Quantitative assessments of radiation-induced toxicity and correlation with RTOG scales and biological equivalent dose in breast cancer

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DOCTORAL THESIS

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List of Abbreviations

WHO: World Health Organization

BCS: Breast conserving surgery

HR: Heterologous reconstruction,

AR: Autologous reconstruction

CF-WBI: Conventional fractionation whole breast irradiation

HF-WBI: Hypofractionation whole breast irradiation

ASTRO: American Society for Radiation Oncology

RTOG: Radiation Therapy Oncology Group

CTCAE: Common Terminology Criteria for Adverse Events

LENT-SOMA: Late Effects Normal Tissue-Subjective, Objective, Management, Analytic

APBI: Accelerated partial breast irradiation

MIB: Multicatheter interstitial brachytherapy

EBRT: External-beam radiotherapy

IORT: Intraoperative radiotherapy

IBTR: Ipsilateral breast tumor recurrence

LDF: Laser Doppler flowmetry

MCI: Microcirculation index

Index

ABSTRACT

Background: Radiation-induced toxicity (RIT) is usually assessed by inspection and palpation. Due to its subjective and unquantitative nature, objective methods are required. This study aimed to determine whether our quantitative tool is able to assess late RIT and establish an underlying BED-response relationship using both subjective and objective assessments. Furthermore, radiotherapy combined with breast reconstruction can reduce the risk of cancer recurrence and increase the survival rate. However, this approach seems to worsen aesthetic outcomes and increase complication rates. The impact of breast reconstruction timing and techniques on clinical outcomes, however, remains unclear.

Methods: Patients were grouped according to the radiation biological equivalent dose (BED) used. A total of 7 groups of patients were recruited into our study. RIT was subjectively evaluated by physicians using the Radiation Therapy Oncology Group (RTOG) acute and late toxicity scores. An objective multiprobe device was also used to quantitatively assess late RIT in terms of erythema, pigmentation, elasticity and skin hydration. For further study, patients undergoing RT and breast reconstruction were divided into 4 groups according to the timing of reconstruction (before radiotherapy, after radiotherapy) and surgical technique (heterologous reconstruction, autologous reconstruction). The median time between radiotherapy and reconstruction, number of revision surgeries, incidence of complications, toxicity, aesthetics and associated clinical risk factors were used to assess the clinical outcomes. The objective multiprobe device was also used to assess RIT.

Results: In 194 patients, in terms of the objective measurements, treated breasts showed

higher erythema and melanin and lower elasticity and hydration than untreated breasts ($p<0.001$, $p<0.001$, $p<0.001$, $p=0.019$, respectively). As the BED increased, Δerythema and Δmelanin gradually increased as well ($p=0.006$ and $p=0.002$, respectively). Regarding the clinical assessment, the increase in BED resulted in a higher acute RTOG ($p<0.001$) and late RTOG toxicity grade ($p<0.001$). As the RTOG toxicity grade increased, the erythema values increased, and the elasticity index decreased ($p=0.003$, $p<0.001$, respectively). For further study, 95 patients undergoing reconstruction and radiotherapy were included. No significant differences in the median time between radiotherapy and reconstruction, incidence of complications, toxicity, or aesthetics were noted between different timings or techniques of reconstruction. Patients undergoing autologous reconstruction needed more revision surgeries to complete reconstruction. However, the total number of surgical procedures was similar between the groups. In a comparison between the treated and untreated breasts by the objective system, radiotherapy produced an increase in erythema and pigmentation and a decrease in elasticity in the treated breast ($p<0.05$ for all parameters). On multivariate analysis, smoking was a significant predictor associated with complications.

Conclusions: The Multi Skin Test Center is a useful tool to assess RIT. Physician-assessed toxicity score and objective measurements revealed that the higher BED was associated with severity of toxicity. Focusing on carefully selecting radiation schedule will be fruitful for patient care. Combined breast reconstruction and radiotherapy seems to be successful regardless of the order of treatment or the type of reconstruction.

RESUMEN

Antecedentes: la toxicidad inducida por radiación (RIT) generalmente se evalúa mediante inspección y palpación. Debido a su naturaleza subjetiva y no cuantitativa, se requieren métodos objetivos. Este estudio tiene como objetivo determinar si nuestra herramienta cuantitativa es capaz de evaluar la RIT tardía y establecer una relación dosis de radiación y RIT utilizando evaluaciones subjetivas y objetivas. Asimismo y dado que la combinación de radioterapia y reconstrucción mamaria parece empeorar los resultados estéticos y aumentar las tasas de complicaciones, hemos utilizado nuestro sistema de evaluación subjetivo para comparar las técnicas de reconstrucción mamaria y la secuencia radioterapia reconstrucción.

Métodos: Las pacientes fueron agrupadas según la dosis de radiación biológica equivalente (BED) utilizada. Se reclutaron un total de 7 grupos de pacientes. La RIT fue evaluada subjetivamente por los médicos utilizando las puntuaciones de toxicidad aguda y tardía del Grupo de Oncología de Terapia de Radiación (RTOG). También se utilizó un dispositivo con varias sondas para evaluar cuantitativamente la RIT tardía en términos de eritema, pigmentación, elasticidad e hidratación de la piel. Para su posterior estudio, las pacientes sometidas a RT y reconstrucción mamaria se dividieron en 4 grupos según la secuencia de reconstrucción (antes de la radioterapia, después de la radioterapia) y la técnica quirúrgica (reconstrucción heteróloga, reconstrucción autóloga). La mediana del tiempo entre la radioterapia y la reconstrucción, el número de cirugías de revisión, la incidencia de complicaciones, la toxicidad, la estética y los factores de riesgo clínicos asociados se utilizaron para evaluar los resultados clínicos.

Resultados: Se reclutaron 194 pacientes y en primer lugar se realizó una comparación de los parámetros objetivos entre la mama irradiada y la no irradiada. Las mamas tratadas mostraron mayor eritema y melanina y menor elasticidad e hidratación que las no tratadas ($p < 0,001$, $p < 0,001$, $p < 0,001$, $p = 0,019$, respectivamente). A medida que aumentaba el BED, el Δeritema y la Δmelanina también aumentaban gradualmente ($p = 0,006$ y $p = 0,002$, respectivamente). En cuanto a la valoración clínica, el aumento de BED dio como resultado unos valores de la escala de la RTOG mayores, tanto de toxicidad aguda ($p < 0,001$) como tardía ($p < 0,001$). La correlación entre las medidas objetivas y subjetivas puso de manifiesto que a medida que aumenta el grado de toxicidad de RTOG, los valores de eritema aumentan y los de elasticidad disminuyen ($p = 0,003$, $p < 0,001$, respectivamente). En el estudio adicional, se incluyeron 95 pacientes sometidas a reconstrucción. No se observaron diferencias significativas en la mediana del tiempo entre la radioterapia y la reconstrucción, la incidencia de complicaciones, la toxicidad o la estética entre los diferentes tiempos o técnicas de reconstrucción. Las pacientes sometidas a reconstrucción autóloga necesitaron más cirugías de revisión para completar la reconstrucción. Sin embargo, el número total de procedimientos quirúrgicos fue similar entre los grupos. En la comparación entre las mamas tratadas y no tratadas mediante el sistema objetivo, la radioterapia produjo un aumento del eritema y la pigmentación y una disminución de la elasticidad en la mama tratada ($p < 0,05$ para todos los parámetros). En el análisis multivariado, el tabaquismo fue el único predictor significativo asociado con complicaciones.

Conclusiones: El Multi Skin Test Center es una herramienta útil para evaluar la RIT, sus valores se correlacionan con las evaluaciones subjetivas realizadas por los médicos y el aumento de dosis (mayor BED) se asocia con la gravedad de la toxicidad. La aplicación de esta herramienta en la evaluación de las pacientes sometidas a reconstrucción y radioterapia pone de manifiesto que no existen diferencias importantes entre los diferentes tipos de reconstrucción y la secuencia de tratamiento, únicamente el hábito tabáquico tiene importancia en la toxicidad.

1.Introduction

1.1 Epidemiology

1.1.1 Epidemiology of cancer

According to estimates from World Health Organization (WHO), cancer is a leading cause of death globally, accounting for an estimated 9.9 million deaths and 19.3 million new cancer cases in 2020. Breast cancer was the most common cancer that has surpassed lung cancer as the leading cause of cancer incidence in 2020 (2.26 million, 11.7%; 2.21 million, 11.4%, respectively), followed by colorectum cancer (1.93 million, 10%), prostate cancer (1.41 million, 7.3%) and stomach cancer (1.08 million, 5.6%) (Figure 1)(1). Lung cancer is the leading cause of death (,18.0%), closely followed by colorectal, liver, stomach, and breast cancer. Among them, for women, the most frequently diagnosed cancer was dominated by breast cancer, and it is also the leading cause of death in women in majority of countries. Due to the aging and growth of the population, as well as the increasing risk factor associated with globalization and socioeconomic development(2), the incidence and mortality of cancer is rapidly growing worldwide.

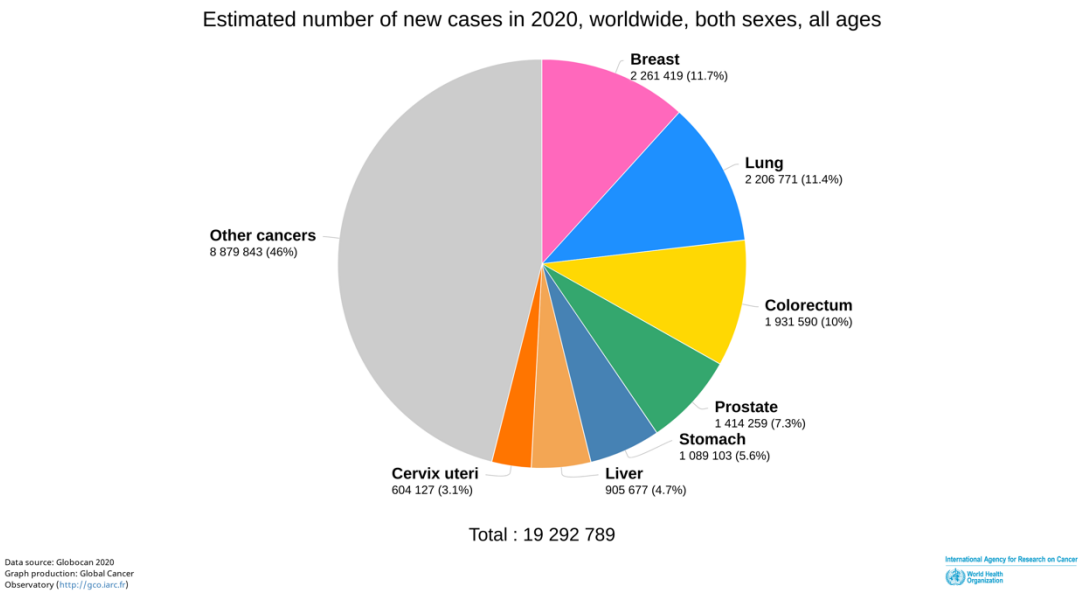


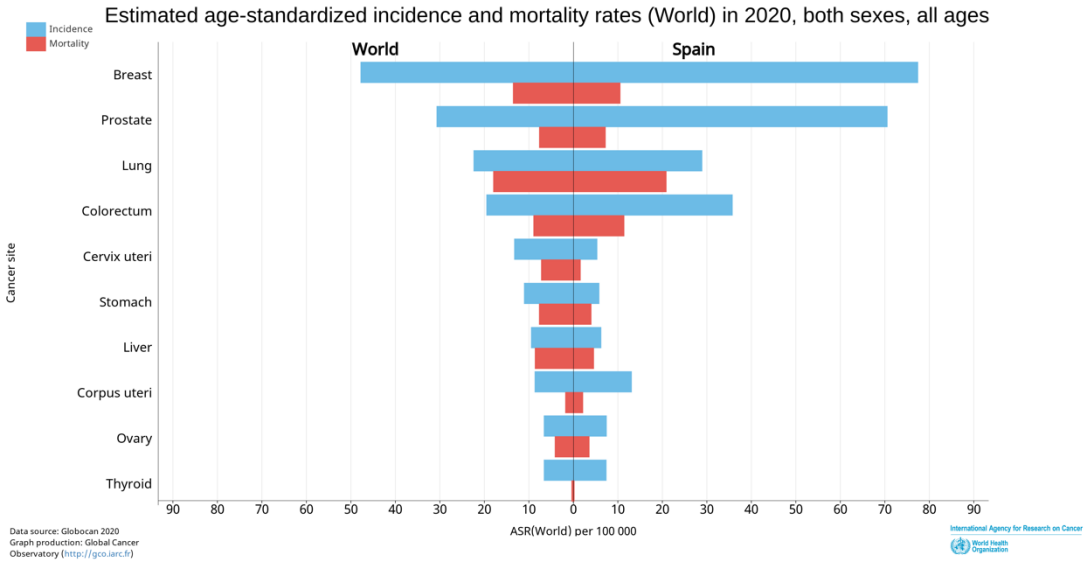
Figure 1. Estimated number of new cases of cancer in 2020.

Source: GLOBOCAN 2020.

1.1.2 Breast cancer in Spain

In 2020, There was 282 thousand new cases of cancer diagnosed in Spain. Figure 2 shows the distribution of cancer incidence and mortality between Spain and all of the world in 2020. It was estimated that 13.6% of breast cancer deaths occur in Spain, while the proportion of the global population was 10.6%. In terms of incidence rate of breast cancer, accounting for 77.5% of Spain and 47.8% of worldwide.

Figure 2. Distribution of cancer incidence and mortality between Spain and all of the world in 2020.



Source: GLOBOCAN 2020.

These variations are likely to be due to the differences in exposure to risk factors (menarche, menopause and first birth histories, breastfeeding, tobacco use, alcohol intake, overweight, lack of physical activities and unhealthy habitus), quality cancer prevention and access to early detection through mammography(3).

1.1.3 Historical development of breast cancer

Breast cancer incidence rates increased rapidly from 1980s to 1990s, which may cause by the changes in prevalence of risk factors and earlier detection of breast cancer by

widespread use of mammographic screening and precise diagnosis. The incidence then declined and stabilized in the early 2000s(4), which possibly due to the increasing mammography and decreasing of menopause hormone therapy(5,6). However, since 2007, there has been a significant increase of breast cancer incidence(7). The explanations of this increasing incidence rate may include the overweight epidemic and the impact of the earlier detection of slow-growing estrogen receptor positive breast cancer through mammographic screening(8–10). The global cancer burden is expected to increase by 47% in 2040 when compared with 2020, and an anticipated 28.4 million new cases will occur, which is a vital barrier to increase life expectancy(1).

1.2 Prevention and detection of breast cancer

In order to reduce the incidence and morbidity of breast cancer, several methods have been implemented. Establishing primary prevention measures for breast cancer, including reduction of obesity and alcohol consumption and encouraging breast-feeding, physical exercises and healthy diet, may impact in decreasing the incidence (Table 1). The earlier detection of breast cancer by widely used mammographic screening may reduce the mortality. WHO guideline recommends that women aged from 50 to 69 years should receive examination through mammography every 2 years(11). However, it may cause overdiagnosis and overtreatment(3,12). And the appropriate and effective treatments are also an important key to reducing incidence and mortality of breast cancer and managing the growing number of cancers.

Table 1: Risk factor of breast cancer.

Risk factors	
Non-modifiable	Modifiable
Gender	Exogenous hormones
Age	Breast feeding
Genetics	Alcohol
Benign breast diseases	Obesity
Endogenous hormones	Physical exercises

Source: own edition

1.3 Breast cancer treatment

1.3.1 Overview of breast cancer therapies

The multidisciplinary treatment of breast cancer includes local treatments (surgery and radiotherapy) and systemic treatments (chemotherapy, hormone therapy, targeted therapy, immunotherapy)(13). Patients may receive one of these treatments or a combination of them. The treatment plans depend on the type and stage of breast cancer, as well as other factors, such as patient's age, overall health, menopausal status and personal preferences.

1.3.2 Surgery and radiotherapy

1.3.2.1 Breast conserving surgery, mastectomy and radiotherapy

Surgery is the primary modality of breast cancer treatment. In 1882, Halsted firstly performed a radical mastectomy(14). Over the years, breast surgeries have transitioned from radical mastectomy to breast conserving surgery (BCS), which is less extreme for patients undergoing breast cancer. The development toward fewer radical approaches has been evidence based. The NSABP B-06 randomized clinical trial compared mastectomy, lumpectomy alone, and lumpectomy with RT for 2163 patients with stage 1 or 2. After 20 years follow-up, no significant differences were found in overall survival. However, the BCS alone group showed a 39.2% of recurrence(15). For patients with early-stage breast cancer, the majority tumor cells can be removed by breast conserving surgery. But some invisible microscopic tumor may remain, which may lead to local recurrence or distant metastases. Radiotherapy after breast conserving surgery (BCS) can destroy the remaining cancer cells. Several randomized clinical trials confirmed the RT plus BCS have similar long-term survival and mortality from breast cancer to mastectomy. This treatment is also related to a satisfactory high local control rates after long-term follow-up and the recurrence rate are lower than those with BCS alone(16–18). Thanks for the progress in modern multidisciplinary treatment of breast cancer, including earlier detection of breast cancer by mammographic screening, development of surgical techniques, examination of margin pathology, improvement of radiation techniques, appropriate patients are able to select BCS plus RT treatment method. Compared to mastectomy, BCS plus RT is associated with a better cosmetic

result, which improves patients satisfactory and quality of life. So, in most developed countries, this protocol is the current standard of care of patients with early-stage breast cancer.

1.3.2.2 Breast reconstruction and radiotherapy

For patients undergoing mastectomy, breast reconstruction not only has a positive effect on body image but also reduces the psychological morbidity of the loss of the breast and increases patient satisfaction.(19) Breast reconstruction can be performed by the following techniques: heterologous reconstruction (HR), e.g., using a permanent implant or tissue expander; or autologous reconstruction (AR), which is performed with the patient's own tissue, including skin, fat and muscle mass, for the sake of obtaining a more natural, symmetrical effect. (20)

Although radiotherapy can reduce the loco-regional and distant recurrence rates of the disease and increase the survival rate,(16,21) at the same time, it affects the aesthetics and increases the risk of complications.(22–24) According to some studies, radiation after reconstruction with implants discreetly worsens aesthetics and increases the risk of complications.(25) Other authors have presented the opposite opinion and considered that the combination of HR and RT is a safe technique with respect to advances in both plastic surgery and RT techniques in the last decade. In many reports, radiation with AR did not entail excessive problems. It is the technique of breast reconstruction that most surgeons choose when patients need RT.(26) AR is associated with reduced mobility and improved cosmetic outcomes in patients who need RT and

is believed to result in a high index of satisfaction.(27) Additionally, the sequence of RT and breast reconstruction does not seem to interfere with the results.(28)

Combination therapy with radiation and breast reconstruction has become increasingly common in recent years.(29) Nevertheless, the complications, toxicities and aesthetic results of those patients are not yet clear and still controversial in some respects.

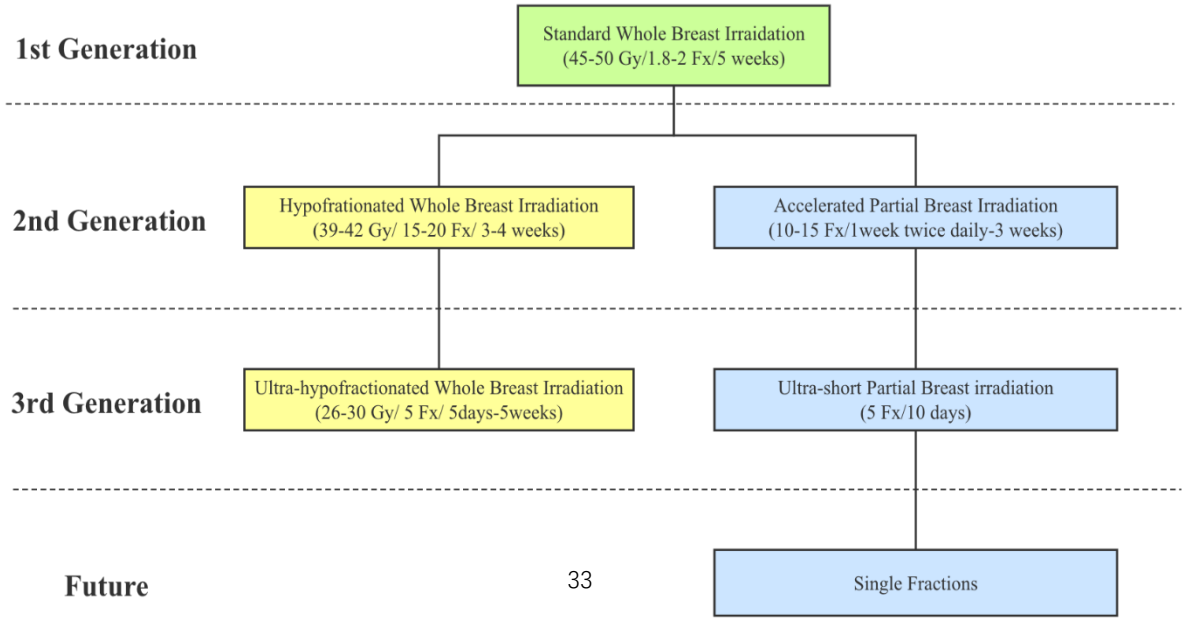
1.3.3 Radiotherapy

After X-rays discovered by Wilhelm Roentgen in the 1895 and Marie Curie finding of polonium radiation in early 1990s, the use of radiation to treat breast cancer was first reported in about 1930(30). Since then, numerous multiple large randomized trials have been explored the need of radiotherapy for breast cancer patients over the past years. The older clinical trials demonstrated that an unacceptably high rates of recurrence was related to breast cancer motility, when omitting radiotherapy(31,32). More recently, clinical trials evaluated the omission of radiotherapy in low-risk patients and found an increased risk of recurrence after long-term follow-up. Studies evaluating the omission of radiation therapy in patients with DCIS also reported increased rates of local recurrence(33,34). According to a meta-analysis of more than 10 thousand patients in 17 randomized clinical trials by the Early Breast cancer Trialists' collaborative group (EBCTCG), radiation therapy after BCS reduced 10-years recurrence from 35% to 19.3% and 15-years mortality from 25.2% to 21.4%(32). Therefore, nowadays, radiation therapy (RT) is provided as an important complementary treatment by using high-energy x-ray or other particles to destroy cancer cells and slow tumor growth, which

improves the local-regional control and reduces the risk of cancer recurrence in clinical practices(15).

The first generation of radiation schedules delivered classically 45-50 Gy in 1.8-2.0 fractions to the whole breast over 5-7 weeks. Although efficacious, the protracted duration of treatment reduces the patients' satisfaction and quality of life. And then, as part of the secondary generation of radiation therapy, hypofractionated irradiation has become the standard treatment. However, a treatment duration of 3-4 weeks is still required. Concurrently, accelerated partial breast irradiation (APBI) is also accepted as an attractive treatment strategy and introduced into clinical practice, which has been explored as a technique to shorten the duration of treatment (1-3 weeks) and extent of the irradiated volume. Meanwhile, in order to explore the possibility of shortening more treatment time and the lower limits of hypofractionated, ultra-short WBI and PBI schedules as the third generation of breast radiotherapy, can complete the treatment in less than 5 days (Figure 3).

Figure 3. Development of fractionated schedule irradiation. Source: own edition



RT is used in following situations: (1) After removing tumor by surgery, RT is usually used to destroy cancer cells that may remain, which helps lower the risk of recurrence (2) When breast cancer cannot be removed by surgery or has spread to the other organs of body, such as bones, lungs, brain and liver, RT is often used to shrink tumors and relieve symptoms. This kind of palliative treatment may reduce pressure, pain and other symptoms, which improves patient's quality of life.

1.3.3.1 Conventional fractionation

With the improvements of radiotherapy planning, over the past decade, many different fractionation schedules and techniques have been applied into clinical practice. The standard RT treatment for early-stage breast cancer has traditionally utilized conventionally-fractionated whole breast irradiation (CR-WBI), which deliver 45-50 Gy in 1.8-2.0 fractions to the whole breast per day over 5 weeks. It can also be related to a boost of 10-16 Gy for1-2 weeks(15),(35). However, this kind of RT regimen cause a substantial time and burden on patients. With the development of RT technologies, other alterative fractionated schedules have been receiving increasing attention, such as hypofractionation and accelerated partial breast irradiation (APBI), which preserve the high local control rates, as well as reduce toxicity and economic burdens to patients and provide convenient care(36,37).

1.3.3.2 Hypofractionation

Previous studies demonstrated that the low α/β of breast cancer, ranging from 2.0 to 4.0 Gy, suggesting that the efficacy of Hypofractionation whole breast irradiation (HF-WBI) are equivalent to CR-WBI(38–40). With this advance in radiation techniques, as an alternative to CR-WBI, the HF-WBI deliver a shorter RT duration by involving a higher daily radiation dose per fraction in reduced number of individual fractions, resulting in reduction of the length of treatment (typically 3-4 weeks). This shorter regimen also reduces the cost of cancer treatment, saving 20-30% when compare with CR-WBI. In terms of the efficacy, safety, toxicity and cosmetic results, hypofractionation have been shown an equivalent outcome with CR-WBI(41–47). Therefore, this shorter and more convenient RT schedules have been employed in clinical practice over the last 20 years. And hypofractionated schedule after BCS has been written into NCCN and the other practical guidelines in recent years.

1.3.3.2.1 Randomized clinical trials of moderate hypofractionation

The first major randomized trial of hypofractionation was carried out by Royal Marsden Hospital and Gloucestershire Oncology Centre (RMH/GOC) in 1986(48,49) (Table 2). 1410 women with T1-3 N0-1 M0 invasive breast cancer, less than 75 years, undergoing BCS with negative margin was included in study. Patients were randomized into one of 3 arms: conventional fractionation group (50.0 Gy/25Fx) and two hypofractionation group (39.0 Gy/13Fx, and 42.9 Gy/13Fx groups). After 10 years follow-up, the local

relapse rates were 12.1% for 50 Gy arm, 14.8% for 39 Gy arm, and 9.6% for 42.9 Gy arm (P=0.027). The changes of breast shape were mild in most of patients, the marked chages in photographic appearance was 10.1% in 50 Gy arms 3.4% in 42.9 Gy arm and 5.6% in 39.0 Gy arm. Distant recurrence and survival rates have not been reported.

The Ontario Clinical Oncology Group (OCOG) in Canada randomly divided 1234 patients into HF-WBI and CF-WBI arms in 1993(47). The eligibility criteria are T1-2 N0 M0 invasive cancers in patients undergoing BCS with negative margin. The maximum width of breast tissue ≤ 25 cm at the central axis is an additional criterion in this trial. Patients undergoing mastectomy and receiving boost and regional nodal irradiation were no included in the recruitment. This trial randomized patient to HF-WBI group at 42.5 Gy in 16 fractions over 22 days versus CF-WBI group at 50 Gy in25 fractions over 35 days. At 10 years, the local recurrence did not reach significant difference between these two radiation schedules, with the trend being lower in hypofractionation arms (6.7% in 50 Gy arm versus 6.2% in 42.5 Gy arm). In term of overall survival, HF-WBI was no inferior to CF-WBI arm (84.6%, 84.4%, respectively), and there were no significant differences in the breast cancer mortality or deaths from other causes between these two arms. The cosmetical outcomes was considered good or excellent in 71.3% patients in CF-WBI and 69.8% patients in HF-WBI, which were no significantly different. Grade II-III skin and subcutaneous toxicities were similar between treatment arms at 10-year follow-up.

The UK Standardization of Breast Radiotherapy Trial (START) consisted of 2 studies: START trial A and B(44–46). Among them, START trial A was initiated in 1999,

which enrolled 2236 patients with T1-3a N0-1 M0 breast cancer, undergoing BCS or mastectomy with margins ≥ 1 mm. Patients were randomized to the CF-WBI control arm of 50 Gy/13fractions/2 Gy or two hypofracionated arms 39 Gy/13 fractions/3.0 Gy or 41.6 Gy/13 fractions/3.2 Gy. After 10 years follow-up, START A trial demonstrated that 41.6 Gy/13 fractions or 39 Gy/13 fractions offered an equivalent outcome with the control regimen (standard schedule of 50 Gy/25 fractions). The primary end point was local control, which was no significantly different between the standard fractionation and hypofractionation arms. The 10-year local recurrence rates were 8.1% and 5.6% in 39 Gy and 41.6 Gy hypofractionated arms, respectively, and 6.7% in the control 50 Gy arm. Similarly, distant relapse rates, disease-free survival rates and overall survival rates did no significantly differ between control arm and two hypofractionated experimental arms. The secondary end point was late toxicity, including changes in breast appearance edema, hardness, telangiectasias, breast shrinkage, shoulder stiffness, which was evaluated by photographs and patient-reports. At 10 years, moderate or marked breast induration, telangiectasia and breast oedema were significantly less common in the 39 Gy/3 fx regimen than 50 Gy /2 fx regimen, while the 41.6 Gy and 50 Gy arms shown a similar late toxicity rates and did not reach significant difference. there were not differences in breast shrinkage, shoulder stiffness and edema between classical fractionation and hypofractionation.

The START B was initiated simultaneously with START A to explore a possibly shortened radiation time for hypofractionated irradiation, which compared 50 Gy in 25 fractions over 5 weeks versus 40 Gy in 15 fractions over 3 weeks. 2215 patients were

recruited with identical eligibility criteria with START A. After 10 years follow up, 40 Gy arm also provided a satisfactory result in local relapse rates when compared to 50 Gy arms (5.2%, 3.8%, respectively).

An interesting finding is that the distant recurrence rates (16.0%, 12.3%, p=0.014, respectively) and overall mortality (19.2%, 15.9%, p=0.042, respectively) were significantly higher in control regimen than HF-WBI regimen. The late toxicity was mild. The late toxicity assessed by photographs and patient's quality of life questionnaires were better on 40 Gy arm. It should be noted that unlike the Canada trial, the UK START trials included a wider variety of patients. Despite the variability of these trials, the breast shrinkage, telangiectasias and edema were less common in hypofrationated arm, which suggested a good result favoring the use of hypofractionation regimen.

Based on the results from the well-powered studies that mentioned above, as well as the other trials and meta-analysis, moderate hypofractionation shows a non-inferiority outcome with regard to local relapse, distant recurrence, mortality, toxicity and cost-effectiveness to classical fractionation. Nowadays, moderate hypofractionation with 15-16 Fx/2.6-2.7 Gy has been accepted as the standard treatment for patients with breast cancer (no regional nodal irradiation) who performed BCS in many countries.

Table 2. Main characteristics and results of four major randomized trials comparing hypofractionated and conventional fractionation whole breast irradiation.

	RMH/GO	OCOG	START A	START B
Sample Size	1410	1234	2236	2215
Years Accrual	1986-1998	1993-1996	1998-2002	1999-2001
Stage Eligibility	T1-3 N0-1 M0	T1-2 N0 M0	T1-3a N0-1 M0	T1-3a N0-1 M0
Mean Age (years)	54.5	Not reported	57.2	57.4
Mastectomy, n (%)	0	0	336 (15)	177(8)
Chemotherapy, n (%)	196 (14)	136 (11)	793 (35)	491 (22)
Boost, n (%)	1051 (75)	0	1,152 (61)	875 (43)
Regional nodal irradiation, n (%)	290 (21)	0	318 (14)	161 (7)
Treatment arms (Gy/fractions)	50/25	50/25	50/25	50/25
	42.9/13	42.5/16	41.6/13	40/15
	39/13		39/13	
Local recurrence, % (95% CI)	12.1 (8.8–15.5) vs. 9.6 (6.7–12.6) vs. 14.8 (11.2–18.3)	6.7 vs. 6.2	6.7 (4.9–9.2) vs. 5.6 (4.1–7.8) vs. 8.1 (6.1–10.7)	5.2 (2.7–5.2) vs. 3.8 (2.7–5.2)
Changes in breast appearance rate, %	35.4 vs. 27.4		42.9 vs. 32.1	42.2 vs. 36.5
Good/excellent cosmesis, %	71 vs. 74 vs. 58	71 vs.70	60 vs. 58 vs.66	61 vs. 66

Abbreviation: RMH/GOC`: Royal Marsden Hospital, Sutton and Gloucestershire Oncology Centre; OCOG: Ontario Clinical Oncology Group; START: Standardization of Breast Radiotherapy Trial.

Source: own edition

1.3.3.2.2 Consensus Guidelines of hypofractionation

The American Society for Radiation Oncology (ASTRO) published a consensus guideline in 2011, which determined that patients ≥ 50 years with T1-2 N0 invasive cancer, undergoing BSC and without chemotherapy was applicable to use hypofractionated whole breast irradiation.

Then in 2018, the ASTRO further expanded the applicable patients for HF-WBI, which was endorsed as a new standard of most patients with early-stage breast. The age, tumour grade and administration of systemic therapy were not the contraindications. Besides, hypofractiontion may be used as an alternative treatment to CF-WBI for patient with DCIS. The European Society of Oncology (ESMO) guideline also recommend hypofractionation as routine radiotherapy for breast cancer.

1.3.3.2.3 Randomized clinical trials of ultra-hypofractionation

In an effort to further shorten and condense the overall irradiated time, ultra-hypofractionated schedules have emerged. Recently, results from UK FAST and FAST-Forward phase III randomized clinical trials have been published(50–52) (Table 3), which were built based on the experience of previous START A and B trials(44–46). Notably, this trial is the first extremely hypofractionation for the experimental arms that have never been explored in breast before.

Table 3. Main characteristics of two ultra-hypofractionated trials

	FAST	FAST-Forword
Sample size	915	4096
Years Accrual	2004–2007	2011–2014
Median follow-up	119.8 months	71.5 months
Stage eligibility	pT1–2 (<3 cm) pN0	pT1–3 pN0–1
Age eligibility	Age ≥ 50 years	Age ≥ 18 years
chemotherapy	No	25% of patients
Surgery	BCS	BCS or Mastectomy
Fractionation arms	50 Gy/2 Gy/5 weeks	40 Gy/2.67 Gy/3 weeks
	30 Gy/6 Gy/5 weeks	27 Gy/5.4 Gy/1 week
	28.5 Gy/5.7 Gy/5 weeks	26 Gy/5.2 Gy/1 week
Boost	No	5–8 × 2 Gy
Primary endpoint	Change in photographic breast appearance	Ipsilateral breast tumor recurrence

Abbreviation: BCS: breast-conserving surgery.

Source: own edition

The UK FAST trials randomized 915 with T1-2, N0, M0 invasive breast cancer after BCS with negative margins and tumor< 3 cm(51). Those with RNI and boost were excluded. Patients were randomly divided into one of three fractionated schedules: one

classical radiation (50 Gy/ 25 Fx) arm or two ultra-short experimental arms (28.5 Gy or 30 Gy in five once-weekly fractions of 5.7 Gy or 6 Gy, respectively). The primary endpoint was change in breast appearance. After long-term follow up, changes in breast appearance, assessed by photography were significantly higher in 30 Gy arm as compared to 50 Gy arm (odds ratio [OR] 1.64, 95% CI 1.08–2.49). there was no significant difference between 28.5 Gy and 50 Gy regimen (OR 1.1, 95% CI 0.7–1.71). normal tissue effects, including shrinkage, induration, telangiectasia and edema, was more common in 30 Gy arm compared with 50 Gy arm($p<0.001$), while there were no significant differences between the 28.5 Gy and 50 Gy arm. In terms of tumor control, which is the secondary endpoint of this trial, there was not powered for statistical comparison, so the results have not yet been published. Estimated cumulative incidence for ipsilateral breast were 0.7% at 5 years and 1.3% at 10 years, difference did not reach statistical significance between these arms (Table 4).

Table 4. Selected results of FAST and FAST-Forword randomized trials.

	Radiation arm	Ipsilateral breast tumor recurrence	Adverse event in breast	Breast shrinkage	Breast induration	Telangiectasia	Edema
		%, HR (95% CI)					
FAST	50 Gy	0.7	33.6	28.5	7.4	3.8	4.8
	30 Gy	1.4, HR 1.36 (0.3–6.06)	50.4, HR 1.79 (1.37–2.34)	40.5, HR 1.71 (1.26–2.32)	15.2, HR 2.22 (1.29–3.84)	5.8, HR 1.55 (0.70–3.45)	13.7, HR 2.98 (1.62–5.48)
	28.5 Gy	1.7, HR 1.35 (0.3–6.05)	47.6, HR 1.45 (1.10–1.91)	33.4, HR 1.22 (0.88–1.68)	18.6, HR 2.14 (1.23–3.71)	5.5, HR 1.35 (0.59–3.09)	8.6, HR 1.78 (0.92–3.43)
FAST-Forward	40 Gy	2.1	26.8	14.9	2.9	3.0	5.5
	27 Gy	1.7, HR 0.86 (0.51–1.44)	35.1, HR 1.41 (1.23–1.61)	19.1, HR 1.34 (1.11–1.62)	6.7, HR 2.40 (1.63–3.54)	4.8, HR 1.61 (1.06–2.44)	10.5, HR 1.95 (1.47–2.59)
	26 Gy	1.4, HR 0.67 (0.38–1.16)	28.5, HR 1.09 (0.95–1.27)	14.6, HR 0.99 (0.81–1.21)	4.3, HR 1.42 (0.93–2.17)	3.5, HR 1.41 (0.92–2.16)	7.5, HR 1.36 (1.01–1.85)

Abbreviation: HR: hazard ratio

Source: own edition

Based on the early results from FAST trial(50), the UK FAST- Forward randomized trial was designed as their second protocol. In Fast-Forward clinical trial, 40 Gy in 15 fractions in 3 weeks were used as a new standard control arm. Using as a very accelerated course, patients also randomly allocated patients into 27 Gy/5 fractions/ 1-week, 26 Gy/5 fractions/1-week in order to test the extremely hypofractionation for completing treatment within 1 week. At 5-year, estimated cumulative incidence of ipsilateral breast tumor relapse was 2.1% for control arm, 1.7% for 27 Gy arm and 1.4% for 26 Gy arm (when 26 Gy compared to 40 Gy, hazard ratio [HR]=0.86, 95% CI: 0.51–1.44; when 27 Gy compared to 40 Gy, HR=0.67, 95% CI: 0.38–1.16). The two experimental arms shown a similar estimated cumulative incidence. It also demonstrated that between 1-week schedules and the 3-week regimen, there was not significant difference in disease-free survival and overall survival. This trial was not powered for subgroup analysis in terms of local recurrence due to the low number of events. The 27 Gy arm shown a significantly higher risk of late toxicity compared to standard arm. The marked or moderate normal tissue effects of lower dose experimental 26 Gy arm were not significantly different to the control arm. The induration of breast in 26 Gy (OR 1.9, 95% CI 1.15–3.14) arm was superior to the 27 Gy arm (OR 2.79, 95% CI 1.74–4.50). Patient-reported toxicity outcomes support the findings that mention above. Moderate or marked toxicity effects was reported more frequently in 27 Gy arm, while the 26 Gy arm was non inferior to 40 Gy arm.

1.3.3.3 Accelerated partial breast irradiation

1.3.3.3.1 Techniques and randomized trials of accelerated partial breast irradiation

Early-stage breast cancer is estimated to account for approximately 60% of breast cancer. The whole breast irradiation after BCS now is well accepted and become a standard of care for these patients. However, due to the assumption that radiotherapy has greater effect in reducing local relapse instead of eliminating possible tumor in remote areas, there is still doubt about whether whole breast irradiation is needed in this kind of patients. In addition, although it is strongly recommended to combine BCS with radiotherapy, there are still 15-30% of patients have not received radiotherapy as part of treatment(53). Physician bias, age, cost-effectiveness, access to health care institution, poor ambulatory status may lead to the underuse of radiotherapy. Therefore, a shortened radiation schedule may resolve these problems and allow more patients to receive radiation therapy(54).

In selected patients with low-risk, accelerated partial breast irradiation (APBI) has emerged as an attractively alternative treatment strategy and introduced into clinical practice. APBI can reduce both the irradiated volume and overall duration of radiotherapy (10-15 fractions/1week twice daily, typically), and targets the tumor bed and margin of adjacent tissue, which not only reduces the normal tissue effects but also provides a satisfactory disease control. Several clinical trials have investigated the efficacy of APBI (Table 5). It showed that APBI was as safe as whole-breast irradiation, and reported a similar toxicity and good/excellent cosmetic results at 5 years follow-

up(55,56). These findings provide increasing evidence for the acceptance of routine employ of APBI.

Table 5. Selected phase 3 APBI clinical trials.

	Patients	Techniques	APBI experimental arm	Control arm	5-year local recurrence
GEC-ESTRO(57)	1,300	MIB	32 Gy /8 Fx or 30.3 Gy/7 Fx	WBI: 50–50.4 Gy in 25/28 Fx + optional 10 Gy boost	MIB:1.44% WBRT: 0.92%
IMPORT-LOW(58)	1,935	EBRT	40 Gy/15 Fx + 36 Gy in 15 Fx to low-risk region or 40 Gy /15 Fx	WBI: 40 Gy/15 Fx	EBRT: 0.5% WBRT: 1.1%
RAPID(59)	2,128	EBRT	38.5 Gy /10 Fx (5–8 days)	WBI: 42.5 Gy/16 Fx. Large breast received 50 Gy in 25 fractions.	EBRT: 3% WBRT: 2.8
NSABP-B-39/RTOG 0413(56)	4,300	EBRT	34 Gy /10 Fx or 38.5 Gy over 10 Fx	WBI: 50–50.4 Gy/25 or 28 Fx + optional 10–16 Gy boost	
ELIOT(60)	824	IORT	21 Gy /1 Fx electrons up to 9 MeV	WBI: 50 Gy/25 Fx + optional 10 Gy boost	IORT: 4.4% WBRT: 0.4%
TARGIT(17,61)	2,232	IORT	20 Gy /1 Fx, low energy X-rays (50 Kv)	WBI: 50 Gy/25 Fx	IORT+WBRT:3.3% WBRT 1.3%

Abbreviations: MIB, multicatheter interstitial brachytherapy; EBRT, external-beam radiotherapy; IORT, intraoperative radiotherapy; WBI, whole-breast irradiation.

Source: own edition

1.3.3.3.2 Brachytherapy

One of the most widely used APBI modalities is multicatheter interstitial brachytherapy (MIB), and it was also the first technique developed. Numerous studies have been conducted (Table 6), in most of them enrolled patients with early-stage breast cancer, T1-2, N0-1, M0, with negative margins. After 4-8 weeks of surgery, 10-20 interstitial catheters were placed at 10-15mm to encompass the lumpectomy cavity by using free-hand or template-guided technique (placing surgical clips as guidance)(55,62).

Table 6. Selected results of multicatheter interstitial brachytherapy studies.

	Patients	Dose/ fraction	IBTR (%)
King *et al.*(63)	51	45 Gy over 4 days or 4 Gy/8 fx	2
Antonucci *et al.*(64)	199	0.52 Gy/h for 96 h or 4 Gy/8 fx or 3.4 Gy/10 fx	5
Arthur *et al.* (65)	99	0.4–0.54 Gy/h for 3.5–5 days or 3.4 Gy/10 fx	4
Ott *et al.*(66)	274	0.6 Gy/h over 5 days or 4 Gy/8 fx	2.9
Polgár *et al.*(67)	45	4.33 Gy /7 fx or 5.2 Gy/7 fx	8.9

Abbreviations: IBTR, ipsilateral breast tumor recurrence;

Source: own edition

In the Group Européen de Curiethérapie/European Society for Radiotherapy and Oncology (GEC-ESTRO) phase 3 trial, 1184 patients with Tis-2a, N0-1mic, M0 breast

cancer, >40 years, at least 20mm of safety margin in all direction were randomized to WBI or APBI arm. A total dose of 50.0-50.4 Gy in 25-28 fractions was delivered in patients allocated to WBI arm. High-dose-rate (HDR) or pulsed-dose-rate (PDR) muticatheter brachytherapy was delivered with 32 Gy/ 8 Fx or 30.3 Gy/ 7 Fx, twice a day in APBI arm. After long-term follow-up, APBI shown a non-inferiority in local control rate compared with WBI (1.4% vs. 0.9%, p=0.42, respectively). At 5 years, local relapse (0.97% or1.07% vs. 1.38% or 1.33%, respectively), disease-free survival (94%, 95%, respectively) and overall survival rates (95.6%, 97.3%, respectively) were similar between control WBI and experimental APBI arms. The accumulative incidence of grade 2-3 toxicity was higher in WBI arm versus APBI arm (10.7% vs. 6.9%, p=0.02, respectively), but cosmetic outcomes was no different(56,57,68).

1.3.3.3.3 External-beam radiotherapy

With the three dimensional-conformal radiation therapy(3D-CRT) beam, patients can be treated in supine or prone with 4-5 non-coplanar beam.

In IMPORT LOW multicenter randomized phase 3 trial(58), 2018 patients were enrolled into 3 arms: 40 Gy in 15 fractions of WBI arm (control arm), 36 Gy in 15 fractions of WBI with simultaneous 40 Gy integrated boost to tumor bed (reduced dose arm), or 40 Gy in 15 fractions to partial breast only (partial-breast arm). In 5 years, local recurrence was 1.1 in control group, 0.2 in reduced-dose arm, and 0.5% in partial-breast arm. Overall survival and cometic outcomes were similar between groups (Table 5).

The RAPID trial(59,69) randomized 2135 patients to 42.5 Gy/ 16 Fx or 50 Gy/25 Fx

arms. Patients in APBI arm were treated with 3-5 non-coplanar conformal fields. After a median follow-up of 8.6 years, APBI demonstrated a similar local relapse rate to WBI (3.0%, 2.8%, respectively). Regarding to the late toxicity, grade 2 (28% of APBI vs. 12% of WBI, $p<0.001$) and grade 3 toxicity rates (4.5% of APBI vs 1% of WBI, $p<0.001$) were significantly higher in APBI arm.

In NSBAP-B-39/RTOG 0413 phase 3 trial(70), 4216 patients were randomized to 50 Gy in 1.8-2.0 Gy WBI arm or 34 Gy in 3.4 Gy using interstitial brachytherapy or 38.5 Gy in 3.85 Gy using 3D-CRT beam APBI arm. After 10.2 years follow-up, cumulative recurrence incidence, disease-free survival, overall survival late grade 3 or greater toxicity were similar between groups. Patient-reported and photographic cosmetic outcomes was not different.

Results of other studies using external beam radiation are shown in table 7.

Table 7 Selected external beam radiation studies

	Patients	EBRT dose (bid)	IBTR (%)	Cosmesis (%) *
Chen *et al.* (71)	94	3.85 Gy/10 fx	1.1	89
Hepel *et al.*(72)	60	3.85 Gy/10 fx	NR	81.7
Vicini *et al.*(73)	58	3.85 Gy/10 fx	6	NR
	102	37.5 Gy/3.75 fx	0	75
Shah *et al.*(74)	192	3.85 Gy/10 fx	0	81

Abbreviations: APBI, accelerated partial breast irradiation; IBTR: Ipsilateral Breast Tumor Recurrence; *: Good/excellent rates (%)

Source: own edition

1.3.3.3.4 Intraoperative radiotherapy

Intraoperative radiotherapy (IOR) has been an exciting development in APBI. Two of the most widely used devices are the Intrabeam (Oberkochen, Germany) and Novac7 (Hitesys, Latina, Italy).

The Novac7 is a mobile accelerator capable of generating vary energies (3 MeV, 5 MeV, 7 MeV and 9 MeV), which had been assessed in Milan Electron IntraOperative Trial (ELIOT)(60). In the trial, 1305 patients >48 years, with tumor diameter ≤ 2.5cm, undergoing BCS were randomized to single-dose IOR arm with electrons with 21 Gy prescribed to tumor bed or 50 Gy in 25 fractions WBI arm. The overall treatment duration was 30-40 min. after median follow-up of 5.8 years, breast recurrence rates were significantly higher in IOR arm than WBI arm (n=35, 4.4%; n=4, 0.4%, $p<0.0001$). no significant difference in overall survival rates. The skin adverse effects were significantly lower in IOR group. After adjustment for potential confounders in multivariate analysis, patients with tumor size >2 cm, more than 4 positive lymph nodes, G3 and triple negative were the significant predictors of increasing risk of recurrences.

1.4 Linear-quadratic (LQ) model, α/β ratio and biologically equivalent dose (BED)

In order to compare the RIT following different radiotherapy regimen protocols and design novel radiotherapy schedules in clinical trials, several iso-effect models have been used to forecast the late responding effects. Among them, the linear-quadratic (LQ) model was adopted to calculate the BED for each fractionation schedule, because of the better description of iso-effect curves(55,56). With this mathematical model, it is possible to forecast the various tissues toxicity in response to different radiation regimens. And compared with the simple dose-response model, the BED-response model is more clinically relevant(39). On this assumption, different fractionation schedules can be directly compared. The α/β ratio in the LQ model represents the fractionation radiosensitivity of the irradiated cells, which values correspond to the different tissues involved(75).

1.5 Radiation-induced toxicity

Radiation therapy is provided as an important complementary treatment, which improves the local-regional control and reduces the risk of cancer recurrence(15). However, in spite of the advances in radiotherapy planning and treatment technology, acute radiation-induced toxicity (RIT) occurs in more than 90% of women. And approximately 30%-40% of post-RT patients will suffer chronic RIT(15,76–78), ranging from dermatitis (erythema), fibrosis (induration), desquamation (moist or dry)

to necrosis. As a result, RIT may affect the function of skin and appearance of breast, which is a key factor impacting on patients satisfaction and quality of life. Nevertheless, due to the high 5-year and 10-year survival rate throughout the past decade (approximate 90%, 80%, respectively)(79–81), patients will live for many years with RIT.

1.5.1 Clinical qualitative toxicity assessment

In most previous studies and current clinical practice, RIT are classified by using the common rating criteria, such as Common Terminology Criteria for Adverse Events (CTCAE), Radiation Therapy Oncology Group (RTOG) scales, World Health Organization (WHO) criteria (Table 9) and Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic (LENT-SOMA) scales (Table 10). These qualitative toxicity scores are subjectively carried out by visual inspections and tactile examinations of physicians, although fast and simple, such assessments are limited to 4 or 5 discrete grades. Generally, grade 0 means an absence of toxicity and grade 4 indicates that the radiation effects led to death(82). In addition, due to the inherent subjective nature, the estimation of skin changes by different physicians may cause inevitable inter-observer and intra-observer variability and lead to a non-negligible significant bias, particularly in multicenter studies(83).

Table 9. Clinician-assessed skin and subcutaneous tissue toxicity scoring criteria

	Grade 1	Grade 2	Grade 3	Grade 4
RTOG				
Skin	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Market atrophy; gross telangiectasia	Ulceration
Subcutaneous tissue	Slight induration (fibrosis) and loss or subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; < 10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis
CTCAE (version 5.0)				
Skin	Faint erythema or dry desquamation;	Moderate to brisk erythema; patchy moist desquamation, moderate edema;	Moist desquamation in areas other than skin folds and creases;	Life-threatening consequences; skin necrosis or ulceration; skin graft indicated
Subcutaneous tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin.	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement.	Generalized induration; associated with signs or symptoms of impaired breathing or feeding
WHO				
Skin and subcutaneous tissue	Erythema	Dry desquamation, vesiculation, pruritus	Moist desquamation, ulceration	necrosis requiring surgical intervention

Abbreviation: CTCAE: Common Terminology Criteria for Adverse Events; RTOG: Radiation Therapy Oncology Group scales; WHO: World Health Organization.

Source: own edition

Table 10. Clinician-assessed skin and breast LENT/SOMA toxicity criteria

		Grade 1	Grade 2	Grade 3	Grade 4
Skin	Pigmentation change	Transitory, slightly	Permanent, marked		
Breast subjective	Pain	Occasional and minimal hypersensation, pruritus	Intermittent and tolerable	Persistent and intense	Refractory excruciating
Breast objective	Telangiectasia	<1 cm^2	1-4 cm^2	>4 cm^2	
	Fibrosis	Barely palpable, increase density	Definite increase intensity and firmness	Very marked density, retraction and fixation	
	Edema	Asymptomatic	Symptomatic	Secondary dysfunction	
	Retraction, atrophy	10-25%	25-40%	40-75%	Whole breast

Source: own edition

1.5.2 Quantitative toxicity assessment

In order to avoid the inter-observer and intra-observer evolution bias, many objective assessment tools have been introduced to monitor skin changes more accurately, including ultrasound(84–88), reflectance spectrophotometer(86,89), Laser Doppler Flowmetry(90,91) and corneometry(92–95) (Table 11). Although these objective techniques hold the advantage of estimating the early tissue response to radiotherapy and providing a better reliable quantification of RIT, however, no tools have been

routinely used in clinical practice or have taken the place of RTOG or CTCAE scales successfully.

Table 11. Selected studies using quantitative toxicity assessments

Study	n	Radiation schemes	Techniques	Quantitative assessment	Qualitative assessment	Correlation
Warszawski et al.(96)	29	CF-WBI: 46-50 Gy/2Gy	Ultrasound	significant differences between treated and untreated breast skin regarding the dermal thickness in early (P<0.001) and in late (P = 0.0018) toxicity.	RTOG	late toxicity were discrepancies between clinical-assessment and ultrasonic changes
Liu et al.(88)	18	CF-WBI: 50.0-50.4 Gy in 1.8 or 2.0 Gy	Ultrasound	Average skin thickness increased from 2.05 ± 0.22mm to 2.61 ± 0.52mm (p<0.001); Pearson coefficient decreased from 0.41 ± 0.07 to 0.28 ± 0.05 (p<0.001); midband fit increased from -0.92 ± 7.35 dB to 0.87 ± 6.70 dB	RTOG	ultrasonographic evolution corresponded with RTOG score
Yoshida et al.(84)	26	CF-WBI: 50.0-50.4 Gy in 1.8 or 2.0 Gy	Ultrasound	Intra-observer ICC for dermal, hypodermal and glandular tissue toxicity was 0.89, 0.74, 0.96, respectively. Inter-observer ICC for dermal, hypodermal, and glandular tissue toxicity was 0.78, 0.74, 0.94 respectively.	RTOG	The ultrasound measurements correlated with RTOG scale
Landoni el al.(97)	89	HF-WBI: 34 Gy /10 Fx/ 3.4Gy	Ultrasound	The mean skin thickness in the irradiated breast vs. contralateral breast (2.13 ± 0.72 mm vs. 1.61 ± 0.29 mm). The mean skin thickness in the treated boost region vs.	CTCv3	The increase of skin thickness in the treated breast and in the boost region were related to fibrosis (G ≥ 1).

				corresponding region of untreated breast (2.25 ± 0.79 mm vs. 1.63 ± 0.33 mm)		
Wengstrom el al.(98)	53	CF-WBI: 50 Gy/ 2 Gy	1.Reflectance spectro-photometer 2. measure digital images (Camera)	Spectrophotometer demonstrated a non-significant reliability coefficient (r=-0.2). The camera provided a significant evidence of reliability in skin erythema measurement.	RTOG	
Schmeel et al.(89)	140	CF-WBI: 50 Gy/ 25 Fx; HF-WBI: 40.05 Gy/ 15 Fx	Reflectance spectro-photometer	Erythema and hyperpigmentation were lower in HF arm (p=0.008, p=0.02, respectively). Patients were also reported less pain and less limitation of day-to-day activities in HF arm (p=0.006, p<0.001, respectively).	CTCAE	HF regimen shown a significantly lower radiation dermatitis when compared with CF arm in CTCAE criteria and objective assessment.
Yamazaki et al.(99)	46 in CF-WBI; 26 in HF-WBI.	CF-WBI: 50 Gy/ 25 Fx; HF-WBI: 42.56 Gy/ 16 Fx	Reflectance spectro-photometer	Radiotherapy decreased the L* value (darker) and increased the a* value (redder) gradually. HF shown a milder color alteration than CF	CTCAE	CTCAE did not show a statistically significant difference between the HF and CF groups
Yoshida et al.(86)	18	CF-WBI: 50.0-50.4 Gy in 1.8 or 2.0 Gy	Spectro-photometer and ultrasound.	Significant changes between the treated and untreated breasts were observed. 27.3% mean increase in skin thickness), 34.1% mean decrease in Pearson coefficient, 27.3% mean increase in melanin, and 22.6% mean increase in erythema	RTOG	All parameters except skin thickness shown correlation with RTOG; Spectrophotometer parameters do not correlate with ultrasound parameters.
Saednia et	90	HF-WBI:	Thermal	Early thermal signals were	CTCAE	Patients with

al.(100)		4250 cGy / fx = 16	imaging device	related to skin toxicity after the 5 RT fraction.		CTCAE>2 associated with higher local increases in skin temperature (p=0 .029).
Sanchis et al.(90)	63	HF-WBI: 40 Gy/ 15 Fx/ 2.67Gy	Laser Doppler flowmetry (LDF)	MCI was positively correlated with the dose (r = 0.647; p < 0.001). Differences in MCI from baseline to the end of radiotherapy were significant (p < 0.001).	CTCAE	Significant changes in MCI values were observed among CTCAE grades (p=0.016)
Nuutinen et al.(101)	21	CF-WBI: 50 Gy/ 25 Fx;	Dielectric constant	Dielectric constant decreased by 31 and 39% in the photon and electron fields skin sites, respectively. Mean dielectric constant was inversely related to erythema.		There was a positive correlation between dielectric constant and clinical fibrosis score.
Huang el al.(102)	101	CF-WBI: 50.0-50.4 Gy in 1.8 or 2.0 Gy	Multi Skin Test Center MC900, corneometer and skin pH meter	Treated breast showed a significant increase in cutaneous blood flow, pigmentation, and skin surface pH, and a decrease in skin hydration.	RTOG, CTCAE and WHO	RTOG, CTCAE and WHO show strong correlation with cutaneous blood flow measurements, but did not showed correlation with skin hydration or pH.
Sekine et al.(93)	43	CF-WBI: 50 Gy/ 25 Fx;	Multi-Display Device MDD4; Corneometer; Tewameter; Mexameter	The quantitative changes of toxicities developed serially from erythema followed by dryness and pigmentation. Radiodermatitis were almost similar course and peak points in subjective and objective measurements.	CTCAE	Melanin index showed significant correlation with pigmentation grades.

Abbreviation: RTOG:Radiation Therapy Oncology Group; CTCAE: Common Terminology Criteria for Adverse Events ; LDF: Laser Doppler flowmetry; MCI: Microcirculation index. Source: own edition.

1.5.2.1 Ultrasound

Ultrasound has been introduced as a complementary or alternative tool for RIT evaluations. This safe and noninvasive tool can objectively assess the changes in skin and subcutaneous tissue microstructures. Generally, three parameters from the radio-frequency signals, including skin thickness, Pearson coefficient and midband fit were used to quantify toxicity. However, the use of ultrasound requires long-term training, which is not conducive to the application of this tool in clinical practice.

In Warszawski et al. study, 29 patients recieved 46-50 Gy/ 2 Gy to whole breast. A ceramic 20 MHz ultrasound was used to evaluate the RIT. Ultrasound significant differences between treated and untreated breast skin regarding the dermal thickness in early ($P<0.001$) and in late ($P = 0.0018$) toxicity. RTOG late toxicity was found discrepancies between clinical-assessment and ultrasonic changes ($K = -0.13$, Pearson's correlation) (96).

In the Liu et al. study, 50.0-50.4 Gy CF-WBI was delivered in 18 patients. All enrolled patients received both ultrasound scans and RTOG toxicity assessment in routine follow-up visits by the same phisician. Ultrasound B-mode images and radio-frequency echo signal were obtained in 4 quadrants of each breast. The value of non-irradiated breast serves as inter-control. After median 22-months follow-up, significant changes were found in irradiated and non-irradiated breast. Average skin thickness increased from 2.05 ± 0.22mm to 2.61 ± 0.52mm ($p<0.001$); Pearson coefficient decreased from 0.41 ± 0.07 to 0.28 ± 0.05 ($p<0.001$); midband fit increased from -0.92 ± 7.35 dB to 0.87 ± 6.70 dB ($p=0.008$). Additional, the ultrasonographic evolution corresponded

with RTOG score and suggested that ultrasound may be used to monitor RIT(88).

Yoshida et al. tested the reliability of ultrasonic assessment of irradiation toxicity. Standard radiation regimen 50.0-50.4 Gy in 1.8 or 2.0 Gy to whole breast was delivered in 26 patients. Among them, 8 patients were assessed for acute toxicity, and 18 patients were measured for chronic toxicity. Ultrasound B-mode images and radiofrequency echo signal were obtained from 4 quadrants of each breast and tumor bed. The untreated breast served as the control. In order to assess intra-observer reliability, one observer analyzed 720 images and then reanalyzed 3 month later. For inter-observer reliability, three observers each analyzed 720 images. The intra- and inter-observer reliability was assessed by intraclass correlation coefficient (ICC). Intra-observer ICC for dermal, hypodermal and glandular tissue toxicity was 0.89, 0.74, 0.96, respectively. Inter-observer ICC for dermal, hypodermal, and glandular tissue toxicity was 0.78, 0.74, 0.94 respectively. The ultrasound measurements correlated with RTOG scale (84).

Landoni et al. reported the possibility to assess RIT with major concern in boost region by ultrasound. Eighty-nine patients received 34 Gy in 10 daily fractions with 8 Gy boost in a single fraction to tumor bed was included in this study. Skin thickness was obtained at the irradiated breast, the boost region and the corresponding locations in the untreated breast. After median 20.5 months follow-up, months. The mean skin thickness in the irradiated breast was higher than contralateral breast (2.13 ± 0.72 mm vs. 1.61 ± 0.29 mm). The mean skin thickness in the treated boost region was also higher than those in the corresponding region of untreated breast (2.25 ± 0.79 mm versus 1.63 ± 0.33 mm). The increase of skin thickness in the treated breast and in the boost region were related

to fibrosis (G ≥ 1)(97).

1.5.2.2 Reflectance spectrophotometer

The reflectance spectrophotometer use L*a*b* coordinate system, which L* indicates lightness and a*and b* are the chromaticity coordinates. The a* value indicates the colors ranging from red to green, and the b* value indicates colors from blue to yellow. The green light with wavelengths of 568nm was used to measure erythema, and red light with wavelengths of 655nm was used to detect pigmentation. A decrease in L* index and an increase in a* values relate with increased erythema and pigmentation. This objective technique for erythema and pigmentation has been used in the measurement of radiation toxicity on several studies(86,89,98,103).

Wengstrom el al. used reflectance spectrophotometer and RTOG scoring system to assess skin erythema. A sample of 53 women was delivered in 50 Gy/ 2 Gy with 6 MV photon beams. The measurements of reflectance spectrophotometer were obtained in five anatomical sections and demonstrated a non-significant reliability coefficient (r=-0.2)(98).

Schmeel et al. also used spectrophotometer to objectively determine acute RIT during HF-WBI and CF-WBI. Radiation dermatitis was evaluated by physician-assessed CTCAE score and patient-reported RISRAS criteria. Besides, skin color was also assessed by spectrophotometer in two arms. HF regimen shown a significantly lower radiation dermatitis when compared with CF arm in CTCAE criteria (mean 1.05 vs.

1.43, p = .024). Based on objective assessment, erythema and hyperpigmentation were lower in HF arm (p=0.008, p=0.02, respectively). Patients were also reported less pain and less limitation of day-to-day activities in HF arm (p=0.006, p<0.001, respectively)(89).

1.5.2.3 Laser Doppler flowmetry

Laser doppler flowmetry (LDF) is a non-invasive method that can assess changes in skin microcirculation. This objective tool provides a real-time cutaneous blood flow measurement to assess acute radiodermatitis by using a skin penetrating infrared laser beam (785nm(90,91).

Sanchis et al. used LDF to assess radiodermatitis in 63 patients who were delivered 40 Gy with IMRT in 15 fractions. Microcirculation index (MCI) was used to characterize variation in distribution of blood perfusion to facilitate comparison. MCI was positively correlated with the dose (r = 0.647; p < 0.001). Differences in MCI from baseline to the end of radiotherapy were significant (p <0.001). Significant changes in microcirculation index values were observed among CTCAE grades (p=0.016)(90).

1.5.2.4 Dielectric constant

Dielectric constant is a quantitative technique for assessment of RIT by visible wavelengths, which consist of an opened-ended probe and a computer-controlled

network analyzer. The analyzer sends the electromagnetic waves into the skin and then measures the reflected waves.

In Nuutinen et al. study, the dielectric constant was evaluated by an electromagnetic frequency of 300 MHz in 21patients who received 50 Gy/ 25 Fx to the whole breast. At 5 weeks, dielectric constant decreased by 31 and 39% in the photon and electron fields skin sites, respectively. Mean dielectric constant was inversely related to erythema. At 2 years, 14 patients were remeasured, and there was a significantly positive correlation between dielectric constant and clinical fibrosis score(101).

1.5.2.5 Multi skin device

The multi skin device generally consist of various probes: a mexameter probe to assess erythema and pigmentation, a corneometrer to detect relative water content of breast skin etc.

Huang el al. enrolled 101 patients into 50.0-50.4 Gy in 1.8 or 2.0 Gy radiation regimen. A Multi Skin Test Center MC900, a corneometer and a skin pH meter were used to assess RIT. Treated breast showed a significant increase in cutaneous blood flow, pigmentation, and skin surface pH, and a decrease in skin hydration. RTOG, CTCAE and WHO show a strong correlation with cutaneous blood flow measurements ($r= 0.70$ for RTOG, 0.68 for CTCAE, and 0.50 for WHO), a moderate correlation with pigmentation ($r=0.4$-0.5), however, showed no significant correlation with skin hydration or pH ($r<0.2$)(102).

In Sekine et al. study, toxicities were measured by A Multi-Display Device MDD4 a corneometer, a tewameter and a Mexameter. A total of 43 patients received 50 Gy in 25 fractions. The quantitative changes of toxicities developed serially from erythema followed by dryness and pigmentation. Radiodermatitis were almost similar course and peak points in subjective and objective measurements. Melanin index showed significant correlation with pigmentation grades. However, there was no significant correlation between skin dryness grade and barrier function(93).

2. Hypothesis

2.1 Principal hypothesis:

The objective multi-probe tool (Multi Skin Test Center MC750) can assess RIT in terms of skin color alteration (erythema, pigmentation), induration and dehydration following different protocols of radiotherapy.

2.2 Secondary hypothesis:

(1) Biologically equivalent dose is associated with radiation-induced toxicity.

(2) The multi-probe objective toxicity measurement is related to subjective clinical RTOG assessment.

(3) The multi-probe objective tool can be used to assess toxicity for patient undergoing breast reconstruction.

(4) Heterologous reconstruction has the similar number of revision surgeries, incidence of complication, toxicity and cosmetic results, compared with autologous reconstruction.

3.Objective

3.1 Principal Objective:

Determine whether our quantitative and multiprobe technique is able to assessment the degree of late RIT in terms of skin color alteration (erythema, pigmentation), induration and dehydration following different protocols of radiotherapy.

3.2 Secondary objective:

(1) Establish an underlying BED-response relationship base on both RIT objective and subjective measurements.

(2) Determinate whether our objective assessment (Multi Skin Test Center MC750) is related to subjective clinical assessment (RTOG).

(3) Determine whether our quantitative technique is able to assess toxicity among a series of patients undergoing radiotherapy and breast reconstruction.

(4) Assessing the median time between radiotherapy and reconstruction, number of revision surgeries, incidence of complications, toxicity, aesthetics and associated clinical risk factors between heterologous reconstruction and autologous reconstruction.

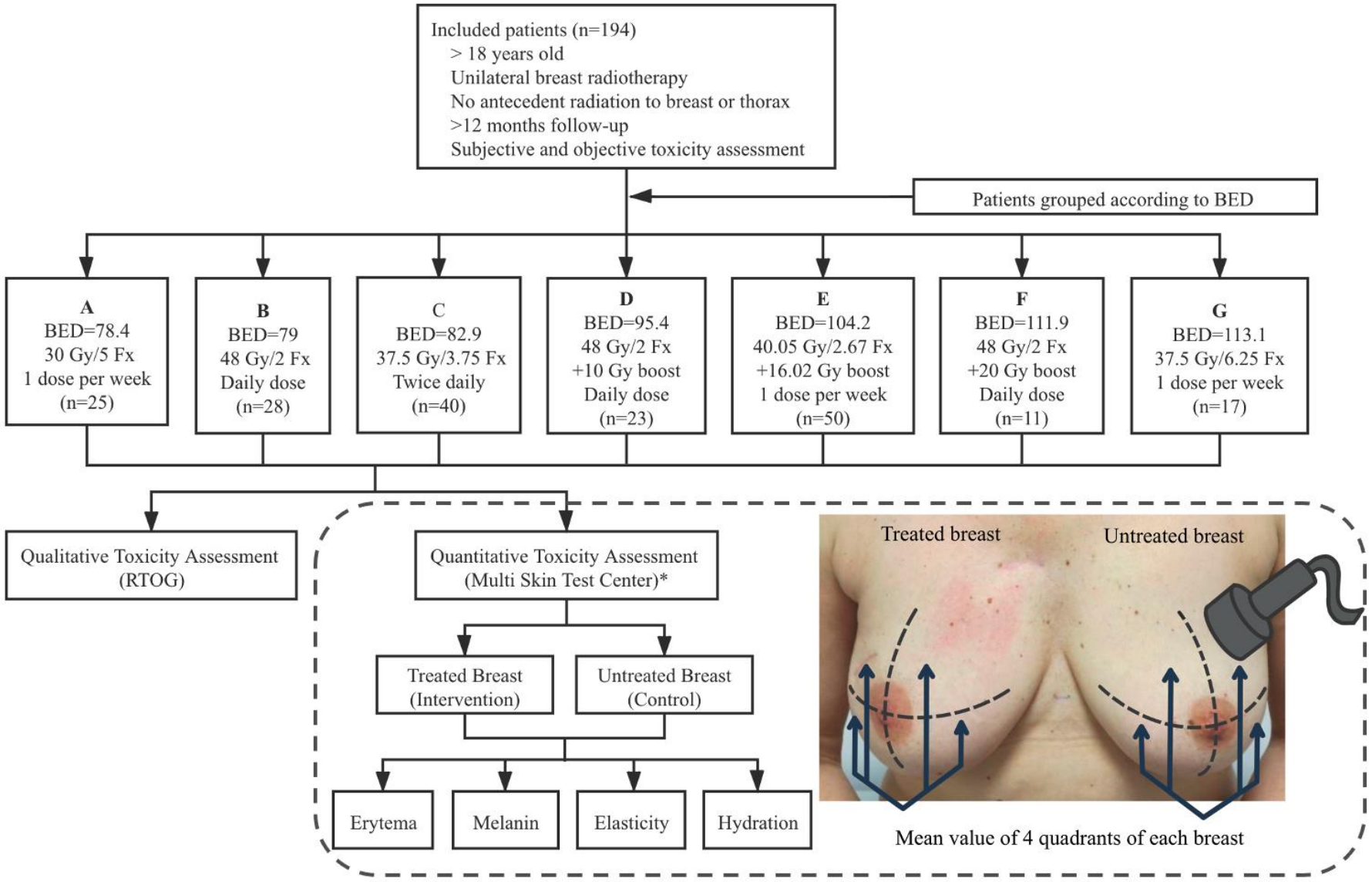
4. Materials and methods

4.1 First study

4.1.1 Patients

Patients were prospectively recruited to this study to assess RIT by means of qualitative and quantitative examination. Patients recruitment based on the following inclusion criteria: patients >18 years old, receiving unilateral breast radiotherapy, follow-up > 12 months, no antecedent irradiation to breast or thorax, accepting subjective and objective toxicity assessment. Exclusion criteria were as follows: follow-up < 12 months, bilateral radiotherapy, prior breast or thoracic radiotherapy, pre-existing skin diseases, skin alterations caused by another treatment, history of allergic skin reaction, refused allocated treatment, no toxicity assessment, withdrawal of consent. Study was approved by Ethic Committee. All patients provided a written informed consent. Radiation-related information and flow chart is shown in figure 5.

Figure 5. Study design and flow chart of participating patients.



In particular, the presence of skin alterations characterized by erythema, contracture and dehydration in breasts.

4.1.2 Radiotherapy

In our study, several fractionation schedules were applied as shown in figure 5. In the conventional fractionation group, 48 Gy at 2 Gy was delivered to the whole breast (CF), with or without an additional 10 Gy (CF+low boost) or 20 Gy (CF+ high boost) at 2 Gy per fraction to the tumor bed. The daily hypofractionation (DHF) schedule consisted of 40.05 Gy in 2.67 daily fractions to the breast, followed by boost dose of 16.2 Gy to the tumor bed; weekly hypofractionated radiotherapy consisted of 30 Gy in 6 fractions of 5 Gy (WHF-low dose) or 37.5 Gy in 6 fractions of 6.25 Gy over 1 week (WHF- high dose). The APBI group was scheduled to receive 37.5 Gy in 3.75 Gy/fraction twice a day, each irradiation separated at least 6 hours (Table 11). All trials delivered radiation schedules according to predefined protocol.

Table 11. Radiated-related information

Treatment Protocol	Patients. No. (n, %)	Total Dose (Gy)	Boost (Gy)	Fractions	Dose per Fraction	BED (α/β=10 Gy) Of Acute Toxicity	BED (α/β=3.1 Gy) Of Late Toxicity
Conventional Fractionation	28（14.1）	48	-	24	2	57.6	79
	23（11.6）	58	10	29	2	69.6	95.4
	11（5.5）	68	20	34	2	81.6	111.9
Moderate Daily Hypofractionation	50（25.1）	56	16.2	21	2.67	70.9	104.2
Weekly Hypofractionation	25 (12.6)	30	-	6	5	45.0	78.4
	17（8.5）	37.5	-	6	6.25	60.9	113.1
APBI	40（20.1）	37.5	-	10 (BID)	3.75	51.5	82.9

Abbreviation: APBI: accelerated partial breast irradiation; BED: Biologically equivalent doses; BID: twice a day.

4.1.3 Clinical toxicity assessment

Patients were subjectively evaluated for acute and late RIT using the RTOG scoring system by physicians. Acute toxicity was measured within 3 months following RT; late toxicity was assessed at least 12 months after finishing RT. The examinations were carried out by visual inspection and palpation of both breasts, ranging from grade 0 (no reaction) to grade 4 (severe toxicity).

4.1.4 Objective quantitative toxicity assessment

A Multi Skin Test Center MC 750 B2 device (CK Electronic, GmbH; Cologne, Germany) was used to detect RIT. This multifunctional device consists of various probes that assess four skin parameters simultaneously for each patient: a mexameter probe for assessing erythema (redness) and melanin (pigmentation), a suction cup probe for assessing elasticity (as the surrogate of fibrosis) and a corneometry probe for assessing skin hydration (the relative water content of the skin of the breast) (Figure 7 and 8). Measurements were obtained from 4 quadrants of each breast, separately in the irradiated breast and the corresponding symmetric regions in the nonirradiated breast (Figure 9). Toxicity values were averaged for each quadrant of the breast with computerized processing to reflect the overall characteristics of the skin and subcutaneous tissues of the whole breast. The entire process of assessing toxicity took approximately 5 minutes per patient. To exclude the bias of the individual skin quality on the toxicity result, we used the absolute difference in toxicity between the treated

and untreated breasts to assess the outcomes (Δerythema, Δmelanin, Δelasticity and Δhydration). The results of the objective assessments were also used to determine whether they are correlated with those of the subjective evaluations.

Figure 7. Probes of multi-probe device from left to right: pigmentation (erythema and melanin), elasticity and hydration probes.

Figure 8. Example of measurement of the erythema and melanin parameters with the corresponding probe.

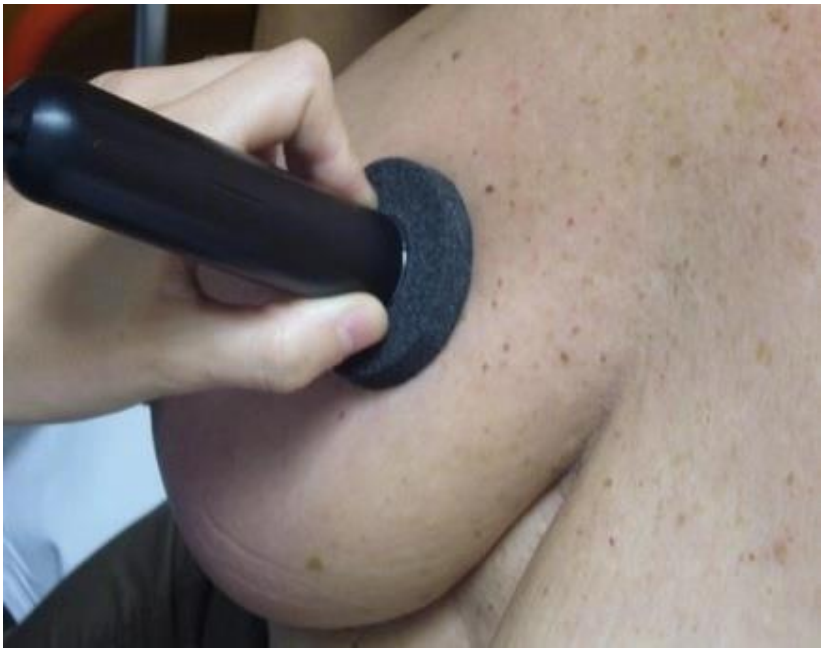
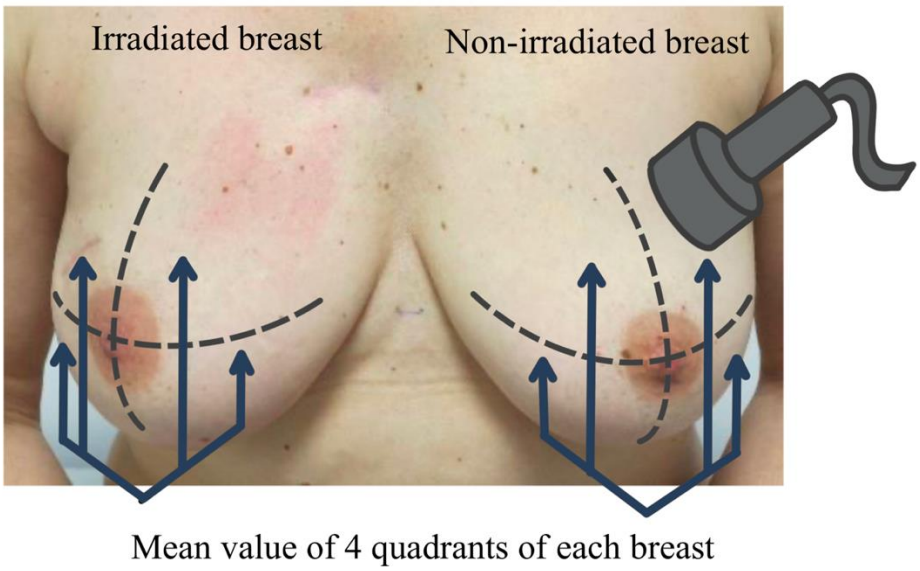


Figure 9. Objective assessment of toxicity by Multi Skin Test Center. Measurements were obtained at 4 quadrants of each breast, separately in irradiated breast and corresponding symmetric regions in non-irradiated breast.



4.1.5 Biological equivalent dose (BED)

Radiation fractionation schedules and their corresponding BED are presented in Table 11. To compare the RITs resulting from different fractionation regimens, the linear-quadratic (LQ) model was adopted to calculate the BED for each radiation schedule. An α/β ratio of 10 Gy for acute toxicity and 3.1 Gy for late toxicity of breast tissue was used to calculate the BED from different radiation schemes. Patients were grouped according to the radiation BED used, and a total of 7 groups (A-G) of patients were recruited into our study. Given the BEDs calculated above, different radiotherapy treatment schedules could be directly compared.

4.1.6 Statistics

The BED and toxicity values are presented as the mean with standard deviation and medians with interquartile ranges. A Wilcoxon signed rank test was used to evaluate the significance of the difference between radiated and non-irradiated breasts. A Spearman correlation coefficient and its significance test were used to identify the relationship between the subjective and objective assessment and determine whether RIT is associated with BED. The correlation coefficient (r) was defined as weak correlation ($0.4 \geq |r| > 0.15$), intermediate correlation ($0.6 \geq |r| > 0.4$) and strong correlation ($|r| > 0.6$). If the $r < 0.15$, we considered that there is no correlation between the two variables. The adjusted associations of radiation schemes and RTOG toxicity scores were studied by ordered logistic regression analysis. Multivariate median regression analysis was used

to identify potential predictors of objectively evaluated toxicity: erythema, melanin, elasticity and hydration. The statistical analysis was performed with Stata (version 15.1; College Station, TX: StataCorp LLC). $p < 0.05$ was considered statistically significant.

4.2 Second study

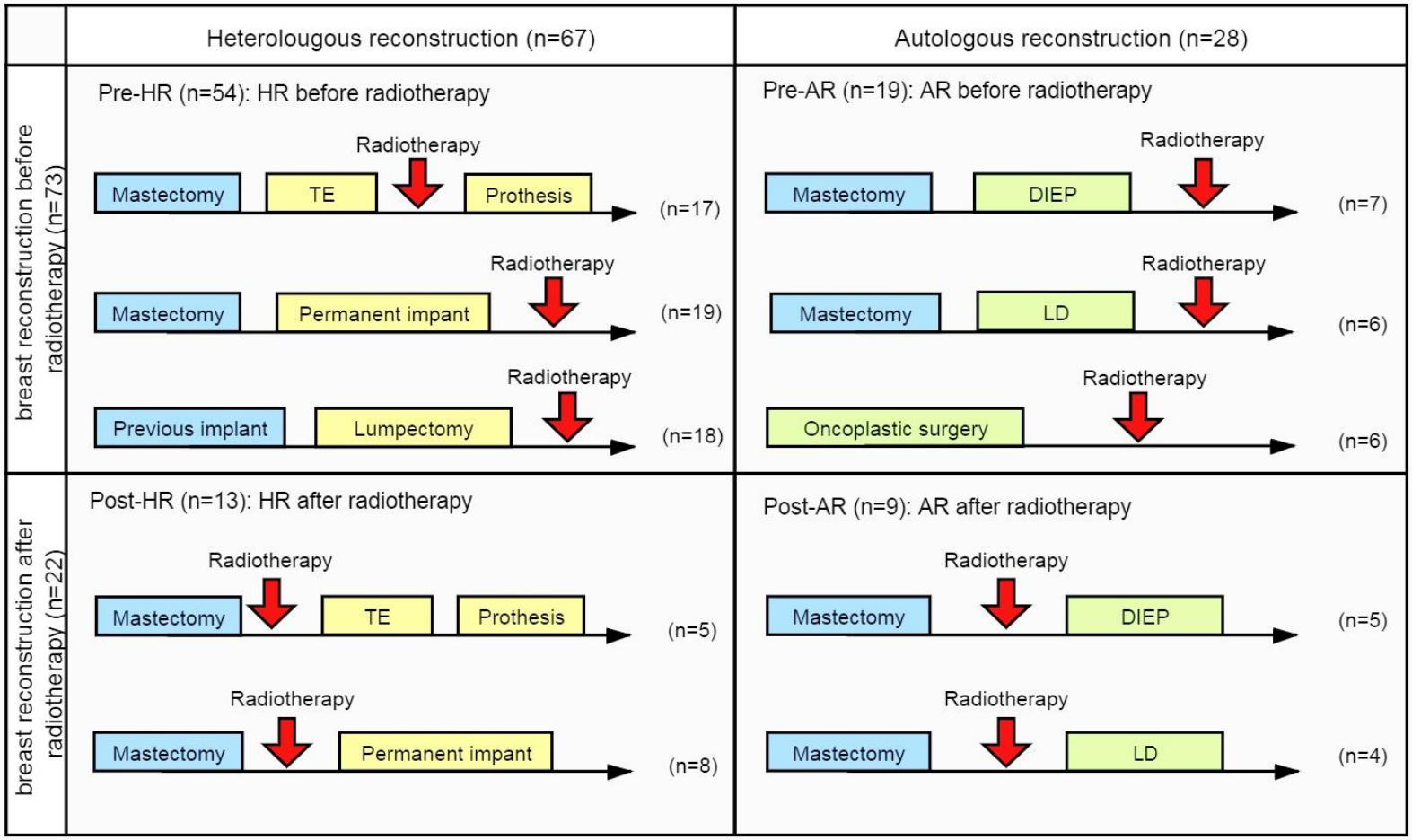
4.2.1 Patients

Ninety-five patients undergoing RT and breast reconstruction were included in this analysis. The choice of reconstruction technique depended on the surgeon's decision and patient's preferences.

4.2.2 Timing and techniques of breast reconstruction

The patients in this study were divided into 4 groups. The pre-HR group included patients undergoing HR (tissue expander and permanent implant) before RT. The pre-AR group included patients undergoing AR (transposition of latissimus dorsi muscle, deep inferior epigastric perforator and oncoplastic surgeries) before irradiation. Patients undergoing HR after RT were included in the post-HR group. Patients undergoing AR after RT were assigned to the post-AR group (Figure 6).

Figure 6. Distribution of groups according the timing and techniques of breast reconstruction.



Abbreviations: pre-HR: heterologous reconstruction before radiotherapy; pre-AR: autologous reconstruction before radiotherapy; post-HR: heterologous reconstruction after radiotherapy; post-AR: autologous reconstruction after radiotherapy; TE: tissue expander; DIEP: deep inferior epigastric perforator; LD: latissimus dorsi flap.

4.2.3 Radiotherapy

48 Gy at 2 Gy was delivered to the whole breast, with or without an additional 10 Gy or 20 Gy at 2 Gy per fraction to the tumor bed.

4.2.4 Measures

We evaluated the effect of treatment by using the median time between RT and breast reconstruction, total number of operations performed for final results, revision surgeries, incidence of complications, toxicity, aesthetics and associated clinical risk factors. This research was approved by the Clinical Research Ethics Committee.

The median time between radiotherapy and reconstruction in patients undergoing post-RT was defined as the time from performing the immediate breast reconstruction surgery or placing the tissue expander (delayed reconstruction) to the beginning of RT, and the median time between radiotherapy and reconstruction in patients undergoing pre-RT was defined as the time from the end of RT to the beginning of breast reconstruction.

The total number of surgical procedures included oncological surgeries (lumpectomy, mastectomy), breast reconstruction surgical procedures and revision surgeries. Revision surgery was defined as any unplanned surgical procedure that was directly related to reconstruction and required a return to the operating room. Among them, fat grafting and nipple-areola complex reconstruction were classified as minor revision

procedures. Other procedures, such as implant removal or replacement, were included as major revision surgeries.

This study analysed the following breast reconstruction complications: capsular contracture, haematoma, infection, fat necrosis and implant failure.

Toxicity was assessed in two ways. First, dermatitis, fibrosis, telangiectasia, palpation pain and lymphedema were evaluated by physicians according to the Radiation Therapy Oncology Group (RTOG) scale of radiation effects, which rates each parameter on a scale from 0 to 4 (0, absence; 4, maximum expression).13 Second, with a multi-probe device (Multi Skin Test Center®, Model MC 750; CK Electronic, GmbH, Cologne, Germany), 4 parameters (melanin, erythema, elasticity and hydration) were measured objectively. The procedure for determining these parameters consisted of performing a measure of each parameters in each of the four breast quadrants in both breasts. The program of this multi-probe device calculates the average of the measurements made of each breast (Supplementary material a-c).

The aesthetic evaluation of the breasts was conducted using the Harvard Scale (excellent, good, fair and poor) by physicians.

4.2.5 Statistics

The regression models included a range of variables likely to be related to complications. Baseline characteristics, demographic variables and surgical data were recorded, including the reconstruction technique, RT timing, age at reconstruction,

laterality of reconstruction, adjunct therapy, receipt of chemotherapy, median time between irradiation and reconstruction, previous implants, hypertension, smoking, and body mass index (BMI). The predictive variables were selected due to clinical relevance. The statistical analysis was performed with the SPSS v26 software package (IBM SPSS, Chicago, IL). Quantitative variables are described as the mean and standard deviation. Student's t-test and ANOVA were used to compare quantitative variables. The Kruskal-Wallis tests was employed to evaluate categorical variables.

Univariate analysis was constructed to identify risk factors associated with complications. The adjusted associations were examined by multivariate logistic regression analysis. Covariables were included if risk factors had a $P < 0.20$ on univariate analysis. Patients with missing covariables were excluded from the multivariate analysis. Patients signed informed consent both for local treatment and also for additional evaluations by objective methods at follow-up.

5.Results

5.1 FIRST STUDY

5.1.1 Patients characteristics and flow chart

Of the 194 patients enrolled in this study, 62 patients received conventional fractionation radiotherapy, 50 patients received moderate daily hypofractionation radiotherapy, 42 patients received weekly hypofractionation radiotherapy, 40 patients received accelerated partial breast irradiation (Table 11).

Patients were grouped according to BED, there were 25 patients in BED=78.4 group, 28 patients in BED=79 group, 40 patients in BED=82.9 group, 23 patients in BED=95.4 group, 50 patients in BED=104.2 group, 11 patients in BED=111.9 group, 17 patients in BED=111.3 group. Patients characteristics, radiation-related information and flow chart is shown in table 12 and figure 5.

Table 12. Patient characteristics and radiation-related information.

Group	Patients. No. (n, %)	Radiation regimens	BED#	Age Mean (±SD)	Interval time* Mean (±SD)
A	25 (12.6)	30 Gy/5 Fx	78.4	81.8 (±6.6)	3.4 (±1.4)
B	28 (14.1)	48 Gy/2 Fx	79	58.2 (±10.9)	3.3 (±1.9)
C	40 (20.1)	37.5 Gy/3.75 Fx (BID)	82.9	66.6 (±6.0)	3.2 (±1.9)
D	23 (11.6)	48 Gy/2 Fx+10 Gy boost	95.4	66.1 (±8.8)	3.0 (±1.9)
E	50 (25.1)	40.05 Gy/2.67 Fx+16.02 Gy boost	104.2	63.7 (±7.9)	3.3 (±0.6)
F	11 (5.5)	48 Gy/2 Fx+20 Gy boost	111.9	54.9 (±12.6)	3.3 (±2.1)
G	17 (8.5)	37.5 Gy/6.25 Fx	113.1	83.7 (±6.6)	9.1 (±2.9)

Abbreviation: BED: Biologically equivalent doses;

#: BED of late toxicity (α/β=3.1Gy).

*: Interval time between radiotherapy and toxicity assessment.

5.1.2 Quantitative assessment

5.1.2.1 Comparison of RIT between irradiated and non-irradiated contralateral breast following different protocols of radiotherapy by objective assessments.

In the comparison of RITs between irradiated and nonirradiated breasts by multiprobe quantitative evaluation, as shown in Figure 10a-d, the treated breast showed significantly higher redness and pigmentation values than the untreated breast: median 21.0 (range 15.9-25.6) vs. 16.8 (range 12.9-20.5), $p<0.001$; 4.5 (range 1.7-11.5) vs. 3.3

(range 1.3-8.4), p<0.001, respectively). The irradiated breast had a greater loss of elasticity than the nonirradiated breast: median 74.5 (range 64.5-80.9) vs. 83.3 (range 78.4-87.3), p<0. 001. There was a similar but significantly different hydration index between the treated breast and untreated breast (median 35.0 (range 27.5-41.1 vs. 35.2 (range 28.8-42.8), p=0.019) (Figure 10 a-d, Table 17).

Figure 10a. Comparison of irradiated breast and non-irradiated breast in erythema.

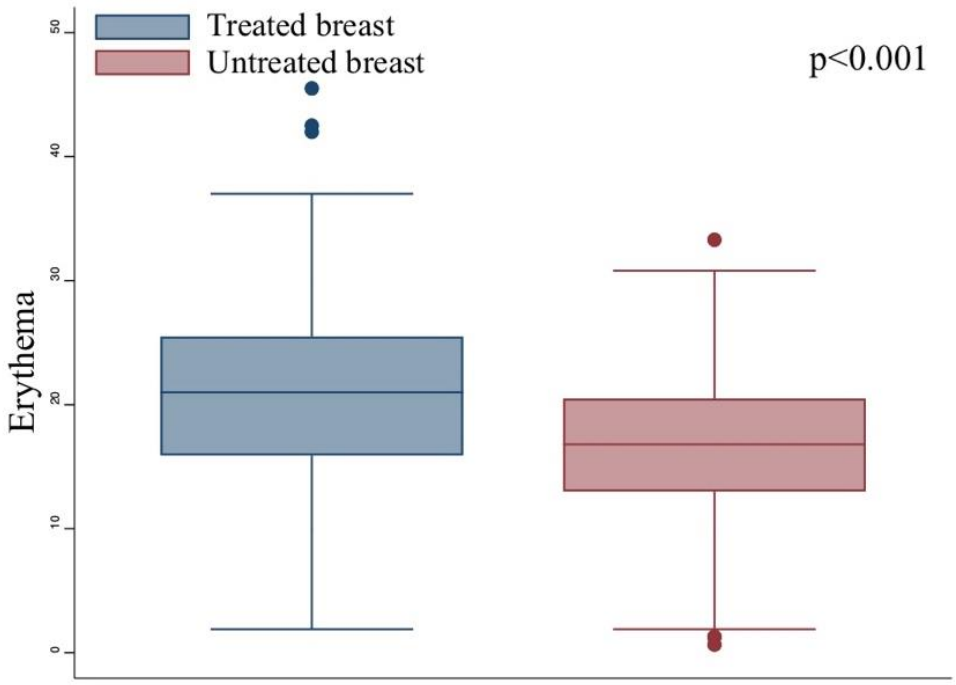


Figure 10b. Comparison of irradiated breast and non-irradiated breast in melanin.

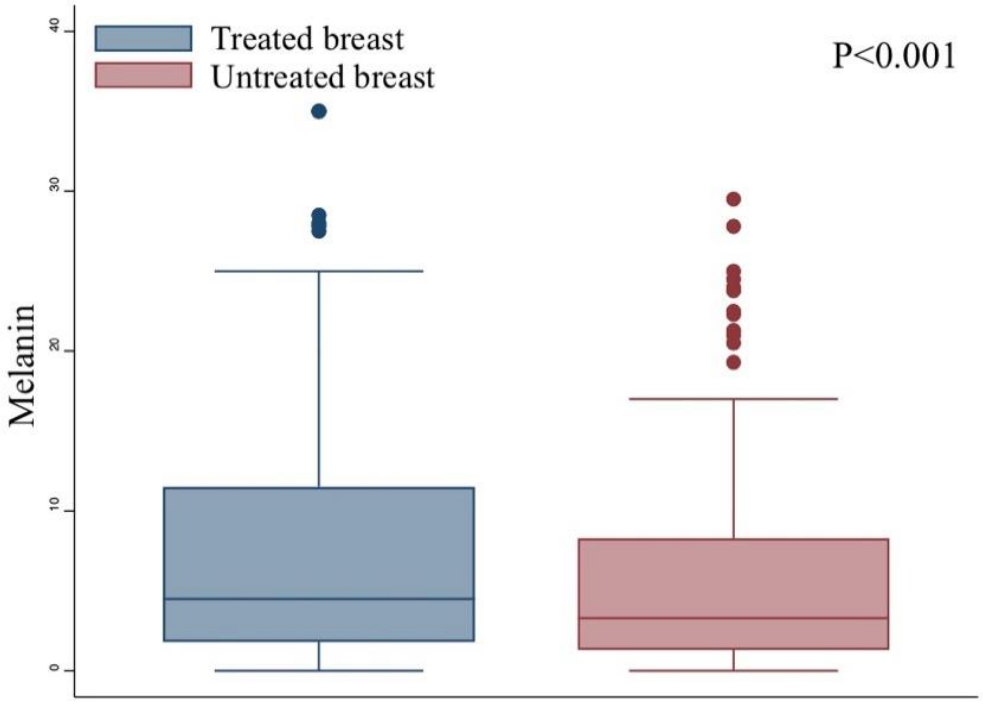


Figure 10c. Comparison of irradiated breast and non-irradiated breast in elasticity.

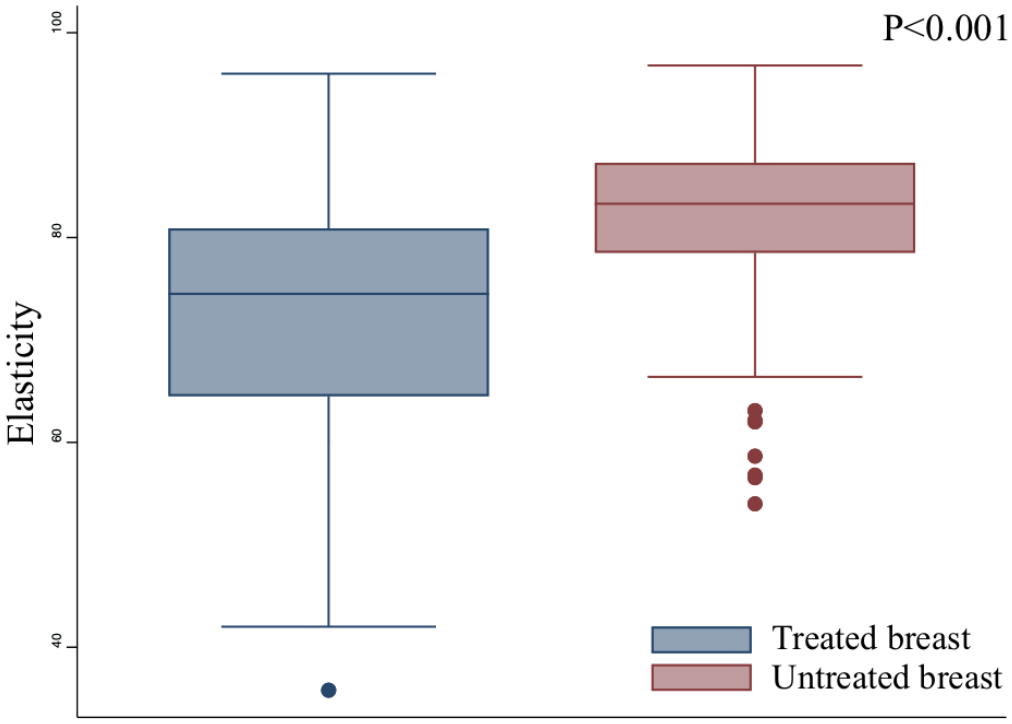


Figure10d. Comparison of irradiated breast and non-irradiated breast in hydration.

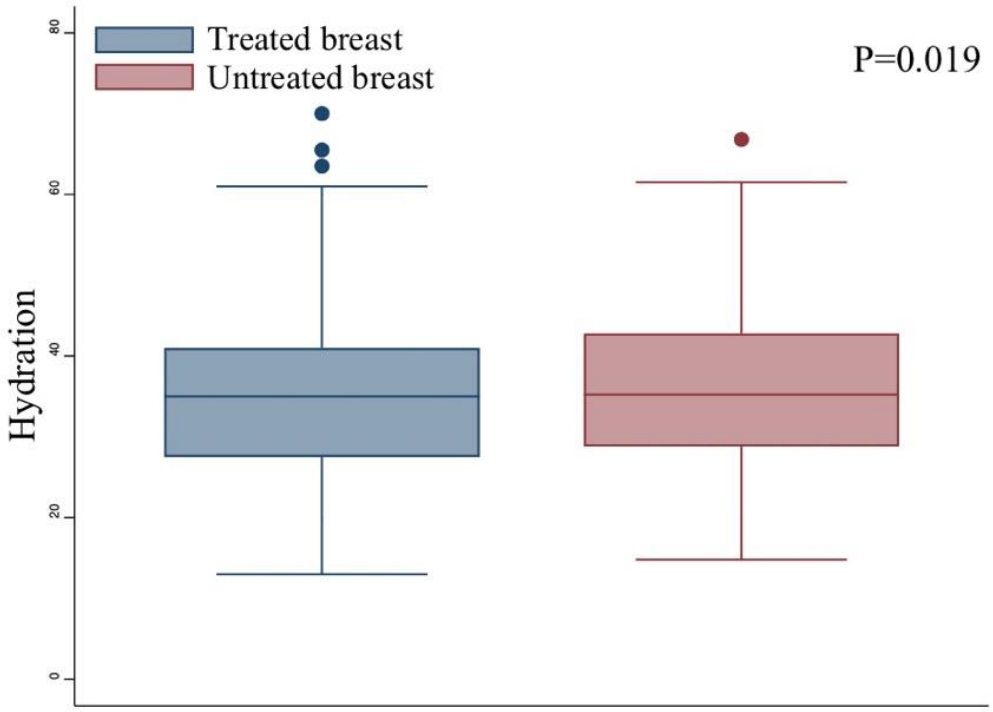


Table 17. Comparison of radiation-induced toxicity between treated and contralateral untreated breast skin

	Four parameters of radiation-induced toxicity		
	Non-irradiated Breast	Irradiated Breast	
	Median (range: Q1-Q3)	Median (range: Q1-Q3)	p
Erythema	16.8 (12.9-20.5),	21.0 (15.9-25.6)	**<0.001**
Melanin	3.3 (1.3-8.4)	4.5 (1.7-11.5)	**<0.001**
Elasticity	83.3 (78.4-87.3)	74.5 (64.5-80.9)	**<0.001**
Hydration	35.2 (28.8-42.8)	35.0 (27.5-41.1)	**0.019**

5.1.3 Qualitative assessment

Based on the clinical-assessed scores, acute skin reactions were noted in 190 of 194 patients (grade 0, 4 cases, 2.1%; grade 1, 105 cases, 54.1%; grade 2, 74 cases, 38.1%; grade 3, 11 cases, 5.7%). No grade 4 toxicity was observed. In terms of late effects, only grade 1 and 2 toxicity were recorded. Physician-assessment reported 126 patients with grade 0 (64.9%), 52 with grade 1(26.8%), and 16 with grade 2(8.2%). No case of severe of grade 3 or 4 toxicity was observed.

5.1.4 BED-RIT relationship based on objective measurements

The BED-RIT relationship based on objective measurements resulted in a significant correlation between the alteration in the erythema and melanin values and the administered BED, as shown in Figure11a-d. The Δerythema and Δmelanin values increased gradually with increasing BED ($r=0.196$, $p=0.006$; $r=0.220$, $p=0.002$, respectively). A decreasing trend was also observed in the Δelasticity index with increasing BED; however, the correlation was not significant ($p=0.055$).

The median Δerythema index of irradiated-breast skin in BED=78.4 was 1.6, in BED=79 was 5.0, in BED=82.6 was 3.5, in BED=95.4 was 4.5, in BED=104.2 was 4.6, in BED=111.9 was 7.2, in BED=113.1 was 4.5. The median Δmelanin index of treated breast in BED=78.4 was <0.0001, in BED=79 was 0.9, in BED=82.6 was 0.5, in BED=95.4 was 0.7, in BED=104.2 was 1.9, in BED=108 was 3.0, in BED=113.1 was

1.5. The median Δelasticity index of irradiated skin in BED=78.4 was -10.5, in BED=79 was -5.8, in BED=82.6 was -9.5, in BED=95.4 was -6.3, in BED=104.2 was -9.1, in BED=111.9 was -10.0, in BED=113.1 was -13.8. The median Δhydration in BED=78.6 was -3.7, in BED=79 was 6.0, in BED=82.6 was -1.25, in BED=95.4 was -3.3, i, in BED=104.2 was -5.5, in BED=111.9 was -3.7, in BED=113.1 was 0.3

Figure 11a. Biological equivalent doses (BED) dependence of Δerythema in patients treated by different protocols of radiotherapy.

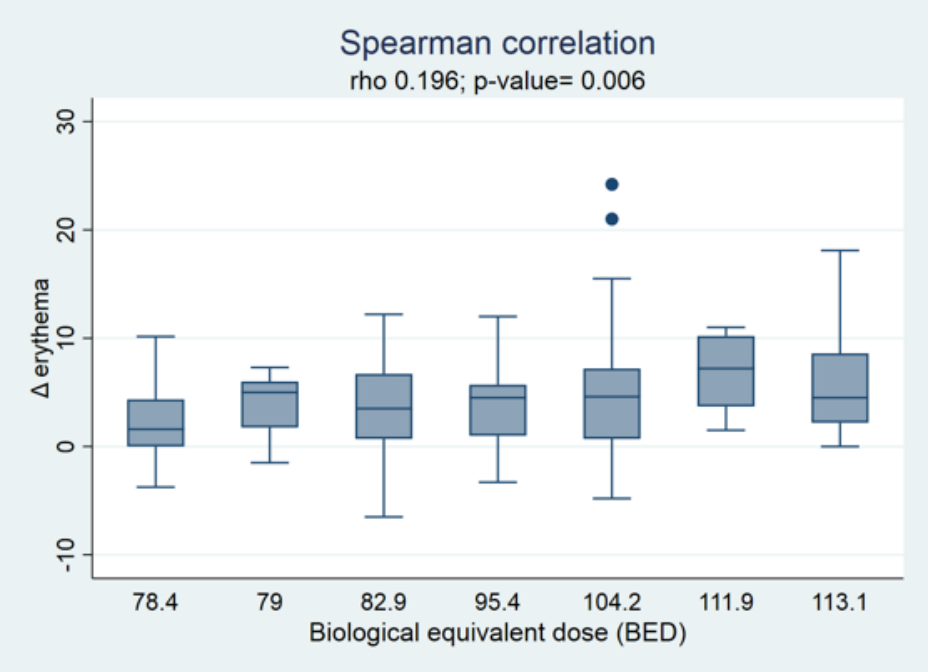


Figure 11b Biological equivalent doses (BED) dependence of Δmelanin in patients treated by different protocols of radiotherapy.

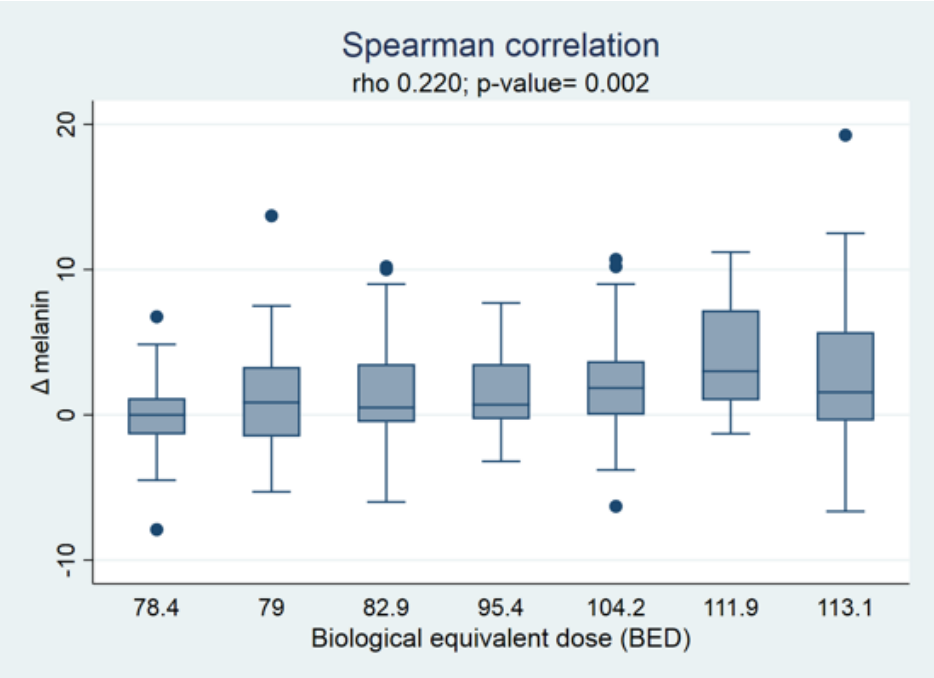


Figure 11c. Biological equivalent doses (BED) dependence of Δelasticity in patients treated by different protocols of radiotherapy.

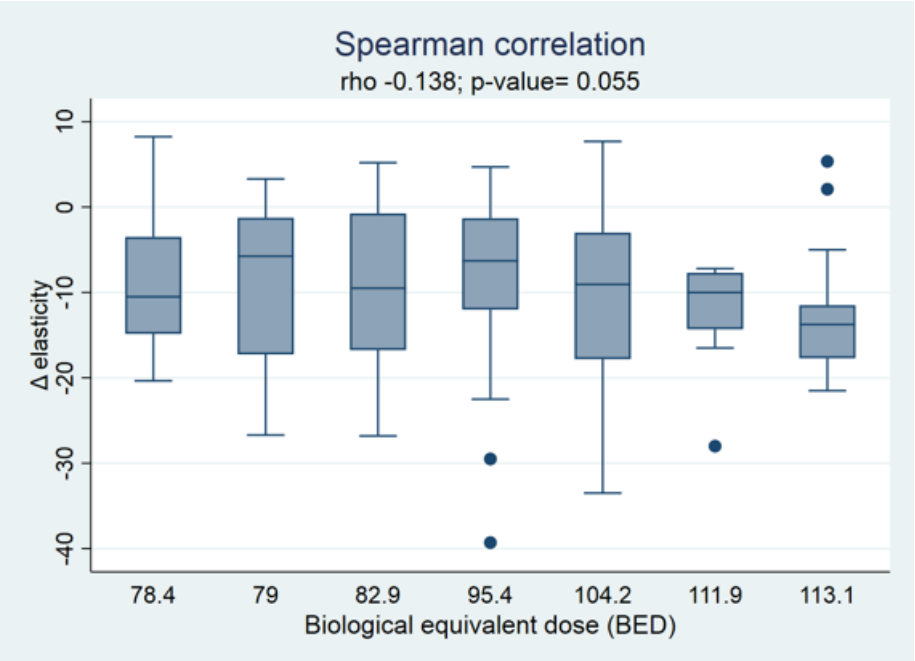
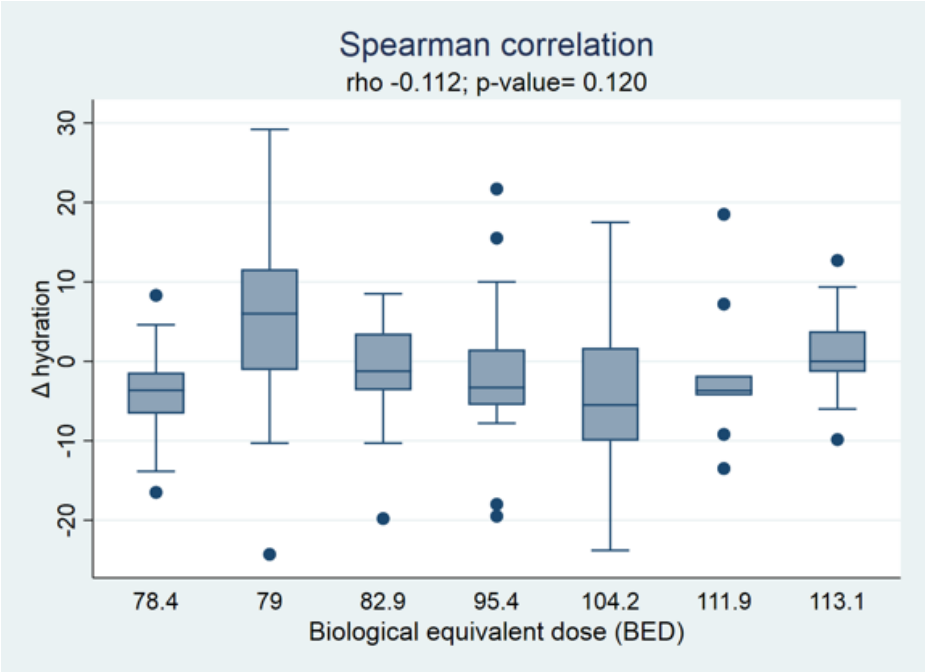


Figure 11d. Biological equivalent doses (BED) dependence of Δelasticity in patients treated by different protocols of radiotherapy.



5.1.5 BED-RIT relationship based on qualitative measurements

Based on qualitative physician assessment, both the RTOG acute toxicity grade (mean BED: grade 0, 82.9; grade 1, 90.0; grade 2, 96.2; grade 3, 104.1, $p<0.001$) and the RTOG late toxicity grade (mean BED: grade 0, 90.8; grade 1, 94.4; grade 2, 105.9, $p<0.001$) increased with increasing BED (Table 13).

Table 13. Mean BED value of Radiation Therapy Oncology Group (RTOG) acute and late toxicity score.

	Acute RTOG toxicity criteria			Late RTOG toxicity criteria		
Grade		Mean BED			Mean BED	
	n (%)	value (± SD) [$]	p	n (%)	value (± SD)	p
0	4 (2.1)	82.9 (0)		126 (64.9)	90.8 (±12.0)	
1	105 (54.1)	90.0 (±12.2)	**<0.001**	52 (26.8)	94.4 (±13.4)	**<0.001**
2	74 (38.1)	96.2 (±12.8)		16 (8.2)	105.9 (±9.9)	
3	11(5.7)	104.1 (±10.7)		0 (0)	-	

Abbreviation: RTOG: Radiation Therapy Oncology Group; BED: Biologically equivalent doses.

$: BED=10 for acute toxicity, BED=3.1 for chronic toxicity.

When grouping schemas in low, medium and high-BED, based on the clinical-assessed acute RTOG scores, non-toxicity (grade 0) was only observed in the low-BED group (n=4). The percentage of patients of grade 1 in low-BED group were higher than the other two group (68.5% in low-BED group vs. 41.9% in median-BED group vs. 39.3% in high-BED group), while the percentage of patients with severe toxicity (grade 3) in the high-BED group was higher than the other two BED groups (1.1% in low-BED group vs. 6.8% in median-BED group vs. 17.9% in high-BED group (Table 14).

Table 14. Radiation Therapy Oncology Group (RTOG) acute toxicity score following different BED radiotherapy protocol.

	acute toxicity n (%)				
Grade	Low-BED	Medium-BED	High-BED	Total	p
0	4 (4.3)	0	0	4 (2.1)	<0.001
1	63 (68.5)	31 (41.9)	11 (39.3)	105 (54.1)	
2	24 (26.1)	38 (51.4)	12 (42.9)	74 (38.1)	
3	1 (1.1)	5 (6.8)	5 (17.9)	11(5.7)	

Abbreviation: BED: Biologically equivalent doses.

BED for late toxicity: low- BED: BED<60; medium-BED: BED>60 and <80; high-BED: BED>80.

In terms of late effects, the percentage of grade 0 in the low-BED group is higher than that in the high BED-group (71.7% vs. 48.7%, respectively). In contrast, the percentage of grade 2 in the low-BED group is lower than that in the high-BED group (0% vs. 17.9%, respectively) (Table 15).

Table 15. Radiation Therapy Oncology Group (RTOG) late toxicity score following different BED radiotherapy protocol.

	Late toxicity n (%)				
Grade	Low-BED (n=53)	Medium-BED (n=63)	High-BED (n=78)	Total (n=194)	p
0	38(71.7)	50(79.4)	38(48.7)	126 (64.9)	<0.001
1	15(28.3)	11(17.5)	26(33.3)	52 (26.8)	
2	0(0)	2(3.2)	14(17.9)	16 (8.2)	

Abbreviation: BED: Biologically equivalent doses.

BED for late toxicity: low- BED: BED<80; medium-BED: BED>80 and <100; high-BED: BED>100.

5.1.6 Comparison of objective assessment (Multi Skin Test Center MC750) to clinical assessment (RTOG)

To investigate whether the color, elasticity and moisture of skin as measured by this multi-probe device correlated with physician-assessment, we compared the four skin parameters with the RTOG toxicity criteria. When excluding patients with grade 0 toxicity (n=4), there were significantly increasing values in the erythema and melanin index with increasing RTOG acute score (p=0.008, p=0.002, respectively). The elasticity value significantly decreased with increasing acute RTOG toxicity score (p=0.028); however, the relationship between hydration and the RTOG toxicity score was not statistically significant.

Figure 12a. Comparison of erythema to Radiation Therapy Oncology Group (RTOG) acute toxicity score.

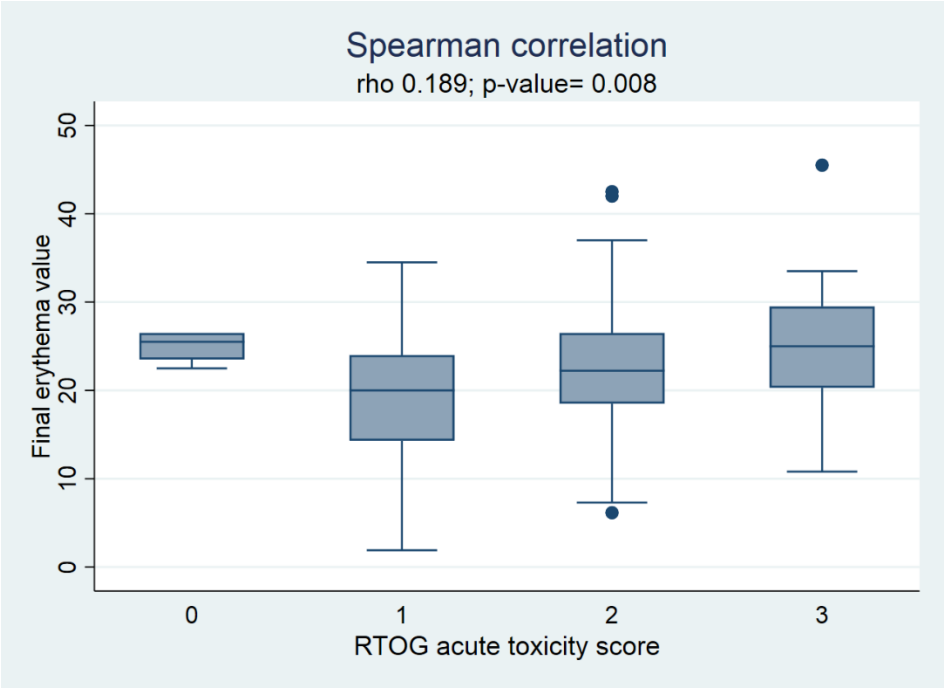


Figure 12b. Comparison of melanin to Radiation Therapy Oncology Group (RTOG) acute toxicity score.

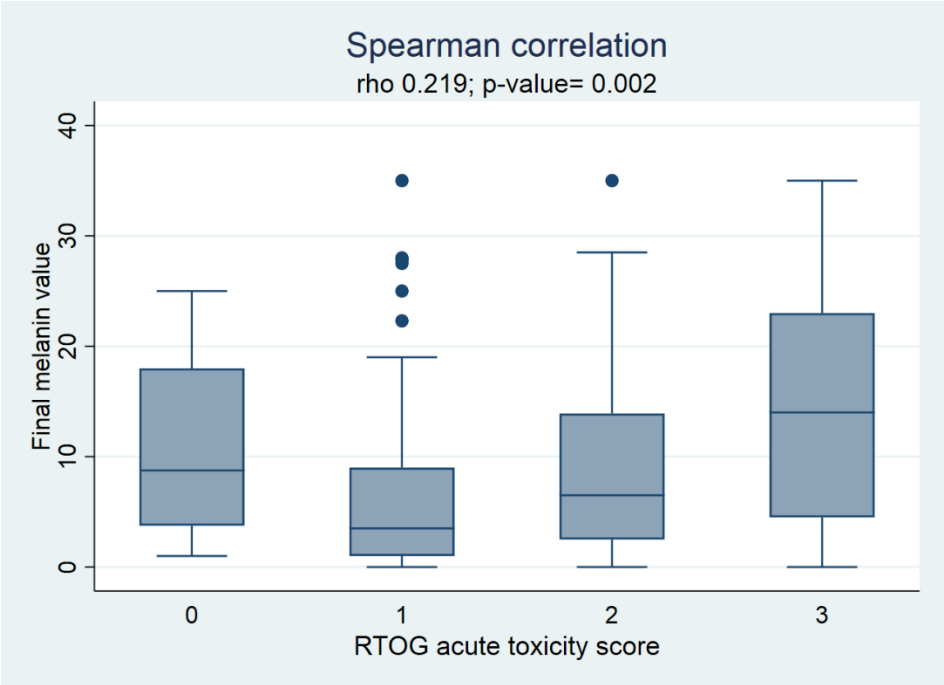


Figure 12c. Comparison of elasticity to Radiation Therapy Oncology Group (RTOG) acute toxicity score.

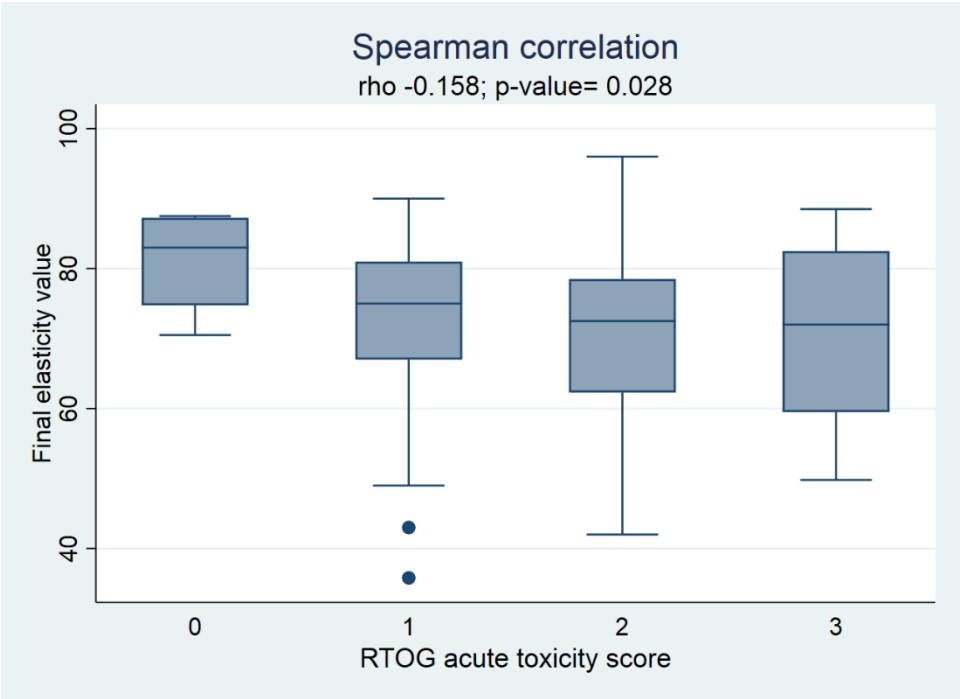
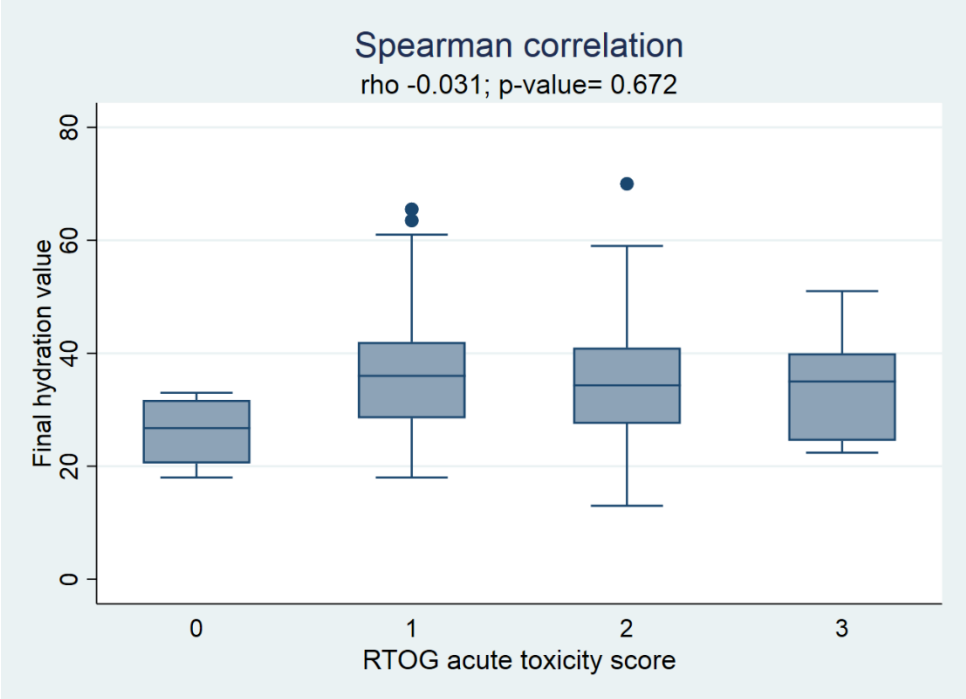


Figure12d. Comparison of hydration to Radiation Therapy Oncology Group (RTOG) acute toxicity score.



There was an increase in erythema and a decrease in the elasticity index with increasing late RTOG toxicity grade ($p=0.003$, $p<0.001$, respectively), while the relationships with melanin and hydration were not significant ($p=0.17$, $p=0.66$, respectively). An average increase of 13.1% in erythema was found among patients with grade 1 toxicity, whereas an increase of 30.6% was found among patients with grade 2, when compared to grade 0. Elasticity index decreased 6.1% for RTOG grade 1, 12.9% for grade 2, when compared to grade 0 ($p=0.006$).

Figure 13a. Comparison of erythema to Radiation Therapy Oncology Group (RTOG) late toxicity score.

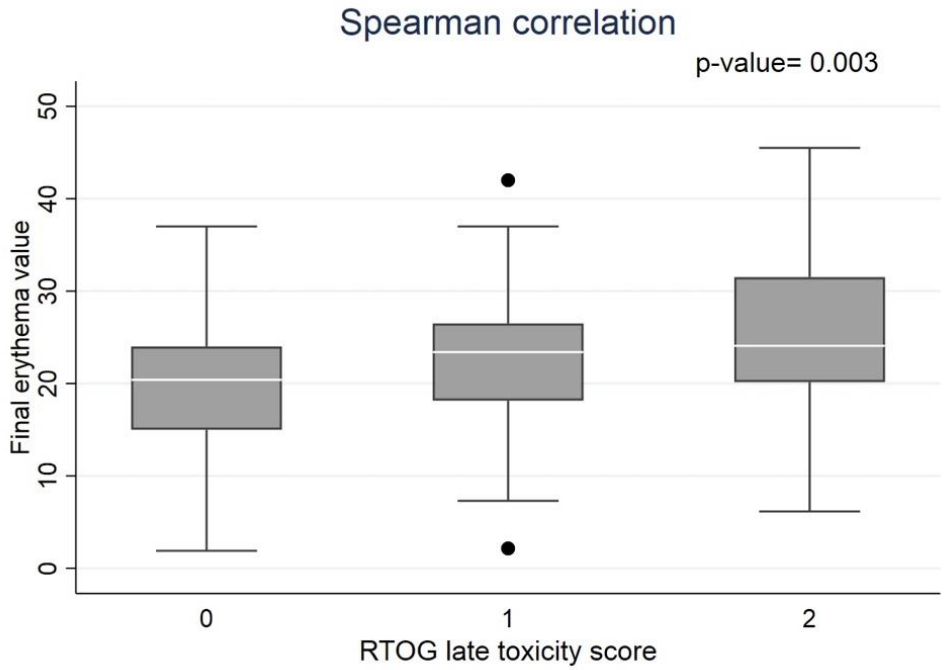


Figure 13b. Comparison of melanin to Radiation Therapy Oncology Group (RTOG) late toxicity score.

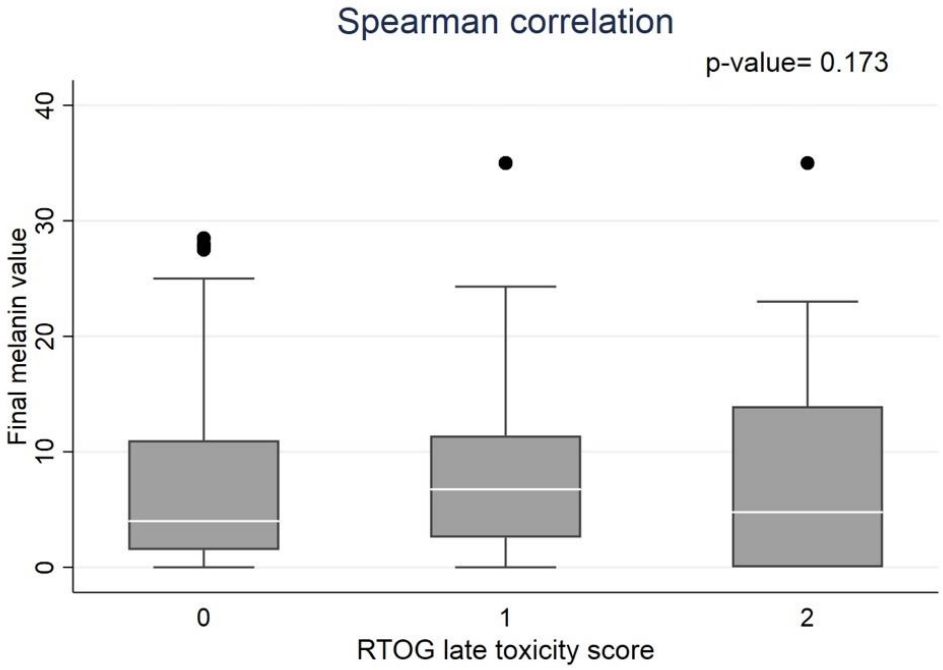


Figure 13c. Comparison of elasticity to Radiation Therapy Oncology Group (RTOG) late toxicity score.

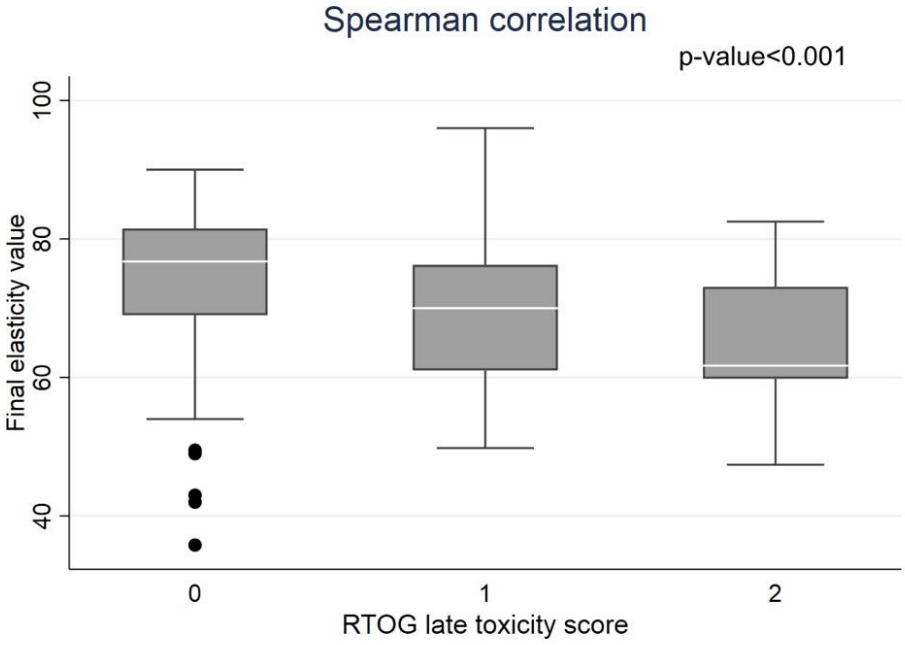
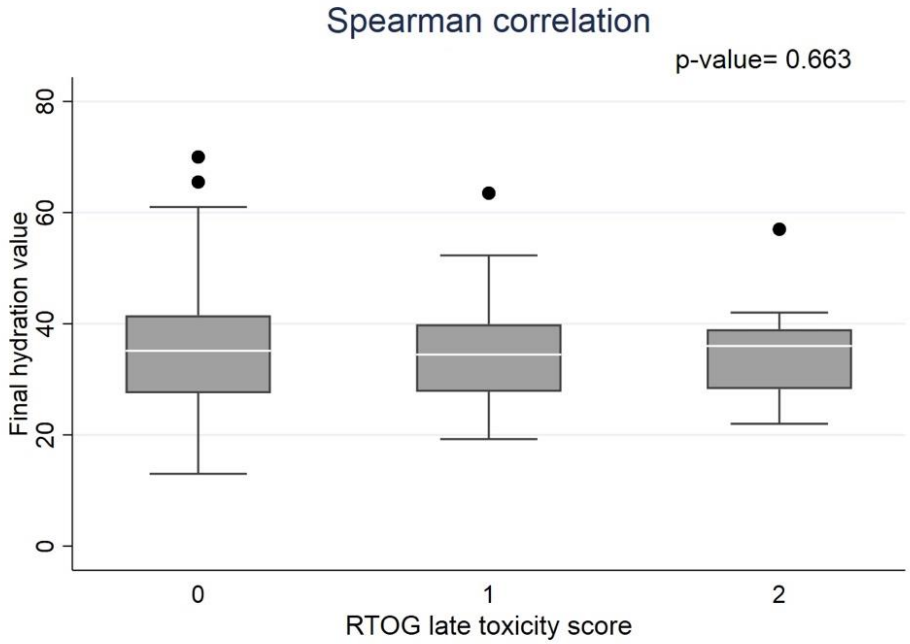


Figure 13d. Comparison of elasticity to Radiation Therapy Oncology Group (RTOG) late toxicity score.



5.1.7 Quantitative evaluation of toxicity by multivariate median regression analysis

After adjustment for possible confounding variables, DHF and WHF-low dose arms were significant predictors of erythema variation in multivariable regression analysis (Coef: 4.00, 95%CI: -0.2-8.3, p=0.06; Coef: -8.41, 95%CI: -14.5 - -2.3, p=0.007). CF + low boost, CF + high boost, DHF, APBI and age were significantly associated with melanin variation (Coef: -5.39, 95%CI: -9.9 - -0.8, p=0.021; Coef:11.12, 95%CI: 5.5-16.7 p<0.001; Coef: -5.76, 95%CI: -9.6 - -1.9, p=0.003; Coef: -6.20, 95%CI: -10.2 - -

2.1, p=0.003; Coef: -0.19, 95%CI: -0.3 - -0.1, p=0.006). The skin elasticity of WHF-high dose regimen was significantly reduced when compared with CF arm (Coef -11.38, p=0.045), and APBI and CF + low boost regimens shown a significantly decreased hydration (Coef: -10.81, 95%CI: -18.5 - -3.2, p=0.006; Coef: -7.36, 95%CI: -14.1- -0.6, p=0.033) (Table 18).

Table 18. Multivariate median regression analyses of different schemes and other clinical associated factors with irradiation-induced toxicity.

	Erythema		Melanin		Elasticity		Hydration	
	Coef	p	Coef	p	Coef	p	Coef	p
Radiation Schemes								
CF	1		1		1		1	
CF + low boost	-0.14 (-5.3-4.8)	0.96	-5.39 (-9.9 - -0.8)	**0.021**	4.45 (-2.7-11.6)	0.22	-10.81 (-18.5 - -3.2)	**0.006**
CF + high boost	1.74 (-4.5-8.0)	0.38	11.12 (5.5-16.7)	**<0.001**	-0.17 (-8.9-8.6)	0.97	-3.64 (-13.0-5.8)	0.45
DHF	4.00 (-0.2-8.3)	**0.06**	-5.76 (-9.6 - -1.9)	**0.003**	-0.66 (-6.6-5.3)	0.82	-4.66 (-11.0-1.7)	0.15
WHF-low dose	-8.41 (-14.5 - -2.3)	**0.007**	-1.97 (-7.4-3.5)	0.47	-3.58 (-12.1-4.9)	0.41	-5.59 (-14.7-3.5)	0.23
WHF-high dose	0.04 (-7.9-8.0)	0.99	-0.90 (-8.0-6.2)	0.80	-11.38 (-22.5 - -0.3)	**0.045**	-2.37 (-14.3-9.5)	0.69
APBI	2.02 (-2.5-6.6)	0.37	-6.20 (-10.2 - -2.1)	**0.003**	2.74 (-3.6-9.1)	0.39	-7.36 (-14.1- -0.6)	**0.033**
Other factors								
Age	-0.06 (-0.2-0.1)	0.49	-0.19 (-0.3 - -0.1)	**0.006**	-0.97 (-0.3-0.1)	0.34	-0.07 (-0.2-0.2)	0.95
Interval time[$]	-0.45 (-0.9-0.5)	0.26	0.33 (-0.3-0.9)	0.33	0.02 (-1.0-1.1)	0.99	-1.14 (-1.8-0.5)	0.26

Abbreviation: Coef: regression coefficient; BED: Biologically equivalent doses; CF: Conventional fractionation; DHF: Moderate Daily Hypofractionation; WHF: Weekly Hypofractionation; APBI: accelerated partial breast irradiation.

[$] Interval time between radiotherapy and toxicity assessment.

5.1.8 Qualitative evaluation of toxicity by multivariate logistic regression analysis

On multivariable regression, after adjusting for possible clinical associated confounding variables, our results revealed that APBI was significant predictor of decreased acute toxicity (OR: 0.11, 95%CI: 0.03-0.47; p=0.003). DHF and WHF-high dose arms were significantly related to the higher late RTOG grade (OR: 2.85, 95%CI: (1.03-7.83); p=0.043, OR: 12.50, 95%CI: 1.83-85.32; p=0.01, respectively) (Table 16).

Table 16. Ordered logistic regression of acute and late RTOG toxicity criteria and radiation schemes

	Acute RTOG toxicity criteria		Late RTOG toxicity criteria	
	OR (95% CI)	p	OR (95% CI)	p
Radiation schemes				
CF	1		1	
CF + low boost	1.72 (0.56-5.24)	0.34	0.46 (0.10-2.05)	0.31
CF + high boost	1.52 (0.36-6.41)	0.57	1.01 (0.21-4.86)	0.99
DHF	1.86 (0.74-4.69)	0.19	2.85 (1.03-7.83)	**0.043**
WHF-low dose	0.70 (0.18-2.74)	0.61	1.43 (0.32-6.52)	0.64
WHF-high dose	2.73 (0.44-16.90)	0.28	12.50 (1.83-85.32)	**0.010**
APBI	0.11 (0.03-0.47)	**0.003**	1.05 (0.34-3.30)	0.93
Other factors				
Age	1.01 (0.97-1.04)	0.66	0.98 (0.95-1.02)	0.41
Interval time[$]	1.02 (0.85-1.22)	0.82	1.07 (0.89-1.29)	0.44

Abbreviation: RTOG: Radiation Therapy Oncology Group; CF: Conventional fractionation; DHF: Moderate Daily Hypofractionation; WHF: Weekly Hypofractionation; APBI: accelerated partial breast irradiation.

[$] Interval time between radiotherapy and toxicity assessment.

5.1.9 Other Radiation-induced toxicity associated clinical factors

The assessment of the role of the original skin condition, age, duration of radiotherapy, interval time between irradiation and toxicity assessment boost, weekly vs. daily radiation schemes and adjuvant hormonal on RIT are shown in figure 14a-d, figure 15a-d, figure 16, figure17a-d, table 19 and table 20, respectively. Pearson correlation coefficient (r) was used to calculate a possible relationship between radiation-induced toxicity and any associated clinical factors. If the $r<0.15$， we considered that there is no correlation between the two variables.

There was a significant correlation between irradiated and contralateral breast in erythema, melanin, elasticity and hydration. The alteration of erythema and melanin in treated breasts was well linear and correlated to the untreated breasts ($r=0.77$, $p<0.001$, $r=0.78$, $p<0.001$, respectively). Elasticity exhibited a moderate correlation between irradiated and non-irradiated breast ($r=0.49$, $p<0.001$). Although the average hydration value of treated and untreated breasts was similar, there was moderate association existed ($r=0.64$, $p<0.001$) (Figure 11 a-d). A negative correlation existed between age and erythema, pigmentation and elasticity ($r=-0.37$, $p<0.001$; $r=-0.23$, $p=0.001$; $r=-0.33$, $p<0.001$, respectively). Erythema and melanin depend weakly on duration of treatment ($r=-0.25$, $p=0.001$; $r=0.22$, $p=0.002$, respectively). No significant correlation was found between hydration and any associated factors included. In terms of RT-associated factors, erythema and elasticity decreased significantly with increasing time interval between irradiation and objective assessment ($r=-0.19$, $p=0.009$; $r=-0.18$, $p=0.013$,

respectively). Erythema index was influenced by the addition of boost irradiation (23.3 vs. 18.8, p<0.001, with and without boost respectively). Patients with daily irradiation demonstrated a significantly higher skin redness and elasticity compared to the group with weekly radiotherapy (12.5 vs. 22.5, p<0.001; 64.2 vs. 76.0, p<0.001, respectively). There was a significant difference in skin elasticity changes as the result of the additional tamoxifen intake (p=0.025).

Figure 14a. Relationship between irradiated breast and non-irradiated breast in erythema

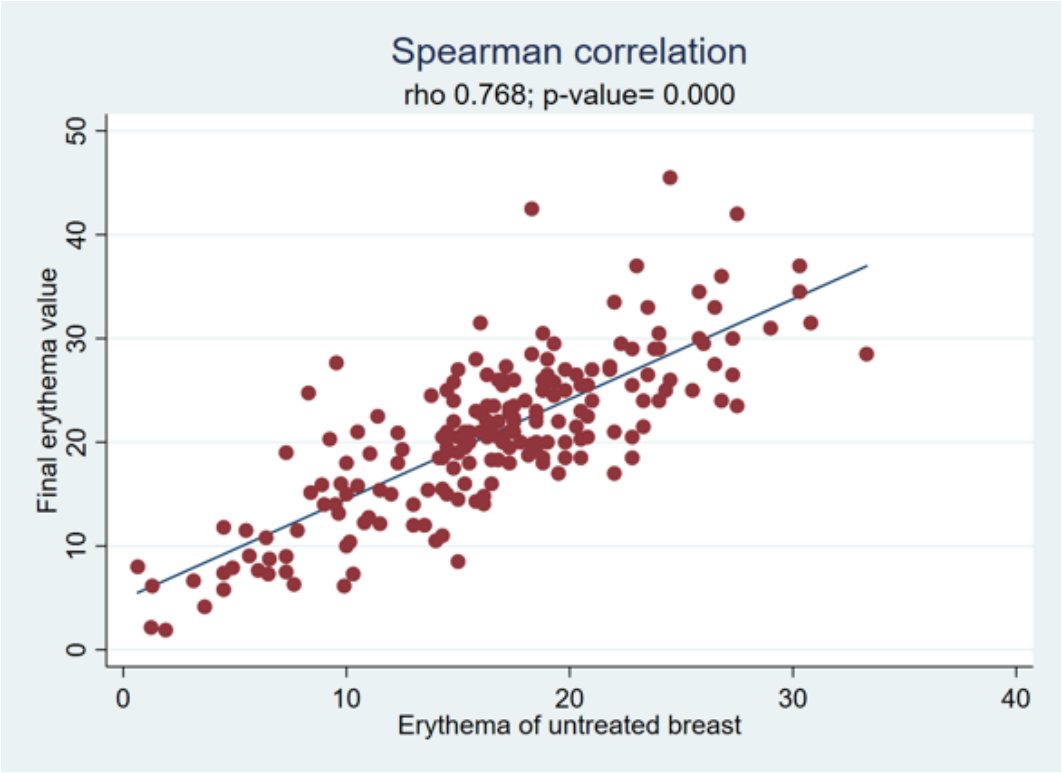


Figure 14b. Relationship between irradiated breast and non-irradiated breast in melanin.

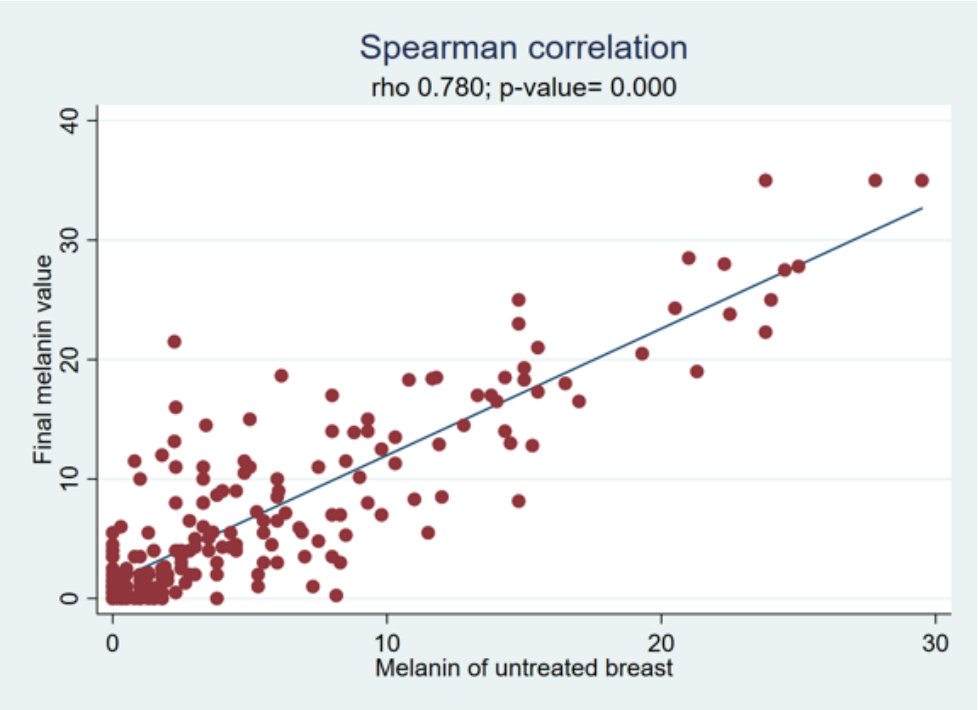


Figure 14c. Relationship between irradiated breast and non-irradiated breast in elasticity.

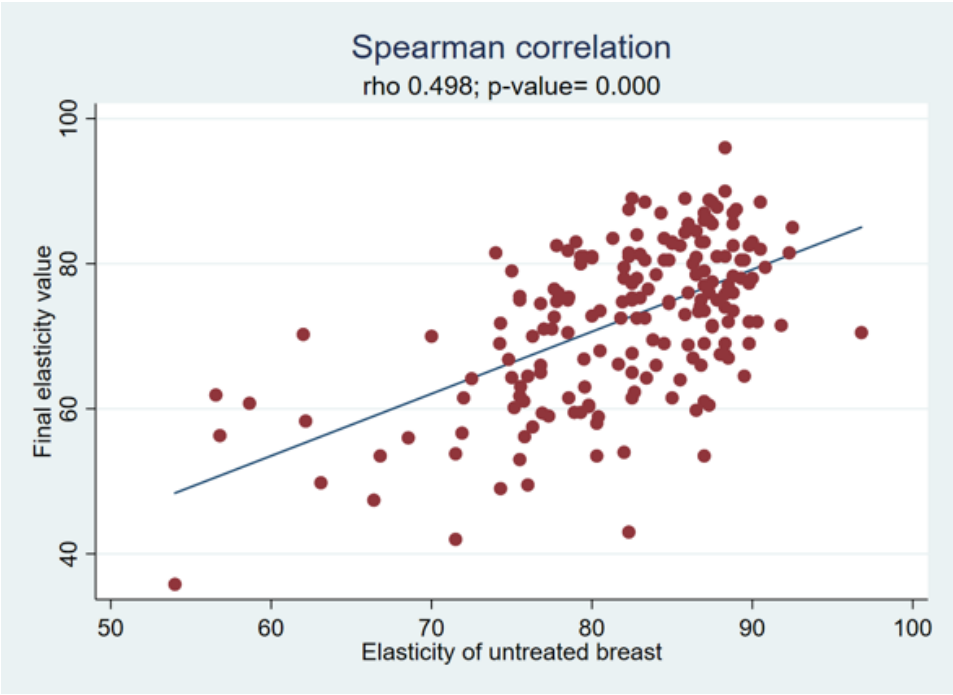


Figure 14d. Relationship between irradiated breast and non-irradiated breast in .

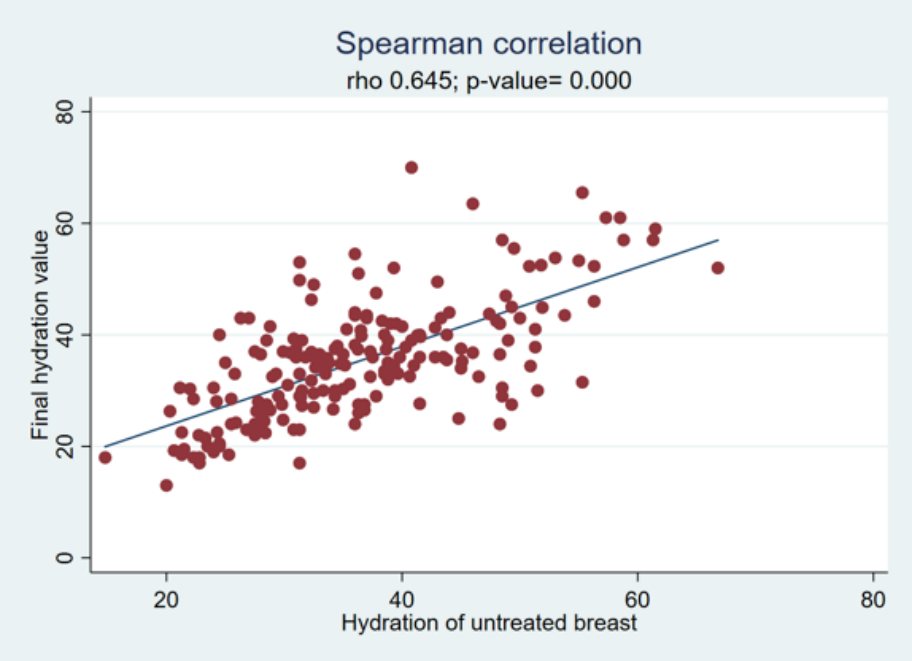


Figure 15a. Correlation between age and erythema.

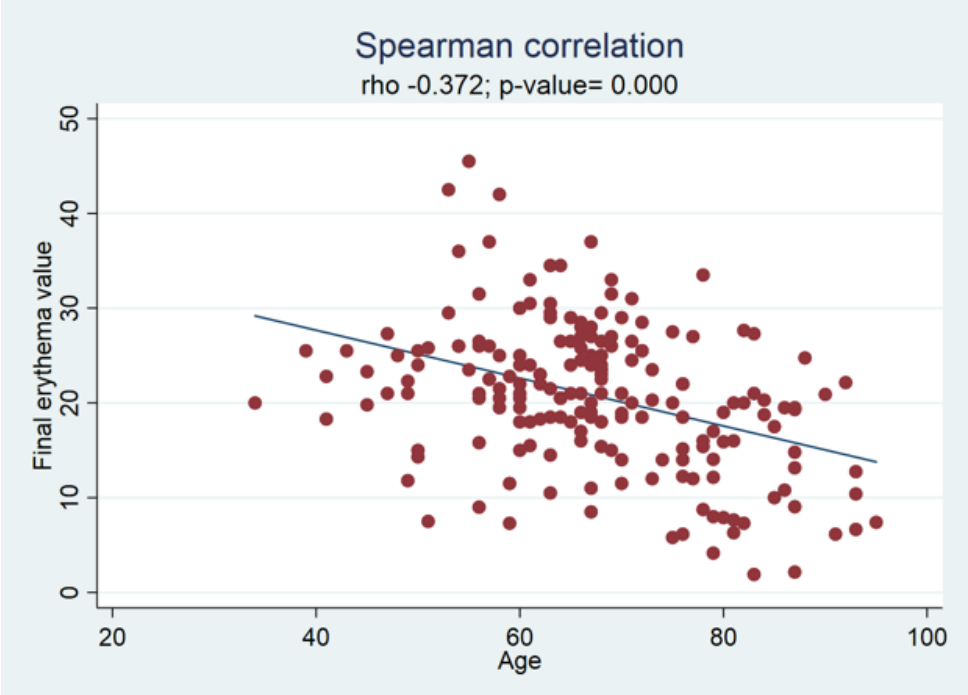


Figure 15b. Correlation between age and melanin.

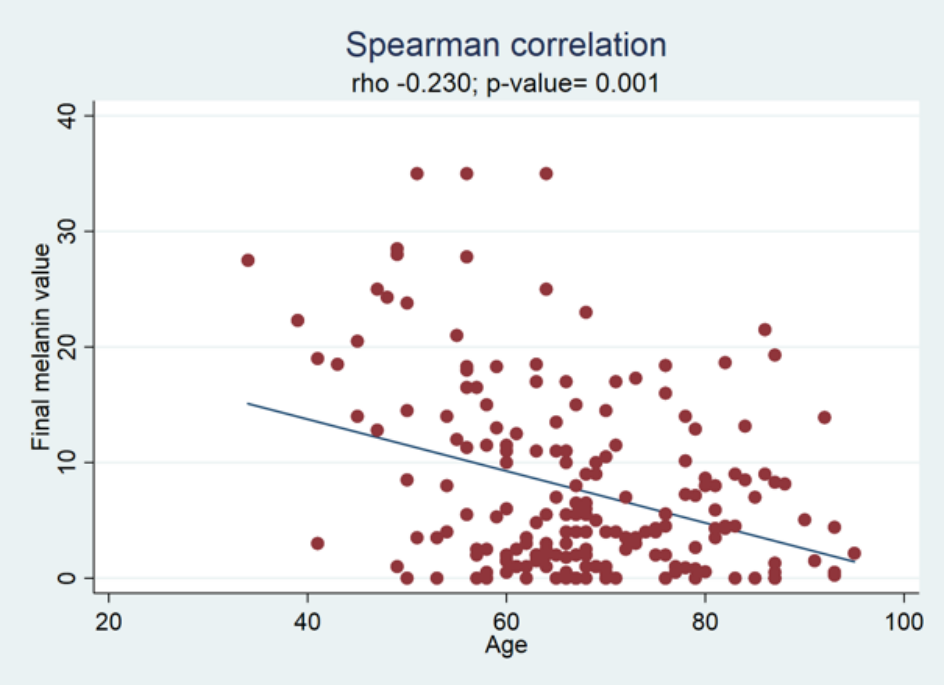


Figure 15c. Correlation between age and elasticity.

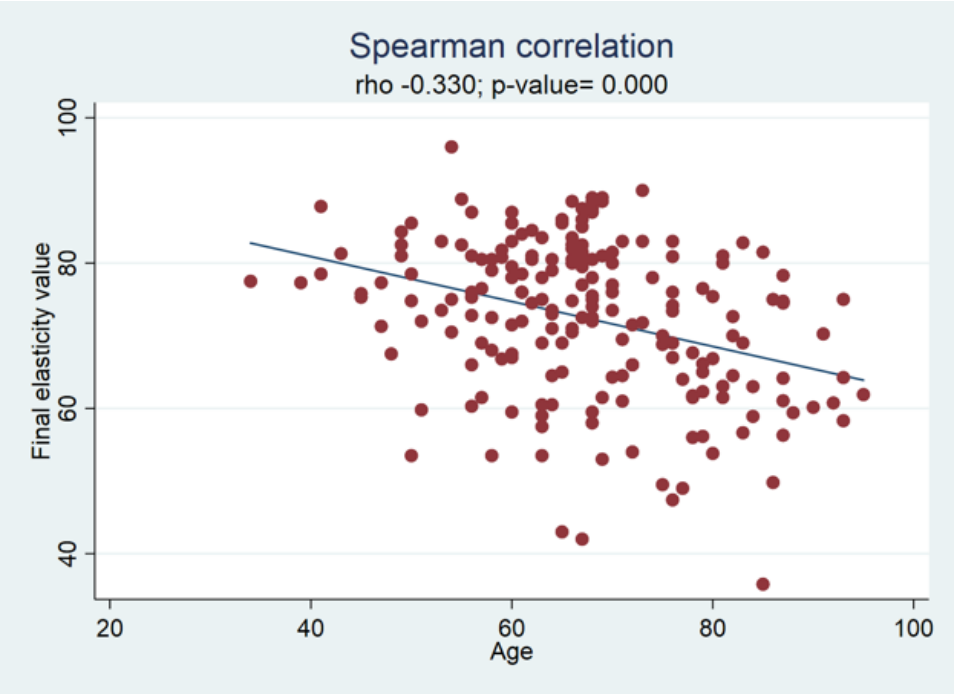


Figure 15d. Correlation between age and hydration.

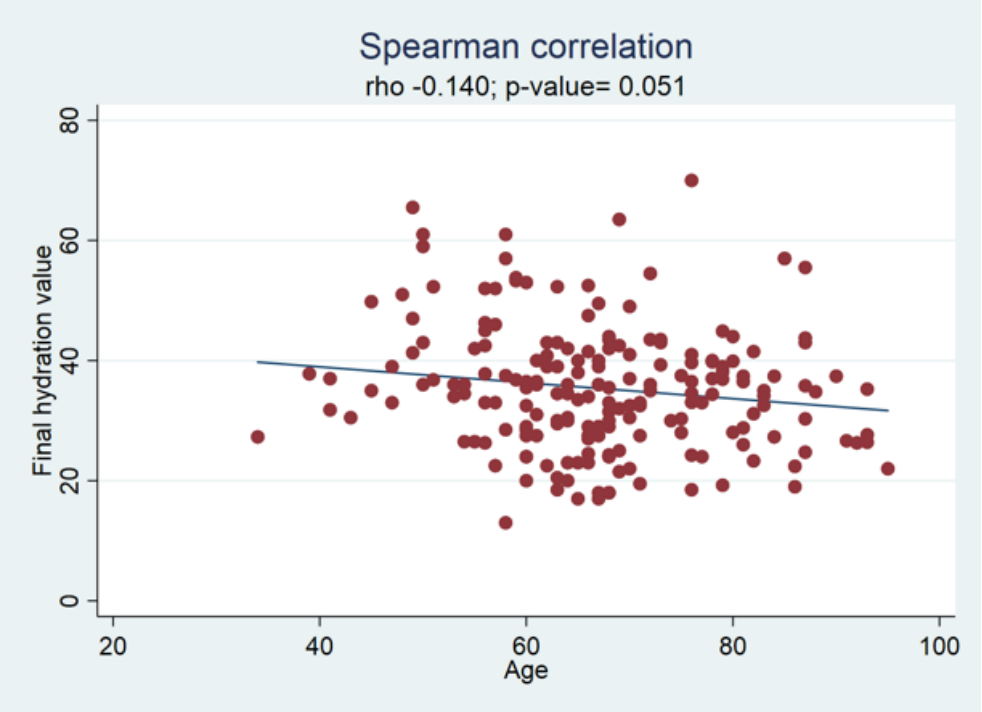


Figure 16a. Correlation between duration of treatment and erythema.

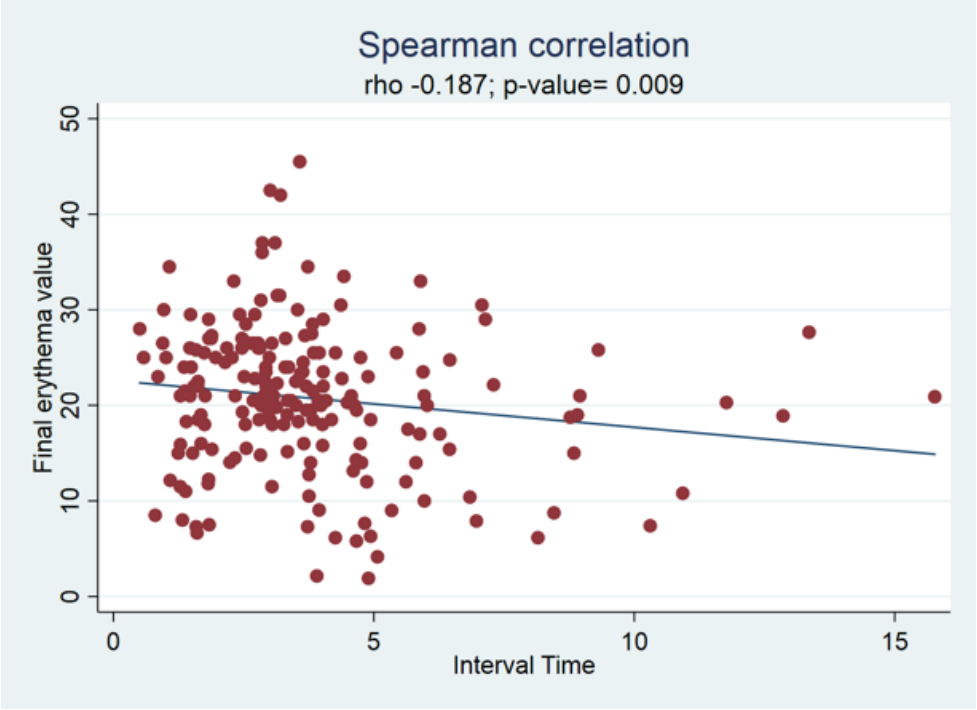


Figure 16b. Correlation between duration of treatment and melanin.

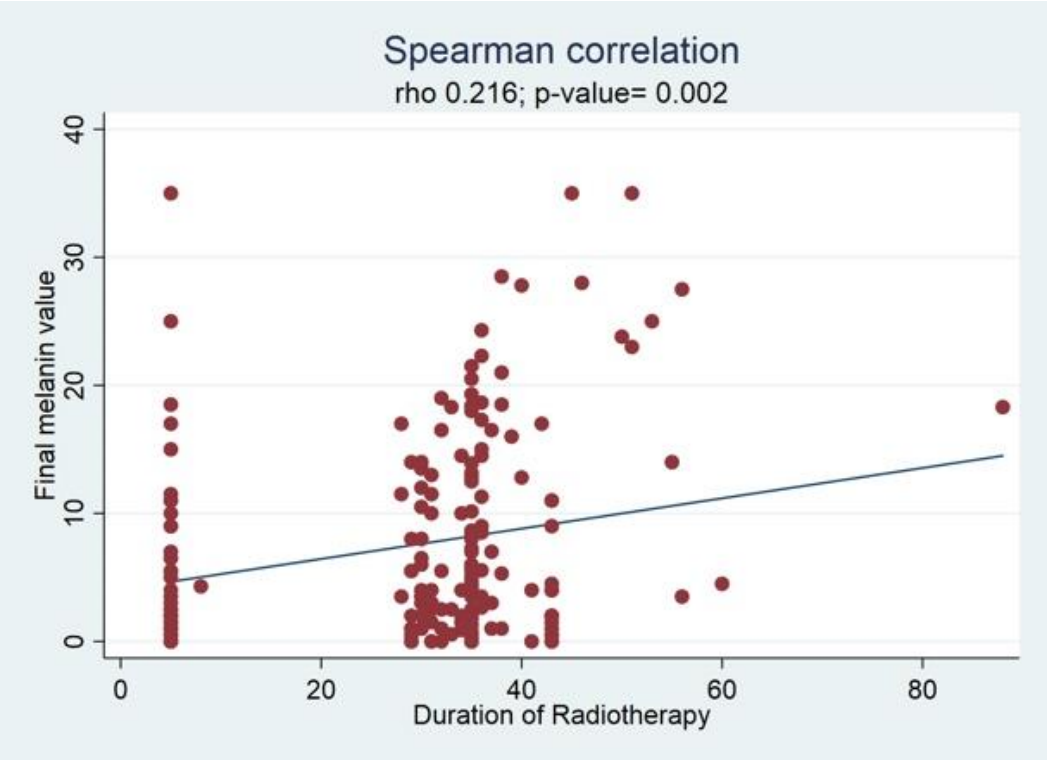


Figure 16c. Correlation between duration of treatment and elasticity.

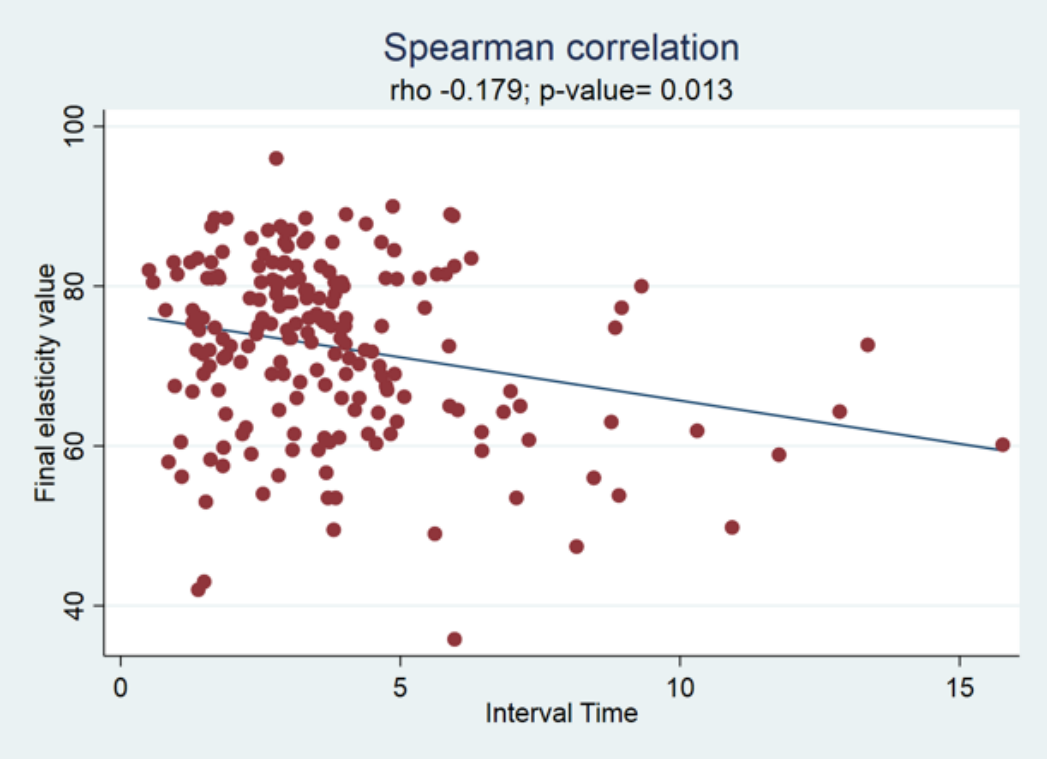


Figure 16d. Correlation between duration of treatment and hydration.

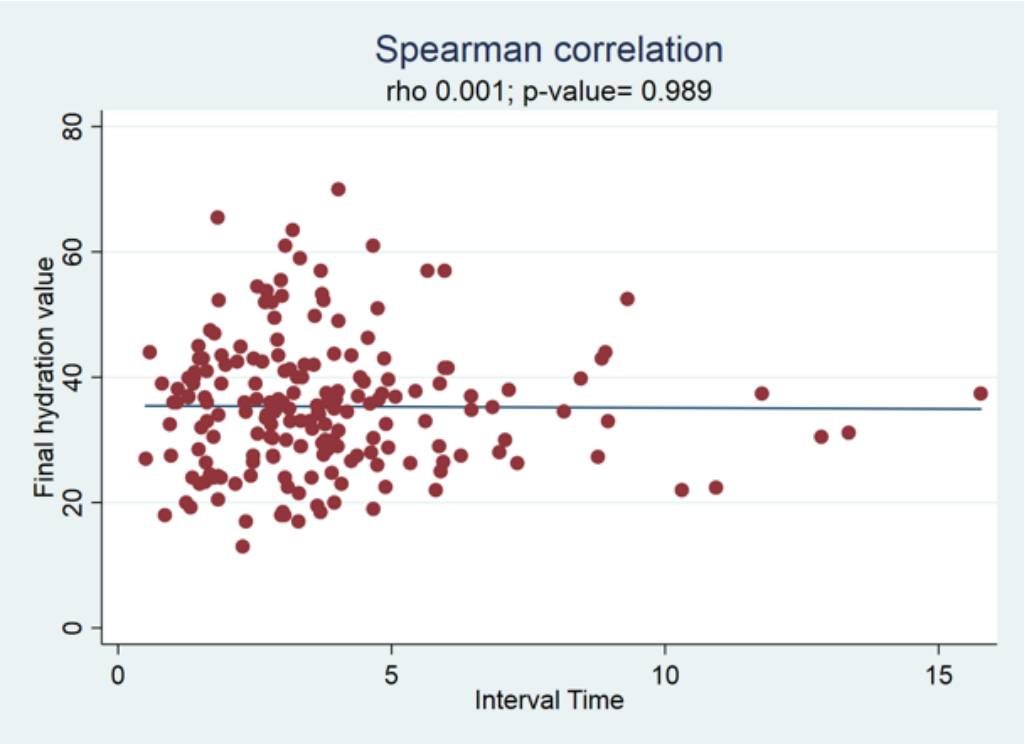


Figure17a. Correlation between erythema and interval time between radiotherapy and toxicity assessment.

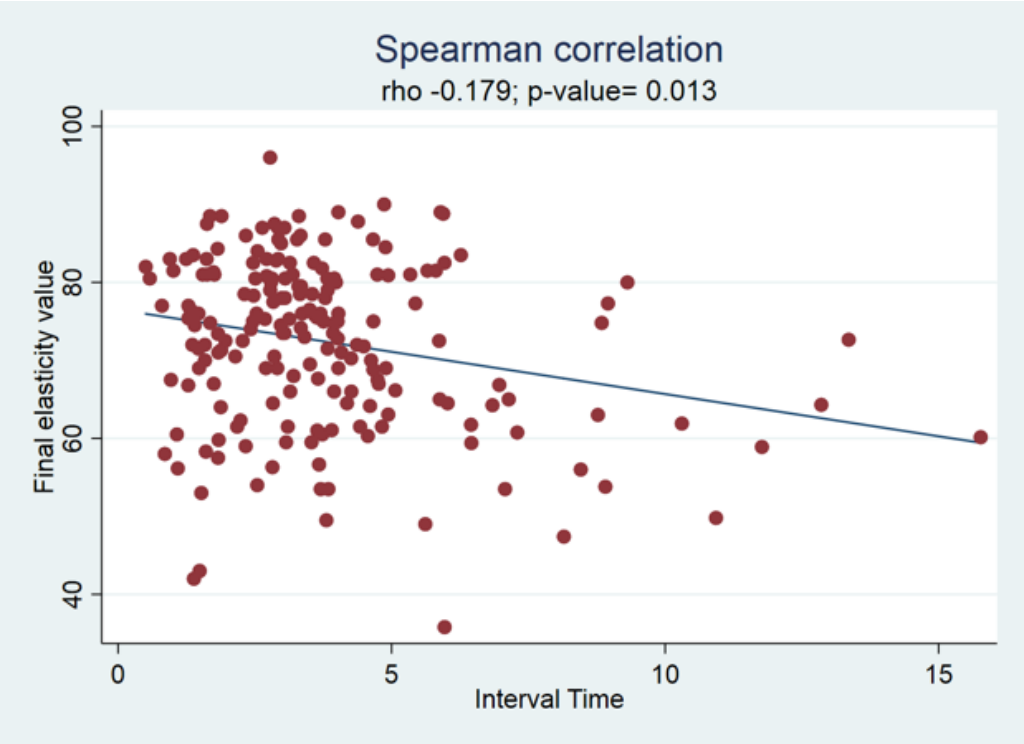


Figure 17b. Correlation between melanin and interval time between radiotherapy and toxicity assessment.

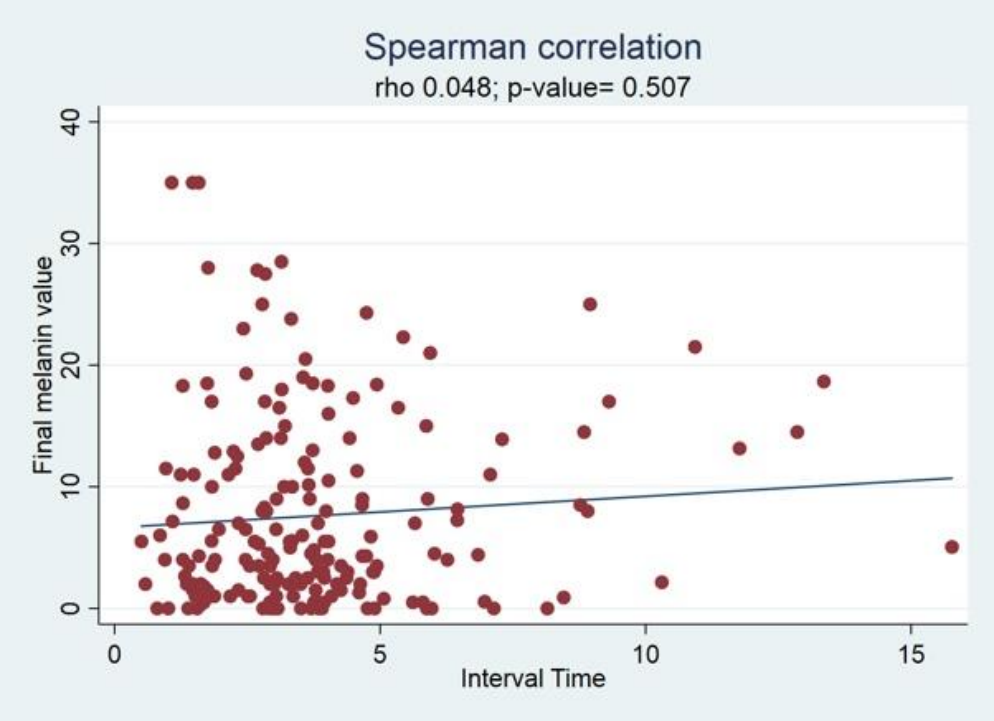


Figure 17c. Correlation between elasticity and interval time between radiotherapy and toxicity assessment.

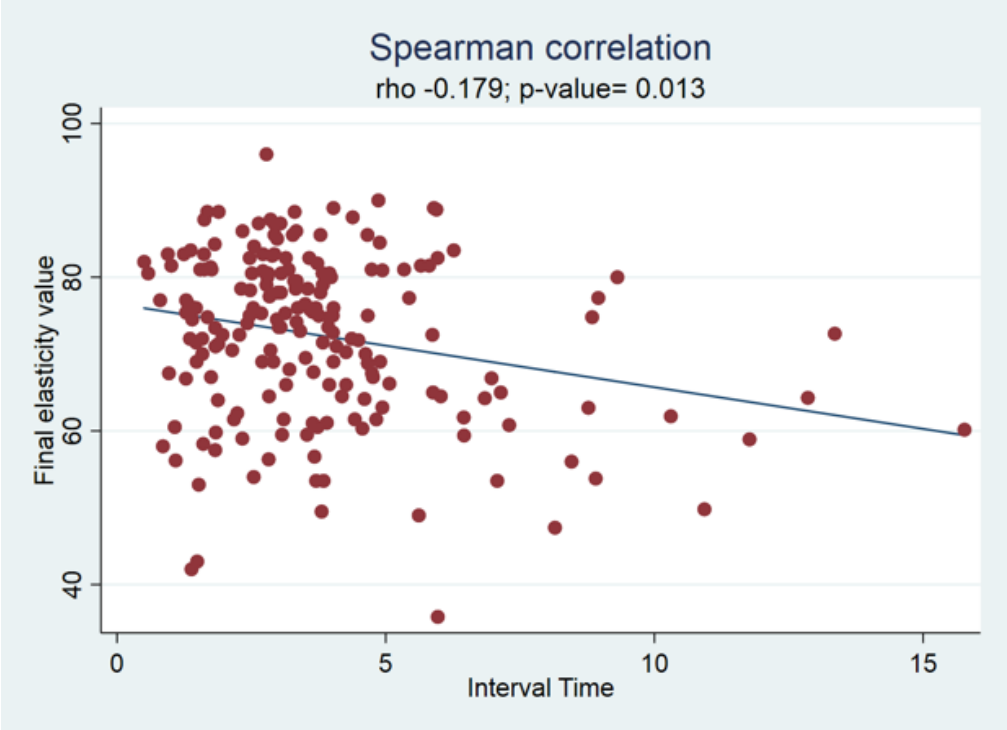


Figure 17d. Correlation between hydration and interval time between radiotherapy and toxicity assessment.

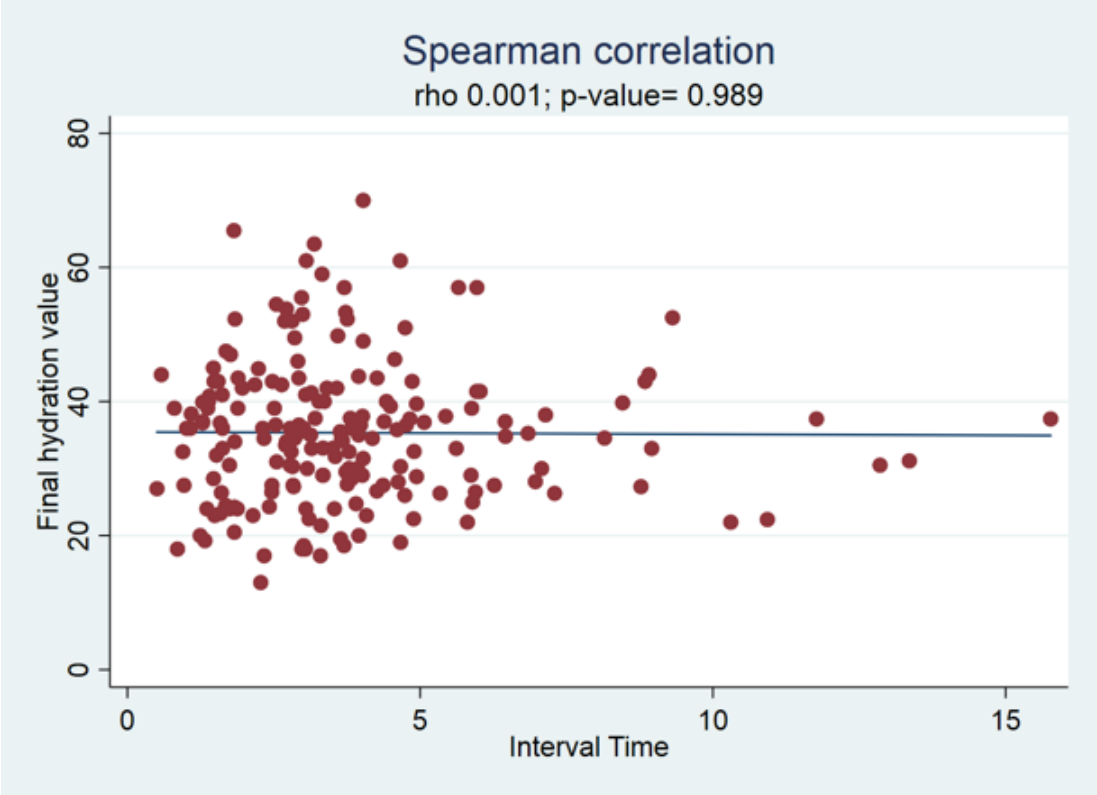


Table 19. Correlation between age, duration of radiotherapy, interval time between irradiation and objective measurement on skin quantitative toxicity assessments.

	Age		Duration of treatment		Interval Time[#]	
	r[$]	p	r	p	r	p
Erythema	-0.37	**<0.001**	-0.25	**0.001**	-0.19	**0.009**
Melanin	-0.23	**0.001**	0.22	**0.002**	0.05	0.51
Elasticity	-0.33	**<0.001**	-0.057	0.43	-0.18	**0.013**
Hydration	-0.14	0.051	0.08	0.27	0.001	0.98

#: Interval time between radiotherapy and objective assessment;

Table 20 Median values of erythema, melanin, elasticity and hydration of irradiated breast depending on boost, weekly vs daily doses, and tamoxifen.

	Boost			Weekly vs Daily[#]			Tamoxifen		
	With (N = 39)	Without (N = 160)		Weekly (N = 45)	Daily (N = 154)		With (N = 32)	Without (N = 167)	
	Median (Q1, Q3)		p	Median (Q1, Q3)		p	Median (Q1, Q3)		p
Erythema	23.3 (20.0, 26.8)	18.8 (12.2, 24.0)	**<0.001**	12.5 (7.7, 18.8)	22.5 (19.0, 26.5)	**<0.001**	20.9 (17.0, 27.0)	21.0 (15.9, 25.5)	0.35
Melanin	4.0 (1.5, 11.8)	5.5 (2.0, 11.5)	0.98	5.3 (1.3, 8.7)	4.0 (2.0, 12.3)	0.31	6.0 (2.0, 10.0)	4.3 (1.6, 11.8)	0.72
Elasticity	76.0 (68.5, 80.9)	72.3 (63.0, 80.9)	0.13	64.2 (59.4, 72.7)	76.0 (69.0, 81.7)	**<0.001**	71.3 (60.5, 79.0)	75.0 (66.1, 81.0)	**0.025**
Hydration	34.8 (27.8, 41.4)	35.4 (27.5, 40.0))	0.82	34.5 (27.6, 39.6)	35.3 (27.5, 41.8)	0.59	31.3 (24.3, 37.4)	35.4 (28.0, 41.8)	0.24

Weekly: weekly hypofractionation; Daily: classical fractionation, moderate daily hypofractionation, and accelerated partial breast irradiation.

5.1.10 Multivariate analysis of radiation-induced toxicity associated clinical factors.

A multivariable regression analysis was used to detect a possible influence of the value of contralateral breast skin, BED, age, boost, interval time between irradiation and toxicity assessment, tamoxifen on irradiated-induced toxicity. In order to prevent the occurrence of collinearity with BED, radiation-related covariables not included in the multivariate regression analysis. The value of contralateral untreated breast skin was still a significant predictor of erythema, melanin, elasticity and hydration in multivariable regression analysis（Coef=0.92, OR=1.12, OR=0.69, OR=0.78, p<0.0001 of all parameter）. Interestingly, on univariate analysis, there was no significant correlation between hydration and BED. However, after adjustment for possible confounding variables, the hydration value significantly associated with the BED increase（Coef=-0.15, p=0.016. Besides, BED remained associated with melanin and elasticity (Coef =0.05, p=0.034, Coef =-0.17, p=0.012, respectively). A correlation was observed between hydration and interval time between radiotherapy and toxicity asessessment (Coef =0.96, p=0.001). Other factors, including age, boost and tamoxifen had no significant influence on the erythema, melanin, elasticity and hydration in the median multivariate regression analysis (Table 21).

Table 21. Multivariate median regression analyses of factor associated with irradiation-induced toxicity.

	Erythema		Melanin		Elasticity		Hydration	
	Coef	p	Coef	p	Coef	p	Coef	p
Age	-0.07	0.07	0.01	0.68	-0.12	0.11	-0.1	0.07
Contralateral[#]	0.92	**<0.001**	1.12	**<0.001**	0.69	**<0.001**	0.78	**<0.001**
BED	0.04	0.35	0.05	**0.034**	-0.17	**0.012**	-0.15	**0.016**
Boost	0.39	0.74	0.35	0.64	-2.1	0.33	-0.23	0.89
Interval time[$]	-0.04	0.84	-0.04	0.73	-0.06	0.87	0.96	**0.001**
Tamoxifen	-1.72	0.15	0.04	0.95	2.6	0.22	1.83	0.3

Abbreviation: Coef: regression coefficient; BED: Biologically equivalent doses

#: Values of erythema, melanin, elasticity and hydration of contralateral non-irradiation breast skin; $: Interval time between radiotherapy and objective assessment;

5.2 Second study

5.2.1 Patient characteristics

Ninety-five patients were included in this study. The median follow-up period was 73.2 months. The mean patient age was 42.8 years at reconstruction. Chemotherapy was administered to 56.8% of patients, while 36.8% of patients received hormonal therapy. Patient characteristics are shown in table 22.

Table 22 Patient and treatment characteristics.

Characteristics	All patients (n=95)	
	n	
Mean age (years; SD)	42.8	7.7
Tumour laterality		
Right	37	38.9 %
Left	48	50.5 %
Both sides	10	10.5 %
Boost		
Yes	22	23.2 %
Adjuvant treatment		
Hormonal therapy	35	36.8 %
Chemotherapy	54	56.8 %
Risk factor		
Smoking	25	26.3 %
Hypertension	11	11.6 %
Diabetes	2	2.1 %
BMI (n=30)		
<25	18	18.8
25.0-29.9	4	4.2
>30	8	8.3
Follow-up (months; SD)	73.2	45.8

Abbreviations: body mass index.

There were 54 pre-HR cases, 19 pre-AR cases, 13 post-HR cases and 9 post-AR cases, according to our distribution of patients depending on the time and type of reconstruction (Figure 6).

5.2.2 Interval time between breast reconstruction and radiotherapy

There was no significant difference in the median time between the different techniques and timing of reconstruction (mean months: 44.4 vs. 26.3, p=0.18; 41.9 vs 29.7, p=0.4, respectively), even when we excluded the 18 patients with previous implants (mean months: 19.6 vs. 26.3, p=0.39; 19.0 vs. 29.7, p=0.2, respectively) (Table 23).

Table 23. Median time (in months) between radiotherapy and breast reconstruction.

	All patients (n=95)			Excluding patients with previous implants (n=77)		
	n	Mean (SD)	P	N	Mean (SD)	p
Reconstruction technique						
Heterologous	67	44.4 (67.3)	0.18	49	19.6 (32.0)	0.39
Autologous	28	26.3 (34.1)		28	26.3 (34.1)	
Timing with respect to reconstruction						
Before reconstruction	73	41.9 (65.9)	0.40	55	19.0 (32.9)	0.20
After reconstruction	22	29.7 (31.6)		22	29.7 (31.6)	

5.2.3 Complications

As shown in Table 24, the overall complication rate was 20%. Complications occurred more frequently in the HR group, although no significant difference was reached (p=0.67). Capsular contracture was the most common complication (16.7%). The pre-HR group showed a higher rate of major revision surgery (20.4%). At least one minor revision procedure was performed by 68.4% and 77.8% of patients in the pre-AR and post-AR groups, respectively. In contrast, 81.5% of patients in the pre-HR group did not require any minor re-operation.

5.2.4 Toxicity outcomes assessed by qualitative and quantitative measurements

Toxicity outcomes were evaluated by physicians in 85 patients. There was no difference in the grade or type of toxicity among the groups (p=0.85, p=0.95, respectively). Dermatitis was the most common form of toxicity (12.9%). The intensity of late toxicity was mild: grade I toxicity occurred in 25.6% of patients. Grade II toxicity occurred in 3 patients, which only existed in the pre-HR group. No cases of grade III or higher chronic toxicity occurred. In addition, to objectively assess toxicity, 31 patients underwent cutaneous analysis using the multi-probe device (Figure 7-9). There were significant differences in the values of erythema, melanin and elasticity between the treated and untreated breasts ($p<0.001$, $p=0.014$, $p<0.001$, respectively). RT produced an increase in erythema and melanin and a decrease in elasticity in the treated breast. Meanwhile, there was no statistically significant difference in hydration ($p = 0.215$)

(Table 24). However, when we compared the erythema, melanin, elasticity and hydration results among the different groups, there were no significant differences.

Table 24. Four parameters (melanin, erythema, elasticity and hydration) were measured in each quadrant of each breast with the multi-probe device.

	Treated breast	Untreated breast	
	Mean (± SD)	Mean (± SD)	**p**
Erythema	19.69(±6.1)	15.6(±5.4)	**<0.001**
Melanin	18.32(±9.4)	16.3(±7.0)	**0.014**
Elasticity	79.9(±7.6)	84.6(±4.3)	**<0.001**
Hydration	42.6(±11.2)	41.2(±11.0)	0.215

5.2.5 Cosmetic outcomes

The aesthetic results were evaluated by physicians in 91 patients. There were no significant differences among the procedures utilized. Good to excellent cosmetic outcomes were observed in 93.4% of all patients and in 100% of patients treated with AR (Figure 25).

Table 25. Reconstruction techniques, complications, revision surgeries, toxicity and aesthetic results according to the timing of irradiation and breast reconstruction techniques.

	Pre-HR (n=54)		Pre-AR (n=19)		Post-HR (n=13)		Post-AR (n=9)		All patients (n=95)		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p**
Complications											
Capsular contracture	9	16.7	0	--	2	15.4	0	-	11	11.6	0.67
Haematoma	1	1.9	1	5.3	1	7.7	0	-	3	3.1	
Infection	2	3.7	0	-	0	-	1	11.1	3	3.1	
Fat necrosis	0	1.9	1	5.3	0	-	0	-	1	1.1	
Implant failure	1	1.9	0	-	0	-	0	-	1	1.1	
Total	13	24.1	2	10.5-	3	23.1	1	11.1	19	20	
Type of revision surgeries											
Major[$]											
Autologous	0	-	2	10.5	0	0	1	11.1	3	3.1	**<0.001**
Heterologous	11	20.4	0	-	0	-	0	-	11	11.6	
Minor [#]	10	18.5	13	68.4	5	38.5	7	77.8	35	36.5	

Abbreviations: pre-HR: heterologous reconstruction before radiotherapy; pre-AR: autologous reconstruction before radiotherapy; post-HR: heterologous reconstruction after radiotherapy; post-AR: autologous reconstruction after radiotherapy; DIEP: deep inferior epigastric perforator; LD: latissimus dorsi flap.

Minor revisions: reconstruction of the areola-nipple complex, fat *grafting*.

$ Major revisions: all other revision surgeries except for minor corrective surgery, such as implant exchange.

Table 25 (continuous). Reconstruction techniques, complications, revision surgeries, toxicity and aesthetic results according to the timing of irradiation and breast reconstruction techniques.

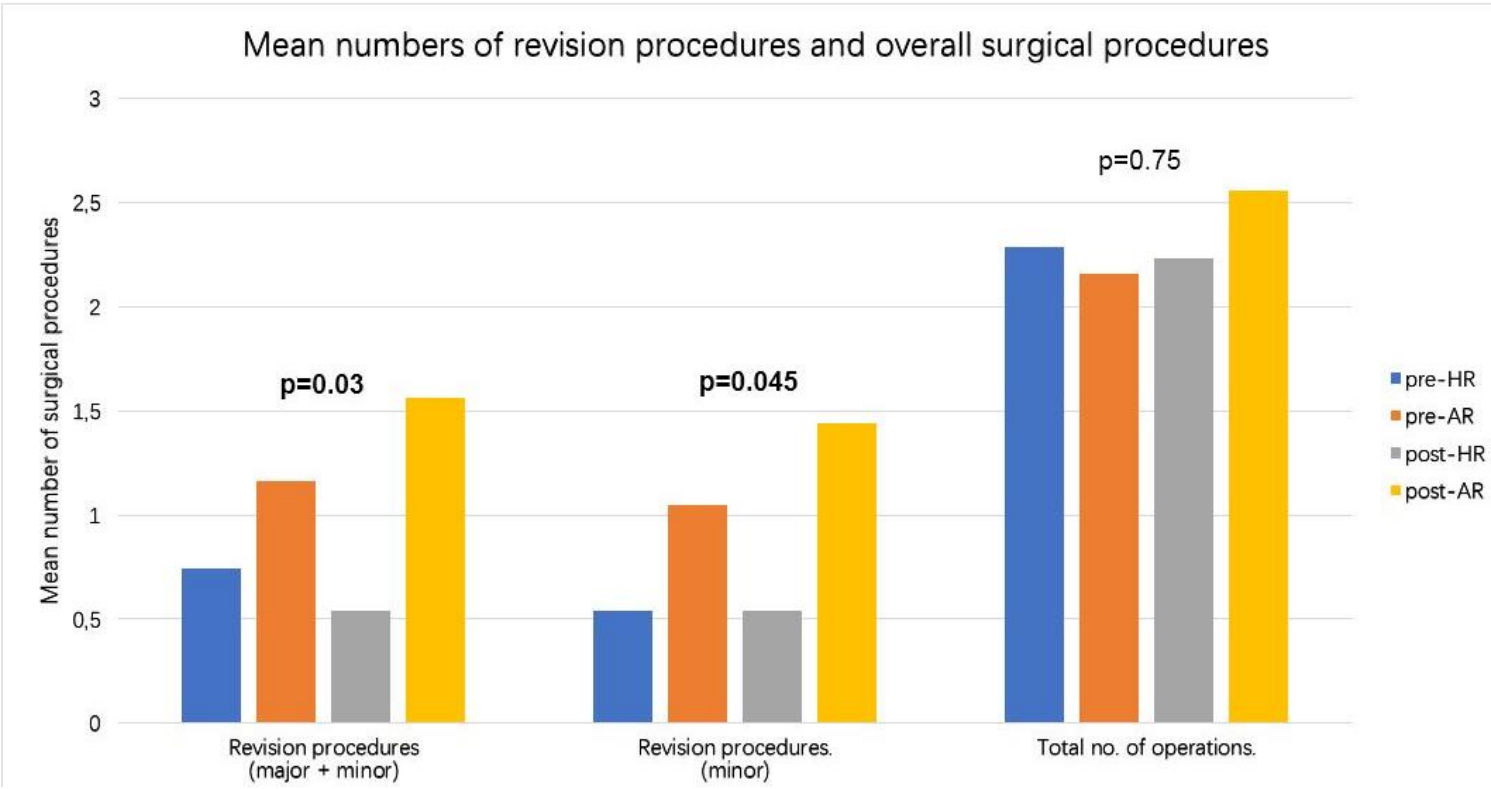
	Pre-HR (n=54)		Pre-AR (n=19)		Post-HR (n=13)		Post-AR (n=9)		All patients (n=95)		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p**
Grade and type of toxicity (n=85)											
Toxicity grade											
I	14	25.9	2	10.5	4	30.8	2	22.2	22	25.6	0.85
II	3	4.9	0	-	0	-	0	-	3	3.5	
Total	17	33.8	2	10.5	4	30.8	2	22.2	25	29.1	
Toxicity type											
Dermatitis	9	16.7	0	-	2	15.4	0	-	11	12.9	0.95
Fibrosis	6	11.1	1	5.3	1	7.7	0	-	8	9.4	
Telangiectasia	0	-	0	-	0	-	1	11.1	1	1.2	
Pain	2	3.7	0	-	1	7.7	0	-	3	3.5	
Lymphoedema	0	-	1	5.3	0	-	1	11.1	2	2.4	
Total	17	33.8	2	10.5	4	30.8	2	22.2	25	29.4	
Aesthetic results (n=91)											
Acceptable											0.17
Excellent	12	24.0	8	42.1	2	15.4	2	22.2	24	26.4	
Good	34	68.0	11	57.9	9	69.2	7	77.7	61	67.0	
Unacceptable								-			
Regular	4	8.0	0	-	2	15.4	0	-	6	6.6	
Bad	0	-	0	-	0	-	0	-	0	-	

Abbreviations: pre-HR: heterologous reconstruction before radiotherapy; pre-AR: autologous reconstruction before radiotherapy; post-HR: heterologous reconstruction after radiotherapy; post-AR: autologous reconstruction after radiotherapy;

5.2.6 Revision procedures and overall surgical procedures

Compared with HR, AR was associated with a significantly higher mean number of unplanned re-operations (p=0.03). Among them, patients undergoing AR also required more additional minor operative revisions for the completion of reconstruction (p=0.045). However, there was no significant difference in the total number of surgical procedures among the study groups (p=0.75) (Figure 18).

Figure 18. revision procedures and overall surgical procedures among patients from four groups



Abbreviations: pre-HR: heterologous reconstruction before radiotherapy; pre-AR: autologous reconstruction before radiotherapy; post-HR: heterologous reconstruction after radiotherapy; post-AR: autologous reconstruction after radiotherapy. Minor revisions included reconstruction of the areola-nipple complex and fat grafting. Major revisions included all other revision surgeries except for minor corrective surgery, such as implant exchange. The total number of surgical procedures included oncological surgeries, breast reconstruction surgeries and revision surgeries.

5.2.7 Univariate and multivariate analysis of risk factors related to radiotherapy and breast reconstruction

On univariate analysis, our results revealed that an older age at reconstruction and smoking were significant predictors of increased complications (OR: 3.11; p=0.047, OR: 1.21; p=0.005, respectively). After adjusting for possible confounding variables, however, only smoking remained associated with complications (OR: 1.2; p=0.01). There was no significant difference in other variables (Table 26).

Table 26. Univariate and multivariate analysis of risk factors related to radiotherapy and breast reconstruction.

	Complication			
	Univariate		**Multivariate**	
	OR (95 %CI)	**p**	**OR (95 %CI)**	**p**
HR	2.61(0.70-9.81)	0.15	2.64(0.57-12.33)	0.22
Pre-RT	1.16(0.34-3.95)	0.81		
Older age [#]	3.11(0.93-8.55)	**0.047**	3.35(0.97-11.57)	0.056
Bilateral	1.85(0.43-7.94)	0.41		
Boost	0.98(0.84-1.14)	0.81		
Chemotherapy	0.91(0.80-1.04)	0.15	0.91(0.79-1.05)	0.31
Median time[$]		0.66		
<6 months	1(reference)			
6-12 months	1.37(0.32-5.79)			
>12 months	0.76(0.23-2.55)			
Previous implant	1.12(0.97-1.29)	0.12	1.06(0.90-1.26)	0.48
Hypertension	0.98(0.80-1.21)	0.87		
Smoking	1.21(1.06-1.38)	**0.005**	1.20(1.04-1.1.38)	**0.01**
BMI≥25	1.6(0.19-13.24)	0.67		

Abbreviations: HR: heterologous reconstruction; pre-RT: radiotherapy before reconstruction; BMI: body mass index.

Age at reconstruction ≥45 years.

$ Median time (in months) between radiotherapy and breast reconstruction.

6. Discussion

6.1 FIRST STUDY

6.1.1 Radiation-induced toxicity

To the best of our knowledge, our series is the first and the largest study that assess late skin parameters (erythema, pigmentation, elasticity and hydration) following 7 different radiotherapy schedules using objective tools. Moreover, this study also analyzed the potential factors associated with RIT based on objective assessment.

The alteration of coloration (erythema and pigmentation), fibrosis and dehydration of the skin son common RIT for breast cancer patients. These RT-associated side effects may impact patient quality of life. In particular, the increasing number of long-term survivors diagnosed with breast cancer makes it necessary to improve the radiotherapy plan to minimize radiation effects on healthy tissues as much as possible. Consequently, ensuring a greater focus on (1) determining whether our quantitative and multiprobe technique is capable of assessing late RIT in terms of skin color alterations (erythema, pigmentation), induration and dehydration following different radiotherapy protocols; (2) establishing an underlying BED-response relationship based on both objective measurements and subjective RIT evaluations; (3) determining whether the measures of our objective assessment tool is related to a subjective clinical assessment of acute and late RIT obtained using the RTOG scale.

6.1.2 Quantitative assessments and comparison of subjective and objective assessments

Currently, different toxicity scales are used to assess RIT. Despite its speed and simplicity, the measurement of skin reactions usually depends on subjective visual and palpation-based tools. The RTOG and CTCAE scores, although valuable and widely used, have many drawbacks, particularly their lack of objective measures, which carries a considerable risk of intra- and interobserver variability(83). Especially in multicenter clinical trials, this variability can lead to discrepancies in toxicity outcomes between different institutions and may limit their value as result measures. In addition, it is widely agreed that with the development of various radiotherapy technologies, quantitative assessments are needed to accurately detect the slight changes in RIT caused by these new technologies. Thus, several studies have attempted to measure RIT by using quantitative methods (Table 26).

Numerous techniques have been developed to objectively assess RIT via the measurement of associated skin characteristics, including ultrasound(84–88,96,97), spectrophotometry(86,89,92), thermal images(100), LDF(90,91), mexameter probes(93,94,102,104), viscoelasticity skin analyzers(105), corneometry(92–95,102) and multiprobe devices, etc(93,101,102,106). Yoshida et al. tested the reliability of the ultrasonic assessment of radiation toxicity and found that the resulting ultrasound measurements of the change in skin thickness were correlated with the RTOG scale score, suggesting that this technique can be used as a reliable method to assess RIT(84). Unlike our assessment, the use of ultrasound requires long-term training, which is not

conducive to its application in clinical practice. Yoshida et al. evaluated radiation dermatitis by a spectrophotometer. CTCAE scales were found to be associated with a* and L* values, which are indicators of skin color alteration. Saednia et al. reported that thermal imaging markers could be used to monitor RIT. Patients with a CTCAE toxicity score>2 demonstrated a significant increase in skin temperature(100). In the study by Huang et al., a LDF was used to successfully measure acute radiation dermatitis, and the resulting quantitative values were shown to be correlated with the RTOG, CTCAE and WHO scores. This study also evaluated the pigmentation and skin hydration of the breast through a multiprobe device. Those clinical scoring criteria were moderate correlated to pigmentation; however, they were not found to be related to moisture analysis(102). Another study by González et al. also used LDF to monitor acute radiation-induced dermatitis. The results showed that the LDF microcirculation index was correlated with the CTCAE scale score(90).

These technologies have been used mainly in the evaluation of acute toxicity; only a small proportion of objective assessment techniques have been used to monitor late toxicity. In our study, late RIT was assessed by a multiprobe device. We used the color (redness and darkness) of skin as an indicator of erythema and pigmentation, skin elasticity as a surrogate for fibrosis and skin moisture content as an indicator of skin hydration. The treated breasts showed higher erythema and melanin and lower elasticity and hydration than untreated breasts. Hydration did not change much after radiation may due to different skin care(107). Subsequently, we compared clinical assessment measurements with our objective evaluations of RIT, and our results agree with those

of the aforementioned studies. Higher erythema and less elasticity are indicators of dermatitis and fibrosis, respectively, the most common signs of late toxicity(107), and were significantly correlated with the RTOG criteria. We suggest that our objective multiprobe measurement system may be used as a reliable clinical tool for assessing RIT.

Furthermore, breasts treated with an RTOG toxicity grade of 0 demonstrated significantly higher values of erythema and melanin and lower values of elasticity than the corresponding nonirradiated breasts. These findings indicate the presence of an underlying but invisible or nonpalpable skin change, suggesting that compared with clinical assessment alone, the multiprobe device can demonstrate more reliable changes with respect to erythema, melanin and elasticity and hydration. Therefore, our objective measurement tool can be used in the assessment of RIT and may be more sensitive than the RTOG scale, as it can detect slight changes in RIT that are difficult to determine by visual or tactile examination.

Table 26. Studies using quantitative toxicity assessments.

Study	n	Median follow-up	Radiation schemes	Biophysical parameters	Quantitative Techniques	Qualitative assessment
Warszawski et al.(96)	29	n=18: ≤ 3 months; n=11: 30 months	CF: 46-50 Gy/2Gy	Skin thickness	Ultrasound	RTOG
Liu et al.(88)	18	22 months	CF: 50.0-50.4 Gy/1.8-2.0 Gy	Skin thickness; hypodermal surface; glandular tissue	Ultrasound	RTOG
Yoshida et al.(84)	26	n=8: < 6 months; n=18: ≥ 6 months	CF: 50.0-50.4 Gy/1.8-2.0 Gy	Skin thickness; hypodermal surface; glandular tissue	Ultrasound	RTOG
Landoni el al.(97)	89	20.5 months	HF: 34 Gy/10 Fx/3.4Gy	Skin thickness	Ultrasound	CTCAE
Wengstrom el al.(98)	53	Acute toxicity (follow-up: N/R)	CF: 50 Gy/2 Gy	Erythema; pigmentation	Spectrophotometer; Measure digital images (Camera)	RTOG
Schmeel et al.(89)	70 in CF; 70 in HF	6 weeks	CF: 50 Gy/25 Fx; HF: 40.05 Gy/15 Fx	Erythema; pigmentation	Spectrophotometer	CTCAE
Yamazaki et al.(99)	46 in CF; 26 in HF	12 months	CF: 50 Gy/25 Fx; HF: 42.56 Gy/16 Fx	Color alteration	Spectrophotometer	CTCAE
Yoshida et al.(92)	118	12 months; subgroup (n=28): 5 years	CF: 48.4-50 Gy/22-25 Fx	Color alteration; skin moisture	Spectrophotometer; Corneometer	CTCAE
Saednia et al.(100)	90	During RT	HF: 42.50 Gy/16 fx	Skin temperature (Dermatitis)	Thermal imaging device	CTCAE
Sanchis et al.(90)	63	3 months	HF: 40 Gy/15 Fx/2.67Gy	Blood flow (Dermatitis)	LDF	CTCAE
Huang el al.(102)	101	Last day of RT	CF: 50.0-50.4 Gy/1.8-2.0 Gy	Blood flow; pigmentation; hydration; skin pH	LDF; Multi Skin Test Center MC900; Corneometer; Skin pH meter	RTOG; CTCAE; WHO
Sekine et al.(93)	43	1 year	CF: 50 Gy/25 Fx;	Erythema, pigmentation; hydration; skin temperature	Multi-Display Device MDD4; (Corneometer; Tewameter; Mexameter); thermometer	CTCAE
Nuutinen et al.(101)	21	5 weeks; subgroup (n=14): 2 years	CF: 50 Gy/25 Fx;	Dielectric constant (Erythema; fibrosis)	Dielectric constant	
Shumway et al.(106)	35	6 weeks	N/R	Erythema	Colorimetric device	Photonumeric scale;

Abbreviation: CF: Conventional Fractionation; HF: Hypofractionation RTOG: Radiation Therapy Oncology Group; CTCAE: Common Terminology Criteria for Adverse Events. RT: Radiotherapy; LDF: Laser Doppler flowmetry.

6.1.3 Radiation schedules

Numerous radiotherapy protocols have been proposed in the past few decades. The classical whole-breast radiotherapy regimen delivers 24-25 fractions at 1.8-2 Gy per day over 5 weeks. What's more, a variety of shorter and more convenient RT schedules have also been employed in clinical practice over the last 20 years. After 10 years follow-up, START randomized trial demonstrated that hypofractionated radiotherapy offered an equivalent outcome with the control regimen (standard schedule of 50 Gy/25 fractions)(107). Whelan TJ, et al also provided a satisfactory result in local tumor control and late toxicity(44,46). Meanwhile, in order to explore the possibility of shortening more treatment time and the lower limits of hypofractionated， FAST-Forward clinical trial randomly allocated patients into 27 Gy/5 fractions/ 1-week , 26 Gy/5 fractions/1-week. It demonstrated that 1-week schedule radiotherapy is non-inferior to the 3-week regimen in terms of tumor control and appears to have mild late toxicity(47). And besides， accelerated partial breast irradiation (APBI) is also accepted as an attractive treatment

strategy and introduced into clinical practice for low-risk breast cancer patients. Several clinical trials investigated the efficacy of APBI. It showed that APBI was as safe as whole-breast irradiation, and reported a similar RIT at 5 years follow-up(50,52). These findings provide increasing evidence for the acceptance of routine employ of APBI.

6.1.4 The linear-quadratic model, α/β ratio and Biological equivalent dose

In order to compare the RIT following different radiotherapy regimen protocols and design novel radiotherapy schedules in clinical trials, several iso-effect models have been used to forecast the late responding effects. Among them, the linear-quadratic (LQ) model was adopted to calculate the BED for each fractionation schedule, because of the better description of iso-effect curves(55,56). With this mathematical model, it is possible to forecast the various tissues toxicity in response to different radiation regimens (Table 27). And compared with the simple dose-response model, the BED-response model is more clinically relevant(39). On this assumption, different fractionation schedules can be directly compared. The α/β ratio in the LQ model represents the fractionation radiosensitivity of the irradiated cells, which values correspond to the different tissues involved(75). In our study, BED values were calculated from different fractionation schedules, including classical whole-breast radiotherapy, moderate daily hypofractionation, weekly hypofractionation and APBI. Patients were grouped according to the irradiation-BED used, and a total of 7 groups of patients were recruited into our study. Since the difference in RIT may be relatively small, this task is not straightforward, a highly accurate and sensitive assessment tool was required. Therefore, we used the Multi Skin Test Center to objectively and quantitatively investigate the underlying relationship between BED and RIT. At the same time, the subjective rating of RTOG was also used to assess the toxicity. The results of objective and subjective methods allowed us to support the impact of BED on late RIT. According to the subjective RTOG score assessment, the increase of BED

resulted in higher RTOG grade. According to the objective assessment, the color alterations of skin correlated to the increase of BED given. And the increase in BED had an impact on the development of fibrosis, however, without significant effect on dehydration. Therefore, based on the results of objective and subjective assessments, we conclude that the lower BED may be critical with respect to the attenuation of RIT in late reaction. This finding also has been confirmed by other clinical trials. In START A and B trial, after 10 years follow-up, moderate or marked breast induration, telangiectasia and breast oedema were significantly less common in the groups with lower BED (39 Gy/3 fx, BED=76.7) and (40 Gy/2.67 fx, BED=74.5) than in the group with higher BED (50 Gy /2 fx, BED=82.3). In FAST trial, at 10 years, normal tissue effects were higher in radiation regimen with higher BED (30 Gy/6 fx, BED=88.1) compared with radiation regimen with lower BED (50 Gy/2 fx, BED=82.3). These results may support us to establish a BED-response prediction equation in further work. In addition, these results also confirm the sensitivity and accuracy of Multi Skin Test Center, which allowed us to detect the slight changes of RIT in relation to minor alteration of radiotherapy schemes used. In the future work, this objective assessment may also be used as a monitoring tool to attenuate toxicity by new radiation technologies.

There are several novel radiation schedules that can reduce hospital visits. The use of the FAST-Forward radiation regimen has rapidly increased for selected low-risk patients (108–112). This low-BED radiation regimen (BED=69.1 α/β=3.1 Gy) may result in a lower possibility of developing RIT according to our RIT-BED relationship.

The COVID-19 pandemic has promoted the adoption of new evidence-based schedules, which, in turn, has prompted us to compare different radiation regimens based on the establishment of a more accurate and sensitive evaluation system. Given the accuracy of our objective assessment, the risk and benefits of different treatment schedules can be discussed, facilitating the sharing of decision-making with patients.

Table 27. Biologically equivalent dose for selected fractionation schedules

Study/Technique	Fractionation schedule	Late toxicity BED(α/β=3.1Gy)
Standard whole breast	48(50) Gy (2.0 Gy/fx)	79(82.3)
Weekly Hypofractionation		
START A	39 Gy (3.0 Gy/fx)	76.7
	41.6 Gy (3.2 Gy/fx)	84.5
START B	40 Gy (2.67 Gy/fx)	74.5
Whelan, et al	42.5 Gy (2.65 Gy/fx)	78.8
Moderate Daily Hypofractionation		
FAST	28.5 Gy (5.7 Gy/fx)	80.9
	30 Gy (6.0 Gy/fx)	88.1
FAST-Forward	26 Gy (5.2 Gy/fx)	69.1
	27 Gy (5.4 Gy/fx)	74.0
APBI		
Livi, et al	28.5 Gy (5.7 Gy/fx)	80.9
Vicini, el al	34 Gy (3.4 Gy/fx)	71.3
RAPID	38.5 Gy (3.85 Gy/fx)	86.3
APBI-IMRT-Florence	30 Gy (6 Gy/fx)	88.1

Abbreviation: BED: Biologically equivalent doses; APBI: accelerated partial breast irradiation.

6.1.5 Multivariable analysis of qualitative and quantitative assessment

In our multivariable analysis, APBI was associated with the lower acute RTOG score in subjective assessment and non-toxicity (grade 0) was only observed in this radiation schemes. Besides, it also shown a lower pigmentation in objective measurement. This is similar to the study by Shah et al. which stated that the rate of grade 3 hyperpigmentation was only 3.8%(113). And several other trials also highlight the safety of this technique, which identified only a 3-4% rate of grade 3 or greater toxicities(73,114). In our study, the WHF-high dose arm demonstrated a greater late toxicity (OR=12.5) in subjective RTOG criteria. Elasticity as the indicator of fibrosis, was lower in this radiation schedule by objective late toxicity assessments. The late reactions reported by other studies were also more of a consequence with WHF-high dose arm than CF protocol. Maher et al. reported a 39% fibrosis rate in WHF arm(38). Similarly the mainly late effects was fibrosis (grade 2-3, 23%) in the study by Ortholan et al(115). Another study by Rovea et al. reported that grade 1 fibrosis consisted of 31.5% of patients(116). However, WHF-low dose arm was associated with a lower erythema in our objective measurement, which revealed a less risk of development of dermatitis. Different radiation schedules can affect the severity of final toxicity. Focusing on carefully selecting radiation schedule may give benefit to reduce RIT. In addition, compared with subjective evaluations, there were more variations in objective assessments related to different radiation schemes. These findings may reveal that our objective tool may be more sensitive than RTOG criteria, so that it can detect the slight changes of RIT that are difficult to determine by visual or tactile examinations.

6.1.6 Radiation-induced toxicity associated-factors

Numerous factors can influence the RIT of the breast. RT-related factors like irradiated dose and volume, dose per fraction, and boost on tumor bed may affect the frequency and severity of RIT. In addition, other extrinsic factors, such as age, adjuvant therapy and interval time also play a role in developing RIT(109–112). Identifying predictive factors can prevent severe RIT. However, no single factor was significant for all researches, and even the opposite conclusions appeared. It may be explained by the following: due to intra-observer and inter-observer variability, clinical studies using subjective evaluation methods to identify irradiation-related toxicity factors may lack accuracy, while the sample size of clinical studies that use objective assessment is usually small, resulting in a lack of statistical power. Moreover, each study included different factors. It is difficult to derive a definitive risk factor for RIT from the existing data. In our study, the color of the breast skin without radiotherapy was a predictor of final toxicity severity (erythema and pigmentation). Poor state of untreated breast skin in terms of elasticity and hydration elevated the final severity of fibrosis and dehydration. Earlier prediction of future color alteration, fibrosis and dehydration of breast skin will be fruitful for patient care. Other factors, including age and interval time had no significant influence on the RIT in the multivariate regression analysis. Due to collinearity, RT- related factors did not include in multivariate analysis.

6.1.7 Advantages of objective assessment

Our objective assessment technique offers several advantages. First, the assessment is fast, straightforward, and noninvasive, and the healthcare workers responsible for operating the device only need minimal training. In contrast, some objective assessment techniques, such as ultrasonography, require longer training periods. Second, it can facilitate the detection of slight changes in RIT that are difficult to determine by visual inspections and palpation measurements. Third, this technique can be used in multicenter clinical trials to avoid potential intra- and inter-evaluator biases while facilitating researchers in comparing their results from those of other members of the scientific community. Fourth, given the continuous innovations in several modern radiotherapy techniques (IMRT, etc.) and the increasing number of different radiotherapy regimens (intraoperative radiotherapy, etc.), a continuous and objective scale allows the accurate detection of the development of RIT to improve the effect of new radiotherapy approaches. Fifth, this device would be used as a potential decision-support tool in clinical practice by avoiding unnecessary radiotherapy for patients at high risk of RIT and help physicians make personalized treatment management decisions in radiotherapy and share them with patients to strike a balance between their benefits and risks.

6.2 SECOND STUDY

For further study for patients undergoing breast reconstruction and RT, there was no significant difference in complications, toxicity or aesthetic results by the timing or technique of reconstruction. AR was related to a significantly higher number of revision surgeries. However, there was no difference in the total number of surgical operations. Smoking was a significant predictor for complications on multivariate analysis.

6.2.1 Timing and techniques of breast reconstruction

The incidence of breast reconstruction has risen in recent years. However, RT has harmful influences on breast reconstruction, leading to undesirable results(117). However, for aesthetic reasons, these radiation-associated complications do not appear to delay or hinder the increase in the rate of breast reconstruction, which may require additional surgical procedures for correction. With this in mind, many authors have explored the relationship between radiation-associated complications and breast reconstruction to reduce the complication rates and obtain optimal reconstructive results. With respect to the breast reconstruction technique, a prospective multicenter cohort study by Jagsi R et al. found that AR was associated with a lower risk of complications than HR(118). Notwithstanding, Wilkins G et al. analyzed 2,234 patients in a multicenter study and found that compared with HR, AR was associated with a higher complication rate.(119) Regarding the effect of radiation timing on complications, some studies have reported that immediate reconstruction had a higher

incidence of complication than delayed reconstruction,(120,121) while other studies have reported no significant difference according to the timing of reconstruction,(121,122) which is similar to the outcomes of our study. These differences may be because not all studies focused on the same types of complications. Despite these distinctions, our study focused on the most common surgery-related complications. Another potential cause of these discrepancies is that the short-term follow-up in some studies may cause chronic complications to be missed. However, the median follow-up period in our study is longer than that in many other investigations. Therefore, almost all acute and chronic complications can theoretically be detected during the observation time.

6.2.2 Complications and risk factors

Although there was no significant difference in the rate of complications among the groups, our multivariate regression model demonstrated that smoking was significantly related to the complication rate ($p=0.01$). This may be because nicotine is associated with increased vasoconstriction and deterioration in microcirculation, while carbon monoxide can decrease blood oxygen transport.(123,124),[26] Our findings are supported by those of many other studies, in which current and long-term smoking were found to cause an increased incidence of complications.(125–129) Therefore, perhaps not all patients are suitable candidates for reconstruction, especially smokers. Patients should be stratified by risk and carefully counselled on the high risks of complications.

Surgeons should also refine the patient and surgical procedure selection processes, even if the patient's preference is more critical. In preoperative counselling, it is particularly important to inform patients in detail about the risk factors related to complications and multiple repair operations that may be necessitated by complications. The overall complication rate in this study was 20%, which is lower than the total average complication rate of many other studies (37%) according to a systematic review.(28) This is probably because in our study, an older age at reconstruction was a significant predictor on univariate analysis (OR: 3.11), with a trend towards significance ($p = 0.056$) after adjustment for multivariate analysis. We included 18 patients with previous breast implants who were younger at the time of reconstruction. In addition, previous implantation and the median time between reconstruction and irradiation did not affect the complication rate on univariate analysis. Therefore, this might explain the lower incidence of complications in this study than in other studies. In addition, it should be noted that these patients with previous implants are often overlooked in this area.

6.2.3 Revision surgery, total number of surgical procedures and aesthetic outcomes

Revision surgery, such as fat grafting**,** can correct uneven or asymmetrical breasts and improve the breast appearance. This increase in aesthetics may improve patient satisfaction and quality of life by fixing an undesirable result of a previous surgery.(130,131) In our findings, patients undergoing AR require more additional surgeries to complete the reconstruction. Just from the perspective of

revision surgery, AR does not seem to be the best choice for patients. However, the present study also demonstrates that patients undergoing AR tend to have better aesthetic results than those undergoing HR (100% versus 85% good to excellent, respectively). A previous study reported by Jugenburg M et al. supports our findings, in which there was a higher aesthetic outcome in patients who underwent AR rather than HR.(129) However, pursuing multiple surgeries will not only increase the operative risk but also lead to a prolonged duration of hospital stay and heavier economic burden. Nevertheless, the total number of surgeries for the completion of reconstruction was similar in AR and HR in our study. Therefore, in terms of comprehensive revision surgery, the total number of surgical procedures and aesthetics, AR is related to better tolerance to irradiation. It also seems to be more cost-effective for patients when these 2 combination therapies are needed.

The decision to perform reconstruction surgery is multifactory. Providing preoperative information has positive effects on patients. Potential risk factors for complications, such as smoking, patients' ability to pay for revision surgeries and patients' expectations of aesthetics, should be taken into consideration in preoperative recommendations. Striking a balance between benefits and risks should occupy a central place in the decision-making process.

6.2.4 Toxicities

In our findings, although the difference did not reach significance, greater irradiation

toxicity was present in the HR groups. This was also shown in a meta-analysis by Barry M et al.(25) In addition, a multi-probe device was utilized to evaluate toxicity more objectively and exactly. With the use of this device, our current findings show that RT produced an increase in erythema and pigmentation and a decrease in elasticity in the treated breast. The use of objective measuring devices can avoid some human errors, for example, missing nuances that the naked eye cannot distinguish. In addition, it may reduce differences caused by low interobserver agreement. Therefore, for further studies on radiation-induced skin toxicity, this objective multi-probe device may be a more appropriate choice. Other researchers can also consider using this objective and quantifiable measurement method to replace the subjective evaluation of radiation-induced reactions and obtain more accurate and objective outcomes. Further prospective studies are required to confirm the reliability of this multi-probe device for the quantitative assessment of radiation-induced toxicity; related outcomes will be published later.

6.3 Limitations

A limitation of first study could be the potential differences of RIT at each time interval. To try to diminish the risk factor of time interval, an ordered logistic multivariate analysis and a median multivariate regression analysis were respectively used to identify the factor of interval time in both subjective and objective assessments. No association was found between RIT and interval time between radiotherapy and toxicity

assessment. Besides, a at least one year of follow-up is considered sufficient for late RIT to be expressed. The mean interval time of our study is 3.9 years. The RIT may have been stabilized according to the study by Chen et al, which found that fibrosis and pigmentation continued to increase for two years after radiotherapy and then stabilized. In addition, the role of adjuvant systemic therapy and the absence of skin care, as well as individual phenotype, genotype and molecular profiles, may also be considered RIT-related factors(76,132–134), but we did not include them in this study. Indeed, among all searched studies, no single factor was shown to be significant, and in certain circumstances, the opposite conclusions were drawn. We expect our sensitive objective assessment tool to provide further clinical evidence and to be used to determine the individual predisposing factors of RIT. Potential limitations of the second study are its retrospective nature, the small sample size and imbalance between the groups. Some potentially confounding factors were not included in the multivariate analysis because of missing data. However, these limitations are common in published comparative series of radiotherapy and breast reconstruction. It is very difficult to propose randomized studies in this group of patients.

7. Conclusions

To our knowledge, this study is the first and largest to assess the RIT following different techniques (CF, DHF, WHF and APBI) based on objective method. We conclude that:

1. The Multi Skin Test Center is a noninvasive, useful and sensitive tool for quantitatively monitoring RIT in patients undergoing radiotherapy for breast cancer.
2. The toxicity results measured by this objective assessment are significantly related to the subjective RTOG toxicity score. A higher BED is associated with the development of more severe toxicity. Meanwhile, this BED-RIT relationship may be used to design novel radiotherapy schedules in clinical trials.
3. The Multi Skin Test Center is able to assess toxicity among patients undergoing radiotherapy and breast reconstruction.
4. RT may be performed successfully regardless of the type or timing of reconstruction when combined with reconstruction. Autologous reconstruction shows better results in terms of toxicity and aesthetics than heterologous reconstruction, although there is no statistical significance. Smoking is a significant predictor of complications for patients undergoing radiotherapy and breast reconstruction.

8. Future lines

Given the accuracy, sensitivity and simplicity of our multiprobe device, in the future work, this objective method may be used as a monitoring tool to evaluate toxicity by new radiation schedules and technologies. And the risk and benefits of different treatment schedules can be discussed, facilitating the sharing of decision-making with patients. Furthermore, the outcomes of BED-RIT relationship may support us to establish a BED-response prediction equation in future work, which may be used to design novel radiotherapy schedules in clinical trials. The role of individual phenotype, genotype and molecular profiles may also be considered as RIT-related factors(3,134). Even though this kind of research is still in its infancy, we expect our sensitive objective assessment tool can provide further clinical evidence and determine the individual predisposing factors of RIT.

We have shown this tool to be useful in several breast cancer scenarios, including breast reconstruction. That is why it can also be useful your applicability to other cancer sites, such as head and neck, which present sever skin toxicity in approximately 23% of patients(135).

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10. Attachments

10.1 First Article

Y. Huang, J. Sanz, N. Rodríguez et al., Quantitative assessments of late radiation-induced skin and soft tissue toxicity and correlation with RTOG scales and biological equivalent dose in breast cancer., Clinical and Translational Oncology, https://doi.org/10.1007/s12094-021-02729-z

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10.2 Second Article

Y. Huang, J. Sanz, N. Rodríguez et al., Effects of radiation on toxicity, complications, revision surgery and aesthetic outcomes in breast reconstruction: An argument about timing and techniques, Journal of Plastic, Reconstructive & Aesthetic Surgery, https://doi.org/10.1016/j.bjps.2021.05.027

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Effects of radiation on toxicity, complications, revision surgery and aesthetic outcomes in breast reconstruction: An argument about timing and techniques

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Summary *Background:* Radiotherapy (RT) combined with breast reconstruction can reduce the risk of cancer recurrence and increase the survival rate. However, this approach seems to worsen aesthetic outcomes and increase complication rates. The impact of breast reconstruction timing and techniques on clinical outcomes, however, remains unclear. For this reason, we aimed to perform a more comprehensive analysis of a series of patients undergoing RT and breast reconstruction.
Methods: Patients were divided into 4 groups according to the timing of reconstruction (before RT and after RT) and surgical technique (heterologous reconstruction and autologous reconstruction (AR)). The median time between RT and reconstruction, number of revision surgeries, incidence of complications, toxicity, aesthetics and associated clinical risk factors were used to assess the clinical outcomes. An objective system of skin toxicity evaluation was performed.
Results: Ninety-five patients were included in this study. No significant differences in the median time between RT and reconstruction, incidence of complications, toxicity or aesthetics were noted between different timings or techniques of reconstruction. Patients undergoing AR

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needed more revision surgeries to complete reconstruction. However, the total number of surgical procedures was similar between the groups. In a comparison between the treated and untreated breasts by an objective system, RT produced an increase in erythema and pigmentation and a decrease in elasticity in the treated breast ($p<0.05$ for all parameters). On multivariate analysis, smoking was a significant predictor associated with complications.
Conclusions: Combined breast reconstruction and RT seem to be successful regardless of the order of treatment or the type of reconstruction.

Introduction

For patients undergoing breast cancer surgery, reconstruction not only has a positive effect on body image but also reduces the psychological morbidity of the loss of the breast and increases patient satisfaction.[1] Breast reconstruction can be performed by the following techniques: heterologous reconstruction (HR), e.g., using a permanent implant or tissue expander or autologous reconstruction (AR), which is performed with the patient's own tissue, including skin, fat and muscle mass, for the sake of obtaining a more natural, symmetrical effect.[2]

Radiotherapy (RT) can reduce the loco-regional and distant recurrence rates of the disease and increase the survival rate.[3,4] At the same time, however, it affects the aesthetics and increases the risk of complications.[5-7] According to some studies, radiation after reconstruction with implants discreetly worsens aesthetics and increases the risk of complications.[8] Other authors have presented the opposite opinion and considered that the combination of HR and RT is a safe technique with respect to advances in both plastic surgery and RT techniques in the last decade. In many reports, radiation with AR did not entail excessive problems. It is the technique of breast reconstruction that most surgeons choose when patients need RT.[9] AR is associated with reduced mobility and improved cosmetic outcomes in patients who need RT and is believed to result in a high index of satisfaction.[10] Additionally, the sequence of RT and breast reconstruction does not seem to interfere with the results.[11]

Combination therapy with radiation and breast reconstruction has become increasingly common in recent years.[12] Nevertheless, the median time between RT and reconstruction, total number of surgeries, complications, toxicity and aesthetic results of those patients are not yet clear and still controversial in some respects. Few studies have analysed the effects of RT on reconstruction performed using different techniques and at different times. Therefore, we aimed to analyse the long-term results of combination treatment with RT and breast reconstruction in a more comprehensive way.

Materials and Methods

Patients

Patients in our care undergoing RT and breast reconstruction were included in this analysis. The choice of reconstruction technique depended on the surgeon's decision and patient's preferences. Patient characteristics are shown in Table 1.

Table 1 Patient and treatment characteristics

Characteristics	All patients (n = 95)	
	n	
Mean age (years; SD)	42.8	7.7
Tumour laterality		
Right	37	38.9%
Left	48	50.5%
Both sides	10	10.5%
Boost		
Yes	22	23.2%
Adjuvant treatment		
Hormonal therapy	35	36.8%
Chemotherapy	54	56.8%
Risk factor		
Smoking	25	26.3%
Hypertension	11	11.6%
Diabetes	2	2.1%
BMI (n = 30)		
<25	18	18.8
25.0-29.9	4	4.2
>30	8	8.3
Follow-up (months; SD)	73.2	45.8

Abbreviations: BMI: body mass index.

Timing and techniques of breast reconstruction

The patients in this study were divided into 4 groups. The pre-HR group included patients undergoing HR (tissue expander and permanent implant) before RT. The pre-AR group included patients undergoing AR (transposition of latissimus dorsi muscle, deep inferior epigastric perforator, and oncoplastic surgeries) before irradiation. Patients undergoing HR after RT were included in the post-HR group. Patients undergoing AR after RT were assigned to the post-AR group (Figure 1).

Measures

We evaluated the effect of treatment by using the median time between RT and breast reconstruction, total number of operations performed for final results, revision surgeries,

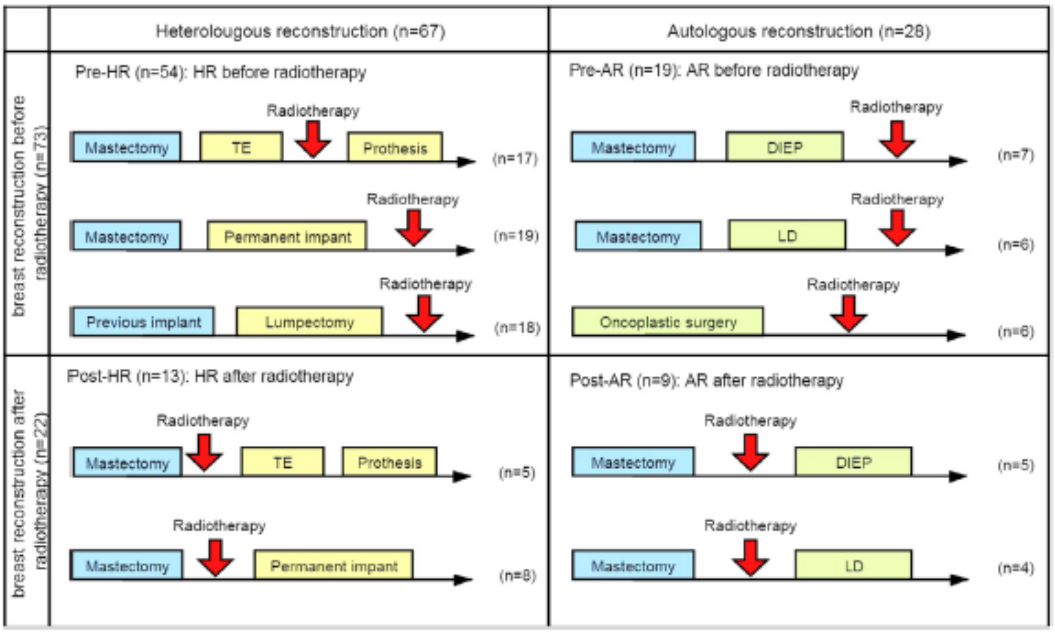

Figure 1 Distribution of groups according to the timing and techniques of breast reconstruction.
Abbreviations: pre-HR: heterologous reconstruction before radiotherapy; pre-AR: autologous reconstruction before radiotherapy; post-HR: heterologous reconstruction after radiotherapy; post-AR: autologous reconstruction after radiotherapy; TE: tissue expander; DIEP: deep inferior epigastric perforator; and LD: latissimus dorsi flap.

incidence of complications, toxicity, aesthetics and associated clinical risk factors. This research was approved by the Clinical Research Ethics Committee.

The median time between RT and reconstruction in patients undergoing post-RT was defined as the time from performing the immediate breast reconstruction surgery or placing the tissue expander (delayed reconstruction) to the beginning of RT, and the median time between RT and reconstruction in patients undergoing pre-RT was defined as the time from the end of RT to the beginning of breast reconstruction.

The total number of surgical procedures included oncological surgeries (lumpectomy and mastectomy), breast reconstruction surgical procedures and revision surgeries. Revision surgery was defined as any unplanned surgical procedure that was directly related to reconstruction and required a return to the operation room. Among them, fat grafting and nipple-areola complex reconstruction were classified as minor revision procedures. Other procedures, such as implant removal or replacement, were included as major revision surgeries.

This study analysed the following breast reconstruction complications: capsular contracture, haematoma, infection, fat necrosis and implant failure.

Toxicity was assessed in two ways. First, dermatitis, fibrosis, telangiectasia, palpation pain and lymphedema were evaluated by physicians according to the Radiation Therapy Oncology Group (RTOG) scale of radiation effects, which rates each parameter on a scale from 0 to 4 (0, absence and 4, maximum expression).[13] Second, with a multi-probe device (Multi Skin Test Center®, Model MC 750; CK Electronic, GmbH, Cologne, Germany), 4 parameters (melanin, erythema, elasticity and hydration) were measured objectively. The procedure for determining these parameters consisted of performing a measure of each parameter in each of the four breast quadrants in both breasts. The program of this multi-probe device calculates the average of the measurements taken of each breast (Supplementary material a-c). We have used this assessment method in previous research in irradiated patients.[14,15]

The aesthetic evaluation of the breasts was conducted using the Harvard Scale (excellent, good, fair and poor) by physicians.[16]

The regression models included a range of variables likely to be related to complications. Baseline characteristics, demographic variables and surgical data were recorded, including the reconstruction technique, time of RT, age at reconstruction, laterality of reconstruction, adjunct therapy, receipt of chemotherapy, median time between irradiation and reconstruction, previous implants, hypertension, smoking and body mass index. The predictive variables were selected due to clinical relevance.

Statistical analysis

Statistical analysis was performed with the software package SPSS v26 (IBM SPSS, Chicago, IL). Quantitative variables are described as the mean and standard deviation. Student's t-test and ANOVA were used to compare quantitative vari-

Table 2 Median months between radiotherapy and breast reconstruction

	All patients (n = 95)			Exclude patients with previous implant (n = 77)		
	n	Mean/SD	p	N	Mean/SD	p
Reconstruction Techniques						
Heterologous	67	44.4 (65.9)	0.18	49	19.6 (27.3)	0.39
Autologous	28	26.3 (14.3)		28	26.3 (14.3)	
Reconstruction timing						
Before reconstruction	73	41.9 (64.3)	0.40	55	19.0 (25.4)	0.20
After reconstruction	22	29.7 (14.2)		22	29.7 (14.2)	

ables. The Kruskal-Wallis test was used to evaluate categorical variables.

Univariate analysis was constructed to identify risk factors associated with complications. The adjusted associations were examined by multivariate logistic regression analysis. Covariables were included if risk factors had a P < 0.20 on univariate analysis. Patients with missing covariables were excluded from the multivariate analysis. A post-hoc power calculation was performed for multiple logistic regression.[17]

Patients signed informed consent both for local treatment and also for additional evaluations by objective methods at follow-up.

Results

Ninety-five patients were included in this study. The median follow-up period was 73.2 months. The mean patient age was 42.8 years at reconstruction. Chemotherapy was administered to 56.8% of patients, while 36.8% of patients received hormonal therapy. Patient characteristics are shown in Table 1. There were 54 pre-HR cases, 19 pre-AR cases, 13 post-HR cases and 9 post-AR cases, according to our distribution of patients depending on the time and type of reconstruction (Figure 1).

There was no significant difference in the median time between the different techniques and reconstruction time (p = 0.18 and p = 0.4, respectively), even when we excluded the 18 patients with previous implants (p = 0.39 and p = 0.2, respectively) (Table 2).

As shown in Table 3, the overall complication rate was 20%. Complications occurred more frequently in the HR group, although no significant difference was reached (p = 0.67). Capsular contracture was the most common complication (16.7%). The pre-HR group showed a higher rate of major revision surgery (20.4%). At least one minor revision procedure was performed by 68.4% and 77.8% of patients in the pre-AR and post-AR groups, respectively. In contrast, 81.5% of patients in the pre-HR group did not require any minor re-operation. Toxicity outcomes were evaluated by physicians in 85 patients. There was no difference in the grade or type of toxicity among the groups (p = 0.85 and p = 0.95, respectively). Dermatitis was the most common form of toxicity (12.9%). The intensity of late toxicity was mild: grade I toxicity occurred in 25.6% of patients. Grade II toxicity occurred in 3 patients, which only existed in the pre-HR group. No cases of grade III or higher chronic toxicity occurred. In addition, to objectively assess toxicity, 31 patients underwent cutaneous analysis using the multiprobe device (Supplementary material a-c). There were significant differences in the values of erythema, melanin and elasticity between the treated and untreated breasts (p<0.001, p = 0.014, and p<0.001, respectively). RT produced an increase in erythema and melanin and a decrease in elasticity in the treated breast. There was no statistically significant difference in hydration (p = 0.215) (Supplementary material c). However, when we compared the erythema, melanin, elasticity and hydration results among the different groups, there were no significant differences. The aesthetic results were evaluated by physicians in 91 patients. There were no significant differences among the procedures utilized. Good to excellent cosmetic outcomes were observed in 93.4% of all patients and in 100% of patients treated with AR.

Compared with HR, AR was associated with a significantly higher mean number of unplanned re-operations (p = 0.03). Among them, patients undergoing AR also required more additional minor operative revisions for the completion of reconstruction (p = 0.045). However, there was no significant difference in the total number of surgical procedures among the study groups (p = 0.75) (Figure 2).

On univariate analysis, our results revealed that older age at reconstruction and smoking were significant predictors of increased complications (OR: 3.11; p = 0.047, OR: 1.21; p = 0.005, respectively). After adjusting for possible confounding variables, however, only smoking remained associated with complications (OR: 1.2; p = 0.01). There was no significant difference in other variables (Table 4). Results from post-hoc power calculation showed a 36.91% power.

Discussion

In our series of patients undergoing breast reconstruction and RT, there was no significant difference in complications, toxicity or aesthetic results by the timing or technique of reconstruction. AR was related to a significantly higher number of revision surgeries. However, there was no difference in the total number of surgical operations. Smoking was a significant predictor for complications on multivariate analysis.

The incidence of breast reconstruction has risen in recent years.[18] However, RT has harmful influences on

Table 3 Reconstruction techniques, complications, revision surgeries, toxicity and aesthetic results according to the timing of irradiation and breast reconstruction techniques

	Pre-HR(n = 54)		Pre-AR(n = 19)		Post-HR(n = 13)		Post-AR(n = 9)		All patients(n = 95)		
	n	%	n	%	n	%	n	%	n	%	p value
Complications											
Capsular contracture	9	16.7	0	-	2	15.4	0	-	11	11.6	0.67
Haematoma	1	1.9	1	5.3	1	7.7	0	-	3	3.1	
Infection	2	3.7	0	-	0	-	1	11.1	3	3.1	
Fat necrosis	0	1.9	1	5.3	0	-	0	-	1	1.1	
Implant failure	1	1.9	0	-	0	-	0	-	1	1.1	
Total	13	24.1	2	10.5-	3	23.1	1	11.1	19	20	
Type of revision surgeries											
Major[$]											
Autologous	0	-	2	10.5	0	0	1	11.1	3	3.1	**<0.001**
Heterologous	11	20.4	0	-	0	-	0	-	11	11.6	
Minor[#]	10	18.5	13	68.4	5	38.5	7	77.8	35	36.5	
Grade and type of toxicity (n = 85)											
Toxicity grade											
I	14	25.9	2	10.5	4	30.8	2	22.2	22	25.6	0.85
II	3	4.9	0	-	0	-	0	-	3	3.5	
Total	17	33.8	2	10.5	4	30.8	2	22.2	25	29.1	
Toxicity type											
Dermatitis	9	16.7	0	-	2	15.4	0	-	11	12.9	0.95
Fibrosis	6	11.1	1	5.3	1	7.7	0	-	8	9.4	
Telangiectasia	0	-	0	-	0	-	1	11.1	1	1.2	
Pain	2	3.7	0	-	1	7.7	0	-	3	3.5	
Lymphoedema	0	-	1	5.3	0	-	1	11.1	2	2.4	
Total	17	33.8	2	10.5	4	30.8	2	22.2	25	29.4	
Aesthetic results (n = 91)											
Acceptable											0.17
Excellent	12	24.0	8	42.1	2	15.4	2	22.2	24	26.4	
Good	34	68.0	11	57.9	9	69.2	7	77.7	61	67.0	
Unacceptable								-			
Regular	4	8.0	0	-	2	15.4	0	-	6	6.6	
Bad	0	-	0	-	0	-	0	-	0	-	

Abbreviations: pre-HR: heterologous reconstruction before radiotherapy; pre-AR: autologous reconstruction before radiotherapy; post-HR: heterologous reconstruction after radiotherapy; post-AR: autologous reconstruction after radiotherapy; DIEP: deep inferior epigastric perforator; and LD: latissimus dorsi flap.

[#] Minor revisions: reconstruction of the areola-nipple complex, fat grafting.

[$] Major revisions: all other revision surgeries except for minor corrective surgery, such as implant exchange.

breast reconstruction, leading to undesirable results.[19] However, for aesthetic reasons, these radiation-associated complications do not appear to delay or hinder the increase in the rate of breast reconstruction, which may require additional surgical procedures for correction. With this in mind, many authors have explored the relationship between radiation-associated complications and breast reconstruction to reduce the complication rates and obtain optimal reconstructive results. With respect to the breast reconstruction technique, a prospective multicentre cohort study by Jagsi R et al. found that AR was associated with a lower risk of complications than HR.[20] Notwithstanding, Wilkins G et al. analysed 2234 patients in a multicentre study and found that when compared with HR, AR was associated with a higher complication rate.[21] Regarding the effect of radiation timing on complications, some studies have reported that immediate reconstruction had a higher incidence of complication than delayed reconstruction,[22,23] while other studies have reported no significant difference according to the timing of reconstruction,[23,24] which is similar to the outcomes of our study. These differences may be because not all studies focused on the same types of complications. Despite these distinctions, our study focused on the most common surgery-related complications. Another potential cause of these discrepancies is that the short-term follow-up in some studies may cause chronic complications to be missed. However, the median follow-up period in our study is longer than that in many other investigations. Therefore, almost all acute and chronic complications can theoretically be detected during the observation time.

Although there was no significant difference in the rate of complications among the groups, our multivariate regression model demonstrated that smoking was significantly related to the complication rate ($p = 0.01$). This may be because nicotine is associated with increased vasoconstriction and deterioration in microcirculation, while carbon monox-

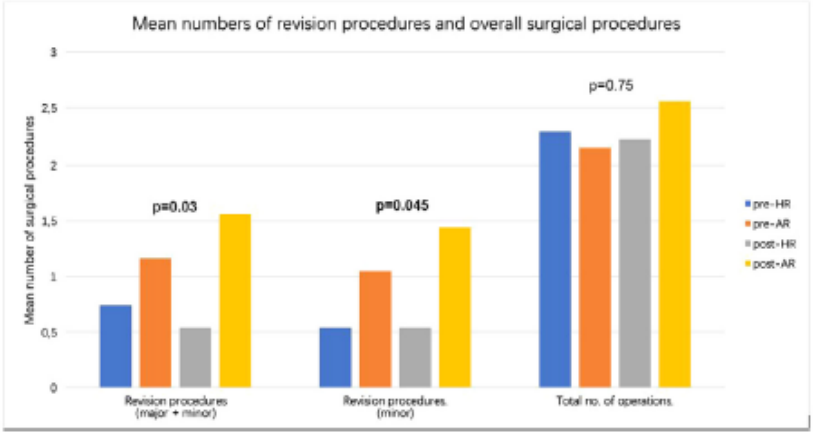

Figure 2 Mean numbers of revision surgeries and overall surgical procedures across the study group.
Abbreviations: pre-HR: heterologous reconstruction before radiotherapy; pre-AR: autologous reconstruction before radiotherapy; post-HR: heterologous reconstruction after radiotherapy; and post-AR: autologous reconstruction after radiotherapy. Minor revisions included reconstruction of the areola-nipple complex and fat grafting. Major revisions included all other revision surgeries except for minor corrective surgery, such as implant exchange. The total number of surgical procedures included oncological surgeries, breast reconstruction surgeries and revision surgeries.

Table 4 Univariate and multivariate analysis of risk factors related to radiotherapy and breast reconstruction

	Complication			
	Univariate		Multivariate	
	OR (95 %CI)	p	OR (95 %CI)	p
HR	2.61 (0.70-9.81)	0.15	2.64 (0.57-12.33)	0.22
Pre-RT	1.16 (0.34-3.95)	0.81		
Older age[#]	3.11 (0.93-8.55)	**0.047**	3.35 (0.97-11.57)	0.056
Bilateral	1.85 (0.43-7.94)	0.41		
Boost	0.98 (0.84-1.14)	0.81		
Chemotherapy	0.91 (0.80-1.04)	0.15	0.91 (0.79-1.05)	0.31
Median time[$]		0.66		
<6 months	1 (reference)			
6-12 months	1.37 (0.32-5.79)			
>12 months	0.76 (0.23-2.55)			
Previous implant	1.12 (0.97-1.29)	0.12	1.06 (0.90-1.26)	0.48
Hypertension	0.98 (0.80-1.21)	0.87		
Smoking	1.21 (1.06-1.38)	**0.005**	1.20 (1.04-1.1.38)	**0.01**
BMI≥25	1.6 (0.19-13.24)	0.67		

Abbreviations: HR: heterologous reconstruction; pre-RT: radiotherapy before reconstruction; and BMI: body mass index.
[#] Age at reconstruction ≥45 years.
[$] Median time (in months) between radiotherapy and breast reconstruction.

ide can decrease blood oxygen transport.[25,26] Our findings are supported by those of many other studies, in which current and long-term smoking were found to cause an increased incidence of complications.[27-31] Therefore, perhaps not all patients are suitable candidates for reconstruction, especially smokers. Patients should be stratified by risk and carefully counselled on the high risks of complications. Surgeons should also refine the patient and surgical procedure selection processes, even if the patient's preference is more critical. In preoperative counselling, it is particularly important to inform patients in detail about the risk factors related to complications and multiple repair operations that may be necessitated by complications. The overall complication rate in this study was 20%, which is lower than the total average complication rate of many other studies (37%) according to a systematic review.[11] This is probably because in our study, older age at reconstruction was a significant predictor on univariate analysis (OR: 3.11), with a trend towards significance ($p = 0.056$) after adjustment for multivariate analysis. We included 18 patients with previous breast implants who were younger at the time of reconstruction. In addition, previous implantation and the median

time between reconstruction and irradiation did not affect the complication rate on univariate analysis. Therefore, this might explain the lower incidence of complications in this study than in other studies. In addition, it should be noted that these patients with previous implants are often overlooked in this area.

Revision surgery, such as fat grafting, can correct uneven or asymmetrical breasts and improve the breast appearance.[32] This increase in aesthetics may improve patient satisfaction and quality of life by fixing an undesirable result of a previous surgery.[33,34] In our findings, patients undergoing AR require more additional surgeries to complete the reconstruction. Just from the perspective of revision surgery, AR does not seem to be the best choice for patients. However, the present study also demonstrates that patients undergoing AR tend to have better aesthetic results than those undergoing HR (100% versus 85% good to excellent, respectively). A previous study reported by Jugenburg M et al. supports our findings, in which there was a higher aesthetic outcome in patients who underwent AR rather than HR.[30] However, pursuing multiple surgeries will not only increase the operative risk but also lead to a prolonged duration of hospital stay and heavier economic burden. Nevertheless, the total number of surgeries for the completion of reconstruction was similar in AR and HR in our study. Therefore, in terms of comprehensive revision surgery, the total number of surgical procedures and aesthetics, AR is related with better tolerance to irradiation. It also seems to be more cost-effective for patients when these 2 combination therapies are needed.

The decision to perform reconstruction surgery is multifactorial. Providing preoperative information has positive effects on patients. Potential risk factors for complications, such as smoking, patients' ability to pay for revision surgeries and patients' expectations of aesthetics should be taken into consideration in preoperative recommendations. Striking a balance between benefits and risks should occupy a central place in the decision-making process.

In our findings, although the difference did not reach significance, greater irradiation toxicity was present in the HR groups. This was also shown in a meta-analysis by Barry M et al.[8] In addition, a multi-probe device was utilized to evaluate toxicity more objectively and exactly. With the use of this device, our current findings show that RT produced an increase in erythema and pigmentation and a decrease in elasticity in the treated breast. The use of objective measuring devices can avoid some human errors, for example, missing nuances that the naked eye cannot distinguish. In addition, it may reduce differences caused by low interobserver agreement. Therefore, for further studies on radiation-induced skin toxicity, this objective multi-probe device may be a more appropriate choice. Other researchers can also consider using this objective and quantifiable measurement method to replace the subjective evaluation of radiation-induced reactions and obtain more accurate and objective outcomes. Further prospective studies are required to confirm the reliability of this multi-probe device for the quantitative assessment of radiation-induced toxicity; related outcomes will be published later.

Potential limitations of this analysis are the small sample size and imbalance between the groups. This current study is also limited by its retrospective nature and the absence of some data from the clinical records. Some potentially confounding factors were not included in the multivariate analysis because of missing data, which may have had an impact on the evaluation of complications.

Conclusions

Our current findings provide information about the incidence of complications, toxicity, aesthetics, total number of surgical procedures, revision surgeries and potential risk factors in patients who decide to undergo reconstruction with RT. In summary, we suggest that combined with reconstruction, RT may be performed successfully regardless of the type or timing of reconstruction. However, AR seems to show better results in terms of toxicity and aesthetics than HR, although there is no statistical significance. Smoking is a significant predictor of complications. We hope that through this information, women will be able to achieve an appropriate risk-benefit balance and make optimal individual decisions.

Conflicts of interest statement

Dr Manuel Algara has received consulting honoraria from Sysmex and Aristo and speaking honoraria from Siemens and Roche.

All the other authors declare not to have any conflict of interest.

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Supplementary materials

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