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Ultrasound Mapping of Lymph Node and Subcutaneous Metastases in Patients with Cutaneous Melanoma: Results of a Prospective Multicenter Study

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Key Words
Melanoma · Sentinel lymph node biopsy · Consecutive complete lymph node dissection

Abstract
Background: Ultrasound (sonography, B-mode sonography, ultrasonography) examination improves the sensitivity in more than 25% compared to the clinical palpation, especially after surgery on the regional lymph node area. ***Objective:*** To evaluate the distribution of metastases during follow-up in the draining lymph node areas from the scar of primary to regional lymph nodes (head and neck, supraclavicular, axilla, infraclavicular, groin) in patients with cutaneous melanoma with or without sentinel lymph node biopsy (SLNB) or former elective or consecutive complete lymph node dissection in case of positive sentinel lymph node (CLND). ***Methods:*** Prospective multicenter study of the Departments of Dermatology of the Universities of Homburg/Saar, Tübingen and Munich (Germany) in which the distribution of lymph node and subcutaneous metastases were mapped from the scar of primary to the lymphatic drainage region in 53 melanoma patients (23 women, 30 men; median age: 64 years; median tumor thickness: 1.99 mm) with known primary, visible lymph nodes or subcutaneous metastases proven by ultrasound and histopathology during the follow-up. ***Results:*** Especially in the axilla, infraclavicular region and groin the metastases were not limited to the anatomic lymph node regions. In 5 patients (9.4%) (4 of them were in stage IV) lymph node metastases were not located in the corresponding lymph node area. 32 patients without former SLNB had a time range between melanoma excision and lymph node metastases of 31 months (median), 21 patients with SLNB had 18 months ($p < 0.005$). In 11 patients with positive SLNB the time range was 17 months, in 10 patients with negative SLNB 21 months ($p < 0.005$); in 32 patients with CLND the time range was 31 months and in 21 patients without CLND 18 months ($p < 0.005$). In thinner melanomas lymph node metastases occurred later ($p < 0.05$). ***Conclusions:*** After surgery of cutaneous melanoma, SLNB and CLND the lymphatic drainage can show significant changes which should be considered in clinical and ultrasound follow-up examinations. Especially for high-risk melanoma patients follow-up examinations should be performed at intervals of 3 months in the first years. Patients at stage IV should be examined in all regional lymph node areas clinically and by ultrasound.

Andreas Blum and Monika-Hildegard Schmid-Wendtner contributed equally to this work.

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Introduction

Melanoma becomes a life-threatening malignancy with the developing of local, regional or distant metastases [1, 2]. Dissemination of metastases occurs in two thirds of these cases through the lymphatic system [3]. Mostly, the regional lymph node group associated to the primary melanoma is involved. A relevant prognostic parameter for further recurrences and survival is the number of affected lymph nodes [1, 4]. Therefore, especially high-risk melanoma patients should be examined in the draining lymphatic areas during the follow-up [5]. Hereby, the ultrasound (sonography, B-mode sonography, ultrasonography) examination improves the sensitivity in more than 25% compared to the clinical palpation, especially after surgery on the regional lymph node area [4, 6–9]. Ultrasound has a high diagnostic accuracy compared to the clinical examination and lower financial costs compared to computer tomography, magnetic resonance tomography or positron emission tomography [4, 5, 8, 9]. But, to guarantee the high diagnostic accuracy trained users and clear defined regional lymph node areas, which are associated to the primary, are demanded. Therefore, this prospective multicenter study was performed to evaluate the distribution of metastases in the draining lymph node areas in melanoma patients during the regular follow-up detected by ultrasound.

Patients and Methods

Patients

Between September 2002 and August 2003, a total of 53 patients (23 women and 30 men) were included in this prospective study by the Departments of Dermatology of the Universities of Homburg/Saar (22 patients), Tübingen (18 patients) and Munich (13 patients) during the follow-up of melanoma patients. Only patients with known primary, detected metastases of lymph nodes or intransit area in ultrasound and proven by histopathology were included. Metastases could be detected either at the first presentation of the patients or during the follow-up. Therefore, patients were included with or without sentinel lymph node biopsy (SLNB) or former elective or consecutive complete lymph node dissection in case of positive sentinel lymph node (CLND). In all centers patients with a positive SLNB received a CLND. Not included were patients with unknown primary melanomas of mucous membranes or organs other than the skin.

Age range of the patients was 32–88 years (mean, 60.6 years; median, 64 years). Tumor thickness range was 0.31–20.0 mm (mean 3.22 mm; median 1.99 mm). Patients' characteristics are listed in table 1. The regular follow-up of melanoma patients included history, physical examination, ultrasound of the scar, intransit and regional lymph node area(s) [5]. Structures suspicious for metastases on ultrasound were surgically removed for histopathologic examination.

Table 1. Characteristics of 53 patients

Characteristics	Number of patients (%)
Sex	
Female	23 (43.4)
Male	30 (56.6)
Tumor thickness, mm	
≤0.75	5 (9.4)
≤0.76–1.50	11 (20.8)
≤1.51–4.00	25 (47.1)
>4.00	11 (20.8)
Unknown	1 (1.9)
Histologic subtypes	
SSM	21 (39.6)
NM	20 (37.7)
LMM	4 (7.6)
ALM	6 (11.3)
Unknown	2 (3.8)
Site of the primary tumor	
Head and neck	7 (13.2)
Trunk	17 (32.1)
Arm	1 (1.9)
Leg	28 (52.8)
Sentinel lymph node biopsy	
Yes	21 (39.6)
No	32 (60.4)
Positiv sentinel lymph node biopsy	
Yes	11 (52.4)
No	10 (47.6)
CLND	
Yes	32 (60.4)
No	21 (39.6)

SSM = Superficial spreading melanoma; NM = nodular melanoma; LMM = lentiginous malignant melanoma; ALM = acrolentiginous melanoma; unknown = subtype not diagnosable in histopathology.

Methods

Ultrasound examinations were performed by all authors using real-time scanners (Homburg/Saar: Sonoline Elegra, Siemens Medical Solutions, Erlangen, Germany; Tübingen: AU4 Diagnostic Ultrasound System, Esaote Biomedica, Neufahrn-Munich, Germany; Munich: SSA-340 A, Toshiba Medical Systems, Neuss, Germany) with a 7.5–13 MHz linear transducer.

In all patients, the examination covered the scar of the primary, its 10-cm surrounding area and the regional lymphatic basin in longitudinal and transverse orientation. At the neck and extremities, this area corresponds to the large blood vessels whereas at the trunk about 30% of melanomas have two or more different lymphatic drainage areas [10–13]. At the proximal part of the extremities the tissue compartment on the lateral and medial region of the main vessels were also scanned. In case the melanoma was located at the head or neck, always both sides of the neck including the supraclavicular region were examined; in case the primary was located at one of the arms, hands or fingers, the axilla and infracla-

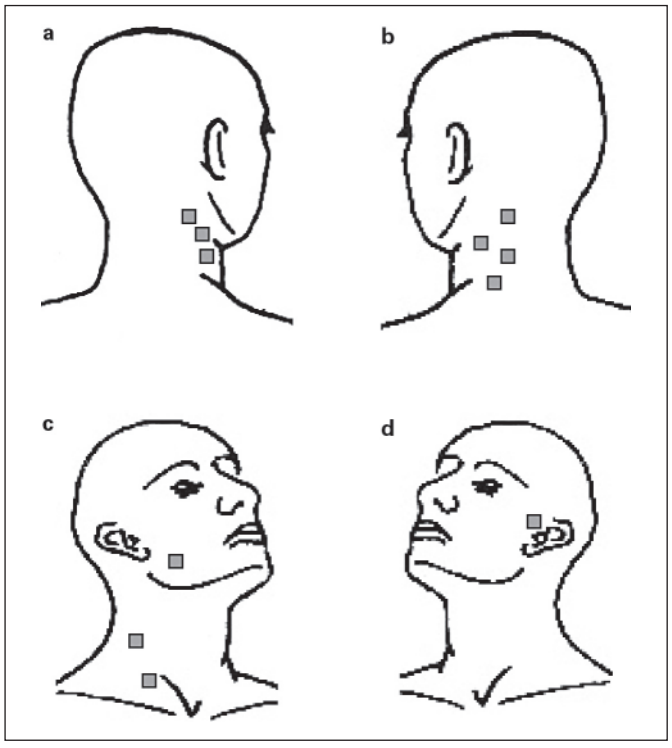

Fig. 1. Lymph node areas at the head. **a** Dorsal right side. **b** Dorsal left side. **c** Ventral right side. **d** Ventral left side. Grey squares indicates melanoma metastases from a primary of the head.

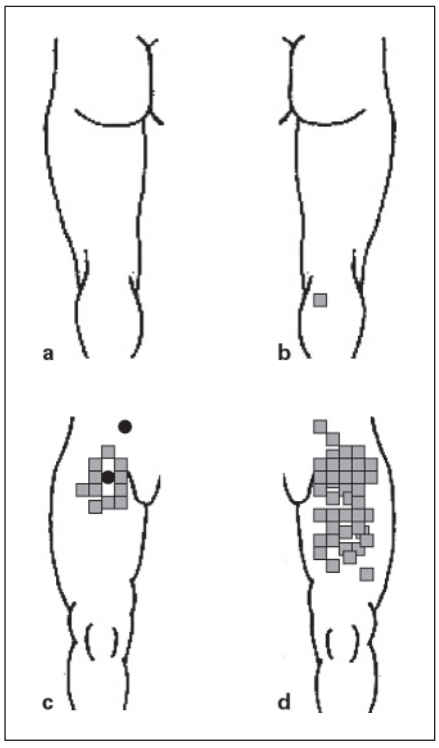

Fig. 3. Lymph node areas at the groin and thigh. **a** Dorsal left side. **b** Dorsal right side. **c** Ventral right side. **d** Ventral left side. Grey squares indicate melanoma metastases from a primary of the thigh, calf, feet or toes and black circles from a primary of the lower belly or back or buttocks.

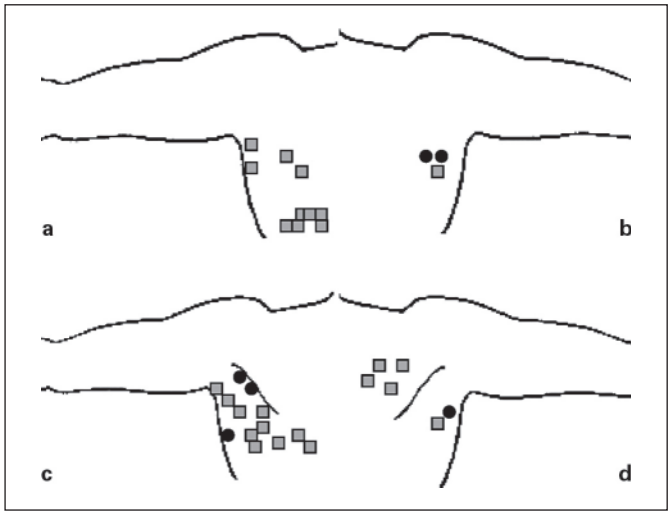

Fig. 2. Lymph node areas at the axilla. **a** Dorsal left side. **b** Dorsal right side. **c** Ventral right side. **d** Ventral left side. Grey squares indicate melanoma metastases from a primary of the lower belly or back and black circles from a primary of the upper thorax or back, shoulder, arm, hand or fingers.

vicular region were examined; with a melanoma at the trunk, both axillas, infraclavicular regions and both groins and in case the melanoma was located at the thigh, calf, foot or toes, the ipsilateral groin was examined.

In every patient this procedure was performed and documented in horizontal and vertical planes. Ultrasound assessment of visible lymph nodes was first based on morphologic criteria (size, shape, echogenicity of the center and cortex of the lymph node). The index according to Solbiati (ratio of maximal and minimal diameters in transversal and longitudinal sonographic sections) was calculated for every lymph node [14]. Lymph nodes were considered as malignant at ultrasound if the following criteria were found [15]: Solbiati index less than two and/or predominance of low echogenicity of the whole lymph node structure and/or lymph node center with low echogenicity and/or asymmetric regions with low echogenicity in the lymph node margin.

In the case of malignant lymph node or subcutaneous metastasis in ultrasound, the exact anatomic position was indicated in a figure (fig. 1–3) for every patient.

The evaluation of data was performed using the statistical package SPSS 11.5.0 (SPSS, Chicago, Ill., USA) for Windows. Statistical testing was performed using Wilcoxon signed ranks test or Mann-Whitney U test. In each statistical analysis, $p < 0.05$ was regarded as statistically significant.

Results

The results of the location of primary and lymph node metastases are given in table 2. In 5 of 53 patients (9.4%) the lymph node metastases were not found in the corresponding lymph node area of the primary melanoma. Patient 11 had her primary at her right foot, followed by metastases in her right groins; during this study a metastasis at her right axilla was detected. Patient 17 had his melanoma at his upper right back with metastases at his right axilla, followed with hepatic and pulmonal metastases; a metastasis was now found in his left axilla. Patient 19 had his melanoma at his right foot, followed by pulmonal metastases; now a metastasis was detected at his right groin. Patient 36 had his melanoma at his ventral right thigh, followed by inguinal metastases; now a metastasis was found in his left axilla. In patient 44, a metastasis was detected about 10 cm above the left groin whereas she had a melanoma at her dorsal left calf.

The distribution of the metastases to the head and neck is presented in figure 1, to the axillas and infraclavicular regions in figure 2, and to the groins and thighs in figure 3. In 6 patients (11.3%) metastases were found at their neck, in 17 patients (32.1%) at the axilla, in 23 patients (43.4%) at the groin, and in 7 patients (13.2%) local subcutaneous metastases (thorax, back, thigh and calf) were diagnosed. In the patients (n = 32), in which a sentinel lymph node biopsy (SLNB) was not performed, the time range between surgery of the primary and lymph node metastases was 27.3–50.5 months (mean, 38.9 months; median, 31 months); in patients with performed SLNB (n = 21) the time range was 15.9–30.2 months (mean, 23.1 months; median, 18 months) ($p < 0.005$). A significant difference in the time range was also found in the group of metastatic (n = 11; 8.0–30.0 months; mean, 19.0 months; median, 17 months) and nonmetastatic (n = 10; 17.1–37.9 months; mean, 27.5 months; median, 21 months) SLNB ($p < 0.005$).

Finally, a significant difference was found between the groups with (n = 32; 24.1–40.6 months; mean, 32.3 months; median, 31 months) and without (n = 21; 17.3–48.8 months; mean, 33.1 months; median, 18 months) consecutive complete lymph node dissection (CNLD) ($p < 0.005$).

The time differences between the surgery of the primary and lymph node metastases are given in table 3. If the melanomas were classified into only two groups (thinner or thicker than 1.50 mm), a significant difference was calculated ($p < 0.05$).

Table 2. Location of primary and lymph node metastases

Patient No.	Location of primary	Location of metastasis
1	upper left back	left axilla
2	forehead left	left cheek
3	ventral left thigh	left groin
4	upper right shoulder	right axilla
5	left foot	left groin
6	right buttock	right groin
7	upper left shoulder	left axilla
8	left shoulder	left axilla
9	left big toe	left groin
10	right proximal arm	right axilla
11	right foot	right axilla
12	ventral left thigh	left groin
13	dorsal left calf	left groin
14	dorsal left head	left neck
15	ventral left calf	left groin
16	ventral left thigh	left groin
17	upper right back	left axilla
18	dorsal right head	right neck
19	left foot	right groin
20	upper left back	left axilla
21	ventral left thigh	left groin
22	ventral right thigh	right groin
23	ventral left calf	left groin
24	dorsal central head	left groin
25	big left toe	left groin
26	dorsal left calf	left calf
27	left foot	left groin
28	dorsal right calf	right groin
29	upper left thorax	left thorax
30	ventral right calf	right groin
31	big right toe	right groin
32	ventral left calf	left groin
33	ventral left thigh	left thigh
34	middle left back	left back
35	ventral left thigh	left thigh
36	ventral right thigh	left axilla
37	ventral right thorax	right axilla
38	middle right belly	right axilla
39	middle right belly	right axilla
40	ventral left thigh	left thigh
41	ventral left thigh	left groin
42	right cheek	right cheek
43	dorsal left calf	left groin
44	dorsal left calf	left groin
45	dorsal left calf	left groin
46	ventral left thigh	left groin
47	upper thorax right	right axilla
48	right neck	right neck
49	right shoulder	right axilla
50	dorsal right head	right neck
51	upper right thorax	right axilla
52	upper right back	right back
53	upper middle thorax	right axilla

Table 3. Time differences depending on thickness of tumor

Tumor thickness	Number of patients (%)	Minimum months	Maximum months	Mean months	Median months
≤0.75 mm	5 (9.4)	23.1	103.7	63.4	49.0
≤0.76–1.50 mm	11 (20.8)	19.9	58.2	39.1	27.0
≤1.51–4.00 mm	25 (47.1)	18.9	41.0	30.0	18.0
>4.00 mm	11 (20.8)	8.2	31.3	19.7	14.0
Unknown	1 (1.9)	16.0	16.0	–	–

Discussion

As far as we know, this was the first prospective study using ultrasound for mapping the distribution of melanoma metastases in regional lymph node areas with or without former surgery. We found a wide distribution in the different areas of proven metastases in histopathology (fig. 1–3). In 8 of 53 patients (15.1%) metastases were found in and around the scar in the subcutaneous tissue. In the head and neck region metastases were found at the glandula parotis, on the cheek and more or less at the area of the great vessels. In the axillary region metastases were found in the axilla and in its wide surrounding. At the back this included the latissimus dorsi muscle and, ventrally, metastases were found in the pectoral muscles and the region of the upper lateral belly. In the groin, a wide distribution of metastases was worked out from the region above the ligamentum inguinale to the distal area of the thigh. Also, metastases were detected medially and laterally to the main blood vessels. Several studies worked out that more than 25% of the lymph node metastases cannot be detected by palpation [4, 8, 9]. One special explanation for this difference between clinical and ultrasound examination could be that the clinical examination is less extensive than the wide area in which metastases could be found.

In 5 of 53 patients (9.4%), metastases were detected in other lymph node regions by using ultrasound. Four of the 5 patients had previous metastases in the regional lymph nodes or even in the organs. So these patients were in stage IV of their disease which could explain the spread of metastases in further regional lymph node areas.

The present data could not be compared with the data about the distribution of sentinel lymph node biopsy (SLNB) [10–13]. Normally, lymphoscintigraphy is performed before surgery of the primary or at least after a small excision biopsy that leads to no or little change in lymphatic drainage. But surgery with recommended safety margins, a SLNB or even a CNLD after positive SLNB have a significant impact on lymphatic drainage. Physicians should be aware of this when they are running clinical and ultrasound follow-up examinations.

Significant differences in the time range to progression were found in the groups with or without sentinel lymph node biopsy and with positive or negative sentinel lymph nodes. In the case of metastatic lymph node(s), an earlier recurrence in the lymph node area was worked out in patients with performed SLNB and patients with positive SLNB. This could also be confirmed that thicker melanomas had earlier lymph node metastases than thinner which has also been reported in the literature [1–5].

However, our data showed that patients with CLND developed lymph node metastases significantly later than patients without CLND. One explanation could be that our collective was too small for analyzing this question. Another explanation could be that due to the CLND micrometastases are not distinguishable by ultrasound. This hypothesis could be supported that the most of high risk melanoma patients had a positive SLNB and underwent a CLND. Probably, this collective might have a benefit of the CLND [16].

In the present study, patients with CLND had longer disease free time concerning lymph or subcutaneous metastatic nodes than patients with positive or negative SLNB (31, 17 and 21 months, respectively). Also here we have to consider that our collective, especially regarding the correlation of affected nodes in CLND or SLNB and tumor thickness, was too small for analyzing this question. In addition, one possible explanation could be that by CLND micrometastases were removed which remained still present in patients with positive or negative SLNB. Studies with a larger data base could be able to answer this question of distribution in the subgroups.

The early detection of subcutaneous and regional lymph node metastases in patients with melanoma is critical for their prognosis [1–4]. Therefore, intensive clinical and ultrasound examination could improve the benefit for patients in the follow-up, especially for high-risk mel-

anoma. The following recommendations are proposed for the ultrasound examination:

Examination from the Scar of Primary to the Regional Lymph Node Area(s). The ultrasound examination should start at the site of the scar of the primary melanoma, followed by the lymphatic drainage area(s). After examination of an area of 10 cm around the scar, the transducer should be moved along the lymphatic vessels to the regional lymphatic region in transversal orientation.

Examination of the Cervical Region(s). The head of the patient should be turned to the opposite site. First, the glandula parotis will be examined in two planes. Then the transducer will be moved to the retroauricular area. The cervical vessels including the surrounding tissue will be examined in a horizontal and a vertical plane from the insertion of the sternocleidomastoidal muscle to the upper thoracic aperture. The evaluation of the submandibular and, finally, the supraclavicular region follows.

Examination of the Axillary and the Infraclavicular Region(s). Patients will be examined in a position with a 120° abduction of the arm. The examination will be performed in a horizontal pattern in cross-sections along the axillary artery, starting from lower axillary region towards the brachial artery and the proximal third of the upper arm, and to the opposite towards the subclavian artery. Finally, the area between the latissimus dorsi (posterior axillary line), the pectoral muscles (anterior axillary line) and the beginning of the upper arm (upper limitation) will be completely evaluated.

Examination of the Groins. The inguinal ligament, inguinal and femoral vessels are the leading anatomic structures for examination of this area. Following the inguinal ligament from the anterior superior iliac spine to the symphysis, the vessels will be crossed. Now the transducer follows the vessels in a horizontal plane 5–10 cm cranial of the inguinal ligament. Caudal of the inguinal ligament, the adductor canal will be completely examined by ultrasound. Lateral and medial of the femoral vessels, the upper third of the thigh will be scanned in two planes.

For patients with high-risk melanoma, clinical and ultrasound examination should be recommended at intervals of 3 months in the first 3–5 years [5]. Weekly self-examination should be demonstrated to the patient which can also lead to an earlier detection of a metastasis. Patients at stage IV should be examined in all regional lymph node areas clinically and with ultrasound. Although the nodal metastases have no significant impact on overall patient survival in stage IV, the ultrasound could be used for monitoring therapies, for providing tumor material for vaccination in clinical studies or for planning surgical intervention to minimize tumor load.

References

1 Balch CM: Cutaneous melanoma: prognosis and treatment results. Semin Surg Oncol 1992; 8:400–404.
2 Schmid-Wendtner M, Baumert J, Schmidt M, Plewig G, Volkenandt M, Hölzel D: Prognostic index for cutaneous melanoma: an analysis after follow-up of 2,715 patients. Melanoma Res 2001;11:1–8.
3 Balch CM, Soong SJ, Murad TM, Smith JW, Maddox WA, Durant JR: A multifactorial analysis of melanoma. IV. Prognostic factors in 200 melanoma patients with distant metastases (stage III). J Clin Oncol 1983;1:126–134.
4 Voit C, Mayer T, Kron M, Schoengen A, Sterry W, Weber L, Proebstle TM: Efficacy of ultrasound B-scan compared with physical examination in follow-up of melanoma patients. Cancer 2001;91:2409–2416.
5 Garbe C, Paul A, Kohler-Späth H, et al: Prospective evaluation of a follow-up schedule in 2,008 patients with cutaneous melanoma: recommendations for an improved follow-up strategy. J Clin Oncol 2003;21:520–529.
6 Nazarian LN, Alexander AA, Rawool NM, Kurtz AB, Maguire HC, Mastrangelo MJ: Malignant melanoma: impact of superficial US on management. Radiology 1996;199:273–277.
7 Rossi CR, Seno A, Vecchiato A, et al: The impact of ultrasound scanning in the staging and follow-up of patients with clinical stage I cutaneous melanoma. Eur J Cancer 1997;33:200–203.
8 Blum A, Schlagenhauff B, Stroebel W, Breuninger H, Rassner G, Garbe C: Ultrasound examination of regional lymph nodes significantly improves early detection of locoregional metastases during the follow-up of cutaneous melanoma. Results of a prospective study in 1,288 Patients. Cancer 2000;88:2534–2539.
9 Schmid-Wendtner MH, Paerschke G, Baumert J, Plewig G, Volkenandt M: Value of ultrasonography compared with physical examination for the detection of locoregional metastases in patients with cutaneous melanoma. Melanoma Res 2003;13:183–188.
10 Uren RF, Howman-Giles R, Thompson JF, et al: Lymphoscintigraphy to identify sentinel lymph nodes in patients with melanoma. Melanoma Res 1994;4:395–399.
11 Rees WV, Robinson DS, Holmes EC, Morton DL: Altered lymphatic drainage following lymphadenectomy. Cancer 1980;45:3045–3049.
12 Morton DL: Sentinel lymphadenectomy for patients with clinical stage I melanoma. J Surg Oncol 1997;66:267–269.
13 Porter GA, Ross MI, Berman RS, Lee JE, Mansfield PF, Gershenwald JE: Significance of multiple nodal basin drainage in truncal melanoma patients undergoing sentinel lymph node biopsy. Ann Surg Oncol 2000;7:256–261.
14 Solbiati L, Rizzatto G, Belotti E: High resolution sonography of cervical lymph nodes in head and neck cancer: criteria for differentiation of reactive versus malignant lymph nodes. Proceedings of the 74th Meeting of the Radiologic Society of North America. Chicago, Radiologic Society of North America, 1988, abstr 113ff.
15 Vassallo P, Wernecke K, Roos N, Peters PE: Differentiation of benign from malignant superficial lymphadenopathy: the role of high-resolution US. Radiology 1992;183:215–220.
16 Cascinelli N, Morabito A, Santinami M, MacKie RM, Belli F: Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme. Lancet 1998 14;351:793–796.