Unpredictability of lymphatic drainage patterns in melanoma patients

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Abstract. We analysed the localisations of sentinel nodes (SN) found with the SN procedure to compare these sites with those that would have been predicted by conventional clinical descriptions of cutaneous lymphatic drainage. We assessed the surplus value of performing the SN procedure in melanoma patients who underwent regional nodal surgery. The SN procedure was performed in 348 patients with melanomas who were referred to our institute between 1993 and 1999. The localisations of the melanomas with the corresponding SNs were meticulously recorded on drawings of the human body and grouped according to the conventional descriptions. Predictability of lymph drainage was defined as the percentage of melanomas whose draining pattern was to the ipsilateral nearest basin, without simultaneous drainage to other basins or to an interval node. In all patients the SN procedure visualised at least one SN. We found 410 lymphatic basins in 347 patients. These basins included basins that could not have been predicted by the conventional clinical descriptions, such as multiple basins and contralateral drainage sites. For the head/neck region, SNs could be found in any of the basins described in the literature. The trunk's drainage predictability depended strongly on the melanoma localisation, ranging from 0% in the midline to 92% in one of the upper quadrants. The lower extremities had a high predictability of almost 100%, and predictability of drainage for the upper extremities ranged from 77% to 100%. In total, 34% of the patients had a cutaneous lymphatic drainage that was unpredictable, either totally or partially. We therefore conclude that an SN procedure is indispensable if the drainage site(s) are to be accurately identified.

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Introduction

Understanding of the anatomy and function of the lymphatic system has been developing ever since the seventeenth century [1, 2]. In 1875, Sappey proposed a concept of cutaneous lymphatic drainage, as is clearly illustrated in his drawings. This concept is still partially useful [3]. However, the structural and functional complexity of the lymphatic system has frustrated attempts to fully comprehend its role in the intricate process of early tumour dissemination. Awareness of the significance of this process has increased since Virchow first formulated the theory that lymph nodes act as defensive barriers in the spread of cancer [4]. In the past century, many attempts have been made to visualise the lymphatic system in patients with a malignancy. Injection of different substances and agents, from mercury to blue dye, resulted in mapping of the lymph vessels and nodes. These lymphangiograms led to the work of Cabanas in 1976, who reported the existence of a "specific lymph node center, the so-called sentinel lymph node" in the lymphatic drainage of the penis [5]. With his work, the sentinel node (SN) concept was born. This SN, in penile cancer, was confirmed to be the first site of lymphatic metastases and frequently the only involved lymph node. A particularly important consequence was that a biopsy of the SN, if negative, could preclude total lymphadenectomy. However, it was not possible to confirm this concept until new techniques were developed to study the physiology of lymphatic drainage. In 1978, Morton elaborated the SN concept by introducing pre-operative cutaneous lymphoscintigraphy (LS) as a method of identifying the

nodal basins at risk of metastases in melanomas. Such a method appeared to be especially necessary in regions from which the direction of flow is unpredictable, like the trunk and head/neck region [6].

Cutaneous LS has provided new insights into cutaneous lymphatic pathways and highlighted the fact that they are clinically unpredictable. When drainage patterns identified by LS were compared with those predicted by clinical experience or historical guidelines according to Sappey, they were found to be discordant in more than 50% of trunk and head and neck primary melanomas [7]. Use of elective lymph node dissection without pre-operative LS may result in inadequate surgery in that there may be failure to remove all basins at risk for metastatic disease or, alternatively, removal of basins that are not draining the area at risk at all.

The SN procedure was introduced in 1992 [8]. The success rate in identifying the SN by this technique was initially approximately 82%. This success rate was improved by the introduction of routine dynamic LS pre-operatively and the intra-operative use of a hand-held gamma probe. Thereafter, reliable information on the lymphatic drainage pattern was obtained, and success rates now reach up to 100% [9]. Probably, almost all nodal basins at risk for metastatic disease can now be identified.

In this study, we analysed the locations of SNs in 348 melanoma patients who underwent an SN procedure in our hospital between 1993 and 1999, and compared these drainage patterns with those predicted according to conventional clinical descriptions of cutaneous lymphatic drainage. In short, we aimed to assess the surplus value of performing an SN procedure in melanoma patients undergoing regional nodal surgery.

Materials and methods

Patients

An SN procedure was performed in 348 consecutive patients with proven clinical stage I (AJCC stages I and II) cutaneous melanoma referred to our institute between August 1993 and September 1999 [10]. There were 158 men and 190 women, with a median age of 49 years (range 6–84). The Breslow thickness was 0.5–1.0 mm in 112 (32%) patients, 1.01–2.0 mm in 141 (40%), 2.01–4.0 mm in 68 (20%) and >4.0 mm in 21 (6%). In six patients (2%) the Breslow thickness was unknown. The median Breslow thickness was 1.78 mm.

The exact location of each melanoma was indicated on a standard drawing. The sites of primary melanomas were head and neck (n=28), trunk (n=146), upper extremity (n=41) and lower extremity (n=133).

Triple-technique SN procedure

Lymphoscintigraphy. All patients pre-operatively underwent dynamic and static LS to establish lymphatic drainage patterns and define the number of afferent lymph vessels and SNs. Technetium-99m-labelled colloidal albumin with a particle size of 3–80 nm was used as the tracer. Two to four intradermal injections with 10 MBq in 0.15 ml saline per injection were given, just adjacent to the scar of the excisional biopsy or re-excision. Dynamic LS was promptly started, collecting 20 images of 60 s each. Static scintigraphy (300 s per image) was performed 2–18 h after the injection to check whether the initial hot spots had retained the tracer. A hand-held gamma detection probe (C-trak, Care Wise Medical Products, Morgan Hill, Calif., USA, or CTC-4, Radiation Monitoring Devices, Watertown, Mass., USA) with settings of 120 keV (lower threshold) and 160 keV (upper threshold) was used in vivo to verify the site of the SN(s). All sites were marked on the skin with indelible ink.

Intra-operative localisation. Surgery was performed 2–24 h after tracer injection. Just before operation, 0.15–0.5 ml of Patent Blue V was injected intracutaneously next to the initial site of the melanoma. The sterile-packed gamma probe was used to establish the site of the incision. The gamma probe and blue dye helped in localising the SN(s) during meticulous dissection, and these nodes were subsequently excised. The result of the pre-operative (dynamic) LS indicated, on the basis of the number and localisation of focal accumulations, how many SNs should be sought and where they should be sought. During surgery, a node was considered an SN if it was stained blue, had an in situ radioactivity count at least 3 times that of the background count or had an ex vivo radioactivity count at least 10 times greater than that of a neighbouring non-sentinel lymph node. On removal of the SN(s), residual radioactivity of the basin was checked with the gamma probe to ensure that all hot nodes had been removed. Residual radioactive lymph nodes were removed if they contained greater than 10% of the SN. After the SN biopsy, a local excision of the primary scar was performed when indicated.

Pathology. The harvested lymph nodes were step sectioned (five levels in total, 250 µm between levels) and examined histopathologically by routine haematoxylin and eosin and immunohistochemical staining for S-100 protein and the melanoma-associated antigen.

If the SN contained metastatic tumour cells, a completion regional lymphadenectomy was performed, when the patient consented, at a later date.

Definition of drainage predictability. For all patients the localisations of melanomas and corresponding SN(s) were depicted in diagrams and ordered according to relevant regions. The method of categorisation of the body into different regions was derived from Sappey (Figs. 1, 2) [3]. Predictability of lymph drainage was defined as the percentage of melanomas whose draining pattern was to the ipsilateral nearest basin, without simultaneous drainage to other basins or to an interval node. Consequently, drainage to a basin other than the ipsilateral nearest one, or to more than one basin or to an interval node was considered unpredictable. Furthermore, by definition, drainage of melanomas located on midlines was also considered unpredictable because in such cases drainage is often to more than one basin. According to clinical experience as documented in the literature, melanomas in the head/neck region have various drainage patterns, with numerous possibilities and often three or four different basins [11]. We therefore defined all head/neck melanoma drainage patterns as unpredictable.

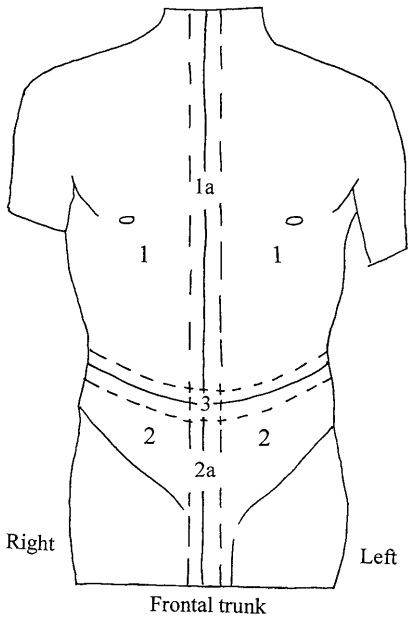

Fig. 1. Categorisation of the frontal trunk into different regions according to Sappey

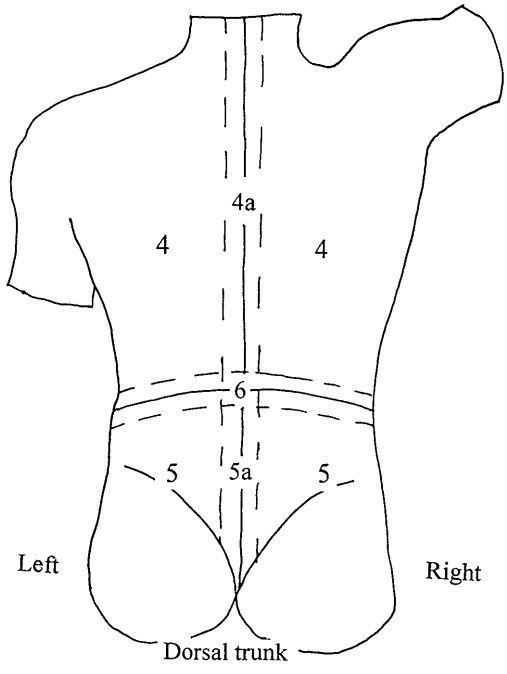

Fig. 2. Categorisation of the dorsal trunk into different regions according to Sappey

Results

In all patients (100%) the pre-operative LS showed at least one focal accumulation on (dynamic) LS. In four patients (1%) the decision was made during surgery not to retrieve the SN, in order to avoid potential morbidity associated with intervention at the location concerned. These locations were the parotid gland in three patients and the deep axilla in the fourth. This yielded an identification rate of 99% (344/348).

Forty-four percent of the patients had only one SN, 38% had two SNs, 13% had three SNs and 5% had four SNs. The mean number of SNs was 1.8.

In 14 of these patients the drainage was first to an interval node. Eighty-two percent of the melanomas drained to one lymph basin, 17% to two basins and 1% to three basins.

Lymph drainage patterns in the 348 patients are now described for all melanoma sites.

Table 1. Lymph drainage patterns of head and neck melanomas

Primary site	Drainage site	No.
Frontal head	Ipsilateral pre-auricular	1
	Ipsilateral parotid	1
	Total	2
Ear	Ipsilateral retro-auricular	2
	Ipsilateral parotid	1
	Ipsilateral anterior triangle	1
	Ipsilateral submandibular/supraclavicular	1
	Total	5
Cheek	Ipsilateral parotid	3
	Ipsilateral jugulodigastric	3
	Ipsilateral retro-auricular	1
	Ipsilateral jugulodigastric/submandibular	1
	Ipsilateral m. sternocleidomasteus	1
	Total	9
Nose tip	Submental	1
	Total	1
Retro-auricular	Ipsilateral anterior triangle	2
	Ipsilateral retro-auricular	1
	Ipsilateral submandibular/parotid	1
	Total	4
Scalp	Ipsilateral posterior triangle	1
	Ipsilateral retro-auricular	1
	Ipsilateral retro-auricular/posterior triangle	1
	Ipsilateral occipital/posterior triangle	1
	Total	4
Neck	Ipsilateral supraclavicular	2
	Ipsilateral posterior triangle	1
	Total	3
Total		28

Head and neck

There were 28 head and neck melanomas; their drainage patterns are shown in Table 1.

Frontal trunk

In total there were 41 melanomas of the frontal trunk; their drainage patterns are shown in Table 2.

Table 2. Lymph drainage patterns of melanomas of the frontal trunk

Primary site	Drainage site	No.	Predictability (%)
Region 1	Ipsilateral axilla	22	
	Other	2	
	Total	24	92
Region 1a	Both axillae	2	
	One axilla	5	
	Total	7	0
Region 2	Ipsilateral groin	1	
	Other	3	
	Total	4	25
Region 2a	Both groins	1	
	Total	1	0
Region 3	Both groins	3	
	One groin	1	
	Other	1	
	Total	5	0
Total		41	56

Table 3. Lymph drainage patterns of melanomas of the dorsal trunk

Primary site	Drainage site	No.	Predictability (%)
Region 4	Ipsilateral axilla	37	
	Both axillae	3	
	Other	10	
	Total	50	74
Region 4a	Both axillae	18	
	One axilla	10	
	Other	2	
	Total	30	0
Region 5	Ipsilateral groin	4	
	Ipsilateral axilla	4	
	Ipsilateral axilla and groin	4	
	Both groins	1	
	Other	1	
	Total	14	29
Region 5a	Both axillae	1	
	One axilla	1	
	One groin	1	
	Both groins	1	
	One axilla/one groin	1	
	Total	5	0
Region 6	Both axillae	3	
	One axilla	2	
	One groin	1	
	Total	6	0
Total		105	39

Above Sappey's line

Left or right side (region 1; n=24). Two patients (8%) had an unpredictable drainage. In one of these cases drainage was to both the ipsilateral axilla and the ipsilateral infraclavicular site. In the other case, drainage was directed towards an interval node, located subcostally, and simultaneously to the ipsilateral axilla.

Midline (region 1a; n=7). Only two patients had a melanoma which drained to both axillae. The other five patients had a drainage pattern to only one of the axillae.

Below Sappey's line

Left or right side (region 2; n=4). The patterns of three patients were unpredictable: in one case drainage was to the ipsilateral axilla, in one case to both the ipsilateral groin and axilla and in the final case to an interval node, located subcostally, and to both the ipsilateral groin and axilla.

Midline (region 2a; n=1). The melanoma of this patient drained to both groins.

On Sappey's line

Midline (region 3; n=5). Five patients had a primary melanoma in the midline of the frontal trunk located exactly on Sappey's line. Three of these melanomas drained to both groins, one drained to only one groin and one drained to both axillae and to an interval node as well.

Dorsal trunk

There were 105 melanomas of the dorsal trunk; their drainage patterns are shown in Table 3.

Above Sappey's line

Left or right side (region 4; n=50). Thirteen patients (26%) had an unpredictable drainage: in three drainage was to both axillae, in two to both the ipsilateral axilla and the ipsilateral supraclavicular zone, in three to the ipsilateral supraclavicular zone, in two to the ipsilateral neck and in one to the contralateral neck. One melanoma drained to three ipsilateral basins: axilla, supraclavicular zone and retro-auricular zone. In one melanoma the only SN was an interval node located subcutaneously on the ipsilateral scapula.

Midline (region 4a; n=30). Eighteen patients had a melanoma which drained to both axillae, while ten had drain-

age to either of the axillae. In one patient drainage was to the axilla and groin on the same side and in the final patient, to one of the supraclavicular zones.

Below Sappey's line

Left or right side (region 5; n=14). Ten patients (71%) had an unpredictable drainage. In four of these patients, drainage was to the ipsilateral axilla and in five to both the ipsilateral axilla and groin. One of the latter five patients had an interval node located just above Sappey's line as well. One melanoma drained to both groins.

Midline (region 5a, n=5). One melanoma drained to one axilla, one to both axillae, one to one groin, one to both groins and one to both the groin and the axilla.

On Sappey's line

Midline (region 6, n=6). Six melanomas were located exactly on Sappey's line in the midline (round L2). Three of these drained to both axillae, two to one axilla and one to one groin.

Upper extremities

There were 41 melanomas of the upper extremities; their drainage patterns are shown in Table 4.

Upper arm (n=24). In four melanomas the pattern was unpredictable. One patient had additional SNs on the m. deltoideus and in the supraclavicular zone and drainage to the axilla. One had an additional SN in the supraclavicular zone and drainage to the axilla. One had two interval nodes on the upper arm and drainage to the axilla. The final patient had drainage to the supraclavicular zone.

Elbow (n=4). None of these four melanomas had an unpredictable drainage pattern.

Lower arm (n=13). Three patients had an unpredictable additional SN in the elbow.

Lower extremities

There were 133 melanomas of the lower extremities; their drainage patterns are shown in Table 5.

Two patients had melanomas with an unpredictable pattern: one had an additional SN in the popliteal fossa and the other had an interval node located just distal to the groin.

Table 4. Lymph drainage patterns of melanomas of the upper extremities

Primary site	Drainage site	No.	Predictability (%)
Upper arm	Ipsilateral axilla	20	
	Other	4	
	Total	24	92
Elbow	Ipsilateral axilla	4	100
Lower arm	Ipsilateral axilla	10	
	Other	3	
	Total	13	77
Total		41	88

Table 5. Lymph drainage patterns of melanomas of the lower extremities

Primary site	Drainage site	No.	Predictability (%)
Upper leg	Ipsilateral groin	50	
	Other	1	
	Total	51	98
Knee	Ipsilateral groin	6	100
Lower leg	Ipsilateral groin	75	
	Other	1	
	Total	76	99
Total		133	98

Discussion

Sappey was one of the first to research the cutaneous lymphatic system. He stated categorically that lymphatic drainage never crosses the midline. This rigid concept was modified for locations on the trunk, and so-called watershed areas were defined. The principal watershed area is a belt-like band extending from just above the umbilicus laterally to the second lumbar vertebra posteriorly; this is called "Sappey's line". In this area, as well as the 5-cm-wide midline area of the trunk, lymph drainage is unpredictable and directed to multiple lymph node basins.

Thompson et al. studied lymphatic drainage patterns in 1,759 melanoma patients between 1986 and 1998, and also demonstrated that reliable clinical prediction of draining node fields is not possible from most sites of the skin, including the watershed areas [12]. In the study by Thompson et al., except in patients with melanomas on an upper or lower limb or the head or neck, cutaneous LS with technetium-99m antimony sulphide colloid as the tracer was performed to establish the draining lymph node field. In the patients included in the early 1990s and later, SN biopsy was introduced, providing even more precise information on the location and number of the SNs.

Table 6. Total number of unpredictable drainage patterns

	No.	%
Head/neck	28	100
Frontal trunk	18	44
Dorsal trunk	64	61
Upper extremities	7	17
Lower extremities	2	1.5
Total	119	34

In our study all patients underwent a triple-technique SN procedure in order to establish the lymph drainage patterns. We compared these lymph drainage patterns with the predicted lymph drainage patterns according to the historical anatomical guidelines of Sappey. The aim of this evaluation was to determine in which percentage of cases the lymphatic drainage turned out to be unpredictable. In these cases lymphatic mapping before nodal surgery was indispensable, because otherwise a wrong basin would have been operated on or a basin at risk for metastatic disease would have been left untouched. Moreover, unsuspected nodal basins and unusual locations of the SN are found, which could not be predicted on clinical grounds [13].

In this study the total percentage of patients in whom lymphatic drainage was unpredictable, either partially or totally, was 34% (Table 6). This percentage included melanomas which drained to more than one basin, melanomas which drained to a contralateral basin and melanomas which drained to an interval node as well. This means that if we had not done the SN procedure in these patients, we probably would have performed an inadequate operation. The results of this study imply that in former studies which compared elective lymph node dissection with a wait and watch approach, surgical procedures could have been performed on the wrong lymph basin in a relatively high percentage of patients; this would have resulted in unrepresentative data and inappropriate conclusions.

According to the literature [11], almost all melanomas located on the head/neck have an unpredictable drainage pattern. In general, the expected drainage of melanomas on the anterior scalp and face is to the lymph nodes of the parotid gland and upper cervical region, whereas melanomas of the posterior scalp tend to spread to the occipital and posterior cervical nodes. Melanomas of the ear and the coronal plane of the scalp may spread to the parotid gland and both the jugular and posterior cervical nodes. However, involved nodes may be found in any of the neck regions. The results of our study are in accordance with these conclusions, in that a significant number of melanomas drained to multiple sites as well as combinations of draining sites. Therefore, accurate prediction of the lymphatic drainage from these locations is very difficult and still unpredictable.

Unpredictable drainage of melanomas located on the trunk occurred in 55% of cases. Especially drainage of melanomas located on the back of the trunk was unpredictable: in total, drainage was unpredictable in 61% of such cases (64/105), and below Sappey's line the figure even reached 79% (15/19).

The melanomas located on the frontal trunk had an unpredictable pattern in 44% of cases (18/41), and below Sappey's line the figure reached 80% (4/5). Sixty-one percent (33/54) of those located in the midline of the trunk (frontal and dorsal) below and above Sappey's line drained to more than one basin. Of those melanomas located on Sappey's line in the midline, which have the potential to drain to four basins, 64% (7/11) drained to more than one basin.

As expected, the percentage of melanomas with a predictable drainage pattern is higher in the extremities. Melanomas on the arms drained only to the axilla in 83% of cases, and 98% of those on the legs drained to the groin. When an unpredictable lymphatic pattern was observed in melanomas of the extremities, it was usually due to drainage to interval nodes. Interval nodes in the arms were found in the elbow, on the upper arm musculature and in the supraclavicular zone, while those on the legs were in the popliteal fossa and on the upper leg musculature. In only 4% (14/348) of the total patient group was drainage first to an interval node, and in 64% of these cases the melanoma was located on the extremities.

We conclude that the triple-technique SN procedure is indispensable in melanoma patients if the regional lymph basin and SN(s) are to be accurately located. In this study, the drainage pattern of the melanoma was unpredictable in 34% of all patients. The unpredictability applies not only to melanomas located within the so-called watershed areas, but to melanomas at all locations. Thus drainage of melanomas on areas of the trunk that would be expected to have a predictable drainage (on a side, outside the watershed area) also appeared highly unpredictable, and even melanomas on the extremities had unpredictable drainage in just over 5% of all cases.

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