European Journal of Cancer (2014) **50**, 2280–2288

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Ultrasound-guided fine needle aspiration cytology as an addendum to sentinel lymph node biopsy can perfect the staging strategy in melanoma patients

Christiane A. Voit [a,e,*,1], Saskia L.M. Gooskens [b,e,1], Petra Siegel [a], Gregor Schaefer [a], Alfred Schoengen [c], Joachim Röwert [a], Alexander C.J. van Akkooi [b,e], Alexander M.M. Eggermont [d,e]

[a] *Department of Dermatology, Charité, Humboldt University of Berlin, Berlin, Germany*
[b] *Department of Surgical Oncology, Erasmus University Medical Center – Daniel den Hoed Cancer Center, Rotterdam, The Netherlands*
[c] *Department of Hematology and Oncology, Armed Forces Hospital, Ulm, Germany*
[d] *Institut de Cancérologie Gustav Roussy, Paris-Sud/Villejuif, France*
[e] *European Organization for Research and Treatment of Cancer (EORTC) Melanoma Group (MG), Brussels, Belgium*

Received 27 March 2014; received in revised form 28 May 2014; accepted 28 May 2014
Available online 3 July 2014

KEYWORDS
Melanoma
Sentinel node
Ultrasound
Fine needle aspiration cytology
Survival
Prognosis

Abstract ***Background:*** Ultrasound guided fine needle aspiration cytology (US-guided FNAC) can identify microscopic involvement of lymph nodes as in breast cancer and avoid surgical sentinel node (SN). Its utility in melanoma patients is controversial and subject of this study.
Methods: Between 2001 and 2010 over 1000 stage I/II consecutive melanoma patients prospectively underwent US-FNAC prior to SN biopsy. 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. FNAC was performed in case of presence of any of these factors. SN tumour burden was measured according to the Rotterdam criteria. All patients underwent SN or lymph node dissection (LND) in case of positive FNAC.
Findings: Mean/median Breslow thickness was 2.58/1.57 mm. Mean/median follow-up was 56/53 months (1–132). SN positivity rate was 21%. US-FNAC Sensitivity was 71% (US only) and 51% (US-FNAC). Sensitivity of US-FNAC was highest for T4 (76%) and ulcerated melanomas (63%). PP, LCE and BS had sensitivity of 69%, 24% and 24% respectively. Sensitivity of

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.

* *Corresponding author at:* Department of Dermatology, Charité, University Medicine, Berlin, Charitéplatz 1, 10117 Berlin, Germany. Tel.: +49 30 450 618230; fax: +49 9491 952616.
E-mail address: christiane.voit@t-online.de (C.A. Voit).
[1] Shared first authorship.

http://dx.doi.org/10.1016/j.ejca.2014.05.027

US-FNAC increased with increasing SN tumour burden. PP was an early sign of metastasis (58% in <0.1 mm metastases). Threshold size of a metastasis for FNAC was 0.3 mm. Five-year survival correlated to US-FNAC status (95% in negative and 59% in positive).

Interpretation: Ultrasound guided FNAC (US-FNAC) according to the Berlin morphology criteria could correctly identify at least half of all tumour positive sentinel nodes, prior to the surgical SN procedure. Peripheral perfusion is an early sign of metastasis, which is very sensitive, but with lower positive predictive value (PPV). It is responsible for the sensitivity of the procedure. Balloon shape is a sign of advanced metastases, with lower sensitivity, but high PPV. US-FNAC sensitivity correlated with increasing T-stage, ulceration of the primary and increasing SN tumour burden. US-FNAC status accurately predicts survival.

1. Introduction

Over recent decades the incidence of malignant melanoma has been rising throughout Europe, the United States of America (USA) and Australia [1–4], but mortality has remained virtually unchanged [4].

The most important prognostic factor of early stage melanomas (stage I/II) is lymph nodal status. Therefore, adequate staging of these patients is very important to be able to determine their prognosis [5,6]. Worldwide, the sentinel node (SN) procedure has been accepted during the past two decades as the most accurate staging procedure [7]. Sentinel node biopsy (SNB) is a surgical procedure with a complication rate between 5% and 10% [8,9]. In the absence of proof that SNB is associated with a survival benefit alternative methods to identify positive SNs are being considered. The diagnostic algorithm of other cancers, such as thyroid and breast cancer, already includes pre-operative ultrasound (US) and fine needle aspiration cytology (FNAC) and it is conceivable to apply this to melanomas.

Previously, we have demonstrated that ultrasound can identify the same node, which is later excised and considered the sentinel node with an accuracy of 79% [10]. Another study by our group has demonstrated that US-FNAC could identify up to 65% of all SN involvement preoperatively [11]. Finally, we have described specific US patterns, which were used to achieve such a high sensitivity, the so called Berlin morphology criteria, which include Peripheral perfusion (PP) as an early sign of involvement followed by loss of central echo (LCE) and balloon shape (BS) as signs of advanced involvement [12].

The number of evaluated patients and their mean and median follow-up have increased significantly. The aim of the current study was to evaluate our increased experience with this modern approach comprising the highest amount of US-FNAC of SNs and to test its application as a completion to SNB. This is especially en vogue with the background of the just now published results of the MSLT1 trial [13], which is literally a confirmation of the results in 2006 and the importance of the non-sentinel node status, which can be assessed by performing completion lymph node dissection (CLND) after a positive sentinel lymph node biopsy (SLNB) [14]; or even – as an alternative-directly after a positive FNAC of the sentinel node.

2. Patient and methods

2.1. Patients

Our prospectively collected database includes all patients presenting with a histopathologically proven primary malignant melanoma (at least 1.00 mm Breslow thickness, or if less, at least Clark IV/V, ulcerated and/or regressed) and who were planned for a sentinel node procedure 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. Recruitment for this study started in 2001, the database now includes over 1500 patients. For the current analyses, we have censored inclusion after the first 1000 consecutive patients with sufficient follow-up (July 2001–November 2010). This cohort includes the first 400 patients, which have been examined exclusively by one ultrasonographist (CV) and whose results have been previously published elsewhere [11,12].

2.2. Methods

All patients were scheduled for a SN procedure in either 1 or 2 day protocol. Patients first underwent a lymphoscintigraphy, which assists the ultrasonographist to better focus their examination. In the timeslot between lymphoscintigraphy and surgery, patients were examined by ultrasound (US) in B-mode and Power Doppler. US is aimed at clearly depicting the location of the suspected SN and at clearly stating whether it seemed to be involved or not. If US depicted a suspicious or malignant SN, FNAC was performed (3–4 repeat FNACs were performed within one procedure) for verification of the lesion. If a clearly malignant