BIJLAGE 1: PROJECTVOORSTEL

PIONEERS IN HEALTHCARE INNOVATION FUND 2020 – RESEARCH PROPOSAL

Voucher type	☐ Technological pioneering in healthcare		☒ Applying technology in healthcare	
Titel				
Verbetering van vrije flap transplantaties met *handheld laser-speckle perfusion imaging*.				
Trefwoorden	Reconstructieve chirurgie	Laser-speckle	Weefsel-imaging	Doorbloeding
Title				
Improving free flap transplantations with the use of handheld laser speckle perfusion imaging				
Keywords	Reconstructive surgery	Laser speckle	Tissue Imaging	Perfusion

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Publieke samenvatting voor publicatie op website en persberichten
Necrose is een ernstige complicatie van een reconstructieve operatie met lichaamseigen weefsel na borstkanker chirurgie. De oorzaak is vaak een ondermaatse doorbloeding van het getransplanteerde weefsel. Er is grote behoefte aan technologie om de doorbloeding objectief, non-invasief, makkelijk en direct te meten. In dit project onderzoeken we of laser speckle die techniek kan zijn. We gaan het door de Universiteit Twente ontwikkelde *handheld* systeem in het ZGT gebruiken tijdens de operatie. Op basis daarvan hopen we uiteindelijk te komen tot een beter eindresultaat voor de patiënt, terwijl we de kosten en moeiten uitsparen waarmee complicaties gepaard gaan.
Public summary to be published online and in press releases
Necrosis is a serious complication in breast cancer surgery with reconstruction using autologous transplanted tissues. Necrosis is caused by a low blood perfusion of the transplanted tissue. Technology is needed to measure perfusion in a real-time and objective manner so surgical strategies can be adjusted directly, preventing complicated sequels. In this project we investigate if laser speckle is a candidate for this. We will use the wireless handheld system developed by the University of Twente within ZGT during surgery. Eventually we hope to achieve a better final outcome for the patient, while saving costs and effort associated with complications.

CURRENT PIHC INVOLVEMENT

Applicants previously granted a PIHC voucher		
Slart, Steenbergen, Van Netten, Van Baal, Meerwaldt en Geelkerken. MIRA Voucher 2015. 'A new field for photoacoustic Imaging: From validation in healthy feet to critical limb ischemia detection in people with diabetes.' Final report submitted November 2017. This research is continued in a NWO/TTW project "handheld perfusion imaging'. Geelkerken, Steenbergen, Wermelink, Van Baal, Meerwaldt, Brusse-Keizer, Kuniyil Ajith Singh: PIHC2019 voucher 'Assessment of the microcirculation using Photoacoustic Imaging in patients with Peripheral Arterial Occlusive Disease'. Project will start soon; delayed because of corona.		
Resubmission of previously non-awarded proposal	☐ yes	☒ no
New technology, similar application (e.g. disease)	☐ yes	☒ no
Similar technology, new application	☐ yes	☒ no

Clinical relevance

Breast cancer is a major life event that occurs to one out of seven women. A skin-sparing mastectomy is one of the treatment options for breast cancer in which the breast gland is removed, and the skin envelope is preserved. Subsequent reconstruction of the breast involves replacing the volume of the breast gland. Breast reconstruction offers improved quality of life, better social and relational functionality. Reconstruction can be performed using either implants or autologous materials. In the latter case, abdominal fat and skin tissue are dissected and transplanted, and its feeding vasculature is reconnected to the internal mammary artery, as a free flap. Figure 1 illustrates this procedure, called DIEP flap which stands for the feeding artery, the Deep Inferior Epigastric Perforator.

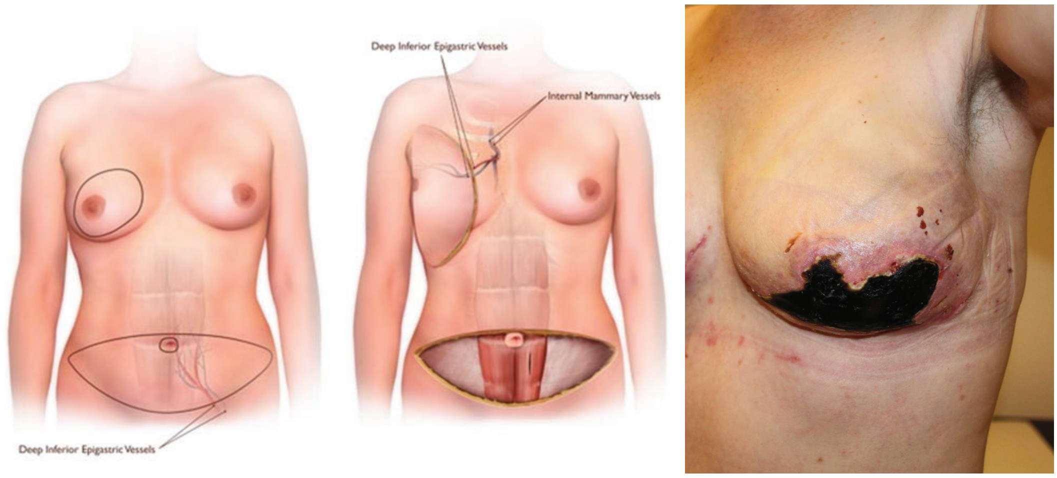

Figure 1. DIEP flap surgery: abdominal fatty tissue is perfused by the abdominal wall artery, removed and reanastomosed to the internal mammary artery deep to the sternum. Right: necrosis as a consequence of insufficient blood supply to the transplanted skin.

In ZGT hospital we perform 60-70 DIEP flaps on a yearly basis. Fortunately, most patients have an uneventful postoperative recovery. This is important as complications lead to dramatic decreases in patient reported satisfaction. In addition, complications cause serious stress to surgeons, and increased visits to clinics lead to increased costs for hospitals and insurance companies. This is why complications need to be reduced to an absolute minimum by aiming for textbook outcome [1].

One of the most serious complications is necrosis of skin due to underperfusion. Perfusion issues in up to 20% of cases are reported [2]. This process can especially occur in breast surgery where relatively large pieces of skin are damaged in mastectomies and autologous breast reconstruction, if the skin envelope receives too little blood to survive or a transplanted autologous flap is too large for the pedicle. In addition, abdominal wall donor site necrosis can occur due to compromised vasculature caused e.g. overly undermining the abdominal flap. Finally, systemic causes including smoking, poor wound healing and obesity increase the chance of poor tissue perfusion and necrosis.

Surgical experience is not reliable enough to predict if poor tissue vascularization will lead to necrosis in the days following breast reconstructive surgery. Moreover, there are no available techniques that can aid a surgeon to monitor skin perfusion preoperatively so she or he can directly adjust the surgical strategy and remove the underperfused tissue, thus preventing necrosis. Hence there is a clinical need for peroperative imaging of the micro perfusion of skin flaps.

A promising technique which has recently been explored is peroperative imaging of tissue using fluorescent intravascular contrast. This technique has been shown to reduce the number of complications (ref.2). A major disadvantage of exogenous fluorescence is the limited time tissue perfusion is measurable before the fluorescence disappears (seconds to minutes).
Laser speckle perfusion imaging (LSPI) is a technology that can provide real-time information of tissue perfusion without contrast agent. It can be used during the entire length of an operation. Furthermore, it provides a more stable and objectively measurable signal compared to fluorescence methods as it does not rely on the signal of a diminishing intravascular agent. In theory, it could

provide superior tissue information compared to exogenous fluorescence techniques.

The aim of this project is to explore and validate the use of handheld LSPI as a technology to detect poor skin perfusion and thus reduce the chance of developing skin necrosis and wound healing delay after mastectomy and breast reconstruction.

Challenge

LSPI is an existing technology that has been explored for measuring flap perfusion [3, 4] However, current devices are all mounted, which makes them bulky and inflexible for use in the operation theatre or bedside. For this reason, the BMPI group of the University of Twente is developing a handheld system. We have to overcome the challenge posed by motion artefacts, which we mainly achieve by a combination of clever beamforming and post processing of results. Click here for a perfusion movie obtained with our system in a psoriatic plaque.
For the research proposed here we need a completely wireless system. This development will be completed in the first stage of this project, after which it will be tested for safety and compliance and introduced in ZGT. Here it will be used for the study outlined below.

Plan of action (incl. study design, timeframe and budget)

1 Preparatory stage: LSPI assembly, researcher training; protocol writing for medical ethical assessment; technical admission procedure for introducing the system in ZGT. (Month 1-3)

2 Training of the researcher for use of the equipment and software, and development of image analysis methodology for this specific application. (Month 1-3)

3 Assessment of threshold values based on [3]. The device used in [3] is available, which allows us to make a comparison of perfusion numbers for both devices using tissue phantoms. (Month 3-4)

4 Exploratory peroperative measurements with the aim to develop a routine in performing the measurements and analysing the peroperatively obtained images. (N=5, Month 5-6)

5 Main study (N=15 patients, month 6-12) of LSPI, comprising:
- Skin of the abdominal wall prior to surgery;
- Idem, perfused on one epigastric artery, imaging of zones of hyperperfusion close to the perforator and comparing it to macroscopically confirmed underperfused areas;
- Idem, during a 3 minute ischemia period just prior to removal of the flap;
- Idem, just after anastomosis, looking at the hyperperfusion state that typically follows anastomosis and reperfusion after 20-30 minutes of ischaemia;
- Comparing surgeon-mapped resections with LSPI mapping of underperfused skin
- Imaging of perfusion of the donorsite, the skin of the abdominal wall that is closed following removal of the flap.

Primary outcome measures:
- % of viable tissue based on laser speckle perfusion image
- Dynamics of perfusion of the flap skin (ischemia – reperfusion) based on LSPI.
- Comparing surgeon's outline of underperfused skin to LSPI assessment
- Comparing surgical outcome of tissue transplants after 4 weeks with LSPI prediction

Roles of project members:
The project researcher will coordinate the METC and technical compliance procedures, patient consent and inclusion, collect patient data, perform the measurements, and analyse the results.
Plastic surgeon H. Rakhorst and oncologic surgeon D. Evers, and other ZGT surgeons, will perform the surgical procedures, make clinical assessments of perfusion and supervise LSPI measurements.
W. Steenbergen and BMPI technician T. Knop will supervise technological aspects, monitor measurement procedures, and analysis of LSPI results. T. Knop will assemble the LSPI device and write documentation (Investigational Medical Device Dossier).

Explanation of the budget: we will hire a technical clinician for 12 months (44kE). Other costs are the medical ethical assessment (2.5 kE) and small instruments and materials (13.5 kE)

Synergy between technological an clinical partners (1+1=3)

There is a perfect and logical complementarity between the partners, in that the University of Twente has developed the method and the device, and will make it wireless. Furthermore, the University of Twente will be strongly involved in developing an application routine in ZGT. ZGT will host the patient measurements under the supervision of their medical staff in close collaboration with UTwente staff.

Expected (short term) milestones, results and output of the project (within 1-1½ years)
Milestone 1: introduction of a wireless handheld laser speckle perfusion imager in ZGT (TRL5-6) *Milestone 2*: conclusions of patient study, e.g. about feasibility, and prediction and prevention of complications. In view of the limited study size, these must be provisory conclusions. Surgeon reported usability of the device will be measured via interviews. *Outputs*: conference paper and journal paper on feasibility of peroperative handheld perfusion imaging for supporting free flap transplant breast surgery.
Long term collaboration of consortium, outcome and continuation of project
All essential stakeholders are present in the consortium. Furthermore this collaboration has been initiated by the clinicians, which emphasises the clinical need. This project but will lay the foundation for a larger study. *We regard a larger study justified if the results for our handheld system are in agreement with those of [3] in terms of a necrosis predictive tendency*. The larger study can be performed within a series of Technical Medicine internships.
Impact on healthcare
Annually in the Netherlands 4500-5000 woman undergo a mastectomy of which 30% undergo a breast reconstruction [5]. Approximately 1200 women will have a DIEP flap surgery, and we expect 120-150 reoperations per year. Specific long term effects of healthcare improvement: • Improved health thanks to better cosmetic result, reduced hospital stay and faster recovery; • Less outpatient clinic visits • Reduction in the number of extra operations (13 kE per operation incl. hospital stay) • Less intense and shorter need for home care, drugs, wound care materials • Faster return to work A commercial (non-handheld) laser speckle device costs approx. 50 kE is much more affordable than a fluorescence based system of >240kE [3] and the costs and disadvantages associated with repeated ICG (contrast agent) injection. Providing means to increase decision making during surgery, will therefore have a tremendous push in the right direction for patients and their families, surgeon, hospital, health insurance and society.
(Potential for) valorisation or implementation
Handheld LSPI has potential for applications where the device needs to be compact and fast, such as transplant surgeries, burn diagnosis (for which evidence of efficacy already exists), and potentially for dermatology (psoriasis). We are in touch with a company with an interest in valorisation. We will prepare a commercial feasibility study with the perspective of creating a spin-off company, e.g. based on the NWO Take Off grant scheme. A patent application will be filed soon to secure IP rights.

References (max. 5)

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2. E.H. Liu *et al.* Plastic and Reconstructive Surgery – Global Open **2019**, 7(4), e2060. DOI
3. J. Zötterman *et al.* Plastic and Reconstructive Surgery – Global Open **2020**, 8(1), e2529. DOI
4. C. To *et al.* Plastic and Reconstructive Surgery **2019**, 143(2), 287e-292e. DOI
5. Nabon Breast Cancer Audit (NBCA), Jaarverslag **2018**. URL

Budget plan	☒ Fill out the format and upload separately
See the budget form and the explanation at the end of the section ‘Plan of Action’.	