UdG
Facultat de Medicina

FINAL YEAR PROJECT

Clinical application of indocyanine green angiography in patients with early stage breast cancer undergoing mastectomy and reconstruction with autologous tissue

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I would also like to thank my family, who have always encouraged me throughout my academic and daily life, for their love and support.

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Acronyms and abbreviations

BCa Breast Cancer

BR Breast Reconstruction

BRAT Breast Reconstruction with Autologous Tissue

DIEP Deep Inferior Epigastric Perforator

EORTC European Organization for Research and Treatment of Cancer

ER Oestrogen Receptors

HER2 Human Epidermal growth factor Receptor 2

ICG Indocyanine Green

ICGA Indocyanine Green Angiography

ICO Institut Català d'Oncologia

IGAP Inferior Gluteal Artery Perforator

LD Latissimus Dorsi

PAP Profunda Artery Perforator

PgR Progesterone Receptors

QoL Quality of Life

SGAP Superior Gluteal Artery Perforator

SIEA Superficial Inferior Epigastric Artery

TDAP Thoracodorsal Artery Perforator

TMG Transverse Myocutaneus Gracilis

TNM Tumour-Node-Methastasis

TRAM Transverse Rectus Abdominis Musculocutaneous

Summary

Background Breast cancer is a major health concern worldwide. Patients diagnosed with early breast cancer undergo breast surgery as part of their treatment strategy. Mastectomy surgeries can result in a reduced quality of life and, for this reason, are often followed by immediate breast reconstruction. Many plastic surgeons consider the use of autologous tissue to be the gold standard. However, breast reconstruction with autologous tissue can result in significant complications such as tissue necrosis, which consequently requires revision surgeries and can worsen patient satisfaction and quality of life.

Objectives To compare the difference in the rate of necrosis after breast reconstruction with autologous tissue between a group of patients studied with indocyanine green angiography in the peri-operative period versus a control group undergoing conventional surgery. To evaluate the quality of life and patient satisfaction between the two groups.

Design and methods This study is a multicentre randomized single-blind clinical trial between two groups of patients. The experimental group will be studied intra-operatively with indocyanine green angiography, thus flap delineation will be guided by the images provided by this method. The control group will undergo surgery without prior imaging, and flap design will be based on theoretical vascular knowledge. Surgeons will complete a data collection form detailing the breast reconstruction and complications during follow-up and patients will be administered three quality of life questionnaires.

Study participants Both groups will be integrated by 225 patients between 25 and 65 years of age, suffering from early stage breast cancer and tributary to mastectomy and breast reconstruction with autologous tissue.

Statistical analysis We will perform a univariate, bivariate and multivariate analysis, taking a 95% confidence interval and a p-value $\leq$0.05 for clinical significance.

Keywords Indocyanine green; indocyanine green angiography; vascularisation; tissue necrosis; breast reconstruction; breast reconstruction with autologous tissue; breast cancer; quality of life.

1 Introduction

1.1 Overview of breast cancer

1.1.1 Epidemiology and clinical relevance

Breast Cancer (BCa) is a major public health concern due to its high prevalence, incidence, and mortality among women worldwide. In 2018 there were almost 2.1 million newly diagnosed cases of female BCa and approximately 630,000 women died from this cause. In the European Union the number of cases amounted to 404,920 with an annual incidence of 144.9/100,000 and a mortality rate of 32.9/100,000. In Spain, BCa is also the most frequent cancer among women, accounting for up to 29% of all new cancers in the female population; as well as being the leading cause of cancer-related mortality within this group (1, 2).

Mammographic screening allows to diagnose early stage BCa, however this translates into an increasing incidence since its introduction, and it continues to rise with the aging of the population (2).

Currently, most BCa are diagnosed at an early stage. Early stage BCa is defined as disease that is confined to the breast or has only spread to the axillary lymph nodes, without metastatic involvement. This definition is based on the fact that early stage BCa is considered curable, with a chance of survival of approximately 70-80%, and increasing over the years. In contrast, advanced disease is defined by metastatic involvement and is not considered curable. Therefore, the main goals of therapy are to prolong survival and control symptoms, while maintaining or improving Quality of Life (QoL) (3).

1.1.2 Classification

Breast tumours are generally classified according to their intrinsic subtype and Tumour-Node-Methastasis (TNM) stage, as these two classifications provide clinically relevant

information on prognosis and management (see annex A.1). For the intrinsic subtype classification, a pathologic evaluation of the primary tumour is required. This should include the following elements: presence or absence of ductal carcinoma in situ, histologic type, grade, immunohistochemistry, Oestrogen Receptors (ER), Progesterone Receptors (PgR), Human Epidermal growth factor Receptor 2 (HER2), and gene expression data. Proliferation markers, such as Ki-67 index which determines the percentage of positively stained tumour cells among the total number of malignant cells assessed, provide additional useful information. According to the forementioned items, the primary tumour can be classified as luminal A, luminal B, HER2-positive or basal-like (also known as triple negative) (2) (see Figure 1.1).

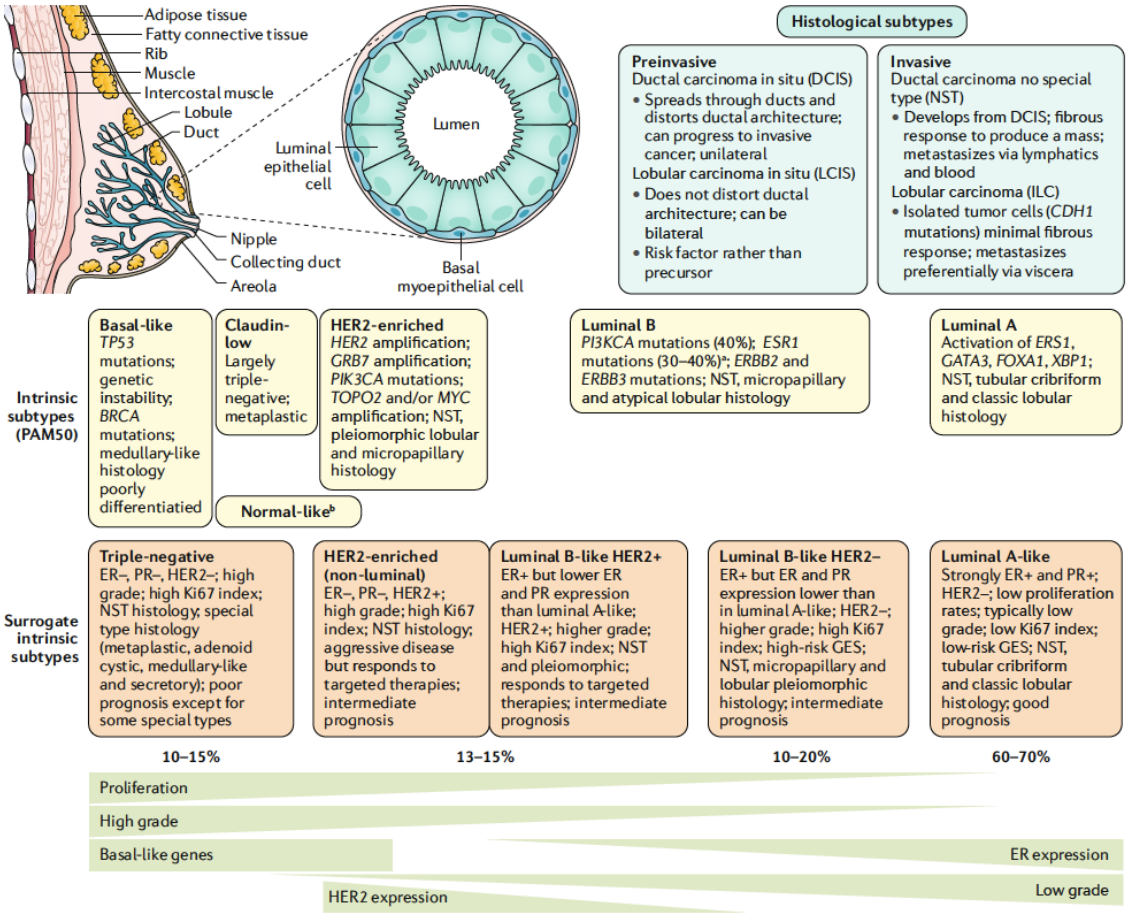

Figure 1.1: Breast cancer histological subtypes. The figure describes histological and molecular characteristics, which have an important implication for therapy. Histological subtypes (top right) are ductal carcinoma no special type (NST) and lobular carcinoma (ILC) with their respective preinvasive lesions ductal carcinoma in situ (DCIS)and lobular carcinoma in situ (LCIS). Intrinsic subtypes are based on histology and immunihistochemistry expression of key proteins: oestrogen receptors (ER), progesterone receptors (PgR) and proliferation marker Ki-67. Tumours expressing ER and/or PgR are termed "hormone receptor-positive"; tumours not expressing ER, PR and HER2 are called "triple-negative". The relative placement of the boxes in green (bottom) align with the characteristics of each tumour subtype. Taken from (3).
-, negative; +, positive; GES, gene expression signature; aESR1 mutations induced by aromatase inhibitor targeted therapy

TNM staging consists of an anatomical classification determined by the size of the tumour, the number of lymph nodes involved and the presence of distant metastases. This staging was first defined in 1959 by the American Joint Committee for Cancer (4) and is useful for BCa management as it defines 4 clinical stages for which different therapeutic approaches may be required.

1.1.3 Diagnosis and therapeutic management

When a breast tumour is suspected, the following tools help achieve a correct diagnostic and prognostic approach (1, 2):

- Anamnesis including personal and family medical history.
- Physical examination focusing on bi-imanual palpation of the breasts and axillary nodes.
- Laboratory tests including haemogram, liver and renal function, alkaline phosphatase and calcium.
- Bilateral mammography and ultrasound of the breasts and regional lymph nodes.
- Core needle biopsy guided with an imaging technique. This study should include evaluation of ER, PgR, HER2 and gene expression. Ki-67 index should also be included, although it is likely to find some inter-observer variability.
- Magnetic resonance imaging should be considered in cases with positive axillary nodes and occult primary breast tumour.
- Extension study with computed tomography scan, bone scan and/or positron emission tomography should be performed when stage III disease is detected or there are signs or symptoms suggestive of metastases.

BCa treatment consists of the combination of local and systemic therapies. The mainstays of treatment are surgery, radiotherapy, chemotherapy, endocrine therapy and molecular targeted therapies, which must however be accompanied by supportive measures. It is highly recommended that the treatment is carried out in specialised breast units or centres by a multidisciplinary and specialised team, as this tends to lead to better results in terms of disease-free survival, overall survival and functional and QoL outcomes. The multidisciplinary team should include medical and radiation oncologists, breast surgeons, breast radiologists, breast pathologists, plastic/reconstructive surgeons and breast nurses (2).

Surgery

The surgical treatment plan for BCa patients is based on multiple factors, such as tumour size and grade, margin extension, appearance on imaging techniques, and patient preference (5).

Breast-preserving surgery

This technique places an incision over the lump, thus minimizing the excision of uninvolved breast tissue. The tumour and a circumferential margin of normal breast parenchyma around it are removed in order to achieve wide negative margins, and the extent of the surgical resection is marked with radiopaque clips to facilitate radiotherapy planning and mammographic follow-up. The wound is then closed in two layers including deep parenchymal sutures and skin sutures (5) (see Figure 1.2).

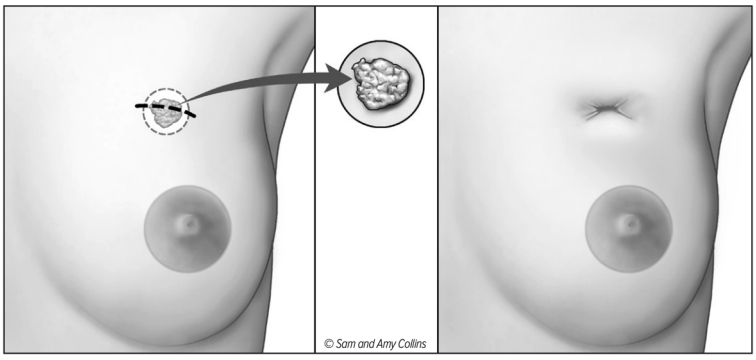

Figure 1.2: Breast-preserving surgery (left) and post-operative appearance (right). Taken from (6).

Mastectomy

BCa is rarely associated with a skin lesion, hence removal of the overlying breast skin is unnecessary in most patients (7). Skin-sparing mastectomy involves excision of all breast tissue with preservation of the skin envelope, allowing for a more natural contour of the reconstructed breast; although in patients with a tumour close to the skin surface, excision of the overlying skin may be considered. A variation of skin sparing-mastectomy is nipple-sparing, which preserves the nipple-areola complex and is considered in patients with tumours remote from the nipple. Nipple and skin-sparing mastectomies are performed by meticulous dissection of the subcutaneous fascia, in order to preserve the dermal blood

supply (see Figure 1.3). The mastectomy specimen is sent to pathology and studied peri-operatively to confirm the adequacy of the excision margins. In all patients undergoing a total mastectomy, immediate Breast Reconstruction (BR) is considered (5, 8).

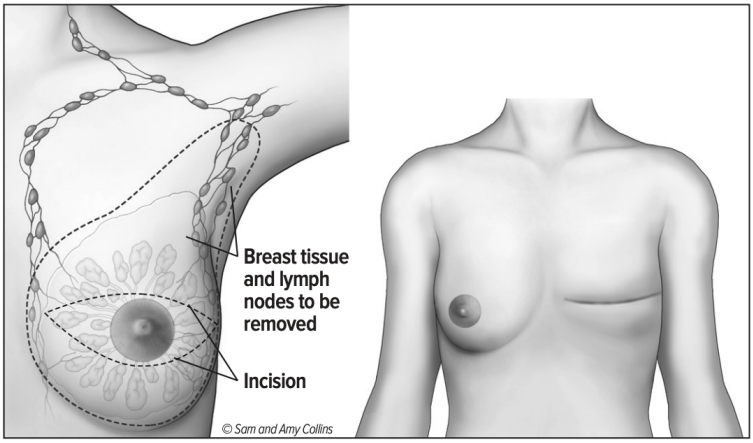

Figure 1.3: Mastectomy (left) and post-operative appearance (right). Taken from (6).

Breast-preserving surgery is similar to mastectomy in terms of patient survival and should be considered as the first treatment option in stages I and II, although the choice of surgical technique should always be individualized (5). However, mastectomy is still the gold standard in the following situations:

- Tumour multicentricity.
- Impossibility of achieving negative surgical margins after multiple resections.
- Small size of the breast in relation to the volume of the tumour.
- Contraindication for radiotherapy.

Sentinel lymph node biopsy is recommended in all patients with clinically negative axillary nodes (cN0) for evaluation of axillary node involvement. Patients with positive lymph nodes will undergo axillary lymph node resection (1, 5).

Adjuvant treatments

Adjuvant radiotherapy should be considered on an individualized basis and offered to all patients treated with breast-preserving surgery as well as those treated with mastectomy with close or biopsy-positive margins, T4 tumours, node-positive T3 tumours and/or $\geq$4 axillary nodes involved.

Systemic adjuvant treatments are often recommended in early stage BCa with the intention of reducing the rate of loco-regional or systemic relapse and mortality. As the variety of clinical subtypes of the primary tumour have different biological, molecular and clinical characteristics, the management of adjuvant treatment depends on the clinic-pathologic classification (1) (see Figure 1.4). Systemic treatment options include chemotherapy, endocrine therapy and molecular targeted therapies.

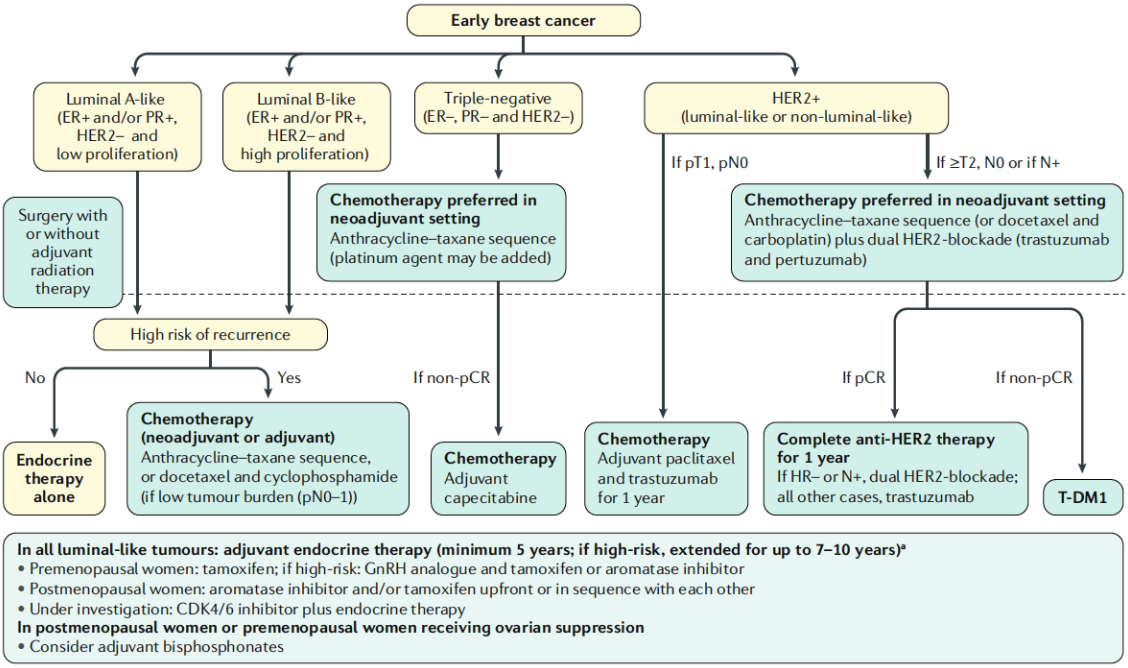

Figure 1.4: Treatment algorithm for early stage breast cancer based on tumour burden and subtype. Taken from (3).
-, negative; +, positive; GnRH, gonadotropin-releasing hormone; HR, hormone receptor; p, pathological; PR, progesterone receptor; N, node status; T, tumour grade; T-DM1, ado-trastuzumab emtansine.

1.2 Breast reconstruction

Mastectomy is for most women a mutilating and deforming procedure which consequently affects their self-image and QoL. Breasts are a powerful symbol of femininity, and their loss can lead to significant psychological consequences.

BR is available today to almost any woman undergoing partial or total mastectomy and can solve some of the complications derived from the surgery. A woman with a successful reconstruction can wear almost any type of clothing and return to a productive and active life. Therefore, the goal of BR is to return the patient to a state as close as possible to

that prior to the mastectomy, seeking a natural shape, smoothness, feel, movement and symmetry to resemble a normal breast. In order to achieve the illusion of normality, nipple and areola reconstruction should also be offered.

The techniques used for BR consist of prosthetic implants, autologous tissue flaps, or combinations of both (5). Ideal candidates for reconstruction are young, healthy, non-obese women, yet older patients may also be candidates depending on their health status and motivation (5, 7).

There is currently a wide variety of techniques for post-mastectomy BR and the decision of the method used depends on the patient, the surgical team and the environment in which the reconstruction is performed. Therefore, plastic surgeons should be familiar with the advantages and disadvantages of each technique and not rigidly commit to one of them (7).

1.2.1 Implant-based breast reconstruction

Expander-implant techniques have been an important method for BR. This technique can be used in patients who have not been previously subjected to radiation and generally consists of a two-step procedure.

The first step involves the insertion of a deflated implant, known as expander, under the mastectomy skin, which is progressively inflated with the aim of stretching the dimensions of the skin envelope and preventing wound contraction after mastectomy (see Figure 1.5). This step can be performed immediately after the mastectomy, although if it is delayed it is preferable to perform the surgery after a minimum of 3 months and once the adjuvant treatments are completed.

The second step consists of replacing the expander with a medium-sized, anatomically shaped silicone implant and making any pertinent adjustments of the contralateral breast.

The advantages of BR with implants include minimal morbidity, reduced surgical time and the absence of donor site morbidity. However, the procedure is not exempt from complications such as implant deflation or malfunction, capsular contracture, reactions

from the implant, visible contour irregularities among others. In addition, a prosthesis will never look as natural as a reconstruction using the patient's own tissue (5, 9).

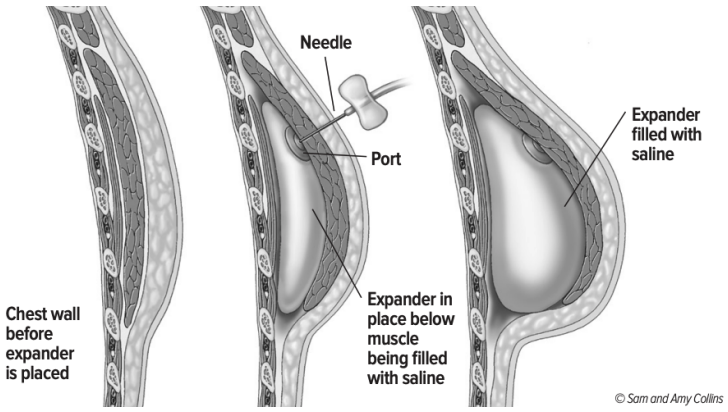

Figure 1.5: Placement of a tissue expander. Taken from (6).

1.2.2 Breast reconstruction with autologous tissue

The use of autologous tissue for BR after mastectomy is considered by many plastic surgeons to be the gold standard, providing women with optimal results and a remarkable QoL without the need for prosthetic materials (10–13).

Pedicled flaps are defined as those in which skin, fat and muscle are transferred over a vascularised pedicle containing a minimum of one artery and one vein that supply blood flow. With the evolution of plastic surgery techniques and the ability to perform microvascular surgery, free tissue transfer allows the design of flaps from remote areas to the breast that can be anastomosed to the internal mammary or thoracodorsal artery and vein or others with similar characteristics. The latter are currently on the rise and perforator-based flaps are considered the first choice for Breast Reconstruction with Autologous Tissue (BRAT).

A variety of flaps obtained from different donor sites have been described, including the following.

Transverse Rectus Abdominis Musculocutaneous (TRAM) flap

The TRAM flap procedure uses skin and subcutaneous tissue from the lower abdominal wall which is transferred to the thorax by tunneling under the skin of the upper abdomen, attached to the rectus abdominis muscle that acts as a blood supply carrier. It is therefore

a pedicled flap which vascularisation relies on the superior epigastric artery and vein.

There is also the possibility of performing a free TRAM flap, which uses the same island of skin from the lower abdominal territory, but requires less sacrifice of the rectus abdominis muscle (see Figure 1.6). Unlike the pedicled TRAM flap, the vascularisation of the free TRAM depends on the lower epigastric artery and vein (5, 6, 10).

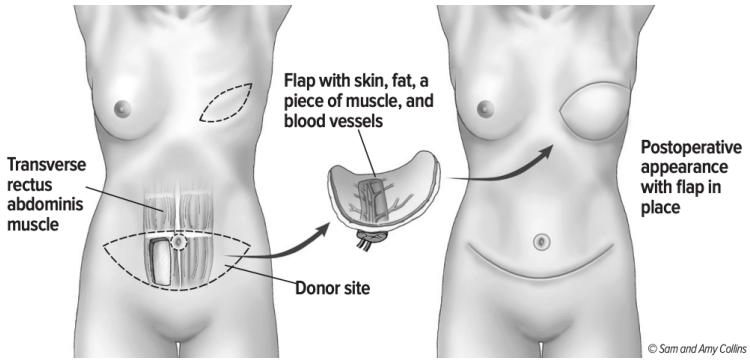

Figure 1.6: Free Transverse Rectus Abdominis Musculocutaneous (TRAM) flap procedure and post-operative appearance. Taken from (6).

Deep Inferior Epigastric Perforator (DIEP) flap

The DIEP flap is a variation of the TRAM flap in which the same palette of skin and fat is transferred from the lower abdomen to the breast, but without the involvement of the rectus abdominis muscle (see Figure 1.7). It consists of a perforator-based flap that relies on the perforator branches of the deep inferior epigastric artery and vein. These vessels are carefully dissected from the rectus abdominis muscle via myotomy, without removing the muscle or fascia, resulting in less injury to the abdominal wall (5, 6, 10).

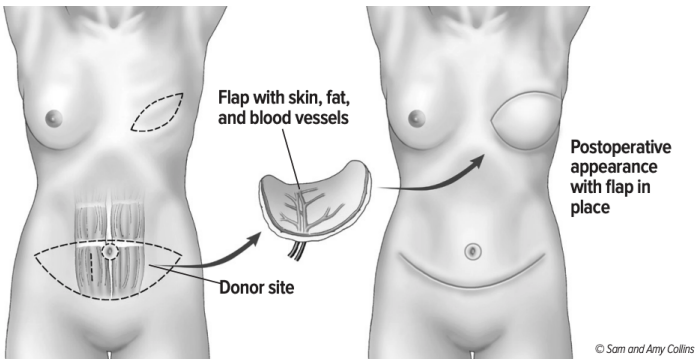

Figure 1.7: Deep Inferior Epigastric Perforator (DIEP) flap procedure and post-operative appearance. Taken from (6).

Superficial Inferior Epigastric Artery (SIEA) flap

The SIEA flap is an alternative option sourced from the abdominal wall as well, consisting of a free adipocutaneous flap perfused by a direct perforator. Its vascularisation is based on the superficial inferior epigastric artery and vein, which gives it the advantage of not requiring a fasciotomy or myotomy, thereby not altering the integrity of the abdominal wall (5, 10).

Latissimus Dorsi (LD) flap

The LD flap uses skin and subcutaneous tissue from the upper back and part or the entire latissimus dorsi muscle (see Figure 1.8). It is a pedicled flap in which the vascularisation is dependent on the thoracodorsal artery and vein. This technique is usually sufficient for small breast volumes, but when the reconstruction volume is larger it may require the placement of a prosthesis or a fat graft to add thickness to the breast (5, 6, 10).

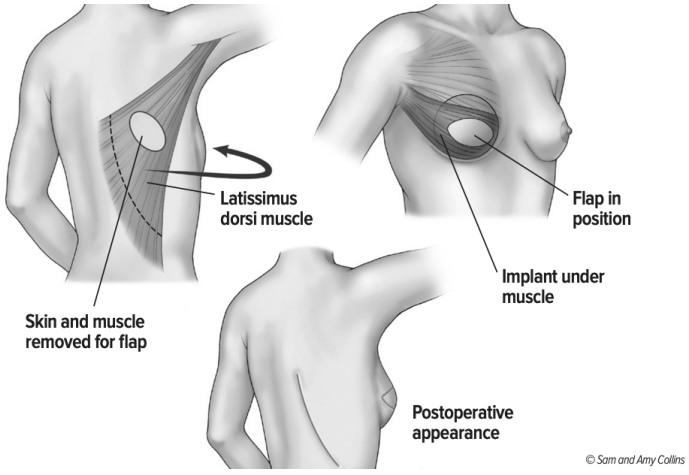

Figure 1.8: Latissimus Dorsi (LD) flap procedure and post-operative appearance. Taken from (6).

Thoracodorsal Artery Perforator (TDAP) flap

The TDAP flap is primarily an option for partial BR, performed as a pedicled flap for laterally-based breast defects. However, it can also be used for total reconstruction in petite women with small volume breasts. As with the LD flap, additional procedures may be used to achieve adequate volume and thickness (10).

Superior Gluteal Artery Perforator (SGAP) and Inferior Gluteal Artery Perforator (IGAP) flaps

GAP flaps use skin tissue from either the upper or lower gluteal region (see Figure 1.9). Depending on the artery and vein that provide blood supply they are divided into SGAP and IGAP, which receive its vascularisation from the superior and inferior gluteal artery respectively (6, 10).

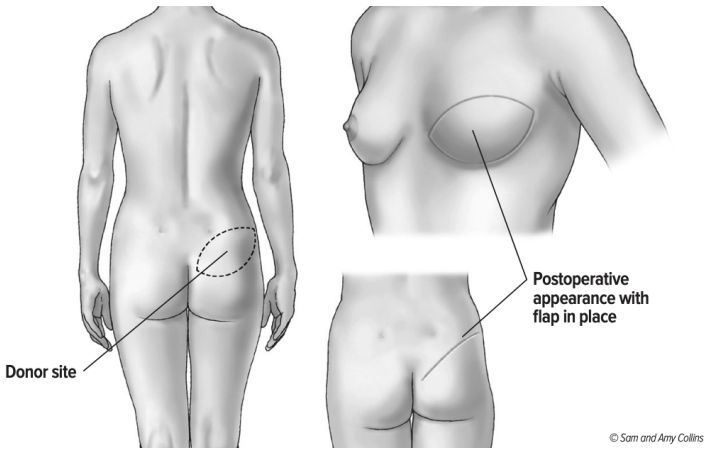

Figure 1.9: Superior Gluteal Artery Perforator (SGAP) flap procedure and post-operative appearance. Taken from (6).

Transverse Myocutaneus Gracilis (TMG) flaps

TMG flaps are composed of tissue from the thigh and gracilis muscle (see Figure 1.10). The blood supply is provided by the gracilis artery and vein, with the possibility of supplementing it with the saphenous vein for additional venous drainage (6, 10).

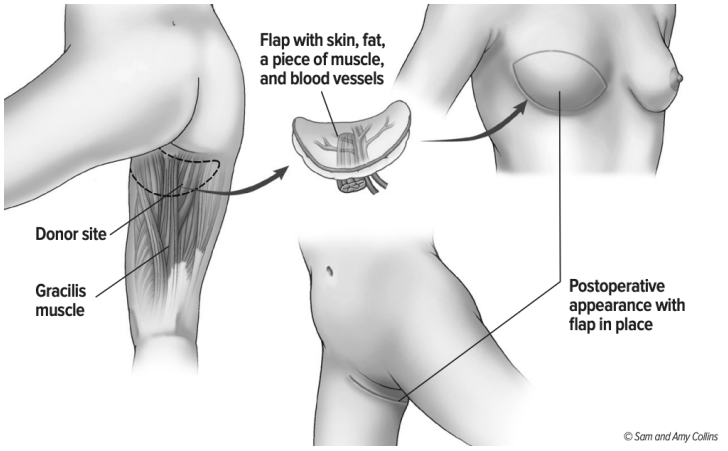

Figure 1.10: Transverse Myocutaneous Gracilis (TMG) flap procedure and post-operative appearance. Taken from (6).

Profunda Artery Perforator (PAP) flap

The PAP flap is based on the deep femoral artery and vein and involves soft tissue from the posterior compartment of the thigh (10).

Table 1.1 shows the vascularisation of the reconstructive flaps for potential use.

Table 1.1: Principal flaps and their respective vascularisation

Type	Flap	Blood supply	Technique
Pedicled flaps	Pedicled TRAM	Superior epigastric artery	Elevation of the flap, tunneling to mastectomy site and insetting and shaping to breast position.
	LD	Thoracodorsal artery	
	TDAP	Thoracodorsal artery	
Free flaps	Free TRAM	Lower epigastric artery	Localization of the best suitable perforator, harvesting of the flap, microvascular anastomosis to recipient vessels, insetting and shaping to breast position.
	DIEP	Deep inferior epigastric artery	
	SIEA	Superficial inferior epigastric artery	
	SGAP	Superior gluteal artery	
	IGAP	Inferior gluteal artery	
	TMG	Gracilis artery	
	PAP	Deep femoral artery	

TRAM, transverse rectus abdominis musculocutaneous; LD, latissimus dorsi; TDAP, thoracodorsal artery perforator; DIEP, deep inferior epigastric perforator; SIEA, superficial inferior epigastric artery; SGAP, superior gluteal artery perforator; IGAP, inferior gluteal artery perforator; TMG, transverse musculocutaneous gracilis; PAP, profunda artery perforator.

1.2.3 Flap design and vascularisation

In patients who undergo BRAT, adequate blood supply to the flap tissue is critical (5). The term "angiosome" refers to a vascular territory for a specific artery and vein. For flap planning, fundamental knowledge of angiosomes allows for proper skin island design. Often, Doppler ultrasound in combination with computed tomography or magnetic resonance angiography are performed on tissues with potential to be used as donor for reconstruction with the aim of identifying the location of perforator vessels (10, 12, 14).

To improve patient outcomes and for the design and delineation of lower abdominal flaps, Hartrampf perfusion zones have been described based on the knowledge of regional vascular anatomy, thus defining four perfusion zones which can vary depending on the location of the perforator vessel, as shown in Figure 1.11.

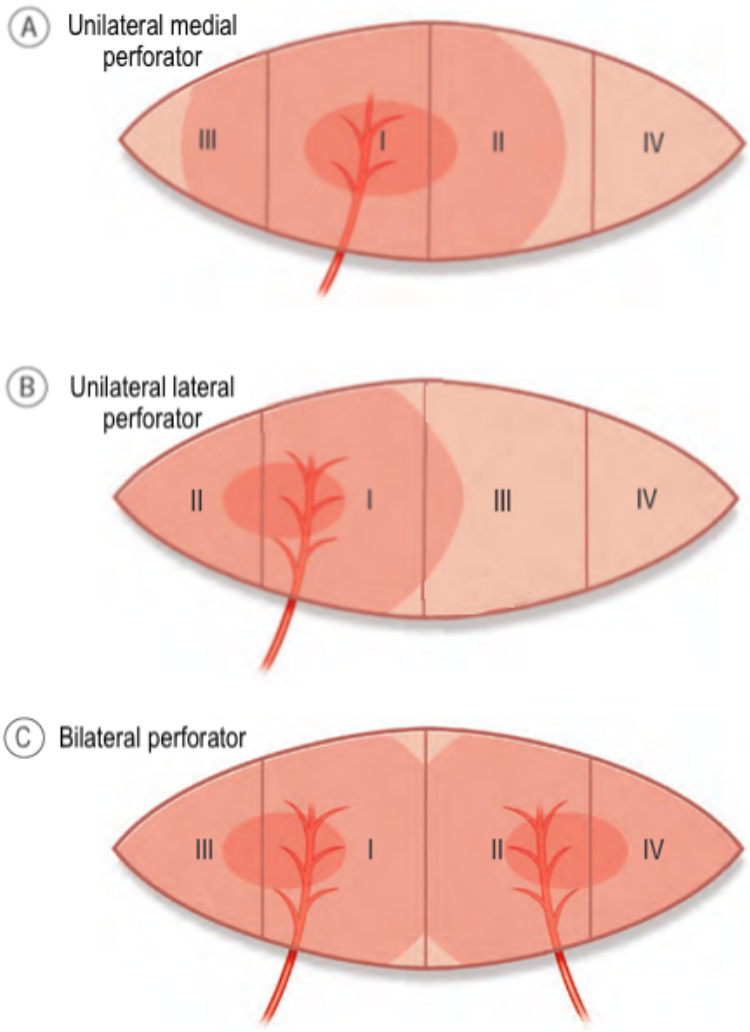

Figure 1.11: Hartrampf perfusion zones in a standard eliptical design of a lower abdominal flap with (A) unilateral medial perforator, (B) unilateral lateral perforator and (C) bilateral perforators. Adapted from (9).

Hence, zone 1 is defined as the location of the flap with the best perfusion, while this decreases towards zones 2 and 3. Zone 4 represents the zone with poorest irrigation and is usually insufficiently perfused. Consequently, zones 1 and 2 are generally preserved, while part of zone 3 and the entire zone 4 are normally discarded (11).

1.2.4 Advantages of immediate breast reconstruction with autologous tissue

Immediate reconstruction usually offers a better cosmetic result compared to delayed reconstruction and has other advantages such as greater efficiency, cost-effectiveness and convenience.

In addition, autologous tissue offers many advantages that implant-based reconstruction cannot, such as longevity and the ability to be predictable and successful in complex cases as prior radiation on the breast or device infection. It also has the added benefit of a more aesthetically pleasing result of both the reconstructed breast and the donor site. Autologous adipose tissue has a consistency very similar to mature breast tissue, which allows the reconstructed breast to behave more naturally. For example, when the patient lies down the breast falls to one side, has a natural movement when the patient runs or walks and has the tendency to become more ptosic over time and to change along with the natural breast if the patient gains or loses weight. Unlike reconstruction with implants, BRAT tends to improve over the years; scars tend to soften and fade, sensation improves and tissue firmness resolves. After the first year of follow-up, additional surgery is rarely needed for patients reconstructed with autologous tissue. Therefore, although BR with implants has low initial costs, the long-term costs are in favor of BRAT (5, 7, 10).

Figure 1.12 shows a pre and post-operative photograph of the same patient, who underwent replacement of an implant for a DIEP flap.

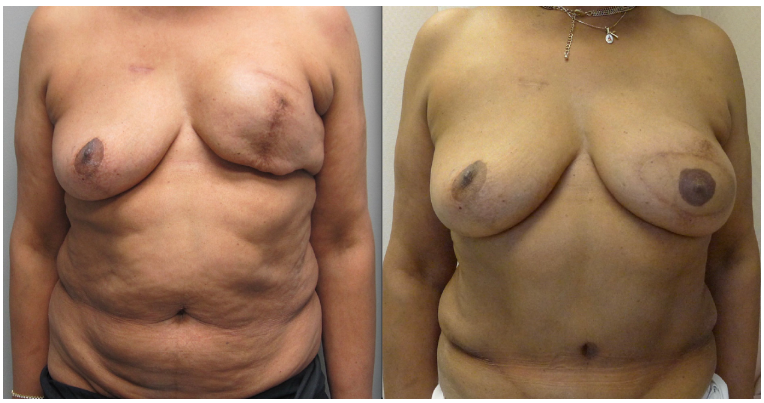

Figure 1.12: Pre-operative photograph of a woman with left breast cancer following prosthetic reconstruction and radiation therapy (left) and post-operative photography following removal of the implant and replacement with a left DIEP flap in the same patient. Taken from (10).

Given the numerous advantages outlined above, immediate reconstruction is the preferred option for almost all patients with early stage tumours who are certain they want to undergo reconstructive surgery, and the use of autologous tissue has become established among patients with skin-sparring mastectomy (5, 7, 10).

1.2.5 Complications associated to breast reconstruction with autologous tissue

The incidence of complications associated with BR is not a negligible issue, as almost half of the patients face at least one complication of any degree during the post-operative period (15). Besides, it has been described that patients who have suffered surgical complications have a significantly worse QoL compared to those who have not (16). Complications resulting from BRAT include:

- Wound complications, including infection, seroma, delayed healing, or haematoma.
- Aesthetic complications, such as breast asymmetry, contour irregularities, contracture, volume loss, poor wound healing and scarring.
- Vascular complications, comprising total flap necrosis, venous distress, partial flap necrosis and fat necrosis.
- Donor site morbidities, including seroma, haematoma, infection, delayed healing, contour deformities or abdominal hernia (the latter only associated with lower abdominal flaps).

Flap necrosis of any degree is a serious complication, as it leads to re-intervention of patients for revision surgery and/or for a second BR with a prosthesis or a new flap (see Figure 1.13). Partial flap necrosis is often caused by poor vascularisation of perforators relative to flap size, and rates can be as high as 20% of procedures using clinical evaluation alone (5, 9, 13, 15, 17).

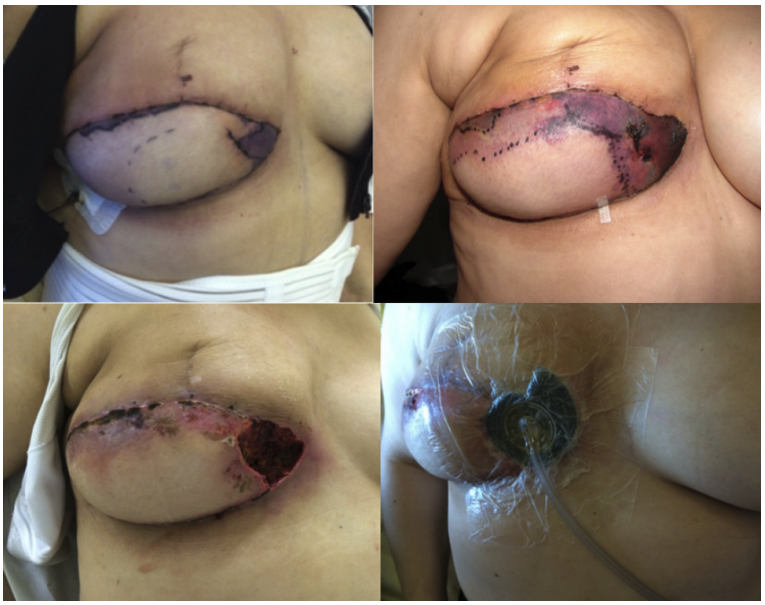

Figure 1.13: Young unsatisfied patient with immediate implant-based reconstruction and radiation therapy. Conversion to autologous tissue respecting patient's wishes: a DIEP flap was performed without any per-operative complication. A few days later, partial venous distress occurred and evolved to partial tissue necrosis, which required trimming and healing. Taken from (13).

1.3 Indocyanine green and fluorescence guided surgery

1.3.1 Features and performance

Indocyanine Green (ICG) is a water-soluble substance, reconstituted in an aqueous solution at pH 6.5 for intravenous injection, that binds to blood proteins and emits energy in the near-infrared (wavelengths between 750 and 810 nm). This iodinated dye has a half-life of 3 to 5 minutes and an excellent safety profile, with negligible adverse effects compared to its benefits, allowing for rapid re-dosing if needed for multiple intra-operative studies. It has a hepatic clearance.

Indocyanine Green Angiography (ICGA) is a form of intra-operative imaging that provides real-time assessment of tissue perfusion and proves to be a minimally invasive, repeatable, standardized, easy-to-interpret, accurate and cost-effective technique. Identifying poorly vascularised skin during surgery can save patients, surgeons and hospitals a considerable amount of complications, time, money and resources. For the angiography, 10 mg (4 mL) bolus of ICG are injected, and images appear within 8 to 10 seconds if

administered via a peripheral line or 5 seconds if administered via a central line, with a total duration of approximately 60 seconds.

Images are captured by a thermal imaging infrared camera to a depth of 3 mm into the tissue and displayed as a grayscale representation in real time. The infrared camera can be a stand-alone device or integrated into a microsurgical microscope. Software analysis allows quantification of relative perfusion values, which requires an additional 2 to 4 minutes. Once the images are stored, it is also possible to convert them from grayscale to a heat map showing "hot" and "cold" spots that correlate with well and poorly perfused areas, respectively (8, 17–21) (see Figure 1.14).

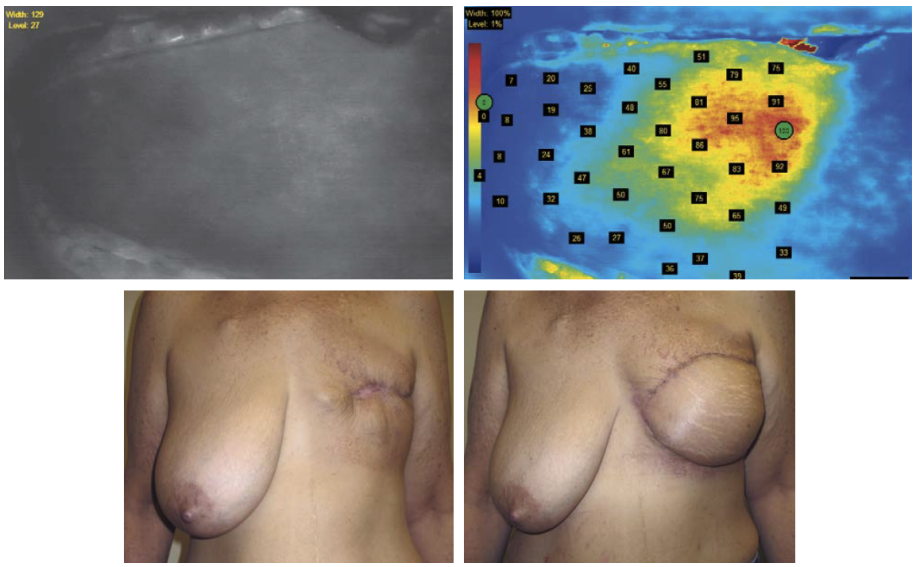

Figure 1.14: Intra-operative indocyanine green angiography revealed two large perforators (3 mm and 2 mm respectively) and a decision was made to perform a DIEP flap based on these two vessels (top). A successful outcome was achieved with anastomosis to the left internal mammary vessels (bottom). Taken from (20).

1.3.2 Clinical applications

ICGA has been a useful tool for the past 50 years, commonly used for the assessment of cardiovascular function, hepatic clearance and retinal angiography, and is recently being extended to other fields such as plastic, cardiac, vascular, general or neurosurgery.

The widespread use of autologous techniques for BR has led to the need for reliable assessment of flap perfusion to allow incorporation of the most perfused portions of the flap and to avoid delayed healing and other complications. Since 2007, this technology

has been used for the evaluation of anastomosis and flap viability of both mastectomy skin flaps and tissue flaps, as well as for the design of large skin paddles (see Figure 1.15). ICGA has been found to have a sensitivity of up to 90% for predicting necrosis of mastectomy flaps, but despite this, there have been no large-scale studies demonstrating its role in improving overall outcomes (19).

Figure 1.15: The video demonstrates the use of indocyanine green angiography for assessment of mastectomy skin flaps and a muscle-sparring latissimus dorsi flap. Taken from (8).

Current applications of ICG in the field of plastic surgery include tools for staging and treatment of melanoma and BCa for example (18, 20, 21):

- Lymphatic pathway localization, used for sentinel lymph node mapping and for staging and treatment of secondary chronic lymphoedema.
- Post-operative follow-up of patients and prediction of patient outcomes.
- Evaluation of the viability of skin-sparing mastectomy flaps prior to immediate reconstruction.
- Evaluation of perfusion of soft tissue flaps used for reconstruction.
- Assessment of the perfusion rate of multiple perforators to aid in the selection of the vessel that provides the most rapid and extensive inflow to the flap.

2 Justification

Breast Cancer (BCa) is a major health concern with high prevalence, incidence and mortality rates (1–3), in which one of the most important pillars of treatment is surgery. Thousands of women undergo mastectomy and Breast Reconstruction (BR) each year, and numerous studies have found that patients who experience surgical complications have significantly worse Quality of Life (QoL) as well as other negative psychosocial outcomes (16). Thus, the incidence of complications and patient satisfaction with the surgical team are important issues to be concerned about.

In the field of reconstructive surgery one of the main considerations is the state of vascularisation of the surgical bed, which is much more relevant when the reconstruction technique uses the patient's autologous tissue (5). Therefore, adequate vascularisation of both the mastectomy flap and the reconstruction flap is necessary to obtain a satisfactory result. Indocyanine Green Angiography (ICGA) is a technique that facilitates real-time visualisation of the vascularisation. This technique has a sensitivity of 90% and is minimally invasive, safe, accurate and cost-effective, making it a potential tool for defining perfusion zones and delineating flaps (19).

The aim of this study is to compare the difference between patients with BCa who are candidates for mastectomy and Breast Reconstruction with Autologous Tissue (BRAT) studied with ICGA and a control group undergoing conventional surgery without prior use of this technique. A few articles have been published determining whether ICGA could help reduce the rate of necrosis after BR surgery. However, many of them have focused on the study of mastectomy flap necrosis and there is still a lack of statistically relevant data in the literature to justify its use and validate it as a safe diagnostic method (17, 22). Unlike previously published papers, we will only include patients undergoing BRAT and evaluate the vascularisation of reconstruction flaps in addition to mastectomy flaps. Furthermore, this work will be designed as a randomized clinical trial and will include a larger sample, with the aim of minimizing bias.

This will be a pioneering study in Catalonia, which will facilitate the extrapolation of the results to Catalan hospitals and help to introduce ICGA for BRAT in this region.

3 | Hypothesis

1. Patients treated with mastectomy and reconstruction with autologous tissue after application of indocyanine green angiography peri-operatively have better results in terms of tissue necrosis compared to those treated with conventional surgical methods.

2. Patients treated with mastectomy and reconstruction with autologous tissue after application of indocyanine green angiography peri-operatively are generally more satisfied with their experience compared to those treated with conventional surgical methods.

4 | Objectives

1. To compare the differences in clinical outcomes between a group of breast cancer patients candidates for mastectomy and reconstruction with autologous tissue studied with indocyanine green angiography in the peri-operative period in contrast to a control group treated with conventional surgical methods; comparing the occurrence of tissue necrosis as the primary outcome.

2. To evaluate the quality of life and patient satisfaction and experience using the validated QLQ-C30, QLQ-BR23 and QLQ-BRECON23 questionnaires developed by the European Organization for Research and Treatment of Cancer (23).

5 | Material and methods

5.1 Design

This will be an analytical single-blind study with a clinical trial design. We will select a sample (see 5.2 and 5.3) and distribute it into two groups, one that will receive a dosage of Indocyanine Green (ICG) peri-operatively, and a control group which will undergo mastectomy and Breast Reconstruction with Autologous Tissue (BRAT) without prior use of ICG. Subjects will be randomly distributed into the experimental and control groups. For the experimental group, doses of 4 mL per image of intravenous ICG will be administered during surgery, and flap vascularisation will be studied in real time using an infrared machine. Surgical planning of the Breast Reconstruction (BR) will be based on the vascularisation observed with the dye, so the surgical team will define the perfusion zones and delineate the flap used for reconstruction. The reconstruction flap used for the surgery will be decided by the surgical team among Deep Inferior Epigastric Perforator (DIEP), Transverse Myocutaneus Gracilis (TMG) or Profunda Artery Perforator (PAP) depending on the patient's constitution and wishes. Patients in the control group, in contrast, will undergo mastectomy and reconstruction using conventional theory-based planning without precise knowledge of the exact distribution of the vascular bed.

Both groups will be followed up during their hospitalisation, 10 days after surgery and at 1, 3, 6 and 12 months. During follow-up, short and long-term complications of the reconstruction flap will be evaluated and reported, with a primary focus on any degree of tissue necrosis. Surgeons will fill a data collection form (see annex A.4) in which they will detail the surgical procedure and complications for each patient. In addition, the questionnaires QLQ-C30, QLQ-BR23 and QLQ-BRECON23, developed by the European Organization for Research and Treatment of Cancer (EORTC) (see annex A.5) (23), will be distributed to all the patients at the 12-month follow-up mark in order to register patient satisfaction with the BR and Quality of Life (QoL). The necrosis rate and the results obtained from the questionnaires of each group will be evaluated and compared by the research team.

5.2 Study population

The population of this study will be based on patients between 25 and 65 years of age, suffering from early stage Breast Cancer (BCa) in Catalonia.

Inclusion criteria:

- Women tributary to mastectomy and BRAT.
- Women receiving neoadjuvant treatments and/or adjuvant radiotherapy.
- Body mass index <30.
- Signed consent form.

Exclusion criteria:

- Medically significant comorbidities.
- Short life expectancy.
- Contraindication to surgery.
- Insufficient autologous tissue to be used for reconstruction.
- Iodine allergy.

5.3 Sample

The sample selection will be carried out in the following hospitals: Hospital Universitari Dr. Josep Trueta (Girona), Hospital Universitari de Bellvitge (Hospitalet de Llobregat) and Hospital Germans Trias i Pujol (Badalona), using the patient lists of the Institut Català d'Oncologia (ICO) as a sampling frame. The sample selection will be probabilistic and aleatory, expecting a response rate of more than 70% of the patients. Patients with a recent diagnosis of BCa who meet the inclusion criteria will be considered eligible to participate in the study.

Sample size

The sample size has been calculated with the help of the GRANMO sample size and power calculator (version 7.12). Considering the literature published so far, the risk of

necrosis is assumed to be 9% in the group studied with Indocyanine Green Angiography (ICGA) and 18% in the group treated with a theory-based BR.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 225 subjects in the experimental group and 225 in the control group are necessary to find a statistically significant difference in proportion, which is expected to be 0.09 in group 1 and 0.18 in group 2. A dropout rate of 2% has been predicted.

Estimated time for sample recruitment

According to the data provided by the plastic surgeons of the three hospitals included, the approximate number of patients per year who would be eligible for the study are:

- 15 to 20 for Hospital Universitari Dr. Josep Trueta.
- 25 to 35 for Hospital Germans Trias i Pujol.
- 110 for Hospital Universitari de Bellvitge.

Considering these numbers, to reach our sample size the estimated time for recruitment of 450 patients is about 3 years.

5.4 Variables

Study variable

Our study variable is the application of ICGA for the assessment of flap vascularity for BRAT in order to properly design and delineate the most perfused skin areas of the reconstruction flaps.

Outcome variable

Our outcome variables are the occurrence of tissue necrosis as a complication of reconstructive surgery, and patient satisfaction and QoL after surgical treatment.

The independent, dependent and covariate variables are described in the table 5.1.

Table 5.1: Description of variables included in the study.

	Variable	**Type**	**Category of values**	**Tests applied**
Independent	ICGA study	Dichotomic qualitative	Yes No	
Dependent	Rate of necrosis	Categorical qualitative	Total flap necrosis Partial flap necrosis Fat necrosis No occurrence of necrosis	Clinical assessment
	Patient satisfaction and QoL	Categorical qualitative	Scoring from 0 to 100	EORTC questionnaires (23)
Covariates	Age	Discrete quantitative	Numerical (years) from 25 to 65	
	BCa stage	Categorical qualitative	I IIA IIB IIIA	Staging tables
	Neoadjuvant and adjuvant treatments	Categorical qualitative	Neoadjuvant treatments Adjuvant treatments Both treatments	
	Body mass index	Continuous quantitative	Numerical $(weight[kg]/height[m]^2)$	
	Smoking habit	Dichotomic quantitative	Yes No	
	Used technique for BRAT	Categorical qualitative	DIEP TMG PAP	Clinical assessment

ICGA, indocyanine green angiography; QoL, quality of life; EORTC, European Organization for Research and Treatment of Cancer; BCa, breast cancer; BRAT, breast reconstruction with autologous tissue; DIEP, deep inferior epigastric perforator; TMG, transverse myocutaneous gracilis; PAP, profunda artery perforator.

5.5 Measuring instruments

In order to measure patient satisfaction and QoL, they will be administered the questionnaires QLQ-C30, QLQ-BR23 and QLQ-BRECON23, developed and provided by the EORTC (23). These three questionnaires are designed and validated to be used together in women diagnosed and treated from BCa after mastectomy, and undergoing all types of BR. Their interpretation is based on individual item scales and measures ranging from 0 to 100, where a high score for each scale represents a higher response level. For example, a high score for the symptom scales represents a high level of symptomatology or problems, whereas a high score for the functional scales represents a high level of functioning or satisfaction. The scales included in these questionnaires are the following:

QLQ-C30

- Global health status/ QoL.
- Functional scales.
- Symptom scales.

QLQ-BR23

- Symptom scales.
- Functional scales.

QLQ-BRECON23

- Symptom scales.
- Functional scales.

For more information on scoring, see the scoring manuals in the annex A.5.

5.6 Statistical analysis

Our research team, consisting of the principal investigators and a professional statistician, will perform the statistical analysis using Statistical Package for the Social Sciences (SPSS) software (version 1.0.0.1406). A 95% confidence interval will be taken, and the results will be considered statistically significant when the p-value is ≤ 0.05.

5.6.1 Univariate analysis

First, a descriptive analysis of the variables will be performed and included in a table. Qualitative variables will be calculated as percentages and rates, while quantitative variables will be calculated as mean and standard deviation, with the assumption that they follow a Gaussian distribution.

5.6.2 Bivariate analysis

After the univariate analysis, to determine whether there is a correlation between the study and outcome variables, the chi-square test of independence will be used for each dependent variable, thus relating:

- Flap necrosis rate comparing the standard flap techniques to the study of flap vascularisation with ICGA.
- Percentage of patient satisfaction and QoL comparing patients undergoing standard flap techniques to the patients undergoing study of flap vascularisation with ICGA.

5.6.3 Multivariate analysis

A multivariate multiple regression analysis will be performed with the aim of studying whether the covariates act as statistically significant factors for our study.

6 | Ethical aspects

This study will be conducted in compliance with the latest revision of the Declaration of Helsinki - Medical Research Involving Human Subjects (2013).

Before the start of the research, this protocol will be submitted to the ethics committee of the three hospitals involved. The project will begin once approval has been received from all committees.

The ethical principles of Beauchamp and Childress will be respected as follows:

- Autonomy: all the participants will be informed about the surgical procedure and the objectives of the research in a clear and understandable way. Additionally, they will be given a written information sheet and a consent form and only those who have signed it will be included in the study. These documents (see annex A.2) will be submitted in advance to the ethics committee for formal approval.
- Non-maleficence: patients who meet the exclusion criteria will be excluded from the project, as they would not benefit from the study procedure.
- Beneficence: the inclusion criteria have been described with the intention of including the patients who will benefit most from the study procedure.
- Justice: all the patients who meet the inclusion and exclusion criteria and who have signed the consent form will be considered equally for participation in the study, ensuring fairness and equality among individuals.

The confidentiality of the participants will be preserved by anonymizing the data collected. All data obtained will be entered and processed in a database to which only the research team will have access.

This study will obey the following laws:

- "Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica."
- "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales."

7 | Study limitations

The design of the present study may have some limitations, including:

- This research attempts to collect a random and probabilistic sample, but only includes patients from the Institut Català d'Oncologia (ICO) databases, as these are contemplated as our sampling frame. Only four hospitals in Catalonia work alongside ICO centers and out of these four, only three of them (those included in the study) perform Breast Reconstruction with Autologous Tissue (BRAT) surgeries. This may generate a sampling bias. To minimize this bias, the sample selection could have been equally probabilistic and random but considering the databases of all the Catalan hospitals with experience in BRAT. However, the proposed solution would increase the budget and complexity of the research.

- For the same reason stated above, by including only three centers, the estimated time for patient recruitment is 3 full years, making the whole project's expected duration five years. If we had included more hospitals, this time would have been shorter.

- A possible observer bias should be considered, as 19 different plastic surgeons will perform the reconstructive surgeries and collect the data. In addition, there is the possibility of errors in data collection and form filling.

- The measurement instruments for the evaluation of the secondary objective of this study are the European Organization for Research and Treatment of Cancer (EORTC) questionnaires (23), the basis of which are the subjective perception of the patients. This may lead to unreliable data.

8 | Working plan and chronology

This study will be carried out by a research team composed of the following:

- General coordinators: Clàudia Brunet and Pau Bosacoma will direct all phases of the research and will pool the data provided by the hospitals.
- Center coordinator: the chief of the plastic surgery service or chief of the breast pathology unit of each center included will coordinate patient recruitment, surgeries and data collection at their center.
- ICO coordinator: there will be a member of the ICO who will be in charge of the management of the patient database in the recruitment phase.
- Professional statistician: a professional statistician will be hired in phase 4 who will be in charge of data collection and statistical analysis.

The estimated time of the study will be 5 years and will include 5 main phases.

Phase 1: Protocol

November 2021 to March 2022. Tasks included:

- Monthly meetings of the general coordinators.
- Literature and background review.
- Drafting and presentation of the protocol.
- Presentation to the ethics committee of the three hospitals involved.
- Possible modifications to the protocol.
- Acceptance by the ethics committee of the Hospital Universitari Dr. Josep Trueta as the center responsible for the study.
- Agreement of participation by the ethics committee at Hospital Universitari de Bellvitge and Hospital Germans Trias i Pujol.
- Explanation of the study and distribution of tasks.

Phase 2: Training of surgeons

First week of April 2022

Surgeons participating in the research will be sent to a one-week training course in which they will practice the application of indocyanine green.

Phase 3: Patient Recruitment and Data Collection

April 2022 to August 2025. Tasks included:

- Patient sampling and invitation to participate in the study. All eligible patients will be interviewed, adequately informed and given a consent form.
- Surgery, follow-up and data collection for each patient.
- Biannual meetings of the general, center and ICO coordinators.

Phase 4: Statistical analysis

August 2025 to November 2025. Tasks included:

- Meeting with the entire research team at the beginning of the phase.
- Data collection and development of an anonymized database.
- Univariate, bivariate and multivariate data analysis.
- Preparation of tables and graphics and interpretation of results.

Phase 5: Final report

September 2025 to March 2026. Tasks included:

- Bimensual meetings with the entire research team.
- Possible modifications and drafting of the final report.
- Presentation of the final report to the scientific community.
- Participation in national congresses of plastic and reconstructive surgery.

A chronogram of the working plan is presented in Figure 8.1.

Figure 8.1: Study chronogram.

9 | Budget

The three included hospitals already own an infrared camera device for the visualisation of Indocyanine Green Angiography (ICGA), and therefore it is not necessary to include this cost in our budget.

The total costs of this study are described in table 9.1.

Table 9.1: Budget.

Item	**Quantity**	**Price per unit (euro)**	**Total price (euro)**
ICG vials	225 vials	90.00	20,250.00
Training course	19 surgeons	700.00	13,300.00
Statistician	240 hours	40.00	9,600.00
Expenses and travel	10 meetings	70.00	700.00
Printing materials	4500 pages	0.02	90.00
National congress expenses	2 attendants	1,500.00	3,000.00
Publication expenses	3 journals	2,000.00	6,000.00
			52,940.00

10 | References

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A Annexes

A.1 TNM and staging tables

Table A.1: Breast cancer staging. Adapted from (4).

	Tis	T0	T1	T2	T3	T4	
N0	0	-	IA	IIA	IIB	IIIB	**M0**
N1	-	IIA *(IB if N1mi)*	IIA *(IB if N1mi)*	IIB	IIIA	IIIB	
N2	-		IIIA	IIIA	IIIA	IIIB	
N3	-	IIIC	IIIC	IIIC	IIIC	IIIC	
Any N	-	IV	IV	IV	IV	IV	**M1**

N1mi, lymph node micro-metastases.

T CATEGORY	T CRITERIA
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)[a]	Ductal carcinoma in situ (DCIS)
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤ 20 mm in greatest dimension
T1mi	Tumor ≤ 1 mm in greatest dimension
T1a	Tumor > 1 mm but ≤ 5 mm in greatest dimension (round any measurement from >1.0-1.9 mm to 2 mm)
T1b	Tumor > 5 mm but ≤ 10 mm in greatest dimension
T1c	Tumor > 10 mm but ≤ 20 mm in greatest dimension
T2	Tumor > 20 mm but ≤ 50 mm in greatest dimension
T3	Tumor > 50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma (see "Rules for Classification")

Figure A.1: American Joint Committee on Cancer Definition of Primary Tumor (T) - Clinical (cT) and Pathological (pT). Taken from (4).

CATEGORY	CRITERIA
cN[a]	
cNX[b]	Regional lymph nodes cannot be assessed (eg, previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I and II axillary lymph node(s)
cN1mi[c]	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral level I and II axillary lymph nodes that are clinically fixed or matted;
	or in ipsilateral internal mammary lymph nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral level I and II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary lymph nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I and II axillary lymph node involvement;
	or in ipsilateral internal mammary lymph node(s) with level I and II axillary lymph node metastases;
	or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)
pN[d]	
pNX	Regional lymph nodes cannot be assessed (eg, not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase-polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary lymph nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel lymph nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary lymph nodes
pN3	Metastases in 10 or more axillary lymph nodes;
	or in infraclavicular (level III axillary) lymph nodes;
	or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive level I and II axillary lymph nodes;
	or in more than 3 axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes;
	or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm);
	or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary lymph nodes by imaging);
	or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Figure A.2: American Joint Committee on Cancer Definition of Regional Lymph Nodes - Clinical (cN) and Pathological (pN). Taken from (4).

CATEGORIES FOR DISTANT METASTASES—CLINICAL AND PATHOLOGICAL (CM0, CM1, PM1)	
M CATEGORY	**M CRITERIA**
M0	No clinical or radiographic evidence of distant metastases[a]
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or and no deposits no greater than 0.2 mm detected microscopically or by using molecular techniques in circulating blood, bone marrow, or other nonregional lymph node tissue in a patient without symptoms or signs of metastases
M1	Distant metastases detected by clinical and radiographic means (cM) and/or histologically proven metastases larger than 0.2 mm (pM)

Figure A.3: American Joint Committee on Cancer Definition of Distant Metastasis (M). Taken from (4).

		UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS		
FACTOR	**5-YEAR DSS, %**	**HR**	***P***	**HR**	***P***	**BIOSCORE POINTS ASSIGNED**
Pathologic stage						
IA/IB	99.1	Referent		Referent		0
IIA	98.0	2.8	.002	2.3	.01	1
IIB	95.6	4.8	<.0001	4.0	<.0001	2
IIIA	95.4	6.8	<.0001	7.2	<.0001	3
IIIC	79.5	26.6	<.0001	19.9	<.0001	4
ER status						
Positive	98.8	Referent		Referent		0
Negative	92.9	4.9	<.0001	2.5	.001	1
PR status						
Positive	98.8	Referent		Referent		
Negative	95.2	4.0	<.0001		NS	
HER2 status						
Positive	97.5	Referent		Referent		0
Negative	98.0	0.8	.5	2.2	.04	1
Nuclear grade						
1	99.8	Referent		Referent		0
2	98.9	5.0	.1	4.0	.2	0
3	95.3	25.0	.001	13.0	.01	1

Figure A.4: The University of Texas MD Anderson Cancer Center Univariate and Multivariate Analyses for Clinic-pathologic Factors Associated With Disease-Specific Survival. Taken from (4).

A.2 Information sheet and consent form

FULL D'INFORMACIÓ PER A LA PACIENT

TÍTOL DE L'ESTUDI	Clinical application of indocyanine green angiography in patients with early stage breast cancer undergoing mastectomy and reconstruction with autologous tissue
INVESTIGADOR PRINCIPAL	Clàudia Brunet i Torres
CENTRE	☐ Hospital Universitari Dr. Josep Trueta ☐ Hospital Universitari de Bellvitge ☐ Hospital Germans Trias i Pujol

Introducció

Ens dirigim a vostè per a informar-la sobre un estudi d'investigació en el qual se la convida a participar. Aquest estudi ha estat aprovat pel Comitè d'Ètica i Investigació Clínica.

La intenció d'aquest document és que vostè rebi la informació correcta i suficient per tal que pugui decidir si accepta o no accepta participar en l'estudi. Li demanem que llegeixi aquest full informatiu amb atenció i ens demani qualsevol dubte que li pugui sorgir.

Participació voluntària

La convidem a participar en aquest estudi ja que ha estat recentment diagnosticada de càncer de mama i rebrà una cirurgia de mastectomia i reconstrucció mamària.

La seva participació en aquest estudi es totalment voluntària i en tot moment pot decidir NO participar. Si decideix participar, en qualsevol moment pot canviar la seva decisió i retirar el consentiment, sense que això suposi un canvi en la seva atenció sanitària.

Objectius de l'estudi

Aquest estudi pretén contestar a dos objectius:

- Avaluar si existeix una diferència en l'aparició de complicacions vasculars de la cirurgia reconstructiva entre un grup de pacients que se sotmetran a un estudi d'imatge durant la cirurgia i un grup control que no se sotmetran a dit estudi.
- Avaluar si existeix una diferència en la qualitat de vida posterior a la reconstrucció de mama entre els mateixos dos grups de pacients.

Descripció de l'estudi

L'estudi inclourà un total de 450 pacients diagnosticades de càncer de mama i en espera de cirurgia de mastectomia i reconstrucció immediata, que hagin rebut o rebran altres

tractaments (radioteràpia, quimioteràpia, etcètera) i tinguin un índex de massa corporal (IMC) de menys de 30.

Per a l'avaluació dels objectius es dividiran les pacients en dos grups:

- 225 pacients al grup 1, que es sotmetran a una prova d'imatge durant l'operació.
- 225 pacients al grup 2, a les quals no es realitzarà aquesta prova d'imatge.

A les pacients del grup experimental se'ls administrarà una o més dosis de 4 mL de verd d'indocianina (colorant) per tal de veure la distribució de la sang del pit reconstruït.

L'assignació de pacients entre els grups es realitzarà de manera aleatòria, per la qual vostè té una probabilitat del 50% d'entrar en qualsevol dels dos grups. Fins a la finalització de l'estudi en cap moment sabrà en quin dels dos grups ha estat assignada.

Activitats de l'estudi

La seva participació en aquest projecte tindrà una durada d'un any, en el qual tindrà:

- 1 visita prèvia a l'operació, on rebrà informació sobre l'estudi i sobre la cirurgia.
- Intervenció quirúrgica de mastectomia i reconstrucció mamària.
- 6 visites de seguiment distribuïdes de la següent manera: en 10 dies del post-operatori i al cap de 1, 3, 6, 9 i 12 mesos. A totes les visites se li avaluarà el pit reconstruït i a l'última visita se li demanarà que respongui a 3 qüestionaris.

Riscs i beneficis

El verd d'indocianina és un colorant autoritzat i comercialitzat per a ús diagnòstic. S'han descrit els següents riscs:

- Espasmes coronaris, nàusees o reaccions al·lèrgiques (< 1/10.000 persones).
- La freqüència de mort per anafilaxi és de menys de 1/330.000 persones.

En cas de rebre verd d'indocianina es pot beneficiar d'una planificació quirúrgica més adequada i de la disminució de complicacions conseqüents a la cirurgia.

Contacte en cas de dubte

Si durant la seva participació té algun dubte o necessita obtenir més informació, pot posar-se en contacte amb el seu cirurgià i amb la investigadora principal.

Se li proporcionarà un paper amb les dades de contacte.

Protecció de dades personals

Tant els responsables de l'estudi com el centre s'asseguraran del compliment de tots els principis contemplats en la normativa de protecció de dades nacional i europea.

Les seves dades seran accessibles només pels membres de l'equip de recerca i s'afegiran a les bases de dades de forma anònima.

CONSENTIMENT INFORMAT

TÍTOL DE L'ESTUDI	Clinical application of indocyanine green angiography in patients with early stage breast cancer undergoing mastectomy and reconstruction with autologous tissue
INVESTIGADOR PRINCIPAL	Clàudia Brunet i Torres
CENTRE	☐ Hospital Universitari Dr. Josep Trueta ☐ Hospital Universitari de Bellvitge ☐ Hospital Germans Trias i Pujol

Jo, _____ (nom i cognoms de la participant)

☐ He llegit el full d'informació que se m'ha entregat sobre l'estudi.
☐ He pogut fer les preguntes pertinents sobre l'estudi.
☐ He rebut suficient informació sobre l'estudi.
☐ He parlat amb l'equip de recerca.
☐ Entenc que la meva participació és voluntària.
☐ Comprenc que puc retirar-me de l'estudi en qualsevol moment, sense haver de donar explicacions i sense que això repercuteixi a la meva atenció sanitària

Rebré una còpia firmada i datada d'aquest full d'informació i consentiment informat.

Presto la meva conformitat per a participar a l'estudi, confirmo que he llegit el full d'informació i estic conforme amb el seu contingut.

Firma de la participant

Data: ___/___/___

Firma de l'investigador

Data: ___/___/___

A.3 Data collection form

FULL DE RECOL·LECCIÓ DE DADES

TÍTOL DE L'ESTUDI	Clinical application of indocyanine green angiography in patients with early stage breast cancer undergoing mastectomy and reconstruction with autologous tissue
INVESTIGADOR PRINCIPAL	Clàudia Brunet i Torres
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Co-variables

Edat	_____ anys
Estadi del càncer de mama	☐ I ☐ IIA ☐ IIB ☐ IIIA
Tractaments neoadjuvants/ adjuvants	☐ Teràpia neoadjuvant (especificar): _____ ☐ Teràpia adjuvant (especificar): _____ ☐ Ambdues (especificar): _____
IMC	_____ kg/m^2
Hàbit tabàquic	☐ No ☐ Sí (especificar): IPA _____
Tècnica quirúrgica	☐ DIEP ☐ TMG ☐ PAP

Grup de la participant

☐ Grup experimental (angiografia amb verd d'indocianina)
☐ Grup control

Dosi de verd d'indocianina (si precisa)

☐ 4 mL
☐ 8 mL
☐ 12 mL
☐ Altres: _____

Complicacions vasculars

☐ Patiment venós. Data: _____

☐ Necrosi total del penjoll de reconstrucció. Data: _____

☐ Necrosi parcial del penjoll de reconstrucció. Data: _____

☐ Necrosi del teixit adipós del penjoll de reconstrucció. Data: _____

☐ Altres: _____ Data: _____

Altres complicacions

ZONA RECEPTORA

☐ Infecció. Data: _____

☐ Dehiscència. Data: _____

☐ Cicatrització lenta. Data: _____

☐ Necrosi de les vores de la ferida. Data: _____

☐ Altres: _____ Data: _____

ZONA DONANT

☐ Infecció. Data: _____

☐ Dehiscència. Data: _____

☐ Cicatrització lenta. Data: _____

☐ Necrosi de les vores de la ferida. Data: _____

☐ Hèrnia abdominal (si DIEP). Data: _____

☐ Altres: _____ Data: _____

COMPLICACIONS ESTÈTIQUES

☐ Asimetria mamària. Data: _____

☐ Irregularitats de contorn. Data: _____

☐ Contractura. Data: _____

☐ Pèrdua de volum. Data: _____

☐ Cicatrització hipertròfica. Data: _____

☐ Altres: _____ Data: _____

Qüestionaris de qualitat de vida

QLQ-C30	_____/100	QLQ-BRECON23	_____/100
QLQ-BR23	_____/100	Mitjana puntuació	_____/100

A.4 EORTC questionnaires

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	Did you have a dry mouth?	1	2	3	4
32.	Did food and drink taste different than usual?	1	2	3	4
33.	Were your eyes painful, irritated or watery?	1	2	3	4
34.	Have you lost any hair?	1	2	3	4
35.	Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36.	Did you feel ill or unwell?	1	2	3	4
37.	Did you have hot flushes?	1	2	3	4
38.	Did you have headaches?	1	2	3	4
39.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40.	Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41.	Did you find it difficult to look at yourself naked?	1	2	3	4
42.	Have you been dissatisfied with your body?	1	2	3	4
43.	Were you worried about your health in the future?	1	2	3	4

During the past four weeks:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
44.	To what extent were you interested in sex?	1	2	3	4
45.	To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46.	Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
47.	Did you have any pain in your arm or shoulder?	1	2	3	4
48.	Did you have a swollen arm or hand?	1	2	3	4
49.	Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50.	Have you had any pain in the area of your affected breast?	1	2	3	4
51.	Was the area of your affected breast swollen?	1	2	3	4
52.	Was the area of your affected breast oversensitive?	1	2	3	4
53.	Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

EORTC QLQ – BRECON23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

The term **'affected'** refers to the breast, which has been, or is about to be, reconstructed.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
54. Have you had numbness or tingling in your arm or shoulder?	1	2	3	4
55. Have you had a problem with fullness under your arm?	1	2	3	4
56. Have you been feeling less sexually attractive as a result of your disease or treatment?	1	2	3	4
57. Have you felt uncomfortable in intimate situations?	1	2	3	4
58. Has the role of your breast in your sexuality been affected by your disease or treatment?	1	2	3	4
59. Has any loss of pleasurable sensations of your breast been a problem to you?	1	2	3	4

During the past week, how SATISFIED have you been with:	**Not at all**	**A little**	**Quite a bit**	**Very much**
60. The size of your affected breast?	1	2	3	4
61. The shape of your affected breast?	1	2	3	4
62. The appearance of the skin of your affected breast?	1	2	3	4
63. The symmetry of your breasts?	1	2	3	4
64. Your cleavage?	1	2	3	4
65. The softness of your affected breast?	1	2	3	4

Please go on to the next page

Answer these two questions ONLY IF your nipple has been <u>PRESERVED.</u>

During the past week, how satisfied have you been with:	**Not at all**	**A little**	**Quite a bit**	**Very much**
66. The appearance of your affected nipple?	1	2	3	4
67. The sensation in your affected nipple?	1	2	3	4

Answer these questions in relation to your breast reconstruction overall.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
68. How satisfied have you been with the appearance of any scars on your affected breast?	1	2	3	4
69. Overall, how satisfied have you been with the result of your breast reconstruction?	1	2	3	4
70. Has the reconstruction of your breast helped you come to terms with your disease or treatment?	1	2	3	4

Answer these questions ONLY IF YOU HAVE HAD A FLAP PROCEDURE (skin/muscle is taken from your back, tummy or buttock to reconstruct your breast).

Please answer the following regarding the area where the skin/muscle was taken from:

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
71. Have you had pain?	1	2	3	4
72. Have you had tightness?	1	2	3	4
73. Have you had any numbness?	1	2	3	4
74. Have you been satisfied with the appearance of the scars?	1	2	3	4

Answer this question ONLY IF you have LOST your nipple and <u>NOT</u> had a nipple reconstruction.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
75. Has the loss of your nipple been a problem to you?	1	2	3	4

Answer this question ONLY IF you HAVE had nipple preserving or reconstructing surgery.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
76. Has the preservation or reconstruction of your nipple helped you come to terms with the disease or treatment?	1	2	3	4

A.5 EORTC scoring manuals

General principles of scoring

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
Thus a **high score for a functional scale** represents a *high / healthy level of functioning*,
a **high score for the global health status / QoL** represents a *high QoL*,
but a **high score for a symptom scale / item** represents a *high level of symptomatology / problems*.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the *raw score*.

2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Coding of the scoring procedure is presented in Appendix 3 for three major statistical packages.

Technical Summary

In practical terms, if items I_1, I_2, ... I_n are included in a scale, the procedure is as follows:

Raw score
Calculate the raw score
RawScore = $RS = (I_1 + I_2 + ... + I_n)/n$

Linear transformation
Apply the linear transformation to 0-100 to obtain the score *S*,

Functional scales: $S = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$

Symptom scales / items: $S = \{(RS - 1)/range\} \times 100$

Global health status / QoL: $S = \{(RS - 1)/range\} \times 100$

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range* = 1.

Scoring the EORTC QLQ-C30 version 3.0

Table 1: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS - 1)/range\} \times 100$$

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$\text{FA } Score = \{(RawScore - 1)/3\} \times 100$$

EORTC QLQ-BR23 Scoring Manual

The **Breast Cancer module** is a supplementary questionnaire module to be employed in conjunction with the QLQ-C30. The QLQ-BR23 incorporates five multi-item scales to assess body image, sexual functioning, systemic therapy side effects, breast symptoms, and arm symptoms. In addition, single items assess sexual enjoyment, future perspective and being upset by hair loss.

The scoring approach for the QLQ-BR23 is identical in principle to that for the function and symptom scales / single items of the QLQ-C30. All scoring information specific to the QLQ-BR23 is presented in Table 1.

Interpretation:
All of the scales and single-item measures range in score from 0 to 100. A high score for the functional scales represents a high/healthy level of functioning, whilst a high score for the symptom scales represents a high level of symptomatology or problems.

Table 1. Scoring the QLQ-BR23

	Scale	Number of items (n)	Item range*	QLQ-BR23 item numbers (I_1, I_2, …, I_n)	Reverse scoring items
Symptom scales / items					
Systemic Therapy Side Effects	ST	7	3	31 – 34, 36 - 38	
Upset by Hair Loss	HL	1	3	35	
Arm Symptoms	AS	3	3	47 – 49	
Breast Symptoms	BS	4	3	50 – 53	
Functional scales / items					
Body Image	BI	4	3	39 – 42	
Future Perspective	FU	1	3	43	
Sexual Functioning	SEF	2	3	44, 45	44, 45
Sexual Enjoyment	SEE	1	3	46	46

* "Item range" is the difference between the possible maximum and the minimum response to individual items. All items are scored 1 to 4, giving range = 3.

SEE, sexual enjoyment, is not applicable if item 45 is "not at all."

HL, upset by hair loss, is not applicable if item 34 is "not at all."

Principle for scoring

1) **Raw score**

For each single-item measure, the score of the concerning item corresponds to the raw score.

For each multi-item scale, calculate the average of the corresponding items.

$$Raw\ Score = RS = \left\{\frac{(I_1 + I_2 + \ldots + I_n)}{n}\right\}$$

Take into account that the scoring of questions 44, 45 and 46 must be reversed prior to statistical analysis.

2) **Linear Transformation**
To obtain the Score S, standardize the raw score to a 0 – 100 range following the appropriate transformation:

Functional scales: $S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$

Symptom scales: $S = \left\{\frac{(RS-1)}{range}\right\} \times 100$

For directions on Missing Data or for more detailed information on the Interpretation of Scores, we redirect to the EORTC QLQ-C30 Scoring Manual (2001).

Reference

Sprangers MAG, Groenvold M, Arraras JI, et al.. The European Organisation for Research and Treatment of Cancer: Breast Cancer Specific Quality of Life Questionnaire Module: First results from a three-country field study. J. Clin. Oncol. 14: 2756-2768, 1996.

This is the revised version of the QLQ-BR23 scoring manual and might slightly differ from the scoring instructions that are presented in the EORTC QLQ-C30 Scoring Manual (2001). Both versions of the scoring manual will lead to the same outcome. Further questions or remarks regarding the scoring algorithms for the QLQ-BR23 can be directed to the QOL Specialist at the Quality of Life Department of the EORTC.

EORTC QLQ-BRECON23 and QLQ-BRECON14 Scoring Manual

The **Breast Reconstruction module** is intended for use alongside the EORTC QLQ-C30 and QLQ-BR23 in women diagnosed and treated for breast cancer before and after mastectomy, and undergoing all types of breast reconstruction.
The QLQ-BRECON23 incorporates six multi-item scales to assess the side effects of disease and surgery, sexual functioning, satisfaction with cosmetic outcomes of the breast, and nipple, donor site symptoms and satisfaction with surgery. Three stand-alone items assess problems with loss of the nipple, reconstruction of the nipple and satisfaction with donor site scars. Fourteen of the items of the QLQ-BRECON23 are applicable to women before undergoing mastectomy and breast reconstruction (QLQ-BRECON14).
For Prophylactic Breast Reconstruction use, please see further below.

The scoring approach for the QLQ-BRECON is identical in principle to that for the symptom scales / single items of the QLQ-C30. All scoring information specific to the QLQ-BRECON is presented in Table 1.

Interpretation:
All of the scales and single item measures range in score from 0 to 100. A high score for the symptom scales and single item represents a high level of symptomatology or problems, whereas a high score for the functional scales and single items represents a high level of functioning or satisfaction.

Table 1. Scoring the QLQ-BRECON

	Scale	Number of items (*n*)	Item range*	QLQ-BRECON item numbers (I_1, I_2, …, I_n)	Reverse scoring items
Symptom scales / items					
Treatment side effects	TS	2	3	54, 55	
Donor site symptoms [a]	DS	3	3	72 - 74	
Loss of nipple [a]	NL	1	3	76	
Functional scales / items					
Sexual functioning	SX	4	3	57 - 60	57 - 60
Satisfaction with breast cosmetic	SBC	6	3	61 – 66	
Satisfaction with nipple cosmetic [a]	SNC	2	3	67, 68	
Satisfaction with surgery	SSU	3	3	69 - 71	
Satisfaction with donor scars [a]	SDS	1	3	75	
Preserve / reconstruct nipple [a]	NP	1	3	77	

* "Item range" is the difference between the possible maximum and the minimum response to individual items. All items are scored 1 to 4, giving range = 3.

[a] Items 67, 68 and 72 to 77 are conditional and must only be scored if applicable to the patient. Scores must be calculated as for missing data (see EORTC QLQ-C30 Scoring Manual).

Principle for scoring

1) **Raw score**
   For each multi-item scale, calculate the average of the corresponding items.

   $$Raw\ Score = RS = \left\{\frac{(I_1 + I_2 + \ldots + I_n)}{n}\right\}$$

   For each single-item measure, the score of the concerning item corresponds to the raw score.
   Take into account that the scoring of questions 57, 58, 59 and 60 must be reversed prior to statistical analysis.

2) **Linear Transformation**
   To obtain the Score S, standardize the raw score to a 0 – 100 range following the transformation:

   $$S = \left\{\frac{(RS-1)}{range}\right\} \times 100$$

For directions on Missing Data or for more detailed information on the Interpretation of Scores, we redirect to the EORTC QLQ-C30 Scoring Manual (2001).

Different use of the questionnaire

- **Pre-mastectomy breast reconstruction questionnaire**
  The first fourteen questions (items 1 to 14) represent the pre-mastectomy breast reconstruction questionnaire: the QLQ-BRECON14. The QLQ-BRECON14 is applicable to women before undergoing mastectomy and breast reconstruction.
- **Post-mastectomy breast reconstruction questionnaire**
  The QLQ-BRECON23, including all items, comprises the post-mastectomy breast reconstruction questionnaire.
- **Prophylactic breast reconstruction questionnaire**
  The QLQ-BRECON23 can be used for prophylactic breast reconstruction as a stand-alone questionnaire. A version of the QLQ-BRECON23 with numbering starting with 1 can be obtained from the Translation Team Leader at the Quality of Life Department at the EORTC.

Reference papers

ZE Winters, V Balta, HJ Thomson, Y Bradberg, A Oberguggenberger, Y Sinove, D Unukovych, M Nava, K Sandelin and H Johansson on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group. Phase III development of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire module for women undergoing breast reconstruction, BJS 2014; 101(4): 371–382.

Winters ZE, Afzal M, Rumpold G, Holzner B, Oberguggenburger A, Vieira RAC, Hartnup S, Filcroft K, Bjelic-Radisic V, Panouilleres M, Rydevik Mani M, King MT and Rutherford C. International validation of the EORTC QLQ-BRECON23 questionnaire assessment for women undergoing breast reconstruction. BJS, Jan 2017, *in press*

Further questions or remarks regarding the scoring algorithms for the QLQ-BRECON can be directed to the QOL Specialist at the Quality of Life Department of the EORTC.


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