Abstract: A method of and determining the extent of a structure (1), such as a non-melanoma skin cancer, in or on the skin of a subject, the method comprising the steps of: placing an index marker (3) on the skin adjacent to the structure (1); positioning an optical coherence tomography device (8) relative to the index marker; using the optical coherence tomography device (8) to image the structure (1) so as to create an image of a cross-section through the skin determining the position of an edge of the structure (1) in the image; and translating that position of the edge in the image to a position on the skin relative to the index marker (3). An associated kit of parts for use in determining the extent of the structure (1) is also disclosed.
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DETERMINING THE EXTENT OF A STRUCTURE ON OR IN THE
SKIN OF A SUBJECT

This invention relates to a method of, a kit for and an index marker for use in the determining the extent of a structure such as, non-exclusively a lesion in or on the skin of a subject.

When mapping the extent of a structure such as a potentially cancerous lesion on or in the skin of a subject at present, current clinical practice is for the clinician to make a number of pen marks around the visible lesion as a guide to a planned clinical excision. The marks are placed at a small distance - the margin - from the visible lesion, based on a combination of experience and a decision regarding the relative merits of conserving tissue as against capturing the tumour, depending on the lesion location.

Optical coherence tomography (OCT) is known as an imaging method, for example, from PCT patent application publications numbers WO2008/068497 and WO2006/054116 and US Patent Number 7 242 833. OCT provides a convenient imaging technology for imaging a few millimetres into the skin of a user, but techniques to date have not provided a particularly convenient method of relating features in images into the corresponding features on or in the subject's skin.

In particular, cancerous lesions come in many shapes and forms, and may show a variety of features under OCT, such as:

- mid-grey, bean-shaped 'nests' in the dermis
- absence of dermal-epidermal junction
- irregularity of or greatly thickened dermal-epidermal junction
- thickened stratum corneum
- homogenous, texture-free, mid-grey dermis
• lack of dark elongated features parallel to surface (blood vessels) in the dermis
• swirls or other large features in the dermis.

By contrast, normal skin generally has under OCT:

• a regular, well defined dermal-epidermal junction
• stratum corneum is very thin or invisible
• a lighter, textured dermis with dark elongated features parallel to surface.

Problems arise in the planning of the excision of lesions due to merely relying on the surgeon's experience. Whether relying upon the visible extent of the lesion on the subject's skin or having carried out some form of internal imaging, if the extent of the lesion beneath the skin relative to its visible extent is not known, then there is a risk that the surgeon will either need to excise more tissue than is necessary, which is unnecessarily traumatic to the subject, or will leave potentially cancerous tissue in place, thus potentially placing the subject in danger of recurrence or spreading of any cancer that they might have. An appropriate balancing of these two risks relies heavily on the skill of the surgeon.

According to a first aspect of the invention, there is provided a method of determining the extent of a structure in or on the skin of a subject, the method comprising the steps of:

placing an index marker on the skin adjacent to the structure;

positioning an optical coherence tomography device relative to the index marker;

using the optical coherence tomography device to image the structure so as to create an image of a cross-section through the skin
determining the position of an edge of the structure in the image;
translating that position of the edge in the image to a position on the skin relative to the index marker.

Thus, by providing an index marker that can be used to provide a correspondence between at least one point in the image that and at least one physical point on the skin, the accuracy with which a user can identify the edge of a structure is increased. Thus, the surgeon removing such a structure can more accurately determine the margin that they wish to leave around the structure, thus allowing the surgeon to leave more undamaged tissue with less chance of leaving potentially malignant or otherwise neoplastic material behind. Less reliance is placed upon the skill and judgement of the surgeon. Alternatively, this method could be used to map how the extent of the structure changes over time, or in any other situation where this information would be of use.

In one embodiment, the index marker will provide a physical reference datum for the optical coherence tomography device, such that the position at which the image is taken is known. Alternatively or additionally, the index marker is visible using the optical coherence tomography device and thus will be visible in the image created by the optical coherence tomography device.

The method may comprise the step of capturing a plurality of cross-sectional images of the skin using the optical coherence tomography device, the plurality of cross-sectional images forming together a three dimensional image of a block of the skin. Typically, the plurality of images will be mutually parallel but spaced apart from one another; the step of using the optical coherence tomography device may comprise positioning the optical coherence tomography device such that the plurality of images are parallel to an estimated edge of the structure,
typically a visible edge of the structure. The images may be consistently spaced from one another.

In this case, with the images sorted so successive images are adjacent, the step of determining the position of the edge of the structure may comprise determining the first or last image in which the structure is visible. By determining which image this is, it will be possible to determine the position of the captured image through the block of the skin. This provides a simple binary test (that is, only whether the structure is present in a given image), and will result in an image number which will correspond to a position on the skin relative to the index marker.

The step of translating the position of the edge may comprise determining the relative position of the index marker and the edge in the image or in the plurality of images, and from that determining the relative positions on the skin of the edge and the index marker. The method may also comprise the step of marking the edge of the structure on the skin, or of marking a margin away from the edge of the structure; even with the inclusion of the a margin (to allow the surgeon to ensure that any cancerous or neoplastic cells are removed), the present method may allow this task to be performed with greater accuracy than previously.

The index marker may be formed of any suitable material that will provide a physical reference datum for the optical coherence tomography device; in one embodiment it may be formed of paper. The index marker may have a self-adhesive backing so that it will stick securely to the skin whilst the method is being carried out. The index marker may be of the form of an annular disc, so that it can be placed over the edge of the structure and optionally provide two points of reference a known distance apart in an image at any orientation of the optical coherence tomography device. The annulus may define a hole through which the optical
coherence tomography device can scan, a circumference of the hole or a point thereon providing the physical reference datum. The index marker may be provided with, or the method may comprise providing the index marker with, an orientation marking that indicates a defined orientation relative to the structure; the orientation marking may provide the physical reference datum. The step of placing the index marker on the skin may comprise attaching the index marker to the skin, for example by using (typically non-permanent) adhesive.

Alternatively, the index marker may comprise a marking on or in the user's skin (for example, an ink mark or a tattoo). Whilst standard ink is not visible in OCT imaging, the ink used may substantially absorb radiation at a wavelength used by the optical coherence tomography device to image the structure. Typically, the wavelength will be in the near infra-red range, preferably around 1300 nanometres. In order to achieve such absorption, the ink may comprise solid particles which absorb substantial quantities of radiation at the wavelength; such particles may be metallic or of plastic materials.

By "substantial" absorbance of radiation at the wavelength, we may mean that the index marker as applied to the user's skin will absorb more than 20%, 25% or 50% of radiation passing through the ink at the wavelength. By "absorb" we can include diffuse scattering, as long as the scattered light is not reflected back to the OCT apparatus. The particles may absorb significantly higher; typically, each particle will absorb at least 90% if not 99% of radiation at the wavelength incident thereon, but the dispersal of the particles within the ink will mean that the overall absorbance of the index marker is lower.

The structure may be any structure the extent of which it is desired to map or excise. For example, the structure may be a mole, tumour,
carcinoma or other lesion or lump; in the preferred embodiment the structure is, or is suspected to be, a non-melanoma skin cancer. The method may be repeated at a plurality of points around the structure.

According to a second aspect of the invention, there is provided a kit for use in determining the extent of a structure on or in the skin of a subject, comprising an optical coherence tomography device and an index marker which can be placed on the skin of the subject.

Thus, by providing an index marker, we provide a point of reference that will allow the correspondence between points in the image created by the optical coherence tomography device and on the skin to be determined. This allows more accurate determination of the position of the edge of a structure on or in the subject's skin to be made.

The optical coherence tomography device may be arranged to capture a plurality of cross-sectional images of the skin, the plurality of cross-sectional images forming together a three dimensional image of a block of the skin. Typically, the plurality of images will be mutually parallel but spaced apart from one another. The images may be consistently spaced from one another. This allows for the position of the edge of the structure to be determined by determining the position of the image in which the structure first or last appears through the plurality of images.

In one embodiment, the index marker will provide a physical reference datum for the optical coherence tomography device, such that the position at which the image is taken is known. Alternatively or additionally, the index marker is visible using the optical coherence tomography device and thus will be visible in the image created by the optical coherence tomography device.
The index marker may be formed of any suitable material that will provide a physical reference datum for the optical coherence tomography device; in one embodiment it may be formed of paper. The index marker may have a self-adhesive backing so that it will stick securely to the skin whilst the method is being carried out. The index marker may be of the form of an annular disc, so that it can be placed over the edge of the structure and optionally provide two points of reference a known distance apart in an image at any orientation of the optical coherence tomography device. The annulus may define a hole through which the optical coherence tomography device can scan, a circumference of the hole or a point thereon providing the physical reference datum. The index marker may be provided with an orientation marking that indicates a defined orientation relative to the structure.

The kit may further comprise a set of instructions instructing the user to act in accordance with the method of the first aspect of the invention.

According to a third aspect of the invention, there is provided an index marker for use in determining the position of a structure on or in the skin of a subject using an optical coherence tomography device, the index marker providing a physical reference datum for images created by the optical coherence tomography device.

The index marker may be formed of any suitable material that will provide a physical reference datum for the optical coherence tomography device; in one embodiment it may be formed of paper. The index marker may have a self-adhesive backing so that it will stick securely to the skin whilst the method is being carried out. The index marker may be of the form of an annular disc, so that it can be placed over the edge of the structure and optionally provide two points of reference a known distance apart in an image at any orientation of the optical coherence tomography device.
device. The annulus may define a hole through which the optical coherence tomography device can scan, a circumference of the hole or a point thereon providing the physical reference datum. The index marker may be provided with an orientation marking that indicates a defined orientation relative to the structure.

Alternatively, the index marker may comprise a marking on or in the user's skin (for example, an ink mark or a tattoo).

There now follows, by way of example only, description of an embodiment of the invention, described with reference to the accompanying drawings, in which:

**Figure 1** shows an index marker being attached to a lesion on the skin of a subject in a first stage of a method according to a first embodiment of the invention;

**Figure 2** shows the index marker of Figure 1 being marked with orientation markings in a second stage of the method referred to with respect to Figure 1;

**Figure 3** shows a scan being taken of the subject's skin, in accordance with a third stage of the method referred to with respect to Figure 1;

**Figures 4a to 4f** show sample images taken through the scan referred to in Figure 3;

**Figure 5** shows the margin of a planned excision having been marked on the subject's skin, in accordance with a fourth stage of the method referred to with respect to Figure 1;
Figure 6 shows the subject's skin lesion after the method referred to in Figure 1 has been repeated at several points around the lesion; and

Figure 7 shows an index marker being applied to a subject's skin in accordance with a second embodiment of the invention.

The accompanying drawings depict the marking of a planned excision of a structure being a lesion 1 on the skin of a subject 2 in accordance with a method according to a first embodiment of the invention. Whilst the lesion referred to herein is a benign lesion, it will serve to explain the invention.

In a first stage (Figure 1), an index marker 3 is attached to the skin surrounding the lesion. The index marker 3 is of the form of a planar annulus, formed of paper with a self-adhesive backing. Such objects are commonly used to reinforce the holes in hole-punched paper. The index marker is placed with its hole 4 over the visible edge 5 (or otherwise suspected edge) of the lesion 1, so that it is attached in the orientation shown in Figure 2 of the accompanying drawings.

In a second stage (Figure 2), a pen 6 is used to mark two orientation markings 7 on the index marker 3. These indicate the directions parallel and perpendicular to the suspected edge of the lesion 1 - in this case, they are placed parallel and perpendicular to the visible edge 5 of the lesion, ninety degrees apart around the index marker.

In the third stage (Figure 3), an optical coherence tomography (OCT) device 8 is used to scan the lesion 1 and the surrounding skin. The OCT device 8 can be any conveniently available OCT device; in the present
embodiment, a VivoSight (RTM) scanner is used, available from Michelson Diagnostics Limited of Maidstone, Kent, United Kingdom.

The OCT device 8 is capable of taking a plurality of cross-sectional scans through the lesion and the subject's skin. Each cross-sectional image is 5 mm wide and 2 mm deep, and fifty such images are taken, such that the cross sections are all parallel with one another, spaced 0.1 mm apart, for a 5 mm spread of scans. Thus, the images thus captured visualise a cuboid block containing the part of the lesion and part of the subject's skin. The OCT device is oriented such that each cross-sectional scan is parallel to the "parallel" orientation marking 7 and centred on the "perpendicular" orientation marking 7, with OCT device being arranged so that the scans are taken through the hole 4, with the first scan being aligned with the edge of the hole adjacent to the "perpendicular" orientation marking 7.

In the fourth stage of the present method, the images thus captured are reviewed. Figures 4a to 4f respectively show a representative sample of the images captured, being images numbers 3, 15, 22, 27, 34 and 43 out of the fifty images captured. The user would at this point inspect the images in order, starting from the image closest to the lesion (in this case, closest to the "perpendicular" orientation marking 7, the numbering of the images starting at 1 and increasing away from that image).

The lesion 1 is visible in several of these images. The user will identify which is the first image in which the lesion is not visible; in the present case we can say that this is image 34 (Figure 4e). Thus, we know that the edge of the lesion 1 is \( \frac{34}{5} \) of the distance from the top of the scan; given 50 scans at a 0.1 mm spacing, in this case the edge is 3.4 mm from the top of the scan.
We have found that it is quicker and easier to search for an image of completely normal tissue that does not show abnormalities than to definitively identify those that do contain an abnormality (such as the abnormalities discussed in the introduction above). Thus, this method simplifies the search for the edge of the lesion, and reduces the skill level required of the user. The user may have already made a scan of an apparently normal, lesion-free area of the user's skin before scanning the lesion; this provides a benchmark for the normal appearance in the OCT images, as what is normal for a given patient may vary wildly from other patients, depending on degrees of sun damage, age, skin type and so on.

The position of the index marker 3 can be used to calibrate the position of the scans on the skin. Because the OCT device 8 is positioned, when scanning, so that the scan is aligned with the hole 4 in the index marker, it is known that the top of the scan is aligned with the top of the hole 4 adjacent to the "perpendicular" orientation marking 7. Thus, in the present case, the edge of the lesion is 3.4 mm down from the top of the hole 4.

The OCT device 8 also projects a visible marker onto the subject's skin. This is positioned halfway through the scan (that is, at image number 25). This marker can be aligned with the "parallel" orientation marking 7, thus giving an alternative physical reference datum on the index marker.

In the present case, the edge of the lesion 3 will be 0.9 mm below the "parallel" orientation marking 7.

As a further alternative, if the index marker is visible using the OCT device 8, then the position of the edge can be determined either from the lateral appearance of the index marker 3 in the scans, or by determining
as was carried out for the lesion 1, which of the scans the index marker 3 appears in at all.

The user can then mark the position of the edge of the lesion 1 on the user's skin, taking into account any margin they wish to leave. It is to be noted that the margin can be much smaller than previously, as it is known more accurately where the edge of the lesion 1 is. Such a mark 9 is shown in Figure 5 of the accompanying drawings.

The method above has marked one edge of the lesion 1. The user would now repeat the method at various points around the lesion 1. In the present case, for a relatively small lesion 1, only four marks are required at roughly 90 degree points around the lesion; larger lesions would require further marks. So, in this case the method would be repeated a further three times with the results shown in Figure 6 of the accompanying drawings, with the marks 9 delimiting the edge of a planned excision. These can then be recorded photographically.

As such, the combination of the index marker 3, the scanner 8 and optionally the pen 6 form a kit for use in carrying out the described method.

This method has been found to be particularly convenient to perform, and reduces the amount of tissue that needs to be excise to safely capture a cancerous lesion. The time taken is approximately one or two minutes per mark 9 and an accuracy of around 1 mm is achievable, which is an improvement on current clinical practice. The method can be used as a stand-alone method for determining the edge of lesions, or can be used as a backup to the present method relying wholly on the surgeon's judgement. By reducing the chances of a cancerous lesion not being fully captured, we would hope to reduce the number of repeat operations
required, thus reducing trauma to the subjects, as does the reduced amount of tissue excision required.

In a second embodiment of the invention, shown in Figure 7 of the accompanying drawings, the equivalent integers to those of the first embodiment have been shown with reference numerals raised by 10. In this embodiment, it is desired to map the extent of a lesion 11 on an area of the subject's skin 12.

Instead of providing a paper index marker as in the first embodiment, a pen 20 is used to draw a circular ring 13 around the lesion, together with two orientation markers 17. The ink 21 used in the pen absorbs strongly at the 1300 nanometre wavelength used in the OCT apparatus used (which is used in the same manner as in the first embodiment of the invention).

The ink 21 is of the form of a visible dye in which is suspended particles which provide the absorbance at the required wavelength. Typically, these particles are of the form of metallic or plastic particles having the necessary absorbance. Such a particle-loaded ink is widely available for the application of temporary tattoos with a sparkling appearance, such as is available from Amazon.co.uk (Amazon Services Europe SARL of Luxembourg) with item reference B001KS13XO.

Such an ink is useful, as standard dye-based inks do not absorb the wavelength used by OCT apparatus to a degree appreciable in the OCT images. By using an ink loaded with suitable particles, the ink marking will appear in the OCT image, thus providing useful registration between the ink marks 13, 17 on the patient's skin and in the OCT image.
CLAIMS

1. A method of determining the extent of a structure in or on the skin of a subject, the method comprising the steps of:
   placing an index marker on the skin adjacent to the structure;
   positioning an optical coherence tomography device relative to the index marker;
   using the optical coherence tomography device to image the structure so as to create an image of a cross-section through the skin;
   determining the position of an edge of the structure in the image;
   translating that position of the edge in the image to a position on the skin relative to the index marker.

2. The method of claim 1, in which the index marker provides a physical reference datum for the optical coherence tomography device, such that the position at which the image is taken is known.

3. The method of claim 1 or claim 2, in which the index marker is visible using the optical coherence tomography device and thus will be visible in the image created by the optical coherence tomography device.

4. The method of any of claims 1 to 3, comprising the step of capturing a plurality of cross-sectional images of the skin using the optical coherence tomography device, the plurality of cross-sectional images forming together a three dimensional image of a block of the skin.

5. The method of claim 4, in which the plurality of images are mutually parallel but spaced apart from one another; the step of using the optical coherence tomography device comprising positioning the optical coherence tomography device such that the plurality of images are
parallel to an estimated edge of the structure, typically a visible edge of
the structure.

6. The method of any preceding claim, in which the step of
5 translating the position of the edge comprises determining the relative
position of the index marker and the edge in the image or in the plurality
of images, and from that determining the relative positions on the skin of
the edge and the index marker.

7. The method of claim 6, further comprising the step of marking the
edge of the structure on the skin, or of marking a margin away from the
dege of the structure.

8. The method of any preceding claim in which the index marker is of
15 the form of an annular disc, the annulus defining a hole through which the
optical coherence tomography device can perform its scan, a
circumference of the hole or a point thereon providing a physical
reference datum.

9. The method of any preceding claim in which the index marker
comprises a marking on or in the user's skin.

10. The method of claim 9, in which the marking comprises an ink
marking comprising ink which substantially absorbs radiation at a
wavelength used by the optical coherence tomography device to image the
structure.

11. The method of claim 10, in which the ink comprises solid particles
which absorb substantial quantities of radiation at the wavelength.
12. The method of any preceding claim, repeated at a plurality of points around the structure.

13. A kit for use in determining the extent of a structure on or in the skin of a subject, comprising an optical coherence tomography device and an index marker which can be placed on the skin of the subject.

14. The kit of claim 13, in which the optical coherence tomography device is arranged to capture a plurality of cross-sectional images of the skin, the plurality of cross-sectional images forming together a three dimensional image of a block of the skin.

15. The kit of claim 14, in which the plurality of images are mutually parallel but spaced apart from one another.

16. The kit of any of claims 13 to 15, in which the index marker provides a physical reference datum for the optical coherence tomography device, such that the position at which the image is taken is known.

17. The kit of any of claims 13 to 16, in which the index marker is visible using the optical coherence tomography device and thus will be visible in the image created by the optical coherence tomography device.

18. The kit of any of claims 13 to 17, in which the index marker is of the form of an annular disc, the annulus defining a hole through which the optical coherence tomography device can perform its scan.

19. The kit of claim 18 as dependent from claim 16, in which a circumference of the hole or a point thereon provides the physical reference datum.
20. The kit of any of claims 13 to 19, in which the index marker is provided with an orientation marking that indicates a defined orientation relative to the structure.

21. The kit of any of claims 13 to 20, further comprising a set of instructions instructing the user to act in accordance with the method of claims 1 to 11.

22. Use of an index marker for in determining the position of a structure on or in the skin of a subject using an optical coherence tomography device, the index marker providing a physical reference datum for images created by the optical coherence tomography device.

23. The use of claim 22, being of the form of an annular disc, the annulus defining a hole through which the optical coherence tomography device can scan, a circumference of the hole or a point thereon providing a physical reference datum.

24. The use of claim 22 or claim 23, in which the index marker is provided with an orientation marking that indicates a defined orientation relative to the structure.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 G01B9/02

According to International Patent Classification (IPC) into both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61B G01B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :
* "A" document defining the general state of the art which is not considered to be of particular relevance
* "E" earlier document but published on or after the international filing date
* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another invention or other special reason (as specified)
* "O" document referring to an oral disclosure, use, exhibition or other means
* "P" document published prior to the international filing date but later than the priority date claimed

19 October 2011 27/10/2011

Date of the actual completion of the international search Date of mailing of the international search report

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## DOCUMENTS CONSIDERED TO BE RELEVANT

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