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DOTTORATO DI RICERCA IN MEDICINA SPERIMENTALE

DEVELOPMENT OF A COMPREHENSIVE PLATFORM FOR TREATMENT OPTIMIZATION IN BREAST RADIOTHERAPY: RESPIRATORY GATING, HEART SPARING, EARLY DETECTION OF CARDIAC DAMAGE.

Relatore:

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1. INTRODUCTION

In the present work, I explored innovative radiotherapy (RT) techniques for treatment optimization in breast cancer patients to spare the heart from radiation exposure and obtain a better and safer treatment strategy.

I have implemented a moderate deep inspiration breast hold (DIBH) radiation technique and prospectively collected data on this treatment to assess the efficacy and advantage of this procedure in left breast cancer treatment.

This study applied a model-based approach to data by calculating the normal tissue complication probability (NTCP) to determine the probability of damage induced on normal tissues for given radiation doses to OAR in terms of cardiac mortality probability.

The second and third parts of the thesis analyzed an alternative heart-sparing technique and a new cardiac damage detection approach. Thus, I described two ongoing trials in which I am our site PI and co-investigator, the first is about cardiac sparing technique for even more selected patients, and the second is about early detection of cardiotoxicity.

In the last part, I introduced a future perspective, with my project-approved proposal on a neoadjuvant RT, a new potential cardiac sparing approach, and an unmet need in our clinical practice.

2. BACKGROUND

Breast cancer is the most common cancer among women. The modern post-surgery treatment with chemotherapy, immunotherapy, radiation and hormone therapy has improved the overall 5-years survival drastically. (1)

Systemic therapy is an essential part of treatment for preventing recurrence in many patients with breast cancer. It includes hormonal-, chemo- and/or biological therapy. Anthracycline-based regimens are one of the most effective according to the stage, tumor grade, molecular subtypes, genomic risk score and patient's preference. Moreover, 20% of breast cancers have ErbB-2 protein overexpression or ErbB-2 gene amplification. These patients benefit from ErbB-2-targeted therapy. (1)

Lumpectomy followed by whole-breast radiation therapy is the standard of care for the treatment of early-stage breast cancer (BC) in order to decrease the risk of disease recurrence and reducing the risk for breast cancer death.(2) Locoregional radiotherapy(RT) is well known to improve local control and overall survival in patients treated with breast conserving therapy (BCT) (3–8).

Part of this gain is counterbalanced by the risk of mortality and morbidity from cardiovascular damage and dysfunction as a result of cardiac exposure to post-surgery treatments. With advances in cancer diagnosis and management techniques, patients are early diagnosed, live longer, and are, therefore, at increased risk of developing long-term complications from the treatment. (9)

Several chemotherapeutic agents (e.g. anthracyclines, trastuzumab) are known to have cardiotoxic effects.(10) Cardiovascular complications from cancer therapy are a very heterogeneous group e.g. myocardial dysfunction, heart

failure (HF), coronary artery disease, valvular disease, arrhythmias, arterial hypertension, etc. One of the most worrisome adverse effects is ventricular dysfunction and heart failure. While the incidence of overt heart failure is less than 5% typically, subclinical left ventricular (LV) dysfunction, defined by a threshold change in LV ejection fraction (LVEF), may be seen in up to 42% of patients with cancer in selected treatment groups. (11–13)

The development of LV dysfunction is associated with poor prognosis and contributes to long-term cardiovascular morbidity and mortality. (14–16)

Cardiotoxicity from breast cancer treatment is the main mortality reason after malignancy in these patients. (17)

It varies among studies and so does the definition of cardiotoxicity. American Society of Echocardiography and European Association of Cardiovascular Imaging Expert Consensus defines cardiotoxicity as a decline of left ventricular ejection fraction (LVEF) ≥10% points with a final LVEF <53%. (18,19)

Echocardiography (ECHO) is currently the standard method for detecting cardiotoxicity, usually by monitoring serial LVEF. Current guidelines suggest ECHO at baseline before potentially cardiotoxic treatment, after the end of anthracycline therapy/before the start of trastuzumab treatment and every three months during trastuzumab treatment.

Radiation-induced cardiotoxicity (RICT) usually develops years after RT, and most of the time it consists of interstitial myocardial fibrosis. Also, RT may be associated with a higher incidence of ischemic heart disease through the development of severe atherosclerotic and non-atherosclerotic disease, complicated by plaque rupture and thrombosis, and potentially with coronary spasm. (18)

The spectrum of RICT, in fact, includes coronary heart disease (prevalence up to 85%), pericardial disease with a prevalence up to 6 – 30% (acute pericarditis, delayed pericarditis, pericardial effusion, and constrictive pericarditis), congestive heart failure, valvular heart disease (prevalence at 10 years: 26% AI, 39% MR, 16% TR and 7% PR

At 20 years: 60% AI, 16% AS, 52% MR, 26% TR, 12% PR), cardiomyopathy (prevalence up to 10%), and arrhythmias (prevalence up to 5%). Vascular injury and myocardial damage from RT can be silent, and in about a half of asymptomatic patients, new myocardial perfusion defects can develop.(20)

More specifically, Coronary Artery Disease usually occurs 10 years after radiation therapy, it is due to epicardial coronary arteries and microcirculatory damage, and sustained inflammation. Involves the left main artery, ostial left anterior descendent coronary artery (LAD) and right coronary artery. Lesions are longer, concentric, and tubular.

Valvular heart disease is due to diffuse fibrosis of the valvular cusps or leaflets, with or without calcification. It consists in an initial regurgitation related to valve retraction; later stenosis related to thickening/calcification.(21)

Cardiomyopathy is due to increased fibrosis in all three layers of the ventricular walls (epicardium, myocardium, and endocardium). May lead to restrictive cardiomyopathy, and rarely to systolic dysfunction.(21)

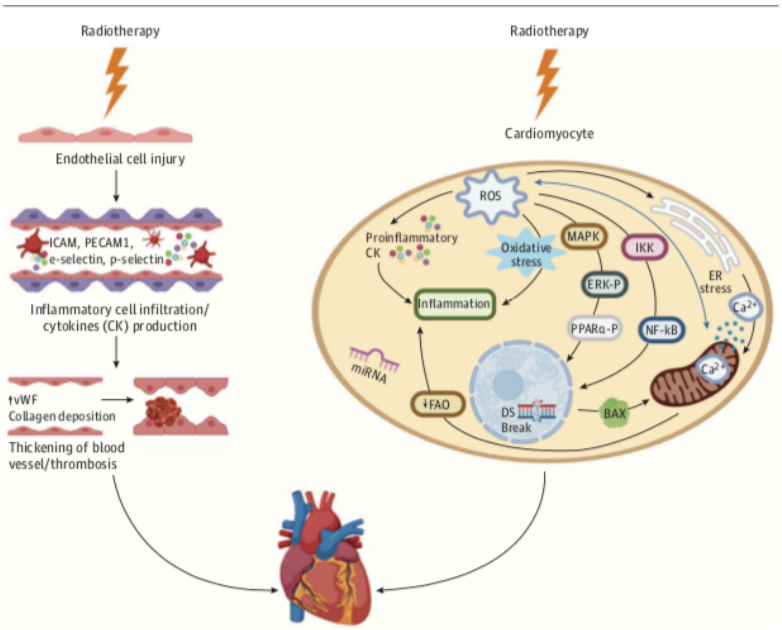


Fig. 1 Overview of Putative Pathogenesis of Radiation-Induced Heart Disease. (62)

Cardiac magnetic resonance (CMR) is the most accurate methodology for the evaluation of volumes and function of heart chambers. Additionally, it is exquisitely capable of providing myocardial tissue characterization, including specifically the presence and extension of myocardial edema and fibrosis.(21)

Serial CMR imaging in women treated for breast cancer with anthracycline-based chemotherapy showed a reduction in LVEF 12 to 24 months after initiating therapy. Few recent studies have suggested that LVEF could start to decline earlier, but the prognostic implications of these early changes are not yet known.

Moreover, breast cancer patients, who receive RT, have an increased risk for acute asymptomatic pericardial effusion, which can also be distinguished by CMR.(22)

CMR is the most sensitive and reproducible measure of LVEF.

Radiotherapy treatment of left-sided breast cancers patients, treated by chemo, results in increased risks of cardiac diseases and ischemic heart events.

Darby et al. (23,24) metanalysis evidenced that there is no “safe” radiotherapy dose to the heart and reported that an increase of 1 Gy to the mean dose to the heart results in a 7.4% relative increase in the risks of major coronary events. This metanalysis also confirmed that RICT begins in the first few years after treatment. (3,23–29) These findings suggest that a tailored RT treatment could be beneficial in some cases, specifically in those patients who are at increased risk of developing a heart disfunction.

Due to these concerns, various strategies to reduce heart dose in patients with left-side breast cancer have been studied, such as the use of a three-dimensional conformal radiotherapy heart block, intensity-modulated radiotherapy(IMRT), lateral decubitus position (30), prone breast technique (31–33), and respiratory gating (34–36).

The increasing use of advanced radiotherapy techniques, IMRT, IGRT, VMAT, allows to conform radiation dose to the target and to avoid or reduce exposure of healthy tissue by limiting the side effects, with the cost of increased low-dose radiation to the organ at risks. Furthermore the spread use of systemic therapies (chemotherapy, hormonal therapy, targeted drugs, and immunotherapy) in the treatment of breast cancer patients, increases the need to deepen the relationship between these therapies, the target dose and the possible development of late complications and underline the needed for a more tailored planification, contouring, innovative treatment (fractions, doses, and timing) and monitoring guidelines.

The aim of my project is to create a model-based approach for cardiac sparing in left-side breast cancer patients adjuvant RT. It will allow to strictly select patients at higher risk of develop treatment-related cardiotoxicity.

3. PRELIMINARY DATA.

3.1 TREATMENT-RELATED CARDIOTOXICITY

- The incidence of cardiotoxicity from trastuzumab is 1,7-20,1% and from anthracycline 3-48%. (18)

The actual incidence of radiation-induced cardiotoxicity is difficult to evaluate. Some studies have found a relative risk of fatal cardiovascular events between 1 and 2.2 in patients with breast cancer. Studies have suggested a synergistic effect on cardiac risk with left breast RT and cardiotoxic chemotherapy. Systolic dysfunction is generally observed when RT is combined with anthracyclines. (37)

The latency of RT-associated cardiac effects ranges from months, for subclinical disorders such as pericarditis, to decades, for clinical diseases such as coronary artery disease (38)

- Rates of major coronary events increase linearly with mean dose to heart by 7.4% per Gray, no threshold. (25) These results on radiation-induced ischemic heart disease were confirmed in a more recent study of breast cancer patients treated with three-dimensional conformal radiation therapy (3D-CRT). (39) Heart damage debut within the first 5 years after RT, continuing into the third decade after RT. (25) Women with pre-existing cardiac risk factors have a higher absolute increase in risk, than other women. (25)

Incidental radiation exposure to the heart during breast radiation therapy (RT) increases the risk of heart disease. There is a dose-response relationship between radiation and acute coronary events. (25,39)

Dose distribution in the heart is not homogeneous; highest cardiac radiation doses can be observed in the apex and the apical-anterior segment, the highest doses are likely to be delivered to the anterior heart, including LAD. (40)

RT-induced LAD disease can contribute to atherosclerotic lesions, which are more extensive than the ones that are typical for carotid bifurcation stenosis. The RT-induced atherosclerotic plaques are often located in long segments of the carotid artery, posing an increased risk for stroke. (20)

- The absolute increase in risk for heart morbidity for a left-sided versus right-sided patient was in the order of 0.4% for acute myocardial infarction, 0.3% for angina, 0.1% for acute pericarditis, 0.2% for valvular heart disease and 0.8% for all heart diseases. The predominance of ischemic heart disease indicates that the coronary arteries and in particular the LAD be a critical structure for the development of late radiation-induced heart morbidity. (41)

Although there was a considerable decrease in doses to the heart over the past few years, radiation-induced heart disease is still a concern due to the improvement in breast cancer patient's survival. (40)

3.2 NTCP MODELS.

- Modern radiotherapy techniques allow unprecedented levels of accuracy, precision, and conformity in target localization, patient setup, and dose delivery thanks to the aid of many different imaging modalities. Contemporary treatment strategies almost always involve delivering higher doses to the targeted tissue with the aim to improve tumor control, but before such approaches can be safely implemented an accurate and reliable knowledge on toxic effects on surrounding tissues has to be secured. With the aim of normal tissue preservation, many models (NTCP) have been proposed to describe radiation-

induced complications mostly focusing on late complications which, being irreversible, are considered to have the highest impact on the patient quality of life. (42)

- Studies have been shown that RT of left breast may increase the normal tissue complications such as cardiovascular disease, and also heart morbidity and mortality. Therefore, some radiobiological evaluation tool, as NTCP are existed which estimate the RT methods.

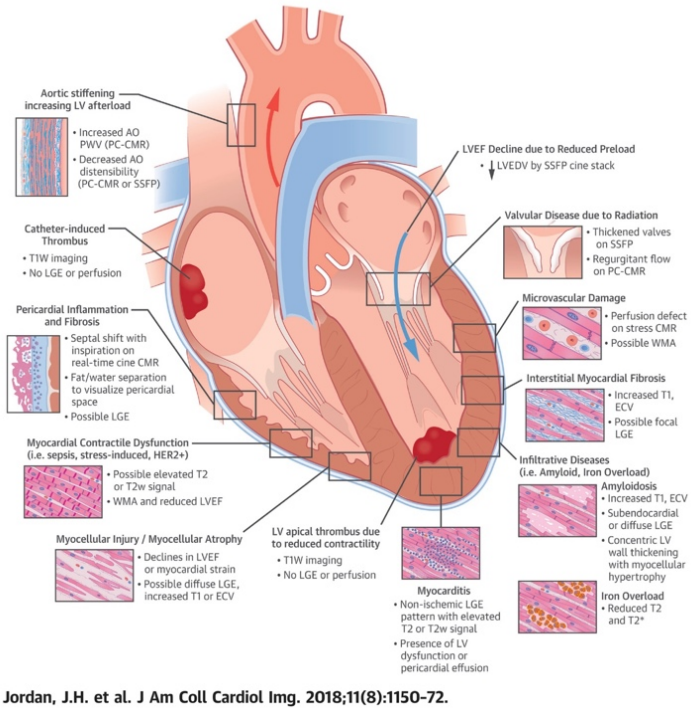
One of the widely used is Lyman-Kutcher-Burman NTCP logistic, and multivariable logistic models (MVL), besides NTCP Model of Heart Valve Dysfunction NTCP model of Coronary stenosis Darby model's and the most recently Van den Boogaard model's which including the volume of the left ventricle receiving 5 Gy (LV-V5) that provide improved prediction of acute cardiac events in patients with breast cancer undergoing radiotherapy have been validated. (39)

3.3 CARDIAC IMAGING

- Echocardiography (ECHO) is currently the standard method for detecting cardiotoxicity, usually by monitoring serial LVEF. In particular, in HER2+ patients treated by trastuzumab. (43) The use of global longitudinal strain (GLS) by speckle tracking echocardiography is strongly recommended because of its feasibility and biological reproducibility. GLS is changing earlier than LVEF, corresponding to myocardial deformation, so this technique could diagnose cardiotoxicity earlier, during subclinical myocardial dysfunction phase. (19) Current guidelines suggest ECHO at baseline before potentially cardiotoxic treatment, after the end of anthracycline therapy/before the start of trastuzumab treatment and every 3 months during trastuzumab treatment.

- Current preliminary experimental data indicate that the decline in contractile function is preceded by CMR evidence of myocardial edema with T2 sequences and T2 mapping. (44)

Cardiac magnetic resonance (CMR) is the most accurate methodology for the evaluation of volumes and function of heart chambers. By CMR it is possible to distinguish asymptomatic pericardial effusion. Finally, CMR is the most sensitive and reproducible measure of LVEF. (22) CMR may differentiate the etiology of a newly identified abnormal myocardial mass, evaluate a pericardial disease process, or determine the cause of a valve leaflet abnormality during the same examination when LVEF is measured. (45)



Jordan, J.H. et al. J Am Coll Cardiol Img. 2018;11(8):1150-72.

Fig. 2 Adverse Cardiovascular Effects Related to Cancer Treatment and Key Cardiovascular Magnetic Resonance Features (45)

3.4 HYPOFRACTIONATED RT

The standard recommended breast cancer radiation dose is 50 Gy in 25 fractions of 2 Gy, five times per weeks, with a boost of 10 to 16 Gy to the tumor bed (46). This fractionation of radiation dose lasts 6 weeks.

Nowadays, the use of hypofractionated schemes has become increasingly common, achieving a shorter treatment course, lower treatment costs, and shorter radiation therapy waiting times (46-48) and it is now a new standard treatment.

Several trials in the literature demonstrated the efficacy and safe of hypofractionated radiation therapy (49-50). The START A and B trials (51,52) and the Canadian Trial (46) showed comparable results between the hypofractionated schemes and the conventional one.

Finally, the UK FAST trial, a randomized trial, compared two different regimens of hypofractionated radiotherapy (28.5 Gy in five fractions and 30 Gy in five fractions over 5 weeks) versus conventional radiotherapy, showing comparable outcomes (53).

4. DEEP INSPIRATION BREATH HOLD.

A deep inspiration causes the flattening of the diaphragm and expansion of the lungs, that pulls the heart away from the chest wall, it is this concept at the base of the Deep Inspiration Breath Hold (DIBH) technique.

During simulation as during treatment, the patient is asked to take a deep breath and holds it till the radiation session is completed.

This means a reduction in heart exposure at the radiation dose.

Currently, there are two very commonly used techniques for DIBH, voluntary DIBH (vDIBH), and moderate DIBH.

In moderate DIBH an active breathing control (ABC) device is used (54), it is based on the utilize of a spirometer which allows for monitoring of air flow throughout the respiratory cycle and stopping air flow at a set threshold volume, helping the patient to hold their breath and volume (54-56).

Moreover, ABC device improve treatment reproducibility by decreasing the variability associated with the procedure, both within a fraction and between separate fractions.

4.1 ACTIVE BREATHING COORDINATOR DEVICE.

ABC is a non-invasive, state of the art technology that helps patients hold breath while they received radiation therapy to keep the lungs filled with air to keep the heart away from the chest wall. (55)

When Active Breathing Coordinator is used during radiation therapy, the patient takes a deep breath before the beam of radiation is delivered.

This deep breath increases the distance between the target PTV breast on the patient’s left side and patient’s cardiac OAR (heart, LAD).

Increasing this distance means there is less risk the heart will receive any incidental radiation during treatment and, therefore, there is less risk of the patient developing radiation-induced heart disease. (56)

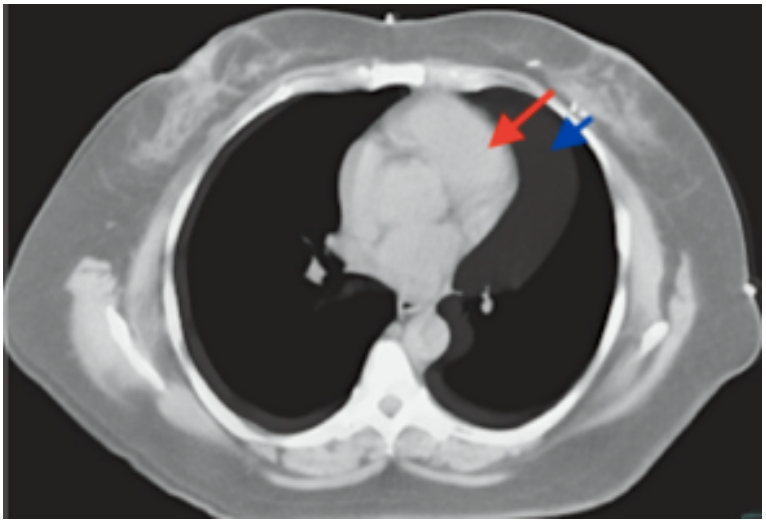


Fig. 3 A fusion CT simulation scan with and without DIBH for one representative patient. Heart displacement from the chest-wall with DIBH (red arrow), in FB (blue arrow).

Usually a breath hold is just 20 to 25 seconds; however, the patient is always in control and can signal she wants to resume breathing at any time if she cannot hold her breath for that length of time.

The ABC device has a nose clip, mouthpiece, tubing and green button.

Before starting CT simulation scan, there is a teaching session about few minutes to learn how to use the ABC device. A small nose clip is put on the patient's nose to avoid involuntary breathing.

The patient also holds a mouthpiece, which is attached to a breathing tube, between her teeth, so that all the air passing through will be read by the machine.

The technicians talk to the patients about how to inhale and hold the breath and exhale, instruct and guide them throughout the treatment process.

They will provide instructions to the patient explaining the steps to the ABC procedure. Position mouthpiece, nose clamp and patient control switch.

Ask patient to take in a big breath and take note as to how many liters are inspired. When the patient is ready, she takes a deep breath. She is asked to press the green button when she is ready to hold breath.

If for any reasons she needs to stop the breath hold, she has to stop pressing down on the green button and the breath hold will stop. When the button is released the balloon, valve is deflated. If the patient presses the button twice in one second, it will send a distress signal that will show up on the laptop screen.

The therapist will stop the treatment. When she has breathed in enough air to inflate her lungs to a pre-determined volume, she is invited to holds her breath.

A small valve in the breathing tube closes so no additional air can enter her lungs during the breath hold. This stops any movement.

A clock in the treatment room allows the patient to see the time remaining. If at any time the patient wants to take a breath, she releases pressure on a switch and the valve automatically opens so she can breathe.

Fig. 4 Active Breathing Coordinator™ Elekta

5. MATERIAL AND METHODS.

Since November 2020, we implemented a moderate Deep inspiration breast hold technique at our department using Active Breathing Coordinator (ABC) device.

Thirty patients included in this analysis were treated from November 2020 to October 2021 at Polyclinic San Matteo.

Pre-radiotherapy planning CT scans were done in Free Breathing (FB) and in DIBH [using Active Breathing Coordinator system (ABC™)] in 30 left sided breast cancer patients.

Collected data for each patient included age, histological primary tumour size, tumour type, nuclear grade, lymphovascular involvement, hormone-receptor status, her2 status.

The medical record for each patient enrolled has been reviewed to obtain clinical data. Were included any woman who underwent left breast RT.

All patients signed written consent for the treatment.

Patients were treated in the supine position, both arms above the head.

The CT was performed 4 – 8 weeks after surgery and before initiating radiotherapy.

3DCRT plans were generated for both scans.

Patients were ineligible for ABC treatment if they were unwilling to undergo device training or were unable to perform a breath hold for 20 seconds. Patient compliance represents a fundamental selection criterion. If a patient has a hearing problem, or a compromised lung function and difficulty in maintaining constant breathing, is not able to undergo ABC simulation.

The technicians trained them with DIBH in detail to ensure perfect implementation during the application of the device.

The breath hold was monitored from the control room, and the CT started once the patient had achieved a satisfactory breath hold (visualized by the laser cross hair overlying the breath hold green mark). If the cross hairs did not overlie, the mark patients were invited to inspire or expire to achieve exact overlay or re-attempt the inspiration.

A simulation CT scan was performed for each patient in Siemens Somaton (Definition AS, Forchheim, Germany) CT scanner and 2 sets of images were taken, one in free breathing (FB) and another in DIBH. The Active Breath Coordinator system from Elekta was used for monitoring respiratory breath-hold where the predetermined threshold of breath-hold volume and duration was set for every individual patient and CT data was acquired without contrast using 3 mm slices.

The FB and DIBH CT scan images were then transferred to our treatment planning system.

The treatment planning was done using Monaco TPS v.5.11 software of Elekta Versa HD machine.

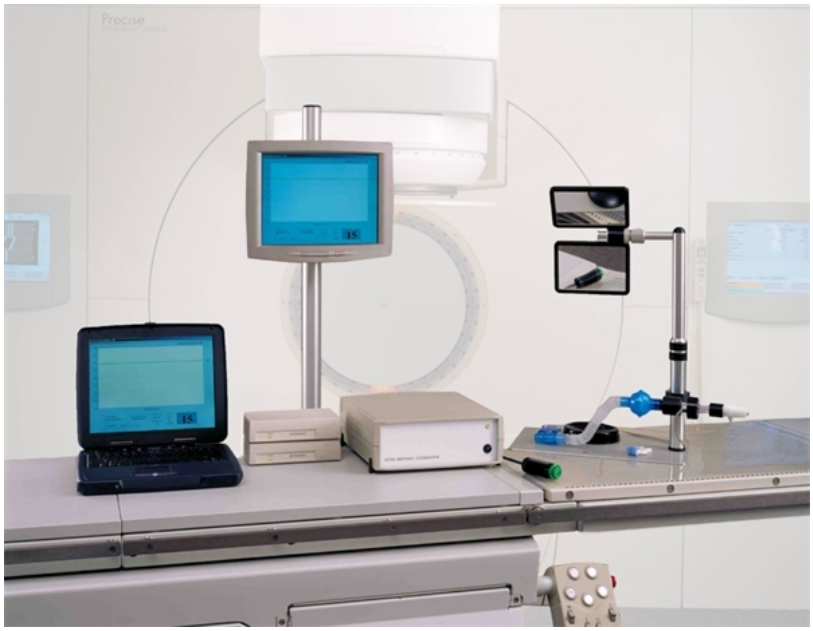


Fig. 5 Active Breathing Coordinator™ component.

5.1 DEFINITION AND DELINEATION OF TARGET AND ORGANS AT RISKS VOLUMES (PTV AND OARS).

Axial computed tomography (CT) images was performed in supine position for all patients.

Target volumes and OARs were contouring using Oncentra treatment planning software.

Target and Organ at Risks (OARs) volumes were contoured on a 0.3 axial CT, either on free-breathing and ABC CT images, according to the RTOG Breast Cancer Atlas (57) and heart contouring guidelines (58).

The clinical target volume (CTV) was defined as the whole left breast. The planning target volume (PTV) was created as the CTV with 5 mm isotropic expansion and then cropped by 5 mm from the skin surface.

The OARs, including the heart, left anterior descending coronary artery (LAD) and left lung, were contoured. The LAD and heart were delineated according to the heart atlas developed by Feng et al. (58).

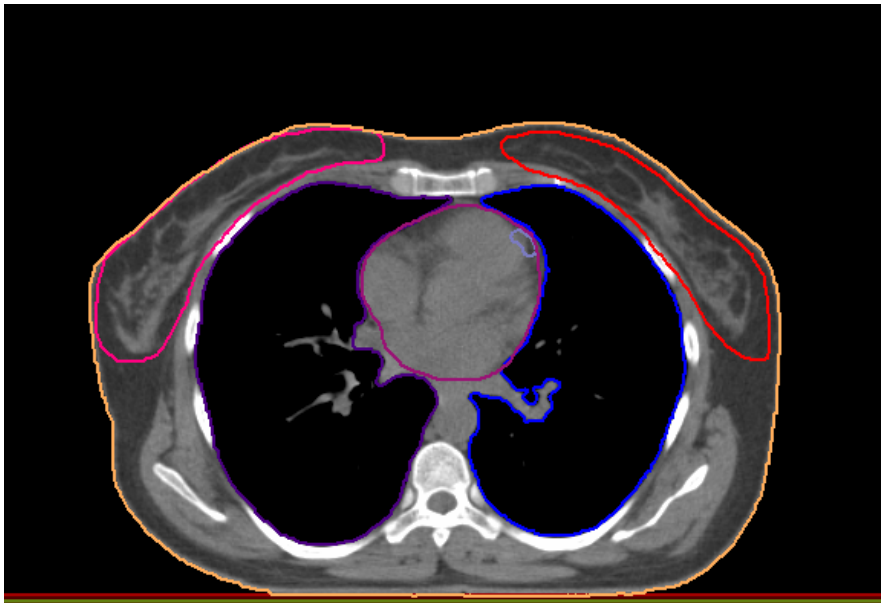
The goals of both treatment plans were 95% of the PTV covered by 95% of the prescribed dose and the hot spot <110% of the prescribed dose. The dose constraints for OARs followed the Quantitative Analyses of Normal Tissue Effects in the Clinic Summary (QUANTEC) guidelines and were optimized to be as low as possible.

Target volumes Breast, SIB and OARs (bilateral lungs, heart, LAD, contralateral breast) were delineated on each CT scan.

Two different 3DCRT plans, for the different treatment ABC and FB, were created and compared.

In the FB contoured CT, heart and LAD are really close to the PTV target, instead in the ABC one, a “safe” distance from these cardiac OAR is achieved. (Fig.6)

a)



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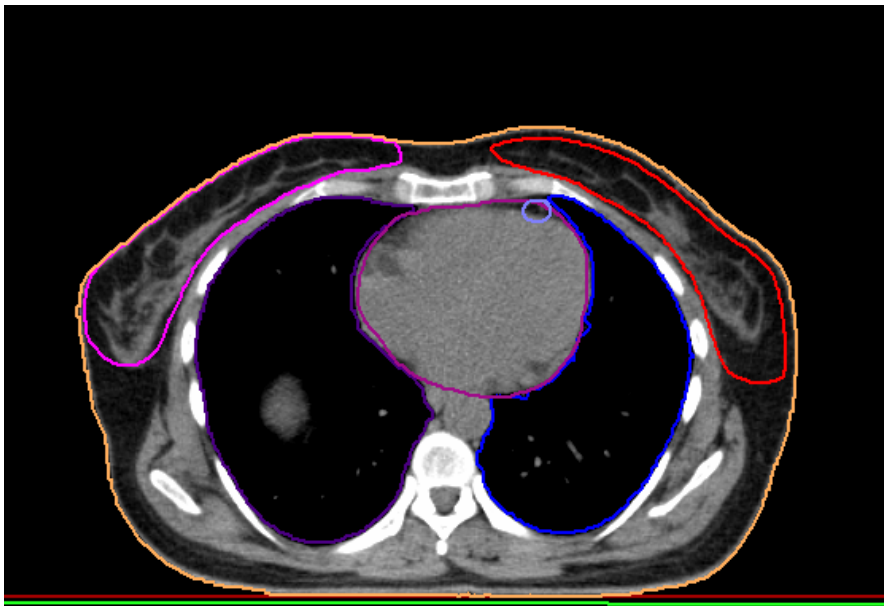


Fig. 6 A contoured Simulation CT with (a) and without (b) ABC for one representative patient. Red: Target breast, Purple: Heart, Lilac: LAD, Blue: Ipsilateral lung.

5.2 TREATMENT PLANNING.

All patients underwent the same hypofractionated schedule of 40.05 Gy in 15 fractions, 5 times a week. In some cases, according to cancer risk factors, a simultaneous integrated boost (SIB) was added with a total dose of 47.55 Gy delivered in the same RT session.

Organ contouring, treatment planning, and dosimetric evaluation were performed on 30 patients, and 60 treatment plans were created and evaluated. Biological evaluation was performed on 60 treatment plans.

By using 3D conformal radiation therapy, breast irradiation was performed with tangential beams and sub-fields to reduce hotspots (preferably not more than 105% of the whole-breast prescription dose). Irradiation of the sib volume was carried out with two or three fields.

Treatment was delivered in all patients using ABC-DIBH technique in Elekta Versa HD Linear accelerator. For image verification, daily kilovoltage cone beam CT was used, and online correction was also carried out.

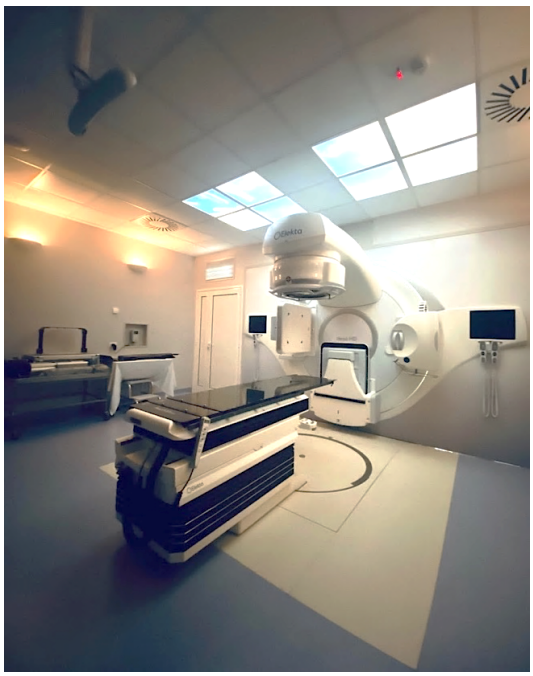


Fig. 7 Elekta Versa HD linear accelerator Fondazione IRCCS Policlinico San Matteo.

6. STATISTICAL ANALYSES.

Dose Volume Histograms (DVHs) were generated for both the plans (FB and DIBH) and the following dosimetric parameters were noted and were compared between the different breathing techniques.

- For the PTV breast and PTV sib: D95% (the percent of the prescription dose covering 95% of the volume).
- As regard OARs: the values of Dmean, V40 for heart; Dmax, Dmean and V20 for LAD; V25, V20 and Dmean for ipsilateral lung.

A standard statistical two tailed paired t-test was used to estimate the statistical significance of the differences between groups. A p-value less than 0.05 was considered statistically significant.

Starting from the differential dose-volume histogram the NTCP values was calculated for heart and it was compared for two different techniques.

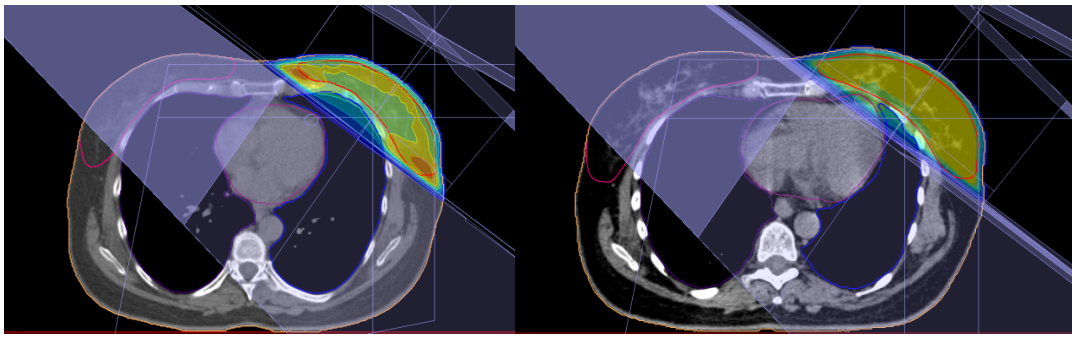
Lyman-Kutcher-Burman logistic and multivariable logistic models (MVL) was chosen in order to evaluate NTCP. The probability for cardiac mortality was calculated using the relative seriality model:

$$NTCP = \left\{1-\prod_{i=1}^{n}[1-P(D_i)^s]^{\Delta V_i}\right\}^{1/s} \quad (1)$$

$$P(D_i) = 2^{-exp\{e\gamma(1-D_i/D_{50})\}} \quad (2)$$

where D_i is the absorbed dose in each dose bin i of the differential dose volume histogram (DVH), D_{50} is the dose resulting in 50% complication probability, γ is the maximum relative slope of the dose–response curve, n is the number of DVH dose bins, $\Delta V_i = V_i/V$ where V_i is the volume of the each dose bin and V is the total volume of the organ. The relative seriality factor, s (range 0 to 1), describes the tissue architecture. Input data for the NTCP calculations with

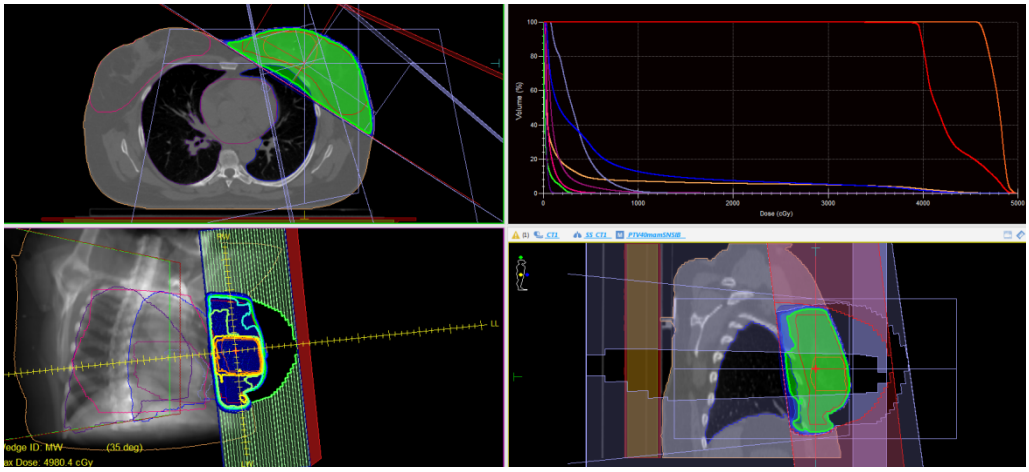
endpoint excess cardiac mortality was taken from Gagliardi et. al. for the entire heart volume: s = 1, γ = 1.28 and D_{50} = 52.3 Gy. (59)



a **b**

Fig. 8 Treatment plan with (a) and without (b) ABC for one representative patient. In section a) Heart and LAD is completely spared, instead without ABC (section b) heart and LAD are involved.

a)



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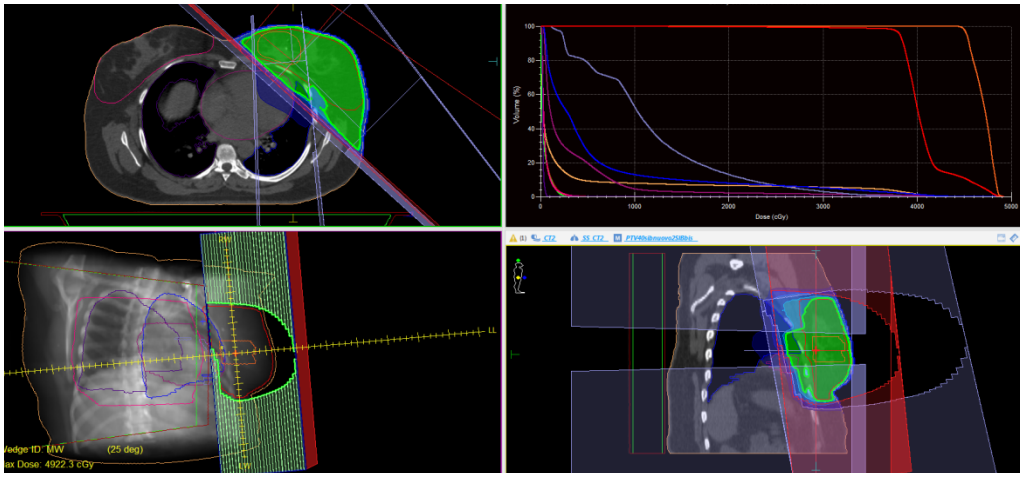


Fig. 9 Treatment plan with (a) and without (b) ABC with a SIB, for one representative patient. In Fig a) Heart and LAD is completely spared, instead without ABC (b) heart and LAD are involved.

7. RESULTS.

7.1 PATIENT AND TREATMENT CHARACTERISTICS

Sixty CT scan data of 30 left sided breast cancer patients, were analyzed.

Patient and treatment characteristics are presented in Table 1.

All patients underwent BCS with sentinel lymphnode biopsy. Median age was 62 yrs (40-80yrs). 20% of the patients received chemotherapy of whom 2 patients, received it as a neoadjuvant treatment. The mean breath-hold volume was 1.1 L and mean duration of breath-hold was 15 s.

Table 1. Patient and treatment characteristics (N = 30).

Patient/Treatment Parameters		**Number**	**Percentage**
Median Age		62 yrs (40-80yrs)	
Median BMI		22 (19,92-25,39)	
Menopausal status	yes	22	73%
	peri	2	7%
	no	6	20%
Tumor	pT1	20	66%
	pT2	5	17%
	YpTis/x	3	10%
	Tis	2	7%
Location of the tumour	QSE	10	33%
	QSI	6	20%
	QQSS	3	10%
	QQII	4	13%
	QC	4	13%
	QQEE	3	10%
Heart Medications		14	47%
Type of surgery done		BCS	100%
Hormone therapy		26	87%
Chemotherapy received		6	20%
Trastuzumab		4	13%
Mean breath-hold volume		1.1 L	
Mean duration of breath-hold		15 sec	

7.2 DOSIMETRIC EVALUATION.

The treatment plans were compared objectively using dose-volume histograms (DVHs) for PTVs and different OARs of interest.

The doses according to the different plans are summarized in Table 2.

Target coverage with the 95% isodose was equal in both the plans. (Fig 10).

The most pronounced and significative difference between the treatment plans are Heart_Dmean, Heart_Dmax and LAD_Dmean and LAD_V20.

Dose differences between DIBH and FB for the heart, LAD, were analyzed.

The differences in dose parameters were calculated as differences between DIBH and FB, normalized to the FB values and expressed as percentage. (Tab.2)

The heart mean dose is lower in DIBH for all patients and decreases significantly from 1.23 ± 0.64 Gy (FB) to 0.90 ± 0.32 Gy (DIBH) ($p < 0{,}0143$).

As regard LAD we obtained a significative sparing either for the Dmax and Dmean and V20Gy:

Dmax drecreases from 20.63 ± 12.42 Gy (FB) to 8.98 ± 5.10 Gy (DIBH) ($p << 0{,}0001$) and Dmean decreases from 4.64± 4.55 Gy (FB) to 2.29 ± 0.86 Gy (DIBH) ($p < 0{,}0073$).

3DCRT dosimetric analysis demonstrated that conventional RT leads to achieve a good treatment planning. The use of ABC reduces heart and LAD volume in the radiation beam leading to a dose reduction in these OAR, as shown in Fig.11 -12.

As regard lung, the absolute irradiated lung volume increases in DIBH due to the increasing the air volume in the periphery. In contrast to the heart, local

density of the lung changes and decreases, with inflation, significantly between FB and DIBH.

The mean left lung volume of all 30 patients was 1292 ± 302 cm3 (mean ± standard deviation (SD)) in FB und 2059 ± 411 cm3 in DIBH.

The total lung mass showed a good accordance between FB and DIBH, whereas the mean lung density decreased from 0.28 ± 0.05 g/cm3 (FB) to 0.18 ± 0.03 g/cm3 (DIBH).

A more accurate model to evaluate the lung dose than the typically DVH is suggested by Markus Oechsner et al (60) that use the dose-mass histogram concept (DMH) and in particular the quantity M20 (the lung mass receiving 20 Gy). While the DVH uses volume elements (voxels) which stay unchanged between FB and DIBH, DMH accounts for density changes inside the voxels. Our treatment planning systems (TPS) offer no option to calculate DMH and doesn't give mass information. So, we decided to obtain a relation between lung mean dose and electron density (ED mean) and between V20(cm3) and ED mean; the distribution of Dmean vs EDmean (Fig.14) and of V20 in function of ED mean are shown in fig.15.

We also derived a new quantity (E), as the product between ED and absolute volume (in cm3), that represents the number of electrons contained in the volume. Consequently, the quantity E20 (ED*V20(cm3)) represents the number of electrons contained in the volume receiving 20Gy. The distribution of V20 in function of E20 and of Dmean vs E20 are represented in figure B e D.

Additionally, we have construct the DEH (Dose-E Histogram) for a sample size of patient (figure 18) and we conduct the dosimetric analyses about lung, V20, V25 and Dmean, and the results are showed in Fig.13.

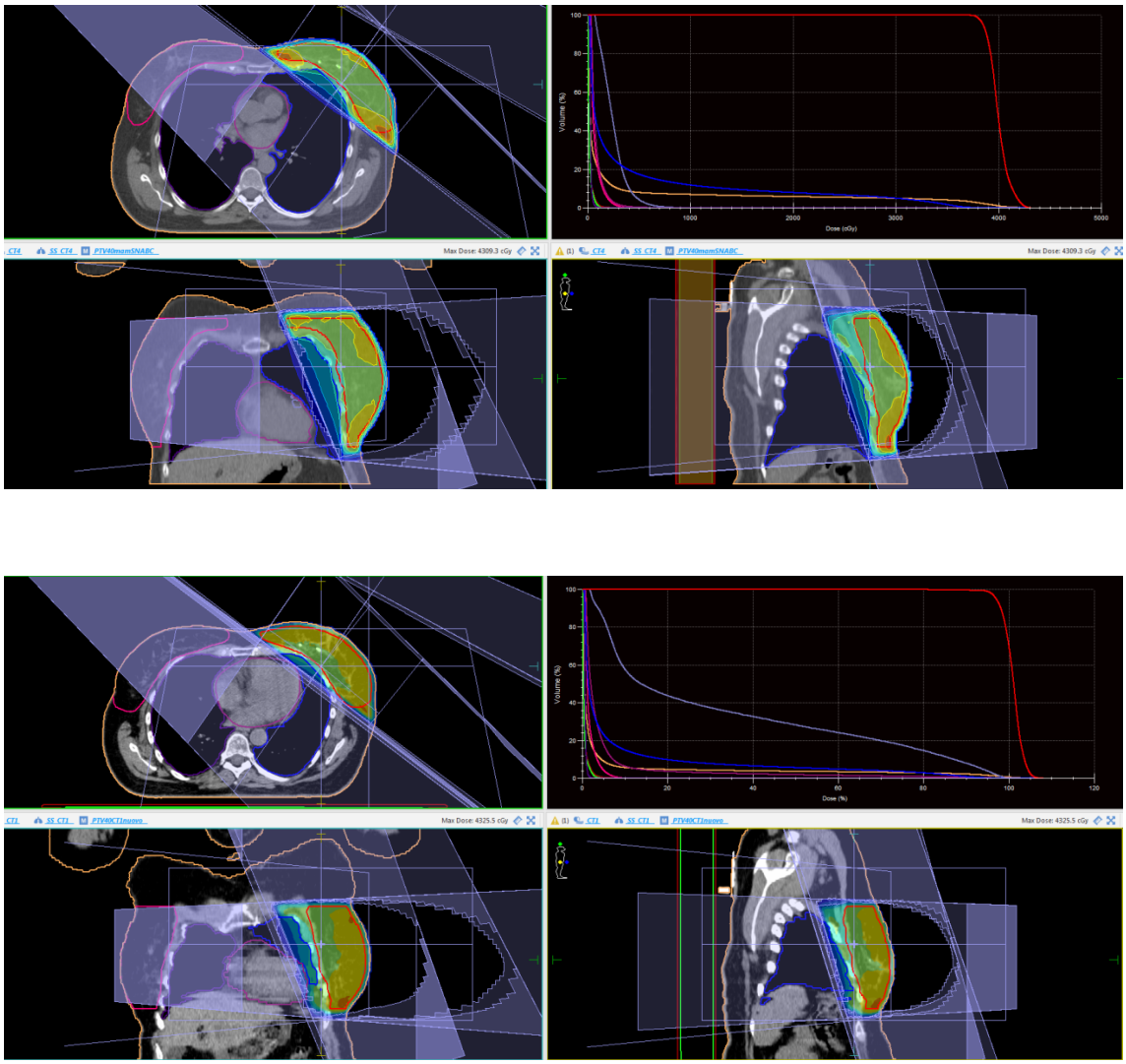


Fig. 10 Treatment plan with (a) and without (b) ABC and DVH dose distribution, showing how the dose to the critical organs is reduced between FB (b) and DIBH (a) for one representative patient.

Table 2. NOTE: Dmax: Maximum dose, Dmean: mean dose, Vx= volume (%) receiving x dose (Gy) or higher.

		PTV (left breast)		SIB		Heart		LAD		
		D95% (Gy)	Dmean (Gy)	D95% PTV(Gy)	Dmean(Gy)	V40Gy (%)	Dmean(Gy)	Dmax(Gy)	V20Gy (%)	Dmean(Gy)
with ABC	mean	38,47	40,98	46,18	47,50	0,00	0,90	8,98	0,00	2,29
	dev.std	0,71	1,14	0,88	0,46	0,01	0,32	5,10	0,00	0,86
without ABC	mean	38,23	40,77	46,04	47,55	0,02	1,23	20,63	1,15	4,64
	dev.std	0,64	0,91	1,06	0,74	0,10	0,64	12,42	3,88	4,55
	p-value	0,2854	0,4336	0,9752	1	0,2802	**0,0143**	**<0,0001**	**<0,000***	**0,0073**
					mean Δ %	-3,33	-18,39	-35,80	-13,33	-31,03
					median Δ %	0,00	-22,37	-57,90	0,00	-37,52
					dev.std	0,18	0,27	0,60	0,35	0,38

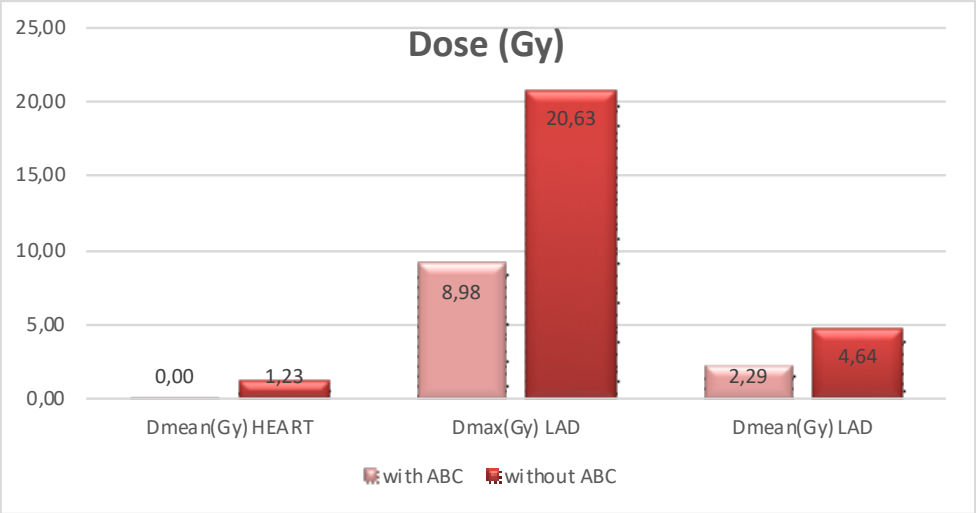


Fig. 11 Heart and LAD Dose comparison between DIBH and FB.

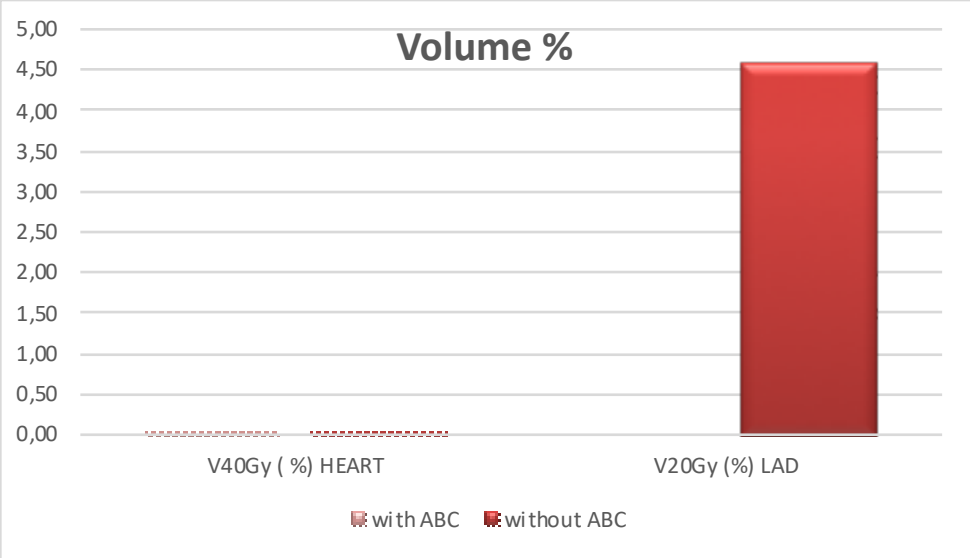


Fig. 12 Comparison of Heart Volume that receive 40Gy and Lad Volume 20 Gy with ABC (pink) and without (red)

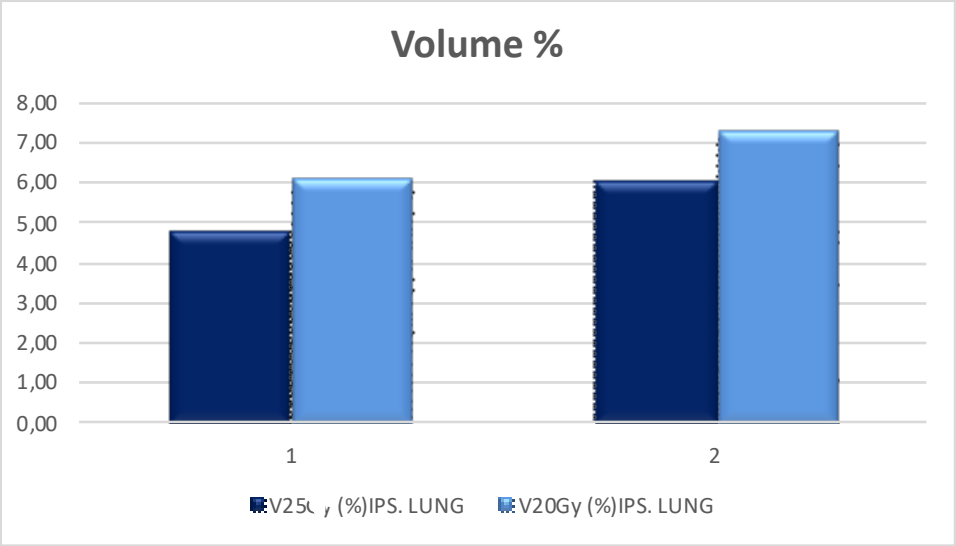


Fig. 13 Comparison of Lung Volume that receive 25 and 20 Gy with ABC (blu) and without (light blu)

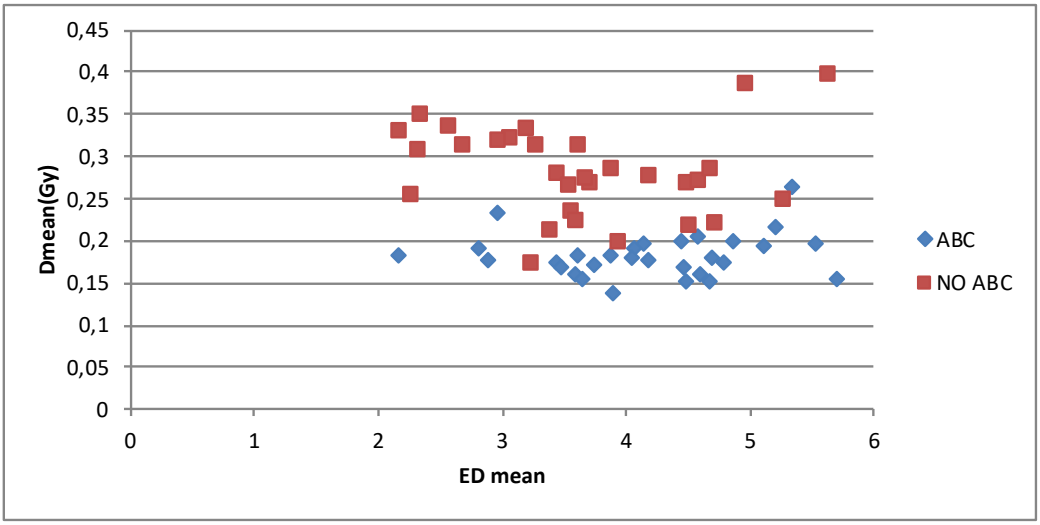


Fig. 14 Distribution of Dmean vs EDmean in ABC and without ABC.

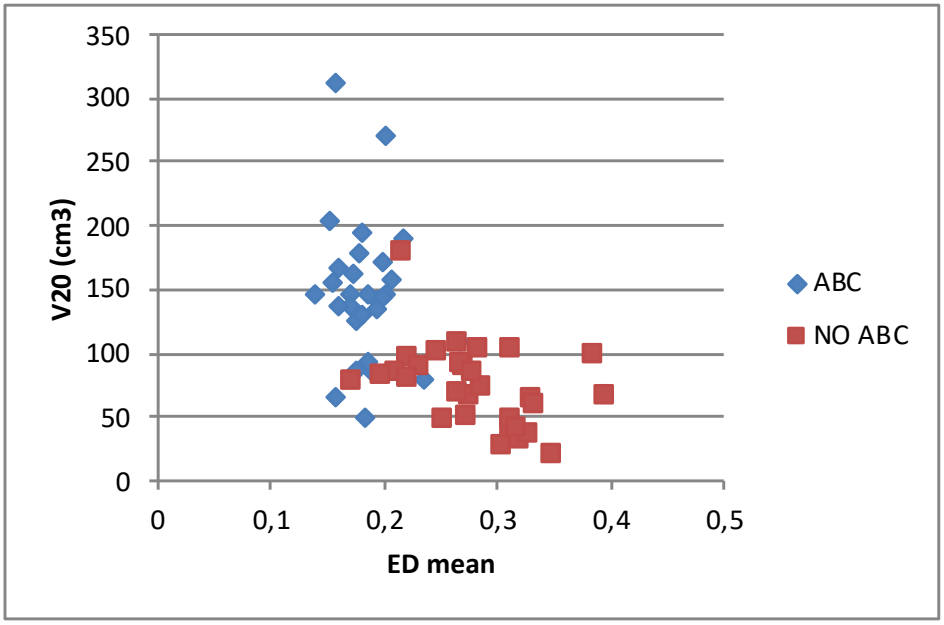


Fig. 15 Distribution of V20 in function of ED mean

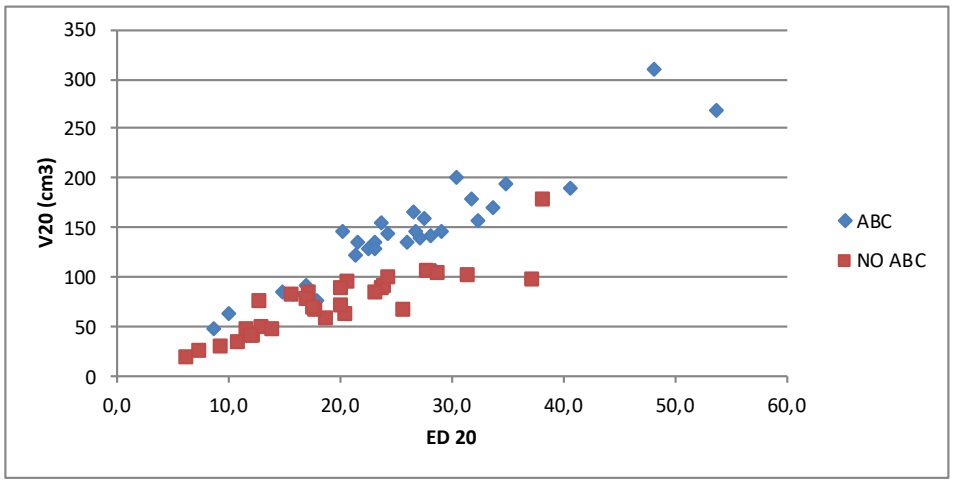


Fig. 16 Distribution of V20 in function of ED 20

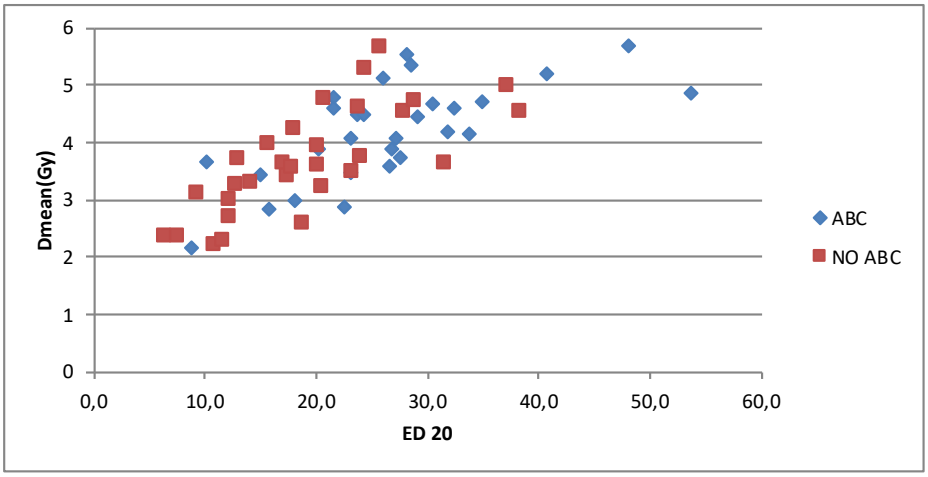
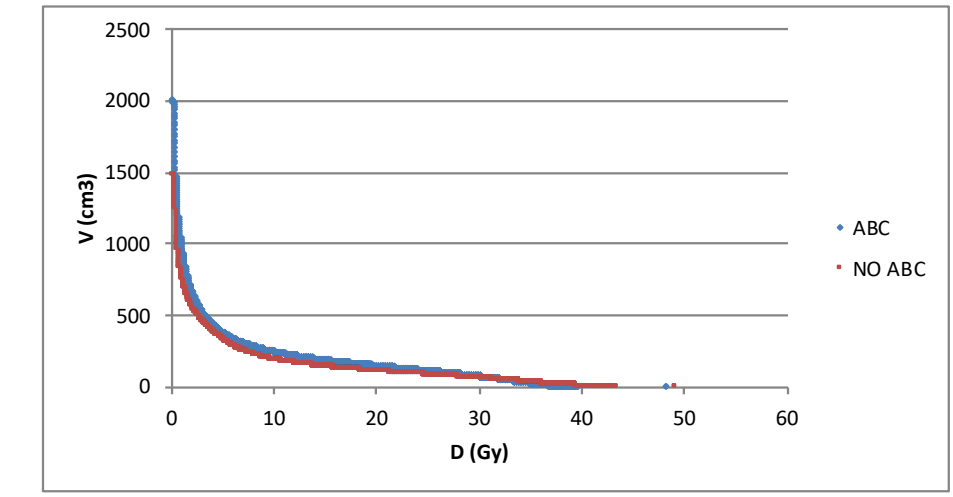
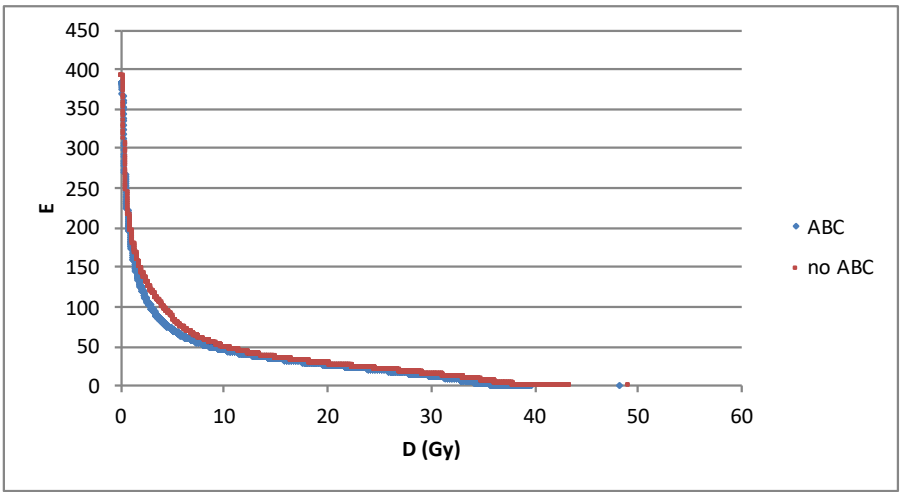


Fig. 17 Distribution of Dmean in function of ED 20



a



b

Fig. 18 DEH (Dose-E Histogram) a: Vcm^3 vs Dose (Gy) b: E vs Dose(Gy).

7.3 NTCP MODEL RESULTS

DIBH reduced the risk for long-term cardiac mortality as showed in table 3.

Table 3 Difference in the risk for long-term cardiac mortality.

	FB	*DIBH*
Excess cardiac mortality probability	0.08	0.04

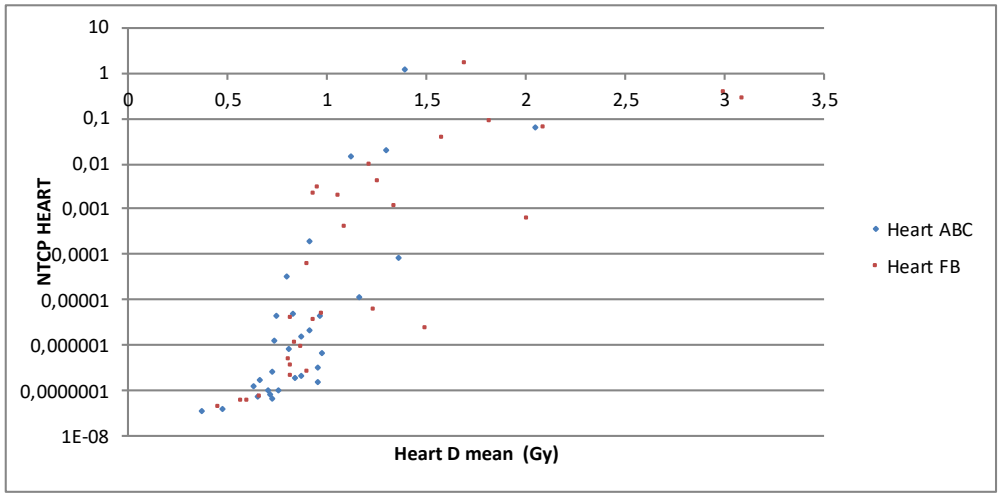


Fig. 19 NTCP Heart Dmean

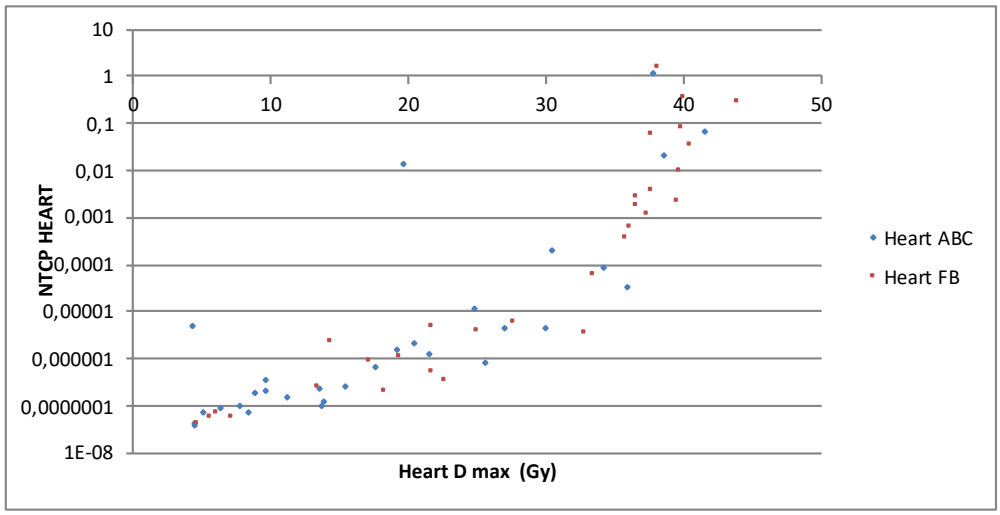


Fig. 20 NTCP Heart Dmax

8. ONGOING TRIAL AND FUTURE PERSPECTIVES.

8.1 PBI PARTIAL BREAST IRRADIATION.

Partial breast irradiation (PBI), as a new clinical indication, by the irradiation of smaller breast volumes can reduce doses to the heart as Lettmaier et al. have shown.

Recent developments in radiation oncology show a move toward a de-escalation strategy for adjuvant radiotherapy in early breast cancer. According to phase 3 trials with an adequate patient selection, partial breast irradiation allows to achieve an acceptable safety profile and a good cosmetic outcome.

Heart exposure to ionizing radiation during RT for BC increases subsequent rates of ischemic heart disease (IHD). The increase is proportional to the mean dose to the heart. Women with pre-existing cardiac risk factors have greater absolute increase in risk from RT. An age >70 years seems to be one of the most significant factors for IHD occurrence, and PBI represents one of several effective strategies to reduce cardiac radiation dose when compared to WBI.

Physical RT properties are different for each partial-breast irradiation technique, substantially altering dose distribution, irradiated volumes, dose homogeneity, and skin doses, all of which may have different clinical outcomes. (61) Specific studies focusing on technical concerns, safety profile, and new relevant end points for patients at low risk of recurrence, such as quality of life, will further help the decision-making process. (62)

At our site, since May 2021, I'm PI of this PBI Phase 3 randomized non-inferiority trial: ExclUsive endocRine therapy Or Partial breast irradiation for women aged ≥70 years with luminal A-like early stage breast cancer (EUROPA): a randomized phase 3 non-inferiority trial.

Study Design

This is a phase 3 randomized controlled trial to compare exclusive PBI with exclusive ET following BCS in low-risk early-stage elderly BC patients. Randomization will be stratified according to the G8 health status screening tool (≤14 versus >14), age at randomization (70-79 versus 80+), and Institution. Patients will be randomized on the basis of local pathology results of the resection specimen from their BCS with or without SNB, showing pT1, clinical/postsurgical N0 (i+), luminal A-like tumors.

Patient population inclusion criteria are:

- Women aged ≥70 years;
- histologically proven invasive unifocal adenocarcinoma of the breast;
- pathological T1 (pT1) stage;
- postoperative negative (no ink) final surgical margins;
- clinical and pathological N0 (cN0 and pN0) stage (isolated tumor cells [i+] allowed);
- any tumor grade (if pT ≤10 mm), G1-2 tumor grade (if pT between 11 and 19 mm);
- luminal A-like biology (immunohistochemistry (IHC)-based on local assessment): ER positive (defined as ≥10%);

Progesterone (PgR) positive (defined as >20%);

Human epidermal growth factor receptor 2 (HER2) negative (score 0 or 1+ and proven negative by in- situ hybridization [ISH] in case of score 2+); and

Ki67 <20% by IHC staining;

- surgically treated with BCS with or without sentinel node biopsy (SNB);
- written informed consent.

An interim analysis for this study is planned when 152 enrolled patients reach the 2-year follow up control.

Actually, 5 patients have been enrolled and PBI confirm to be a feasibile and a good OaR sparing technique, consistent with literature data, with a heart V3Gy < 10%.

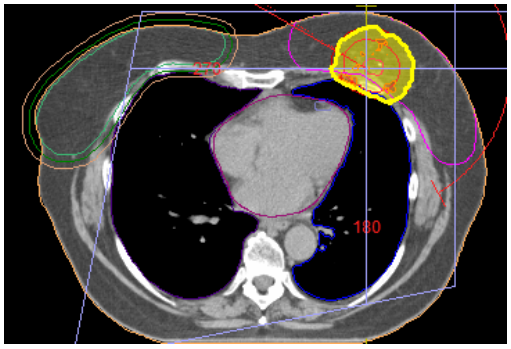


Fig. 21 A breast cancer left PBI.

8.2 EARLY DETECTION OF CARDIOTOXICITY

I'm co-investigators of this multicenter, observational prospective longitudinal study:

Early Detection Of Cardiotoxicity From Systemic And Radiation Therapy In Breast Cancer Patients. A Multicenter Observational Prospective Longitudinal Study

To our knowledge, this study is the first longitudinal prospective one which includes 200 patients. Its primary endpoint is to evalute myocardial oedema on CMR after cardiotoxic systemic therapy and radiation therapy in predicting the incidence of cardiotoxicity.

It is important to distinguish these high-risk patients who need intensive cardiovascular screening during and after cardiotoxic treatment. Our purpose is to find these risk group patients when the toxicity is still subclinical and reversible and prevent the subclinical toxicity with protective drugs administered to the right patient at the right time.

This study is designed to evaluate myocardial edema on CMR after radiation therapy and cardiotoxic systemic therapy in predicting the incidence of cardiotoxicity.

Stage I-III female breast cancer patients, who are planning on starting neo/adjuvant therapy for breast cancer are enrolled.

Baseline blood tests will be taken, physical examination, CMR, ECG and ECHO will be done, proper medical history, including current medications of the patient and family history of CVD will be taken. If baseline hs-CRP ≥10 mg/l, another blood test will be checked after 2 weeks.

ECHO will be done on Philips Epiq or General Electic Vivid E95 and Cardiac Magnetic Resonance will be performed with Siemens Skyra 3T or a 1.5T scanner (MAGNETOM Aera, Siemens AG).

Patients receiving cardiotoxic chemotherapy will be drown blood before and if possible 24 hours after chemotherapy administration.

Patients who get anthracycline, have an ECHO and ECG after the end of this treatment.

During trastuzumab, blood will be taken before every administration (every 3 weeks) and ECHO will be done after every 4 cycles (every 3 months).

Before the beginning of radiotherapy, blood tests will be taken, CMR and ECHO will be done. Patients who receive trastuzumab concurrently with RT will continue visits as described above. Biomarkers will be taken in the middle of RT.

2 weeks +/-3 days after the end of RT, blood tests will be taken, CMR and ECHO will be done. Six weeks after the end of RT, biomarkers will be measured. If hs-CRP ≥3mg/l, ECHO will be done. Patients will be followed at least until 10 years after the end of RT.

12 months after the end of RT blood tests for measuring biomarkers and ECHO and CMR will be checked.

During treatment, if a patient gets symptomatic heart failure or decline of LVEF greater than 10% points, with a final LVEF <53% on ECHO, patient will be referred to cardiologist and specific treatment as described by guidelines will be prescribed.

Primary Endpoint

The aim of this study is to assess the role of myocardial oedema on CMR (T2 mapping) after radiation and cardiotoxic systemic therapy in predicting the incidence of cardiotoxicity, defined as by consensus guidelines (decline of LVEF ≥10% points with a final LVEF <53%) measured on CMR and ECHO over the time window of 12 months from the end of radiation therapy.

Secondary Endpoints

1. To detect GLS decrease >15% from baseline, measured on Echo over the time window of 12 months
2. To see if the changes in biomarkers will correlate with LVEF measurements, assessed by ECHO and CMR
3. To see if the changes in biomarkers will correlate with GLS measurements, assessed by ECHO
4. To compare the time to the biomarker's positivity to the time to the decrease in GLS >15% and/or decline of LVEF ≥10% points with a final LVEF <53% measured on Echo.
5. To find out if patients with increased baseline biomarkers will develop cardiotoxicity, identify predictors of cardiotoxicity by multivariable analysis

6. To detect major cardiovascular events (defined as acute myocardial infarction, hospitalization due to heart failure, atrial flutter/fibrillation, ventricular tachycardia) or death due cardiac problems during the follow up
7. To assess the role of fibrosis on CMR (T1 mapping with evaluation of extracellular volume) after cardiotoxic radiation therapy and /or systemic therapy in predicting the incidence of cardiotoxicity.
8. To detect incidence of acute asymptomatic pericarditis after radiation therapy, measured on CMR
9. To investigate if the area of the edema on CRM correlates with RT dose distribution
10. To assess the incidence of myocardial oedema on CMR (T2 mapping) after radiation therapy and cardiotoxic systemic therapy measured on CMR and ECHO over the time window of 12 months from the end of radiation therapy.

The recruitment period is 2-3 years until the needed number of patients have been enrolled. Each patient will be followed until 12 months after the end of radiation therapy. Then, patients will be followed for 10 years. Our center has enrolled 5 patients to date.

8.3 NEOADIUVANT RADIATION TREATMENT.

Neoadjuvant RT may be a valuable strategy to achieve major pathological responses and de-escalate breast conservative treatments leading to a better quality of life. This could represent an attractive option in the setting of early-stage breast cancer patients with positive estrogen receptors, and in the treatment of inoperable locally advanced breast cancer (LABC) too. Concerning locally advanced setting, recent studies demonstrated that neoadjuvant RT is an effective down-sizing treatment, allowing surgical resection regardless of

systemic treatment performed. There is a clear unmet need for a neoadjuvant role of RT in breast cancer treatment. Even more than PBI, this RT approach could allow an optimum heart sparing treatment, by irradiating a really small and well-defined PET-based PTV.

Rationale:

The majority of local recurrences occur in close proximity to the original tumor location. Neoadjuvant RT holds several advantages over adjuvant RT: treatment target is better oxygenated, surrounding normal tissues receive reduced doses because of a smaller target volume, and of course a greater ability to recognize and to delineate the disease. This strategy might also lead to major pathological responses, which could be possible correlated to a lower risk of recurrence. It could allow a huge OAR spare.

Moreover, the irradiated breast tissue will be surgically removed, and this is likely to lead to reduced fibrosis and improved cosmetic outcome. Considering that treatment volume has been associated with adverse cosmetic outcome, this might be an important advantage of a preoperative approach. In locally advanced disease this approach may allow for a single-staged surgical procedure, with mastectomy and immediate autologous reconstruction.

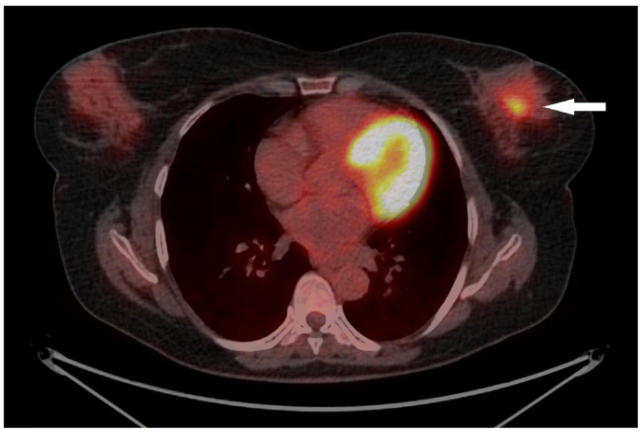


Fig. 22 A breast cancer single nodule highlighted by Breast PET/CT.

Objective

- To investigate the feasibility of a neoadjuvant single fraction of BGRT in Early-Stage Breast Cancer (ESBC). The main aim is to explore a 21 Gy Stereotactic PET-guided fraction in a pilot trial, as a preliminary step to further clinical investigations. (group 1)
- To investigate the feasibility of a neoadjuvant BGRT in LABC. To evaluate breast and lymph node rates of pCR with a short-course BGRT. (group 2)

A representative sample of clinical T1c-T2(<3cm) N0 as early breast cancer (group1), and stage II-III breast cancer patients as LABC (group 2), will be enrolled in this feasibility study.

Inclusion criteria group 1:

- Unifocal tumors with a margin of at least 1 cm or greater on conventional imaging from the chest wall and from the skin,
- Invasive ductal carcinoma histological subtype (which had a significantly higher 18F-FDG uptake),
- No lymph vascular invasion on diagnostic ultrasound,
- estrogen receptor positive,
- BRCA negative.

Inclusion criteria group 2:

- inoperable LABC,
- Invasive ductal carcinoma histological subtype (which had a significantly higher 18F-FDG uptake).

this study seeks to

1) characterize FDG profiles in order to determine what proportion of these primary breast tumors would be suitable for BgRT with a single-dose preoperative RT.

2) characterize FDG profiles in order to determine what proportion of these locally advanced breast tumors would obtain a pCR by BgRT with a short course preoperative RT.

2) Combine anatomical features with metabolic characteristics

3) Develop robust treatment plans

4) Evaluate a dosimetric analysis

5) Estimate overall treatment time

Research Plan

- Identify around 25 patients who could perform a diagnostic FDG PET/CT prior to treatments based on primary tumor characteristics (San Matteo University Hospital)
- Assess the FDG profile on the diagnostic FDG PET/CT performed prior to treatment by measuring the SUVmax, SUVpeak, SUVmean, SUVbackground, and other relevant parameters (San Matteo University Hospital and Reflexion Medical)
- Correlate BgRT treatment planning dosimetry studies, as a precursor to commencing clinical BgRT treatments for primary breast cancer (Reflexion Medical, San Matteo University Hospital)

- The American research committee approved my proposal. It was approved in October 2021.

9. DISCUSSION

This study aimed to develop a comprehensive platform for treatment optimization in breast radiotherapy: respiratory gating, heart sparing, early detection of cardiac damage.

It is well known that breast radiation treatment has increased over the past decades, improving survival for patients with breast cancer; there is still concern regarding the possible adverse effects of radiotherapy on long-term outcomes in terms of increased risk of CV disease. (62)

Even more advanced techniques are adopted trying to preserve the heart from possible radiation sequelae. In this project, I explore different heart sparing techniques.

The first approach I described is a DIBH one. By using the ABC device, we achieved an optimum heart sparing breast treatment.

Our results showed the dosimetric benefit of the DIBH technique over free breathing technique in reducing cardiac OARs doses (heart and LAD), confirming literature knowledge. (63)

Indeed, the dosimetric analysis from our study showed a significant reduction in Dmean, V40 for heart. Also, a significant reduction in mean and maximum LAD doses and LAD volume that receive 20Gy were observed. These findings are in correspondence with data existing in the literature. (63)

The advantage of DIBH is to decrease the heart volume included in the irradiation fields by deplacing it, decreasing both the mean and the maximum heart dose, and LAD dose too, in a statistically significant way. (64)

Furthermore, the hypofractionated regime of 40Gy in 15 fractions, as a relatively new standard schedule, for whole breast irradiation after breast-conserving surgery,

comfirm to be safe and feasible, in ABC treatment too, and allowed to achieve a good dosimetric OAR sparing.

Furthermore, we applied the Lyman-Kutcher-Burman logistic, and multivariable logistic models in order to evaluate NTCP and assess cardiac mortality risk, and our results underline a major saving with DIBH treatment, data consistent with literature. (60)

This study showed that treatment of left-sided breast cancer in DIBH reduced the DVH-based heart and LAD dose.

Regarding lung, instead, there is a change in lung density inside the voxels between FB and DIBH. Therefore, a more accurate model to evaluate the lung dose than the typically DVH is suggested by Markus Oechsner et al. (60) that use the dose-mass histogram concept (DMH) (65-66) and, in particular, the quantity M20 (the lung mass receiving 20 Gy). While the DVH uses volume elements (voxels) that stay unchanged between FB and DIBH, DMH accounts for density changes inside the voxels.

Our treatment planning systems (TPS) offer no option to calculate DMH and give mass information.

So, we analyzed a relation between lung mean dose and electron density.

Furthermore, regarding the irradiated lung mass despite an increase in absolute irradiated left lung volume in DIBH, when considering the changes in the local density of the lung, with a DEH-based analysis, we found results are in agreement with those in FB.

Partial-breast irradiation has been introduced as a further breast RT treatment. It could represent a good heart sparing strategy for selected low-risk patients.

Several large phase 3 trials have demonstrated the noninferiority of partial breast vs. whole-breast irradiation in terms of local recurrence and similar or decreased

toxic effect using different available techniques (67-70). In this regard, Europa trial enrollment is ongoing, for elderly women affected by low-risk early breast cancer, a challenging setting regarding prognosis and potential comorbidities, thus minimizing treatment to maintain health-related quality of life without compromising survival is extremely important.

10. CONCLUSION

In summary, radiation treatment with DIBH allows reducing the dose delivery to the surrounding normal structures. In particular, it means a good reduction in cardiac doses due to the increase of the distance between target and heart, as shown by our data and also confirmed by other authors.

Respiratory control confirms to be the most practical and successful approach to minimizing the radiation dose to the heart.

Patient compliance is fundamental for the proper development of this approach.

Results of the ongoing trials could add important information, both as regards the role of Magnetic Resonance in early detection of possible cardiac damage, early detection and intervention could prevent the progression of heart failure to an advanced-stage disease requiring advanced therapies; as the efficacy and good sparing of partial breast irradiation, achieving a better quality of life, especially in older frailty women.

A new role of RT, in a PET-guided neoadjuvant setting instead of adjuvant, is under investigation, and it could allow even better-tailored treatment for our patients.

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"Quando curi una malattia puoi vincere o perdere.
Quando ti prendi cura di una persona, vinci sempre"