Efficiency of Presurgical Basal Cell Carcinoma margin mapping using Optical Coherence Tomography

Study Protocol

V04

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Rationale:

Basal Cell Carcinoma (BCC) is the most common malignancy in humans. Its incidence is continuously increasing. The head and neck areas are most commonly affected due to their increased lifetime exposure to sun compared to other body parts. BCC is often treated by surgical excision which has high cure rate compared to other treatment modalities, but leaves a visible scar which can affect the quality of life of the patient, depending on the location and size of the excision. Mohs Micrographic Surgery (MMS) was developed to minimize the size of the surgical excision whilst maintaining very high cure rate. The main drawback of MMS is that repeated surgery procedures may be required to eliminate all of the tumour using specialist resources located at the clinic.

Optical Coherence Tomography (OCT) allows non-invasive in-vivo imaging of superficial skin lesions. It is in routine clinical use for diagnosis of BCCs, and the diagnostic sensitivity and specificity is well established in published multi-centre trials. A further potential application of OCT is the pre-surgical mapping of the lateral margins of BCC. If the margins of a BCC were accurately known prior to commencing an MMS treatment, the treatment could be performed much more quickly, resulting in shorter patient stays and more efficient use of surgical and operating room resources. Previously published research has already shown that OCT mapping of BCC margins is more accurate than clinical assessment; the objective of the present study is to demonstrate that pre-surgical mapping of BCC margins with OCT is also more efficient.

Hypothesis:

That presurgical margin mapping of BCCs with OCT results in a reduction of the number of MMS surgery stages to < 1.4 without adversely impacting clinical outcome.

Objectives:

Primary Objective:

- Show that the average number of MMS stages by using pre-surgical margin mapping with OCT is < 1.4

Secondary Objectives:

- Validate that the reduction in MMS stages by use of OCT mapping does not result in an increase in the size of the surgical defect

- Show that the average time taken to perform OCT margin mapping is < 5 minutes for lesions of area < 2 cm2

Tertiary Objectives:

- For those lesions for which OCT margin mapping did not result in a single stage operation:

o Determine the proportion of each BCC subtype (nodular, superficial, or infiltrative BCC)

o Determine the proportion for which the first surgery stage had margins that were not clear (i) laterally (ii) in depth

o Determine whether anatomical location is a factor

Population:

Inclusion criteria:

- 200 patients with biopsy-proven BCCs who have been referred for MMS
- Adults > 18 years of age
- Informed consent

Exclusion criteria:

- Patients with BCCs larger than 6 cm2

Study Design:

Interventional Randomised Controlled Trial (RCT)

Previously published research [1-5] has shown that, under controlled conditions, OCT mapping of BCC margins is more accurate than clinical assessment and so is expected to produce a reduction in the number of MMS stages. However, the efficiency of the technique, in terms of the reduction in MMS stages versus the additional time required to OCT map the lesion, has not been quantified.

This RCT is designed to quantify the improvement in efficiency, and validate that it is more efficient than standard MMS. The study comprises two Arms, one is the OCT arm and one is the Control Arm. In the OCT Arm, OCT is used to map the tumour margins and the resulting number of MMS stages is recorded.

In the Control Arm, standard MMS is performed.

In order to be completely sure that the reduction in MMS stages using OCT has not been obtained at the cost of increasing the amount of tissue excised, all tumours are also mapped at initial consultation, prior to randomization, by a second observer. See Figure 1 Outline Protocol below.

Figure 1. Outline Protocol

Initial Steps

1. Informed consent is obtained from eligible patients

2. Observer #1 (not the surgeon) maps the extent of the BCC tumour using OCT. The time taken, size and shape of the mapped border is recorded.

3. The OCT marks are removed and the patient is asked to return at a later date for the surgical procedure

4. Patients are randomized into two groups, A. OCT Arm and B. Control Arm

A. OCT Arm

5. Observer #2 (the Mohs surgeon) maps the extent of the BCC tumour using OCT. The time taken, size and shape of the mapped border is recorded.

6. The Mohs surgeon performs Mohs surgery using the marked OCT mapped borders as the first stage estimate. The number of MMS stages is recorded.

B. Control Arm

7. Standard Mohs surgery is performed, using clinical assessment for the first MMS stages

Final Observations

8. Finally, prior to closure of the wound, the size of the surgical defect of all lesions is measured by tracing the extent on squared transparent paper and also photographed with a scale. The subtype of the BCC from the Mohs histology is recorded (nodular / superficial / infiltrative / other)

Avoiding Bias:

The initial OCT mapping, prior to randomization, by another Observer who is not the surgeon, is to detect any bias on behalf of the surgeon who might consciously or unconsciously increase the size of the excision in the OCT Arm (therefore unnecessarily increasing the amount of healthy tissue excised) in order to reduce the number of MMS stages. This first Observer does not know which Arm the patient will end up in and so will simply do their best to map the tumour as accurately as possible. It is then straightforward to compare their results (size of mapped margins) with the surgeon's to confirm the absence of any bias. Their OCT mapping results will also be compared with the size of the final surgical defect (for all lesions) to confirm that (as in all previous studies) OCT mapped borders are no larger than the final surgical defect by conventional MMS.

Case Number Estimation:

N=200 patients will be included in the study (100 in each arm).

According to published literature, the average number of MMS stages per lesion is in the range 1.5 to 1.7 [6]. Previous studies with small numbers of patients in non-RCT conditions indicate that presurgical margin mapping with OCT reduces the average number of stages to approximately 1.2 [1-5]. Analysis by a qualified statistician has shown that assuming the true value is 1.2, then 83 patients in the OCT arm will be sufficient to show that the average number of MMS stages is < 1.4 with a confidence level of 95% ($P<0.025$). This study will be performed with 100 patients in each arm in order to exceed this criterion and show that OCT mapping improves on standard MMS with 1.5 – 1.7 stages.

Termination Criteria:

The patient will be excluded from the study on personal demand (see informed consent).

Start and Duration

The study is designed for 2 years starting immediately after approval by ethics committee. Recruitment will be 2 patients per week.

Study-related interventions

The OCT device is CE marked and has been on the market in first and second generations since 2011. A methodology for using OCT to map the lesion margins has been developed since 2011 and results published [refs] and then further optimized.

The study involves manual measurement of the lesion at 3 stages (on clinical assessment, after OCT mapping, and after surgery. The measurement procedure is very simple and involves placing transparent squared paper over the lesion and tracing the extent. This procedure is a well-established technique for measuring the extent of wounds

In the OCT arm of the study, the Mohs surgeon will make a first incision using the marked OCT margins as the first estimation of the tumour border.

Risks and adverse effects

There are no risks or adverse effects from the OCT mapping procedure or lesion measurement procedure.

The OCT scanner is a CE marked device using a low power, eye-safe, Class I laser for the scanning process. The scan does not exposure the patient to any unsafe optical radiation.

For this study, the CE-marked OCT scanner has been modified by the addition of a non CE-marked prototype Marking Accessory ('Marker'). This Marker produces a small dot of ink on the subject's skin at the centre of the OCT scan when a trigger is depressed by the operator. The ink is approved for use in surgical markers. The Marker contacts the skin but is cleaned between each patient using disinfectant wipes. After mapping and before surgery the patient's skin is prepared in the normal manner, so there is no risk of infection. As the Marker is not CE-marked, MHRA approval of its use is being obtained.

Data and Analysis

The following data and analysis will be performed:

1. Primary Objective

- The average number of MMS stages will be calculated for each arm by dividing the total number of MMS stages for all the patients in the arm, by the number of patients in the arm. The 95% confidence levels for each arm will be calculated.

2. Secondary Objectives

- The area of lesions will be obtained from the tracings of the mark obtained by placing a transparent TegaDerm™ adhesive dressing over the mark, removing it (with ink transferred) and pasting on to squared graph paper and then counting the number of squares inside the traced borders.

- The area of the surgical defect will be obtained by placing OpSite™ squared adhesive dressing over the defect prior to commencement of repair, using an ink marker to trace the defect on the dressing, and then counting the number of squares inside the traced borders.

- The following will be calculated

i. The mean, r.m.s. and maximum difference between the area of the OCT map made by Mohs surgeon and the area of the OCT map made by Observer #1, for lesions in the OCT Arm

ii. The mean, r.m.s. and maximum difference of the area of the OCT map made by Observer #1 and the area of final surgical lesion in the Control Arm.

From (i) we will quantify the difference between the Mohs surgeon and Observer's OCT mapping, and whether the Mohs surgeon's margins are consistently smaller or larger.

From (ii) we will determine whether the Observer's margins are smaller or larger than the final surgical lesion, and from (i) then show whether the surgeon's margin are expected to be smaller than the final surgical lesion, and by how much.

Figure 2. Schematic of process showing the areas.

Finally, the average time taken to OCT map lesions will be calculated:

- For all lesions
- For lesions, divided into the following subcategories by clinically visible lesion size:
  - < 2.0 cm2
  - 2.0 – 4.0 cm2
  - > 4.0 cm2

3. Tertiary Objectives

The results for all lesions in the OCT arm which took more than 1 MMS stage will be analysed as follows:

Calculate the proportions of each BCC subtype (nodular, superficial, or infiltrative BCC, or other) as a % of the total

Calculate the proportion for which the first surgery stage had margins that were not clear (i) laterally (ii) in depth (iii) both

Calculate the proportions of lesions in each of the following anatomical locations: nose, periocular, perioral, ear, other facial location, neck, trunk, limbs.

Privacy Statement

Anonymization of patient data is compulsory (see privacy policy statement)

References

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