# Three-dimensional visualisation of lymphatic drainage patterns in patients with cutaneous melanoma

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See Reflection and Reaction page 755

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## Summary

**Background** **Lymphoscintigraphy accurately maps lymphatic drainage from sites of cutaneous melanoma to the draining sentinel lymph nodes. The Sydney Melanoma Unit has accumulated lymphoscintigraphy data from over 5000 patients with cutaneous melanoma over more than 15 years, collectively revealing patterns of skin lymphatic drainage. We aimed to map these data onto a three-dimensional computer model to provide improved visualisation and analysis of lymphatic drainage from sites of cutaneous melanoma.**

**Methods** **Lymphoscintigraphy data from 5239 patients with cutaneous melanoma were collected between July 27, 1987 and Dec 16, 2005. 4302 of these patients had primary melanoma sites below the neck, and were included in this analysis. From these patients, two-dimensional lymphoscintigraphy data were mapped onto an anatomically based three-dimensional computer model of the skin and lymph nodes. Spatial analysis was done to visualise the relation between primary melanoma sites and the locations of sentinel lymph nodes.**

**Findings** **We created three-dimensional, colour-coded heat maps that showed the drainage patterns from melanoma sites below the neck to individual lymph-node fields and to many lymph-node fields. These maps highlight the inter-patient variability in skin lymphatic drainage, and show the skin regions in which highly variable drainage can occur. To enable interactive and dynamic analysis of these data, we also developed software to predict lymphatic drainage patterns from melanoma skin sites to sentinel lymph-node fields.**

**Interpretation** **The heat maps confirmed that the commonly used Sappey's lines are not effective in predicting lymphatic drainage. The heat maps and the interactive software could be a new resource for clinicians to use in preoperative discussions with patients with melanoma and other skin cancers that can metastasise to the lymph nodes, and could be used in the identification of sentinel lymph-node fields during follow-up of such patients.**

## Introduction

Cutaneous melanoma is a potentially fatal disease which has increased in incidence over recent decades in most people of European background.[1] Detection of metastatic melanoma in the regional lymph nodes has major implications for treatment and prognosis. Sentinel lymph-node biopsy (SLNB)[2] is used to detect whether melanoma cells have metastasised to the sentinel lymph nodes (SLNs), which are defined as any lymph node receiving direct lymphatic drainage from a primary tumour site. SLNs are located by preoperative lymphoscintigraphy, which involves imaging the lymphatic drainage from a primary melanoma site to the SLNs through a radioactive tracer injected into the skin.[2]

SLNB has substantially improved the accuracy of lymph-node staging in patients with melanoma and has been shown in the large Multicentre Selective Lymphadenectomy Trial (MSLT-I) to improve disease-free survival.[3] In this trial of 1269 patients with primary melanoma of intermediate thickness, the mean 5-year disease-free survival was 78·3% (SE 1·6) in the SLNB group and 73·1% (SE 2·1) in the observation group (hazard ratio [HR] for recurrence, 0·74; 95% CI 0·59–0·93; p=0·009). This trial also showed an improvement in overall survival for patients with metastatic nodal disease who had an immediate complete surgical clearance of the entire lymph-node field[3] (ie, all lymph nodes located within the region where the SLN is located, for example, the axilla or groin). In patients with nodal metastases, the 5-year survival was higher in those who had immediate lymphadenectomy compared with those in whom lymphadenectomy was delayed (72·3% [SE 4·6] *vs* 52·4% [SE 5·9]; HR for death 0·51; 95% CI 0·32–0·81; p=0·004).

However, not all centres have access to lymphoscintigraphy, and clinical follow-up in patients with melanoma then relies on predictions of lymphatic drainage based on historical assumptions that are probably incorrect in 30% of individuals.[4]

Lymphoscintigraphy studies have confirmed that lymphatic drainage of the skin is highly variable between patients, with very few areas of the skin from which lymphatic drainage is clinically predictable.[5] For over 100 years, patterns of lymphatic drainage from the skin were predicted from the work of Sappey,[6] whose 1874 atlas stated that lymphatic drainage never crossed the midline of the body nor a theoretical horizontal line drawn around the waist through the umbilicus. These concepts were challenged in the 1970s, 1980s, and 1990s, largely due to work in patients with melanoma by the use of lymphoscintigraphy, which showed that lymphatic drainage frequently occurs across Sappey's lines, and that, although skin sites usually drain to ipsilateral lymph-node fields, contralateral drainage is not uncommon.[7–12]

The Sydney Melanoma Unit (SMU), Australia, has done preoperative lymphoscintigraphy on more than 5000 patients with cutaneous melanoma.[4] The centre's database includes the precise location of the primary melanoma and the location of every SLN in each patient, located through lymphoscintigraphy. These data have allowed drainage patterns to be tabulated and two-dimensional displays to be generated relating melanoma sites to draining lymph-node fields.[5,13] We aimed to improve the visualisation of these data by developing a three-dimensional model of human skin onto which the data could be mapped. The current study presents the first results of this mapped data; construction of this three-dimensional model and mapping procedures have been reported previously.[14]

## Methods

### Mapping lymphoscintigraphy data

We constructed a three-dimensional finite element model of human skin with the use of anatomical images from the Visible Human dataset,[15] which was created from a male cadaver. A detailed description of the geometry development and associated metrics was outlined in our previous study.[14] In brief, the shape of the human skin surface was modelled by breaking it up into small regions called "skin elements"; a total of 886 of these curved units, each quadrilateral or triangular in shape, were required to mathematically describe the entire skin surface in three-dimensional space. At present, the model excludes the head and neck because the Visible Human dataset has an abnormally short neck region that does not allow adequate mapping of primary melanoma sites onto it. A head and neck model based on another three-dimensional dataset is being developed because lymphatic drainage of skin on the head and neck is very complex[16] and a highly detailed model is required. The Visible Human dataset also had to be manipulated to allow visualisation of all surfaces of the upper limbs.[14] This manipulation resulted in the palms of the hands being oriented posteriorly in our three-dimensional model, rather than the standard anatomical orientation (in which the palms are facing forwards). 43 distinct lymph-node fields have also been placed within the three-dimensional model.[14] In the work presented here, each node field has been displayed as a single point that represents an approximate anatomical midpoint of the field, with the exception of the interval lymph-node field,[17] which is displayed separately outside the three-dimensional representation of the body. Node fields located in the head and neck region are also located outside the existing three-dimensional skin model; however, their geometric position is based on Visible Human data.

Lymphoscintigraphy data from 5239 patients with cutaneous melanoma, collected between July 27, 1987 and Dec 16, 2005, had already been entered into a database. The location of the primary melanoma site in each patient had been recorded using a two-dimensional grid placed over outlines of an idealised human body viewed from different perspectives.[4,13] After each patient was imaged by use of the appropriate protocol, clinicians from the SMU manually recorded the primary melanoma site on one of these two-dimensional grids by referencing previously recorded clinical drawings of the primary melanoma site, and also visually inspecting the tumour site location. For our studies, these melanoma-site coordinates were mapped onto the skin elements in our three-dimensional model by use of techniques that we have previously reported.[14] Melanoma sites above the neck could not be mapped onto the skin model because the model did not have a head and neck mesh, and consequently, only primary melanoma sites that were located below the neck were used in this current analysis. The density of the melanoma sites recorded in the database was higher than the density of the skin elements in the three-dimensional model, so several melanoma sites have been placed within each three-dimensional skin element (webfigure). For each patient in the database, the location of the SLNs that drained the primary melanoma site located by lymphoscintigraphy were recorded and assigned to one or more of 43 discrete lymph-node fields. As described previously,[5,13] a substantial number of patients had SLNs located in more than one lymph-node field. Patients who showed highly atypical drainage patterns were checked for previous surgery, and if they had undergone previous surgery were excluded from this analysis.

See Online for webfigure

### Data fitting and statistical analysis

To create maps of lymphatic drainage patterns, patients were selected from the database based on the drainage pattern of interest—eg, patients showing drainage to an SLN in the right axilla. For each melanoma skin site, the number of patients fulfilling this drainage pattern was divided by the total number of patients at that skin site, to derive a percentage likelihood value for drainage to the specified node field from that skin site. These discrete percentage likelihood values were then fitted as a field over the skin model, to give a smoothed and continuous representation of the discrete field values.[18] This field was then visualised by colour-coded heat maps. Mathematically, the fitting process was established by minimising the difference between each discrete datapoint's field value and its nodally interpolated field value on the skin mesh. During fitting, a smoothing term was introduced to account for noise in the data, and the discrete data values were weighted according to the frequency of points at each skin site.[18] The weights ensured that areas of skin with more data present would have an increased effect on the resulting fitted field, and that outlying values would not skew the results.

The model also enabled the visualisation of SLN positions for each skin site. Melanoma sites on each skin element were grouped together to calculate patterns of lymphatic drainage from that region of skin. The number of melanoma sites located on each skin element and the percentage likelihood that melanomas on each element