BMJ Open

Study protocol of the BASINEL Study: a pragmatic randomised controlled trial investigating treatment versus no treatment of low-risk basal cell carcinomas in older persons

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To cite: Van Coile L, Verhaeghe E, Ongenae K, *et al*. Study protocol of the BASINEL Study: a pragmatic randomised controlled trial investigating treatment versus no treatment of low-risk basal cell carcinomas in older persons. *BMJ Open* 2022;**12**:e063526. doi:10.1136/bmjopen-2022-063526

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-063526).

Received 06 April 2022
Accepted 13 September 2022

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ABSTRACT

Introduction Basal cell carcinomas (BCCs) represent 70% of all skin cancers. These tumours do not metastasise but are locally invasive if left untreated. There is a high incidence of BCC in the elderly, and clinicians frequently face important treatment dilemmas. The approach to BCC in the elderly should be investigated thoroughly.

Methods and analysis Data on health-related quality of life (HrQoL), survival and complication rate will be examined in a treatment and a non-treatment arm (1:1 allocation). In the non-treatment arm, in vivo biological behaviour of low-risk BCCs in elderly patients will be examined. The main objective is to combine tumour characteristics with demographic data, in order to determine whether treatment will positively affect the patients' HrQoL within a predetermined time frame.

A monocentric randomised controlled trial (RCT) was designed at the Ghent University Hospital. The study population consists of patients with the minimum age of 75 years and a new diagnosis of (a) low-risk BCC(s). Patients in the treatment arm will receive standard care. Patients in the non-treatment arm will be closely monitored: the tumour will be intensively evaluated using multispectral dermoscopy, reflectance confocal microscopy and high-definition optical coherence tomography. All patients will be asked to fill in a questionnaire concerning their HrQoL at consecutive time points. Patient-reported side effects will be evaluated via an additional questionnaire.

Primary outcomes will include the difference in HrQoL and the difference in complication risks (treatment vs non-treatment) at different time points of the study. Secondary endpoints are the evolution of the BCCs in the non-treatment arm and the long-term survival in both study arms. Tertiary endpoint is the treatment effectiveness in the treatment arm. The sample size calculation was performed and resulted in a target sample size of 272 patients in this study with a 1:1 allocation.

Ethics and dissemination Subjects can withdraw from participating in this study at any time for any reason without any consequences. Approval for this study was received from the Ethics Committee of the Ghent University Hospital on 26 August 2021.The results of this RCT will be submitted for publication in one or more international, peer-reviewed medical journals, regardless of the nature of the study results.

Trial registration number ClinicalTrials.gov (NCT05110924).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a randomised controlled trial investigating the health-related quality of life and treatment outcomes, as well as survival, in patients receiving treatment versus no treatment for their low-risk basal cell carcinoma (BCC) at an older age.
⇒ In vivo biological behaviour of BCCs will be evaluated with the use of in vivo imaging techniques, with no risk of scarring bias after skin biopsies.
⇒ Ethical considerations of not treating a BCC are the main study limitation.

INTRODUCTION

Skin cancer is by far the most frequent cancer worldwide, and epidemiological data confirm that currently one out of five men and one out of sixwomen in the Netherlands will develop a skin cancer before the age of 85 years.[1] There is a high burden of skin cancer care in daily dermatological practice, and previous research by our group indicated that an even more spectacular increase in patients with skin cancer can be expected in the next 20 years.[2] Basal cell carcinomas (BCCs), part of the keratinocyte cancers (KCs), represent 70% of all skin cancers and are non-aggressive; these tumours generally do not metastasize but can be locally invasive tumours if left untreated. The high incidence of skin cancer in the elderly is evident since carcinogenesis due to sun exposure is a cumulative process, and experimental studies have shown that aged patients are less likely to

repair DNA damage due to ultraviolet exposure.[3] Because of the high incidence of BCC in the elderly, clinicians are frequently faced with important treatment dilemmas due to logistical problems, morbidity and limited life expectancy in this often frail population. Globally, an estimated 524 million people in 2010 were aged 65 years or older (or 8% of the world population), and by 2050, this absolute number is expected to triple (1.5 billion), representing 16% of the global population.[1 4 5] In this way, optimising our care for elderly and healthy ageing should be a number one priority in the next decennium, as also stated by the WHO.

The best approach to treat BCC in older persons should be investigated thoroughly, since current data on biological behaviour of these tumours are absent and most guidelines are based on studies in young patients. Our group also pointed out the urgent need for this research in a recent perspective.[6] Consequently, the elderly are often overtreated or undertreated because of a lack of data on the biological tumour heterogeneity, the effectiveness of the treatment and the complication risks in this specific population. Several observational studies have shown that most non-melanoma skin cancers (NMSCs) (69%) were treated with extensive surgery regardless of patients' life expectancy.[7] In the USA each year, more than 100 000 patients are treated for BCC in their final year of life.[8] In certain patients, an active surveillance or watchful waiting (WW) strategy can potentially be the best choice. Despite frequently seen as similar options, WW differs from active surveillance in some important things. In WW, the patient will not be followed at consecutive time points. WW carries a palliative non-aggressive intent and does not include routine monitoring or procedures.

The current study will be a randomised controlled trial (RCT) in elderly patients with at least one low-risk BCC. A low-risk BCC in this study is defined as a BCC which is located on the trunk or the limbs (excluding the hands and the feet) and with a maximal diameter of the tumour of 3 cm. The study will allow us to propose a more appropriate treatment and follow-up for elderly patients with low-risk BCCs. We will examine the possibility of not treating all BCCs by collecting data on the quality of life (QoL), the complication risk and the in vivo biological behaviour of low-risk BCCs in elderly patients using state-of-the-art imaging techniques. The concept of not treating all BCCs in the elderly would be novel in the field of dermatology. Currently, all growth data and knowledge of the biological behaviour of BCCs are based on retrospective studies or very small prospective studies in patients awaiting surgery. The overall goal is to collect reliable clinical data in elderly patients in order to develop a personalised approach and a new innovative, cost-effective care pathway for the treatment of BCC in an ageing population.

METHODS AND ANALYSIS

Data collection procedure

Outcomes

The main study outcome is to determine difference in health-related quality of life (HrQoL) (measured as health utility index) and complication rates between both study arms (treatment vs no treatment) at different times of the study. This will provide important information on the impact of (not) treating a BCC in elderly patients (>75 years). In addition, at the time point of 10 years after inclusion date, survival will be evaluated and compared between the two groups with evaluation of the cause of death.

Secondary treatment effectiveness (recurrence rate at 36 months) in the treatment arm and the possible growth and histological evolution of the BCCs in the non-treatment arm will be evaluated.

Hypotheses

- Treatment of low-risk BCCs in elderly patients will impact patients' HrQoL more than the tumour itself.
- Treatment of low-risk BCCs in elderly patients comes with a higher complication rate than the tumour itself.
  - In elderly patients with low-risk BCCs, survival rates do not differ between patients who receive a treatment and patients who do not receive a treatment for their tumour.

Objectives

- Primary objectives:
  - To determine the impact on the HrQoL in elderly patients with low-risk BCCs in the treatment versus the non-treatment arm.
  - To determine the complication rate in elderly patients with low-risk BCCs in the treatment versus the non-treatment arm.
- Secondary objectives:
  - To determine the survival of elderly patients with low-risk BCC in the treatment versus the non-treatment arm.
  - To evaluate the in vivo natural behaviour and growth of the BCCs in the non-treatment arm (nested observational study).
- Tertiary objective/exploratory endpoint:
  - To determine treatment effectiveness (recurrence rates of the BCCs after 36 months) of the different (standard of care) therapies administered in the treatment arm (nested observational study).

Study design

This study will be a monocentric RCT.

Population

Patients aged 75 years and older with a new diagnosis of (a) low-risk BCC(s) consulting at the Department of Dermatology of the Ghent University Hospital.

Inclusion criteria

Patients with the age of 75 years or older with a new diagnosis of at least one BCC localised on the trunk or on the limbs (with the exception of BCCs on the hands and/or the feet).

No minors or incapacitated persons will be enrolled in this study.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Patient is unable to provide consent.
2. Patient is unable to understand the task and questionnaires.
3. Patient is immunocompromised.
4. Patient has a genetic skin cancer syndrome.
5. The BCC has a diameter of more than 3 cm.
6. The BCC occurs in a skin site that underwent radiotherapy in the past.
7. Patient has a history of malignant melanoma or other types of NMSC (with the exception of KC)).
8. Patient has had a high-risk squamous cell carcinoma (SCC) during the last 2 years or a SCC in the head and neck region during the last 2 years.

Recruitment procedure

Patients will be consecutively recruited in the Ghent University Hospital. Start of recruitment from 1 December 2021 with, after inclusion, at least 36 months of follow-up.

They will be given thorough information about the study objectives and the protocol. A written informed consent form will be collected for all participants (online supplemental file: patient consent form (in Dutch)).

If the patient gives consent to participate in the study, the dermatologist or study nurse fills out part 1 of the data collection (demographic information and clinical data) in the data capturing system REDCap. Additionally, the phone number and the email address of the patient will be asked because there will be consecutive moments in the study where the patient will be asked to fill in a questionnaire. After the dermatologist or the study nurse filled in the first part of the data collection, the patient will go through the stratification and randomisation process and will be randomly allocated to either the treatment or the non-treatment arm of the study.

Stratification and randomisation procedure

Randomisation process will take place via REDCap.[9] REDCap is a secure web application for building and managing online surveys and databases. In REDCap, state-of-the art authentication and authorisation can be used to ensure data security. Network transmission (data input, submitting surveys, surfing the web, etc) in REDCap is protected via Transport Layer Security encryption. This ensures that the sent information cannot be tapped or changed during transmission. The REDCap application and associated database are located on secure servers behind the Ghent University Hospital application layer firewall (reverse proxy) and on Ghent University server.

The randomisation module within REDCap allows researchers to randomly assign participants to specific groups. This module can be turned on during project creation. A randomisation model defines how the subjects in the study are randomised. REDCap allows to define the type of randomisation, which will be a stratified randomisation in our study. This ensures that different groups are balanced.

In REDCap, the field that has been specified for randomisation will display a 'Randomise' button in the data entry screen. Pressing the 'Randomise' button, the value of a random group will be assigned. The random group field will become read-only and the value cannot be changed. Also, the strata field become read-only and cannot be changed.

Randomisation scheme

1. Diagnosis of at least one low-risk BCC.
2. Age ≥75 years.
3. No exclusion criteria.
4. Stratification:
   - Charlson Comorbidity Index (<3, ≥3).
   - Randomisation 1:1.

Flow of the study

The first part of the study includes the input of the demographic info and clinical data by the research team. Afterwards, the stratification and randomisation step will take place and patients will be allocated to the treatment or the non-treatment arm. A schematic study flow can be found in figure 1.

We will compare standard treatment versus no treatment head-to-head (1:1 allocation) in a RCT:

1. Treatment arm: evaluation of HrQoL (Basal and Squamous Cell Carcinoma Quality of Life (BaSQoL) instrument, EQ-5D-5L and time trade-off task (TTO)), evaluation of treatment effectiveness, possible complications and survival data.
2. Non-treatment arm: evaluation of HRQoL (BaSQoL, EQ-5D-5L and TTO), evaluation of possible complications, survival data and follow-up of BCCs with in vivo imaging (multispectral dermoscopy (MSD), reflectance confocal microscopy (RCM) and high-definition optical coherence tomography (HD-OCT)).

Patients allocated to the treatment arm will receive diagnostic investigation(s) as in standard care to establish the diagnosis of a BCC. This will include clinical and dermoscopic examination of the lesion and (in most cases) a skin biopsy to confirm the diagnosis of a BCC and to determine the histological subtype. Specific for the study, patients will be asked to fill in a questionnaire concerning their HrQoL (the disease-specific BaSQoL, the generic EQ-5D-5L and the TTO) and concerning possible complications (patient-reported side effects (PRSEs)) through email (REDCap) or by phone. In the case where patients have a skin biopsy and this shows

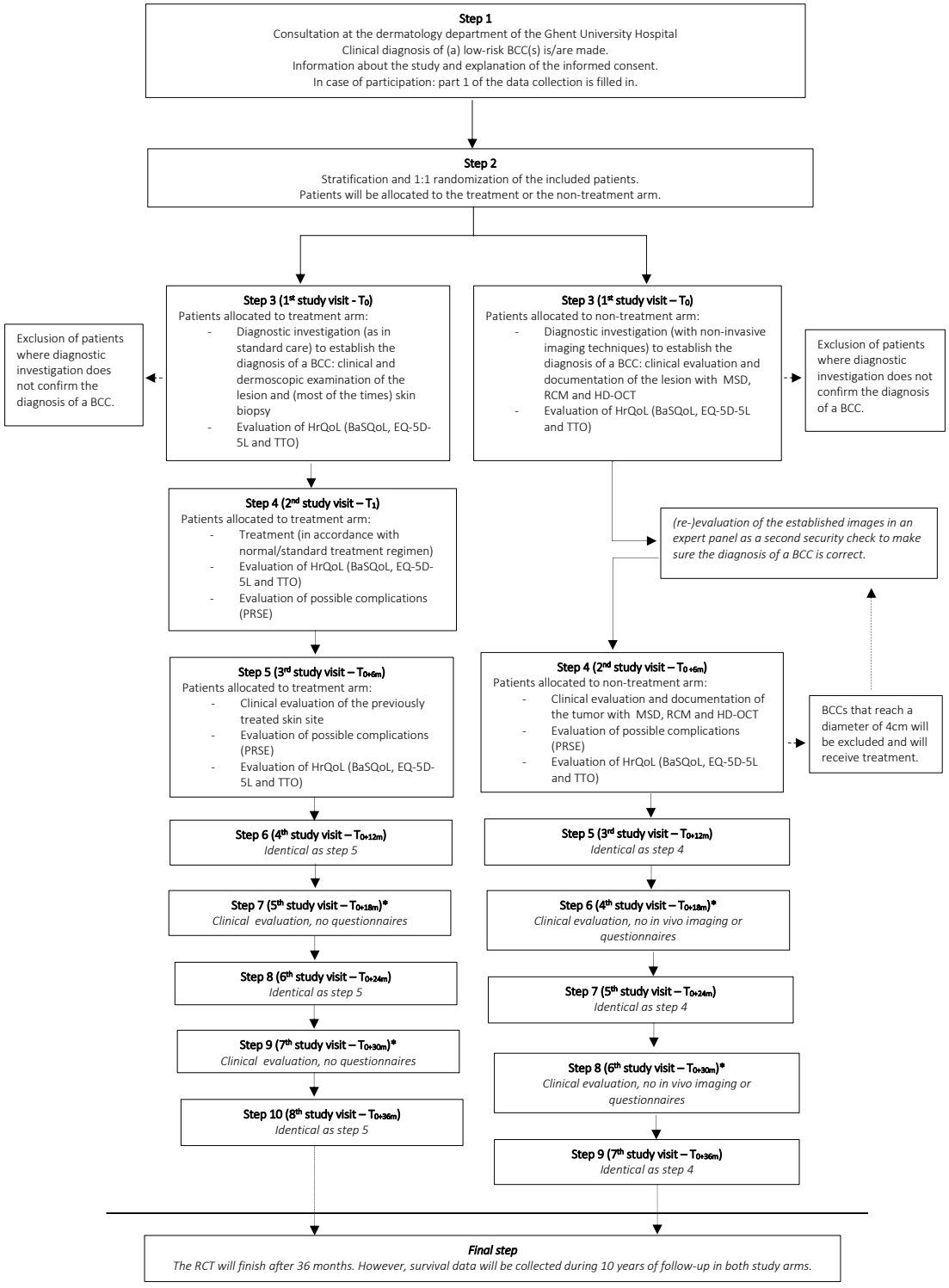

Figure 1 Stepwise procedure of patient inclusion and data collection. *Frequency of follow-up is in accordance with the current guidelines used for follow-up of KCs at the Ghent University Hospital. Patients who need to be followed every 6 months (more than one BCC or a history of BCC or SCC) will also consult at T_{18} and T_{30}. However, these visits will only provide clinical evaluation. BaSQoL, Basal and Squamous Cell Carcinoma Quality of Life; BCC, basal cell carcinoma; HD-OCT, high-definition optical coherence tomography; HrQoL, health-related quality of life; KCs, keratinocyte cancers; MSD, multispectral dermoscopy; PRSE, patient-reported side effect; RCM, reflectance confocal microscopy; RCT, randomised controlled trial; SCC, squamous cell carcinoma; TTO, time trade-off task

the suspicious lesion is not a BCC, these patients will be excluded. After this step, enrolled patients will receive treatment of their BCC in accordance with the normal/standard treatment regimen. The treatment (ie, surgery, topical treatment or CO_2-laser) will be performed by an independent dermatologist of our department who is

blinded and is not aware of the patient's participation in this study. After the treatment, a new questionnaire (via email or by phone) will be sent out to capture the patient-reported HrQoL (EQ-5D-5L, BaSQoL and TTO) and possible PRSEs. Afterwards, the patients will be followed every 6–12 months for a follow-up period of 36 months with a clinical evaluation of the previously treated skin site and evaluation of possible complications. After the visit at 6, 12, 24 and 36 months, the patient will again be asked to fill out the HrQoL questionnaires and complications questionnaire.

Patients allocated to the non-treatment arm will also receive diagnostic investigations to establish the diagnosis of a BCC. In this study arm, the diagnostic investigation will be performed by non-invasive imaging techniques (MSD, RCM and HD-OCT) to confirm the diagnosis of a BCC and to determine the histological subtype. Patients will be asked to fill out a questionnaire concerning their HrQoL (BaSQoL, EQ-5D-5L and TTO) through email or by phone. Important to point out is the possible exclusion of certain patients after this step. This will be the case in patients where the in vivo imaging techniques show that the suspicious lesion is not a BCC. There is also a second security check build in this study arm: a (re-)evaluation of the established images will take place in an expert panel to make absolutely sure the diagnosis of a BCC is correct. When there is doubt, the patient will be excluded from the study and will receive standard diagnostic measures and treatment if necessary. Afterwards, the patients in this arm will be followed every 6–12 months for a follow-up period of 36 months. Because of the indolent nature of these skin tumours, a follow-up period of 36 months seems necessary to allow a correct estimation of the growth of the BCC. Every study visit, there will be a clinical evaluation of the tumour. At the follow-up visits of 6, 12, 24 and 36 months, a new documentation of the tumour with MSD, RCM and HD-OCT will be performed. At these time points, patients will also be asked to fill in the HrQoL questionnaires and complications questionnaire. Because of ethical reasons, a maximum tolerable diameter of the tumour has been defined in advance: BCCs in the non-treatment arm that reach a diameter of 4 cm will be excluded and will receive treatment. Patients can be enrolled in the study with a maximum diameter of their BCC of 3 cm (cfr. exclusion criteria). However, in the non-treatment arm, a possible growth of the tumour can be seen. Because of ethical reasons and to make sure a treatment of the BCC remains (technically) achievable, we decided to exclude BCCs that reach a diameter of 4 cm during the study and to propose treatment. Patients in the non-treatment arm who decide to withdraw from participating in this study or patients lost to follow-up will be contacted by our research team. These patients will be invited to our department to discuss the treatment options for their BCC. If the patient prefers not to treat their BCC, we will inform their general practitioner about the discontinuation of the study and the patient's choice not to treat their BCC. Of course, also in these patients, a further yearly clinical follow-up is advised. In both study arms, the follow-up within the RCT (with the collection of HrQoL data and data on the complication risks) will end after 36 months. However, survival data will be collected once more after 10 years of follow-up in both study arms. Of course, all patients are well informed to contact our department if their lesion would grow or change rapidly, or would cause symptoms.

Special situations

- Patients who develop a new KC during follow-up in the study:
  a. If the KC is a low-risk BCC (according to the study criteria): patients remain in the previously allocated study arm and the newly diagnosed BCC receives the same approach (treatment or non-treatment).
  b. If the KC is a high-risk BCC (according to the study criteria) or another type of KC (excluding actinic keratosis): patients will receive treatment for the newly diagnosed tumour. Because of interference with the assessment of the HrQoL and the complication risks, these patients will be excluded from the RCT starting from the time point the new lesion has been diagnosed. The initial low-risk BCC can, in the non-treatment arm, still be followed with in vivo imaging for the nested observational study concerning the natural behaviour and growth of these low-risk BCCs.
- If patients develop an exclusion criterion during study follow-up, he/she will also be excluded from the further study.

Interventions

Questionnaires

Basal and Squamous Cell Carcinoma Quality of Life instrument

The BaSQoL instrument is a disease-specific validated QoL questionnaire for patients with KC. It consists of 16 questions in 5 dimensions (worries, appearance, behaviour, diagnosis and treatment and other people) rated on a 4-point Likert scale. Mean duration to complete the BaSQoL is 5–10 min (timings are based on estimations).

EQ-5D-5L

The EQ-5D-5L is a standardised instrument developed by the EuroQol Group as a measure of HrQoL that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of a descriptive system and the EQ Visual Analogue Scale. The five dimensions are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression rated on five response levels. It takes patients 1 min to fill in the complete questionnaire (timings are based on estimations).

Time trade-off task

This direct valuation of own health requires the patient to imagine two hypothetical life courses: to remain in their current health during the following 10 years or to live in perfect health for shorter duration. The utility is then calculated as the proportion of years in perfect health.

Mean duration to complete the TTO is 1 min (timings are based on estimations).

Patient-reported side effects questionnaire

In this questionnaire, possible complications after treatment of the BCC or possible complications due to the tumour itself will be questioned. This questionnaire consists of a list of commonly reported side effects that has been developed on the basis of literature review as well as by panel discussion with subspecialised dermatologists in this matter. Participants will be asked if they have experienced symptoms of which they believe these symptoms could be a side effect from the allocated treatment for their BCC or from their BCC itself. The following complications have been listed: pain, itch, bleeding/haematoma, infection, functional complications, aesthetic concerns and anxiety. There will also be room for the patient to fill in additional remarks or comments. Mean duration to complete the PRSE is 1 min (timings are based on estimations).

In vivo imaging techniques

Reflectance confocal microscopy

RCM is a non-invasive optical imaging tool that allows imaging of skin lesions in vivo at nearly histological resolution. The combination of dermoscopy with RCM allows the dermatologist to improve the accuracy of diagnosis of a skin cancer without the need of taking a skin biopsy and thus leading to fewer biopsies taken from benign skin lesions.[10]

RCM uses a near-infrared laser (830 nm wavelength) to produce high-resolution images based on differences in the reflection and backscattering of light from the examined tissue section. It allows nuclear and cellular imaging of the skin with a typical lateral (horizontal) resolution of 0.5–1 µm and an axial (vertical) resolution between 3 and 5 µm, to a depth of about 150–200 µm depending on the anatomical site.[10] The imaging in depth is performed by the RCM by creating in real time a stack of images at the same horizontal plane at different depths, creating an image from the stratum corneum down to the underlying papillary dermis, which is called an optical biopsy.

In this study, the VivaScope 3000 (Lucid-Tech, Henrietta, New York, USA) will be used. This is a CE-labelled device and will be used in this study within the intended use. It is a handheld RCM device. The field of view with this handheld device is however limited to 1000×1000 µm^2. We need to address that imaging resolution decreases below a depth of 100–150 µm. This results in the fact that RCM is restricting accurate diagnostic interpretation to the epidermis and superficial dermis.[10]

RCM can be used as a second-level examination in equivocal skin lesions. It can improve the ability to differentiate benign from malignant skin lesions, thus reducing the number of unnecessary biopsies by 50%–70%. The reduction of unnecessary biopsies also leads to a decrease in the associated morbidity and healthcare expenditures.[10]

A meta-analysis in 2016 showed good results for the diagnostic accuracy of RCM in detecting BCC. In this meta-analysis, the RCM showed a pooled sensitivity of 91.7% and a pooled specificity of 91.3%. Another, more recent meta-analysis in 2019 showed a pooled sensitivity of 92% and a pooled specificity of 93% for the detection of primary BCC. This indicates that RCM is a sensitive and specific tool for the in vivo diagnosis of BCC.[11 12]

Multispectral dermoscopy

The current standard of care in dermatology is the use of a dermatoscope to allow better visualisation of the structures of lesions underneath the stratum corneum. The dermatoscope used in daily practice is usually based on white light imaging.

MSD is based on illumination of the skin with narrowband light sources with different wavelengths. Each of these wavelengths is differently absorbed by skin chromophores, such as pigment or (de)oxygenated blood. With conventional, white light dermoscopy, the visualisation is limited up to the epidermis/dermis intersection layer. MSD allows to visualise deeper into the skin, up to 2 mm depth.[13]

In this study, Demetra (Barco, Belgium) will be used. This is a CE-labelled device and will be used in this study within the intended use. It is a flexible, wireless handheld device that provides multispectral dermoscopic examination. It is also possible to document the tumour with this device by making dermoscopic, close-up and clinical overview images with it. With this device, the surface of the lesions will be analysed and followed over time.

High-definition optical coherence tomography

HD-OCT is a non-invasive imaging technique that allows real-time high-definition cross-sectional visualisation of tissues reaching up to a 1 mm depth. This device has a resolution of 1–3 µm.[14] OCT is based on the principle of interferometry and uses infrared light (1300 nm) projected onto the skin to produce an image based on the sum of the different light refractions caused by the different optical properties of structures in the skin. In this study, the Skintell (Agfa, Belgium) will be used. This is a CE-labelled device and will be used in this study within the intended use. A meta-analysis in 2018 showed a pooled sensitivity of 92.4% and a pooled specificity of 86.9% concerning the diagnostic accuracy of OCT in BCC.[15] HD-OCT provides imaging with a high lateral and axial resolution, making it possible to visualise specific three-dimensional images with real-time scanning. It will be used to determine the depth of the BCC.

End of study

After 36 months, the intensive follow-up within the study will end. Patients who were allocated to the non-treatment arm will have to choose whether or not they want a treatment for their BCC. The primary principle is that all patients in the non-treatment arm will receive treatment for their BCC after the 36 months of follow-up. However,

patients are free to choose themselves if they prefer not to treat their BCC. A further yearly clinical follow-up will be advised in both cases. At T_0+10 years, the survival rates between patients who did receive treatment for their BCC and patients who did receive treatment for their BCC will be evaluated. This is a secondary endpoint and purely observational in nature; no sample size calculations will be done for this.

Withdrawal of individual subjects

Subjects can withdraw from participating in this study at any time for any reason without any consequences. Patients can decide to adjust their BCC approach at any time. Because the assessment of the HrQoL is one of the most important endpoints in this study, patients who choose actively for a treatment or an active surveillance approach will be excluded from the study. Of course, they will be followed afterwards at our department, but not within study setting. In order to achieve the required sample size, in case of a drop-out, this individual will be replaced to attain 115 subjects per study arm. Missing values due to tumour progression could lead to less overall tumour burden, and these missing data will be corrected for using joint modelling methods.

Sample size calculation

The sample size calculation was performed using SAS (version 9) power and sample size. A sample size of 104 per group yields 80% to detect a clinically relevant difference in HRQoL of 0.03 (health utility index), assuming a SD of 0.0768. Assuming a drop-out rate up to 30% (patients will be excluded from the RCT if they develop a high-risk BCC or another type of KC (excluding actinic keratosis) during study follow-up), 136 patients are required in each group. This means a total of 272 patients are required in this study with a 1:1 allocation.

Study risks

A known important risk in this study could be selection bias. However, we will try to reduce this type of bias by consecutively and consistently proposing study participation to every patient who meets inclusion criteria. The first data (demographic and clinical data) will be collected before the randomisation process. After the randomisation, patients allocated to the treatment arm will receive treatment corresponding to standard treatment regimen. The dermatologist treating the patient will not be aware of the patients' participation in the study. This will ensure that the evaluation of the HrQoL after the treatment cannot be influenced.

Of course, also a drop-out of patients or missing data are a potential risk in any clinical trial. After correct reporting, several analyses will be performed to evaluate the effect of missing data such as the intention-to-treat analysis and a worst-case scenario analysis.

Because the intervention in this study includes a non-treatment arm, a possible growth of the non-treated BCCs can be seen. These tumours are usually indolent. The follow-up of these lesions will be intensive and thorough using MSD, RCM and HD-OCT. Because of ethical reasons, a maximum tolerable diameter of the tumour has been fixed in advance. BCCs in the non-treatment arm that reach a diameter of 4 cm will be excluded and will receive treatment. This leads to the risk of drop-out due to tumour burden limit. However, statistical analyses will compensate in order not to underestimate the tumour growth in the nested observational study in the non-treatment arm.

Statistical analysis

Statistical analysis will be performed for interim analyses after the 18-month follow-up visit in this study as well as when data collection has been completed after the 36-month follow-up visits. The analyses will of course be performed after data cleaning.

All statistical tests will be two tailed, and p values of <0.05 will be considered statistically significant. Analyses will be performed by the investigators of the study group, in collaboration with the Department of Statistics of the Ghent University. The latest version of SPSS statistics (IBM Corp) will be used.

Statistical analyses used to compare groups will contain largely descriptive statistics between the two study arms. Baseline characteristics of all enrolled patients will be reported per randomisation group and will be illustrated in a baseline table. The following characteristics will be reported: age, gender, skin type, number of KCs in the past (excluding actinic keratosis), comorbidities (assessed by the Charlson Comorbidity index), tumour location, tumour size, tumour histology and baseline health utility score (derived from the EuroQol 5 dimensions questionnaire). Dichotomous variables will be summarised as proportion of patients with the count divided by the total number of evaluated patients. Continuous variables will be summarised as mean with SD in case of normal distribution and as median with IQR in case of non-normal distribution. Differences between the study arms will be analysed using the X^2 test, the independent t-test or the Mann-Whitney U test. All complications will be reported per study arm. The occurrence of complications will be gathered by questioning the patients as well as screening the patients' medical record. Complications will be assessed on patient level and X^2 test will be used to compare the outcomes between the study arms. In the case >25% of patients have multiple complications, assessment will be performed on complication level (n per patient) using multivariable Poisson regression analysis. Changes in health utility over time will be reported. Health utility scores, derived from the EQ-5D-5L, will be available at baseline, after treatment (in the treatment arm) and at 6, 12, 24 and 36 months of follow-up. The follow-up data will be assessed by repeated measurement analysis with baseline data as covariate, using a generalised linear mixed model. The results will be displayed per study arm in a graph. X^2 tests will be used to compare the HrQoL between the study arms. Table 1 gives an

Table 1 Overview of the study hypotheses, outcomes, instruments and planned statistical analysis

Hypotheses	Outcomes/items	Instruments	Statistical analysis
$H0=T\,arm_{HrQoL}>n-T\,arm_{HrQoL}$	QoL	BaSQoL EQ-5D-5L TTO	Unpaired t-tests
$H0=T\,arm_{complications}<n-T\,arm_{complications}$	Pain Bleeding Infection Implications on daily activities Aesthetical worries Anxiety	VAS (PRSE questionnaire) Y/N (%) (PRSE questionnaire) Y/N (%) (PRSE questionnaire) Y/N (%) (PRSE questionnaire) Y/N (%) (*q13–15 BaSQoL*) Y/N (%) (*q6–8 BaSQoL+q5 EQ-5D-5L*)	X^2 tests
$H0=T\,arm_{survival}\neq n-T\,arm_{survival}$	Survival	Time to death	Kaplan-Meier curves Cox regression analysis

BaSQoL, Basal and Squamous Cell Carcinoma Quality of Life; HrQoL, health-related quality of life; PRSE, patient-reported side effect; TTO, time trade-off task; VAS, Visual Analogue Scale.

overview of the hypotheses, outcomes, instruments and planned statistical analysis.

The relation between specific patient characteristics or clinical data and high utility indices will be explored to identify additional patient characteristics or clinical data that are associated with a better QoL. These additional analyses will be performed using logistic regression with and without study arm as covariables.

Main analyses will be performed according to the intention-to-treat principle to avoid bias. To preserve benefit of randomisation, all randomised participants should be included in the analysis. This means all patients will be analysed in the intention-to-treat analysis according to their initially assigned study arm after randomisation. Differences in patient characteristics between patients lost to follow-up and enrolled patients will be assessed. In case of potentially meaningful differences, a worst-case scenario will be run, in which all patients lost to follow-up in the treatment arm will be considered to have a health utility index of 1 and all patients lost to follow-up in the non-treatment arm will be considered to have a health utility index of 0.97. Moreover, per-protocol analysis will be performed. All subjects from the intention-to-treat population without protocol violations and deviations regarding (non-)treatment will be included in the per-protocol population.

Based on the sample size calculation, we need to include a total of 272 evaluable patients (136 per study arm) in this study. Patients are evaluable if they are not excluded due to protocol violation in eligibility or consent and if data on outcome at 36 months are available. To reach the appropriate sample size and targeted power in this study, patients not fulfilling these criteria will be replaced.

Patient and public involvement

During the design of this study and the development of the study protocol, a small group of patients with low-risk BCCs who consulted our department were informed about our study and were asked for feedback. Their input was taken into account in the further development process of this study protocol.

ETHICS AND DISSEMINATION

Ethics and auditing

This study is approved by the Ethics Committee of the Ghent University Hospital (BC-10076). Informed consent material is available in Dutch with the approved study protocol. A data management plan was thoroughly described; this is available upon request.

Dissemination and protocol amendments

The results of this RCT will be submitted for publication in one or more international, peer-reviewed medical journals, regardless of the nature of the study results. Coauthorship will be determined based on substantial contributions. Any amendment on the study protocol will be reported to the Ethics Committee of the Ghent University Hospital.

Contributors LVC and IH drafted the manuscript and designed the figures. LVC and IH designed the trial in collaboration with EV, KO and LB. All authors revised the final version of the article before submission.

Funding This research project was funded by the Innovation and Clinical Research Fund of the Ghent University Hospital. The research activities of IH are supported by a postdoctoral fellowship of the Scientific Research Foundation-Flanders (number: 12Y2420N). The research activities of LVC are supported by a predoctoral fellowship of the Scientific Research Foundation-Flanders (number: 1S69921N).

Disclaimer The funding sources had no role in the literature study, no role in preparation, review or approval of the manuscript; and no role in the decision to submit the manuscript for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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