IJCRM
International Journal of Contemporary Research In Multidisciplinary

*Research Article*

# Breast Cancer Between Radiomics and Adaptive Radiotherapy

**Virginia A.Cirolla[1*], O.Lora[2]**
[1]MD,PhD in Oncology, UOC of Oncological Radiotherapy University of La Sapienza/IOV Padua, Italy
[2]UOC Radiotherapy University of Padua, Italy

**Corresponding Author:** * Virginia A.Cirolla

**Abstract**

The breast is a complex structure located between the chest wall and the skin. It consists mainly of glands and adipose tissue. The mammary glands, called lobules, join together to form lobes. In one breast there can be 15 to 20 such lobes. Breast cancer is a potentially serious disease caused by the uncontrolled growth of certain cells within the breast gland, which become malignant and have the potential to spread to surrounding tissues and, over time, to distant organs. In theory, all cells in the breast can give rise to a tumor. In most cases, breast cancer is caused by glandular cells (lobules) or those that form the wall of the ducts. In Italy, breast cancer is the most common neoplasm, representing 30.3% of all cancers affecting women and 14.6% of all cancers diagnosed. Although the incidence has increased, especially in younger women, mortality is decreasing, with a 6% reduction in 2020 compared to 2015. Breast cancer remains the leading cause of cancer death in women. Breast cancer treatment has undergone significant changes over time. Years ago, the standard approach was a complete mastectomy, which involved removing the entire breast gland. However, at the end of the 20th century, the surgeon U. Veronesi demonstrated the effectiveness of quadrantectomy, which involves the surgical removal of only the quadrant affected by the disease, preserving a large part of the breast tissue. This is a conservative approach linked to the use of radiotherapy to treat any microscopic residues. Continuous studies have shown that patients treated with mastectomy and those who underwent quadrantectomy had similar rates of recurrence. Today, conservative surgery is widely used and requires a personalized approach for each patient. The removal of the axillary lymph nodes occurs only in case of positivity, and mastectomy is limited to cases in which it is strictly necessary. Radiotherapy targeted to the breast affected by the lesion reduces the risk of recurrence. These advances in the diagnosis and treatment of breast cancer demonstrate how much medicine is advancing in the management of this disease.

**Manuscript Information**

- **ISSN No:** 2583-7397
- **Received:** 22-05-2024
- **Accepted:** 15-07-2024
- **Published:** 02-08-2024
- **IJCRM:**3(4); 2024: 121-128

- **Plagiarism Checked:** Yes
- **Peer Review Process:** Yes

**How to Cite this Manuscript**

Virginia A.Cirolla, O.Lora. Breast Cancer Between Radiomics and Adaptive Radiotherapy. International Journal of Contemporary Research in Multidisciplinary.2024; 3(4): 121-128.

**KEYWORDS:** breast cancer, breast cancer therapies, ART radiotherapy and breast cancer.

Cardiovascular risk remains one of the main causes of death in patients treated for breast cancer with chemotherapy. Cardiac complications can in fact compromise the survival of these subjects.The American Cardiology Society has classified cardiotoxicity in women with breast cancer undergoing chemotherapy with anthracyclines and anti-HER2 therapies, into stages ranging from A to D.Women who are in stage A high risk or asymptomatic B are those for whom the risk of developing cardiotoxicity may change. The early identification of the development of cardiac toxicity is therefore an indispensable tool for increasing survival and quality of life of these patients. For this reason the use and identification of new serum markers of early cardiac damage is so essential and plays a crucial role in the research and support of chemotherapy treatments. An analysis carried out on patients who did not have cardiac risks showed how NRG1 and Gal 3 undergo significant variations depending on the degree of toxicity of the therapy administered, in proportion to the degree of myocardial stress suffered by the cardiac muscle.

Breast cancer is influenced by various risk factors: among the non-modifiable factors, age is a key element. The risk of developing breast cancer increases as you age. Most cases affect women over 50. Regarding family history, it is estimated that between 5% and 7% of breast cancers are hereditary, caused by genetic mutations transmitted by parents. The best-known genes are BRCA1 and BRCA2, responsible for approximately 50% of hereditary forms of breast cancer. Hormones play an important role in determining breast cancer risk and represent modifiable risk factors. An early first menstrual period (before age 12) or a late menopause (after age 55) may increase the risk. The absence of pregnancies and the use of certain oral contraceptives or hormone therapies during menopause may also contribute to the increased risk. Most modifiable risk factors are linked to lifestyle and behavior. Overweight, obesity and alcohol consumption, often related to a diet high in fat and sugar and low in fruit and vegetables, play a significant role. Conversely, breastfeeding can reduce the risk of breast cancer. Understanding these risk factors can help you adopt a lifestyle that can reduce your risk of developing breast cancer.

**Many types of carcinomas originate from epithelial cells of the breast:**

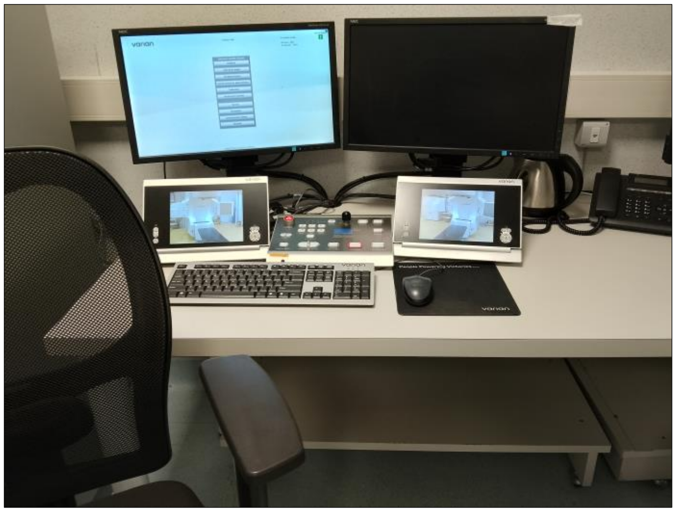
- Ductal carcinoma is triggered by the uncontrolled proliferation of duct cells, it is the most common type of breast cancer. Its ability to spread beyond the duct wall is a very important aspect that must be considered in its treatment.
- Lobular carcinoma, starting from the lobules, is less common, it can be present in both breasts or in multiple places within the same one, which can make treatment more complex.
- Intraductal carcinoma in situ is a non-invasive form of cancer, because the cancer cells are still inside the ducts and have not spread further. This type of cancer usually has a favorable prognosis if treated appropriately.
- Other less frequent forms of carcinoma, such as tubular, papillary, mucinous, and cribriform, often have favorable prognoses. Knowing the types of breast cancers is critical to diagnosis and treatment.

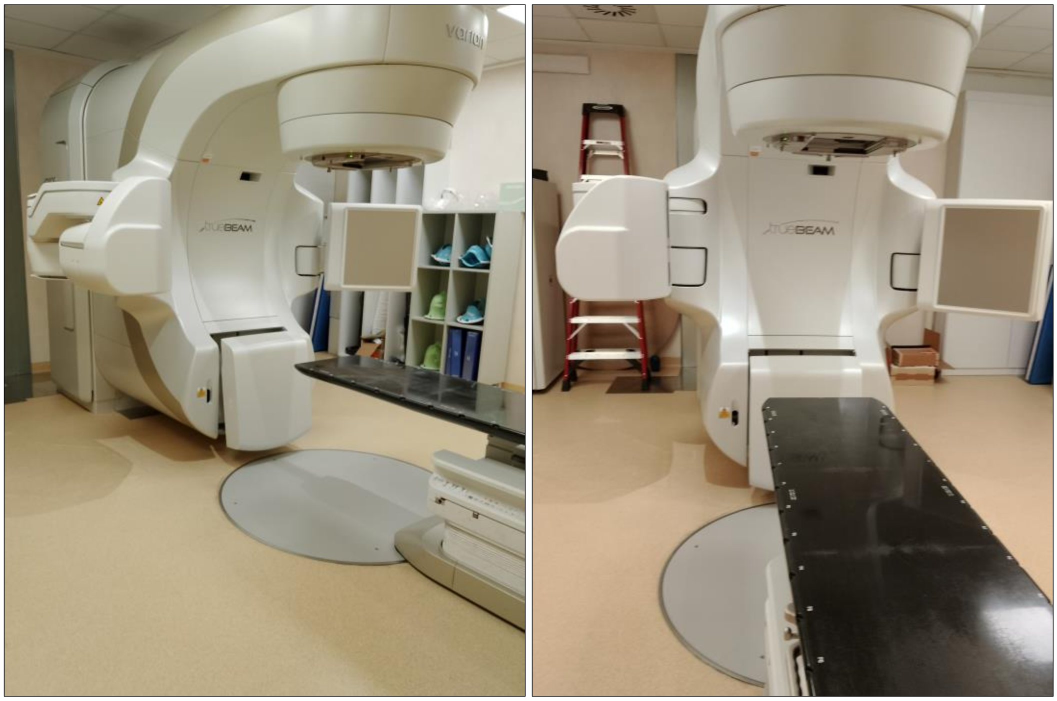
**Radiotherapy of breast cancer**

Radiotherapy is a branch of medicine that uses mega voltaic ionizing radiation to treat cancer. It plays an essential role in the treatment of neoplastic diseases to achieve complete remission. It can be used as an exclusive treatment or in combination with other therapies such as surgery, chemotherapy or hormone therapy. It is a precise, painless, integrated, safe and above all non-invasive treatment. RT is targeted at specific areas of the body, often involving only very limited and limited areas. The number of sessions, called fractionations, varies depending on the type of tumor and the location, from a single session up to several weeks of therapy. For the development of this study, dedicated to the treatment of left breast cancer, we are interested in external beam radiotherapy. This is the most common technique used for left breast cancer.

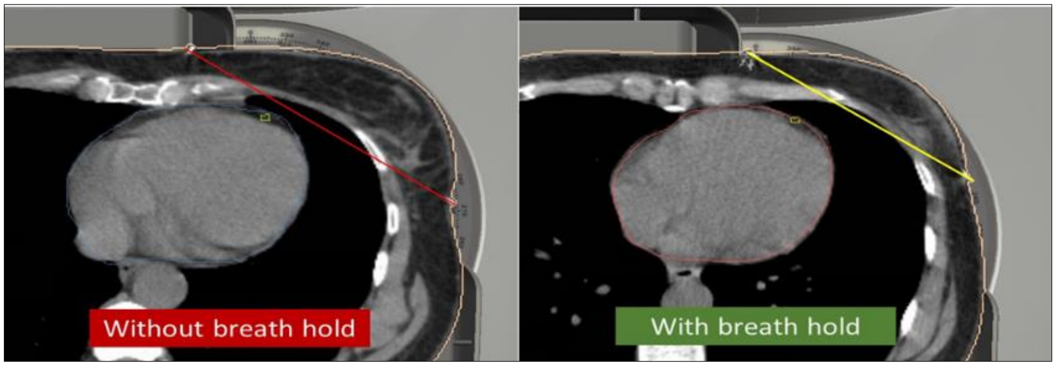
High energy photons generated by linear accelerators (LinAc) are used. External beam RT includes 3D conformal radiation therapy, which uses multiple photon fields to irradiate the tumor area, sparing surrounding healthy tissue.

VMAT (Volumetric Modulated Arc Therapy) is an advanced radiotherapy technique that has revolutionized the approach to tumor treatment. Unlike traditional techniques, VMAT is characterized by continuous rotation of the linear accelerator around the dosimetric isocenter throughout the treatment. This rotation, through the use of the MLC complex, allows the angle, shape and intensity of the beam to be dynamically adapted in a three-dimensional way to adhere to the lesion with extreme precision, maximizing the therapeutic effect on the tumor. Through the precision that characterizes it, this technique minimizes the risk of damaging the healthy organs surrounding the lesion, thus improving the patients' quality of life. VMAT radiotherapy sessions are extremely shorter than traditional techniques, making the treatment more pleasant for patients. The beam model we use to treat breast cancer is a 6 MV photon beam from a Varian True Beam linear accelerator. VMAT plans consist of several arcs with the isocenter located approximately at the center of the planning target volume (PTV). The PTV is limited to the skin anteriorly and the ribs posteriorly. These treatment plans were planned in medical physics starting from the centering CT scan and the contours carried out by the radiotherapists.






WBI (whole breast irradiation) usually includes the BH (breath hold) technique which allows to reduce the dose to the heart in patients with left breast cancer. PBI (partial breast irradiation) is used for patients at low risk of recurrence. The total dose of breast cancer radiotherapy treatment is commonly around 50 Gy in 25 fractions (2 Gy per fraction) for WBI. Alternatives with hypofractionated treatments have been studied with similar results in terms of efficacy and tolerability. Modern RT manages to minimize toxicity and preserve the aesthetics of the breast. Patients may experience changes in the appearance of the breasts and hardening of the tissues.




**Radiotherapy visit**

The first stage involves an initial meeting with a radiotherapy expert. During this visit, the professional examines the patient's clinical file, discusses the diagnosis and radiotherapy plan, answers the patient's questions and shares information on potential side effects following treatment. During this phase it is decided whether or not there is a need to proceed with radiation treatment and the patient's entire treatment path is traced.

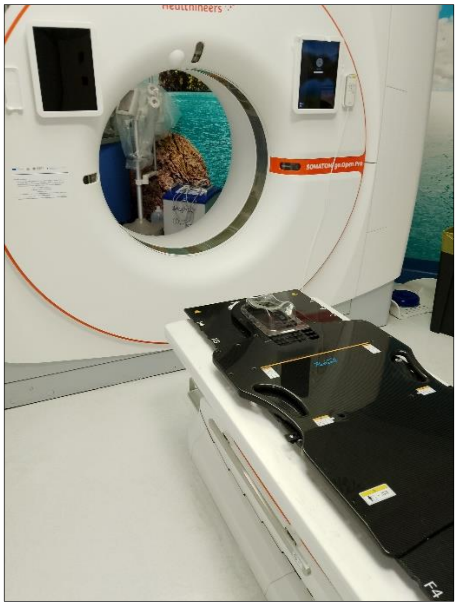
**Simulation**

The simulation phase in radiotherapy treatment is a fundamental part of the process. The planning of the treatment plan starts from here. The steps that characterize this phase are:

- **Patient positioning:** the medical radiology technician positions the patient in such a way as to guarantee the repeatability of the treatment. She is positioned on the treatment table in a comfortable and specific position, with her arms above her head, aided by an immobilization device called a breast board. The patient must be positioned precisely and reproducibly during each treatment session.
- **Immobilization systems:** if necessary, immobilization systems are used that help keep the patient in the desired position. These devices reduce the risk of involuntary movements during treatment.
- **Centering CT:** imaging scans, usually computed tomography (CT), are performed to identify the body

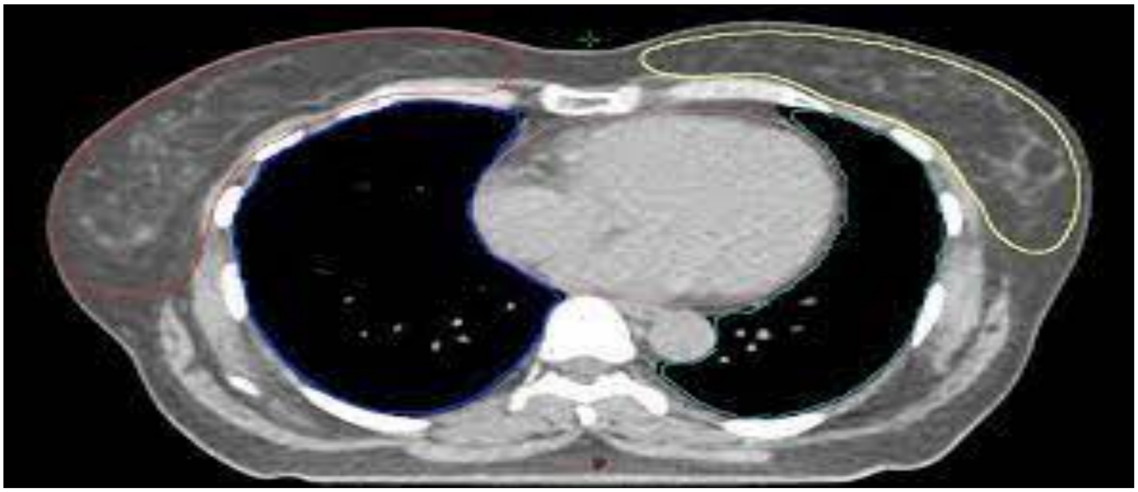
volumes to be irradiated and the organs at risk to be protected. These scans provide precise visual guidance for treatment planning.

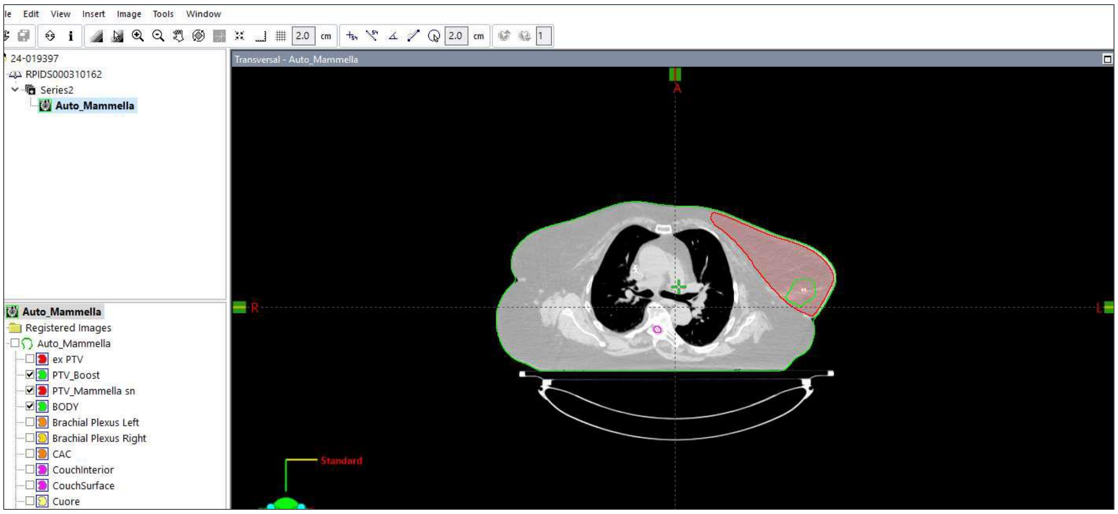
- **Metallic landmarks:** the technician applies metallic landmarks visible in the scans. These landmarks are essential to highlight useful reference points during planning and treatment. For example, they can be used to mark where the radiation beam should be directed.
- **Point tattoos:** at the end of the scan, point tattoos (ink) are performed. These tattoos are further permanent and fundamental reference points to ensure good reproducibility of positioning throughout the treatment period. In this way, the simulation ensures that radiotherapy treatment is precisely targeted to target areas, minimizing exposure of healthy organs and ensuring the safety and effectiveness of the treatment.



**Contour**

The contouring process carried out by the radiotherapist is a crucial phase in planning the radiotherapy treatment. During this phase, the doctor precisely identifies and delimits the contours of the "targets" (the areas to be irradiated) and the "organs at risk" (the sensitive structures that must be protected from irradiation and therefore receive reduced doses of radiation) . This accurate delineation of the contours allows the planning software (TPS) to optimize the dose distribution, in order to ensure the required coverage of the target volume, while trying to spare the surrounding organs. This process is highly personalized for each patient being based on the anatomy acquired with the 14 simulation CT scan. Precision in contouring is essential to ensure an effective and safe treatment.



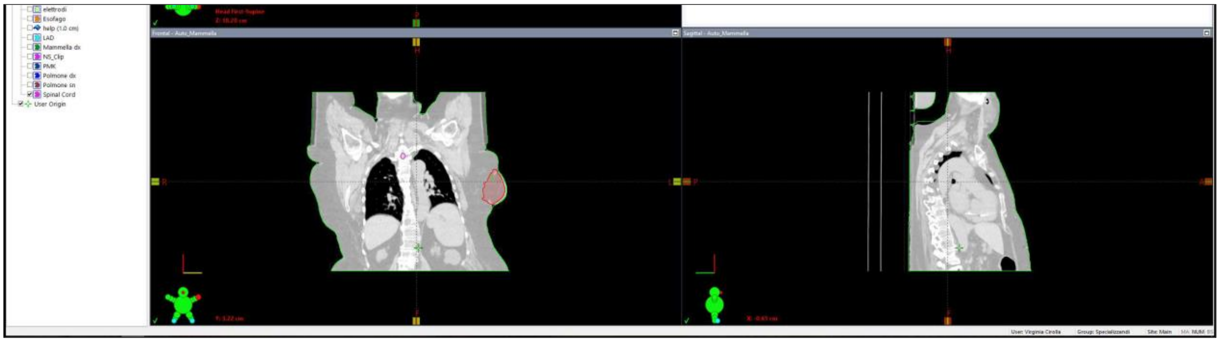



**Target**

The radiotherapy volumes relating to the lesion defined by the radiation oncologist, during the contouring phase, are [ICRU Report 50]:

- **GTV (Gross Tumor Volume):** represents the volume of the palpable or visible neoplasm, i.e. the tumor itself which is demonstrable.
- **CTV (Clinical Target Volume):** is larger than GTV and includes the visible tumor along with the microscopic or subclinical extension of the disease that needs to be treated. It is designed to ensure that all relevant tumor cells are covered by radiotherapy.
- **PTV (Planning Target Volume):** it is even broader and includes the CTV with safety margins around it. These margins take into account treatment-related uncertainties, including physiologic movements and changes in the shape and position of the CTV during therapy. The PTV is used in defining treatment fields.
- **IM (Internal Margin):** is the margin added to the CTV to compensate for physiological movements and changes in the size, shape and position of the CTV during treatment.
- **SM (Set-up Margin):** takes into account uncertainties related to patient positioning during treatment.
- **TR (Treated Volume):** This is the volume that receives a specific dose of radiation prescribed by the radiation oncologist to achieve the treatment goal.
- **IV (Irradiated Volume):** represents the volume that receives a significant dose of radiation in relation to the tolerance of the surrounding tissues.

These different volumes are critical to ensuring that radiation treatment is precisely targeted to the tumor, minimizing irradiation of healthy organs and maximizing treatment effectiveness.



**OAR**

The organs at risk in the treatment of left breast cancer are mainly the heart, lung and contralateral breast. They are located in close proximity to the target and if hit by high doses can cause serious consequences for the patient's health. There are techniques that allow these structures to be safeguarded, limiting the radiation of their volume as much as possible. In our center a VMAT treatment plan in BH (breath hold) is used with the use of a Virtual Bolus. The VMAT technique allows you to conform the beam precisely and homogenize the dose on the lesion of interest, allowing the sparing of adjacent organs. The peculiarity of the use of Breath Hold is that it can reduce the ITV (internal target volume), this is because by taking into consideration only one moment of the various positions of the lesion during breathing the target is considered almost stationary. It will be irradiated only at that exact moment of breathing so as to reduce the PTV as much as possible, allowing the entire volume of lung parenchyma in which the target would move during all respiratory acts to be excluded from irradiation. The position in which the target is located during the delivery of the beam, defined during the development of the treatment plan, is summarized and recognized only if the patient breathes with the same frequency. The respiratory trace recorded in the bunker must be the same as that acquired during the centering CT scan. The conditions must be recreated so that the lesion is in the position planned by the physicist. In our center the BH technique is performed with the patient in maximum inspiration, for various reasons. The first is that the patient feels much calmer and more comfortable holding their breath with the air inside their lungs, allowing them to perform longer apneas. During inhalation the diaphragm lowers, the heart thins and moves downwards, allowing it to exit the treatment field. When the air is inside the lung there is a greater interaction between it and the photons, this allows the lung parenchyma to be safeguarded.

**Lung**

Pulmonary toxicity following radiotherapy is a side effect that can occur in two distinct and related phases:

**Radiation Pneumonia:** is an early inflammatory reaction that develops 4 to 12 weeks after the conclusion of radiotherapy. It involves the irradiated lung and results in a number of pathological changes, including alveolar cell death and the accumulation of inflammatory cells within the interstitial space. Symptoms of RP may include fever, cough, difficulty breathing, and fatigue.

**Radiation Fibrosis:** represents a late and irreversible event that occurs more than six months after the conclusion of radiotherapy treatment 18. In this condition fibroblasts proliferate and there is an accumulation of collagen in the lung tissues, leading to a loss of the normal architecture of the lung. RF can cause irreversible reduction in lung function, chronic dyspnea, and respiratory distress.

**Heart**

Cardiac irradiation in breast cancer treatments can lead to long-term consequences, although modern technologies have helped reduce the risk of these side effects. One of the main harmful effects of cardiac irradiation is damage to the coronary arteries. This can lead to the development of coronary artery disease (CAD), with symptoms emerging 5 to 10 years after treatment. To reduce the risk of CAD, it is recommended to keep the average heart dose below 5 Gy, the V20 Gy below 10% and the dose to the coronary region below 20 Gy. These limits may vary depending on the patient's situation and the radiotherapy technique used. It is important to note that long-term monitoring and management of patients who have undergone cardiac irradiation are essential to identify symptoms early and prevent more serious complications. Modern radiotherapy always tries to minimize irradiation of surrounding healthy tissues, including the heart, to minimize side effects.

**Planning**

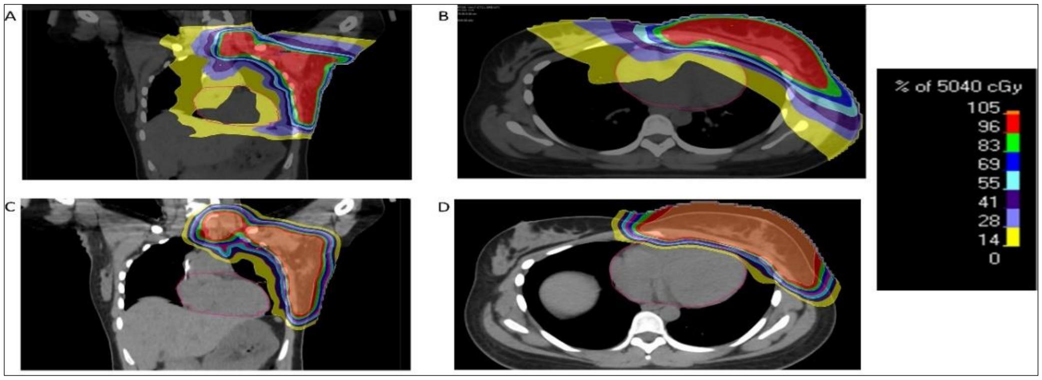
Radiation treatment planning for breast cancer is an intricate and highly personalized process. This process includes several crucial stages:

**Optimization phase:** This phase is characterized by the use of inverse planning, where the radiation beam intensity profile is automatically determined after defining the clinical objectives for each identified volume. The main objective is to maximize the effectiveness of the treatment of the neoplasm and minimize the irradiation of the surrounding healthy tissues in accordance with the dose constraints established by the doctor.

**Calculation phase:** During this phase, the treatment planning system (TPS) calculates the dose distribution based on the optimized treatment plan. This distribution is overlaid on simulation CT scans, on which target sites, OARs, and other anatomical structures have been contoured. This complex and carefully planned procedure is critical to ensuring targeted and safe radiotherapy treatment for breast cancer, while ensuring effectiveness in controlling the disease.

**Delivery**

Once the planning of the treatment plan is completed, the patient begins the treatment period. This involves daily radiotherapy sessions, Monday to Friday, for several weeks. Each individual radiotherapy session is short, generally lasting only a few minutes. During daily treatments it is essential that the patient is positioned in the same position and with the same precision used during the simulation phase. For this purpose, the same immobilization systems that were chosen previously are used.



**Patient positioning**

A crucial step is the use of IGRT (Image-Guided Radiation Therapy), which allows you to verify the accurate positioning of the patient before each treatment. This verification occurs through image acquisition directly in bunkers, these can be two-dimensional (KV/KV or MV/KV) or three-dimensional (CBCT - Cone Beam CT). These images are then overlaid on the CT scans obtained during the simulation. If the alignment between the verification images and the simulation scans is not adequate, immediate adjustments are made. This may involve slight shifts in the patient's position or adjustments to the radiation beam. The main objective is to ensure that the treatment precisely hits the target area, corresponding to the neoplasm, while minimizing the involvement of surrounding healthy tissues. This attention to detail and constant verification of positioning during each radiotherapy session are essential to ensure effective and safe treatment for the patient

**IGRT**

Image-guided radiotherapy (IGRT) represents a major advance in the precision and effectiveness of radiotherapy. It uses sophisticated machinery equipped with radiological image acquisition systems, such as accelerators equipped with Cone-Beam CT. These systems allow high resolution images to be obtained before each treatment session directly in the bunker, allowing a precise assessment of the position of the tumor and surrounding organs.

**This approach offers several significant advantages**

**Precision:** ability to detect small variations in the position of the target allows extremely precise radiotherapy, minimizing the involvement of surrounding healthy organs.

**Error correction**: possibility to correct any set-up and organ-motion errors due to involuntary body movements. Fundamental to ensure that the treatment hits the area of interest exactly.

**Reduction of side effects:** IGRT reduces the risk of affecting surrounding healthy organs, allowing a lower incidence of side effects associated with traditional radiotherapy.

**High radiation doses:** the ability to deliver higher doses safely improves therapeutic efficacy, increasing the likelihood of disease control. The process begins with positioning the patient on the therapy table according to the coordinates defined during the simulation CT. Subsequently, a 3D image is acquired via CBCT and overlaid with the CT image obtained during the initial simulation. Any discrepancies are recorded, identified and automatically corrected before the actual treatment is carried out. IGRT represents an important advance in the personalization of radiotherapy treatments, improving the effectiveness and safety of radiotherapy for patients.

Radiotherapy is a local treatment that uses ionizing radiation to intervene on the tumor mass, both for curative and palliative purposes. The data shows that approximately 60% of patients affected by cancer undergo at least one cycle of radiotherapy during the therapeutic process. In recent years, thanks to Research and the use of Artificial Intelligence, it has become possible to personalize radiotherapy treatments based on the needs of the individual patient, with an improvement in disease control and a decrease in the toxicity of the treatment. Adaptive radiotherapy (ART) is an advanced form of radiotherapy that involves adapting the radiotherapy treatment to changes in the patient and the pathology they suffer from. This is a complex treatment, which aims to ensure the patient receives the most personalized care possible and which allows greater precision in irradiating the tumor by adapting to the patient's anatomy.

This technique is possible thanks to the use of radiological images, which allow us to monitor changes in the patient's body and tumor day by day during treatment. The objective of the new treatment protocols is to combine adaptive radiotherapy with radiomics, a form of Artificial Intelligence capable of providing valuable information on the characteristics of tumors starting from radiological images. (PET TC RMN).

Artificial Intelligence allows us to reach where the human eye cannot: thanks to a series of biological and radiological markers we can now define in advance what the patient's outcome will be. Each patient must be treated according to the type of response that his body could give and Artificial Intelligence helps radiation oncologists to predict this response.

**UNIQUE (ART)**

## REFERENCES

1. Ellis IO, Allison KH, Dang C, Gobbi H, Kulka J, Lakhani SR, Moriya T, Quinn CM, Sapino A, Schnitt SJ, Sibbering DM, Slodkowska E, Yang W, Tan PH. Invasive carcinoma of the breast histopathology reporting guide. International Collaboration on Cancer Reporting; 2021. Sydney, Australia.
2. Yu TT, Lam SK, To LH, Tse KY, Cheng NY, Fan YN, Lo CL, Or KW, Chan ML, Hui KC, Chan FC. Pretreatment prediction of adaptive radiation therapy eligibility using MRI-based radiomics for advanced nasopharyngeal carcinoma patients. Front Oncol. 2019 Oct 16;9:1050.
3. Tran WT, Jerzak K, Lu FI, Klein J, Tabbarah S, Lagree A, Wu T, Rosado-Mendez I, Law E, Saednia K, Sadeghi-Naini A. Personalized breast cancer treatments using artificial intelligence in radiomics and pathomics. J Med Imaging Radiat Sci. 2019 Dec;50(4)
4. Tanaka S, Kadoya N, Sugai Y, Umeda M, Ishizawa M, Katsuta Y, Ito K, Takeda K, Jingu K. A deep learning-based radiomics approach to predict head and neck tumor regression for adaptive radiotherapy. Sci Rep. 2022 May 27;12(1):8899.
5. Yang M, Liu H, Dai Q, Yao L, Zhang S, Wang Z, Li J, Duan Q. Treatment response prediction using ultrasound-based pre-, post-early, and delta radiomics in neoadjuvant chemotherapy in breast cancer. Front Oncol. 2022 Feb 7;12:748008.