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Loco-Regional Adjuvant Radiotherapy in Breast Cancer
Retrospective Analysis of the Toxicity and Impact of the COVID-19 Pandemic

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LOCO-REGIONAL ADJUVANT RADIOTHERAPY IN BREAST CANCER: RETROSPECTIVE ANALYSIS OF THE TOXICITY AND IMPACT OF THE COVID-19 PANDEMIC

Mémoire présenté pour l'obtention
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Loco-regional adjuvant radiotherapy in breast cancer: retrospective analysis of the toxicity and impact of the COVID-19 pandemic

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Abstract

Background: Radiotherapy for breast cancer has evolved over the past few years. Initially, radiotherapy for patients with early breast cancer was performed by delivering a total dose of 50 Gy, i.e., 25 fractions of 2.0 Gy. Gradually, different treatment schedules were developed offering shorter schedules with lower total doses. According to the current ESTRO-ACROP recommendations, the standard of care is the 15-fraction START schedule which can be used regardless of the area to be irradiated. But the occurrence of COVID-19 pandemic has prompted Ste-Elisabeth hospital to treat all node-positive breast cancer patients over 65 years of age with a shorter 5-fraction FAST schedule, i.e., one fraction per week for five weeks, based on French retrospective data and long experience. However, currently, FAST-Forward ultrahypofractionation with 5-fraction radiotherapy (one fraction per day) is still not recommended in the axillary area for safety reasons and the FAST schedule is not mentioned.

Aim: The hypothesis behind this research project is that the toxicity associated with loco-regional radiotherapy according to the 5-fraction FAST schedule is not superior to the toxicity observed with loco-regional radiotherapy according to the 15-fraction START schedule.

Methods: A retrospective analysis, conducted between 2018 and 2021, including 205 breast cancer patients treated with loco-regional radiotherapy according to the FAST (87 patients) or the START (118 patients) schedule within the Ste-Elisabeth hospital was carried out. Patient data from medical records were entered into a database and then used to assess the toxicity between the two cohorts. A descriptive analysis of the population as well as an analysis of overall survival and progression-free survival were also performed.

Analysis: The two cohorts were comparable except for age and ECOG performance status. The FAST cohort was, on average, ten years older than the START cohort and therefore had a lower ECOG

performance status. No significant difference was observed in terms of overall survival, progression-free survival, or toxicity between the two cohorts.

Conclusion: Loco-regional radiotherapy according to the FAST schedule does not appear to be inferior to loco-regional radiotherapy according to the START schedule after a combined median follow-up of 28.9 months. However, prospective randomized trials are needed to confirm these results and to hope the validation of the FAST schedule in the axillary area in the future.

Keywords: Breast cancer, Adjuvant radiotherapy, Hypofractionation, Lymph nodes, Toxicity.

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Table of Content

List of abbreviations

BC: Breast Cancer
WHO: World Health Organization
IDC: Invasive Ductal Carcinoma
ILC: Invasive Lobular Carcinoma
DCIS: Ductal Carcinoma In Situ
LCIS: Lobular Carcinoma In Situ
AJCC: American Joint Committee on Cancer
ER: Estrogen Receptor
PR: Progesterone Receptor
BCS: Breast-Conserving Surgery
RT: Radiotherapy
NCI: National Cancer Institute
CTCAE: Common Terminology Criteria for Adverse Events
NTE: Normal Tissue Effects
ESTRO-ACROP: European Society for Radiation and Oncology Advisory Committee in Radiation Oncology Practice
SIB: Simultaneous Integrated Boost
SLN: Sentinel Lymph Node
SLNB: Sentinel Lymph Node Biopsy
ALND: Axillary Lymph Node Dissection
COVID-19: Coronavirus Disease 2019
SE Hospital: Ste-Elisabeth Hospital
CHU UCL: Centre Hospitalier Universitaire UCLouvain
GDPR: General Data Protection Regulation
BMI: Body Mass Index
RSW: Réseau Santé Wallon
PFS: Progression-Free Survival
OS: Overall Survival
AE: Adverse Event
OR: Odds Ratio
aOR: adjusted Odds ratio
UOQ: Upper Outer Quadrant
PY: Person-Years
HR: Hazard Ratio
aHR: adjusted Hazard Ratio
UZ Ghent: University Hospital of ghent

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in women. [1] In 2020, according to the World Health Organization (WHO), 2.2 million breast cancers were registered around the world. [2] In Belgium, this represents 10.596 new cases for the same year. [1] In view of these figures, the WHO has defined two strategies for the early detection of BC. [3] The first is early diagnosis, which means detecting symptomatic individuals as early as possible. The second is screening, which involves testing healthy individuals to identify those with cancer but that are still asymptomatic. [4] The earlier BC screening is done, the higher the chance of recovery. In Belgium, a screening mammogram is offered to women between the ages of 50 and 69, which is when starting preventive treatment could have a real impact on the chances of recovery. This free examination, called "Mammotest", is the most effective screening method. In addition to the Mammotest, women are also advised to perform a monthly breast self-examination to detect any abnormalities in size, shape, or appearance. [5,6] At present, the screening methods associated with the multidisciplinary side of its management allow observing, at 5 years, a survival probability of 91.9%. [7]

1. Diagnosis

Since there are a variety of treatment options, it is important for clinicians to be able to accurately characterize each cancer in order to guide the best treatment choice. [8] Among the prognostic factors that may guide treatment, nodal status, tumor size, hormone receptor status, and histological type can be mentioned. [9]

1.1. TNM staging system

The nodal status as well as the size of the tumor are parameters included in the TNM staging system, which allows understanding the extent of the cancer. This system, developed by American Joint Committee on Cancer (AJCC), is based on three characteristics of the tumor, namely the size of the tumor (T), the number of lymph nodes affected (N), and the presence of metastasis (M). Each of these parameters will be evaluated independently and will be assigned either a letter X, if the parameter in question could not be evaluated; a 0 signifying respectively the absence of tumor, the absence of positive lymph nodes, or the absence of metastasis; or a number ranging from 0 to 4 for T, from 0 to 3 for N, or from 0 to 1 for M, referring to the extension of the tumor. Following the evaluation of these three parameters, five stages of breast cancer, ranging from 0 to IV, can be derived. (Table.1) The higher the stage, the larger the cancer will be and the more it will have spread to other parts of the body. [10,11] In general, for stages I, II, and III, curative treatments are used in order to completely cure the cancer, while for stage IV, i.e., terminal stage, palliative treatments are preferred to prolong the life expectancy of these patients and improve their quality of life. [12]

TNM staging can be assessed at different times during the management of patients with BC, allowing the distinction between cTNM and pTNM. The cTNM corresponds to clinical staging, i.e., prior to the initiation of any treatment and usually based on physical examination, whereas the pTNM refers to post-chirurgical staging, which is the result of an anatomo-pathological examination of a tissue or a biopsy. [11,13]

Stage	Tumor (T)	Nodes (N)	Metastasis (M)
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1	M0
	T1		
IIA	T0	N1	M0
	T1		
	T2	N0	
IIB	T2	N1	M0
	T3	N0	
IIIA	T0	N2	M0
	T1		
	T2		
	T3	N1	
		N2	
IIIB	T4	N0	M0
		N1	
		N2	
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Table.1. TNM staging system – AJCC 8th edition

1.2. Hormone receptor status

It is estimated that about 70% of BC are hormone sensitive. [14] This means that the cancer cells have hormone receptors on their surface, making the cancer dependent to hormones. The two hormones involved are estrogen and progesterone, two female hormones known to stimulate the growth and proliferation of cancer cells. To be considered hormone-sensitive, cancer cells must have estrogen receptors (ER) and/or progesterone receptors (PR). Hormone receptors-positive breast cancer are treated with hormone therapy to decrease the level of hormone and slow down the tumor progression. [15,16]

1.3. Histological types

There are different histological types of breast cancer, which can be characterized according to where the cancer cells begin to grow. We can distinguish between invasive breast cancer (or infiltrating), characterized by infiltration of the cancer into the breast tissue, and non-invasive breast cancer (or in situ), where the cancer has not spread to the surrounding tissue and remains localized within the ducts or lobules of the breast. Among invasive BC, the two most common are Invasive Ductal Carcinoma (IDC) and Invasive Lobular Carcinoma (ILC), depending on whether the cancer has spread from breast ducts or from breast lobules respectively. Regarding non-invasive BC, the two main types are Ductal Carcinoma In Situ (DCIS) and Lobular Carcinoma In Situ (LCIS), also named depending on location from which the cancer has spread. [7,17] In general, carcinoma in situ is considered as the precursor of invasive carcinoma. The treatment chosen will therefore aim to prevent this progression to invasive carcinoma. [18]

In terms of proportion, IDC is the most frequently observed and represents 85% of breast cancers. The second most common histology is ILC in 10% of cases. Finally, and in the same proportion, it is LCIS (2,5%) and DCIS (2,5%). [19]

2. Breast cancer treatment

The management of BC is based on a multidisciplinary approach, which means that rather than using one particular treatment, a collaboration between several treatment options will be preferred in order to minimize recurrence. [20]

Currently, the first-line treatment is surgery and the two commonly used techniques in BC are mastectomy and breast-conserving surgery (or lumpectomy). With mastectomy, the entire breast is removed, whereas with breast-conserving surgery (BCS), not only is the tumor removed, but also a margin of healthy tissue surrounding it to ensure that all cancer cells are removed. [21] Different studies, [22,23] conducted over the years, have shown that mastectomy can be considered equivalent to BCS when followed by radiotherapy. The decision to use one technique over the other must therefore be based on factors other than survival rates. Among these factors, tumor size, breast size and patient's preference appear to be the most important. The fear of recurrence as well as the postoperative body image seem to be non-negligible factors that will influence the patient's preferences and will, therefore, have an impact on the final decision. [24,25]

As mentioned above, surgery, either mastectomy or BCS, is performed as first-line treatment. However, the multidisciplinary aspect of BC management allows other treatment options to precede or complete surgery. Any treatments that are performed prior to surgery will be referred as neoadjuvant treatments, and it may include chemotherapy, hormonotherapy, or endocrine therapy. These treatments may be prescribed to decrease the size of the breast tumor to promote BCS rather than mastectomy, for example. [26] Conversely, all treatments prescribed after surgery will be indicated under the term of adjuvant treatments. This may include chemotherapy, hormonotherapy, or radiotherapy.

The first traces of mastectomy date back to the end of the 19th century, when William Halsted documented his first interventions. [27] For many years, mastectomy was considered the standard of care for patients with BC, but for some years now, BCS followed by postoperative radiotherapy (adjuvant radiotherapy) has become the preferred treatment in hospitals. This evolution can be explained by the improvement of screening methods that allow the detection of cancers at earlier stages, but also by the publication of studies that prove that the use of radiotherapy after BCS is just as effective as mastectomy alone. [20]

Among these studies, the NSABP B-06 randomized trial compared total mastectomy with lumpectomy with or without adjuvant radiotherapy. In this 1976 trial, 2 163 women were enrolled and assigned to one of three groups: total mastectomy, lumpectomy without radiation, or lumpectomy with radiation. Adjuvant radiotherapy consisted of 50 Gy of radiation to the breast, but no radiation to the lymph nodes. After a 20-year follow-up, only data from 1 851 women were available. No significant difference was observed when comparing disease-free survival, distant-disease-free survival, and overall survival between the three groups. But this study demonstrated that a significant difference ($P<0.001$) could be observed in terms of recurrence when comparing lumpectomy without radiation to lumpectomy plus breast radiation. (Fig.1) [28]

Other studies [29,30,31] have also shown that adjuvant radiotherapy reduces local recurrence and improves overall survival in patients. As a result, adjuvant radiotherapy has become a standard of care for patients with breast cancer who have already been treated with BCS as a surgical method.

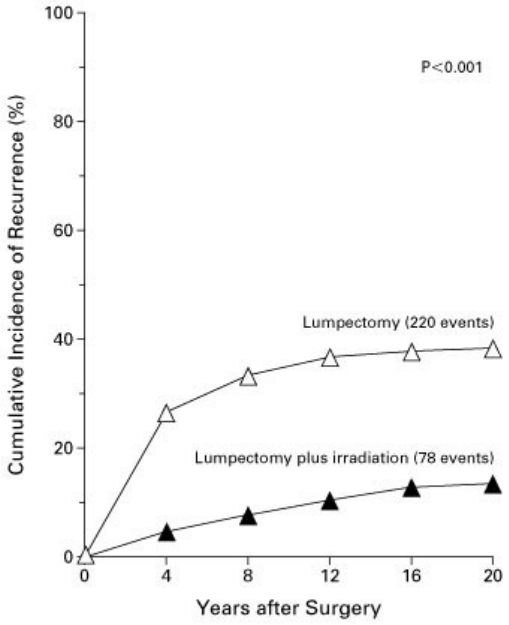


Figure 1. Cumulative Incidence of a First Recurrence of Cancer in the Ipsilateral Breast during 20 Years of Follow-up among 570 Women Treated with Lumpectomy Alone and 567 Treated with Lumpectomy plus Breast Irradiation.

3. Radiotherapy

Radiotherapy (RT) is a treatment that uses high-energy radiation to destroy cancer cells. [32] The rays, qualified as ionizing, form ions and deposit energy in the cells they encounter, causing damages within them. The lesions, which can be direct or indirect, essentially affect the genetic material, thus preventing them from dividing and replicating. However, radiation damage does not specifically affect cancer cells but also normal healthy cells. Fortunately, the majority of damage in healthy cells is effectively repaired by complex repair mechanisms such as homologous or non-homologous recombination. The repair mechanisms in cancer cells are not as efficient as those in healthy cells, and radiation damage usually results in cancer cell death. [33,34] To minimize the exposure of normal cells to radiation, the irradiation area should be centered on the tumor, as much as possible, and should try to minimize the inclusion of healthy tissue margins.

Neoadjuvant RT, which is performed before surgery, has the primary goal of reducing the size of the tumor. While adjuvant RT, which takes place after surgery, is intended to destroy tumor cells that may have persisted following the surgical procedure. [33] Four areas can be irradiating depending on the location of the tumor and how it has spread. These are the tumor bed, the whole breast, the chest wall, and the lymph nodes.

In general, RT is well-tolerated by patients, but since the radiation does not exclusively affect cancer cells, several side effects may be observed. For BC, the most common side effects are radiation dermatitis, breast edema, hyperpigmentation, and fibrosis. These side effects can occur at any time during the process, so it is possible to distinguish between acute, subacute, and late toxicities. A toxicity is considered acute if it appears at the end of the treatment, subacute if it occurs between 4-6 months post-RT and late if it occurs after one year. [35]

In addition to specifying whether these side effects occur in the short, medium, or long term, it is important to be able to quantify and report them correctly. For this purpose, the National Cancer Institute (NCI) has created the Common Terminology Criteria for Adverse Events (CTCAE), a standard that allows the evaluation of toxicities in a correct way (Table.2). This evaluation system makes it possible to grade the side effects, on a scale from 1 to 5, according to their severity. A grade 1 side effect is generally mild, asymptomatic and does not require any particular intervention, while a grade 5 side effect is responsible for the patient's death. [36,37]

ACUTE (End of Treatment)					
	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Acute radiation dermatitis	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin fold and creases: moderate edema	Moist desquamation in areas other than skin fold and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Odynophagy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences: urgent operative intervention indicated	Death
SUBACUTE (4-6 M)					
Breast pain	Mild pain	Moderate pain; limiting activities of daily living	Severe pain; limiting self care	-	-
Breast edema	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic, operative intervention indicated	-	-
LATE (> 12M)					
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Hyperpigmentation	Hyperpigmentation covering <10% body surface area; no psychosocial impact	Hyperpigmentation covering >10% body surface area; associated psychosocial impact	-	-	-
Skin induration	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; limiting activities of daily living	Severe induration, unable to slide or pinch skin;	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Telangiectasia	Telangiectasias covering <10% body surface area	Telangiectasias covering >10% body surface area; associated with psychosocial impact	-	-	-
Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting activities of daily living	Severe symptoms; limiting self care activities of daily living	-	-
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting activities of daily living	Severe symptoms; limiting self care activities of daily living		

Table 2. 5th version of the CTCAE related to breast cancer

3.1. Changes in radiotherapy fractionation

Since the discovery of X-rays by William Röntgen in 1895, and their use as a cancer treatment shortly thereafter, radiotherapy has evolved, and different schedules have been developed. [33] These RT schedules differ from each other in the number of fractions and total doses. It is, therefore, not always clear which schedule to apply to a particular patient, as the patient's characteristics, the type of cancer or the area to be treated are factors that may influence the choice.

For years, the standard RT schedule for early breast cancer was to deliver 50 Gy in 25 fractions over five weeks, i.e., 5 fractions of 2.0 Gy per week. Gradually, other studies have proposed alternative schedules combining lower and lower total doses with a lower and lower number of fractions.

One of the first trials to challenge the standard 50 Gy schedule was the START-B trial (UK Standardization of Breast Radiotherapy: Trial B). This randomized phase III trial was designed to compare the efficacy of two adjuvants RT schedules. Between 1999 and 2001, 2 215 women

with early breast cancer and a median age of 57 years were enrolled in the START-B trial. 92% of them had previously received BCS, while the remaining 8% had received a mastectomy. These women were randomly assigned to one of two treatments schedules. In the first group, women were treated with the standard RT schedule of 50 Gy in 25 fractions (2.0 Gy/fraction for five weeks), while women in the second group were treated with an alternative hypofractionated schedule of 40 Gy in 15 fractions (2.67 Gy/fraction for three weeks). Lymph node irradiation was performed in 161/504 node-positive women. After a 10-year follow-up, no significant difference was observed in terms of local-regional tumor relapse and disease-free survival when comparing the two schedules. This means that the 15-fraction hypofractionated schedule does not appear to be inferior to the standard 25-fraction RT schedule. [38]

After presentation of these results, hypofractionated adjuvant RT in 15 fractions has become a standard in the management of patients with early breast cancer.

A second study that has had an impact is the FAST study, a phase III randomized controlled trial conducted in the UK. Between 2004 and 2007, 915 women with invasive early breast cancer, all over 50 years of age, node-negative and having previously received BCS were enrolled in the FAST study. The purpose of this trial was to compare 25-fraction RT with two alternative 5-fraction hypofractionated schedules. Once included, these women were randomly assigned to one of three groups of adjuvant whole breast radiotherapy. In the first group, the control group, women received 50 Gy in 25 fractions of 2.0 Gy. Women in the second group were treated with hypofractionated RT of 30 Gy in 5 fractions over five weeks (1 fraction of 6.0 Gy/week), while women assigned to the third group received hypofractionated RT of 28.5 Gy in 5 fractions, also over five weeks (1 fraction of 5.7 Gy/week). Since all 915 women in the study were node-negative, no lymph node irradiation was performed. After a follow-up of 10 years, no significant difference was observed in terms of normal tissue effects (NTE: breast shrink, breast induration, telangiectasia, breast edema) when comparing RT delivered in 50 Gy with the one delivered in 28.5 Gy (Fig.2). But, for hypofractionated RT in 30 Gy, the NTE was statistically higher ($P<0.001$). Thus, hypofractionated RT delivered in 28.5 Gy is radio-biologically comparable to RT in 15 fractions. [39]

The third study is the FAST-Forward study, which attempted to compare the standard 15-fraction schedule with two hypofractionated 5-fraction schedules delivered over one week. According to the authors, there was no reason to believe that the current standard 15-fraction schedule could represent the lower limit of hypofractionated RT in breast cancer. The FAST-Forward study, a phase III randomized trial, accepted men and women at least 18 years old with invasive breast carcinoma who had undergone BCS or mastectomy. In total, between 2011 and 2014, 4 096 patients were included and randomized into one of three arms of this UK-based trial. The first arm included 1 361 patients treated with the standard 40 Gy schedule in 15 fractions. The second arm included 1 367 patients treated with a hypofractionated RT of 27 Gy, delivered in 5 fractions over one week (1 fraction of 5.4 Gy/day). Patients in the last arm were treated with a 26 Gy schedule, delivered in 5 fractions over one week (1 fraction of 5.2 Gy/day). No lymph node irradiation was performed. The primary endpoint of this study was ipsilateral breast tumor relapse, and no significant difference was observed between the standard 15-fraction and the alternative 5-fraction schedule. [40] In view of these results, ultrahypofractionation (26 Gy in five fraction) can also be recommended to treat patients with breast cancer. [41]

NTE End Point	Moderate/Marked Events/Total[a] (%)	KM Estimate (95% CI) of Cumulative Incidence (%) of Moderate/Marked Events		Hazard Ratio (95% CI)	Comparison With 50 Gy, P[d]	Comparison Between 30 Gy and 28.5 Gy, P[d]
		5 Years[b]	10 Years[c]			
Any NTE in the breast[e]						
50 Gy	88/301 (29.2)	20.1 (15.9 to 25.1)	33.6 (27.5 to 40.8)	1		
30 Gy	134/304 (44.1)	37.2 (31.9 to 43.0)	50.4 (44.0 to 57.1)	1.79 (1.37 to 2.34)	< .001	
28.5 Gy	116/298 (38.9)	27.9 (23.1 to 33.6)	47.6 (40.6 to 55.2)	1.45 (1.10 to 1.91)	.008	.099
Breast shrink						
50 Gy	69/301 (22.9)	13.7 (10.2 to 18.2)	28.5 (22.2 to 36.1)	1		
30 Gy	104/304 (34.2)	27.4 (22.7 to 33.0)	40.5 (34.3 to 47.4)	1.71 (1.26 to 2.32)	< .001	
28.5 Gy	79/298 (26.5)	17.9 (13.9 to 22.9)	33.4 (27.0 to 40.9)	1.22 (0.88 to 1.68)	.232	.025
Breast induration						
50 Gy	19/301 (6.3)	4.8 (2.9 to 8.0)	7.4 (4.7 to 11.4)	1		
30 Gy	40/304 (13.2)	9.2 (6.4 to 13.1)	15.2 (11.3 to 20.3)	2.22 (1.29 to 3.84)	.003	
28.5 Gy	38/298 (12.7)	9.2 (6.3 to 13.2)	18.6 (12.7 to 26.7)	2.14 (1.23 to 3.71)	.006	.864
Telangiectasia						
50 Gy	10/301 (3.3)	2.1 (1.0 to 4.5)	3.8 (2.0 to 7.0)	1		
30 Gy	15/304 (4.9)	4.1 (2.4 to 7.2)	5.8 (3.5 to 9.7)	1.55 (0.70 to 3.45)	.288	
28.5 Gy	13/298 (4.4)	2.2 (1.0 to 4.8)	5.5 (3.2 to 9.5)	1.35 (0.59 to 3.09)	.460	.721
Breast edema						
50 Gy	14/301 (4.6)	4.4 (2.6 to 7.4)	4.8 (2.9 to 8.0)	1		
30 Gy	40/304 (13.2)	12.8 (9.5 to 17.2)	13.7 (10.2 to 18.2)	2.98 (1.62 to 5.48)	< .001	
28.5 Gy	24/298 (8.0)	6.8 (4.4 to 10.3)	8.6 (5.8 to 12.6)	1.78 (0.92 to 3.43)	.084	.043
Other						
50 Gy	14/301 (4.6)	3.5 (1.9 to 6.4)	6.5 (3.4 to 12.5)	1		
30 Gy	37/304 (12.2)	8.1 (5.5 to 11.8)	14.1 (10.4 to 19.1)	2.80 (1.51 to 5.18)	< .001	
28.5 Gy	25/298 (8.4)	6.4 (4.0 to 9.9)	9.9 (6.7 to 14.4)	1.88 (0.98 to 3.62)	.054	.123

Abbreviations: KM, Kaplan-Meier; NTE, normal tissue effects.
[a]Follow-up NTE data available for 903/915 patients.
[b]Rate estimated at 5 years and 3 months.
[c]Rate estimated at 10 years and 3 months.
[d]*P* value for pairwise log-rank test.
[e]Any NTE in the breast includes shrinkage, induration, telangiectasia, and edema

Figure 2. Survival Analysis of Moderate/Marked Physician-Assessed Late NTE by FAST fractionation Schedule

The difficulty in applying the appropriate RT schedule for a particular patient has prompted The European Society for Radiation and Oncology Advisory Committee in Radiation Oncology Practice (ESTRO-ACROP) to create a standard with various practical recommendations (Table.3). This consensus, created by a group of experts, agrees on different aspects of hypofractionation, side effects, health-related quality of life in order to benefit BC patients. It is based on evidence-based medicine, and it provides recommendations for patient selection, radiation dose, and number of fractions in early BC. Thus, according to ESTRO-ACROP, 15-fraction RT (or moderate hypofractionation) can be offered to any patient regardless of the region affected. Regarding 5-fraction hypofractionated RT in one week (or ultrahypofractionation), it can be offered for whole breast, tumor bed, and chest wall irradiation, but cannot be offered for lymph node irradiation for the FAST-Forward schedule in one week. [42]

Reducing the number of fractions has many advantages, not only for the patient, but also for the hospital's RT department. It increases the quality of life of patients by allowing them to visit the hospital less frequently and return to their normal lives sooner. From the hospital's point of view, it improves the capacity of the department with a reduced schedule per patient. [42,43]

3.2. Boost

In some cases, and regardless of the RT schedule selected, some patients may be prescribed what is called additional boost irradiation. These boost doses allow the former tumor bed to be irradiated with a higher dose in order to improve local control and reduce the risk of recurrence. [44,45]

***Panel:* Final consensus statements**

1. Whole breast irradiation

a Moderate hypofractionated whole breast irradiation should be offered regardless of age at breast cancer diagnosis, pathological tumour stage, breast cancer biology, surgical margins status, tumour bed boost, breast size, invasive or pre-invasive ductal carcinoma in situ (DCIS) disease, oncoplastic breast conserving surgery, and use of systemic therapy

b Ultrahypofractionated (26 Gy in five fractions) whole breast irradiation can be offered as (1) standard of care or (2) within a randomised controlled trial or prospective registration cohort

2. Chest wall irradiation

a Moderate hypofractionation can be offered for chest wall irradiation without breast reconstruction

b Moderate hypofractionation can be offered for chest wall irradiation regardless of time and type of breast reconstruction

c Ultrahypofractionation (26 Gy in five fractions) for chest wall irradiation without breast reconstruction can be offered as (1) standard of care or (2) within a randomised controlled trial or prospective registration cohort

d Ultrahypofractionation (26 Gy in five fractions) for chest wall irradiation after breast reconstruction can be offered within a randomised controlled trial or prospective registration cohort

3. Nodal irradiation

a Moderate hypofractionation should be offered for nodal irradiation

b Ultrahypofractionation (26 Gy in five fractions) should not be offered for nodal irradiation until ongoing trials results are reported

4. Partial breast irradiation–patient selection for external beam radiotherapy

Low risk-features suitable for partial breast irradiation are: luminal-like subtypes small tumour (≤3 cm), absence of lymph vascular space invasion, non-lobular invasive carcinoma, tumour grade 1–2, low-to-intermediate grade DCIS (sized ≤2·5 cm with clear surgical margins ≥3 mm), age at diagnosis 50 years or more, unicentric or unifocal lesion, clear surgical margins (>2 mm), node negative (including isolated tumour cells), and no use of primary systemic therapy and neoadjuvant chemotherapy

5. Partial breast irradiation–dose and fractionation

a Moderate hypofractionation (40 Gy in 15 fractions) and ultrahypofractionation (26–30 Gy in five fractions) represent acceptable schedules for external beam partial breast irradiation

b Twice a day external beam partial breast irradiation dose and fractionations similar to those used in the RAPID trial should not be offered

DCIS=ductal carcinoma in situ.

Table 3. Current recommendations for radiotherapy in early breast cancer

Radiation boost is generally recommended for at-risk patients, defined as patients with a higher risk of local recurrence. This may include young patients, those with positive margins after tumor resection, or those with hormone receptor-negative cancer. [46] These boost doses can either be added at the end of RT schedule (called sequential boost), which inevitably lengthens the duration of the treatment, or they can be integrated into the different RT sessions. The latter situation, called Simultaneous Integrated Boost (SIB), offers the advantage of irradiating the former tumor bed with higher doses without increasing the total number of sessions.

Currently, and according to ASTRO, sequential boost doses are recommended over SIB, after adjuvant RT in breast cancer, outside the context of clinical trials. [47] However, in clinical practice, hypofractionated adjuvant RT with integrated boost sessions (SBI technique) is increasingly preferred. [44] This decision is supported by several studies [48,49,50] that have shown that adjuvant RT with SIB is not associated with severe toxicities and is generally well tolerated.

4. Lymph nodes

The breast contains a high number of lymph nodes (30-50), all involved in the body's defense and resistance to disease. [51,52] These nodes are colonized by immune cells such as lymphocytes and macrophages to allow these small immune organs to carefully filter the contents of the lymph that passes through them. Almost all the drainage of the breast takes place within two lymph nodes groups, called the axillary lymph nodes and the internal mammary nodes. However, the main culprit is the axillary lymph node, which alone drains about 75% of the lymph from the breast. [53]

The axillary lymph nodes can be divided into three levels, all located in the axillary fossa. The first level (level I) is formed by lymph nodes lateral and inferior to the pectoralis minor. The lymph nodes of level II are located deep to the pectoralis minor, while the nodes belonging to the third level (level III) are rather medial and located deep to the medial border of the pectoralis minor. [54] Other lymphatic groups can also be identified, such as the subclavicular group or the lymph nodes belonging to the supraclavicular group, but they play a lesser role compared to the previous groups. [53]

Lymph nodes are one of the most common sites of metastasis in BC. Cancer cells, present in the primary tumor, can break away and spread to invade one or more homolateral lymph nodes, via the lymphatic circulation. When malignant cells, initially originating from the tumor bed, are found in one or more lymph nodes, these nodes are called positive (pN+). Node invasion is considered as a prognostic factor of the disease and is it therefore important to know the nodal status when a breast cancer is diagnosed. [55]

4.1. Management of positive lymph nodes

Sentinel Lymph Node (SLN) is the first lymph node to which the breast will drain, which means that it will also be the first node to be invaded by migrating malignant cells. SLN analysis is the first step in determining the nodal status of a particular patient. [56] To do this analysis, a Sentinel Lymph Node Biopsy (SLNB) is performed, which is a technique that determines whether the cancer is only found locally, i.e., in the breast, or if it has spread beyond, i.e., in the lymph nodes. To do this, a tracer is injected into the tumor and will allow, via its drainage at the first lymph node relay, to identify the SLN. Once identified, the sentinel lymph node is surgically removed and sent to a laboratory for analysis of its status. [57] If cancer cells are found within the SLN, and it is positive, it may mean that other lymph nodes located upstream may also be positive. In this case, Axillary Lymph Node Dissection (ALND) and/or lymph node irradiation may be considered.

4.1.1. Lymph node irradiation (or loco-regional radiotherapy)

As mentioned above, lymph node irradiation is frequently performed using the moderate hypofractionation, 40 Gy in 15 fractions (2.67 Gy/fraction for three weeks). Indeed, the lymph node region remains, at present, the only area for which it is not recommended to use 5-fraction radiotherapy in one week. This is mainly due to the potential toxicities that could be observed following the exposure of single doses that are too high in the lymph nodes (5.7 Gy once a week for the FAST schedule compared to 2.67 Gy five times a week for the moderate schedule). These potential toxicities may include lymphedema, brachial plexopathy and shoulder

immobility. [35] Lymphedema occurs when, following the removal or irradiation of lymph nodes, the lymphatic system is no longer able to drain the axillary area properly, resulting in an accumulation of lymph. [58] Brachial plexopathy is a rarely observed neurological disorder that may occur following radiation to the brachial plexus. [59] This plexus, formed by the ventral branches of the last four cervical nerves and the first thoracic nerve, is responsible for the motor and sensitive innervation of the upper limbs. [60,61] Thus, the main symptoms of brachial plexopathy can be numbness, paresthesia, or lymphedema. [59] Finally, the impaired shoulder is an alteration of shoulder movements that can be observed when irradiation, at single doses too high, leads to fibrosis of the pectoral muscles, and/or other muscles of the chest wall. Damage to the ligaments, cartilage and nerves in this area may also be involved in the occurrence of this alteration. [35]

5. The impact of COVID-19

For many years now, Ste-Elisabeth Hospital (SE Hospital) has offered loco-regional RT according to the FAST schedule (5 fractions of 5.7 Gy over five weeks) to breast cancer patients over 75 years of age. The reasons why this hospital has preferred to use the FAST schedule, despite the ESTRO-ACROP recommendations, are mainly due to the results published by Ortholan *et al.* [62] In this study conducted between 1987 and 1999, 150 patients with a median age of 78 years were included, of whom 33.8% were node positive. This study was designed to evaluate the long-term effects of hypofractionated RT in five weekly fractions in the elderly. The interest of this study is that 31.8% of patients received lymph node irradiation according to this schedule with a total dose of 27.5 Gy divided into 5 fractions of 5.5 Gy. However, the results specifically obtained for patients irradiated at the lymph node level were not described in this paper.

In the ESTRO-ACROP recommendations, the ultrahypofractionated FAST-Forward schedule is not recommended for the axillary region, while the 5-week FAST schedule is not mentioned. However, it is specifically the FAST schedule that the SE hospital has chosen to use for loco-regional irradiation. To date, the hospital remains convinced of the importance of allowing time for healthy tissue to regenerate. Indeed, as mentioned at the beginning, radiation damage affects both cancerous and healthy cells. [33] However, by using a FAST-Forward schedule (5 fractions of 5.2 Gy over one week), healthy tissues are exposed to a single high dose of radiation on a daily basis, whereas using the FAST schedule ensures that healthy tissues have time to regenerate before starting a new RT session.

During the emergence of the COVID-19 pandemic in Belgium, hospitals were instructed to reduce unnecessary patient attendance in health care facilities, in order to prevent the spread of the virus. [63] To continue to offer RT to breast cancer patients and at the same time limit their attendance in the department, SE hospital has decided to lower the current eligibility threshold of 10 years. Thus, since the first wave of COVID-19, loco-regional RT according to the FAST schedule is also offered to patients older than 65 years, especially if they present a geriatric profile. However, this change does not affect all patients between 65 and 75 years of age, as only a portion of them will be treated with 5-fraction hypofractionated loco-regional RT. The factors that will have an impact on the decision to undertake one treatment schedule rather than the other are mainly the clinician feeling of the physician, the patient's profile and wishes, and the reassuring data cited above. Examples of patients who may benefit from loco-regional RT

under the FAST schedule include patients with a geriatric profile or patients who are too frail to travel five times a week for three consecutive weeks.

Thus, since the emergence of COVID-19, and with a few exceptions, all patients over 75 years of age are treated with loco-regional RT in 5 fractions. Patients between 65 and 75 years of age are analyzed on a case-by-case to see if the FAST schedule would be suitable for them. However, no patients under 65 years of age are eligible for this adjuvant RT schedule, due to the limited follow-up of this 5-fraction schedule, which is shorter than the life expectancy of younger patients. Indeed, the current results of the FAST study do not allow sufficient insight to predict toxicities that may occur in 20-30 years. Therefore, for younger patients, it is preferable to keep a standardized RT, the 15-fraction RT, in order to guarantee the quality of the treatment provided over the long term.

In addition to the results presented in the literature and the occurrence of COVID-19, the ability for patients to access INAMI reimbursement also impacted the SE hospital's interest for the FAST schedule.

The extension of this schedule to a younger population has many benefits for both the patients and the radiotherapy department. The reduction in the number of sessions, the increase in machine availability, and the reduction in scheduling have resulted in fewer patients in the hospital. But this treatment schedule needs to be evaluated in a prospective study. At present, a randomized controlled multicentric trial comparing 5 and 15 fractions has been accepted by the ethics committee and is about to start.

Objectives

The main hypothesis on which this master thesis is based is that the toxicity observed with hypofractionated loco-regional radiotherapy in 5 fractions according to the FAST schedule is not superior to loco-regional radiotherapy according to the 15-fraction schedule.

All the analyses intended to answer the hypothesis will be carried out on two distinct cohorts of patients. The first cohort, considered as the control, will be composed of all patients treated for breast cancer with loco-regional radiotherapy according to the 15-fraction schedule, within the SE hospital between 2018 and 2021. The second cohort will be composed of all patients also treated during the last four years at SE hospital, but who received loco-regional irradiation with the 5 fraction FAST schedule.

The first analysis performed will be a purely descriptive analysis to determine whether the two cohorts studied are comparable. This analysis will focus on different criteria specific to the patient and her cancer. The collection of these criteria will be possible thanks to the creation of a database and its completion with the data present in the medical records of each patient included in the analysis.

In a second step, the evaluation of overall survival and progression-free survival will be performed on these two cohorts to test the hypothesis. This will allow to compare the two treatment schedules between them in order to know if there is a difference between the two at the loco-regional level.

Finally, the last analysis that will be performed in this master thesis and that will allow to provide results regarding the hypothesis will be the analysis of toxicity. Toxicity will be evaluated and compared within the two groups through the collection of side effects observed for each of the patients. To provide a complete analysis, the eleven toxicities that may be observed following radiotherapy for breast cancer will be analyzed, evaluated, and entered by grade in the database.

Any additional analysis that we would like to carry out because it could provide additional information to the initial hypothesis will be added as a subsidiary analysis.

Methods

This retrospective analysis, conducted over a period from January 1, 2018 to December 31, 2021, was based on data from cohorts of patients from one of the following six hospitals: CHU UCL Ste-Elisabeth, CHU UCL Mont-Godinne, CHU UCL Dinant, CHR Namur, St-Luc Bouge, and CHR Auvelais. All radiotherapy sessions are performed at the Ste-Elisabeth site.

1. Patient Selection

All BC patients, who have been treated with loco-regional RT according to the FAST schedule (5 fractions), over the period 2018-2021, were first identified. In a second step, all BC patients also treated over the same period but with loco-regional RT according to the START schedule (15 fractions) were identified. These patients will be part of the control group and must be at least 65 years old. As the loco-regional RT according to the FAST schedule is currently not proposed for patients under 65 years of age, we decided to only include patients over 65 years of age in the START group. With this criterion, it is trying to have comparable cohorts as much as possible in order to limit the age bias. After identification of these BC patients, several inclusion/exclusion criteria were applied. For the moment, this represents 220 patients.

1.1. Inclusion Criteria

The inclusion criteria included only female patients; who were at least 65 years old at the time of the first session of RT; and who had loco-regional breast tumor or loco-regional breast recurrence requiring lymph node irradiation.

1.2. Exclusion Criteria

The exclusion criteria included all male patients; all patients younger than 65 years at the time of the first RT session; patients who have not had an axillary procedure and with irradiation of area 1 only; and all patients with a history of homolateral RT reported in their medical records.

After application of these criteria, 205 patients were included in this retrospective study. The remaining 15 patients were excluded for the following reasons. (*Fig. 3*) This represents an exclusion of 6.82% of the patients initially identified.

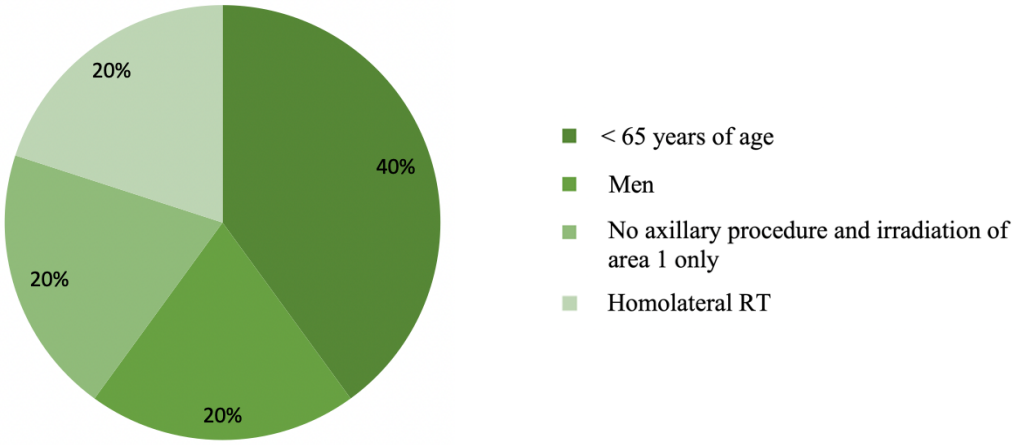


Figure 3. Proportion of exclusion by reason

Of the 205 patients included, 118 are in the START control group as they received the 15-fraction lymph node irradiation, while the remaining 87 patients are in the FAST group corresponding to the 5-fraction loco-regional irradiation.

2. Development of the database

A first version of the database was created based on the opening of the first five medical records. The literature and feedback from various clinicians at SE hospital also helped in its creation. This version was developed in an Excel format mainly to allow easier and quicker modification according to the content of these medical records. As soon as the parameters encoded in the Excel format seemed appropriate for the assessment of toxicity between the two cohorts, they were submitted to some of the Ste-Elisabeth's radiotherapists for validation. Once approved, the content of the Excel format was exported and definitively encoded in REDCap.

REDCap is a web-based application that allows the creation of online databases, allowing for secure data collection. [64] The decision to use REDCap, instead of Excel, for the final encoding is mainly due to practical and security reasons. Although Excel is an easy-to-use program known to all, it remains a software that allows data overwriting or data modification too easily and without automatic backup. Moreover, with Excel, it is not possible to work with several people on the same file, which is what we wanted to do in this study. Therefore, to ensure a better robustness of the collected data, the REDCap application, which allows the creation of a secure database with automatic backup, and which can be filled simultaneously by different users, will be preferred. In addition, REDCap allows to provide targeted access to specific users, which has made possible to comply with the GDPR regulation when transferring data to the statistician in charge of the analyses, without disclosing the names of the patients.

The final version of the database (Annex. 1) can be divided into five different parts. The first part, called the description, contains specific information about the patient, such as name, surname, date of birth, date of diagnosis, or the site from which the patient comes. Also included in this part are the different risk factors (smoking, diabetes, breast size, BMI) that are associated with breast cancer.

The second part focuses on the different characteristics of the cancer at the time of diagnosis. Laterality and quadrants are two parameters that allow the precise location of the tumor in the breast. The histology of the cancer, its grade and its pro-operative TNM are also included in this second part.

The third part is composed of the different treatments that have been put in place to treat the cancer. There is precise information on adjuvant/neoadjuvant treatments, on surgery and the axillary procedure performed, on the post-operative TNM, and on post-operative toxicities (lymphedema and arm mobility). The treatment section also includes details on radiotherapy: the schedule used (START-B or FAST), the duration of the irradiation, information about a boost dose and the site irradiated.

In the fourth section, information is provided on toxicities that occur after radiotherapy sessions. This section analyses the eleven toxicities that can be observed following irradiation of the breast and lymph nodes. These toxicities are acute dermatitis, dysphagia, breast pain, breast edema, breast atrophy, hyperpigmentation, breast induration, telangiectasia, homolateral arm edema, plexitis and homolateral arm pain. Of these toxicities, some are more frequently

observed than others, as is the case for acute dermatitis, arm oedema, hyperpigmentation, and breast induration. [35] Other toxicities are much less frequent, such as telangiectasia, plexitis or dysphagia, and are only observed in certain cases. But to provide more robust results, the evaluation of all these toxicities seemed more appropriate than selecting only the most common ones.

The last part concerns information on the survival of these patients. It includes the date of the last oncology visit, the date of the recurrence (if there was a recurrence) with details of its location, and the date of the last visit or death if there was a death.

3. Completion of the database

Data entry into the database was performed between July 11, 2022 and September 13, 2022. All data, specific to each patient, were extracted from medical records thanks to the OmniPro software and the Réseau Santé Wallon (RSW). OmniPro is a software that has allowed the computerization of medical records, while the RSW is a platform that allows the sharing of computerized health documents between various health care providers in order to have the complete health history of the patient. [65]

All information related to the description part (name, site, risk factors, …) was usually easily found in the medical record in the antecedent's section. For the diagnosis and treatment part, the information could be found in different places depending on the affiliation site of the patient. When the patient came from the SE hospital, a special section called "Clinique du sein" was filled in and contained all the information related to breast cancer, with some exceptions. But when the patient came from one of the other five hospital sites, the information related to diagnosis and treatment had to be searched for in the entire record. Information related to post-radiation toxicity was usually found in either the radiotherapy and/or oncology and/or radiology consultations. To ensure that no details were missed, all consultations related to these three departments were precisely analyzed. However, not all side effects that wanted to be evaluated were explicitly mentioned and evaluated in the medical records. In this case, we asked several clinicians why they were not mentioned and apparently, most of them only mention the toxicities that they observed during visits. We therefore made the decision to encode all unmentioned toxicities as "NA". Finally, for the last part of this database, namely the survival part, it is in the RSW that most of the information was searched. Indeed, to find the date of the last news, rather than trying to find the date of the last consultation in the medical record, we looked for a date related to a blood test done recently, or a COVID-19 test done in the last few days.

Of course, in some cases, the information could not be found either in the medical record or in the RSW. In this case, the specific field in the database remained empty and this lack of information was qualified as missing data.

The information in the medical record can also be interpreted differently from one person to another. To try to minimize this interpretation bias, a file with instructions in case of doubt was created (Annex. 2) and a triple check was performed in order to increase the robustness of the data collected. This was possible thanks to the colored dots proposed in the REDCap functionalities. It is possible to assign a colored dot to each of the five parts of the file created in the database, indicating its status. A red dot means that the part in question is not complete, a yellow dot means that it has not yet been verified, while the last dot, the green one, indicates

that the part in question is complete within the medical record. In addition to giving a status of each part, it is also possible with REDCap to lock a part. For this triple verification, the first person who was in charge of encoding the information in the database had to assign the status 'incomplete' once the file was created. The second person, in charge of verifying the information encoded in the file, could have the choice between two labels. If he agreed with the data encoded, the status 'complete' was assigned to the file, but in case of disagreement, the yellow 'unverified' label was assigned. The last person double-checked all the encoded information. If he agreed with the information provided in the database, he could lock the file which meant that the file was ready to be analyzed. If there was a disagreement, this person had to reopen the medical file in OmniPro to make a decision and then lock the document.

Once the REDCap file was completed, verified, and validated for each patient's data, statistical analyses were performed to compare the two treatment schedules.

4. Statistical Analysis

All statistical analyses were performed by Professor Bihin using the 'R' software. Since the results presented in this thesis will be published in a medical journal, all analyses were performed by a statistician to ensure that they are appropriate and provide robust results.

The initial hypothesis of this thesis was that the toxicity related to loco-regional RT observed with the FAST schedule is not superior to the toxicity observed with the START schedule. To test this hypothesis, complex and simple statistical analyses were performed on 5 main questions:

1. Comparison of baseline characteristics of the two cohorts

First, a purely descriptive analysis of the population was performed in order to compare the two cohorts in the baseline. To do this, the relative frequency of a particular event, for all the criteria encoded in the database, was performed in both groups. The differences for each event between the two cohorts were then assessed using the Chi^2 test or the Fisher's test. Depending on the criteria evaluated, the degrees of freedom could vary between 1 and 6. Given that the confidence interval is 95%, the significance thresholds could vary between 3.84 and 12.59 respectively.

2. Comparison of survival according to the schedule received

Progression-Free Survival (PFS) and Overall Survival (OS) between the two groups were assessed using survival curves determined by the Kaplan-Meier method. A comparison of the risks of death between the two groups was also assessed by relating the logarithm of the risk of death to the age of the patient. The covariate "presence or absence of hormone receptors on the surface of cancer cells" was also added to this evaluation, making this model a multivariate model. This allowed the evaluation of the potential relationship between the presence of hormone receptors, the age of the patient, with the risk of death in BC patients.

3. Comparison of toxicity according to the schedule received

The proportion of occurrence of each of the eleven toxicities that may be observed following loco-regional radiotherapy, was evaluated between the two cohorts. In order to perform this

analysis, the most important grade observed for a particular toxicity was taken for each individual. The risk of occurrence of an adverse event (AE) for each group was compared using the odds ratio (OR). Two ORs were evaluated; the first one (OR1) corresponds to the risk of occurrence of an AE of grade 1 or higher while the OR2, corresponds to the occurrence of an AE of grade 2 or higher. Afterwards, an adjusted odds ratio (aOR) taking into account three covariates allowed the evaluation of the influence of chemotherapy, axillary procedure and irradiated volume on the occurrence of toxicities in each of the two cohorts. Finally, a P-value, considering these three covariates, was calculated using logistic regression.

4. Sensitivity analysis

In the statistical analysis, all AEs reported as NA were converted to grade 0 side effects. To consolidate this decision, a sensitivity analysis was performed to exclude all side effects encoded as NA and to consider only those toxicities explicitly mentioned as grade 0, 1, 2, 3, 4, or 5 in the medical records. If both scenarios are consistent, it could be concluded that NA-encoded AEs were effectively unlisted because they were absent.

5. Subsidiary questions

a. Relationship between risk factors and global toxicity (after adjustment for chemotherapy, axillary procedure, and irradiated volume)

An additional descriptive analysis was performed, relating the different BC risk factors to the global toxicity experienced by these patients. To do this, two cohorts were compared to see if the presence of higher side effects could be correlated with the presence of risk factors. The first cohort consisted of all patients who experienced a grade 1 side effect, whereas the second cohort included only patients who experienced a grade 2 or higher side effect. Since this is a purely descriptive analysis, the analyses performed here are identical to those performed in question 1.

b. Comparison of the proportions of patients with relapse among those who died according to the schedule received

It is also a descriptive analysis showing the proportion of patients who died among those who relapsed from cancer. The analyses will therefore be identical to questions 1 and 5a.

c. Comparison of median follow-up according to the schedule received

Finally, the follow-up time of patients in the two cohorts was also analyzed in order to compare the two groups.

Analysis

The results will be analyzed following the order of the questions mentioned in the statistical analysis section above.

1. Comparison of baseline characteristics

This analysis is presented in five different tables, grouped by distinct criteria, and allows us to identify differences between the two cohorts. The results are presented as the proportion of individuals for each criterion, except for the parameters age, BMI, and irradiated volume where it represents the average of the observed values. The confidence intervals are set at 95%.

1.1. Risk factors

	Sample size	FAST (N=87)	START (N=118)	*P* value
Age (years)	205	78.00	68.00	< 0.001
ECOG				
0	204	0.18	0.47	< 0.001
1		0.69	0.51	
2		0.10	0.02	
3		0.02	0.00	
Old tobacco	205	0.16	0.12	0.384
Active tobacco	205	0.08	0.09	0.750
BMI	183	27.700	27.400	0.754
Diabetes	205	0.23	0.12	0.034
Breast size				
No information	205	0.71	0.62	0.233
A		0.01	0.01	
B		0.09	0.09	
C		0.13	0.19	
D		0.02	0.08	
E		0.03	0.01	
Hormone receptors	205	0.76	0.82	0.266

Table 4. Comparison of risk factors between the FAST and START cohorts

When analyzing the age of the patients in the two groups, it is observed that the patients included in the FAST group are on average 10 years older than the patients in the START group. As mentioned above, this does not seem surprising since loco-regional RT according to the FAST schedule was not routinely offered to patients under 75 years of age, which inevitably increases the mean age of this group. Since there is a significant difference between the two cohorts, this means that differences in survival between the two groups could be partly explained by the age factor, although at this stage it is too early to conclude anything.

A significant difference is also observed when comparing the ECOG performance status between the two cohorts. A high-performance index means that the patient is less independent and has more difficulty performing daily activities, compared with a lower performance status, which corresponds to an active patient who can perform activities without restriction. The difference between the two groups is probably explained by the age difference between the two groups. Indeed, the patients belonging to the FAST cohort are older and therefore more fragile than the patients in the START cohort.

No significant differences were observed for the parameters “old tobacco, active tobacco, BMI, and proportion of hormone receptors-positive” between the two cohorts. However, nearly one in four patients in the FAST cohort appeared to be diabetic compared to nearly one in ten patients treated with the START schedule (*p*-value of 0.034). Type 2 diabetes is the most common type of diabetes in the world (90% prevalence). Risk factors include age, obesity, and sedentary lifestyle for example. Thus, one of the reasons that could explain the difference is the presence of older and more inactive people in the FAST group compared to the START group. [66,67]

No conclusion can be drawn for the "breast size" factor because of the high proportion of missing data observed. This is mainly due to the fact that the SE hospital is the only one among those analyzed that encodes all information related to the chest circumference. The other five hospitals generally do not.

Globally, the two cohorts studied are quite similar and only the age factor can, for the moment, explain any difference between them.

1.2. Treatments

	Sample size	FAST (N=87)	START (N=118)	*P* value
Neodjuvant treatments				
None	205	0.64	0.64	0.390
Chemotherapy		0.20	0.26	
Hormonotherapy		0.14	0.08	
Other		0.02	0.01	
Adjuvant treatments				
None	205	0.18	0.13	0.394
Chemotherapy		0.08	0.05	
Hormonotherapy		0.71	0.77	
Other		0.02	0.05	
Concomitant treatments	205	0.07	0.03	0.249
Axillary procedure				
None	205	0.02	0.04	0.597
Dissection		0.76	0.70	
SLN		0.22	0.25	
Irradiated volume (cm3)	205	59.800	66.175	0.528

Table 5. Comparison of treatments between the FAST and START cohorts. SLN=Sentinel lymph node.

In general, most breast cancer patients do not receive neoadjuvant therapy before surgery. Of those who do, 20-25% receive chemotherapy and a smaller proportion receive hormone therapy. Based on these figures, chemotherapy seems to be more prescribed in the START cohort, i.e., in younger patients, whereas hormone therapy seems to be more indicated for older patients in the FAST cohort. However, the difference between the two groups is too small to be considered significant. The category "other" usually refers to targeted therapy and, as the table shows, this was hardly ever performed in these patients regardless of the group.

Regarding adjuvant treatment, we can see that the majority of patients, no matter the group, received hormone therapy after surgery. This is not surprising given that, as shown in *Table. 4*, nearly 80% of patients have hormone receptors on the surface of their cancer cells, making the tumor hormone dependent. Although there was no significant difference between the two groups, the proportion of patients treated with hormone therapy after surgery is slightly higher in the START group. One explanation that may support these results is that, in general, triple-negative (hormone-insensitive) cancers are found in a higher proportion in older patients. This table also shows that in about 15% of cases, no adjuvant therapy is prescribed, while in less than 10% of cases chemotherapy is offered.

Axillary Lymph Node Dissection (ALND) is the most performed axillary procedure, and this is logical as all patients included in this analysis had lymph node involvement. A smaller proportion (about 25%) only received SLNB despite having positive nodes. In fact, recent studies [68,69] have shown that SLNB is just as effective in terms of overall survival and relapse-free survival as ALND. Thus, for patients with relatively small lymph node involvement, SLNB is more recommended than in the past.

No significant difference was observed between the irradiation volume of one group compared to the other. On average, both groups were irradiated with a volume of 60 cm^3.

1.3. Quadrants

	Sample size	FAST (N=87)	START (N=118)	*P* value
UIQ	205	0.08	0.15	0.119
UMQ		0.10	0.08	0.648
UOQ		0.46	0.39	0.316
LIQ		0.06	0.09	0.346
LOQ		0.13	0.11	0.720
Nipple area		0.20	0.08	0.021
EOQ		0.09	0.07	0.524
EIQ		0.07	0.07	0.974
Central		0.02	0.00	0.098
Whole breast		0.02	0.03	0.911
Axillary recurrence at first presentation		0.02	0.02	0.757

Table 6. Comparison of the location of the tumor between the FAST and START cohorts. UIQ=upper inner quadrant; UMQ=upper median quadrant; UOQ=upper outer quadrant; LIQ=lower inner quadrant; LOQ=lower outer quadrant; EOQ=equatorial outer quadrant; EIQ=equatorial inner quadrant.

The proportion of tumors found in the Upper Outer Quadrant (UOQ) is clearly higher than the proportion of tumors found in the other quadrants. This is consistent with other studies such as that of Rummel *et al.* [70] At present, we do not really know the factors that could explain the preferential occurrence of the tumor in the UOQ, even if, by looking at the literature, several hypotheses can be put forward. The most frequently encountered hypothesis has been the use of underarm deodorants. Indeed, antiperspirant cosmetics are composed of aluminium salts, an active ingredient considered genotoxic and capable of causing DNA damage. In addition to this, it turns out that aluminium salts could also be considered as a metallestrogen, i.e., a metal capable of interfering with the action of estrogens, a hormone already known to be linked with breast cancer. [71,72]

The proportion of tumor found in the other quadrants is much lower and the difference is generally not significant between the two groups except for the nipple area.

1.4. Histology

	Sample size	FAST (N=87)	START (N=118)	*P* value
IDC	205	0.48	0.58	0.147
ILC		0.25	0.19	0.252
NST		0.36	0.36	0.905
DCIS		0.13	0.03	0.005
LCIS		0.06	0.03	0.242

Table 7. Comparison of histology between the FAST and START cohorts. NST=No special type.

For the statistical analyses, IDC and NST were considered as two distinct histology. However, it turns out that these two types want to describe the same type of cancer and IDC and NST will henceforth be described under the common term “invasive ductal carcinoma”. Thus, 84% of IDCs are observed for the FAST group and 95% for the START group.

As shown in the literature, IDC is the most common histology in breast cancer and accounts for about 80-90% of cancers. It is followed by ILC with a prevalence of about 15-20% and is in turn followed by DCIS and LCIS in equal proportions (about 5%). [19] From these figures, it can firstly be observed that younger patients in the START cohort tend to have more invasive ductal carcinoma than FAST patients, although this cannot be considered a significant difference. Secondly, it can also be seen, but this time with a significant difference between the two cohorts, that FAST patients are more prone to DCIS compared to patients in the START cohort. However, for both of the above observations, this cannot be correlated with what is found in the literature. In general, the proportion of patients with invasive carcinoma (IDC in this case) increases with the age of the patient, which is not the case here. [73,74] This is also inconsistent with the results observed for DCIS. Normally, one would expect patients in the younger cohort (START) to have more ductal in situ carcinoma than those in the FAST cohort. A second reason that might contradict these results is the fact that carcinomas in situ are considered invasive precursors and are therefore mainly diagnosed by mammography. It should be recalled that screening mammography in Belgium is offered to women aged between 50 and 69 years. However, the average age of the women in the FAST cohort is 78 years. We would therefore tend to think that women over 69 years of age perform fewer mammograms than younger women. Therefore, the proportion of DCIS in the FAST cohort should be smaller than that observed here.

1.5. Pre-operative and post-operative TNM

	Sample size	FAST (N=87)	START (N=118)	*P* value
Pre-operative T				
0	198	0.02	0.01	0.509
1		0.25	0.28	
Is		0.01	0.01	
2		0.46	0.52	
3		0.07	0.08	
4		0.18	0.08	
X		0.01	0.02	
Pre-operative N				
0	197	0.48	0.41	0.767
1		0.40	0.41	
2		0.05	0.06	
3		0.05	0.08	
X		0.02	0.04	
Pre-operative M				
0	201	0.90	0.88	0.741
1		0.08	0.08	
X		0.02	0.04	
Post-operative T				
0	201	0.06	0.11	0.534
1		0.31	0.36	
Is		0.01	0.02	
2		0.38	0.36	
3		0.20	0.14	
4		0.05	0.02	
Post-operative N				
0	201	0.09	0.17	0.446
1		0.71	0.65	
2		0.14	0.13	
3		0.05	0.05	
X		0.01	0.00	
Post-operative M				
0	202	0.91	0.91	0.427
1		0.08	0.05	
X		0.01	0.03	

Table 8. Comparison of pre-operative and post-operative TNM between the FAST and START cohorts

1.5.1. Pre-operative TNM

The majority of patients (about 50%), regardless of the group, had a tumor between 2 and 5 cm in diameter before surgery (T2). About 25% of the patients had a tumor of 2 cm or less in diameter (T1). About Tis, as only pN+ patients were included in the analysis, in situ should not normally be found. However, this was found in 1% of patients, but this does not seem

inconsistent as it is quite possible to find it in 2 of the 198 patients assessed. Very few of the tumors found were larger than 5 cm and it was impossible to assess the size of the tumor pre-operatively in 2% of patients (Tx).

Concerning the lymph nodes, almost all patients belonged to either the cN0 or cN1 group. cN0 means that no tumor cells were found in the patient's lymph nodes, which is quite logical since it is mainly in the post-operative period, i.e., after surgery, that these cells are found and that the lymph node involvement can be quantified. cN1 means that nodes containing cancer cells were already found pre-operatively, mainly by ultrasound or cytopuncture. For about 10% of the patients, the stage cN3 or cN4 was found and for 3% of the patients, the nodal status could not be assessed.

Very few metastases were found in the patients pre-operatively, but for all criteria (size of the tumor, nodal status, metastases) no significant difference was observed between the two cohorts.

1.5.2. Post-operative TNM

The post-operative results are quite similar to the pre-operative results with still a predominance of patients in the pT2 and pT1 groups. Then, as for the pre-op results, pT3 patients are found next (15-20%) but are this time followed by pT0 patients. Indeed, the proportion of patients in whom no tumor is found has increased in the post-operative period compared to the pre-operative period. This is possible because a number of patients, prior to surgery, have already received neoadjuvant treatments to reduce the size of the tumor. The smaller tumor can then be completely removed leaving healthy margins behind. Finally, for the same reasons as in the pre-operative analysis, a very low amount of pTis is found in these pN+ patients.

When looking at the lymph node results, the proportion of patients with negative lymph nodes has decreased compared to the pre-operative analyses. This is consistent with what was previously explained about the fact that node status is discovered at the time of lymph node sampling. It also explains that the proportion of patients belonging to the pN1, pN2, pN3 groups increased. And finally, for one patient, the lymph node status could not be assessed, and this was probably because no lymph node sampling was performed and that the lymph node irradiation was sufficient on its own.

Post-operative metastatic results did not differ from pre-operative results and as with pre-operative analyses no significant differences were observed between the FAST and START cohorts.

2. Comparison of survival

For the survival analysis, overall survival (OS) and progression-free survival (PFS) were assessed and compared between each of the two cohorts. For each of the two analyses, we find firstly a Kaplan-Meier survival curve showing the risk of occurrence of the event "death or progression" over time. In a second step, a multivariate model was created and adjusted with the covariates age and presence or absence of hormone receptors in order to observe their impact on the risk of death or progression in patients.

2.1. Comparison of overall survival

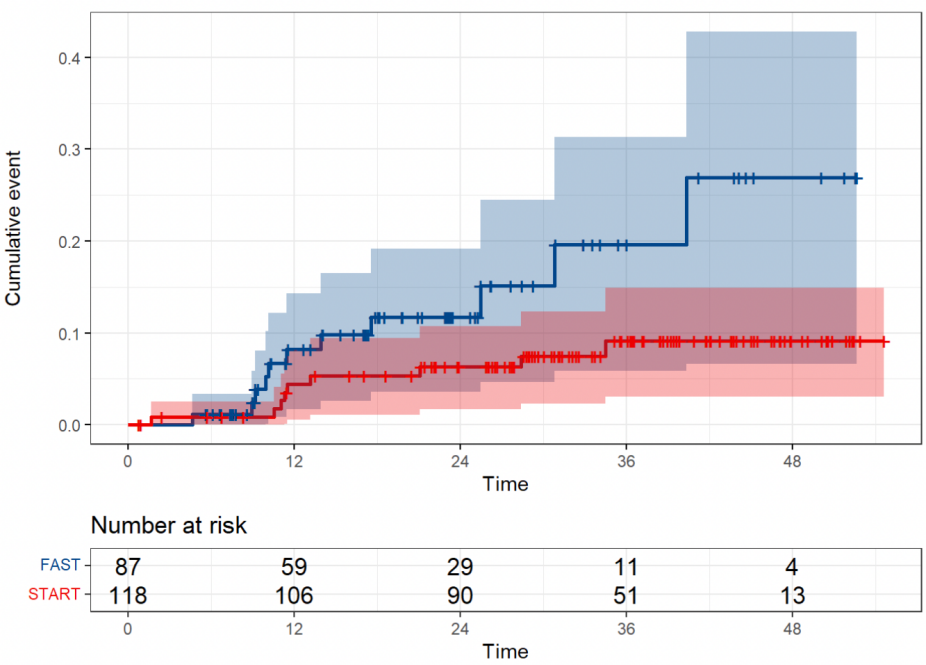


Figure 4. Overall Kaplan-Meier survival curves for patients treated with loco-regional radiotherapy according to the FAST and START schedules.

On the Kaplan-Meier survival curve, the occurrence of death is represented by an upward growth of the curve while the censoring of a patient, related to his loss of sight, is represented by a vertical line. Confidence intervals, set at 95%, are represented by the blue and red bands for the FAST and START groups, respectively.

Logically, the number of patients at risk of death in both cohorts decreases over time because the proportion of patients who died and were lost to follow-up increases over time. Thus, when we look at the number of patients for whom follow-up is still assured after 36 months, this represents 11 patients for the FAST cohort, or 12.6%, and 51 patients for the START cohort, or 43.2%.

This first survival curve also shows that after 48 months, the proportion of patients who died in the FAST cohort is close to 10%, while the proportion of deaths in the START group is about 25%. In other words, this means that after 48 months, there is still a 90% survival in the START cohort, compared to about 75% in the FAST cohort. However, the cause of death of these patients remains unknown and it is therefore impossible to know whether these deaths are related to breast cancer or not.

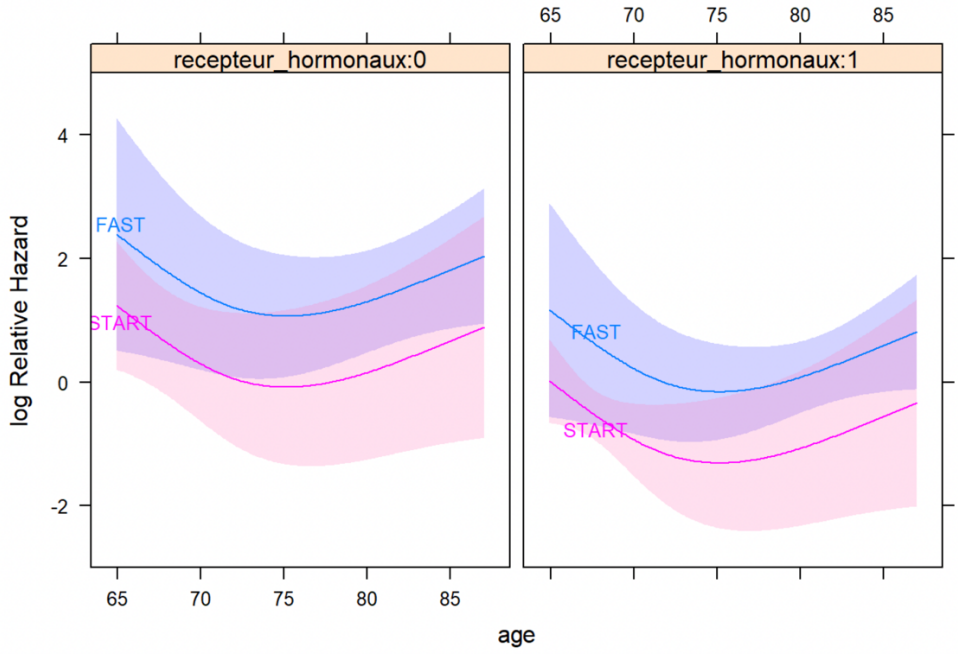
The advantage of this representation is that it is easy to see the difference in survival between the FAST and START cohorts. The disadvantage is that it could be thought that this difference is related to the treatment given (START or FAST loco-regional RT) whereas it could be related to the age difference between the two groups or to other characteristics. Indeed, by looking at the age-related mortality tables for 2021 in Belgium, the probability of a 78-year-old Belgian woman dying is 2.43 times higher than the probability of a 68-year-old woman. (*Table.9*) [75] At this point, we should only consider this figure as a descriptive analysis of the proportion of

deaths between the two groups and we cannot conclude that the observed difference in death is related to the treatment.

2021	BELGIQUE Femmes						
Age exact (X)	Population moyenne (px)	Décès observés (dx)	Taux de mortalité (Tx)	Probabilité de décès (QX)	Survivants (Lx)	Décès de la table (Dx)	Espérance de vie (EX)
68	**64006**	**692**	**0,010811**	**0,010753**	**898676**	**9664**	**19,31**
69	61902	716	0,011567	0,011500	889012	10224	18,52
70	60457	759	0,012554	0,012476	878788	10964	17,73
71	59805	805	0,013460	0,013370	867825	11603	16,94
72	59274	870	0,014678	0,014570	856222	12476	16,17
73	58675	909	0,015492	0,015373	843746	12971	15,40
74	57594	1010	0,017537	0,017384	830776	14442	14,63
75	52636	1034	0,019644	0,019453	816334	15880	13,88
76	47619	1051	0,022071	0,021829	800454	17473	13,15
77	45316	1122	0,024759	0,024455	782981	19148	12,43
78	**40772**	**1078**	**0,026440**	**0,026093**	**763832**	**19931**	**11,73**

Table 9. Mortality tables for Belgian women in 2021.

2.1.1. Multivariate model



Schedule	Events	PY	Rate	HR	aHR	lower	upper	*P*-value
FAST	11	200.2	5.49	2.54	3.16	0.70	14.18	0.13
START	9	388.1	2.32	*NA*	*NA*	*NA*	*NA*	*NA*

Figure 5. Comparison of risk of death between the FAST and START cohorts controlling for age and "hormone receptor" co-variates (multivariate model). PY=person-year; HR=hazard ratio; aHR=adjusted hazard ratio.

In this multivariate model, age and hormone receptor factors were considered. On the x-axis, the age factor is represented, whereas on the y-axis, this is the logarithm of the age-adjusted risk of death that is represented.

- *Reading of the curves:*

The curves show a u-shaped relationship between risk of death and age. This means that above and below the age of 75, the risk of death increases. However, looking at the different confidence bands, we observe a great imprecision given their rather large width, which does not allow us to extrapolate the results obtained to the population of patients with breast cancer. *Figure. 5* also shows that the presence of hormone receptors results in a slightly lower risk of death than the population of patients without these hormone receptors.

And so, even considering the covariates age and hormone receptors, we see that the risk of death is still higher in the FAST cohort than in the START cohort.

- *Reading of the table:*

The event of death occurred in 11 patients in the FAST cohort and in 9 patients in the START cohort. The follow-up is 200 person-years (PY) for the FAST cohort while it is 388 PY for the START cohort. Considering these two criteria, it is possible to calculate the incidence rate of death in each group. It is equal to 5.49 and 2.32 for the FAST and START groups respectively. This means that for 100 person-years, 5 and 2 "death" events are expected, respectively.

The Hazard Ratio (HR) is the ratio of the risk of death in the FAST group to the risk of death in the START group. HR is equals to 2.54, which means that the risk of death is 2.54 times higher in the FAST group. However, when this value is adjusted for the covariates age and hormone receptors, which is the adjusted hazard ratio (aHR), the risk of death is now 3.16 times higher in the FAST group. This means that considering age and hormone receptors does not explain the difference in survival between the two groups, although it is not significant.

2.2. Comparison of progression-free survival

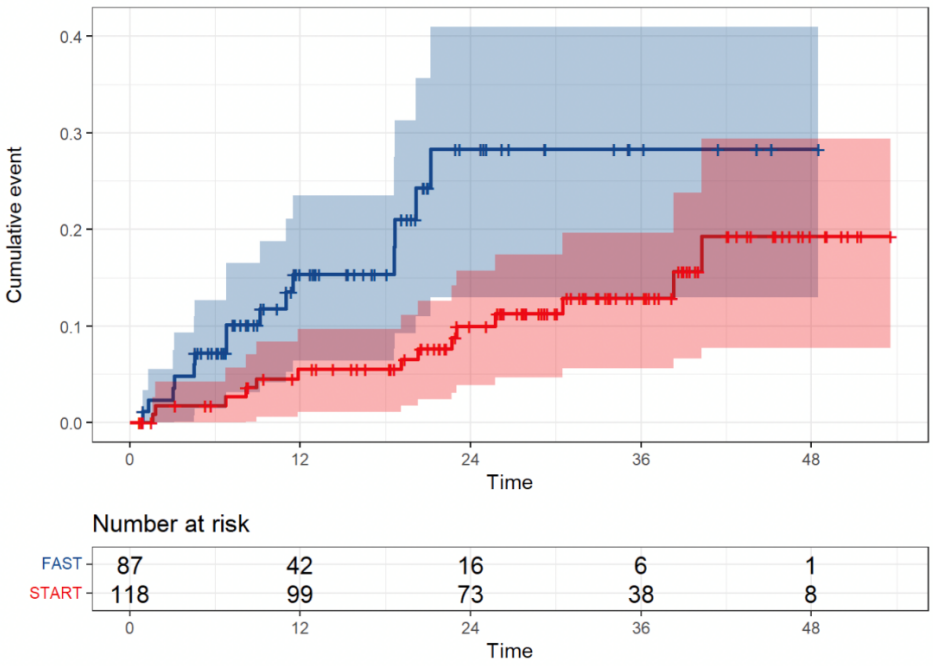
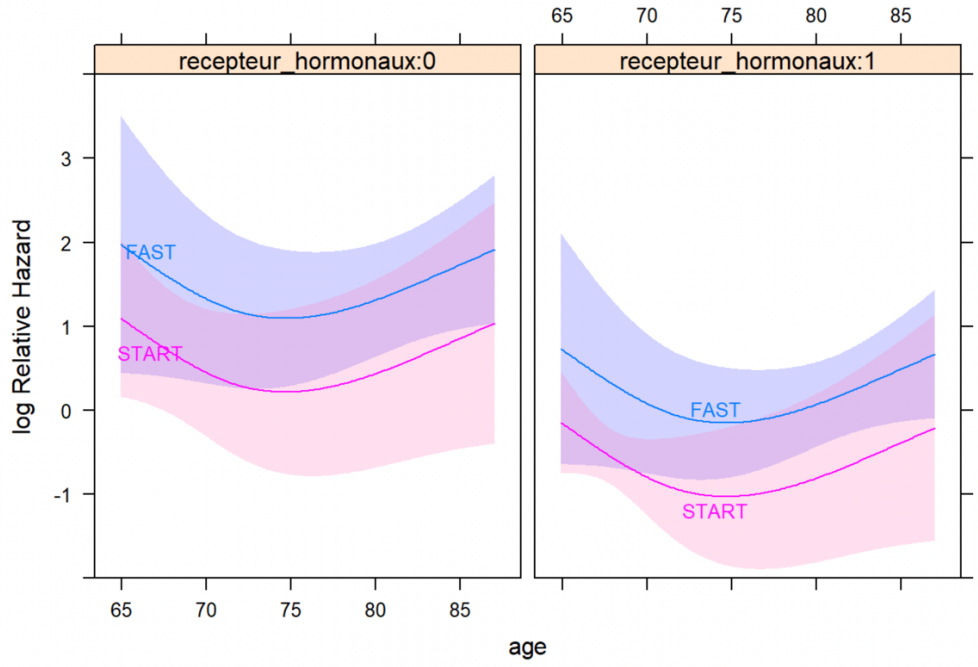


Figure 6. Progression-free Kaplan-Meier survival curves for patients treated with loco-regional radiotherapy according to the FAST and START schedules.

The progression-free survival curve can be read in the same way as the overall survival curve. This means that the upward growth always represents the occurrence of the event, represented here by either death or progression, while the vertical bar represents the loss to follow-up.

After 48 months of follow-up, progression or death was observed in 30% of patients in the FAST group and 20% in the START group. The progression-free survival curve does not change beyond the first 24 months for patients in the FAST cohort. This means that for the 16 people still being followed up after the first two years, none of them relapsed or died. This is consistent with the fact that most relapses occur within the first two years.

2.2.1. Multivariate model



Schedule	Events	PY	Rate	HR	aHR	lower	upper	*P*-value
FAST	15	109.7	13.67	2.59	2.40	0.75	7.72	0.14
START	14	275.4	5.08	*NA*	*NA*	*NA*	*NA*	*NA*

Figure 7. Comparison of progression-free survival between the FAST and START cohorts controlling for age and "hormone receptor" co-variates (multivariate model). PY=person-year; HR=hazard ratio; aHR=adjusted hazard ratio.

- *Reading of the curves:*

Reading the curves gives the same results as reading the overall survival curve, except that here the event is progression or death and not just death. However, it can be observed that the difference between the risk of progression/death adjusted for the presence of hormone receptors seems to be slightly greater between the two groups than in the overall survival analysis. Indeed, the presence of hormone receptors seems to reduce the risk of event for the START group compared to the FAST group.

- *Reading of the table:*

In the same way as in the previous analysis, the number of events and the person-year follow-up will be used to calculate the incidence rate. For the progression-free survival analysis the incidence rate is equal to 13.67 for the FAST group and 5.08 for the START group. This means that for 100 PY, it is estimated that 13 "death or progression" events will occur in the FAST group versus 5 events in the START group.

The HR, which considers the number of events, but also the time at which these events occur, is equal to 2.59, which means that the risk of progressing or dying is 2.59 higher in the FAST group. But once adjusted for covariates age and hormone receptors, this risk remains similar, and it equals to 2.40. This means that the two co-variates applied cannot explain the observed differences between the two groups.

However, as it was the case for the overall survival analysis, the confidence intervals are so wide that hypothesizing that the FAST group has a greater risk of the event is as consistent as hypothesizing that the two groups have similar risks. To refine these figures, randomized clinical trials involving large numbers of individuals are needed.

3. Comparison of toxicity

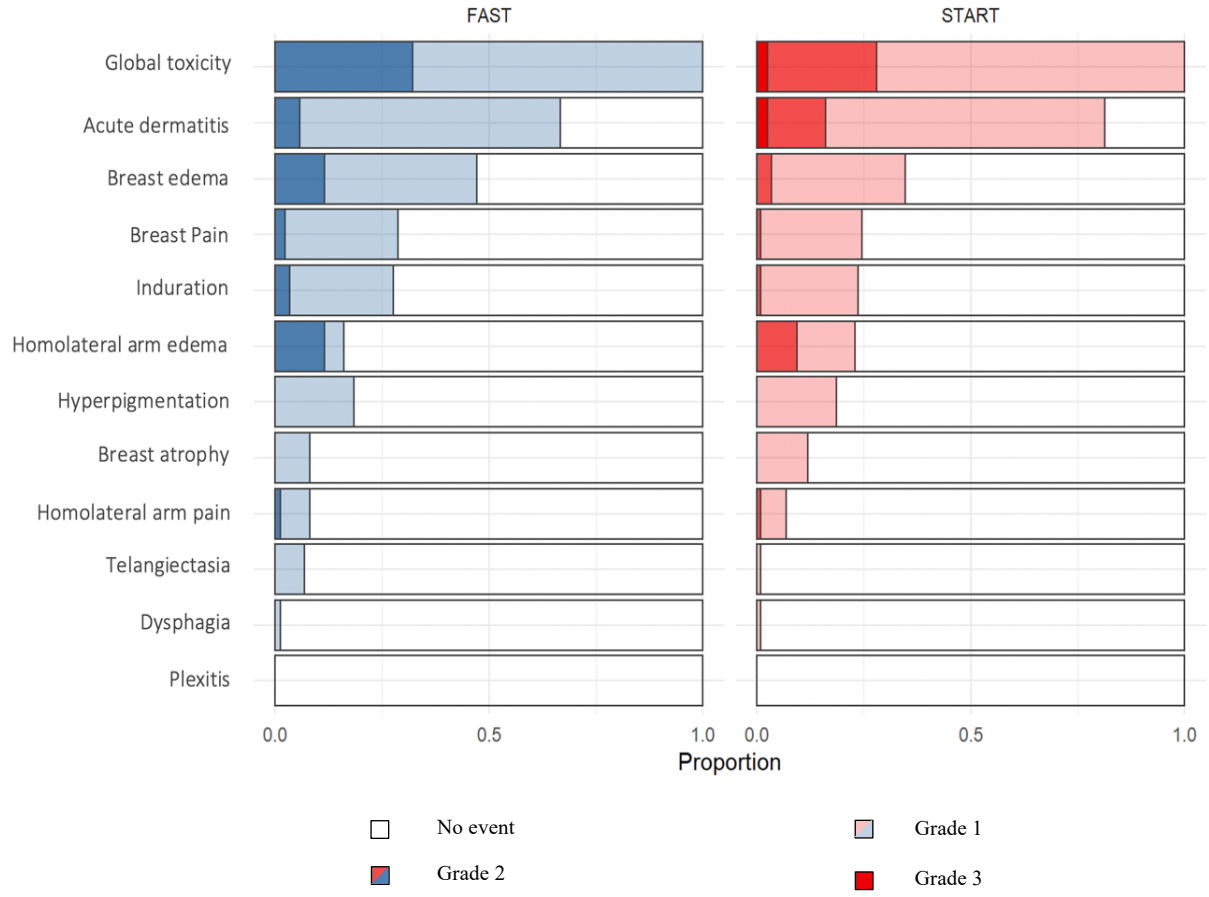


Figure 8. Proportion of toxicities occurring in the FAST and START groups.

	F0	F1	F2	F3	S0	S1	S2	S3	OR1	aOR1	Lower1	Upper1	*P*-value1	OR2	aOR2	Lower2	Upper2	*P*-value2
Global toxicity	0	59	28	0	0	85	30	3	*NA*	*NA*	*NA*	*NA*	*NA*	0.82	0.98	0.86	1.12	0.76
Acute dermatitis	29	53	5	0	22	77	16	3	2.18	1.17	1.03	1.32	0.02	3.15	1.11	1.01	1.22	0.03
Breast edema	46	31	10	0	77	37	4	0	0.60	0.88	0.76	1.01	0.07	0.27	0.93	0.86	1.00	0.04
Breast pain	62	23	2	0	89	28	1	0	0.81	0.98	0.86	1.12	0.79	*NA*	*NA*	*NA*	*NA*	*NA*
Induration	63	21	3	0	90	27	1	0	0.82	0.96	0.85	1.09	0.55	*NA*	*NA*	*NA*	*NA*	*NA*
Homolateral arm edema	73	4	10	0	91	16	11	0	1.55	1.08	0.96	1.21	0.20	0.79	0.99	0.91	1.08	0.85
Hyperpigmentation	71	16	0	0	96	22	0	0	1.02	1.02	0.91	1.15	0.68	*NA*	*NA*	*NA*	*NA*	*NA*
Breast atrophy	80	7	0	0	104	14	0	0	1.54	1.04	0.95	1.14	0.38	*NA*	*NA*	*NA*	*NA*	*NA*
Homolateral arm pain	80	6	1	0	110	7	1	0	0.83	1.00	0.93	1.08	0.94	*NA*	*NA*	*NA*	*NA*	*NA*
Telangiectasia	81	6	0	0	117	1	0	0	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Dysphagia	86	1	0	0	117	1	0	0	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Plexitis	87	0	0	0	118	0	0	0	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*

Figure 8. Proportion of toxicities occurring in the FAST and START groups (continued).

The comparison of toxicity between the two groups was performed by multivariate analysis, adjusted with the covariates: chemotherapy, axillary procedure performed, and volume irradiated. To assess toxicity, the eleven toxicities as well as the global toxicity were analyzed, considering the grade at which they occurred. Global toxicity refers to the occurrence of any of the eleven toxicities at any time.

Looking at the graph in *Figure. 8,* all the patients included in this retrospective analysis had at least one of the eleven toxicities. For about 66% of the patients, it was grade 1, for about 33% it was grade 2, and a very small proportion was grade 3 toxicities. It can also be seen that the proportion of patients with breast edema, breast pain, induration, and telangiectasia appear to be slightly higher in the FAST cohort. In addition, the higher grades also appear to be more pronounced in this group, although these toxicities are generally temporary and reversible. However, no grade 3 toxicities were observed in this cohort.

The table in *Figure. 8* shows the proportion of events by grade and cohort. Columns F0, F1, F2, and F3 correspond to the proportion of events for grades ranging from 0 to 3 for the FAST cohort. Similarly, columns S0 through S3 correspond to the proportion of toxicities for each grade of the START cohort. For example, we note that the proportion of patients with acute dermatitis is higher in the START group. However, the analysis of acute dermatitis is somewhat biased since it is a toxicity that usually appears within the first week after irradiation, and most elderly patients are not seen within this first week. Therefore, a large number of dermatitis may not have been identified.

In the table, the odds ratio can also be found, which corresponds to the risk of occurrence of a side effect of grade 1 or higher in the FAST cohort compared to the START. Thus, if we take acute dermatitis as an example, an OR1 of 2.18 means that the risk of seeing a side effect of grade 1 or higher appear to be 2.18 times higher for the START group than for the FAST group. However, OR1 corresponds to the univariate analysis, and is therefore purely descriptive because it does not consider the different covariates. Next to OR1, we find the adjusted Odds ratio (aOR) which is equal to 1.17. This means that once the three covariates are adjusted, the risk of observing a grade 1 or higher event in the START group is only 17% higher than in the FAST group. Lower 1 and upper 1 refer to the confidence interval.

Looking at the p-value for the acute dermatitis event, there is a significant difference between the two cohorts but this, as mentioned above, can be explained by the absence of a follow-up visit around the first week for the older patients.

The OR2 is the risk of developing a grade 2 or higher event between the two cohorts. For acute dermatitis, OR2 is equal to 3.15 which means that the risk of developing a grade 2 or higher dermatitis is 3.15 times higher in the START group compared to the FAST group. aOR2, once adjusted for covariates, is almost equal to 1 which means that once the three covariates are considered, the risk of developing a grade 2 or higher event is not higher in the cohort START compared to the FAST cohort. Again, there is a significant difference between the two cohorts, but this is again explained by the lack of visits in the first week after RT.

Overall, in terms of observed toxicity, there is no great difference between the two cohorts and the loco-regional irradiation with either the FAST or the START schedule can be considered equivalent. To reinforce this simplified analysis, a second complex analysis was performed but will not be presented in this master thesis. This complex analysis takes into consideration the time with which the event occurs; death as a competitive risk that prevents the event from

occurring; and the transient nature of some side effects. However, the results of this second analysis led to the same conclusion as the present analysis and therefore reinforce the idea that loco-regional RT administered in 5 fractions or 15 fractions can be considered equivalent.

4. Sensitivity analysis

The sensitivity analysis in which all missing data had to be excluded could not be performed because this represented between 75% and 99% of the dataset included in the analysis. This is because physicians, in their practice, generally only describe the side effects they observe, and all unobserved events are not mentioned in the medical records. However, the more complex toxicity analysis that was not presented leads to the same conclusion as the toxicity analysis described above. This therefore reinforces the overall message of this work.

5. Subsidiary questions

5.1. Relationship between risk factors and global toxicity (after adjustment for chemotherapy, axillary procedure, and irradiated volume)

	Sample size	Grade 1 (n=144)	Grade 2 or higher (n=61)	*P* value
Age	205	72	72	0.830
ECOG				
0	204	0.36	0.31	0.663
1		0.57	0.62	
2		0.05	0.07	
3		0.01	0.00	
Old tobacco	205	0.14	0.13	0.883
Active tobacco	205	0.10	0.07	0.464
BMI	183	27.100	28.800	0.014
Diabetes	205	0.16	0.18	0.717
Neodjuvant treatments				
None	205	0.67	0.59	0.300
Chemotherapy		0.24	0.23	
Hormonotherapy		0.09	0.15	
Other		0.01	0.03	
Adjuvant treatments				
None	205	0.13	0.20	0.333
Chemotherapy		0.06	0.07	
Hormonotherapy		0.78	0.67	
Other		0.03	0.07	
Concomitant treatments	205	0.06	0.02	0.161
Axillary procedure				
None	205	0.01	0.10	0.002
Dissection		0.72	0.74	
SLN		0.27	0.16	
Hormone receptors	205	0.81	0.77	0.570
Breast size				
No information	205	0.72	0.51	0.041
A		0.01	0.02	
B		0.06	0.16	
C		0.13	0.23	
D		0.06	0.05	
E		0.01	0.03	
Irradiated volume (cm3)	205	62.50	60.00	0.765
IMC irradiation	205	0.42	0.38	0.597
Irradiation of area 1	205	0.51	0.56	0.569

Table 10. Proportion of risk factors by grade of toxicity. SLN= Sentinel lymph node; IMC=Internal mammary chain.

This analysis assessed the potential association between the occurrence of grade 1 or grade 2 or higher events with different risk factors associated with breast cancer.

No significant differences were observed when comparing the frequency of occurrence of the different grades with the majority of risk factors (age, ECOG performance status, smoking, diabetes, adjuvant/neoadjuvant or concomitant therapy, hormone receptors or radiation-related factors). Conversely, a significant difference ($P < 0.05$) could be observed for BMI, axillary procedure, and breast size factors. However, for the "breast size" factor, no conclusion can be drawn due to the large proportion of missing data.

For the BMI factor, this could mean that patients with a high BMI could have a higher risk of developing high-grade toxicities compared to patients with a low BMI. For the axillary procedure, patients who received no intervention appear to be more likely to develop high-grade toxicities (Grade 2 or higher). Conversely, patients who receive the SLN appear to be more likely to have low-grade toxicities (Grade 1). This means that performing the sentinel lymph node biopsy alone could reduce the risk of developing a high-grade toxicity. Axillary dissection, however, did not appear to impact the grade of events.

However, to really conclude that these two factors impact the grade of toxicity, further studies with larger numbers of subjects need to be conducted.

5.2. Comparison of the proportions of patients with recurrence among those who died according to the schedule received

	FAST (N=11)	START (N=9)	*P* value
Recurrence	0.64	0.67	0.888

Table 11. Proportion of recurrence among deceased patients for the FAST and START cohorts.

Firstly, it can be observed that of the 205 patients included in the analysis, approximately 10% of deaths occurred. Of these deaths, about 65% had a recurrence. However, no significant difference can be observed when comparing the proportion of patients who died and had recurrences in the FAST group with the START group.

5.3. Median follow-up

	FAST (N=76)	START (N=109)	Combined (N=185)	*P*-value
OS time	19.8	34.1	28.9	<0.001

Table 12. follow-up time of patients in the FAST and START cohorts and overall follow-up time when combined.

The follow-up time is the time between the date of the first radiotherapy session and the date of last news. The latter is usually the last date found in the patient's medical record but can also be the date of death if the patient has died.

There is a significant difference between the two groups and patients in the START group generally have twice the length of follow-up as patients in the FAST group. This median follow-up of less than two years for the FAST cohort is because loco-regional RT according to this schedule has only been offered to patients over 65 years of age since the COVID-19 pandemic.

Conclusion

Since its inception, breast RT has continued to evolve, offering shorter and shorter schedules using lower and lower total doses. Numerous clinical trials, such as the START-B, FAST, and FAST-Forward trials, have demonstrated that these new schedules can be considered non-inferior to the standard of care and have also allowed for the continuous updating of treatment schedules. At present, moderate hypofractionated RT (15 fractions of 2.67 Gy) is considered the current standard of care. However, five-fraction hypofractionated RT can also be used for tumor bed, whole breast or chest wall irradiation, but has not yet been validated for lymph node irradiation for safety reasons.

At the SE hospital, loco-regional RT according to the FAST schedule had been offered for some years to patients over 75 years of age. But the arrival of the COVID-19 pandemic was an opportunity for the SE hospital to expand the population eligible for this treatment schedule. This decision resulted in fewer patients in the hospital in order to meet the containment measures taken during the course of the year 2020.

The present retrospective analysis, which attempted to demonstrate that the toxicity observed with loco-regional radiotherapy according to the FAST schedule is not greater than that observed with loco-regional radiotherapy according to the 15-fraction schedule, succeeded in meeting its primary objective. Indeed, comparison of overall survival, progression-free survival, and toxicity showed no significant differences between the two treatment schedules. The results presented in this analysis also allow us to observe a potential causal relationship between the grade severity of an observed side effect and BMI or axillary procedure performed on a specific patient. Thus, having a high BMI and not receiving an axillary procedure would increase the risk of developing higher grade toxicities.

Among the limitations of our analysis, the comparison of toxicity in two different groups, each composed of patients of different ages, can be cited. Although attempts were made to minimize this analytical bias by including only START patients over 65 years of age, patients in the FAST cohort were on average 10 years older than patients in the START group.

Another limitation of this analysis may be due to the loss of sight that may be associated with some patients. The first reason for which loss of sight may be observed is that all radiotherapy sessions, regardless of the site included in this analysis, are conducted at SE hospital. It happens that some patients, after having completed the radiotherapy, return to their original site (CHR Namur, CHU UCL Godinne, CHU UCL Dinant, CHR Auvelais, St-Luc Bouge) for their follow-up sessions. The accessibility of these data, which are therefore carried out on different sites, is therefore not necessarily guaranteed. The second reason that could explain a loss of sight is that it happens that some patients, for unknown reasons, do not show up for certain visits. This can lead to a gap in the medical records of these patients as well as a gap in our analysis at certain key dates.

The short follow-up time represents another analytical limitation to our work. Indeed, the longest follow-ups that we could observe are patients who were treated in 2018. However, it is clear that the occurrence of adverse events may be longer term, i.e., beyond this period. This analysis will therefore present the results of short/medium term lymph node toxicity.

Thus, in order to validate the FAST radiotherapy schedule in the axillary area, the results presented in this analysis must be verified by large-scale randomized controlled trials.

The first study that might provide answers is the Yo-Hai5 study, a randomized controlled trial conducted by the University Hospital of Ghent (UZ Ghent). This randomized clinical is based on the results of a matched case analysis performed in UZ Ghent and published in 2020. [76] In this analysis, 71 patients with a mean age of 73 years, and previously treated with BCS, were included for adjuvant RT according to the FAST schedule. Node-positive patients could be included in this study. If indicated, some patients could receive SIB of 6.2 - 6.5 Gy, or loco-regional radiotherapy in case of positive nodes. The latter consisted in irradiating the lymph nodes with a dose of 5.4 Gy/fraction, for a total of 5 fractions, and was performed in 28% of cases. The control group, with which this cohort was compared, consisted of 71 patients from the same hospital, but whose breast cancer had been treated with adjuvant RT in 15 fractions. The aim of this analysis was to compare different toxicities (retraction, breast edema, telangiectasia, fibrosis out and in the tumor bed, etc.) between these two groups, 24 months after the end of RT. The occurrence of breast edema, fibrosis in the tumor bed and pigmentation was comparable between the two groups. Breast retraction, telangiectasia and pain were significantly ($P< 0.05$) less observed in the 5-fraction group, whereas the occurrence of fibrosis was higher in this group.

To try to substantiate these results prospectively, UZ Ghent has launched the Yo-Hai5 study, still in the recruitment phase, which will attempt to compare 15-fraction lymph node irradiation with 5-fraction lymph node irradiation (delivered over ten days) on a total of 488 patients. The primary objective of this study, conducted in collaboration with SE Hospital, is to evaluate breast shrinkage over a two-year period. As secondary objectives, the Yo-Hai5 study will attempt to evaluate several parameters such as acute and late toxicity, loco-regional and distant tumor control, and patient reported outcomes.

However, even though our study remains a retrospective analysis of a small number of patients, and that we will have to wait a few more years to obtain the results of Yo-Hai5, the results presented in this study remain very promising in many respects. First, suggesting that loco-regional radiotherapy according to the FAST schedule is equivalent to the START schedule would allow many hospitals to reduce the number of sessions associated with loco-regional radiotherapy to benefit both the hospital and the patients. From the patient's point of view, it would allow him/her to reduce the number of appointments and thus lighten the physical and emotional burden of RT sessions. From the hospital's point of view, it would allow a reduction in costs since the availability of the machines is increased and the schedule of the sessions is lightened. [77] If it turns out that lymph node irradiation with the FAST schedule is not inferior to the START schedule, hospitals could start offering this treatment schedule to younger patients, as long as patient safety is still ensured. This would further reduce the costs of the hospital associated with the radiotherapy service.

On a larger scale, validation of axillary radiotherapy with the FAST schedule could also be beneficial for developing countries. These countries are areas of the world where the number of RT machines and physicians is somewhat limited. Being able to treat patients with the FAST schedule would allow them to treat a larger number of patients than they are currently able to.

In conclusion, the results presented in this analysis are promising, although they need to be confirmed by randomized clinical trials such as the Yo-Hai5 trial.

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Supplemental information

Annex. 1

Description

Record ID	_____
Information patient	
Nom	_____
Prénom	_____
Date de naissance	_____ (Y-M-D)
Date de diagnostic	_____ (Y-M-D)
Site	◯ CMSE ◯ Godinne ◯ Dinant ◯ CHR Namur ◯ Saint-Luc Bouge ◯ CHR Auvelais
Facteurs de risque	
Tabac ancien	◯ Yes ◯ No
Tabac actif	◯ Yes ◯ No
Diabète	◯ Yes ◯ No
Echelle de statut de performance ECOG	◯ Patient entièrement actif, capable d'effectuer les mêmes activités pré-morbides sans restriction ◯ Patient restreint dans ses activités physiques, mais ambulatoires et capables d'effectuer des activités légères ou sédentaires ◯ Patient ambulatoire et capable de s'occuper de lui, mais incapable d'effectuer des activités debout plus de la moitié de la journée ◯ Patient capable de soins limités, alité ou au fauteuil plus de la moitié de la journée ◯ Patient complètement handicapé, ne pouvant s'occuper de lui. Totalement alité ou confiné au fauteuil
Taille	_____ (cm)

Masse	(kg)
IMC au diagnostic	
Bonnet	
Age au diagnostic	

Diagnostic

Radiothérapie	
Latéralité (N+) gauche	◯ Yes ◯ No
Latéralité (N+) droite	◯ Yes ◯ No
Radiothérapie du sein controlatéral	◯ Yes ◯ No
Moment de la radiothérapie du sein controlatéral	◯ Concomitant ◯ Antécédent
QSI _____ QSM _____ QSE _____ QII _____ QIM _____ QIE _____ RM _____ QEE _____ QEI _____ Central _____ Sein entier _____ Uqext _____ Récidive axillaire en première présentation _____	
CCI _____ CLI _____ NST _____ DCIS _____ LCIS _____	
Autres histologies	◯ Yes ◯ No
Grade histologique	◯ Grade 0 ◯ Grade 1 ◯ Grade 2 ◯ Grade 3
Récepteur hormonaux	◯ Yes ◯ No
Triple négatif	◯ Yes ◯ No

TNM preop	
T	◯ 0 ◯ I ◯ Is ◯ II ◯ III ◯ IV ◯ x

N	◯ 0 ◯ I ◯ II ◯ III ◯ x
M	◯ 0 ◯ I ◯ x

Traitement

Traitement néo adjuvant	◯ Aucun ◯ Chimiothérapie ◯ Hormonaux ◯ Autre
Précisez le type de traitement néo adjuvant	_____
Chirurgie	◯ Pas de chirurgie ◯ Tumorectomie ◯ Mammectomie
Geste axillaire	◯ Pas de geste ◯ Curage ◯ GSN
Nombre de ganglions analysés	_____
Nombre de ganglions prélevés lors du curage	_____
Marge	◯ R0 pour marge négative ◯ R1 pour marge positive
Traitement systémique post-chirurgie	◯ Yes ◯ No
Précisez le type de traitement post-chirurgie	_____

Post-opération

T	◯ 0 ◯ I ◯ Is ◯ II ◯ III ◯ IV ◯ x
N	◯ 0 ◯ I ◯ II ◯ III ◯ x
M	◯ 0 ◯ I ◯ x
Mobilité du bras	◯ Normale ◯ Limitée

Lymphoedème du bras homolatéral	◯ No ◯ Yes ◯ NA
Date de début de la radiothérapie	_____ (Y-M-D)
Date de fin de la radiothérapie	_____
Protocole	_____
Boost	◯ Yes ◯ No
Fractionnement du boost	_____
Traitement concomitant	◯ Yes ◯ No
Précisez le traitement concomitant	_____
Traitement adjuvant	◯ Aucun ◯ Chimiothérapie ◯ Hormonaux ◯ Autre
Précisez le traitement adjuvant	_____

Site ganglionnaire irradié

CMI _____
I _____
II _____
III _____
IV _____

Toxicité

Date de visite _____
(Y-M-D)

Dermatite aiguë _____
Dysphagie _____
Douleur du sein _____
Oedème du sein _____
Atrophie mammaire _____
Hyperpigmentation _____
Induration _____
Telangiectasie _____
Oedème du bras homolatéral _____
Plexite _____
Douleur du bras homolatéral _____

Autres toxicités ◯ Yes ◯ No

Précisez l'autre toxicité _____

Survie

Date de la dernière visite oncologique	_____ (Y-M-D)
Follow-up visite	_____ (mois)
Récidive	◯ Yes ◯ No
Date de récidive locale	_____
Date de récidive ganglionnaire	_____
Date de récidive controlatérale	_____
Date de récidive à distance	_____
Date de dernière nouvelle ou date de décès	_____ (Y-M-D)
Follow-up (vivant ou décès)	_____ (mois)
Décès	◯ Yes ◯ No

Annex. 2

1. Description

- If the day is not specified for any date and only the month is known, the first day of the month is taken by default.
- Date of diagnosis: take the date of cytopunction if indicated, otherwise take the date of magnetic resonance imaging or transfer to the breast clinic.
- ECOG performance index: take the one known before the diagnosis and not after.
- Height and weight: Go to the anesthesiology section and take the one around the diagnosis.

2. Diagnostic

- Always take the most recent histology and grade before starting treatment.
- If more than one TNM is indicated, take the one with the highest number.
- In case of new cancers, take the characteristics of the current cancer and not the previous one.

3. Treatment

- Axillary gesture: always take the most recent one. If a GSN was removed and a curage was performed afterwards, encode curage in the database.
- Arm mobility: if physiotherapy is needed, it means that the mobility is limited. If it is indicated acceptable, it is thus considered limited.
- If breast tumor in both breasts, we take the information of the breast that received the RT and if both breasts, we select the breast that received the highest boost dose.
- For the start and end dates of the RT, we take the dates written in the free text after the last RT session.

4. Toxicity

- If no information is mentioned about a toxicity for a particular visit, "NA" is indicated by default.
- As soon as a visit is indicated in the medical record, it is added to the database even if it means 10 visits for the same patient. It is better to have too much information than not enough.
- Excellent skin tolerance = acute demartite 0.
- If the toxicity is between two grades, the higher grade is taken by default.
- Breast edema: if the patient has had physiotherapy, it is automatically a grade 2.

5. Survival

- Date of last ontology visit: any visit during which toxicity was assessed, even if it was not necessarily an oncology visit.
- Since "retractile scarring" is often mentioned in medical records, it was decided to indicate it in the "other toxicity" section