status could be expected, and was tested in a separate model 2 without SN status. All statistical analyses were performed with SPSS version 21 (IBM Corporation, Armonk, NY, USA). P values of less than 0.05 were considered as significant.

Results

Baseline features of the first 1000 US-FNAC cases have been described previously elsewhere.[27] After quality control (where 2 duplicate cases were excluded and 6 cases were identified concerning patients with a second primary melanoma and a second US-FNAC) eight consecutive study patients were added to the cohort to restore a sample size of 1000 patients (1006 cases) for the current analyses. Patient and tumor features are displayed in Tables 1 and 2. Mean/median follow-up was 66/61 months (IQR 40–95).

Survival

5-year and 10-year Kaplan–Meier estimated MSS was significantly better for patients with negative US and FNAC: 90% (SE 1%) vs. 51% (SE 5%) for US-FNAC positive patients; and 85% (SE 2%) vs. 34% (SE 6%) respectively (both $p < 0.0001$) (Fig. 1A). This difference in MSS remained significant in the group of SN-positive patients: 5-year MSS 71% (SE 5%) for US-FNAC negative patients vs. 51% (SE 5%) for US-FNAC positive patients and 10-year MSS 65% (SE 7%) vs. 33% (SE 6%) (both $p < 0.0001$) respectively (Fig. 1B). Since there was only 1 SN negative patient with positive US-FNAC (whom turned out to have a false negative SNB), no log-rank test comparison could be performed for SN negative patients. The corresponding 5-year and 10-year Kaplan–Meier estimated DFS rates for all patients were 84% (SE 3%) for US-FNAC negative patients vs. 33% (SE 5%) for US-FNAC positive patients, and 79% (SE 2%) vs. 24% (SE 6%) (both $p < 0.0001$) respectively (Fig. 2).

There were 778 both US (and/or FNAC) negative and SN negative patients. Of these patients, 49 (6%) developed regional lymph node metastases. False negative rate (FN/(FN + TP)) was 49/(49 + 119) = 29%. The median time interval to nodal basin failure was 28 months (interquartile range 19–44 months). The majority of these patients had either a NM (n = 23) or a SSM (n = 21, 2); 2 patients had an ALM; 1 patient a LMM; and in 2 patients exact histology data were not available.

Table 1
Baseline characteristics of all melanomas (1006 in 1000 patients).

Characteristic	n (%) or mean/median (range)
Gender	
Female	435 (43)
Male	571 (57)
Histological subtype	
SSM	601 (60)
NM	242 (24)
LMM	37 (4)
ALM	44 (4)
Unknown	82 (8)
T stage	
T1 (≤1.00 mm)	294 (29)
T2 (1.01–2.00 mm)	309 (31)
T3 (2.01–4.00 mm)	233 (23)
T4 (>4.00 mm)	170 (17)
Ulceration	
Absent	763 (76)
Present	243 (24)
SNs removed	1.72/1 (1–13)
SN result	
Negative	797 (79)
Positive (incl. 43 direct LND for pos. FNAC)	209 (21)
Immediate LND (after pos. FNAC)	43 (4)/43/209 (21)
SN tumor burden Rotterdam criteria	(n = 209)
<0.1 mm	32 (15)
0.1–1.0 mm	63 (30)
>1.0 mm	64 (31)
Immediate LND or unknown	50 (24)

Baseline characteristics of all melanomas with n and percentage or mean/median and range. Abbreviations: US, ultrasound; SSM, superficial spreading melanoma; NM, nodular melanoma, LMM, lentigo maligna melanoma; ALM, acrolentiginous melanoma; SN, sentinel node; LND, lymph node dissection, pos., positive; FNAC, fine needle aspiration cytology.

Table 2
Ultrasound and fine needle aspiration cytology results.

PP	
Absent	670 (67)
Present	273 (27)
Unknown	63 (6)
LCE	
Central echo present (normal)	798 (79)
Central echo wandering to rim	97 (10)
Central echo lost	66 (7)
Unknown	45 (5)
BS	
Absent	887 (88)
Present	53 (5)
Unknown	66 (7)
US results	
US benign	683 (68)
US suspect	247 (25)
US malignant	76 (7)
FNAC results	n = 341
Benign	252 (74)
Malignant	89 (26)
US/FNAC results	
Normal US/FNAC negative	681 (68)
PP at US	206 (20)
BS/LCE and/or FNAC positive	119 (12)

Ultrasound results of all 1006 melanomas. Abbreviations: PP, peripheral perfusion; LCE, loss of central echo; BS, balloon shape; US, ultrasound; FNAC, fine needle aspiration cytology.

Classification of patients according to Berlin ultrasound morphology criteria showed that patients with a suspicious US (i.e. presence of PP or beginning LCE = 'wandering to the rim') had a slightly worse 5-year MSS than patients with a normal US; and patients with a clearly malignant US (i.e. presence of BS or total LCE) had the poorest survival: 5-year MSS 91% (normal US, SE 1%) vs. 81% (suspicious US, SE 3%), and vs. 55% (malignant US, SE 6%), and 10-year MSS 86% (SE 2%) vs. 74% (SE 4%) and 38% (SE 8%) (all $p < 0.0001$) (Fig. 3).

The unadjusted and adjusted HRs for 5-year MSS are shown in Table 3.

US-FNAC results were categorized as follows: US normal and FNAC negative; US suspicious and FNAC negative; US positive and/or FNAC positive. After adjustment for SN status, gender, age, Breslow thickness, primary tumor location, histology type, and ulceration in model 1, suspicious US was no prognostic indicator, but positive US-FNAC did remain as a prognostic indicator for worse MSS.

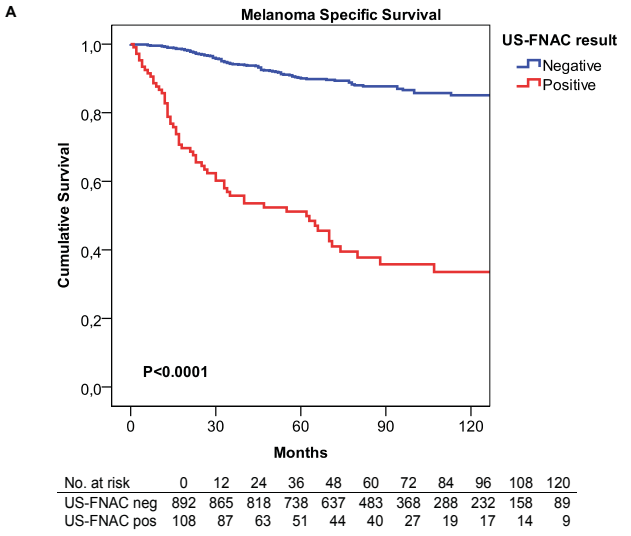
A second model was formed with SN tumor burden. An interaction term was calculated for SN tumor burden and US-FNAC result since they were found to be significantly correlated.[27] In a simple model with US-FNAC result and SN tumor burden, the interaction term was not significant (data not shown). The unadjusted and adjusted hazard ratios for 5-year MSS for model 2 are shown in Table 3. In this model, US-FNAC was no prognostic indicator.

Discussion

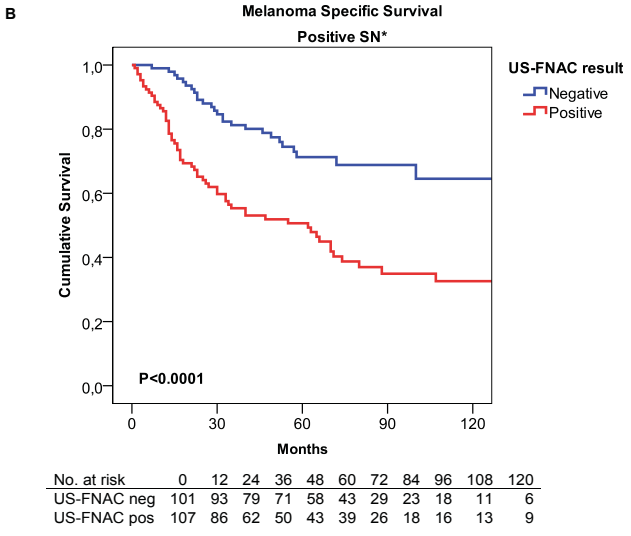
This study is the largest to date reporting on the value of preoperative assessment of the SN with US morphologic criteria in combination with FNAC in melanoma patients. We present the long-term follow-up results of this matured cohort of 1006 US-FNAC examinations in 1000 patients described previously by Voit et al.[27]

Crude 5-year estimated MSS was significantly worse for patients with suspicious US (PP or wandering of the central echo to the rim) and for patients with malignant US (BS or LCE) as well as for the combined result of a positive US and/or FNAC (Figs. 1 and 3).

The unadjusted HR for a suspicious US in absence of a positive FNAC was slightly higher than the reference value of a normal US (and negative FNAC), although not significant. The unadjusted HR for a malignant US and or a positive FNAC was significantly higher compared to patients with a normal US (Table 3). In model 1, adjusted HR for positive US-FNAC remained as prognostic indicator with a HR of 1.80 ($p = 0.019$), while in model 2, where a more detailed classification of SN tumor burden according to the Rotterdam criteria was applied, positive US-FNAC



No. at risk	0	12	24	36	48	60	72	84	96	108	120
US-FNAC neg	892	865	818	738	637	483	368	288	232	158	89
US-FNAC pos	108	87	63	51	44	40	27	19	17	14	9



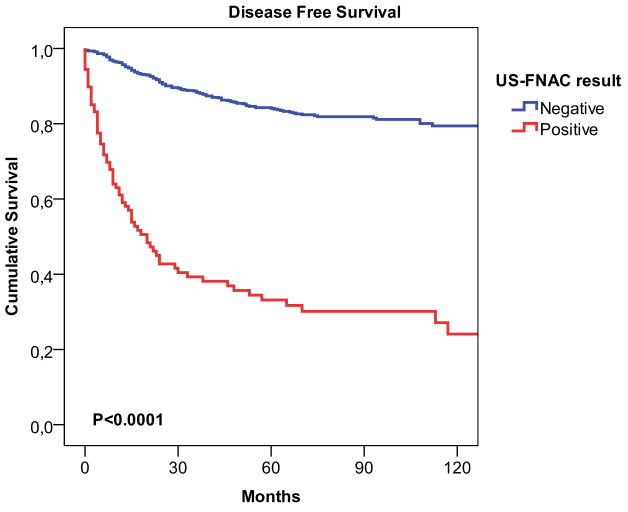
No. at risk	0	12	24	36	48	60	72	84	96	108	120
US-FNAC neg	101	93	79	71	58	43	29	23	18	11	6
US-FNAC pos	107	86	62	50	43	39	26	18	16	13	9

Figure 1. Estimated Kaplan–Meier melanoma specific survival of all patients (A) and of SN positive patients only (B) for ultrasound (US) – fine needle aspiration cytology (FNAC) negative result (blue line) and for US-FNAC positive result (red line) compared with the log-rank test.

was not a significant prognostic indicator, despite the still slightly elevated HR of 1.52 ($p = 0.144$).

Voit et al. found that US-FNAC outcome was clearly correlated with SN tumor burden; preoperative US-FNAC correctly identified 61% of SNs with a tumor burden of >1.0 mm as malignant, and up to 91% of the patients who proceeded directly to LND was correctly identified as SN-positive.[27] This can explain why a positive US-FNAC result is a relevant prognostic indicator for MSS after adjustment for SN status and other prognostic indicators in model 1, and not in model 2 where SN tumor burden already is a covariate.

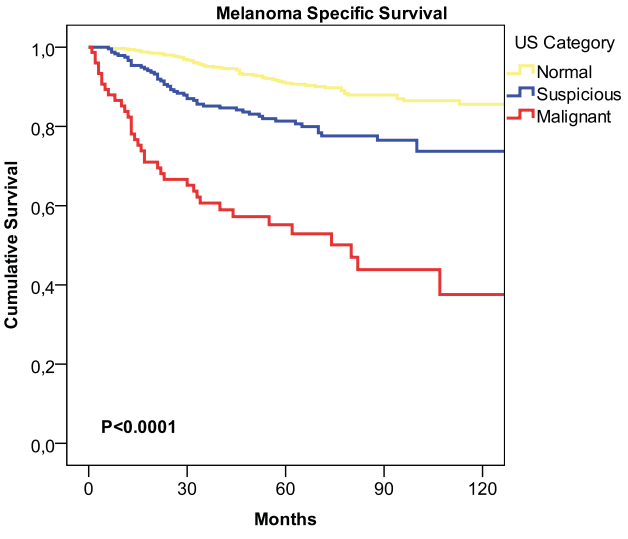
Routine US-FNAC in breast cancer patients has shown to upstage a significant amount of patients preoperatively, sparing them an unnecessary SNB in up to 18%.[15] The fact that US-FNAC results remain as prognostic indicator



No. at risk	0	12	24	36	48	60	72	84	96	108	120
US-FNAC neg	892	839	771	689	585	449	332	266	213	148	80
US-FNAC pos	108	61	40	34	30	26	19	13	13	10	7

Figure 2. Estimated Kaplan–Meier disease free survival of all patients for ultrasound (US) – fine needle aspiration cytology (FNAC) negative result (blue line) and US-FNAC positive result (red line) compared with the log-rank test.

after a median follow-up of 5 years in this large cohort emphasizes the potential to incorporate the Berlin US morphology criteria combined with FNAC as was done with the Rotterdam criteria in staging of melanoma patients in this paradigm shifting era with upcoming systemic therapies for melanoma. Especially in light of current adjuvant



no. at risk	0	12	24	36	48	60	72	84	96	108	120
US normal	679	663	631	570	493	369	281	217	176	122	66
US suspicious	245	230	204	179	158	128	94	77	61	45	29
US malignant	76	59	46	40	30	26	20	13	12	5	3

Figure 3. Estimated Kaplan–Meier melanoma specific survival of all patients for ultrasound (US) category normal (yellow line), suspicious (blue line) and malignant (red line) compared with the log-rank test.

Table 3
Cox proportional hazards regression analysis for melanoma specific survival (n = 1000).

Variable	Univariable			Multivariable model 1			Multivariable model 2		
	HR	95% CI	p-Value	HR	95% CI	p-Value	HR	95% CI	p-Value
SN status									
Negative	Ref			Ref			–		
Positive**	6.52	4.73–8.98	<0.0001*	3.65	2.37–5.63	<0.0001*	–		
SN tumor burden									
Negative	Ref			–			Ref		
<0.1 mm	1.04	0.33–3.29	0.954	–			0.96	0.30–3.11	0.942
0.1–1.0 mm	5.94	3.72–9.49	<0.0001*	–			4.67	2.81–7.79	<0.0001*
>1.0 mm	8.09	5.28–12.4	<0.0001*	–			3.89	2.78–8.46	<0.0001*
Direct LND/missing	12.1	7.74–19.0	<0.0001*	–			4.25	2.08–8.65	<0.0001*
US-FNAC									
Both neg.	Ref			Ref			Ref		
US susp & FNAC neg	1.45	0.93–2.26	0.100	1.13	0.71–1.78	0.617	1.20	0.76–1.90	0.426
US malig/FNAC pos	7.56	5.31–10.8	<0.0001*	1.80	1.10–2.96	0.019*	1.52	0.87–2.65	0.144
Gender									
Female	Ref			Ref			Ref		
Male	1.39	0.99–1.93	0.053	1.48	1.04–2.11	0.029*	1.45	1.02–2.08	0.041*
Age									
Cont.	1.01	0.99–1.02	0.136	1.01	1.00–1.02	0.045*	1.01	0.99–1.02	0.064
Location									
Extremity	Ref			Ref			Ref		
Trunk	0.95	0.67–1.35	0.782	1.12	0.76–1.64	0.567	1.10	0.74–1.62	0.641
Head & neck	1.72	1.08–2.75	0.022*	2.33	1.43–3.79	0.001*	2.27	1.38–3.74	0.001*
Breslow									
Cont.	1.11	1.10–1.13	<0.0001*	1.06	1.00–1.08	<0.0001*	1.06	1.03–1.09	<0.0001*
Ulceration									
Absent	Ref			Ref			Ref		
Present	3.19	2.32–4.39	<0.0001*	1.53	1.07–2.19	0.019*	1.51	1.05–2.17	0.026*
Histology									
SSM/LMM	Ref						Ref.		
NM/ALM	2.88	2.08–4.00	<0.0001*	1.47	1.01–2.12	0.042*	1.53	1.06–2.22	0.024*
Unknown	1.14	0.54–2.37	0.735	1.07	0.51–2.24	0.859	1.04	0.49–2.17	0.928

Multivariable model 1 was adjusted for: gender, age, primary tumor location, Breslow thickness, ulceration status, histologic subtype, SN status (including 43 patients with direct lymph node dissection), and US-FNAC result. Multivariable model 2 was adjusted for: gender, age, primary tumor location, Breslow thickness, ulceration status, histologic subtype, SN tumor burden and US-FNAC result. A p-value of <0.05 was considered statistically significant (marked with an *).

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; SN, sentinel node; Ref, reference; Cont., continuous; SSM, superficial spreading melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; ALM, acrolentiginous melanoma; US-FNAC, ultrasound-fine needle aspiration cytology result; neg., negative; susp, suspicious; malig, malignant; pos, positive. ** Positive SN patients include 43 patients undergoing direct lymph node dissection after positive US-FNAC.

therapy (trials), in a field which lacked effective systemic therapy until 2010, the need for early and easy staging is desired by patients and physicians. As described previously by Voit et al.,[26,32] this might be a cost-effective baseline staging for pT3-4 melanomas and/or primary ulcerated melanomas.[33]

Limitations

PP and beginning LCE were no prognostic indicators, nonetheless these are helpful signs in selecting which patients should undergo FNAC as well in order to further differentiate between a negative or positive US-FNAC result. As was described previously, sensitivity of combined US-FNAC was significantly higher than in other studies, possibly due to the fact that the threshold to perform FNAC because of a suspicious US Berlin criterion was lower than in other performed studies.[27]

The correlation between US-FNAC and SN tumor burden may color survival outcome of US-FNAC status, causing significant differences in survival which may be more based on SN tumor burden than on US-FNAC status. Potentially US-FNAC can best be seen as an indicator of high SN tumor burden. Ultimately all patients undergoing US-FNAC will undergo a SNB or direct LND in case of positive US-FNAC, thus no potential nodal involvement will be missed. Histology of SN or dissected lymph nodes will still be used for pathological staging; but patients can skip and be spared a potentially unnecessary SNB in case of positive US-FNAC.

As all US-FNAC negative patients underwent a SNB, no answer can be given on whether these patients would have

developed nodal basin failure over time if no SNB was performed, not taking into account the patients that turned out to be false negative after SNB. The 29% false negative rate and regional nodal recurrence rate in US-FNAC and SN negative patients is comparable to other reports,[7,34] which is reassuring.

One of the limitations of this study is that all US-FNACs were performed by a select group of 3 dedicated ultrasonographists, of whom one performed the first 400 alone. The reproducibility of US-FNAC results by another study team has yet to be investigated. Efforts have been made to educate others in recognizing and utilizing the Berlin morphology criteria for targeted US-FNAC of the SN by organizing EORTC Melanoma Group sentinel node ultrasound courses since 2012. More recently the GULF trial, a prospective multicenter study has started (Dutch trial registry number NTR5193, www.trialregister.nl). In this feasibility study 120 patients eligible for SNB (melanoma and breast cancer patients) will undergo gamma-probe and US guided FNAC of the SN prior to surgical removal of the SN, with sensitivity of the gamma-probe guided US-FNAC as main objective. Additionally, US images of all SNs will be classified according to the Berlin criteria.

Despite this drawback, US-FNAC of the sentinel node has proven to be accurate and sensitive in detecting patients with possible lymph node involvement prior to surgery, and has the potential to become a part of standard preoperative diagnostic work-up like in breast cancer.

Conclusions

The long-term results of this study support the step-wise approach to melanoma patients. In case of positive FNAC and/or clearly malignant US (BS and/or LCE) they can be spared a SNB. In case of PP and negative FNAC, patients could be offered continue US surveillance or SNB for higher risk primary tumors. Completely US-FNAC negative patients might only require follow-up and no SN staging, with continue US surveillance as addendum for high risk T3/4 and/or ulcerated primaries.

Ethical approval information

Ethical Approvals: # 45/95 Ethics committee of the University of Ulm, # 1367/00 of the Ethics Committee of the Charité, Medizinische Fakultät der Humboldt Universität Berlin and Amendment EA1/023/06.

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Conflicts of interest statement

AE has received honoraria from and a consulting role for BMS, Incyte, GSK, MSD and Celldex, all unrelated to the current study. He has received travel expenses from BMS, Incyte, GSK and MSD, all unrelated to the current study.

The remaining authors have no conflicts of interest pertaining to the current manuscript.

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