ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

DOTTORATO DI RICERCA IN

ONCOLOGIA, EMATOLOGIA E PATOLOGIA

Ciclo 38

**Settore Concorsuale:** 06/I1 - DIAGNOSTICA PER IMMAGINI, RADIOTERAPIA E NEURORADIOLOGIA

**Settore Scientifico Disciplinare:** MED/36 - DIAGNOSTICA PER IMMAGINI E RADIOTERAPIA

# ANALYSIS OF ANATOMICAL PARAMETERS IN THE RADIOTHERAPY OF BREAST CANCER

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Esame finale anno 2026

# INDEX

# Acronyms and Abbreviations

2D: Two-Dimensional
3D: Three-Dimensional
3D-CRT: Three-Dimensional Conformal Radiation Therapy
AI: Artificial Intelligence
BEV: Beam's Eye View
BRCA: BReast CAncer genes
CBD0: Contralateral Breast Distance at 0 degrees
CDH1: CaDHerin-1
CI: Confidence Interval
CLD: Central Lung Distance
cm: centimetres
CP: Control Point
CT: Computed Tomography
DFS: Disease Free Survival
DIBH: Deep Inspiration Breath Hold
DRR: Digitally Reconstructed Radiographs
DVH: Dose Volume Histogram
FP: Forward Planning
Gy: Gray
h-IMRT: hybrid IMRT
IMRT: Intensity Modulated Radiation Therapy
IP: Inverse Planning
IRST: Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori"
kV: kilovolt
LAD: Left Anterior Descending artery
LINAC: LINear Accelerator
MD: Radiation Oncologist
MHD: Maximum Heart Distance
MHL: Maximum Heart Length
MLAD: Maximum LAD Distance
MLC: Multi Leaf Collimator
MLD: Maximum Lung Distance
MLL: Maximum Lung Length
mm: millimetres
MU: Monitor Unit
MV: MegaVolt
OAR: Organ At Risk
OR: Odds Ratio
PTEN: Phosphatase and TENsin
PTV: Planning Target Volume
ROI: Region of Interest
RT: Radiation Therapy
SGRT: Surface Guided Radiation Therapy
SIB: Simultaneous Integrated Boost
SKT11: Serine/Treonin Kinase 11
S&S: Step-and-Shoot
TP53: Tumoral Protein 53
TPS: Treatment Planning System
VMAT: Volumetric Modulated Arch Therapy
V"n": Percentage of OAR volume receiving "n"Gy
Vol: Volume
Vol LAD 80%: Volume of LAD receiving at least 80% of dose prescription
vs: Versus

# Abstract

## Introduction

Breast cancer is the most diagnosed neoplasm in women. At the Istituto Romagnolo per lo Studio dei Tumori “Dino Amadori” (IRST) in Meldola patients are treated with several radiotherapy techniques (Linac based treatment with static or MLC modulated fields, and Tomotherapy). The most often used fractionation in the treatment of breast cancer without lymph node involvement is 40.05 Gy in 15 fractions. Planners' and clinicians' experiences determine which radiotherapy approach is the best for each patient. In this study we would like to identify a parameter system that will allow identifying a priori the optimal radiotherapy approach for each patient undergoing breast radiotherapy.

## Material and methods

Thirty patients were enrolled from June 2023 to June 2025 based on the following criteria: patients who have previously been treated for breast cancer at IRST’s Radiotherapy Facility; treated region: Left Breast; fractionation scheme of 40.05 Gy in 15 fractions. Three different treatment plans were produced for each patient with different planning approaches such as 3D-CRT (Conformal Radiotherapy), Intensity Modulated Radiotherapy (IMRT), and hybrid strategy (3D-CRT+IMRT). Each analyzed technique was scored from 1 (best) to 3 (worst) in blind by three Radiation Oncologists with proven experience. Then, 2D and 3D anatomical parameters with a crucial role in the choice of the best radiotherapy technique were extracted for each patient. Statistical analyses were performed to identify a correlation between anatomical parameters and treatment plans’ scoring.

## Results

IMRT was selected in 73% of patients, the hybrid approach in 27%, while 3D-CRT was never selected. The overall percentage agreement among the three clinicians was 45.6% (95% CI: 32.3-58.8%). The median Central Lung Distance (CLD) (p=0.009), Maximum Lung Distance (MLD) (p=0.002), Maximum Heart Distance (MHD) (p=0.005), Target Length in slices (p=0.009), Curvature Volume (p=0.02), Volume of Left Anterior Descending Artery receiving 80% Dose prescription (Vol LAD 80%) (p=0.03), Maximum LAD distance (MLAD) (p=0.004) were significantly lower in patients for whom the hybrid technique was selected as the best plan compared to those for whom IMRT was selected. Univariate logistic regression found that CLD, MLD, MHD, MLAD, target length and curvature were associated with a higher likelihood of the Hybrid technique being selected as the optimal plan.

An explorative multivariate logistic regression was conducted using three of the statistically relevant factors (MLD, MHD, Curvature volume) selected by clinicians. It confirmed the trend of the univariate analysis. A trend of an independent association between MLD and MHD was observed.

## Conclusions

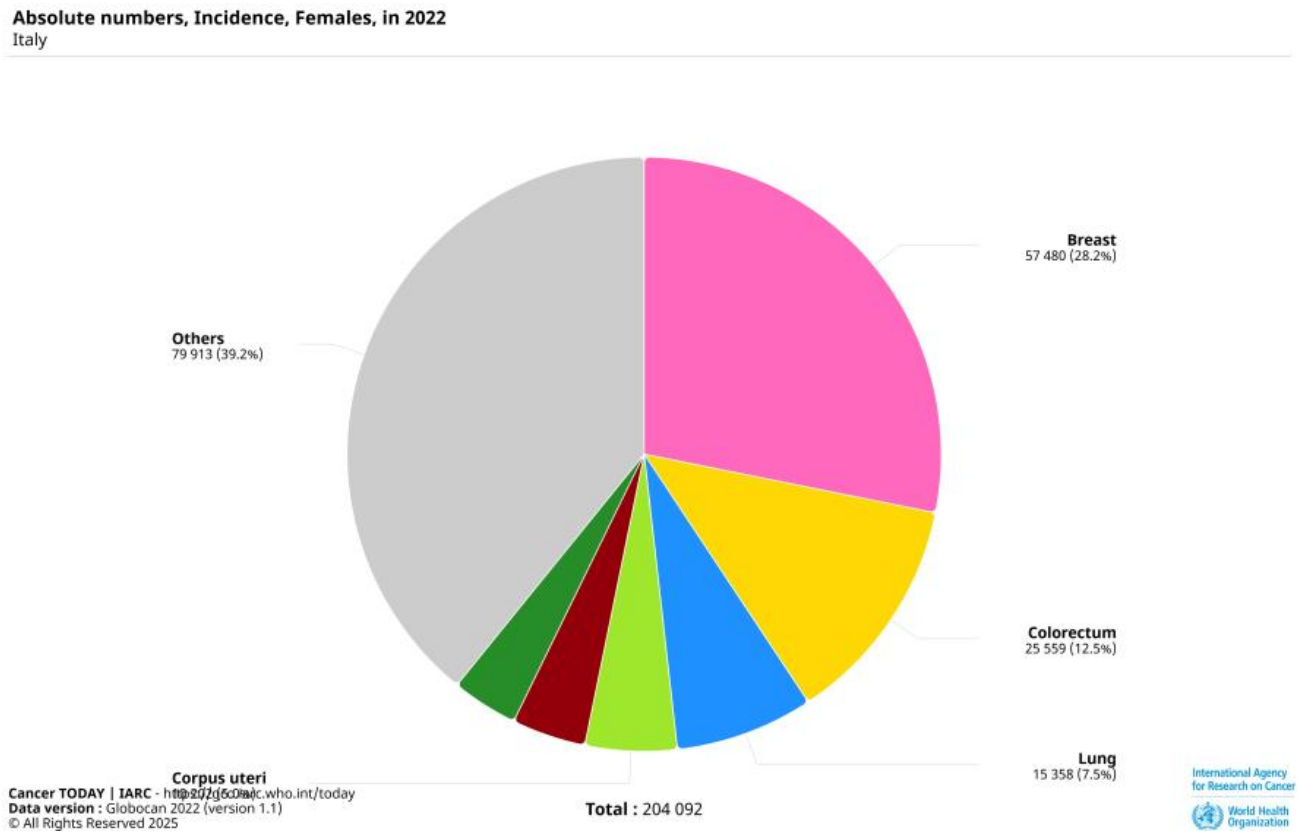
This study identified a set of anatomical parameters able to guide the a priori selection of the optimal planning strategy. Our research showed how crucial it is to develop a parameters-based model for selecting the most effective radiation treatment for patients with breast cancer. Larger prospective and multicenter investigations are assured.

# 1. Introduction

## 1.1. Epidemiology of breast cancer

Breast cancer is the most diagnosed neoplasm in women, accounting for around 1/3 of all malignant tumour diagnosed in women worldwide. In 2022 in Italy, 57480 new cases of breast cancer in women have been diagnosed (28.2%) and 15455 death for breast cancer (17.2%) have been identified, representing the leading cause of cancer death in women as shown in Figure 1a and 1b.

**Figure 1a. Incidence of female cancers [1]. Breast cancer is in pink colour.**



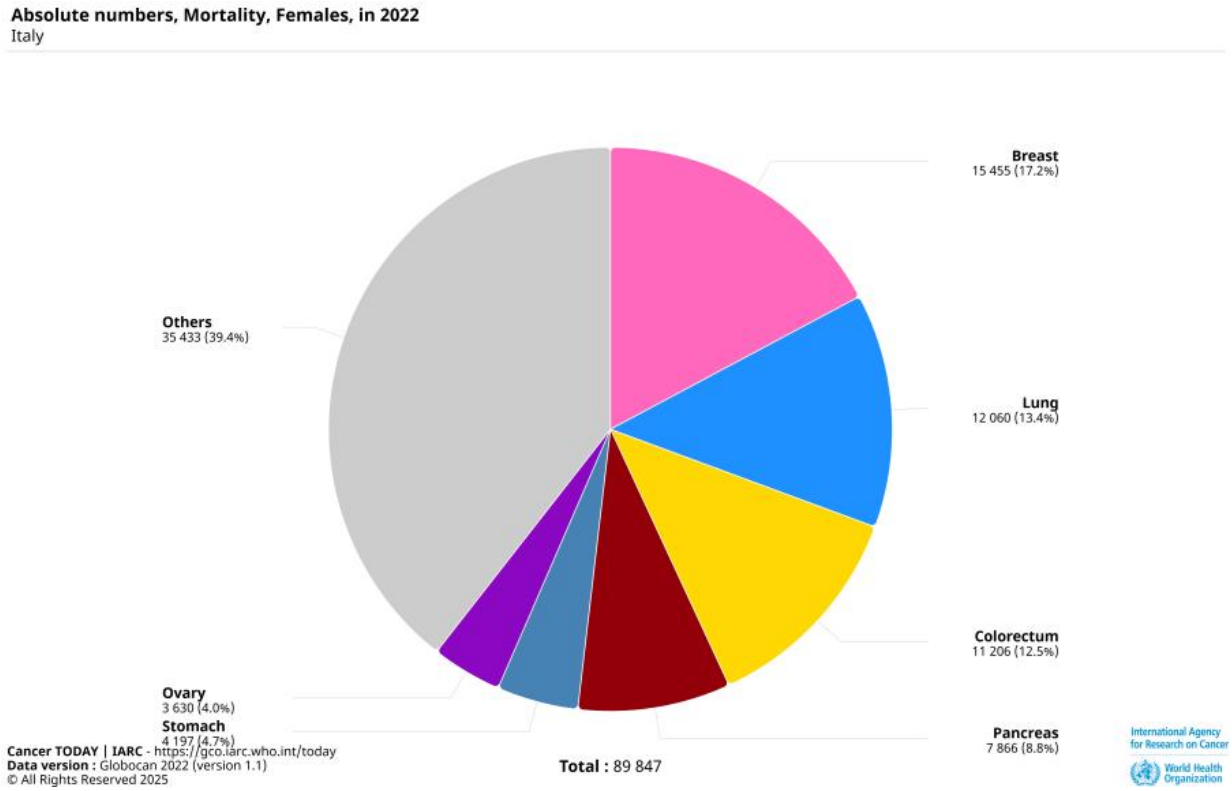



**Figure 1b. Mortality of female cancers [1]. Breast cancer is in pink colour.**

Breast cancer is etiologically, histopathologically and genetically a heterogeneous disease with both hereditary predispositions and non-hereditary factors [2], [3], [4]. The majority of breast cancer refers to mammary carcinoma from ductal or lobular cells in the mammary epithelial tissue. Malignant transformation is due to accumulation of mutations in regions of the genome that are involved in control of cell growth and division, DNA repair and programmed cell death [5]. These mutations could be inherited but mostly are spontaneous, indeed familial occurrence is estimated at 5–10% of all cases[1].

Breast cancer is divided in four clinical stages I, II, III and IV in the tumour–node–metastasis staging system [3] that provide information on aggressiveness of cancer and the extent of invasion [12] (Figure 2).

[1] BRCA1 and BRCA2 are high-penetrance genes which are linked with inherited breast cancer susceptibility, but also TP53, PTEN, CDH1 and SKT11 are found [6]. Lower penetrance genes and genes linked to susceptibility to sporadic breast cancer are described in literature [7], [8], [9], [10]. Important risk factors in the develop of breast cancer include age >55 years, earlier onset of menarche, later menopause, dense breast tissue (more glandular and fibrous tissue) and benign breast conditions (squamous and apocrine metaplasias, fibrosis, adenosis, mastitis or fat necrosis) [7]. Other conditions that could induce higher risk of breast cancer were: first pregnancy after age 30, who did not breastfeed or never had children, hormonal replacement therapy, obesity, low physical activity and unhealthy living habits such as cigarette smoking and alcohol consumption [11].

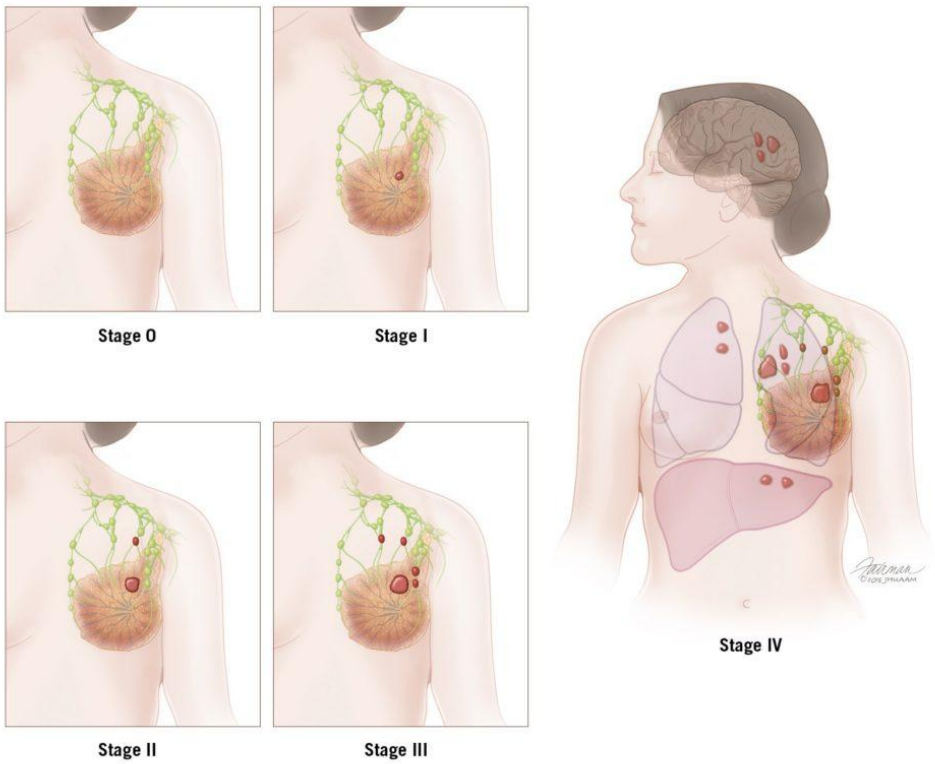



**Figure 2. Breast cancer staging [13].**

Pre-cancerous and invasive breast cancer stages are divided in several histopathological subtypes:

- Non-invasive (in-situ) types of breast tumours remain in a particular location of the breast, without being spread into surrounding breast tissue, lobules or ducts [3]. The two main types of in situ cancers are recognized: ductal carcinoma, which represent 80% of pre-cancerous forms, and lobular carcinoma accounting for the next 20% [14].
- Invasive breast cancer grows invasively into surrounding breast tissue, spread into lymph nodes and other organs. Two main types consists of invasive lobular carcinoma and invasive ductal carcinoma. There are also tumours that are mixed forms of carcinomas. Lobular and ductal carcinoma are heterogeneous groups that can be divided in several subtypes.
- Special types of breast tumours, a category containing rare and histologically or clinically distinct breast cancer.

Breast tumour cells spread by lymph and blood. Tissues mostly affected by metastasis include brain, bones, lungs, and liver. Breast cancer metastases, display certain organotropism, which, in addition to histological origin, is also determined by molecular subtype [10].

## 1.2. Breast cancer therapy path

The treatment options for breast cancer include surgery, radiation therapy, and systemic treatments like chemotherapy, hormone therapy, targeted therapy, or immunotherapy. Surgery, when possible, represents the standard treatment in breast cancer, which allows for organ preservation in most early stage breast cancers. In particular, in the last decades a conservative surgery has been developed for the in situ carcinomas, replacing in most of the cases the radical mastectomy [15], [16]. The multidisciplinary treatments for patients with operable breast cancer combine local, i.e. surgical and radiation therapies, with systemic treatments including a wide range of drugs. Systemic therapy is very important for improving disease-free survival (DFS) based on the control of micro-metastases with the potential to spread throughout the body.

Radiotherapy (RT) plays a crucial role in the multidisciplinary approach of breast cancer. Indeed, most of the breast cancer patients with in situ or invasive tumour is eligible for conservative surgery associated with post surgery (adjuvant) RT treatment on the whole breast remained that is actually the gold standard treatment [17].

## 1.3. Radiotherapy and Breast cancer

Literature data demonstrated that RT had a positive impact on patients outcome reducing the probability of relapse compared to surgery alone [18], [19].

Furthermore, significant evidence has been building on safe strategies to decrease the duration, length, dose, and cost of RT, while maintaining oncologic and cosmetic outcomes [18].

In the advanced stages of breast cancer, literature evidence continues to support a wide indication for adjuvant radiotherapy with a local control benefit of 60% to 70% reduction in recurrence and a 10% improvement in absolute survival [19], [20], [21].

Over the last several years, multidisciplinary guidelines have been updated to standardize breast cancer management with respect to margin status, use of post mastectomy radiation therapy, and use of advanced therapies, including accelerated partial breast radiation therapy [22], [23], [24], [25]. Moreover, the use of hypofractionated treatment is also gaining importance because of the ability to treat patients with a shorter course of therapy and the presence of comparable toxicity profiles, thus adding value and cost savings to the management of breast cancer [26].

In order to increase survival, reduce tumour recurrence and minimize treatment-related toxicities, breast cancer RT must balance between tumour reduction and healthy tissues protection.

## 1.4. Radiation-induced toxicity to organs at risk in breast cancer

Radiation-induced cardiac toxicity is a well-established and clinically significant consequence of RT, particularly in the management of breast malignancies. The anatomical region in which the mammalian gland is located, i.e. the thoracic district, is composed by several organs at risk (OARs). Indeed, a series of treatment-related side effects could arise from a RT treatment. In addition to that, all structures in the thoracic region (such as heart and lungs) have physiological movements that add some critical issues in the treatment of breast cancer with RT. Moreover, their close proximity to breast cancer target, depending on the patient' anatomy, is an additional cause of complication for this type of local treatment [17].

Patients undergoing left-sided breast irradiation are particularly at risk because of the close proximity of the heart to the treatment field, which raises mean heart doses and increases the likelihood of adverse cardiac events such heart failure and coronary artery disease [27], [28]. Even low to moderate mean heart doses give an additional risk of severe coronary events, demonstrating the dose-dependent and linear link between cardiac dose and toxicity. For instance, it has been demonstrated that the excess risks of major coronary events increase by over 20% for every additional gray (Gy) of mean cardiac dosage [29].

In the past, breast RT planning simply contoured the entire heart as an OAR. However, research has demonstrated that even when the mean cardiac dosage falls within permissible bounds, the left anterior descending artery (LAD) can still receive large doses, underscoring the necessity of its distinct identification [30]. Since 2011, literature studies started to suggest evaluating the LAD dosage in addition to the heart. LAD delineation's frequent use as a distinct OAR was supported by its demonstrated consistency and reliability by 2016 [31]. Because of its front anatomical location, the LAD frequently gets larger doses than the rest of the heart, which makes it especially vulnerable to radiation-induced damage [30], [32], [33]. Clinical evidence indicates that greater mean and maximum LAD doses are linked to a higher risk of cardiac events; higher event rates are correlated with thresholds such as mean LAD dose > 2.8Gy and maximum > 6.7Gy [32]. Incorporating the LAD into treatment planning and optimization algorithms considerably lowers its radiation dose without sacrificing target coverage, according to recent dosimetric and clinical studies [32], [33], [34].

In breast cancer radiation therapy, ipsilateral lung damage is a known risk, with radiation pneumonitis and pulmonary fibrosis being the primary issues. The amount of lung volume exposed to radiation and the radiation dose are directly related to the likelihood and seriousness of these side effects. One of the most reliable indicators of both acute and late lung damage is V20 (percentage of

lung volume receiving 20 Gy). To reduce the incidence of radiation pneumonitis, a number of studies advised maintaining the ipsilateral lung V20 below 30%. Some even indicated even lower thresholds (e.g., <26%) for hypofractionated regimens. [35], [36], [37], [38].
Also mean lung dose is considerated as a key predictor of lung toxicity. An elevated risk of lung toxicity is linked to a mean lung dosage exceeding 10–15 Gy. For safety the mean dose should be kept between 10.5 and 15 Gy [35], [38], [39], [40].
Additional toxicities associated with this type of treatment are dermatitis [41], modifications in breast volume, scars and skin changes [42] or fat necrosis [43].

## 1.5. Radiotherapy techniques on linear accelerator (LINAC)

Since the beginning of RT in clinic, breast cancer has been one of the most treated cancer because of its high incidence. To date the most common device which delivers RT to breast cancer patient is linear accelerator (LINAC).
Different planning and treatment techniques are available on LINAC, each one with its strengths and weaknesses.
Since 1980s and 1990s, the development of Computed Tomography (CT) scanners and Treatment Planning Systems (TPS) has enabled multiplanar visualization of the patient's anatomy, allowing for greater precision in defining treatment beams by providing a better estimate of the relationships between OARs and target structures. Traditional two-dimensional techniques have thus given way to the emergence of 3D conformal therapy (3D-CRT).
Furthermore, the introduction of collimation systems consisting of multiple leaves, called multi-leaf collimators (MLC) has allowed for a further increase in terms of precision in the conformation of the dose to the tumour volume, resulting in the 3D-CRT technique as it is known today. With 3D-CRT, both beam entrance and conformation (i.e. MLC configuration, wedges, angulations and relative weight) are manually derived by the operator, in the so call direct planning process. The number of beams ranges from 2 up to 4 fields (2 major fields + 2 compensative with lower relative weight).
From 2000s and 2010s, the advent of more sophisticated TPS able to perform forward planning, opened the path for more modulate techniques, with fixed beam entrance (Intensity Modulated RadioTherapy, IMRT) or delivered dynamical on an arc (Volumetric Modulated Arch Therapy, VMAT). Indeed the forward planning is able to backward calculate the optimal beam aperture starting form a desired dose distribution described by the operator.

Firstly IMRT was developed as an evolution of 3D-CRT technique, consisting in the delivery of radiation to the patient via fields that have non-uniform radiation fluence [44], [45], [46]. This feature allows more conformality and less high radiation dose to radiosensitive normal tissues close to the lesion even if they lie within a concavity in the Planning Target Volume (PTV) [47], [48]. Intensity modulation is possible by dividing a field into small beams, segments or Control Points (CPs) [49]; with different MLC configuration and different dose rate (i.e. monitor units/CPs) for each segment. Due to the computational complexity IMRT treatments are optimized with inverse planning technique (IP), starting with dose prescription and dose constraints on OARs and resulting in beam and segments' conformation and weight. IMRT step-and-shoot technique (segmental MLC) involves the dose being delivered in static segments: MLC leaves are positioned to form a segment, the beam is turned on and irradiates, then turned off while the leaves move to the next segment. This process is repeated until treatment is complete. Compared to the sliding window technique (dynamic), step-and-shoot is simpler to verify, requires fewer monitor units (MU), and reduces scatter dose, while maintaining comparable target coverage and protection of organs at risk [50].

Arc therapies, in particular VMAT, were developed from IMRT techniques: in addition to dose modulation gantry rotation during dose delivery was implemented.

In particular each treatment arc is divided into a defined number of arc portion (defined as VMAT CPs). For each CP a MLC conformation is set by TPS from IP technique, due to an increment of technical complexity [51].

While optimal beam aperture are derived automatically by the TPS, the irradiation technique (i.e. IMRT, VMAT, combined 3D-CRT and modulated technique), number of beams and beams entrances should be determined by the operator. In comparison with conventional 3D-CRT, IMRT and VMAT enhance target coverage and reduce high-dose exposure to organs at risk; however, this modulation generally enlarges the volume of tissue receiving lower doses, often referred to as the low-dose bath [52], [53], [54]. Furthermore, IMRT and VMAT typically require a higher number of MUs than 3D-CRT, which has been associated with an increased out-of-field dose and a potentially greater risk of secondary cancer induction. This aspect should be carefully considered when selecting a treatment technique, particularly for patients with good prognosis or long expected survival [55], [56].

The most commonly used treatment techniques in breast cancer radiotherapy are accelerator-based: 3D-CRT, IMRT and VMAT. The IMRT and VMAT have been developed in the last 20 years, thanks to software and hardware implementation [57], [58], [59].

Other radiotherapy techniques were developed linked to particular radiotherapy accelerator, such as Tomotherapy, which is an advanced radiotherapy technique that combines the precision of CT with

modulated and rotational radiation delivery. Tomotherapy uses a linear accelerator mounted on a circular gantry (similar to a CT scanner) that rotates around the patient. During treatment, the patient is slowly moved thru the gantry while a fan-shaped radiation beam rotates and is modulated by a multileaf collimator. This allows the dose to be delivered in a helical manner, ensuring homogeneous and precise coverage of the tumour target [60]. However, in centres where a standard LINAC is available, the Tomotherapy is nowadays used for limited cases of breast cancer RT.

## 1.6. Personalised radiotherapy in breast cancer

An accurate treatment delivery involves a personalized approach and takes into account different factors: choice of treatment technique, the position on treatment couch, choice of immobilization system, patient-related parameters (tumour volume, comorbidities, body mass index, the volume and position of the OARs with respect to the target) and the quality of dose distribution conformed to target volume geometry [61], [62]. Several factors have been reported in literature to influence the final outcome of a treatment plan, for example: tumour volume and lymph nodes involvement [63], the number of fields and field geometry, irradiation of healthy tissue areas, overdosed and underdosed regions of tumour volume, dosimetry of OARs [64]. OARs-related parameters should be taken into account in the assessment of the treatment plan and their importance is given by the OAR located nearby the tumour volume, such as the heart and ipsilateral lung for breast cancer target. Literature data showed studies that evaluated heart and lung parameters based on digitally reconstructed radiographs (DRR) [65], [66] or treatment field [52], [67], [68]. These parameters (maximum heart length - MHL, maximum heart distance - MHD, maximum ipsilateral lung length - MLL and maximum ipsilateral lung distance - MLD) could affect dose and irradiated OAR volume. Tumour location has a great role importance in breast cancer irradiation, indeed left and right-sided breast cancer patients involve different radiation-induced risks, leading to differences in the anatomical location of critical organs. Therefore, evaluation of dosimetric indicators for each patient category and their correlation with patient-related parameters can offer important information regarding optimization of breast cancer radiotherapy [62].

## 2. Aim of the project

At the Istituto Romagnolo per lo Studio dei Tumori “Dino Amadori” (IRST) in Meldola, patients are treated with several radiotherapy techniques (3D-CRT, IMRT, Tomotherapy). The most often used fractionation in the treatment of breast cancer is 40.05 Gy in 15 fractions (2.67 Gy/session), according to literature studies [69]. The optimal approach is often determined by the planner's and clinician's expertise, typically starting with the 3D-CRT technique that is the simplest, increasing the complexity if dose constraints and dose distribution acceptance are not reached using a trial and error approach. The 3D-CRT tangential plans target and all the characteristics (opening of the collimator, relative weight and angle of the wedge filter) are set by the planner with a direct planning technique (Forward Planning or FP). If the dose limits for OAR are not satisfactory or there are issues in dose distribution (i.e. an high involvement of posterior healthy tissues at underarm level), treatment plans are performed with different techniques. The IMRT technique step-and-shoot (S&S) delivery is chosen as alternative to 3D-CRT and provide for the use of a higher number of fields (maximum 8). Using an IP technique, we try to find dose value, dose distribution and histogram dose volume wanted through imposing dose limits to OAR or to structures created ad hoc for planning (named “ghost” or “help”).

The hybrid technique has been used since 2020 at IRST and consists of the delivery of no more than 80% of the prescription dose in 3D-CRT mode and the dose remaining of two or more IMRT step-and-shoot field (usually set with the same entry angle than 3D-CRT field) [59].

If the hybrid approach is not able to reach the dosimetric goals, a full IMRT approach is then used.

Actually, the RT plan and RT technique that will be used for each breast patient’s treatment is defined by physicist’s and clinicians’ experience during RT plan approval session. The absence of a standardized method with defined anatomical parameters, could led to operator dependent choices and time consuming procedure. With the increased number of cancer patients requiring RT treatment, the optimisation of required time in treatment planning is crucial. Moreover, standardization and parameters able to guide through the best treatment approach is required in the view of personalized treatment strategies. For these reasons in this study we would like to identify a parameter system that will allow identifying a priori the best optimal radiotherapy approach for each patient undergoing breast radiotherapy at our centre. The aim of this project is to identify a parameter system that allows to a priori find and guide which radiotherapy technique could be the most useful for each breast cancer patient treated at IRST centre. To reach this aim, a score will be assigned to different treatment plans by three blinded clinicians with proven experience in the field of RT and anatomical parameters will be extrapolated for each patient.

# 3. Materials and methods

## 3.1. Study design and patient cohort

Thirty patients with breast cancer were enrolled in the present study conducted at IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori," Meldola, Italy.
Inclusion criteria were:

- patients already treated with fractionation regimen of 40.05 Gy in 15 fractions [69] in the Radiotherapy Unit at IRST in Meldola;
- diagnosis of breast cancer in the left breast.

Left breast was chosen as inclusion criteria because of its ipsilateral position to the heart (which is one of the most important OAR) [70], [71].
The study was approved by the local Ethical Committee (protocol code: IRST174.27 PaRTyB) in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference of Harmonization. Written informed consent was obtained from all patients.

## 3.2. Patient immobilisation and CT acquisition

To date at IRST, after the first medical examination and RT prescription, a setup CT is acquired, useful to define the patient positioning that has to be maintained for the whole treatment process. In this study all patients' were set up in supine position with "Posirest™-2" [72] for chest and arm immobilisation and "KneeFix-2™" [73] to maintain knees slightly bent and the back resting on the CT bed. All CT scans were acquired with the same scanner, a Siemens "SOMATOM go. Open pro™" [74] in free breathing.
CT scans were acquired with the same standard fixed exam protocol:

- Slice thickness: 3mm
- Pitch: 0.80
- Voltage: 120 kV
- Scout: Postero-Anterior
- Rotational time: 0.35
- Acquisition: from top to bottom (from gonion to bottom liver)

All patient were marked with 3 tattoos on thorax skin (one on Median Sagittal Plane, one on the left side and one on the right), marking the points in which the laser optical references cross for the subsequent radiotherapy sessions [75].

All OARs, except for LAD, were automatically contoured on CT data sets by a tool integrated in the CT scanner. Target contouring and OARs contouring check were performed by radiation oncologists of the Radiotherapy Unit in IRST on Treatment Planning System (TPS) software Pinnacle³ (16.2.1 version).

## 3.3. Radiotherapy techniques and plan optimisation

According to clinical practice, three radiotherapy techniques for treatment plan were evaluated: 3D-CRT, IMRT (S&S) and a hybrid technique (3D-CRT+IMRT), from here called h-IMRT or hybrid. All plans were calculated with 6 MV energy beams.

The breast 3D-CRT technique consists of at least two opposed radiation fields (medial and lateral) tangential to the breast wall using a MLC to conform the dose closely to the target (Figure 3). Wedges were also used to compensate for tissue curvature. The tangential asset allows to maximise target volume dose coverage and dose sparing to healthy tissue around target volume and OARs such as heart, left anterior descending coronary artery (LAD), lungs and contralateral breast [76], [77], [78], [79].

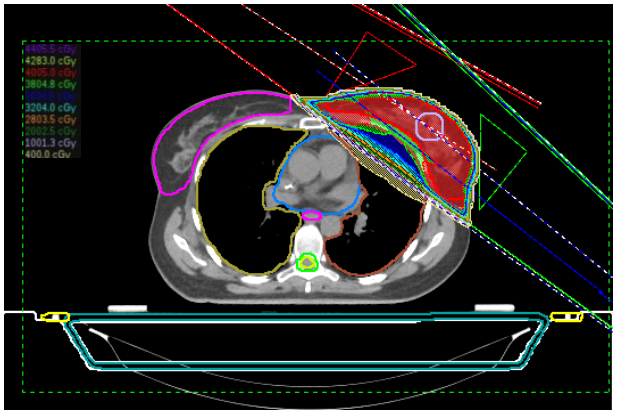



**Figure 3. 3D-CRT dose distribution and fields' asset**

In this study compensatory fields, additional lightly weighted subfields, were used for example in larger or irregularly shaped breasts to homogenise dose distribution, reducing hot spots and acute skin toxicity [77], [78], [79], [80], [81]. In particular a maximum of two accessory fields were set with maximum relative weight 9% with 3 fields setting and 5% with 4 fields setting.

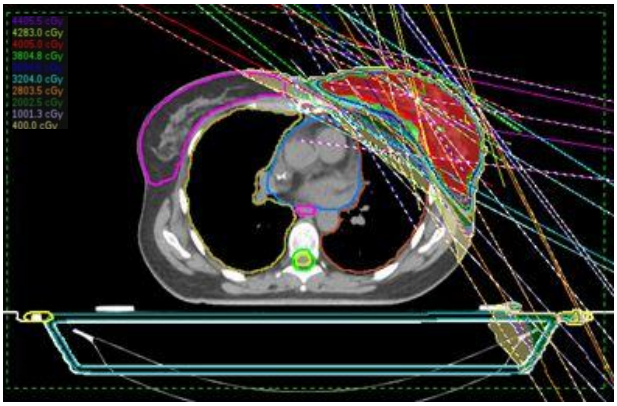



**Figure 4. IMRT dose distribution and fields' asset**

Target coverage in 3D-CRT fields was assured by opening MLC with 8mm margin around target structure to take penumbra into account and estimate patient's breathing movement [82], [83] and with a margin of 2.5 cm between the MLC and target in anterior (air side) direction [84].

At IRST the complete IMRT setting is made by 8 step-and-shoot fields (4 medial and 4 lateral), with different orientations and 10 CPs per field set (Figure 4); for this reason all IMRT plans of this study were planned with eight beams setting, with a total of 80 CPs (Figure 5).

The collimator orientation was set 0° for each field. The beams' entrances were initially standard (medial: 305°,315°,325°, 345°; lateral: 100°,120°,130°,140°), spanning over the lateral and medial entrance beam that would be used for a 3D-CRT 2 beams configuration (e.g. angles =310° medial, 125° lateral). If necessary beam entrance angles were then adjusted by a maximum of ±20° based on single patient anatomy. IMRT was then optimised with IP.

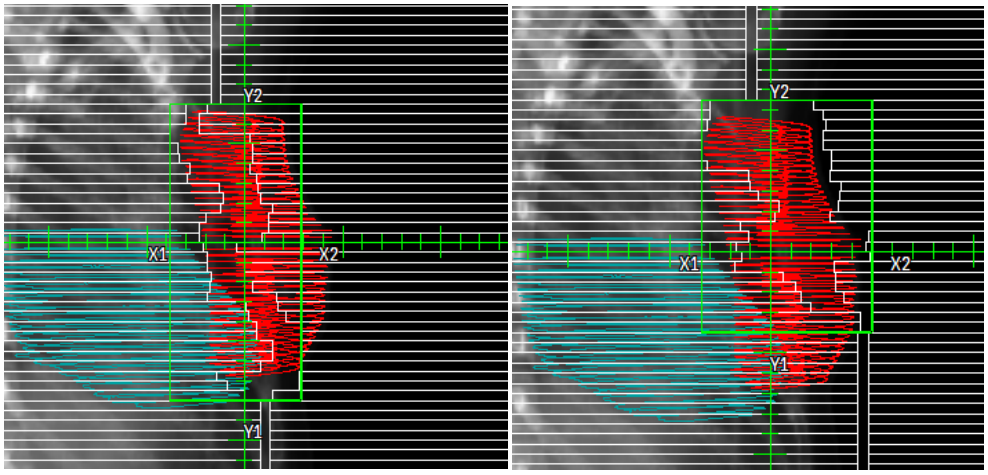



**Figure 5. Different MLC position in BEV in 2 different CPs of IMRT field: white lines indicate MLC leaf position**

H-IMRT (Figure 6) consists of a fusion of 3D-CRT technique planned in FP and IMRT technique optimised in IP. First a 3D-CRT plan is planned in FP. Then the 3D-CRT's dose contribution is set to 60-80% of the total dose prescription (40.05 Gy in 15 fractions) [85]. The remaining dose contribution is compensated by adding a maximum of 3 step-and-shoot IMRT fields with 10 CPs per field. IMRT fields' beam entrances are usually set

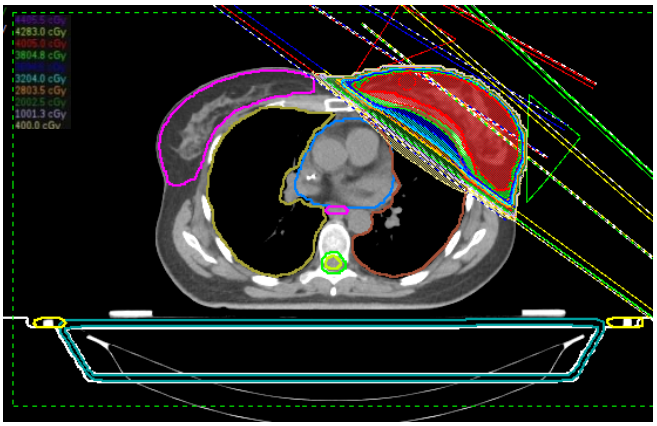


**Figure 6. Hybrid dose distribution and fields' asset**

equal to the 3D-CRT beam orientation, or spanning over ±10°.

All RT simulations (plans) were optimised on TPS using a calculation grid 0.3x0.3x0.3 $cm^3$ voxel covering all OARs structures with Cone Collapsed Convolution algorithm.

At IRST an internal protocol for 40.05Gy/15 fractions in breast treatment was developed based on literature studies and on clinical experience.

Each RT plan was optimised trying to reach the following dose constraints for target and OARs structures:

- **Target:**
  - Coverage 98% (3925 Gy) dose prescription at 98% volume ($1^{st}$ goal) – coverage 95% (3805 Gy) of dose prescription at 95% volume ($2^{nd}$ goal);
  - 107% (4285 Gy) dose prescription at 1% volume ($1^{st}$ goal) - 110% (4405 Gy) of dose prescription at 1% volume ($2^{nd}$ goal).
- **Contralateral breast:**
  - Mean dose<1.5 Gy ($2^{nd}$ goal: < 3Gy) [86], [87];
  - D max<6 Gy ($2^{nd}$ goal: < 10Gy) [86];
  - V5 Gy<15 % [88], [89], [90].
- **Homolateral lung:**
  - Mean dose<5 Gy ($2^{nd}$ goal: <8 Gy) clinical experience [87], [88]
  - V20 Gy<10 % [86];
  - V16 Gy<15% ($2^{nd}$ goal: <20%) [91], [92];
  - V8 Gy<35% [91], [92];
  - V4 Gy<50% [86], [92].
- **Contralateral lung:**
  - Mean Dose<2 Gy [87];
  - V4 Gy<5% [86].
- **LAD:**
  - V17 Gy<1 % ($2^{nd}$ goal: <2%) [86], [93]
- **Hearth:**
  - Mean dose<3Gy ($2^{nd}$ goal: <4Gy) [86], [87];
  - V35 Gy<1% [86], [94];
  - V17 Gy<5 % [86], [94];
  - V8 Gy<10 %.
- **Tyroid:**
  - Dose max<0.8 Gy.

Efforts were made in every plan to fulfil the limits as best as feasible. While not every plan was able to fully address every limitation, the second goal of target coverage (coverage 95% (3805 Gy) of dose prescription at 95% volume) was prioritised.

## 3.4.Anatomical parameters

Anatomical and clinical parameters with a crucial role in the choice of the best radiotherapy technique were evaluated based on literature data and clinical practice [95], [96].
Two-dimensional (2D) parameters were calculated on 3D-CRT medial tangential fields - except for Contralateral breast distance - with DRR images visualization and CT data set using TPS (Figure 7, 8, 9, 10) for an Elekta VERSA HD were [65], [68], [97]:

- **Maximum Hearth Length** (MHL, cm): The maximum crano-caudal length from the top hearth slice involved in the tangential fields to the bottom one;
- **Maximum Heart Distance** (MHD, cm): the maximum width of the heart in the tangential fields (from tangent fields jaw position to the edge of hearth contour);
- **Maximum LAD Distance** (MLAD, cm): the maximum width of the LAD in the tangential fields (from tangent fields jaw position to the edge of LAD contour);

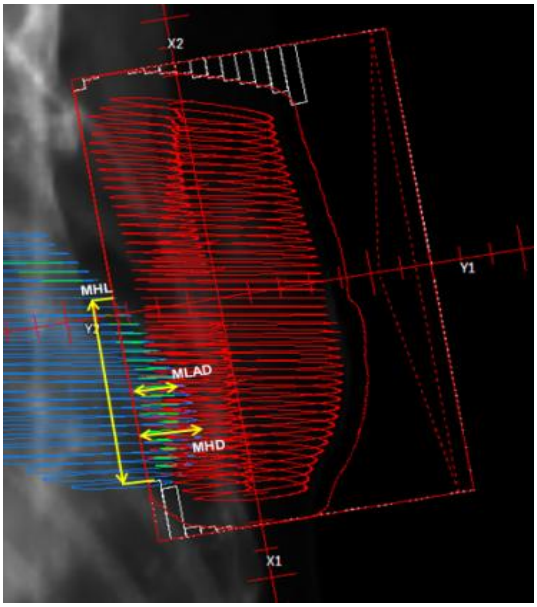


**Figure 7 DRR with heart and LAD 2D parameters in beam's eye view (BEV)**

- **Central Lung distance** (CLD, cm): The distance measured from the medial field border to the edge of the lung contour at the central axis on the tangential field;

- **Maximum Lung Distance** (MLD, cm): the maximum width of the ipsilateral lung in the tangential fields (from tangent fields jaw position to the edge of lung contour);
- **Maximum Lung Length** (MLL, cm): The maximum crano-caudal length from the top ipsilateral lung slice involved in the tangential fields to the bottom;
- **Target length**:
    - Distance from target top slice to bottom slice (number of slices x 0.3cm);
    - Target length on longitudinal axis of tangential fields on DRR (cm);

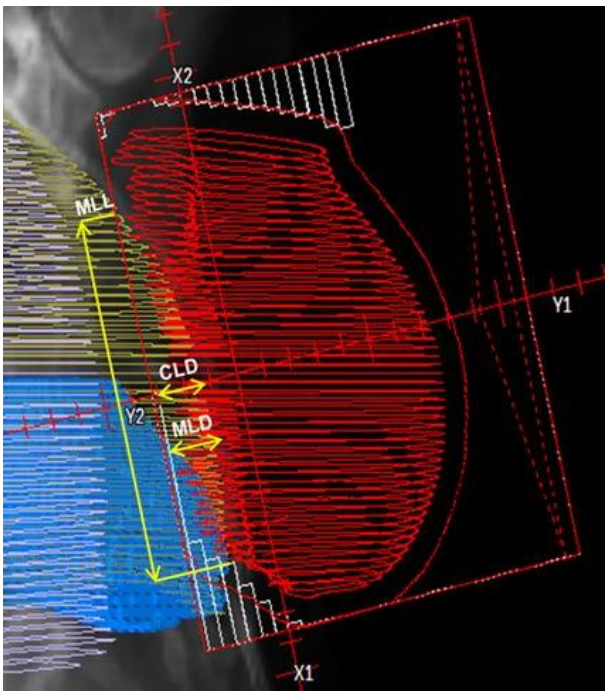



**Figure 8. DRR with lung 2D parameters in BEV**

- **Contralateral breast distance** (CBD0, cm) was calculated using DRR at 0 degrees: distance from the most medial margin of the right breast and the most medial target's margin.

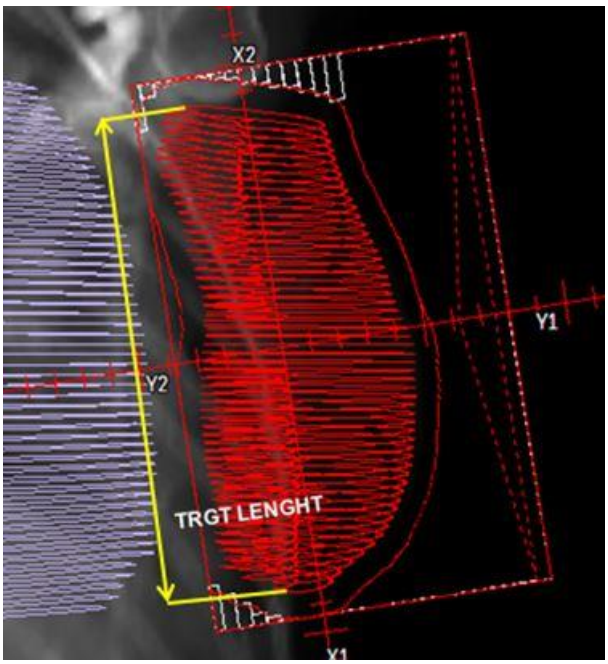



**Figure 10. DRR with target length in BEV**

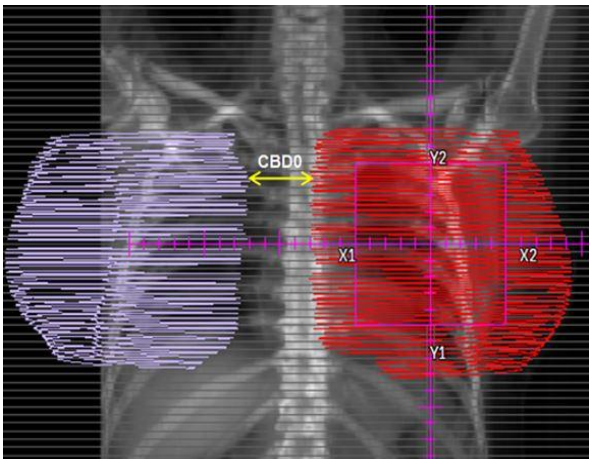



**Figure 9. DRR 0° with CBD0**

3D parameters measured using TPS's volume computation tool were:

- **Heart volume** ($cm^3$);
- **Lung volume** ($cm^3$);
- **Target volume** ($cm^3$);
- **Target curvature volume** (cm3): Region of interest (ROI) structure indicating the level of curvature of the target structure. This ROI was calculated as the region between the line of target margins and target's posterior region in each slice on transverse plane (Figure 11);
- **LAD ISO 80%** ($cm^3$): LAD volume receiving more than 80% of the dose prescription in 3D-CRT plan;

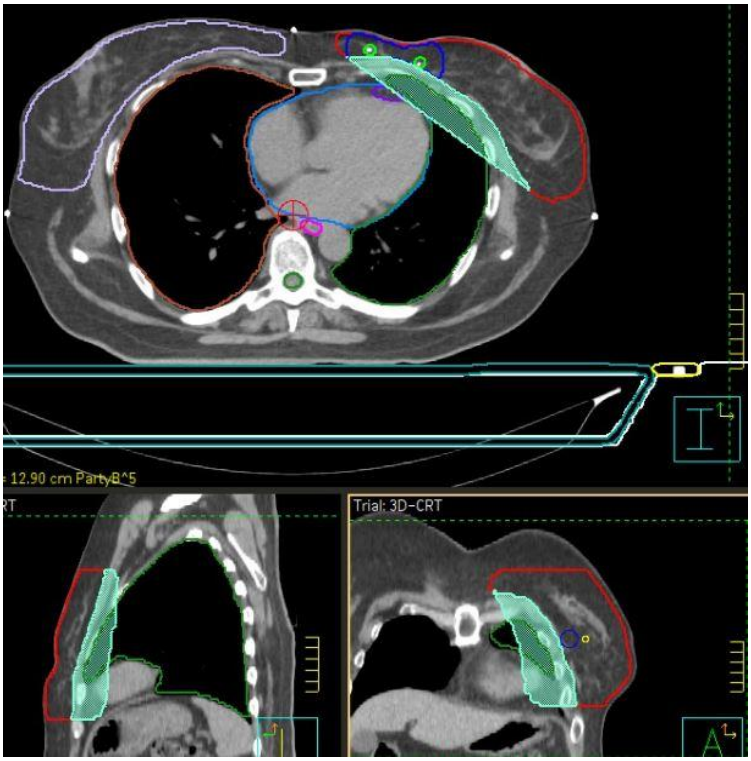



**Figure 11. Curvature volume (colorwash acquamarine) in multiplanar view**

- **Lateral tissue** ($cm^3$): healthy tissue located in poster lateral position compared to target irradiated by 3D-CRT tangential fields. To obtain this volume, a ROI was drawn on the axial slices with the posterior border being the proximal margin of the lateral tangential field, the medial border being its perpendicular and the 8 mm expansion of the target, and the anterior and lateral borders being the "body" structure, as shown in Figure 12.

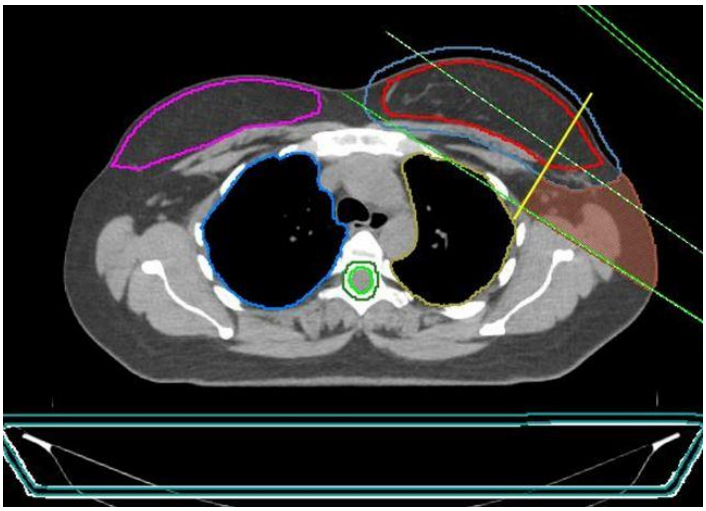


**Figure 12. Lateral tissue (colorwash brown) o transverse plane**

## 3.5. Treatment scoring

Three Radiation Oncologists (MDs) in blind with proven experience evaluated the three treatment plans (3D-CRT, IMRT and h-IMRT) produced for each patient enrolled.
Scoring process was performed reflecting the real-world plan approval process. In particular dose volume histogram (DVH), 3D dose distribution on CT data sets and compliance of internal protocol dose constraints for each plan were evaluated. A score was assigned as follows:

- "1" for the best treatment plan;
- "2" for the second best treatment plan;
- "3" for the last choice of treatment plan.

By performing the median score over all clinicians of each treatment plan, the plan achieving score 1 was selected as the best treatment option for the patient. If no plan achieved a median score of 1, the patient was included in the test set for the parameter signature. This situation typically occurs when each treatment plan has been rated once as the best, once as the second-best, and once as the worst. In such cases, there is no clear collective preference — the patient is therefore classified as uncertain.
The scores allowed us to draw up a ranking of the best treatment plans. The median score determined the optimal plan for each patient.

## 3.6.Statistical analysis

All statistical analyses were performed by Biostatistics Unit using R software (version 4.4.2) and Stata (version 15). A two-sided p-value $<0.05$ was considered statistically significant.
Continuous variables, namely the quantitative anatomical parameters, were summarized as median and range. Categorical variables, including RT technique and clinician-assigned rankings, were reported as frequencies and percentages.
For each patient, the three treatment plans (3D-CRT, IMRT, and Hybrid technique) were independently scored by three clinicians (1 = best, 2 = second best, 3 = worst). The median score for each plan across clinicians was calculated, and the plan with a median score of 1 was designated as the optimal treatment. In cases where no plan achieved a median score of 1 (indicating an equal distribution of rankings) the case would have been classified as "uncertain" and excluded from

comparative analyses; however no such cases occurred. This use of the median was chosen as a robust, non-parametric synthesis of clinician rankings.

Inter-rater agreement among clinicians in plan selection was assessed using percent agreement and Cohen's kappa coefficient (κ). Percent agreement represents the proportion of cases in which clinicians selected the same plan, however, it does not account for agreement occurring by chance. Cohen's κ quantify the degree of agreement beyond chance by comparing the observed agreement with the agreement expected under random allocation of ratings, thereby providing a chance-corrected measure of inter-rater reliability. Kappa values range from –1 to 1, with higher values indicating stronger agreement. Following Landis and Koch [98], κ values <0 indicate poor agreement, 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and >0.80 almost perfect agreement. Ninety-five percent confidence intervals for κ were computed using standard asymptotic methods. Comparisons of continuous parameters between groups (i.e., Hybrid vs IMRT) were performed using the Wilcoxon rank-sum test, while categorical variables were compared using the Pearson chi-square or Fisher's exact test. The Wilcoxon rank-sum test is a non-parametric method that compares the distribution of a continuous variable between two independent groups without assuming normality, making it suitable for small samples. The Pearson $\chi^2$ test evaluates the association between categorical variables, while the Fisher's exact test is applied when sample sizes are small (when expected cell counts were <5 in at least 80% of cells).

Univariate logistic regression models were fitted to estimate the association between each parameter and the likelihood of selecting the Hybrid technique rather than IMRT. Given the limited sample size and the small number of Hybrid cases (i.e., outcome events), particular attention was paid to the risk of model overfitting in multivariable logistic regression analyses. In small datasets, including an excessive number of predictors relative to the number of events may lead to unstable coefficient estimates, inflated effect sizes, and reduced model generalizability. To enhance model stability and interpretability, the number of variables included in the multivariable model was therefore intentionally restricted. An exploratory multivariable logistic regression model was constructed including three parameters related to OARs dose and toxicity [71], [99] selected a priori based on their clinical relevance. This parsimonious approach was adopted to ensure a clinically meaningful and methodologically robust assessment of potential independent associations. Odds ratios (ORs) of univariate and multivariable logistic regression models were estimated using the original measurement scale of each variable and were not standardized. This choice was made to preserve clinical interpretability, allowing the estimated effect to be directly interpreted per unit increase in the corresponding anatomical or dosimetric parameter. Results of all logistic regression models are reported as ORs with 95% confidence intervals (CIs) and corresponding Wald p-values.

# 4. Results

## 4.1. Patient population overview

Thirty patients were enrolled from June 2023 to June 2025. Median age was 60 years (range: 45-77 years).

3D-CRT, IMRT and h-IMRT were evaluated for all patients.

The IMRT technique was chosen as the first choice (score=1) for 22 patients (73%), h-IMRT for 8 patients (27%). 3D-CRT technique was never selected as the best treatment plan (Table 1).

**Table 1. Clinicians' choice for each patient.**

| Patient | best_plan | Patient | best_plan |
|---|---|---|---|
| ParTyB.1 | hybrid | ParTyB.16 | imrt |
| ParTyB.2 | hybrid | ParTyB.17 | imrt |
| ParTyB.3 | imrt | ParTyB.18 | hybrid |
| ParTyB.4 | imrt | ParTyB.19 | imrt |
| ParTyB.5 | imrt | ParTyB.20 | imrt |
| ParTyB.6 | hybrid | ParTyB.21 | imrt |
| ParTyB.7 | imrt | ParTyB.22 | imrt |
| ParTyB.8 | imrt | ParTyB.23 | imrt |
| ParTyB.9 | hybrid | ParTyB.24 | imrt |
| ParTyB.10 | imrt | ParTyB.25 | hybrid |
| ParTyB.11 | imrt | ParTyB.26 | hybrid |
| ParTyB.12 | imrt | ParTyB.27 | imrt |
| ParTyB.13 | imrt | ParTyB.28 | imrt |
| ParTyB.14 | hybrid | ParTyB.29 | imrt |
| ParTyB.15 | imrt | ParTyB.30 | imrt |

## 4.2. Clinicians Concordance

Overall, the three clinicians gave the same assessment in 45.6% of cases (95% CI: 32.3–58.8%) as shown in Figure 13. When accounting for agreement that could occur by chance, the Cohen's kappa coefficient ($\kappa = 0.16$; 95% CI: 0.01–0.33) indicated only a slight level of concordance among evaluators.

When considering each pair of MDs separately, MD1 and MD2 showed agreement in 33.3% of cases (95% CI: 15.4–51.2%), and MD1 and MD3 in 30.0% (95% CI: 12.6–47.4%). In both pairs, concordance remained low after adjusting for agreement expected by chance ($\kappa = 0.12$ and $\kappa = 0.09$, respectively). The pair MD2 and MD3 showed a higher raw agreement of 73.3% (95% CI: 56.5–90.1%), although the corresponding Cohen's kappa ($\kappa = 0.37$; 95% CI: −0.01–0.74) still indicated only a fair level of agreement, possibly influenced by the small sample size and variability in the evaluations.

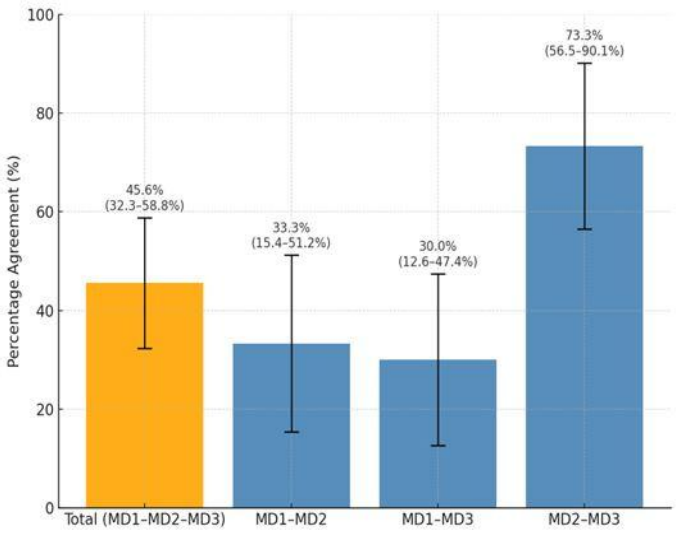



**Figure 13. Clinicians concordance (total and pairwise)**

## 4.3.Parameters distribution

A comparison of parameter distributions was performed to assess differences between patients for whom IMRT or the hybrid technique was selected as the best treatment plan (Table 2, Figure 14).

The median CLD (p=0.009), MLD (p=0.002), MHD (p=0.005), Target Lenght in slices (p=0.009) and MLAD (p=0.004) were significantly lower among 2D parameters in patients for whom the hybrid technique was selected as the best plan, compared to those for whom IMRT was selected.

Among 3D metrics, patients for whom the hybrid approach was chosen as the best plan had significantly lower median Target Volume Curvature (p=0.02) and VOL LAD 80% (p=0.03), than patients for whom IMRT was chosen.

These results suggest that patients with lower values of these parameters were more likely to be addressed to the hybrid technique as the optimal treatment.

Violin plots (Figure 14) show the distribution of one statistically significant parameter (MHD), and one non-statistically significant parameter (Lateral Tissue).

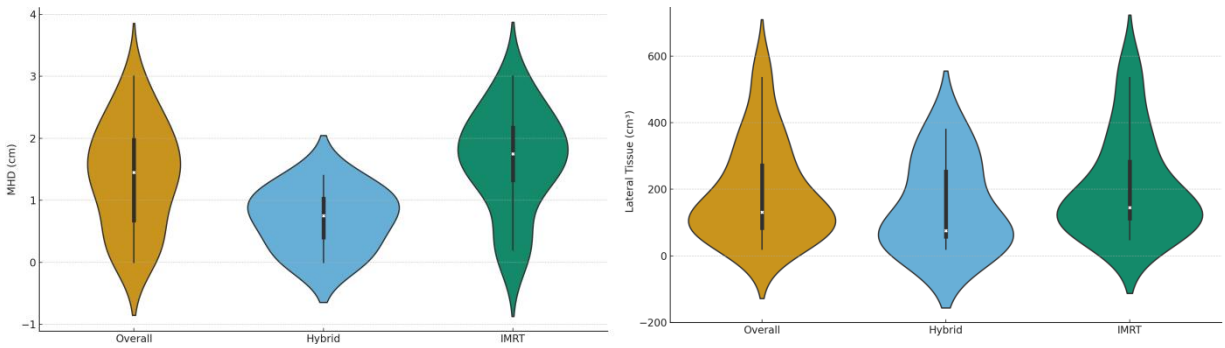



**Figure 14. Violin plots of MHD and Lateral tissue. In orange overall, in lightblue Hybrid and in green IMRT**

**Table 2. Parameters distribution. * Wilcoxon rank-sum test was used to compare the parameter values among patients for whom the selected best plan was the hybrid technique and those for whom it was IMRT.**

| Parameters | Overall (N=30) | Hybrid (N=8) | IMRT (N=22) | *p** |
|---|---|---|---|---|
| **LUNG – median, min-max** | | | | |
| **CLD (cm)** | 2.1, 1-3.4 | 1.8, 1.2-2.1 | 2.4, 1-3.4 | **0.009** |
| **MLD (cm)** | 2.4, 1.2-3.6 | 1.9, 1.2-2.2 | 2.6, 1.2-3.6 | **0.002** |
| **MLL (cm)** | 14.35, 7.7-17.6 | 14.1, 7.9-15 | 14.7, 7.7-17.6 | 0.07 |
| **VOLUME ($cm^3$)** | 1235, 910-2131 | 1548, 910-1845 | 1215, 916-2131 | 0.07 |
| **HEART – median, min-max** | | | | |
| **MHL (cm)** | 5.8, 0-8.9 | 4.3, 0-8.5 | 6.8, 0-8.9 | 0.05 |
| **MHD (cm)** | 1.45, 0-3 | 0.75, 0-1.4 | 1.75, 0-3 | **0.005** |
| **VOLUME ($cm^3$)** | 625, 421-840 | 607, 433-808 | 647, 421-840 | 0.42 |
| **CONTRALATAERAL BREAST– median, min-max** | | | | |
| **CBD0 (cm)** | 3.7, 2.6-7.1 | 4.1, 2.8-6.9 | 3.6, 2.6-7.1 | 0.27 |
| **TARGET – median, min-max** | | | | |
| **VOLUME ($cm^3$)** | 752, 169-2341 | 566, 169-1593 | 787, 382-2341 | 0.14 |
| **LENGTH (N.slices x 0.3cm)** | 13.8, 10.2-19.2 | 12.2, 11.1-14.7 | 14.4, 10.2-19.2 | **0.009** |
| **LENGTH on DRR (cm)** | 15.2, 12-19.7 | 14.1, 12.3-16.4 | 15.9, 12-19.7 | 0.05 |
| **CURVATURE VOLUME ($cm^3$)** | 156, 46-335 | 141, 103-152 | 205, 46-335 | **0.02** |
| **LAD – median, min-max** | | | | |
| **Vol lad 80% ($cm^3$)** | 0.29, 0-6.38 | 0.025, 0-0.4 | 0.85, 0-6.38 | **0.03** |
| **MLAD (cm)** | 0.9, 0-2.4 | 0.05, 0-0.9 | 1.1, 0-2.4 | **0.004** |
| **LATERAL TISSUE – median, min-max** | | | | |
| **VOLUME ($cm^3$)** | 131, 20-562 | 76, 20-379 | 145, 49-562 | 0.14 |
| **AGE – median, min-max** | | | | |
| **YEARS** | 60, 45-77 | 59, 50-77 | 61, 45-77 | 0.86 |

## 4.4. Univariate logistic regression

The univariate logistic regression complements the group comparison analysis by estimating the strength and direction of the association between each parameter and the likelihood of selecting the Hybrid technique (Table 3).

**Table 3. Univariate logistic regression.**

| Parameters | OR | 95% CI | P |
|---|---|---|---|
| **LUNG** | | | |
| **CLD (cm)** | 0.09 | 0.01-0.54 | **0.02** |
| **MLD (cm)** | 0.05 | 0-0.36 | **0.02** |
| **MLL (cm)** | 0.80 | 0.56-1.09 | 0.16 |
| **VOLUME (cm3)** | 1.00 | 1-1.01 | 0.07 |
| **HEART** | | | |
| **MHL (cm)** | 0.73 | 0.51-0.99 | 0.06 |
| **MHD (cm)** | 0.17 | 0.03-0.6 | **0.01** |
| **VOLUME (cm3)** | 1.00 | 0.99-1 | 0.40 |
| **CTRL BREAST** | | | |
| **CBD0 (cm)** | 1.60 | 0.75-3.76 | 0.23 |
| **TARGET** | | | |
| **VOLUME (cm3)** | 1.00 | 1-1 | 0.24 |
| **LENGTH (n. slices x 0.3cm)** | 0.48 | 0.23-0.84 | **0.02** |
| **LENGTH on DRR (cm)** | 0.60 | 0.33-0.99 | 0.07 |
| **CURVATURE VOLUME (cm3)** | 0.98 | 0.96-1 | **0.04** |
| **LAD** | | | |
| **Vol lad 80% (cm3)** | 0.05 | 0-0.61 | 0.20 |
| **MLAD (cm)** | 0.08 | 0.007-0.46 | **0.02** |
| **LATERAL TISSUE** | | | |
| **VOLUME (cm3)** | 1.00 | 0.99-1 | 0.33 |
| **AGE** | | | |
| **YEARS** | 1.01 | 0.93-1.11 | 0.76 |

Lower LUNG CLD (OR=0.09, 95% CI:0.01-0.54, p=0.02), MLD (OR=0.05, CI:0-0.36, p=0.02), MHD (OR=0.17, 95% CI:0.03-0.6, p=0.01), target length in slices (OR=0.48, 95% CI:0.23-0.84, p=0.02), curvature volume (OR=0.98, 95% CI:0.96-1, p=0.04) and MLAD (OR=0.08, 95%, CI:0.007-0.46, p=0.02), were associated with a higher likelihood of the Hybrid technique being selected as the optimal plan.

## 4.5. Multivariate logistic regression

A multivariate logistic regression was performed to verify whether the parameters that were significant in the univariate analysis remained independently associated with the clinicians' choice of treatment plan.

An explorative multivariate logistic regression was then conducted using three of the statistically relevant factors (MLD, MHD, Curvature volume) selected by clinicians. The choice was made based on the clinical relevance of each parameter.

Given the limited sample size and the resulting loss of power in the 3-variable logistic regression model (MLD, MHD, and curvature volume), additional 2-variable models were fitted for each pair of parameters (MLD with MHD, MHD with curvature and MLD with curvature) to explore the potential independent effects (Table 4).

All multivariate models confirmed the same direction of effects as in the univariate analyses. Although none of the parameters reached statistical significance, a trend toward an independent association of MLD was observed both in MLD-MHD (OR=0.9, 95% CI 0.003-0.83, p=0.08) and MLD-curvature (OR=0.10, 95% CI 0.003-0.78, p=0.09) models.

**Table 4. Multivariate logistic regression.**

| Multivariate | 3 parameters MLD-MHD-CURVATURE | | | 2 parameters MLD-MHD | | | 2 parameters MHD-CURVATURE | | | 2 parameters MLD-CURVATURE | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **OR** | **95% CI** | **P_Value** | **OR** | **95% CI** | **P_Value** | **OR** | **95% CI** | **P_Value** | **OR** | **95% CI** | **P_Value** |
| **MLD (cm)** | 0.11 | 0.002-1.34 | 0.19 | 0.09 | 0.003-0.83 | 0.08 | | | | 0.10 | 0.003-0.78 | 0.09 |
| **MHD (cm)** | 0.34 | 0.04-2.01 | 0.26 | 0.30 | 0.04-1.47 | 0.16 | 0.26 | 0.04-1.04 | 0.09 | | | |
| **CURVATURE VOLUME ($cm^3$)** | 0.996 | 0.96-1.03 | 0.82 | | | | 0.99 | 0.96-1.005 | 0.23 | 0.99 | 0.96-1.01 | 0.37 |

## 5. Discussion

Radiotherapy represents a gold standard treatment in breast cancer. The developments of new technologies and techniques for radiotherapy treatment have played an important role in the mammalian gland treatment. A lot of steps forward have been pushed by the high incidence of this pathology [100].

Plan personalisation has become a key point to be considered according to the individual patient's tumour characteristics, with the aim to improve treatment efficacy and reduce radiation-induced side effects [101]. Different treatment techniques could be used for breast cancer RT irradiation, by the use of different assets of beam entrances and configurations. Nowadays, the choice of the best treatment approach is mainly based on single operator experience and often reached with a trial and error process. The possibility to have some information that a priori could guide this choice may provide a great advantage. In view of this, a set of anatomical parameters were assessed in the current study and compared to three different treatment techniques (3D-CRT, IMRT and h-IMRT) for breast cancer RT. Whereas IMRT and h-IMRT were chosen as the best treatment technique by clinicians in 73% and 27% respectively, 3D-CRT was never selected as best treatment. This could be attributed to different causes. First, the choice to consider only left side cancer patients, may have a strong impact on this choice, as the requirement to spare the heart and the LAD may impact on an additional constraint of OAR sparing compared to right side breast patients. Second, the machine geometry employed for planning treatment: our study was conducted with an Elekta VERSA HD machine that is designed with a wedge filter that only works perpendicularly to MLC leaves. As a result, in 3D-CRT designs, MLC conformations are only partially functional: wedge filter orientation has the thickest section on the distal target side and the thinnest on the proximal target side, whereas MLC leaves work on the target longitudinal axis. This asset prevents MLC from performing optimally while attempting to conform the 3D-CRT field closer to the target structure. With other LINACs (e.g. Varian) the combined configuration of MLC and wedge orientation is different. Another probable reason is related to the 3D-CRT technique: during treatment field delivery, MLC is in a static position, and intensity modulation is not possible in place of intensity modulated approaches (IMRT and h-IMRT), that provide additional degrees of freedom where OAR sparing is crucial, as for heart structure in left side breast cancer patients. In addition some studies have reported that h-IMRT has a better homogeneity and conformation (i.e. decreasing the percentage of dose outside the target in the posterolateral region) than 3D-CRT technique [102]. These considerations and 3D-CRT treatment fields' geometry (tangential orientation) may partially explain an increase in the percentage of high doses outside the target, in

particular in the patient's lateral region, making the 3D-CRT a suboptimal technique for these patients. Each plan was scored considering patient's age and clinical conditions. In few cases dose protocol constraints were not reached for some OARs (hearth V35, LAD V17 and 110% dose prescription at 1% volume) but target coverage's 2nd goal was guaranteed.

Novel measurements not previously reported in the literature were made on CT data sets in addition to the most commonly used anatomical parameters (MHD, MHL, and CLD): lateral tissue volume, target volume curvature, CBD0, Vol lad 80%, and MLAD. In particular, the last two parameters are linked to LAD, which is frequently assessed also in right-sided breast treatments since it has emerged as an organ of interest in the treatment of breast cancer [103]. The contralateral breast measurement (CBD0) was made on DRR at 0° to maximise the precision of distance calculation: small differences in 3D-CRT field orientation (1 or 2 degrees) could have led to high differences in contralateral breast distance calculation. The other novel parameters were created as a result of clinicians' observation during plan optimisation and approval.

The results of our study highlighted the presence of a set of anatomical parameters able to discriminate between the choice of hybrid technique compared to IMRT, in particular lower CLD, MLD, MHD, Target Length in slices, MLAD, Curvature Volume and VOL LAD 80%. The increase of the value of these parameters is associated with a probability to choose for a more modulated treatment approach (IMRT in place of h-IMRT). Therefore the advantage is the possibility to measure these parameters for the single patient and evaluate the probability of the most adequate treatment approach for this single patient. Univariate analysis showed that all these parameters were statistically significant apart from the VOL LAD 80%. We hypothesized that this could be due to the parameter's small volume (a small variation of this parameter could lead to different clinical choice), a weak indication for LAD involvement in the tangential field (MLAD is a more precise 2D parameter), and a parameter link to dose distribution (is less dependent on anatomical geometry than other parameters).

Univariate and multivariate analyses showed concordant directions of effect (OR < 1 for MHD, MLD and target curvature). However, due to the limited number of cases in the hybrid group, the 2- and 3-variable models lacked power: therefore, statistical independence of predictors cannot be demonstrated. Non-significant p-values should be interpreted as a consequence of limited power rather than as evidence of no effect. A whole multivariate analysis was not performed due to the limited sample size (N=30) and the number of events in the smaller outcome category (Hybrid technique, N=8), which would not allow a stable estimation of multiple covariates without the risk of overfitting.

These findings suggest a course of action to personalise treatment in patients with unfavourable geometry, in particular in breast cancer where breathing and heart position affects dose to OARs.
Unexpectedly, we showed a low level of inter observation agreement among the three clinicians. This finding supports the importance of investigating the unmet clinical need of standardizing the choice of the best radiotherapy technique through a well defined set of anatomical parameters. Moreover, it suggests that plan approval could be performed by more than two clinicians.
Several reports and studies defined and stressed the importance of dosimetric indexes [46], [104], [105], [106]. Since our goal is to capture the real-world treatment planning and approval process we did not examine dosimetric indices in our study.
The interplay effect, defined as the dynamic interaction between respiratory motion and modulated beam delivery, represents a critical source of uncertainty in thoracic and breast radiotherapy. To define treatment accuracy during free breathing the 3D-CRT fields had a 8mm margin around target structure and 2.5 cm in the anterior projection (air side) [83]. The same option was not available in our TPS (Pinnacle v 16.2.1) for IMRT forward planning. Different studies have investigated the interplay effect for IMRT and VMAT modulated treatment modalities. The reviewed studies consistently show that respiratory motion induces a temporal averaging of static dose distributions, resulting in dose "smoothing" along the motion trajectory and fraction-to-fraction variability that depends on the delivery dynamics [107], [108], [109], [110], [111].
The expected (mean) dose remains largely unaffected, but spatial heterogeneity increases, particularly for single-fraction or highly modulated deliveries. Fractionation has a mitigating role: statistical averaging across multiple fractions substantially reduces the dosimetric deviations observed in individual sessions, making the cumulative dose distribution close to the static plan in conventional regimens. However, this compensation is less effective in hypofractionated schedules (e.g. 5 fractions) or for small boost volumes. Plan robustness strongly depends on modulation complexity, aperture regularity, and fluence smoothing. Mitigation strategies able to manage breath interplay effect include Deep Inspiration Breath Hold (DIBH), respiratory gating, 4D dose accumulation, and robust planning approaches. Collectively, these techniques effectively minimise interplay-induced uncertainties [107], [108], [109], [110], [111].
Breath hold acquisition and treatment methods have been developing in recent years, particularly the DIBH for breast treatment with surface guided radiotherapy (SGRT) [112], [113], [114]. Several studies sought to determine the impact of irradiation conditions (under DIBH or free breathing) by examining correlations between OARs dosimetry and tumour volume [115] or by comparing treatment planning-specific parameters (heart volume, lung volume, heart chest wall length, height, chest depth, central lung distance, heart chest wall distance, maximum heart depth, and lung

orthogonal distance) with OARs dosimetric parameters (heart and LAD mean and maximum dose and contralateral and ipsilateral lung dose volumes) [116], [117]. These studies found that the DIBH technique improves treatment outcomes because it reduces the dose to OARs [62]. In particular hearth and his structures (LAD): diaphragm lowering during deep inspiration turns away hearth from the target region [118], [119], [120], [121], [122].

At IRST, few patients have been enrolled to be treated with DIBH with SGRT thanks to SGRT system implementation (Sentinel™) since January 2025. This new asset could lead to DIBH as the gold standard for our future breast treatments. Due to the recent introduction of DIBH at our Institute, our study was performed using free breathing CT simulation acquisitions. However, the findings of our study were geometrical considerations that could be used and derived also for DIBH. Thus, different values of anatomical parameters (in particular hearth and LAD parameters) and technique choices by clinicians were expected, in particular for 3D-CRT technique. Although 3D-CRT was never selected as the best treatment in this study, it could be the most useful one in the breath hold treatments due to time reduction in treatment delivery [123].

Many studies explored the use of VMAT with different assets (partial arc, reduced bowtie arcs and hybrid 3D-CRT/VMAT) in breast cancer treatment as an alternative solution to IMRT and conformal radiotherapy [109], [119], [124], [125]. At our institution we treat the left breast with VMAT technique in few cases (treatments with Simultaneous Integrated Boost, patients with challenging anatomy, DIBH). In the future we would like to include VMAT technique to check clinicians' preferences considering the innovation of this technique as difference in treatment time from IMRT, with similar dosimetric results [125].

In recent years Artificial Intelligence (AI) has been applied in all human fields, including medicine [126]. With this study we paved the way for developing an AI-based tool which can read a patient's CT data set, calculate anatomical parameters objects of this study and automatically predict the best treatment solution based on the patient's anatomy and the institution's treatment techniques and technologies. The objective for the future is to provide a personalised radiation treatment that can be used on each patient according to their clinical and anatomical characteristics.

Finally, we would like to highlight some limitations of our study: first of all the limited number of patients evaluated for each group, which should be taken into account when transposing the results. However, similar other studies with a small number of patients were reported in the literature which, nevertheless, presented valuable information regarding treatment techniques comparison [62]. The absence of dosimetric indices was explained above, however for a more comprehensive analysis, a study that integrates anatomical parameters and dosimetric indices will be performed in the future. Furthermore, while this study was retrospective and only included one cancer institute,

the findings are relevant to our world or something comparable. Last, the extensions of VMAT technique, as well as Simultaneous Integrated Boost (SIB) prescription and DIBH techniques may provide an additional strength on the present work and could represent a future expansion of the present investigation.

Our research showed how crucial it is to develop a parameters-based model for selecting the most effective radiation treatment for patients with breast cancer. Multicenter and larger prospective investigations are assured.

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