



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

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## Summary

*Lancet Oncol* 2007; 8: 806–12

Published Online

July 20, 2007

DOI:10.1016/S1470-

2045(07)70176-6

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**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.<sup>1</sup> Detection of metastatic melanoma in the regional lymph nodes has major implications for treatment and prognosis. Sentinel lymph-node biopsy (SLNB)<sup>2</sup> 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.<sup>2</sup>

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.<sup>3</sup> 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;  $p=0\cdot009$ ). 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<sup>3</sup> (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;  $p=0\cdot004$ ).

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.<sup>4</sup>

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.<sup>5</sup> For over 100 years, patterns of lymphatic drainage from the skin were predicted from the work of Sappey,<sup>6</sup> 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.<sup>7–12</sup>

The Sydney Melanoma Unit (SMU), Australia, has done preoperative lymphoscintigraphy on more than 5000 patients with cutaneous melanoma.<sup>4</sup> 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.<sup>5,13</sup> 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.<sup>14</sup>

## 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,<sup>15</sup> which was created from a male cadaver. A detailed description of the geometry development and associated metrics was outlined in our previous study.<sup>14</sup> 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<sup>16</sup> 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.<sup>14</sup> 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.<sup>14</sup> 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,<sup>17</sup> 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

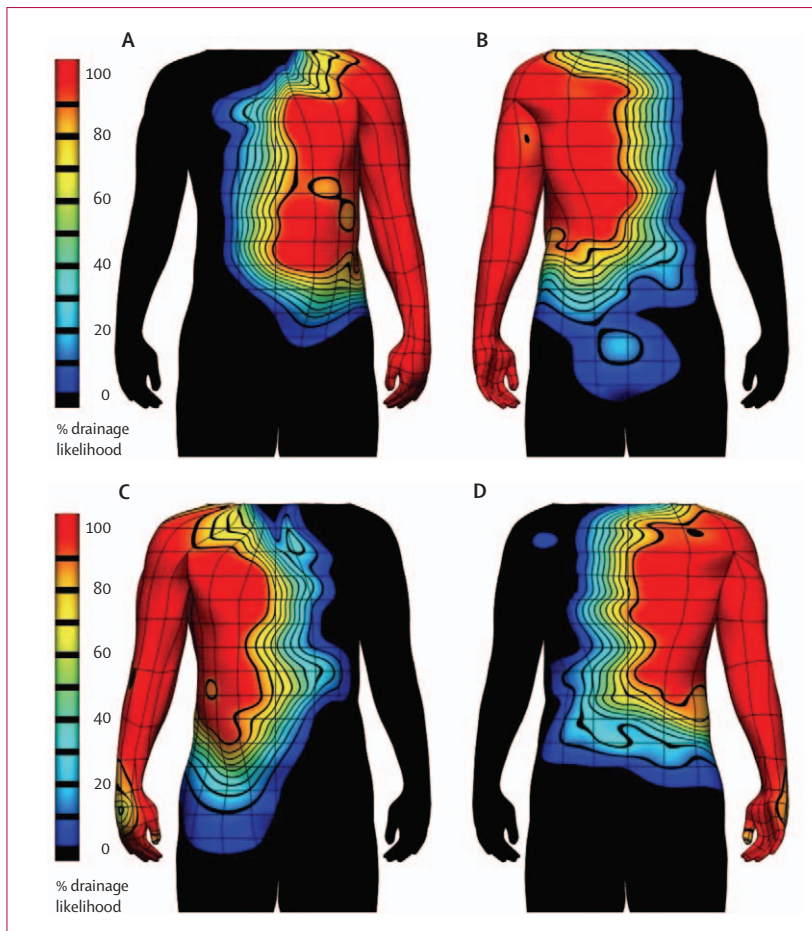
different perspectives.<sup>4,13</sup> After each patient was imaged by use of the appropriate protocol, clinicians from the SMU manually recorded the primary melanoma site on one of these two-dimensional grids by referencing previously recorded clinical drawings of the primary melanoma site, and also 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.<sup>14</sup> 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,<sup>5,13</sup> 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.<sup>18</sup> 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.<sup>18</sup> 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



**Figure 1:** Heat maps showing percentage likelihood that a primary melanoma site will show lymphatic drainage to axillary lymph-node fields

Drainage to the left axillary lymph-node field (A, B); and the right axillary lymph-node field (C, D). Regions of skin with no lymphatic drainage to this lymph-node field are coloured black. A and C are anterior views and B and D are posterior views.

would drain to specific lymph-node fields was calculated. The percentage likelihood values often sum to more than 100% because patients can have lymphatic drainage to more than one SLN.

#### Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, writing of this report, or the decision to publish the report. HMR had full access to all the data (including raw data) and had final responsibility for the decision to publish.

## Results

### Spatial heat maps visualising lymphatic drainage

Heat maps were analysed from 4302 evaluable patients. Heat maps were generated on the three-dimensional skin model to visualise the percentage likelihood that any skin region will drain to a particular lymph-node field. Although only the heat maps for drainage to the axillae and groins are discussed below, maps of drainage to

epitrochlear, popliteal, and triangular intermuscular space node fields have also been generated, and are available to view can be viewed online at <http://www.bioeng.auckland.ac.nz/melanoma/>.

Figure 1 shows heat maps generated for the left and right axillary lymph-node fields, and shows the percentage likelihood that skin sites will have lymphatic drainage to SLNs within these fields. The heat maps shown here visualise anterior and posterior views only; however, selected lateral views can be viewed online. These heat maps are based on 1639 patients with SLNs in the left axilla and 1597 patients with SLNs in the right axilla; these represent the largest number of patients with lymphatic drainage to any one lymph-node field within this dataset, and highlights that the most common site for melanomas is the skin of the back, an area that usually drains to one or both axillae. Ten patients (five with drainage to the left axilla and five with drainage to the right axilla) could not be plotted on the current model because their cancers were located on the neck.

These heat maps confirm that skin sites on the arm or torso above the umbilicus commonly drain to the ipsilateral axillary lymph-node field. However, the heat maps also quantitatively show that lymphatic drainage often occurs across Sappey's lines, both across the midline and across the umbilical meridian. The heat maps for the two axillae are not exactly the same as each other, but they do have sufficient commonality to show the skin regions in which drainage to the ipsilateral axilla is almost certain, and the range of sites where drainage to the ipsilateral or contralateral axilla should be considered possible or probable. A small number of anomalous patients account for the most dramatic asymmetries, as indicated by contour lines. For example, two patients with primary melanomas on the left anterior torso and one patient with a primary melanoma on the right anterior torso showed direct lymphatic drainage solely to interval nodes, decreasing the percentage of drainage to the ipsilateral axillary lymph-node field below 100% in those regions (figure 1). Two patients with primary melanomas near the right posterior wrist (figure 1) show drainage to a right epitrochlear and an interval SLN, respectively, and a patient with a primary melanoma on the right thumb showed unusual drainage to the right infraclavicular and right cervical level IV lymph-node fields, bypassing the right axilla.

An important note is that previous nodal or other major surgery can alter a patient's skin lymphatic drainage. Two patients who had previously undergone right axillary dissection before lymphatic mapping were excluded from analysis: one of these patients showed drainage from the right anterior torso to a right internal mammary lymph node, and the other patient showed contralateral drainage from the right arm to an SLN in the left axilla, and drainage to SLNs in the right supraclavicular fossa and upper mediastinal lymph-node fields.

We did not check the records of all 4302 patients for previous surgery, so some patients who had previous

surgery have not been removed from the analysis. However, we estimate that the number of such patients would be less than 1% of the patients in this study; this estimate is based on the knowledge of nuclear medicine physicians at the SMU regarding the patients imaged by lymphoscintigraphy in their database.

The data in figure 1 show a difference between the drainage patterns from the left and right sides of the body. To establish whether a true difference between the left and right sides of the body exists, more data will be required.

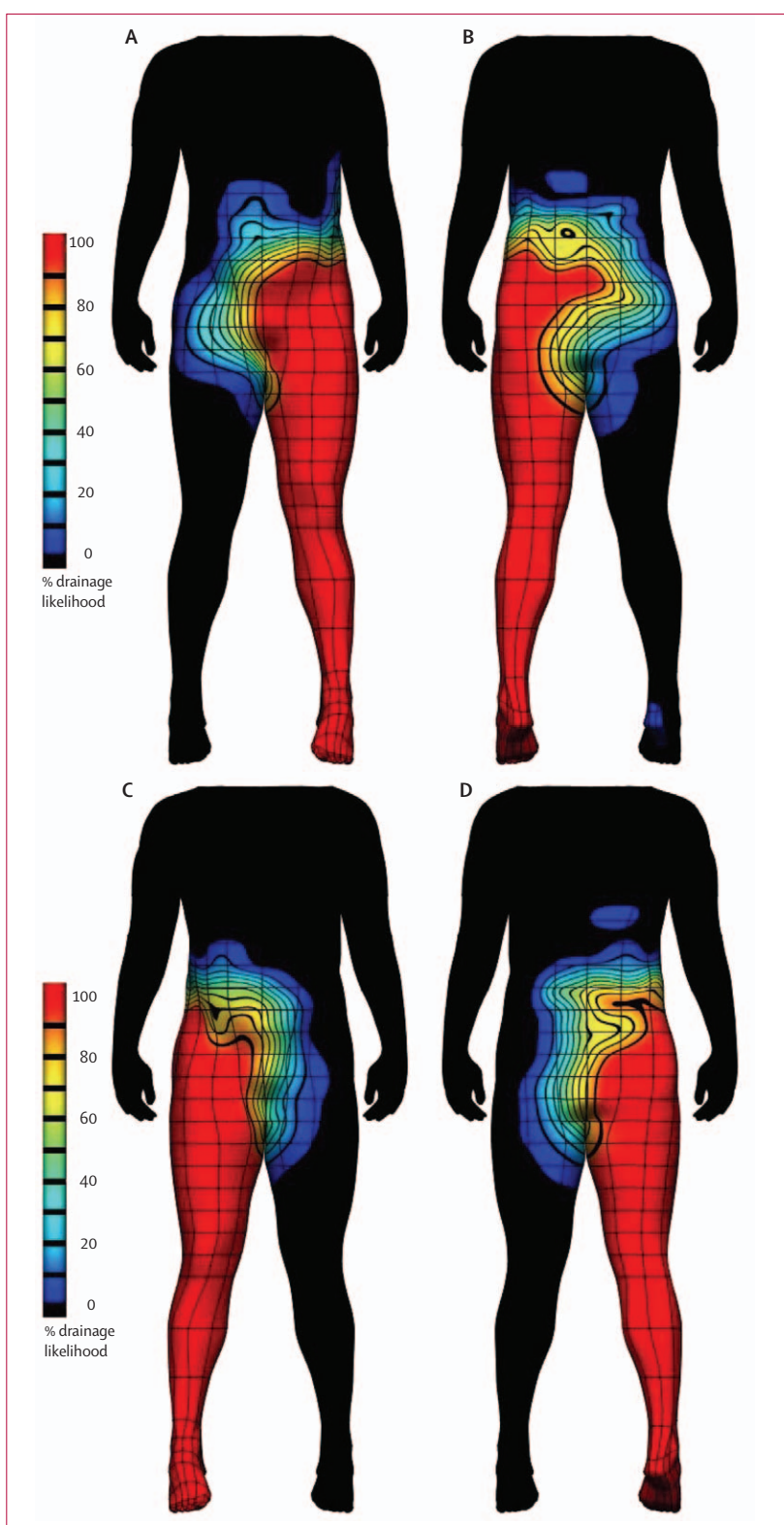
Heat maps that show drainage to the left and right groin lymph-node fields are shown in figure 2. The groin was the second most common SLN field in the database, with 780 patients showing drainage to the left groin and 758 patients showing drainage to the right groin.

As in the axillary heat maps, drainage across Sappey's lines is noted to occur often, but a very distinct region drains almost always to the ipsilateral groin. All primary melanoma sites on the left lower limb have lymphatic drainage to SLNs in the left groin and all right lower limb melanoma sites have drainage to the right groin lymph-node field (figure 2). Melanoma sites might also show drainage to interval lymph nodes or to the popliteal lymph-node field; however, the data show that for these sites, drainage always occurs to the groin as well.

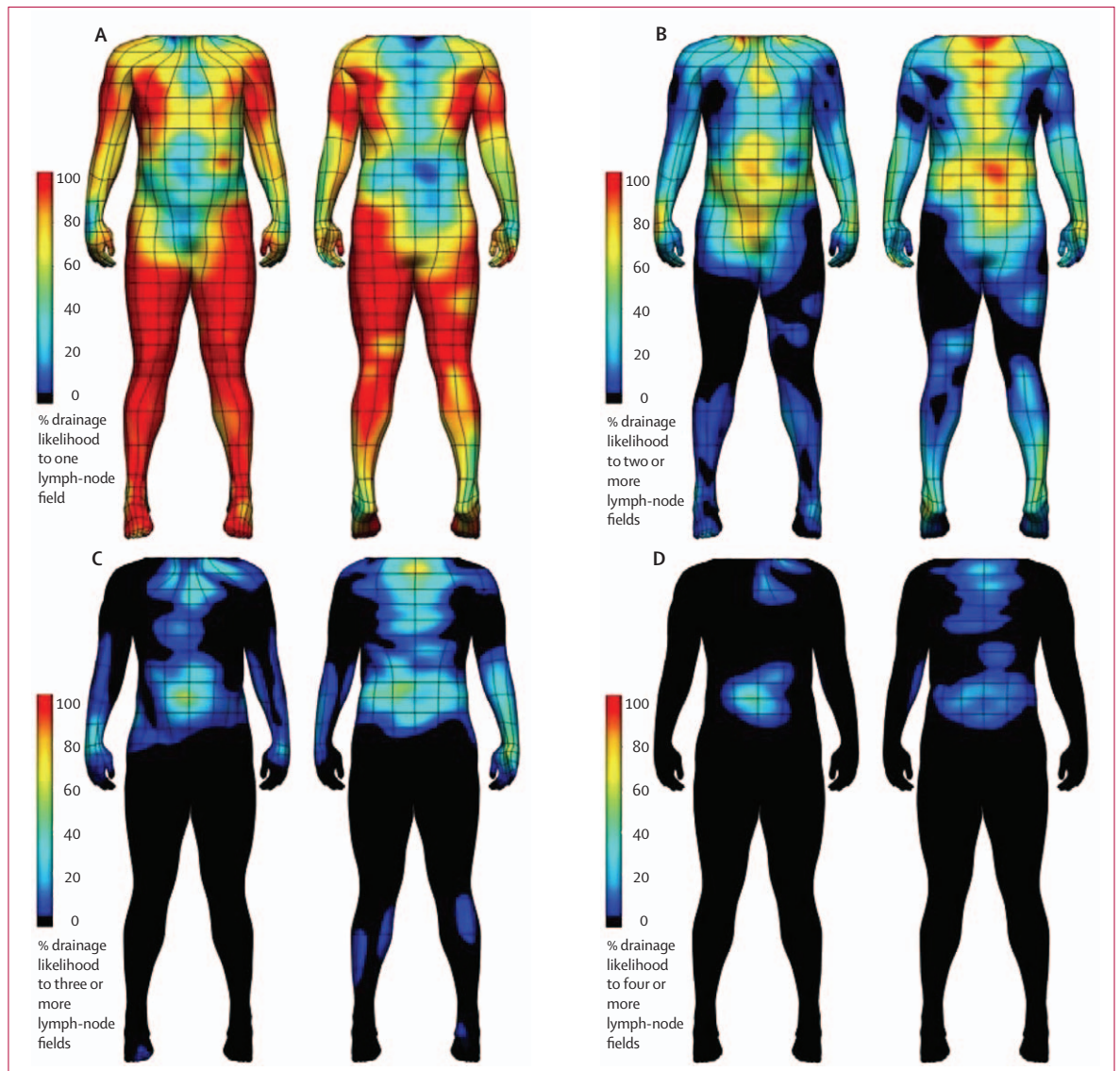
The heat maps show that lymphatic drainage of the lower limbs is highly predictable. Previous studies have shown that drainage to the contralateral groin can occur if the ipsilateral groin has been disturbed by previous nodal surgery.<sup>19</sup> One patient who had previous excision biopsy of lymph nodes in the right groin had a primary melanoma on the distal right leg, which showed contralateral drainage to the left groin and ipsilateral drainage to the right groin. This patient was excluded from this analysis. However, contralateral drainage without previous nodal surgery can occur. One patient with a melanoma on the right heel (figure 2) had contralateral drainage to the left groin and ipsilateral drainage to the right groin and right popliteal lymph-node fields. This was the only patient in the database without previous surgery who did not show exclusive drainage to the ipsilateral groin lymph-node field.

The upper regions of the groin lymph-node field show some asymmetry. We noted that the density of primary melanoma sites in the skin regions near the groin is especially low (webfigure), and the heat maps over these regions are based necessarily on extrapolations from the nearest skin regions in which data from patients with melanoma are available. The asymmetry noted in the heat maps probably indicates the sparsity of data in these regions.

Heat maps have also been generated for skin sites that have drainage to different numbers of lymph-node fields. Figure 3A shows regions of skin that have drainage to only one lymph-node field, and figure 3B illustrates the probability that drainage from a region will be to more than one lymph-node field. These data show the regions of skin where lymph-node drainage is most predictable.



**Figure 2:** Heat maps displaying the percentage likelihood that lymphatic drainage will occur to groin lymph-node fields. Drainage to left groin lymph-node field (A, B); and right groin lymph-node field (C, D). A and C are anterior views and B and D are posterior views.



**Figure 3: Percentage likelihood that a primary melanoma site will show lymphatic drainage to one or more lymph-node fields**  
 Drainage to one lymph-node field (A); two or more lymph-node fields (B); three or more lymph-node fields (C); and four or more lymph-node fields (D). For each image, left is anterior view and right is posterior view.

For example, figure 3A shows large red regions on the legs indicating that melanoma sites in these areas of skin drained to a single lymph-node field, in this instance, the ipsilateral groin. Whereas figure 3B shows that there are some areas of skin in which drainage is never to a single lymph-node field (the red areas on the upper and lower back) and are therefore highly unpredictable. In figure 3C and 3D, the complexity of drainage patterns from certain areas of skin is shown by the probability that drainage from regions of skin will be to at least three (figure 3C) or at least four (figure 3D) lymph-node fields. For example, more than 20% of patients in some of these areas drained to at least four different lymph-node fields (figure 3D). The regions with the highest likelihood of

drainage to many lymph-node fields are close to Sappey's lines (figure 3C and 3D). However, regions outside the torso, most notably on the distal leg and especially the hand and forearm, can also drain to three or more lymph-node fields (figure 3C). Skin sites that commonly drain to many lymph-node fields do not always drain to the same subset of fields (data not shown). Nonetheless, for those areas of skin with complex drainage patterns, the subset of lymph-node fields with noted drainage can still be identified and the relative likelihood of drainage to each field can be calculated.

We also did a preliminary analysis of the effects of sex and age on patterns of skin lymphatic drainage. The results indicated sex-specific differences in the distribution

of primary sites, which affect the frequency of drainage to particular lymph-node fields. However, when the same primary sites were compared, no sex-specific differences in the patterns of drainage were apparent. Preliminary analysis similarly suggests that age does not affect the pattern of lymphatic drainage from each skin site, although age can affect the primary melanoma site locations. For example, the relative frequency of melanoma on the head is increased in older patients compared with younger patients, and is most probably consistent with the increased sun exposure due to less hair coverage. Further analysis of sex, age, and other features of the data are underway in an ongoing study.

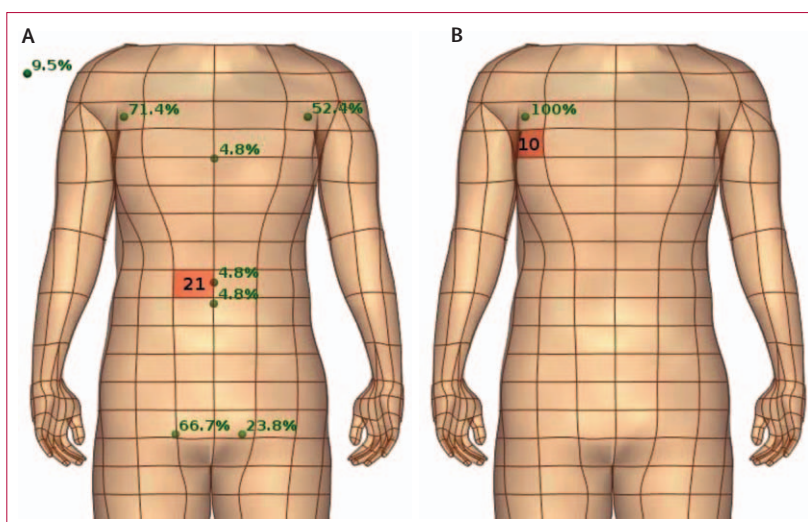
### Interactive computer software to predict lymphatic drainage

To further predict lymphatic drainage, we developed interactive computer software to enable regions of skin on the three-dimensional model to be selected so that SLN field locations would be displayed. Figure 4 shows the lymphatic drainage from two separate skin regions on the back by the use of our software. Figure 4A shows a region of skin near the midline and waist of the posterior torso, where 21 patients in the dataset had cutaneous melanoma. Eight potential SLN field locations are shown when clicking on this skin region, showing that lymphatic drainage from this site is especially difficult to predict. The likelihood of lymphatic drainage occurring to each of those eight lymph-node fields is displayed on the model (the lymph-node field depicted outside the body represents interval lymph nodes). By contrast, figure 4B shows a region of skin near the left axilla with a much simpler drainage pattern, showing 100% likelihood of having an SLN in the left axilla based on ten patients who had a melanoma at this site. This software can also display the SLN field names or the number of patient cases draining to each particular lymph-node field, instead of the percentage likelihood values.

### Discussion

We aimed to integrate the SMU's large lymphoscintigraphy dataset from patients with cutaneous melanoma, and present that data in concise and instructive three-dimensional formats. The three-dimensional models that we generated quantitatively show how patterns of lymphatic drainage from skin differ from traditional anatomical descriptions.

From clinical experience gained at the SMU over the past 15 years, for patients with melanomas that are 1.0 mm or more in Breslow thickness, the most accurate staging of the regional lymph nodes is achieved by use of high-resolution lymphoscintigraphy to locate the sentinel lymph nodes and then undertaking selective biopsy of these lymph nodes with blue dye and an intraoperative gamma-detecting probe. We believe that this is desirable in all patients; however, this approach is not possible in some circumstances, including: in geographical areas in



**Figure 4: Interactive SLN software**

A selected posterior torso element left of the midline near the waist shows complex lymphatic drainage to eight potential SLN fields calculated from 21 patients (A). Drainage is 71.4% and 52.4% likely to drain to the left or right axilla respectively, 9.5% likely to drain to an interval lymph node, 4.8% likely to drain to either the intercostal, retroperitoneal, or paravertebral lymph-node fields, and 66.7% and 23.8% likely to drain to the left or right groin lymph-node fields, respectively. Another posterior torso element selected with more straightforward lymphatic drainage (B). All ten patients showed lymphatic drainage solely to the left axillary lymph-node field.

which nuclear medicine facilities are unavailable; or situations in which lymphatic mapping is thought to be unreliable due to the unavailability of suitable small particle radiocolloids. Under these circumstances, we believe our model will be clinically useful. The interactive computer software especially should help in planning ultrasonography or clinical follow-up by identifying the appropriate lymph-node fields that need to be monitored and should also be helpful in discussions with patients before surgery when gaining informed consent. The software will show possible variability in lymphatic drainage from the precise point on the skin on which the melanoma exists.

A further clinical application of this model would be if lymphoscintigraphy showed drainage from the melanoma site to an SLN, but did not show drainage to a lymph-node field that the model predicted for 90–100% of patients. In this situation, this other predicted lymph-node field should also be monitored during clinical and ultrasonography follow-up because in some patients with clinically normal lymph nodes, metastatic occlusion of a lymphatic collector can prevent a true SLN receiving radiocolloid on lymphoscintigraphy.<sup>20</sup> Another use of this model and the interactive displays is for teaching medical and nursing undergraduates and postgraduate surgical trainees.

We acknowledge that lymphoscintigraphy is not perfect, but the method is highly reproducible<sup>21</sup> and is probably the cause of a metastatic SLN being missed in under 1% of patients overall. Lymphoscintigraphy remains the best way to identify the location of SLNs for subsequent biopsy. Therefore, the technique is a reliable method of establishing

skin lymphatic drainage, and inaccuracies in the heat map and web-based software displays should be small.

Although the SMU has the world's largest lymphoscintigraphy database, it is not without limitations: patients with previous surgery were not removed from the analysis. The number of such patients is estimated to be less than 1% based on the knowledge of RFU of patients in the lymphoscintigraphy database (Uren RF, personal communication), but has not been assessed quantitatively.

An absence of patients with melanoma in some skin regions on the three-dimensional model means that lymphatic drainage patterns cannot be calculated accurately for these regions (the total number of patients for each skin element is displayed graphically in the webfigure, with the number of patients with melanoma at each individual skin site ranging from 1 to 16). To make this explicit, the interactive software shows the number of patients that form the basis of the percentage likelihood values displayed, to minimise overinterpretation where there is a paucity of available data. Similarly, heat maps could not be calculated accurately and visualised for all SLN fields due to insufficient data, or where most melanoma sites were located on the head or neck, which cannot currently be mapped onto the skin model. Ultimately, we hope that these limitations will be at least partly addressed as the dataset grows, and after a head and neck skin model is created. We are developing an interface for our three-dimensional model to allow input of both melanoma and SLN sites, which should facilitate case-by-case accrual of new data into the dataset.

In summary, lymphoscintigraphy on a large number of patients with primary cutaneous melanoma has accumulated a large amount of information on the lymphatic drainage of the skin. Disseminating this information effectively to clinicians will be assisted by developing new methods for its display. We have established methods for displaying lymphoscintigraphy data on a three-dimensional computer model that should be useful to clinicians and medical educators. By making the data available to clinicians and others through online software, the information might help in the management of individual patients with melanoma and other skin cancers that have the propensity to spread to lymph nodes.

#### Contributors

PRD and JFT conceived and initiated the study. RFU and JFT provided access to the SMU lymphoscintigraphy database. RFU collected and recorded the data in the database. NPS conceived the approach and methods for mapping and analysing the data. NPS and PRD obtained funding and gave study supervision. HMR created the anatomical model, mapped the data for three-dimensional visualisation, did the statistical analysis, created the figures, and wrote the initial draft of the report. SAB assisted with data visualisation and the creation of figures. All authors approved the final version of the report.

#### Conflicts of interest

The authors declared no conflicts of interest.

#### Acknowledgments

This study was supported by the Maurice Wilkins Centre for Molecular Biodiscovery, the New Zealand Foundation for Research Science and Technology, and the Wellcome Trust.

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