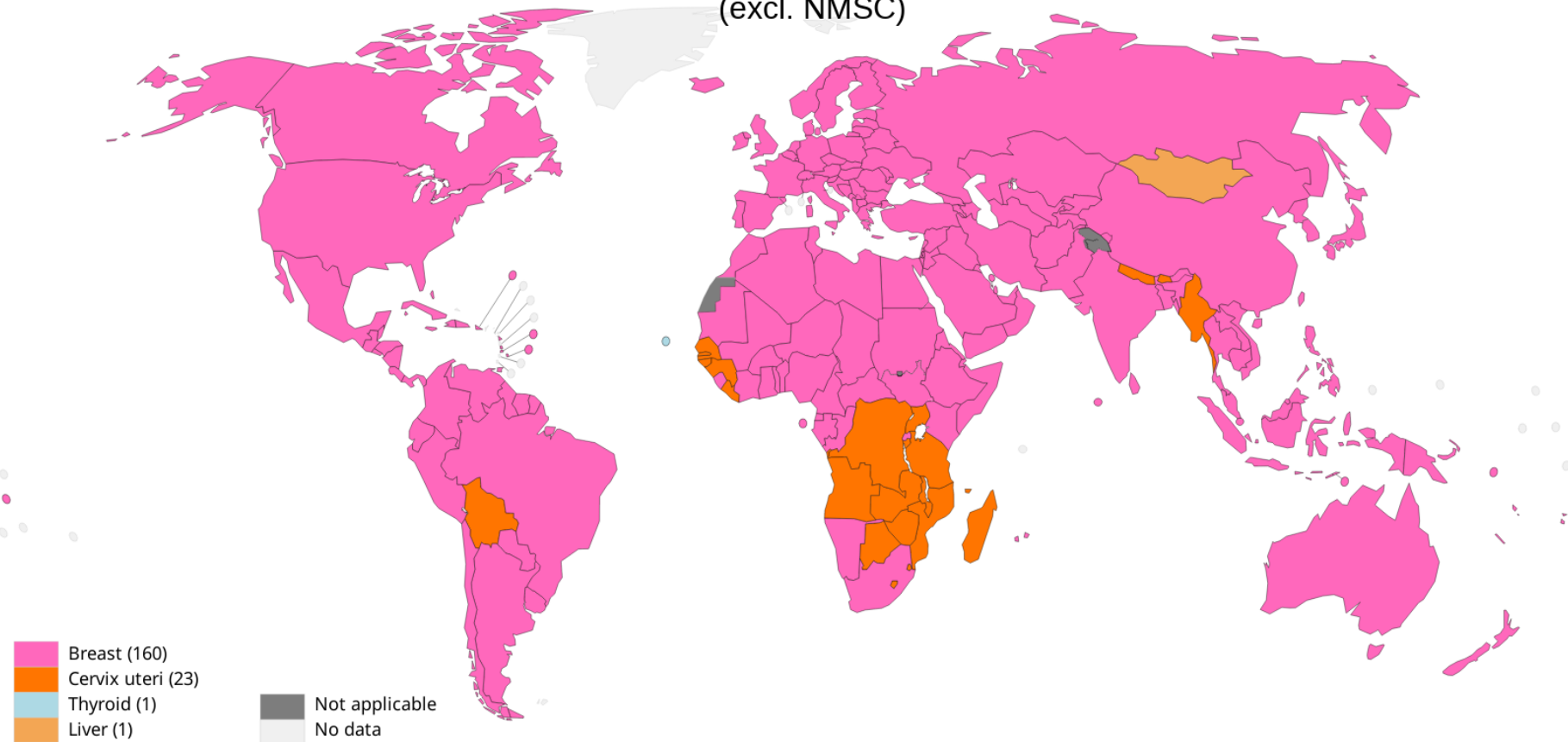




Radiation therapy of patients with breast cancer

Assist Prof Neda Milosavljević
Assist Prof Marija Živković Radojević

Top cancer per country, estimated age-standardized incidence rates (World) in 2020, females, all ages (excl. NMSC)



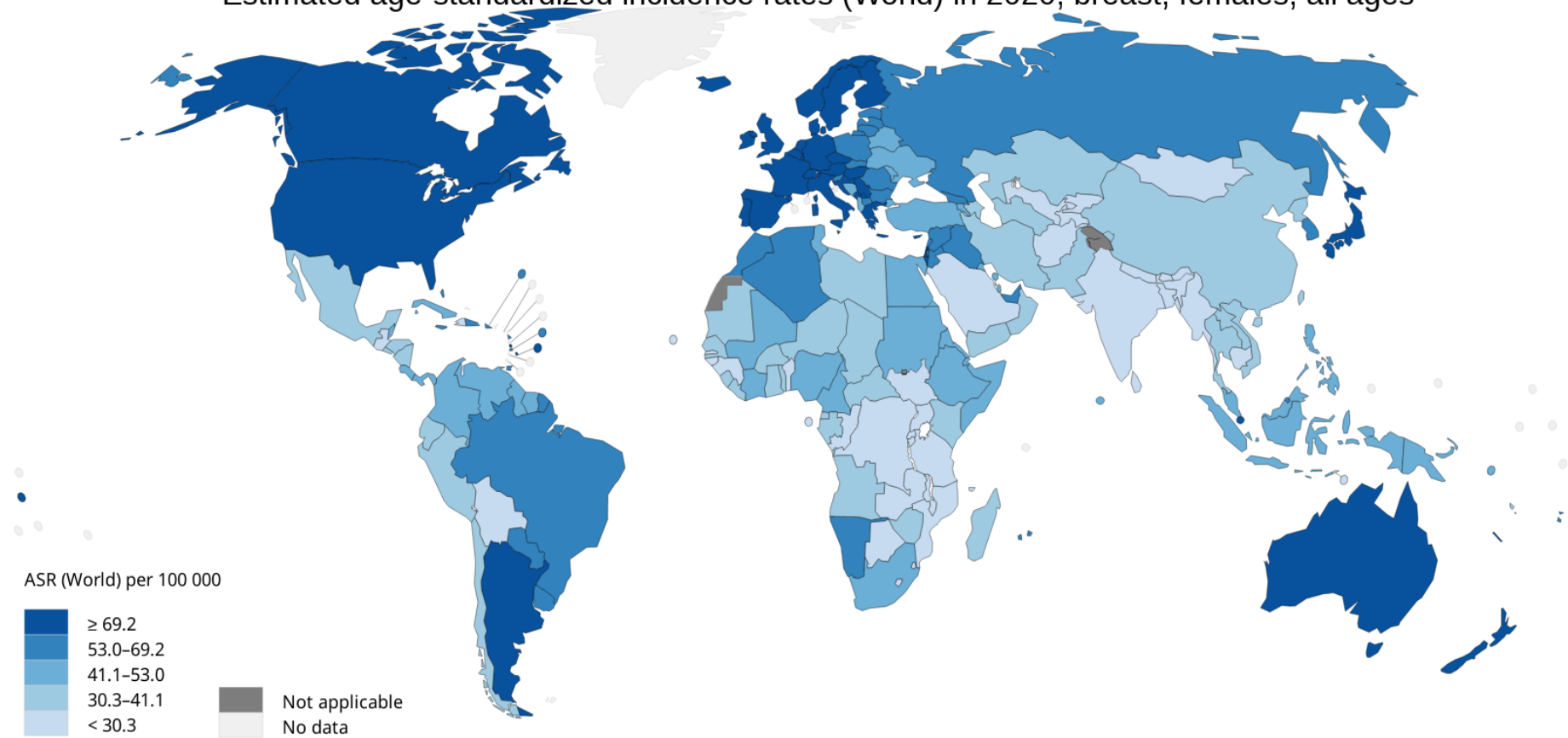
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Data source: GLOBOCAN 2020
Map production: IARC
(<http://gco.iarc.fr/today>)
World Health Organization



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Estimated age-standardized incidence rates (World) in 2020, breast, females, all ages



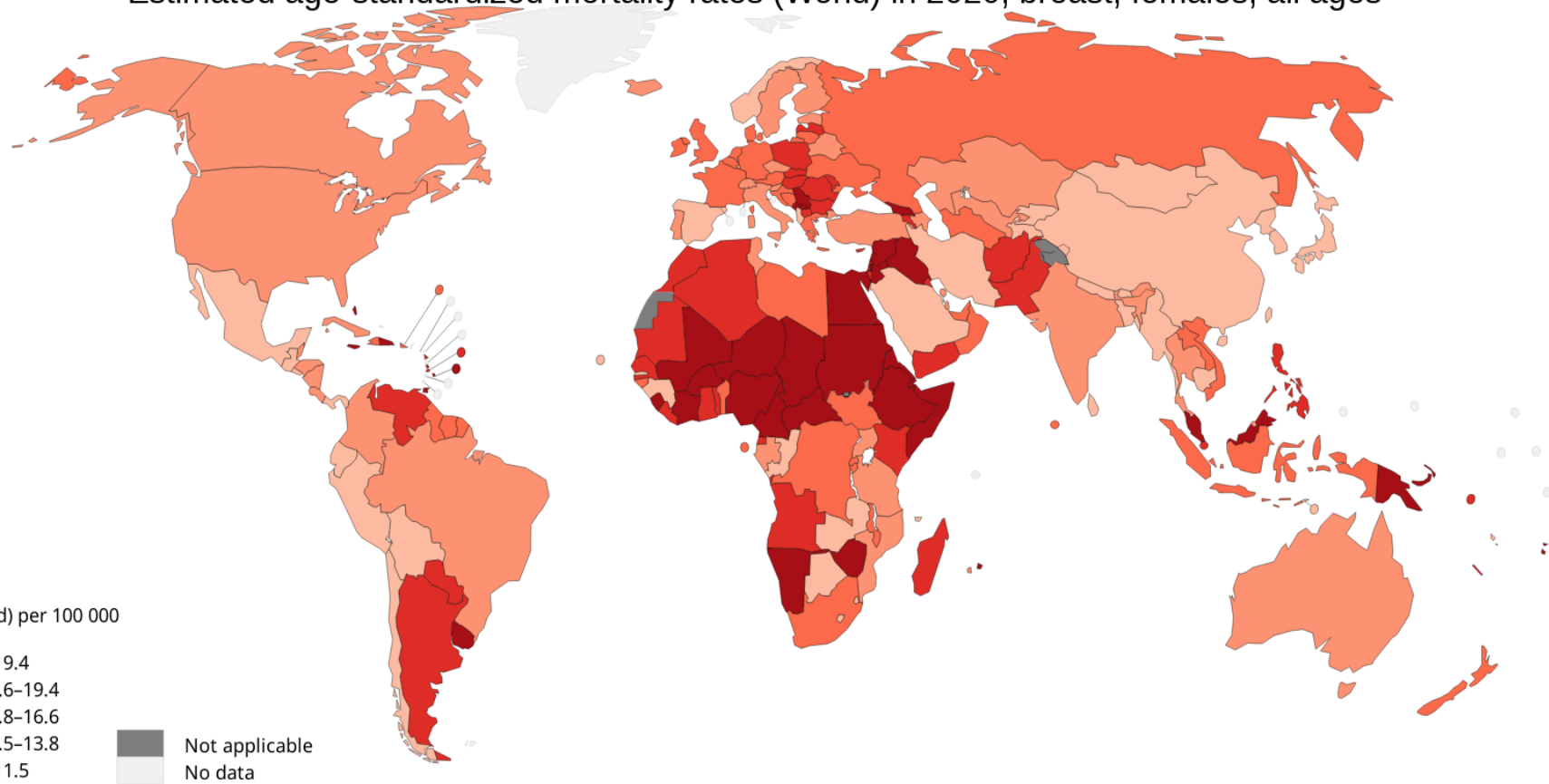
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Data source: GLOBOCAN 2020
Map production: IARC
(<http://gco.iarc.fr/today>)
World Health Organization



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Estimated age-standardized mortality rates (World) in 2020, breast, females, all ages



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Data source: GLOBOCAN 2020
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World Health Organization



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BE IN THE *know*
KEEP YOUR RISK *low*

You **can't** control:



AGE



GENDER



RACE



GENETICS

You **can** control:



DIET



EXERCISE



DRINKING

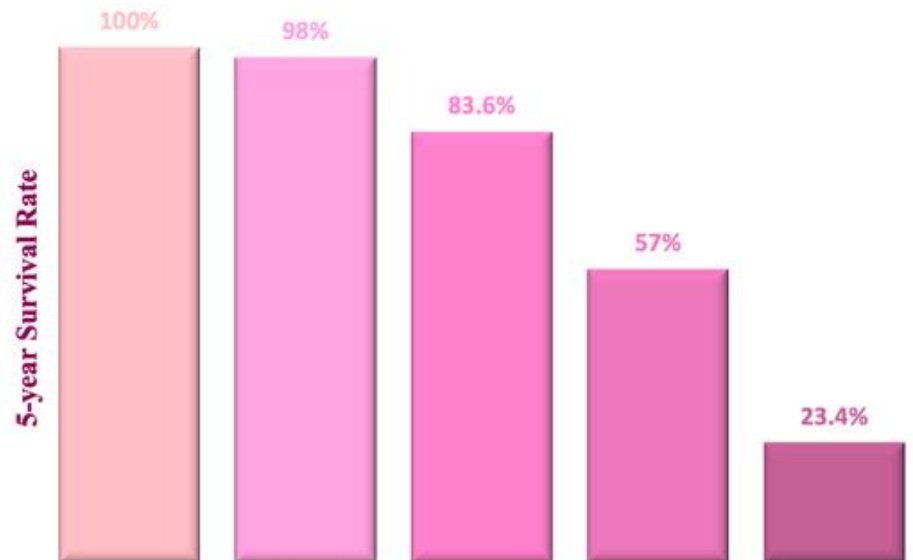


SMOKING

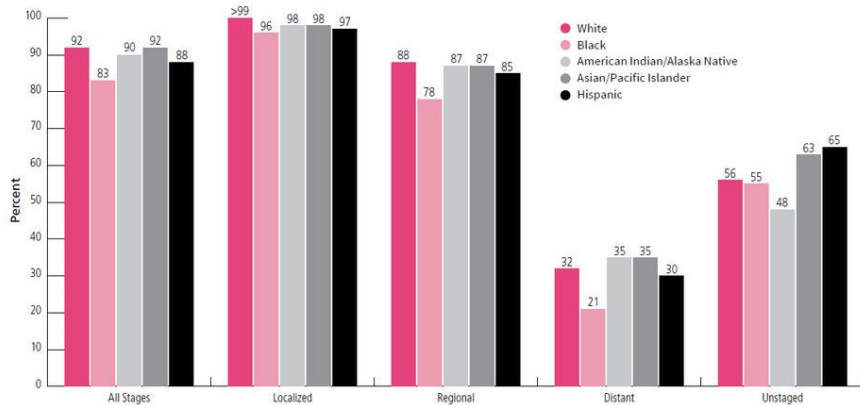
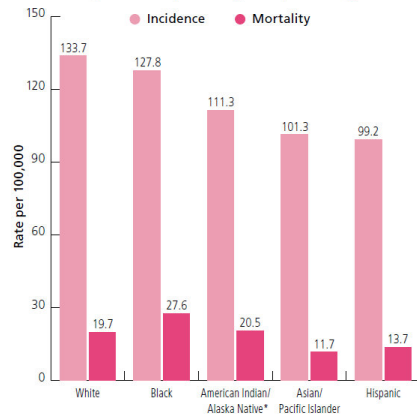
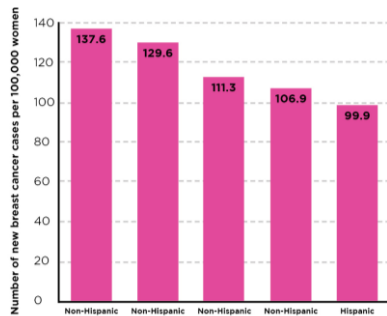
1 IN 8 WOMEN



Will develop breast cancer in their
lifetime



	Stage 0	Stage I , II	Stage I , II	Stage III	Stage IV
Classification	In situ	Early-Stage Invasive (Local)	Early-Stage Invasive (regional)	Locally Advanced	Metastatic
Characteristics	Confined within breast gland(s)	Confined twithin breast area	Spread to lymph nodes	Spread to Lymph node	Cancer spread beyond breast region
Tumor Size	Very Small	2-5 cm	2-5 cm	5 ≥ cm	Variable



“

Among younger women, Black and non-Hispanic Black women have higher rates of breast cancer compared to white and non-Hispanic white women. Among older women, white and non-Hispanic white women have higher rates of breast cancer compared to Black and non-Hispanic Black women.”



“Black women still have a 4% lower incidence rate of breast cancer than White women but a 40% higher breast cancer death rate”.

“Black women have the lowest survival for all subtypes of breast cancer”.

Breast Cancer Myths Versus Facts

Breast cancer is one of the better-known and more-talked-about cancers, but there are still many misconceptions.



BREASTCANCER • ORG

MYTH: If I don't have a family history of breast cancer, I won't get it.

MYTH: Wearing a bra can cause breast cancer.

MYTH: Carrying your cell phone in your bra can cause breast cancer.

MYTH: Annual mammograms guarantee that breast cancer will be found early.

MYTH: Early-stage breast cancer rarely recurs.

MYTH: Breast cancer only happens to middle-aged and older women.

MYTH: If you maintain a healthy weight, exercise regularly, eat healthy, and limit alcohol, you don't have to worry about breast cancer.

MYTH: Using underarm antiperspirant can cause breast cancer.

MYTH: Consuming too much sugar causes breast cancer.

MYTH: Breast cancer always causes a lump you can feel.

MYTH: All breast cancer is treated pretty much the same way.

MYTH: When treatment is over, you're finished with breast cancer.

Left and Right Sided Breast Cancer 1

H. Tulinius^a, H. Sigvaldason, G. Ólafsdóttir

Patients with an affected first degree relative were of 2.54 fold risk of developing contralateral primary breast cancer, but women with no affected relative were at a reduced risk (not significant). Patients with right sided breast cancer are more likely to have a relative with breast cancer. The breast cancer status of the relatives did not influence the risk of death, so a better survival of familial cases could not be shown.

- the larger size of the left breast
- early detection of tumors in those who are righthanded
- breastfeeding from the right breast more often than the left


www.nature.com/scientificreports

scientific reports

OPEN Left sided breast cancer is associated with aggressive biology and worse outcomes than right sided breast cancer

Yara Abdou^{1,2}, Medhavi Gupta³, Mariko Asakura³, Kristopher Attwood⁴, Opyrchal Mateusz⁵, Shigra Gandhi⁶ & Kazuaki Takabe^{1,2,3,4,5,6,7}

[Check for updates](#)



Department of Breast Diseases & Cancer Care

Breastfeeding

can lower breast cancer risk, especially if a woman breastfeeds for longer than 1 year. There are several reasons why breastfeeding protects breast health:

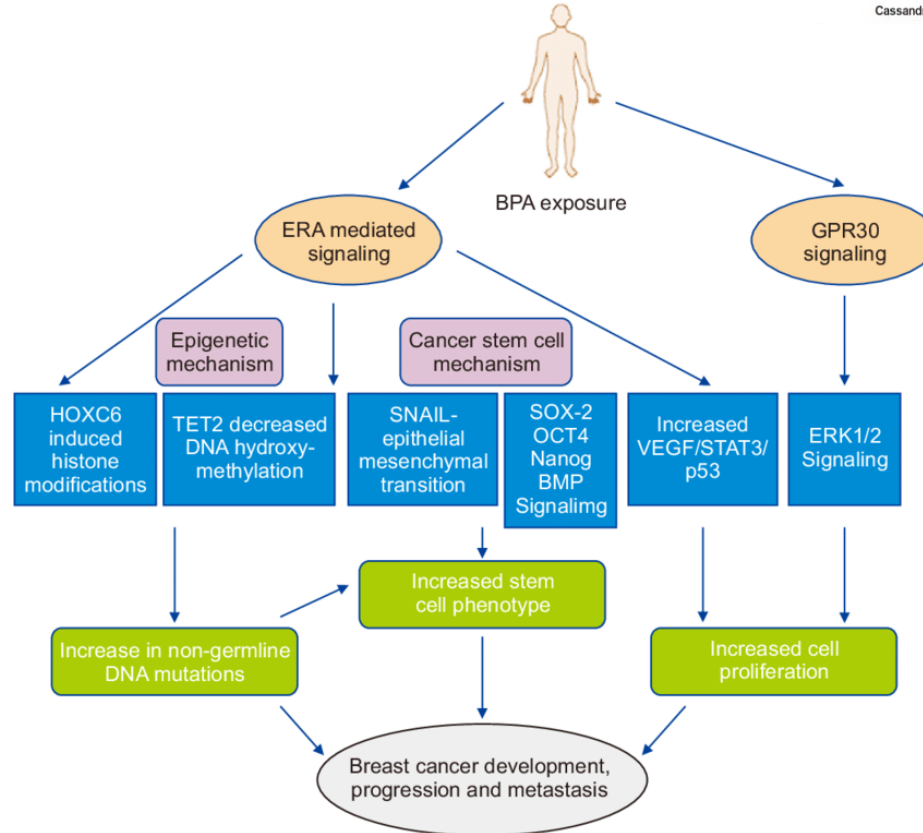
- making milk 24/7 limits breast cells' ability to misbehave
- most women have fewer menstrual cycles when they're breastfeeding (added to the 9 missed periods during pregnancy) resulting in lower estrogen levels
- many women tend to eat more nutritious foods and follow healthier lifestyles (limit smoking and alcohol use) while breastfeeding

PRATIKSHA HOSPITAL

Plastic – not so fantastic

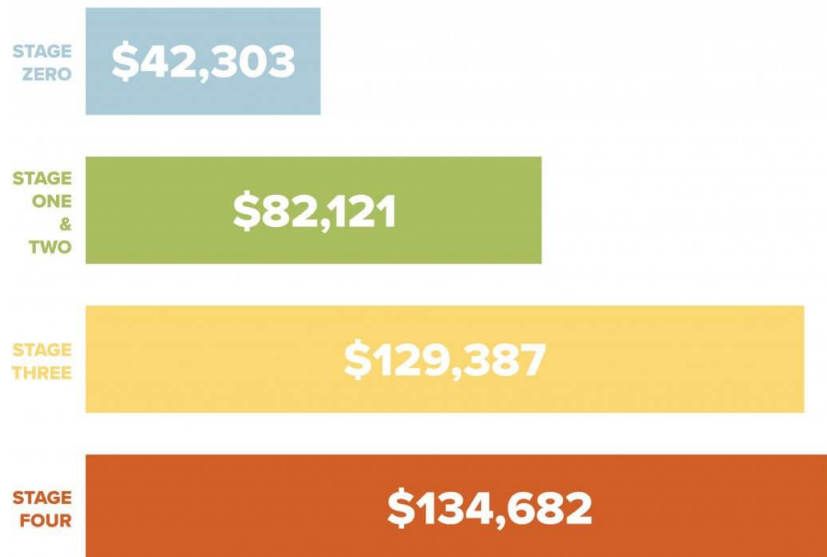
Understanding the Mechanistic Link between Bisphenol A and Cancer Stem Cells: A Cancer Prevention Perspective

Cassandra Winz^{1,2}, Nanjoo Suh^{1,3}



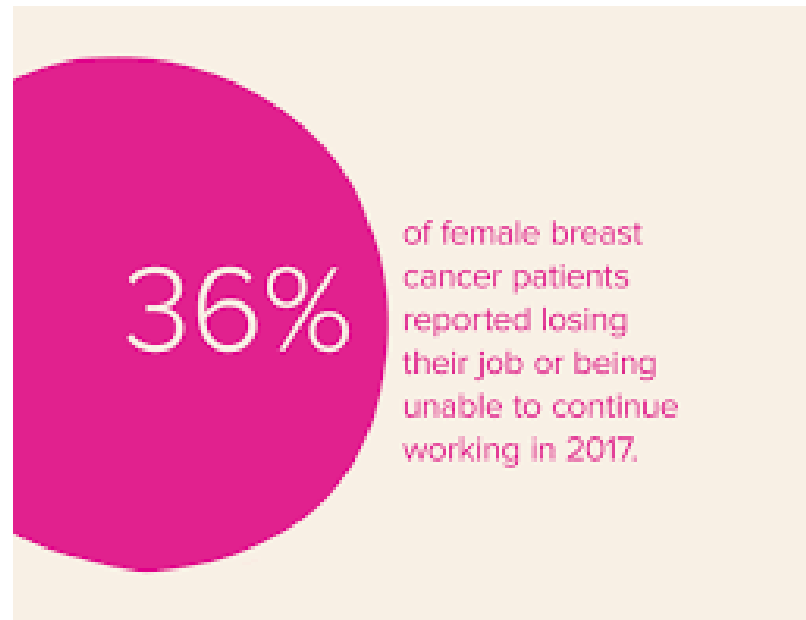
Special Report: The Cost of Breast Cancer Care

Relative Cost of Breast Cancer By Diagnosis



Breast Cancer Has Huge Economic Effects

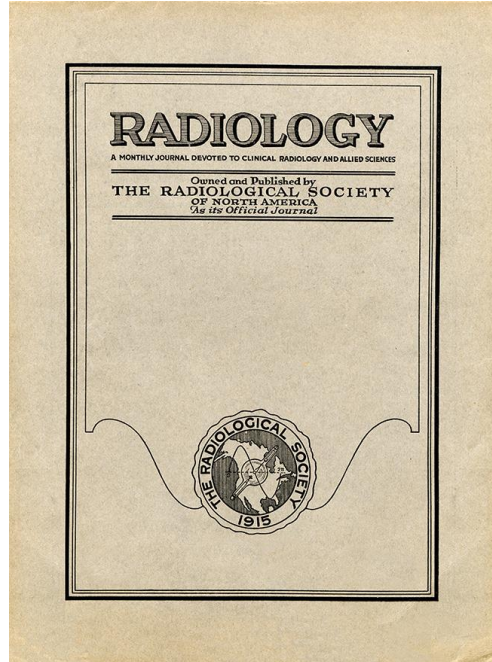
In 2020, costs associated with breast cancer were estimated at \$16.5 billion. To put that into perspective, if you saved \$100 per day, it would take you more than 450,000 years to reach that total.



Priority in the Therapeutic Use of X-rays

Emil H. Grubbé

Published Online: Aug 1 1933 | <https://doi.org/10.1148/21.2.156>



Review Article

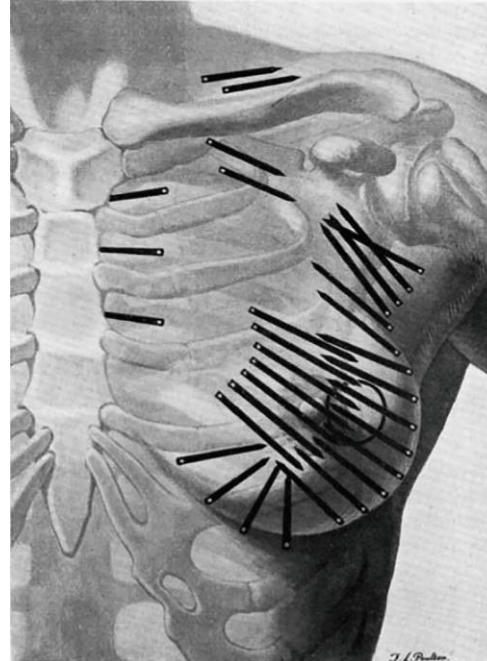
Evolution of radiotherapy techniques in breast conservation treatment

John Boyages^{1,2}, Lesley Baker²



GLAND SURGERY

pISSN: 2227-684X
eISSN: 2227-6875



RADIUM TREATMENT OF BREAST CANCER 415

THE RADIUM TREATMENT OF CARCINOMA OF THE BREAST.

By GEOFFREY KEYNES,
ASSISTANT SURGEON, ST. BARTHOLOMEW'S HOSPITAL, LONDON

THE RADIUM PROBLEM.

THE radium problem in the treatment of carcinoma of the breast is exactly the same as that which faces purely operative treatment—how to extirpate completely the cells of the primary growth and all secondary growths that may conceivably be accessible. Advance in the surgery of the breast dates from 1867, when Charles Moore,¹ of the Middlesex Hospital, criticized the methods of removal of the breast then practised. He advocated the wide removal of skin and underlying tissues, and of the main lymphatic glands draining the breast. He also enunciated the principle of the centrifugal dispersion of the disease. Since his time the work of Mitchell Banks, Samuel Gross, Halsted, Sampson Handley, and Cheate (to mention only some of the

“unnecessarily drastic operations are thereby eliminated, and to many women the saving of the breast is of the greatest psychological significance”

obvious local extension of the growth beyond the limits of operation, adhesion of the growth to the chest wall, involvement of lymphatic glands other than those in the axilla, or the presence of metastases in other parts of the body.

The radium problem may therefore be resolved into a series of questions which it is my object in this paper to make some attempt at answering:—

1. Can the primary growth in the breast be eradicated by radium?

VOL. XIX.—NO. 75.

27

Breast cancer therapy

Local/Locoregional therapy

- SURGERY
- RADIOTHERAPY

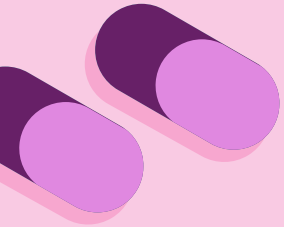
Systemic therapy

- CHEMOTHERAPY
- IMMUNOTHERAPY
- HORMONOTHERAPY



Radiotherapy indications

- Radiotherapy after breast conserving therapy (BCT)
- Radiotherapy of hemithorax
- Radiotherapy of regional lymphatics
- Radical radiotherapy of the breast cancer

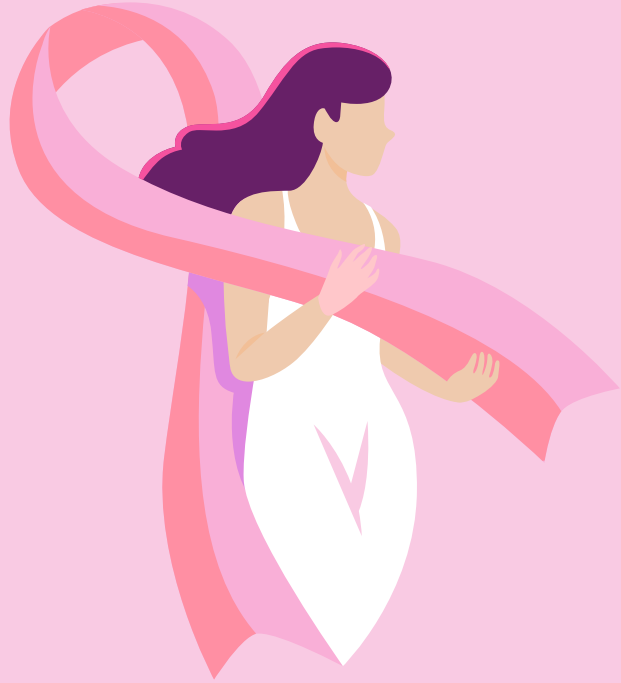


AIM = Local/locoregional treatment

- **Curative RT** – Local/locoregional disease control (better overall survival without relapsing)
- **Palliative RT** – Quality of Life improvement

Radiotherapy

- Transcutaneous radiotherapy
- Brachytherapy
- Intraoperative radiotherapy



Transcutaneous radiotherapy



PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy

- It is important to individualize RT planning and delivery.
 - ▶ 3-D CT-based treatment planning should routinely be utilized to delineate target volumes & organs at risk, and assess dose distribution across the entire treatment volume.
 - ▶ Radiation to the breast/chest wall and nodal regions is generally delivered with single energy or mixed energy photons \pm electrons.
 - ▶ Treatment planning should be optimized to maximally improve homogeneity across the target volume while minimizing dose to organs at risk.
 - ▶ Additional techniques such as respiratory control (deep inspiration breath-hold), prone positioning, and cardiac blocks may also be used to try to further reduce dose to heart, lung, and adjacent normal tissue.
 - ▶ At a minimum, weekly imaging to verify treatment setup should be utilized. More frequent imaging may be needed for selected cases with inconsistent reproducibility. Image-guided radiation therapy (IGRT) may be utilized with deep inspiration breath-hold (DIBH) technique to reduce normal tissue exposure of the heart, lung or liver.
 - ▶ Dose-volume histograms (DVHs) should be used to evaluate, dose and constraints to normal tissues (ie, heart, lung), and planning target volumes (PTVs).
- It is common for RT to follow chemotherapy when chemotherapy is indicated.

Whole Breast Radiation

- Target definition is the breast tissue at risk.
- RT dosing:
 - ▶ The whole breast should receive a hypofractionated dose of 40–42.5 Gy in 15–16 fractions; in selected cases 45–50.4 Gy in 25–28 fractions may be considered.
 - ▶ A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions.
 - ▶ Ultra-hypofractionated WBRT of 28.5 Gy in 5 (once-a-week) fractions may be considered for selected pts over 50 years following BCS with early-stage, node-negative disease, particularly those in whom a boost is not intended.^{a,b}
- Lumpectomy cavity boost can be delivered using enface electrons, photons, or brachytherapy.

Basic steps in the implementation of radiotherapy treatment

- Multidisciplinary tumor medical board (TMB) decision
- First examination and interview
- Preparation for CT simulation / processing
- CT simulation
- Delineation of organs at risk (OAR) and target volumes
- Radiotherapy planning
- Accuracy check and plan verification
- Positioning
- Treatment implementation
- Quality assurance procedures
- Monitoring of side effects during and after completed radiotherapy treatment

Transcutaneous radiotherapy

Depending on the size and shape of the target volume and the adjacent organs at risk, breast tumor radiotherapy is performed using various radiation techniques on a linear accelerator (LINAC), with photon energies ranging from 4 to 6 MV and electrons of appropriate energy (usually 6 to 15 MeV).

Aligning the geometry of radiation beams directed from multiple directions with the irregularly shaped parts of the body (neck, chest, breast) and variations in the shape of the target volume and surrounding organs at risk requires **precise positioning** and **immobilization** of patients during the radiation delivery and the selection of optimal radiation techniques.

Positioning and immobilisation

1. Supine position

- Flat position
- Incline position

2. Prone position

3. Lateral decubitus

Positioning in the supine position on a flat surface – WING BOARD

- An immobilization device that is easy to apply and comfortable for the patient.
- Made of carbon fibers.
- In the middle, there is a space for a headrest. On the lateral sides, the board bends in the shape of "wings," providing support for the arms in elevation and extension.
- At the top, there is a handgrip holder for raising the arm, which moves along both horizontal and vertical axes.



Positioning in the supine, incline position – BREAST BOARD

- a) Inclination is performed until the breast lifts from the lateral side of the chest.
- b) By elevating the ipsilateral or both arms, the breast is stabilized in the desired position. Care is taken to avoid the formation of skin folds in the folds.
- c) Data on the degree of inclination, position, height, and rotation of the k axial supports are entered into the positioning and immobilization chart



Positioning in the supine, incline position – BREAST BOARD

The angle of arm elevation depends on:

- The patient's ability to comfortably lift her arms.
- Skin folds in the supraclavicular region - folds influence the skin's reaction to radiation.
- In CT planning, the CT opening determines the degree of elevation.



Additional immobilisation devices

For the purpose of immobilizing the irradiated breast and positioning the healthy breast, we can use **thermoplastic masks**, which are molded to the shape of the patient's body and secured to the immobilization device.

The created masks should not alter the natural shape of the breasts by compression, but they should also not be



Additional immobilisation devices

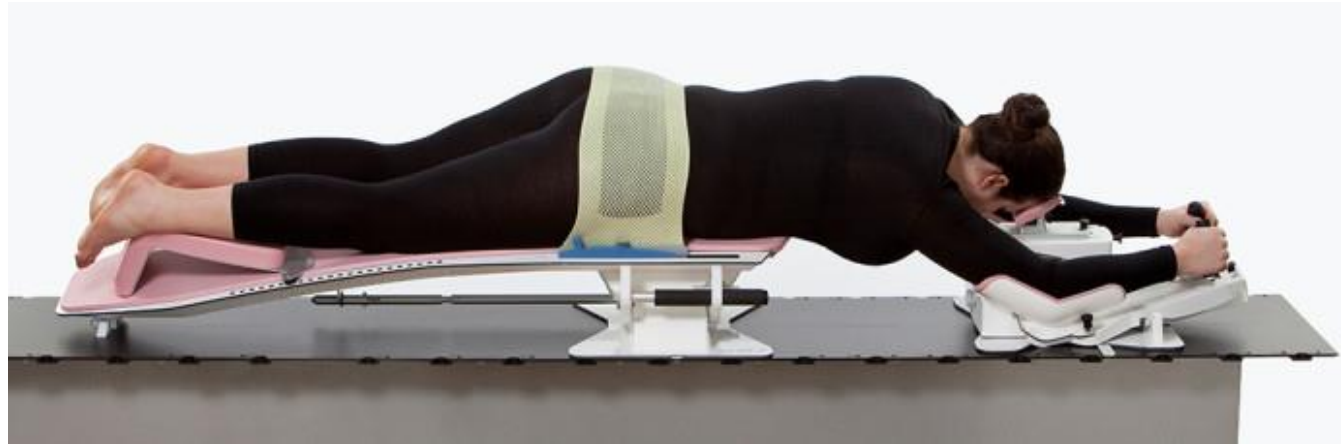
Vac-Lok™ cushion provide the possibility of easier and more precise repositioning.

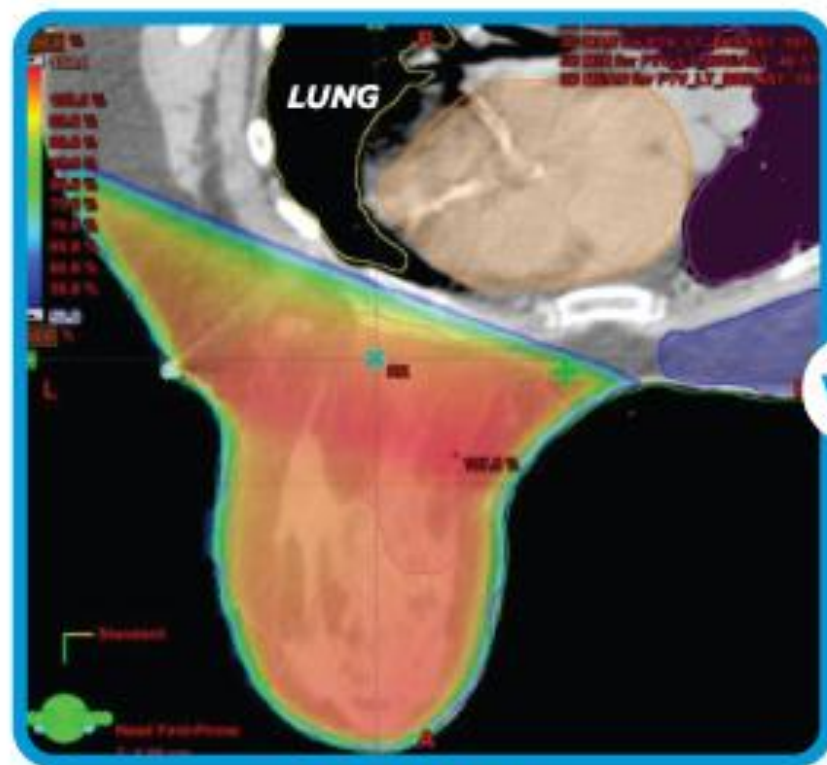
Vac-Lok™ cushions are reusable.

Vac-Lok™ cushions can be combined with other immobilization devices.



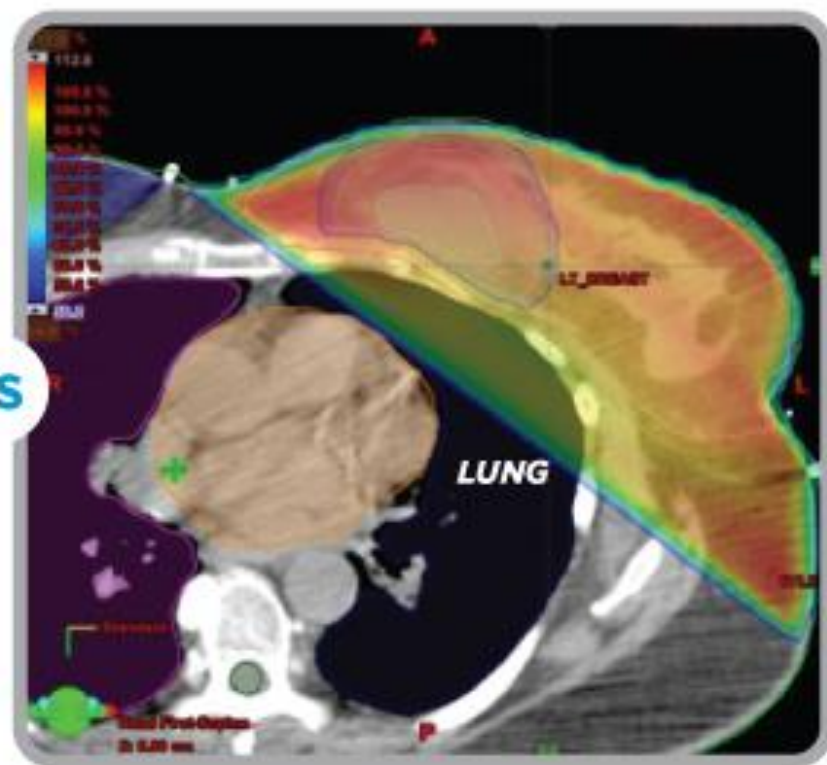
Positioning in the prone position



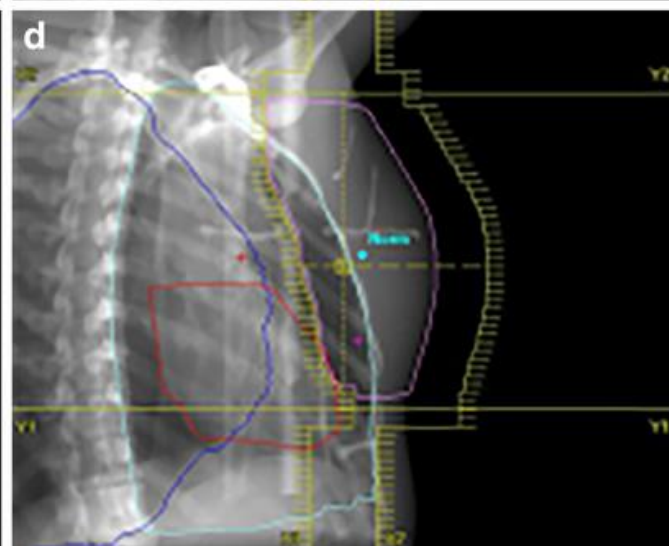
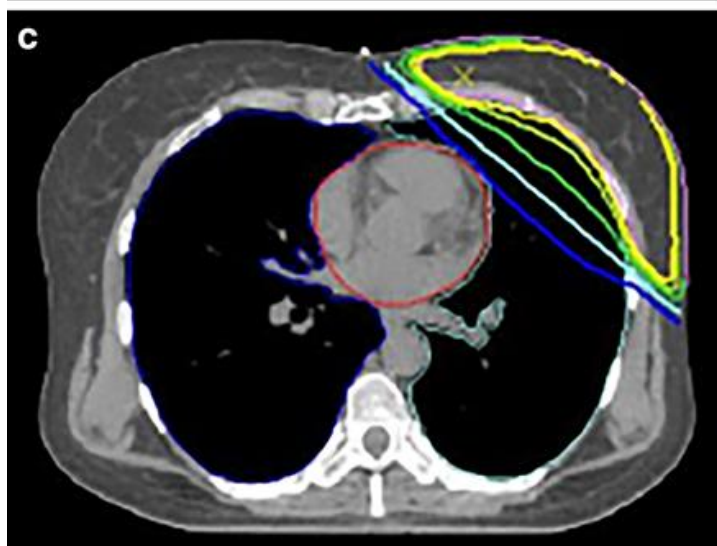
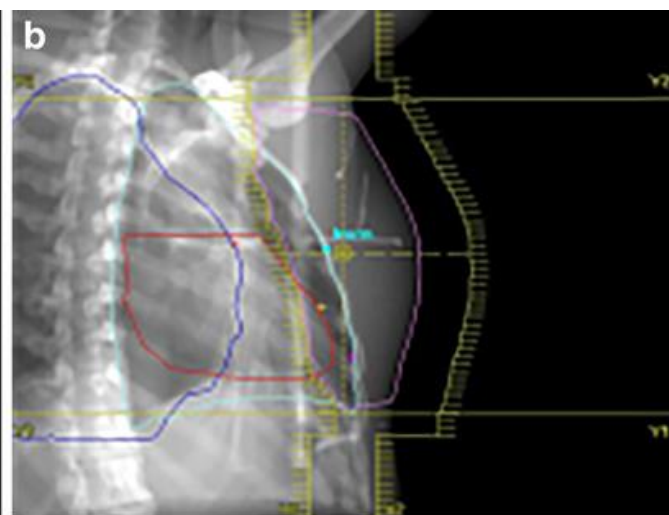


PRONE

VS



SUPINE



Target volume delineation

- **Gross Tumor Volume (GTV):** the visible part of the tumor (or lymph node), based on the performed clinical-diagnostic procedures. After a surgical treatment (R0 resection) the GTV is not visible.
- **Clinical Target Volume (CTV):** zone of microscopic spread of malignant cells around the visible part of the tumor (CTVt). CTVn is defined around enlarged regional lymph nodes (GTVn), it includes at least the entire anatomical group of lymph nodes to which the involved node belongs.
- **Planning Target Volume (PTV):** the margin that covers the interfractional/intrafractional variations of the CTV position in relation to the geometry of the beam/radiation field, and is caused by: variations in precision, physiological movements.

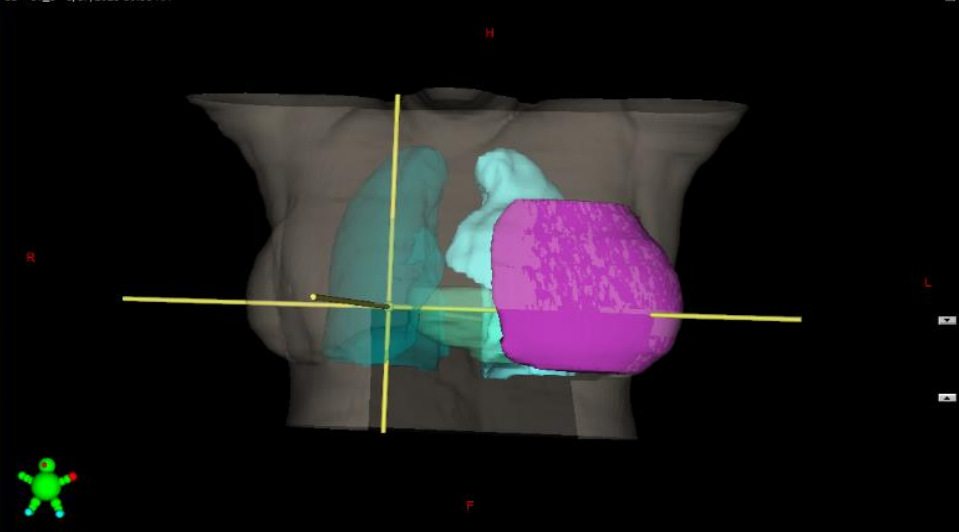
Target volume delineation

- Healthy, surrounding tissues, whose sparing/radiosensitivity is taken into account when creating a radiation plan and carrying out radiotherapy Treatment
- Additional volume around OAR (PRV - Planning Risk Volume)
- 3D model of the "virtual patient", with a volumetric representation of the geometry of the target volume and the spatial relationships of the target volume and the OAR

Transversal - CT_1 - 3/17/2021 10:51 AM



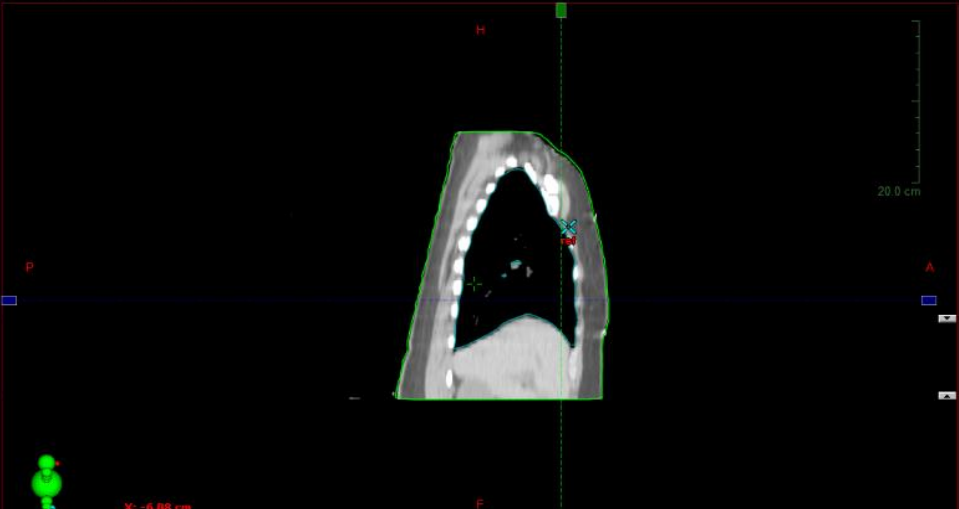
3D - CT_1 - 3/17/2021 10:51 AM



Frontal - CT_1 - 3/17/2021 10:51 AM



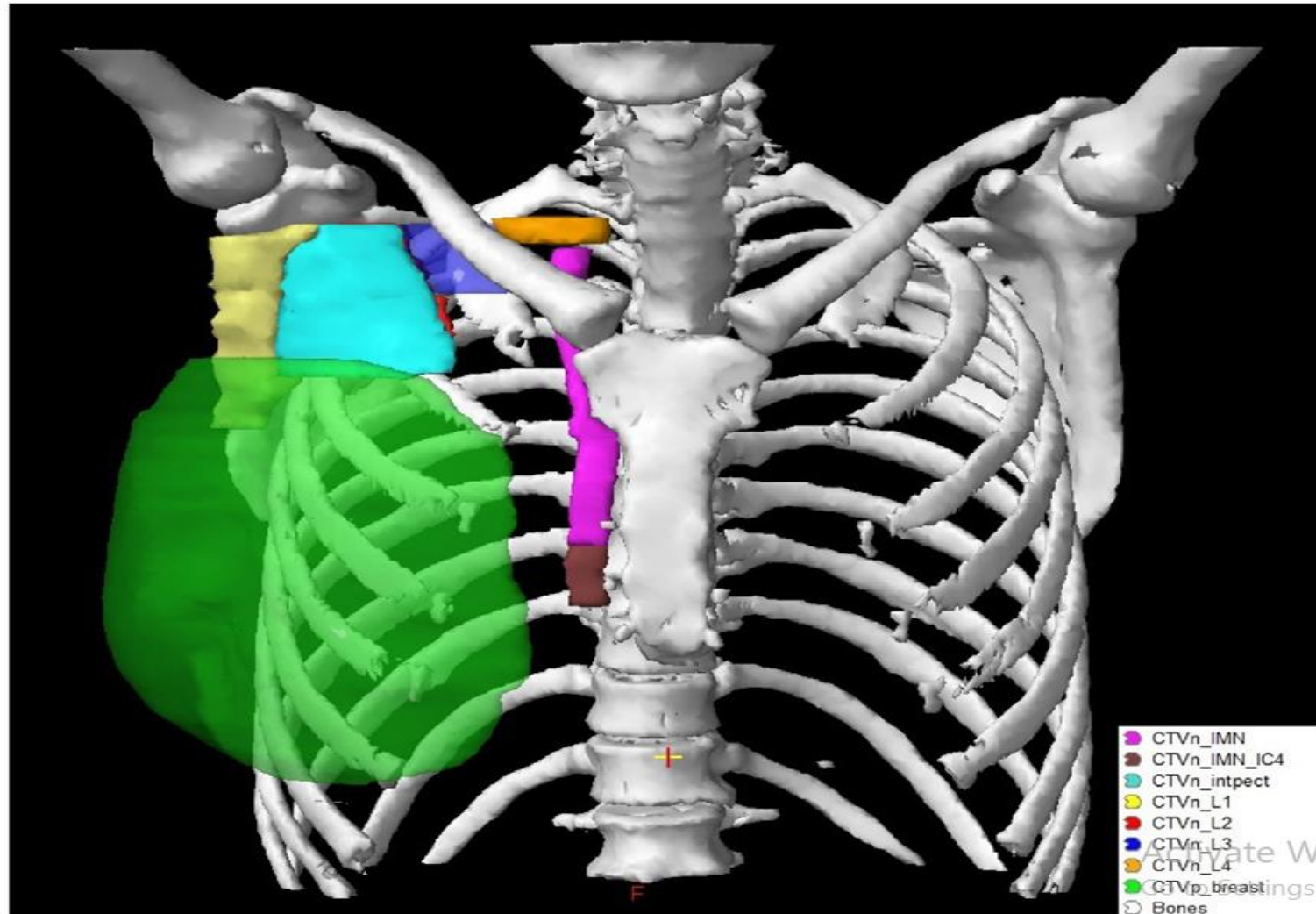
Sagittal - CT_1 - 3/17/2021 10:51 AM



Breast Cancer Atlas for Radiation
Therapy Planning:
Consensus Definitions



Borders per region	Axilla level 1 CTVn_L1	Axilla level 2 CTVn_L2	Axilla level 3 CTVn_L3	Lymph node level 4 CTVn_L4	Internal mammary chain CTVn_IMN	Interpectoral nodes CTVn_interpectoralis	Residual breast CTVp_breast	Thoracic wall CTVp_thoracic wall
Cranial	Medial: 5 mm cranial to the axillary vein Lateral: max up to 1 cm below the edge of the humeral head, 5 mm around the axillary vein	Includes the cranial extent of the axillary artery (i.e. 5 mm cranial of axillary vein)	Includes the cranial extent of the subclavian artery (i.e. 5 mm cranial of subclavian vein)	Includes the cranial extent of the subclavian artery (i.e. 5 mm cranial of subclavian vein)	Caudal limit of CTVn_L4	Includes the cranial extent of the axillary artery (i.e. 5 mm cranial of axillary vein)	Upper border of palpable/visible breast tissue; maximally up to the inferior edge of the sterno-clavicular joint	Guided by palpable/visible signs; if appropriate guided by the contralateral breast; maximally up to the inferior edge of the sterno-clavicular joint
Caudal	To the level of rib 4 – 5, taking also into account the visible effects of the sentinel lymph node biopsy	The caudal border of the minor pectoral muscle. If appropriate: top of surgical ALND	5 mm caudal to the subclavian vein. If appropriate: top of surgical ALND	Includes the subclavian vein with 5 mm margin, thus connecting to the cranial border of CTVn_IMN	Cranial side of the 4th rib (in selected cases 5th rib, see text)	Level 2's caudal limit	Most caudal CT slice with visible breast	Guided by palpable/visible signs; if appropriate guided by the contralateral breast
Ventral	Pectoralis major & minor muscles	Minor pectoral muscle	Major pectoral muscle	Sternocleidomastoid muscle, dorsal edge of the clavicle	Ventral limit of the vascular area	Major pectoral muscle	5 mm under skin surface	5 mm under skin surface
Dorsal	Cranially up to the thoraco-dorsal vessels, and more caudally up to an imaginary line between the anterior edge of the latissimus dorsi muscle and the intercostal muscles	Up to 5 mm dorsal of axillary vein or to costae and intercostal muscles	Up to 5 mm dorsal of subclavian vein or to costae and intercostal muscles	Pleura	Pleura	Minor pectoral muscle	Major pectoral muscle or costae and intercostal muscles where no muscle	Major pectoral muscle or costae and intercostal muscles where no muscle
Medial	Level 2, the interpectoral level and the thoracic wall	Medial edge of minor pectoral muscle	Junction of subclavian and internal jugular veins – >level 4	Including the jugular vein without margin; excluding the thyroid gland and the common carotid artery	5 mm from the internal mammary vein (artery in cranial part up to and including first intercostal space)	Medial edge of minor pectoral muscle	Lateral to the medial perforating mammarian vessels; maximally to the edge of the sternal bone	Guided by palpable/visible signs; if appropriate guided by the contralateral breast
Lateral	Cranially up to an imaginary line between the major pectoral and deltoid muscles, and further caudal up to a line between the major pectoral and latissimus dorsi muscles	Lateral edge of minor pectoral muscle	Medial side of the minor pectoral muscle	Includes the anterior scalene muscles and connects to the medial border of CTVn_L3	5 mm from the internal mammary vein (artery in cranial part up to and including first intercostal space)	Lateral edge of minor pectoral muscle	Lateral breast fold; anterior to the lateral thoracic artery	Guided by palpable/visible signs; if appropriate guided by the contralateral breast. Usually anterior to the mid-axillary line



- CTVn_IMN
- CTVn_IMN_IC4
- CTVn_intpect
- CTVn_L1
- CTVn_L2
- CTVn_L3
- CTVn_L4
- CTVp_breast
- Bones

Activate Windows

Go to Settings to activate Windows.

Indications for adjuvant radiotherapy for ductal carcinoma in situ (DCIS) are as follows:

✓ **DCIS** after breast-conserving surgery, except when all three conditions are met:

1. Tumor < 10mm
2. Low/intermediate nuclear grade
3. Margins > 2mm

✓ **DCIS** after radiotherapy, adding a tumor boost for individuals under 40 years old or if margins are less than 2mm.

Indications for adjuvant radiotherapy for invasive breast carcinoma (Stages I-III) are as follows:

- ✓ **Early invasive breast cancer T1, T2, N0 (EIBC) after breast-conserving surgery,** radiotherapy can be omitted in patients over 70 years of age if they are receiving adjuvant endocrine therapy, provided all the following conditions are met:
 - ✓ Tumor size less than 2 cm
 - ✓ Tumor-free resection margins
 - ✓ G1/G2
 - ✓ N0
 - ✓ Positive hormone receptors (ER+)

✓ **EIBC** - Adding a tumor boost is recommended for women under 60 years old and those with poor prognostic parameters (at least one): positive axillary lymph nodes, LVI+, margin less than 1 mm, G3, extensive DCIS component, positive margins with no planned tumor re-excision. Boost omission is permissible for patients meeting the following criteria:

- a. ≥ 60 years old,
- b. Small, low-grade tumor
- c. Negative resection margin favorable tumor biology when hormonal therapy is planned

✓ **EIBC - After mastectomy**, if there is a combination of multiple risk factors:

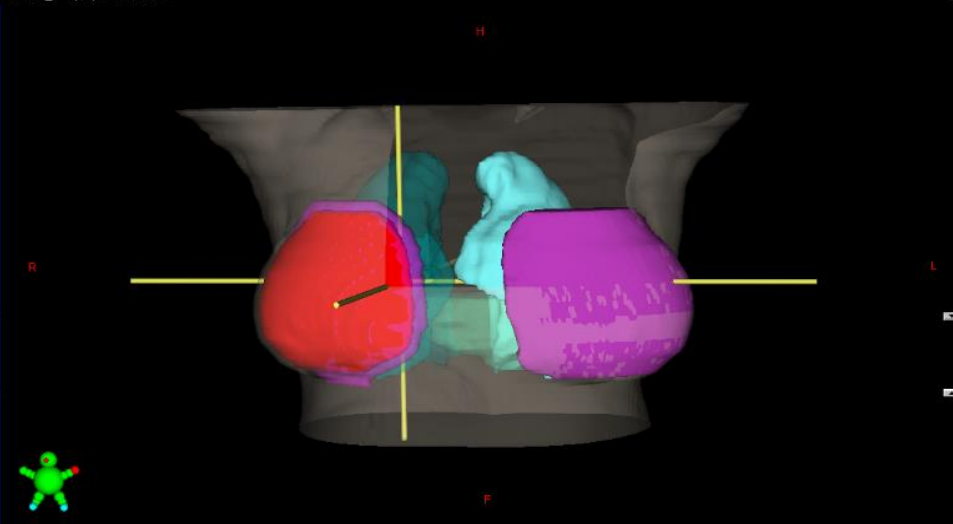
- Positive margins
- G3
- Multicentric/multifocal tumor
- Extensive LVI
- Centrally or medially localized tumor
- Young age (<40 years)
- Unfavorable molecular profile
- 1-3 positive lymph nodes with the presence of extracapsular invasion or in younger women

Locally Advanced Breast Cancer (LABC) after breast-conserving surgery

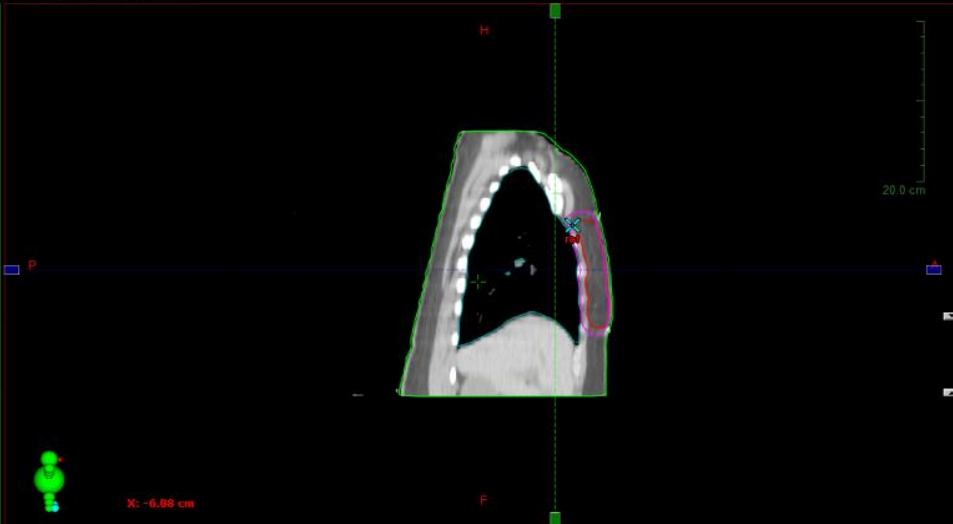
Locally Advanced Breast Cancer (LABC) after mastectomy if any of the following conditions are met:

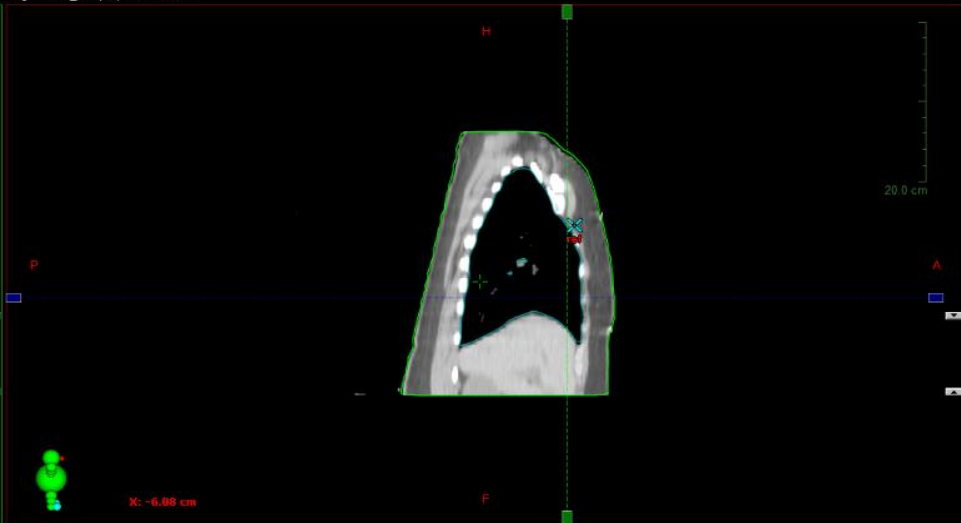
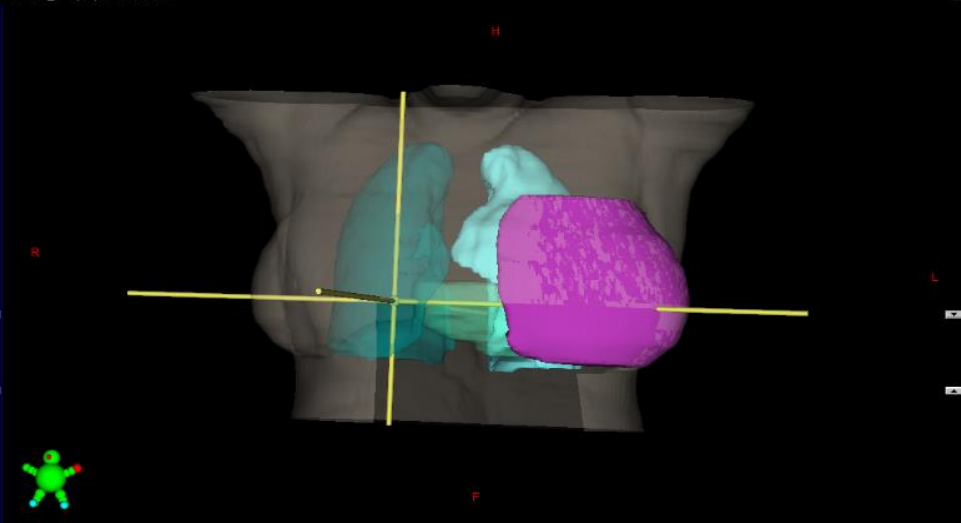
- Tumor size > 5cm
- Invasion of the skin or chest wall (T4)
- Positive margins
- Recurrence of the chest wall
- More than 4 positive lymph nodes
- No lymphadenectomy/inadequate sentinel node (SN+) without lymphadenectomy (macrometastasis)
- 1-3 positive lymph nodes and poor prognostic factors (younger than 40 years, T3, G3, LVI+)

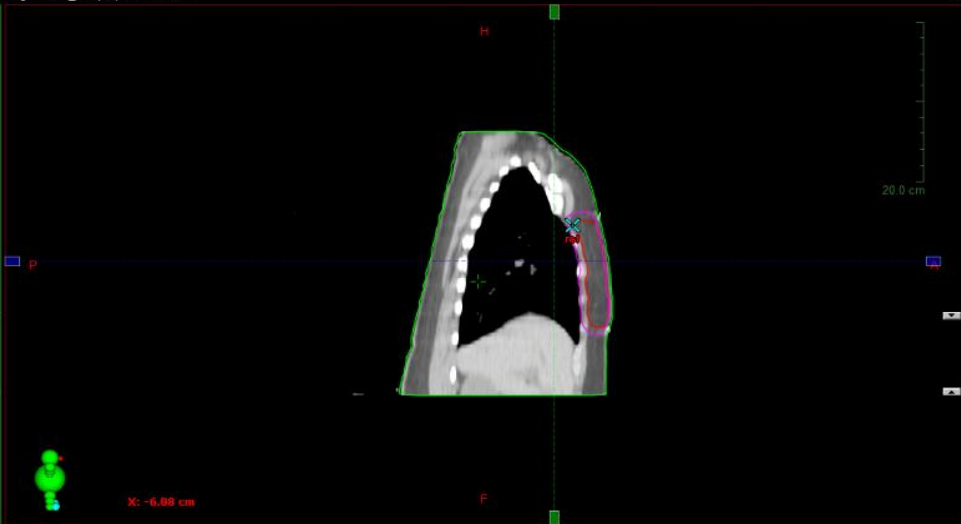
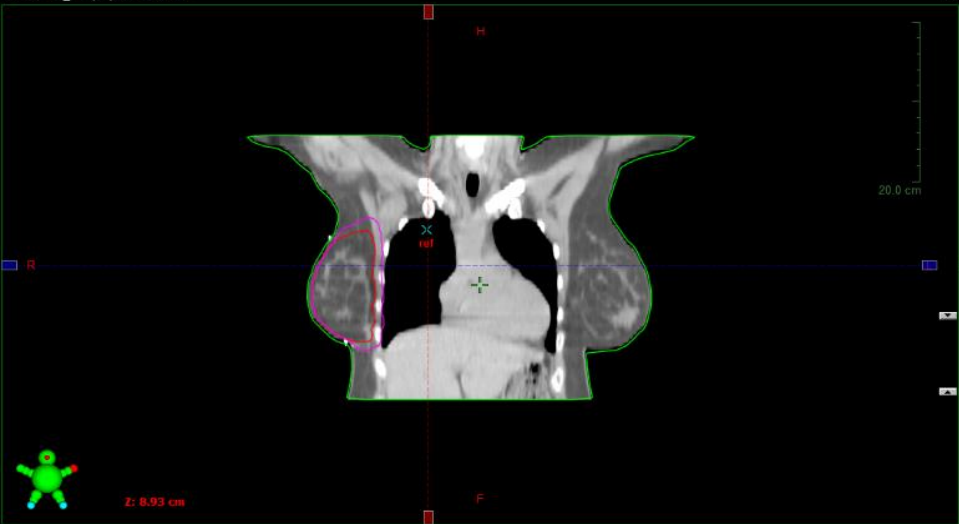
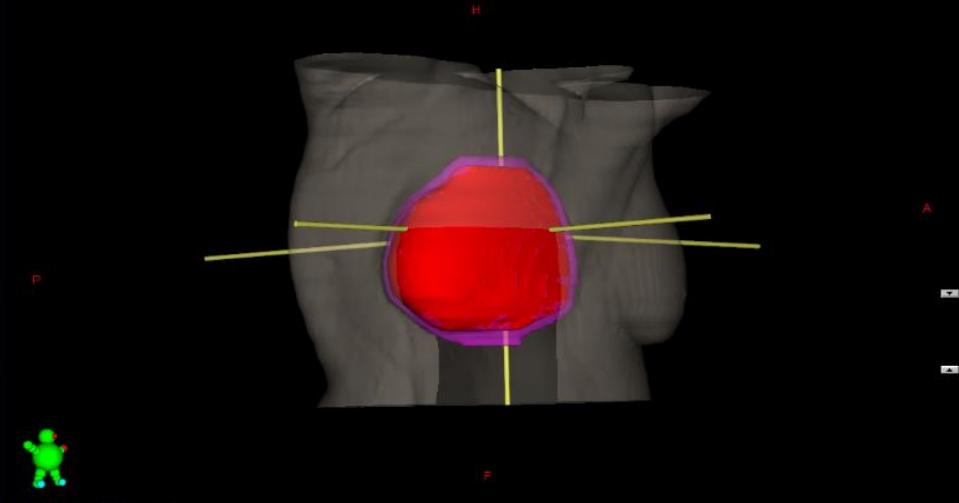
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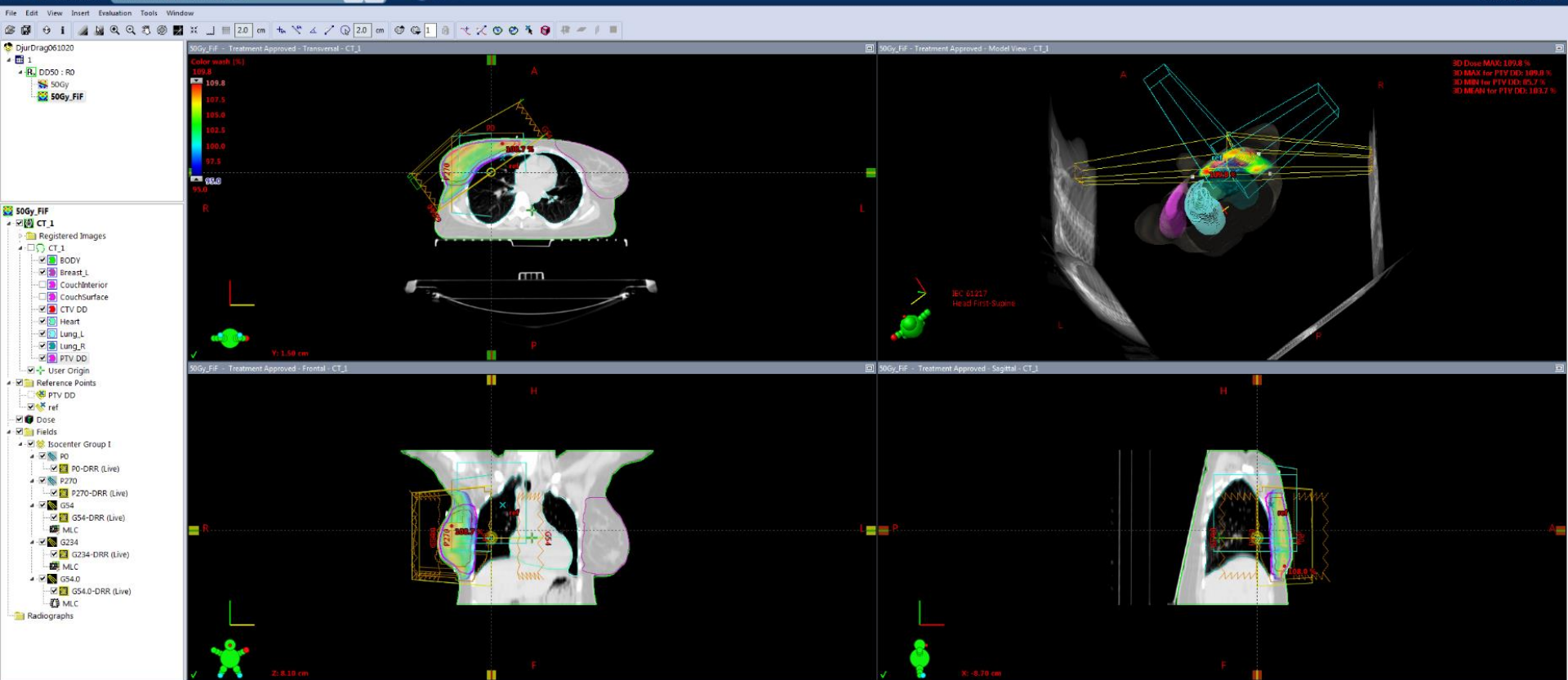


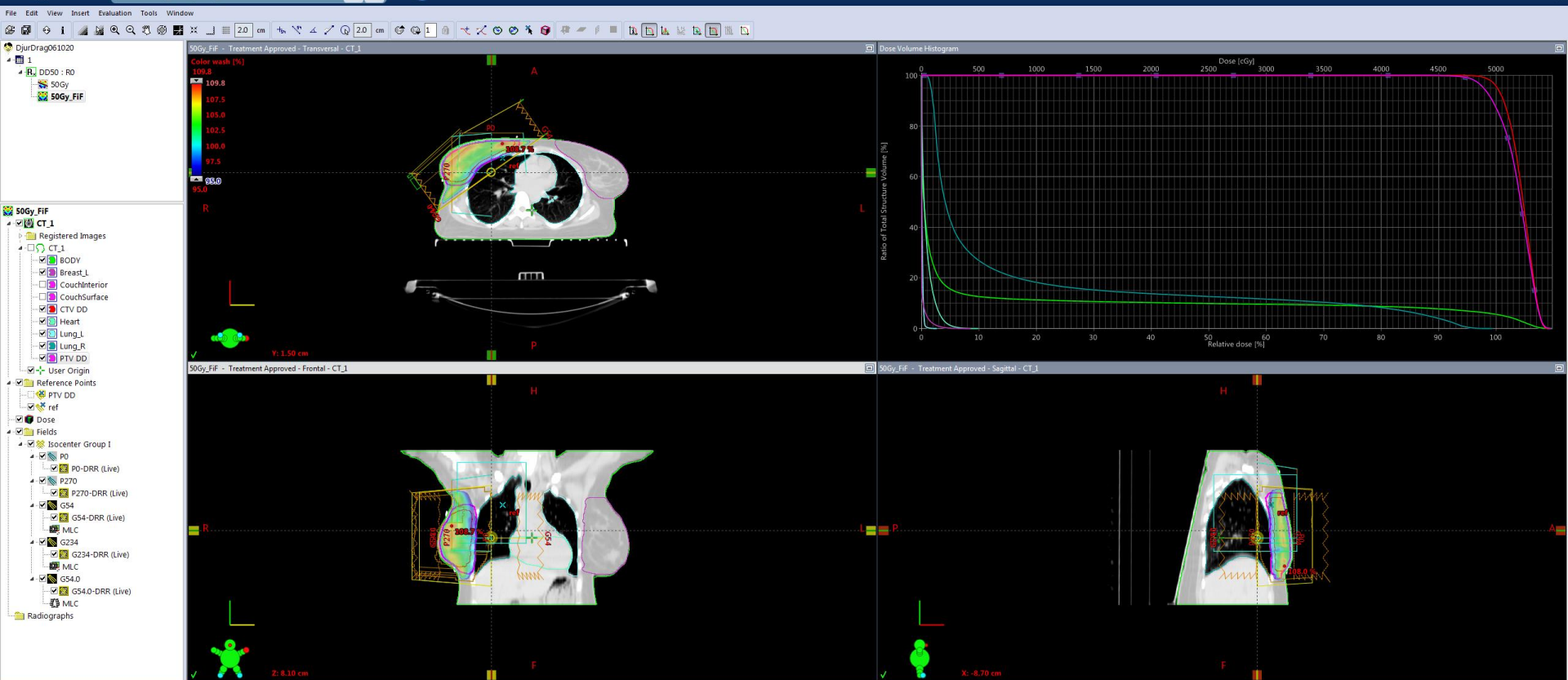
☐ Sagittal - CT_1 - 3/17/2021 10:51 AM



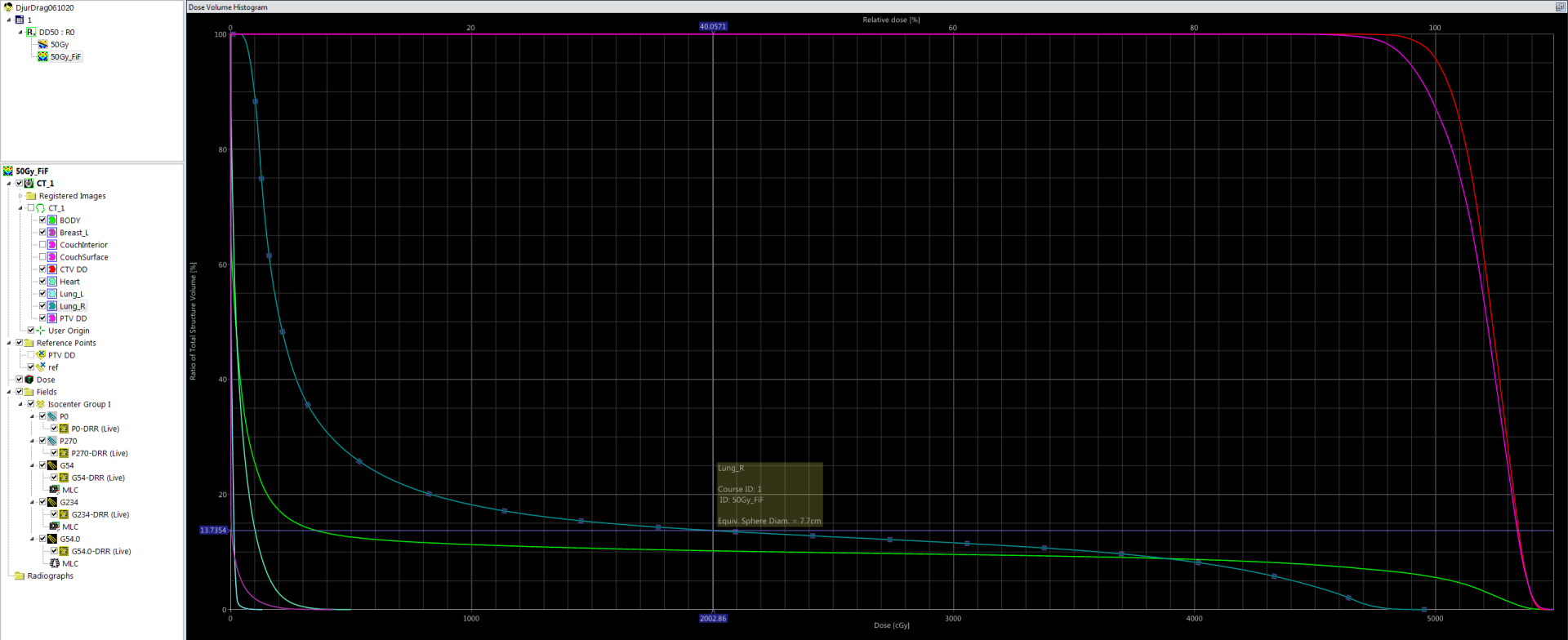




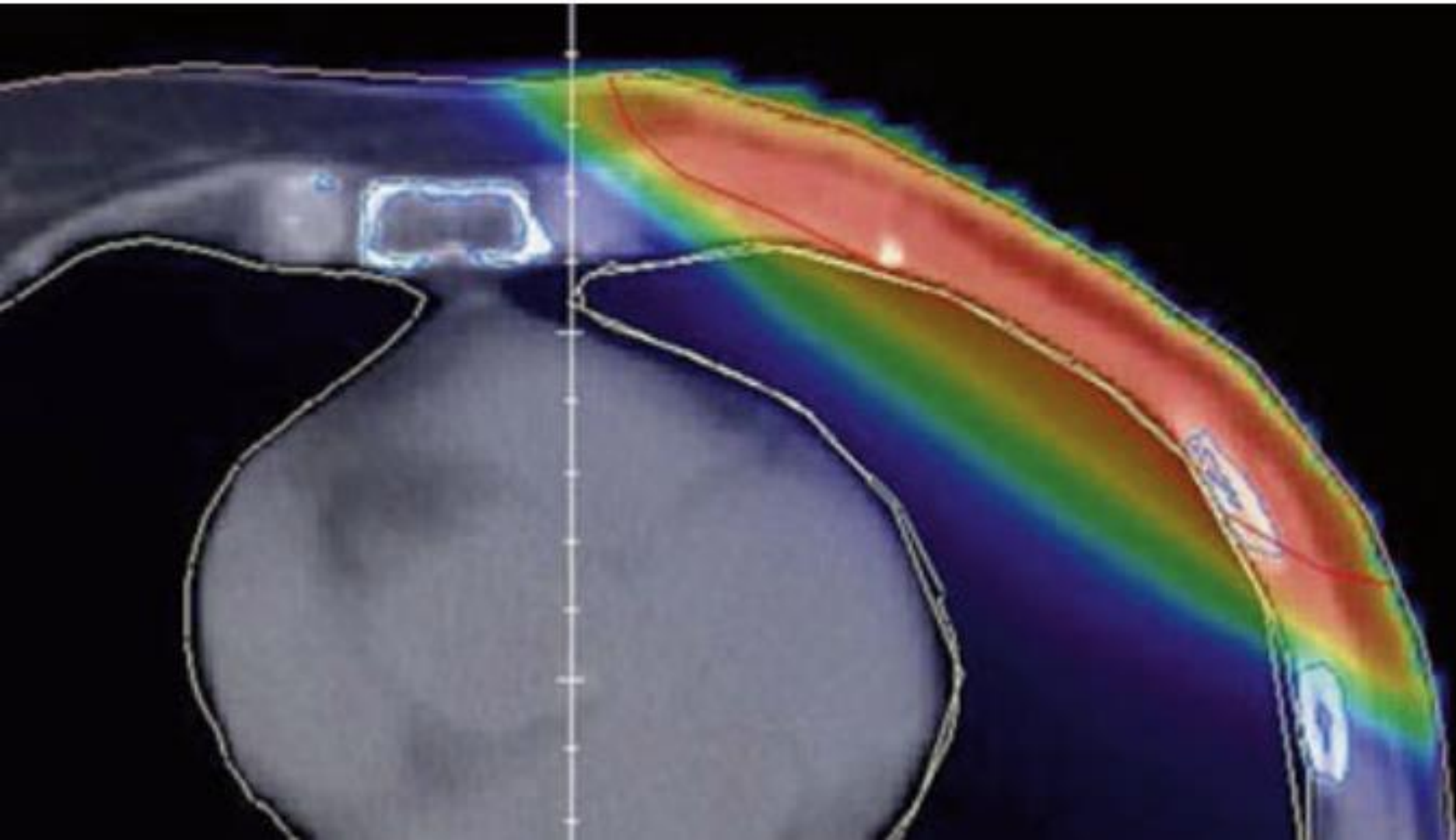




Fields	Dose	Reference Points	Dose Statistics								
Show DVH	Structure	Approval Status	Plan	Course	Volume [cm ³]	Dose Cover [%]	Sampling Cover [%]	Min Dose [%]	Max Dose [%]	Mean Dose [%]	
<input checked="" type="checkbox"/>	BODY	Approved	50Gy_FIF	1	22542.5	100.0	100.3	0.0	109.8	10.9	
<input checked="" type="checkbox"/>	Lung_L	Approved	50Gy_FIF	1	1389.6	100.0	100.0	0.0	2.7	0.1	
<input checked="" type="checkbox"/>	Lung_R	Approved	50Gy_FIF	1	1746.9	100.0	100.0	0.8	99.3	16.0	
<input checked="" type="checkbox"/>	Heart	Approved	50Gy_FIF	1	486.4	100.0	100.0	0.0	10.0	0.9	
<input checked="" type="checkbox"/>	Breast_L	Approved	50Gy_FIF	1	1291.6	100.0	100.0	0.0	8.6	0.1	
<input checked="" type="checkbox"/>	CTV DD	Approved	50Gy_FIF	1	833.1	100.0	100.0	90.6	109.3	104.4	
<input checked="" type="checkbox"/>	PTV DD	Approved	50Gy_FIF	1	1102.6	100.0	85.7	100.0	109.8	103.7	



Dose		Reference Points	Dose Statistics								
Show DVH	Structure	Approval Status	Plan	Course	Volume [cm ³]	Dose Cover [%]	Sampling Cover [%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]	
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<input checked="" type="checkbox"/>	Lung_L	Approved	50Gy_FIF	1	1389.6	100.0	100.0	0.0	135.3	5.8	
<input checked="" type="checkbox"/>	Lung_R	Approved	50Gy_FIF	1	1746.9	100.0	100.0	38.5	4967.2	799.9	
<input checked="" type="checkbox"/>	Heart	Approved	50Gy_FIF	1	486.4	100.0	100.0	0.0	499.7	45.3	
<input checked="" type="checkbox"/>	Breast_L	Approved	50Gy_FIF	1	1291.6	100.0	100.0	0.0	428.3	7.1	
<input checked="" type="checkbox"/>	CTV DD	Approved	50Gy_FIF	1	833.1	100.0	100.0	4530.2	5467.4	5221.7	
<input checked="" type="checkbox"/>	PTV DD	Approved	50Gy_FIF	1	1102.6	100.0	100.0	4283.6	5487.5	5185.6	





PRINCIPLES OF RADIATION THERAPY

Post-mastectomy Radiation (including breast reconstruction)

- The target includes the ipsilateral chest wall and the entire mastectomy scar ± drain sites.
 - Regional nodal RT is typically delivered with the chest wall. See below.
- In the case of cT3N0, high-risk features for considering PMRT include, but are not limited to, young age and/or LVI.
- Based on anatomic considerations and presence of reconstruction, various 3-D-, IMRT, or VMAT techniques using photons and/or electrons are appropriate.
- PMRT details and dosing:
 - The routine use of bolus is not recommended. Bolus should be considered in the use of IBC or clinical-pathologic situations where the dose to the skin may not be adequate.
 - Chest wall scar boost of 10-16 Gy/fx at 1.8 to 2.0 Gy/fx total 5-8 fractions may be delivered with or without bolus using electrons or photons.
 - Chest wall RT dose is 45-50.4 Gy at 1.8-2 Gy/fx in 25-28 fractions. Patients not undergoing breast reconstruction may alternatively receive 40 Gy at 2.67 Gy/fx or 42.5 Gy at 2.66 Gy/fx

Regional Nodal Radiation

- For supra/infra-clavicular and axillary nodes, prescription depth varies based on the patient anatomy.
- Regional nodes should be contoured when considering regional nodal RT. Refer to breast atlases for contouring guidelines.^{c,d}
- RT dosing:
 - Regional node dose is 45–50.4 Gy at 1.8–2 Gy/fx; patients not undergoing breast reconstruction may alternatively receive 40 Gy at 2.67 Gy/fx or 42.5 Gy at 2.66 Gy/fx
 - A supplemental boost of RT can be delivered to grossly involved or enlarged lymph nodes (ie, internal mammary, supra/infra-clavicular) that have not been surgically removed.

RT with Preoperative or Adjuvant Systemic Therapy

- In patients treated with preoperative systemic therapy, adjuvant RT is based on the maximal disease stage (ie, clinical stage, pathologic stage, tumor characteristics) at diagnosis (before preoperative systemic therapy) and pathology results after preoperative systemic therapy.
- Sequencing of RT with systemic therapy:
 - It is common for RT to follow chemotherapy when chemotherapy is indicated. However,
 - CMF (cyclophosphamide/methotrexate/fluorouracil) is the only standard regimen that can be given concurrently with RT.
 - Capecitabine is typically given after completion of RT.
 - Olaparib should be given after completion of RT.
 - Available data suggest that sequential or concurrent endocrine therapy with RT is acceptable. Due to compounding side effects, initiating endocrine therapy at the completion of RT may be preferred.
 - ◊ Abemaciclib should be initiated after completion of surgery/RT/chemotherapy, concurrently with endocrine therapy.
 - Adjuvant HER2-targeted therapy ± endocrine therapy may be delivered concurrently with RT.

Lymph node irradiation

Radiation therapy to locoregional lymph nodes reduces the rate of locoregional recurrence of breast cancer, as well as the rate of distant recurrences. Adjuvant radiotherapy to the axilla (Levels I and II) is recommended based on the following clinical indications:

1. Inadequate axillary dissection (<7 lymph nodes).
2. If 7, 8, or 9 lymph nodes were excised and found negative, assessment is based on other risk factors.
3. Rest after axillary dissection.
4. If axillary dissection was not performed.
5. Sentinel node (SN) biopsy positive without further dissection.
6. Presence of extracapsular tumor spread.
7. Always for 4 or more positive lymph nodes.
8. For 1-3 positive lymph nodes and the presence of risk factors, i.e., if at least one of the following conditions is met:
 1. Woman younger than 40 years
 2. LVI+
 3. High grade (HG) 3
 4. T3 (tumor over 5 cm)
 5. Poor biological profile (HER2+ or triple-negative)

Optional:

If ALL the criteria are met, nodal irradiation can be omitted (1) (Level of evidence A, Recommendation category II):

- T1/T2
- ≤ 2 positive nodes
- Breast-conserving surgery performed
- Planned whole breast irradiation
- No preoperative chemotherapy received

If pN0, nodal irradiation can be optionally applied for:

central/medial localization or tumors >2 cm if the following conditions are met: < 40 years of age and the presence of lymphovascular invasion (Level of evidence B, Recommendation category II).

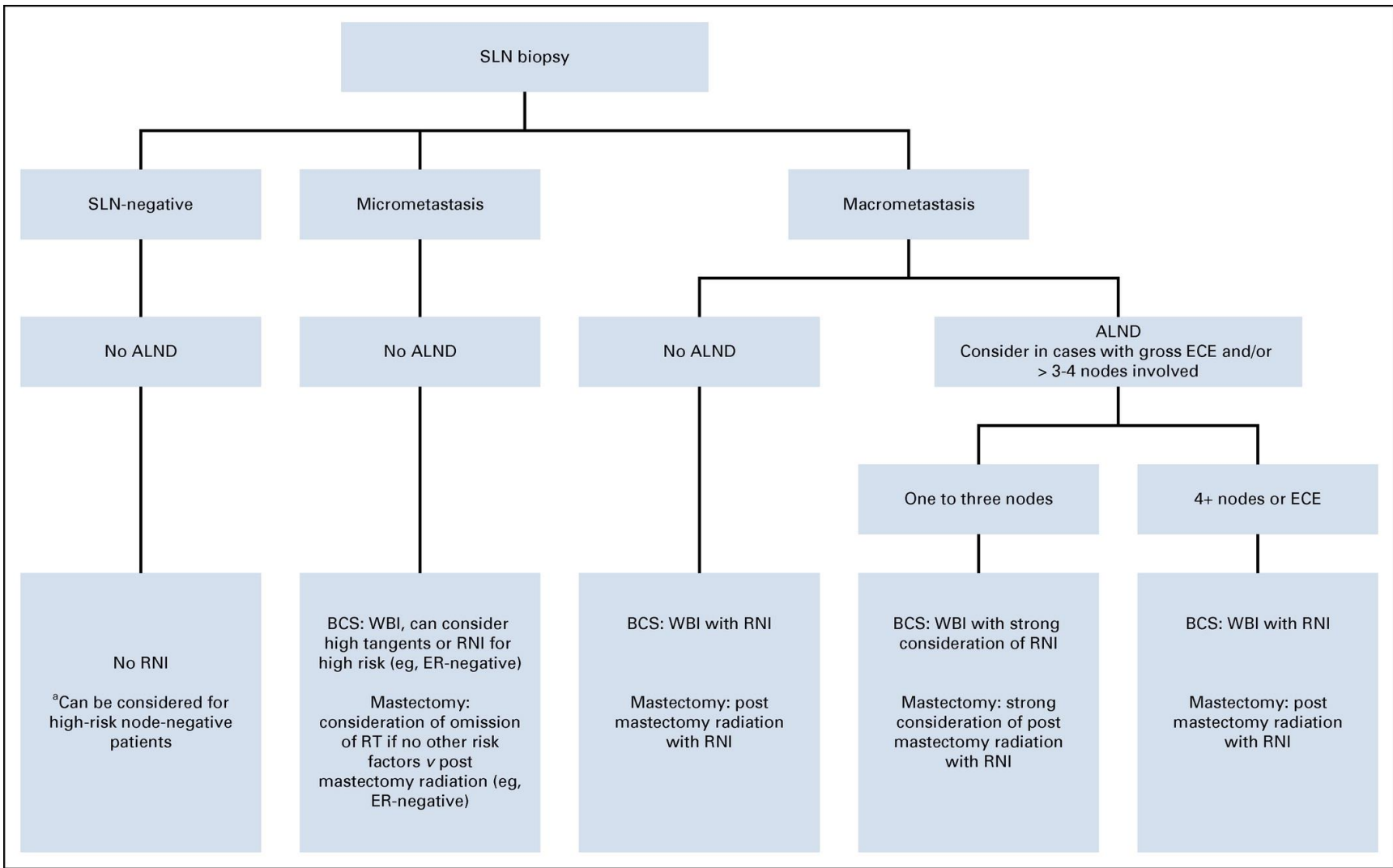
Adjuvant radiotherapy to the **supraclavicular region** is recommended in the following clinical indications:

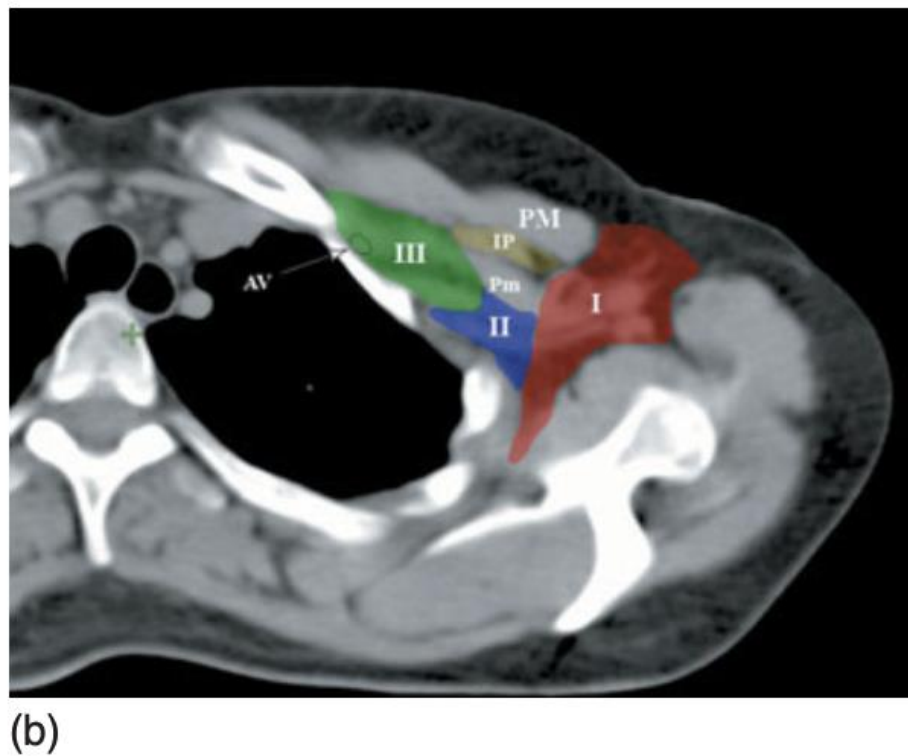
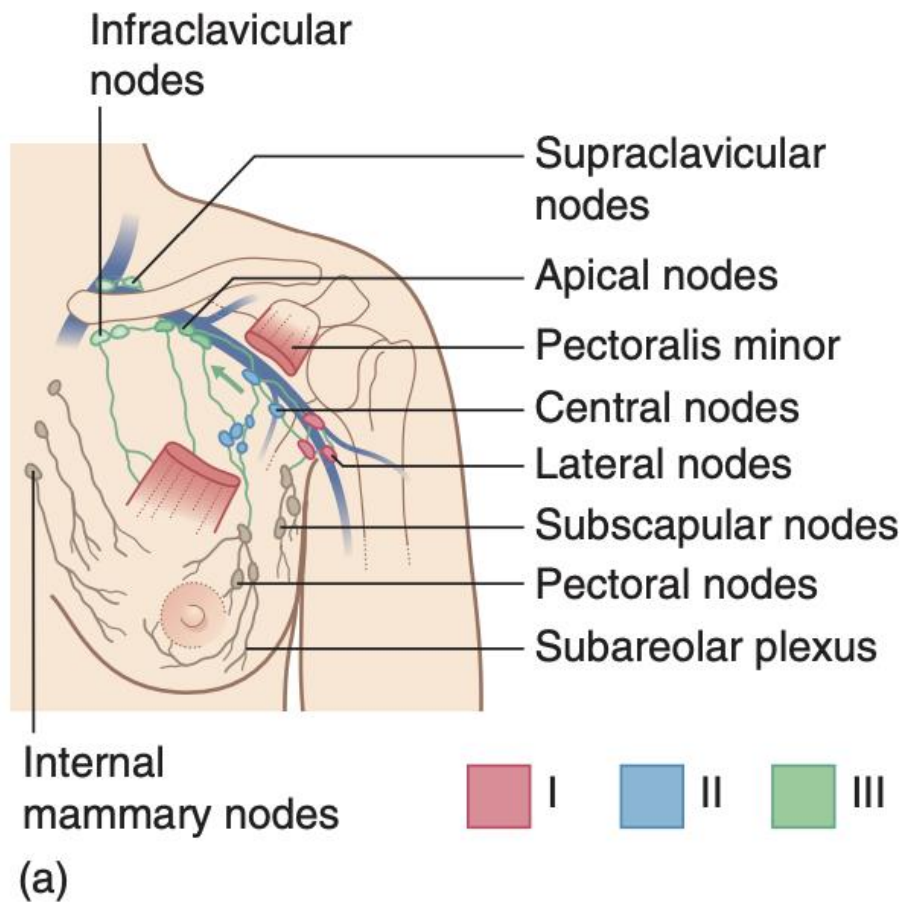
1. Four or more positive lymph nodes.
2. Inadequate axillary dissection (<7 lymph nodes).
3. For 1-3 positive lymph nodes with other high-risk factors, fulfilling at least one condition (<40 years old, LVI+, G3, T3).

Adjuvant radiotherapy to the **internal mammary artery** region is recommended according to the following indications:

1. When the tumor is localized in the medial quadrants of the breast or centrally, with positive lymph nodes in the axilla.
2. For tumors larger than 3 cm, pN0, and central/medial localization.

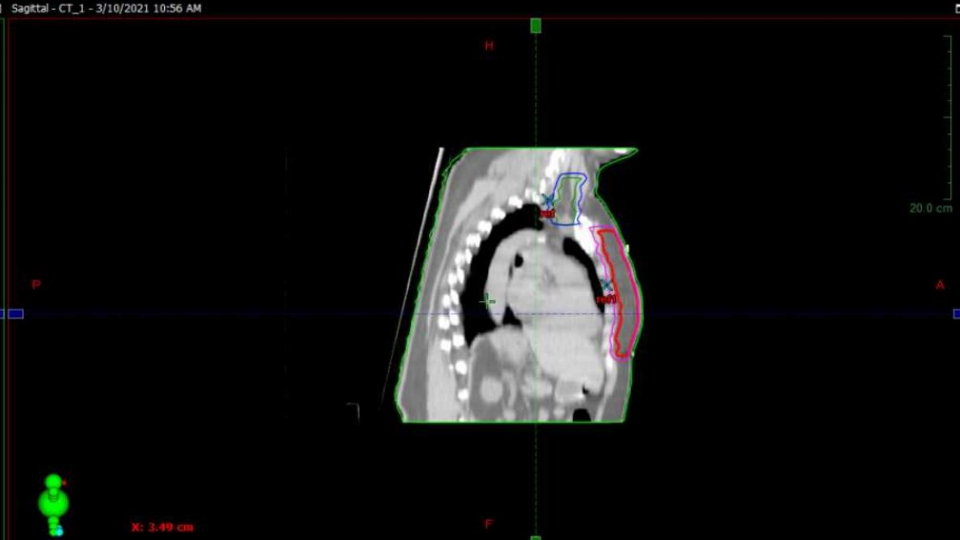
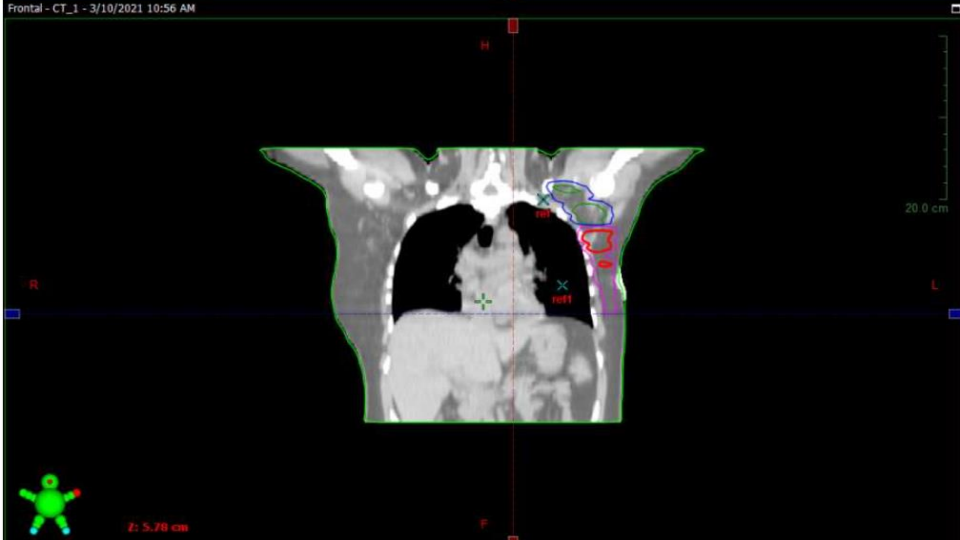
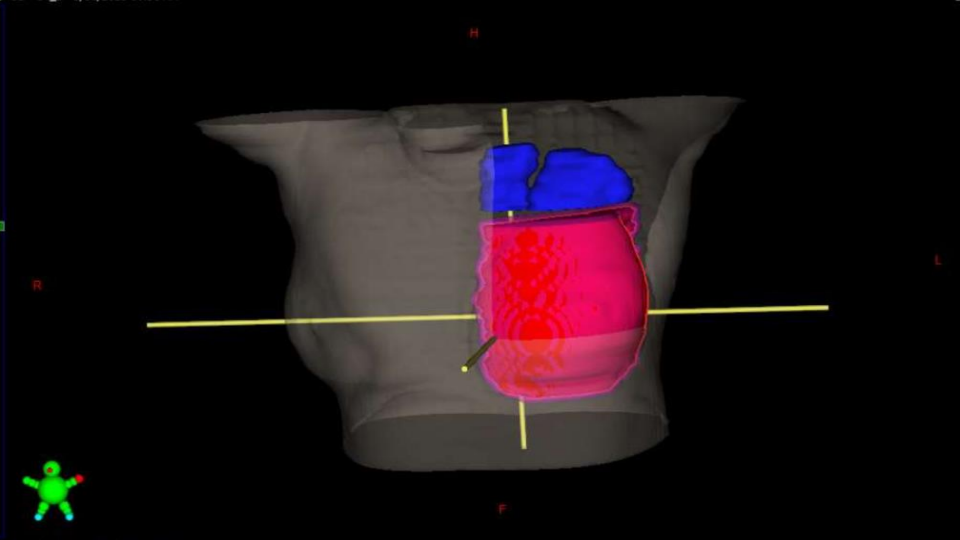
Optional: If there are four or more positive axillary lymph nodes, regardless of tumor localization.

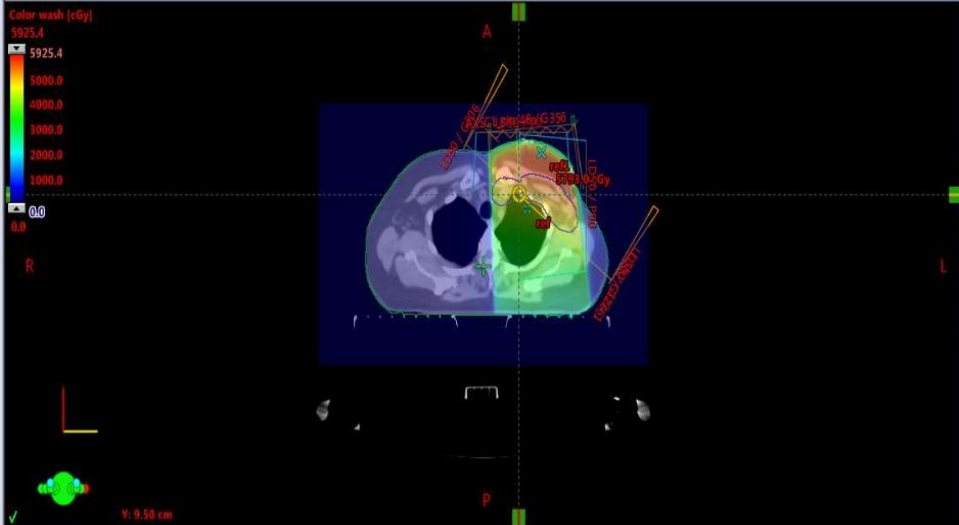




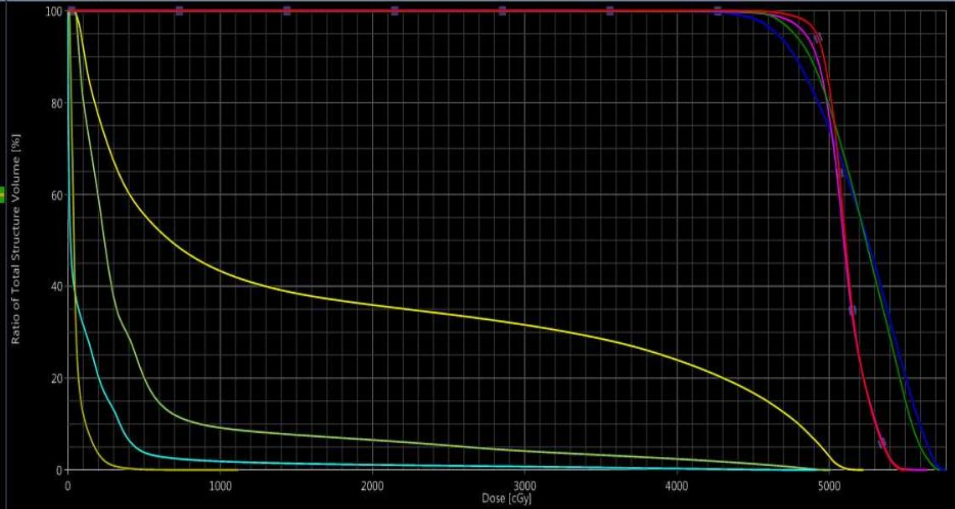
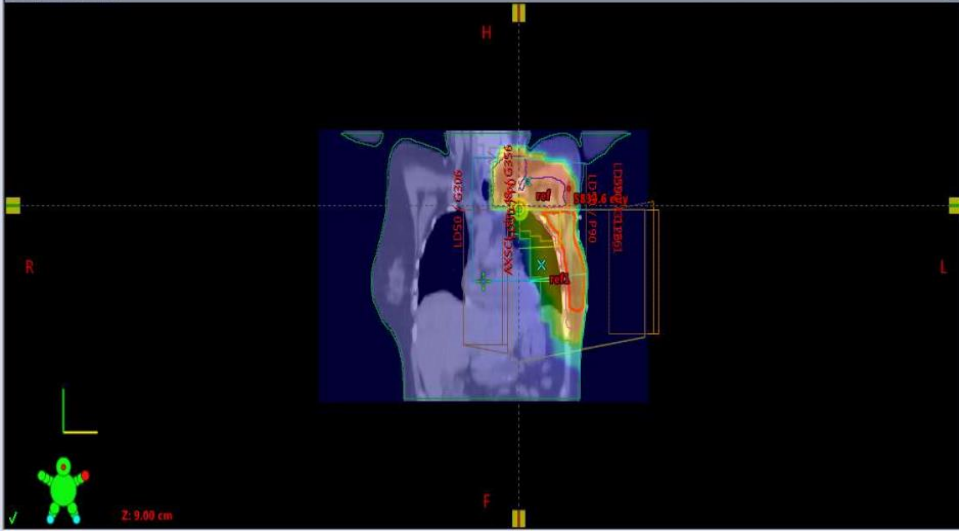
Lymph Node Radiotherapy Instead of Extended Axillary Surgery – the New Standard?

Peter Niehoff Silla Hey-Koch

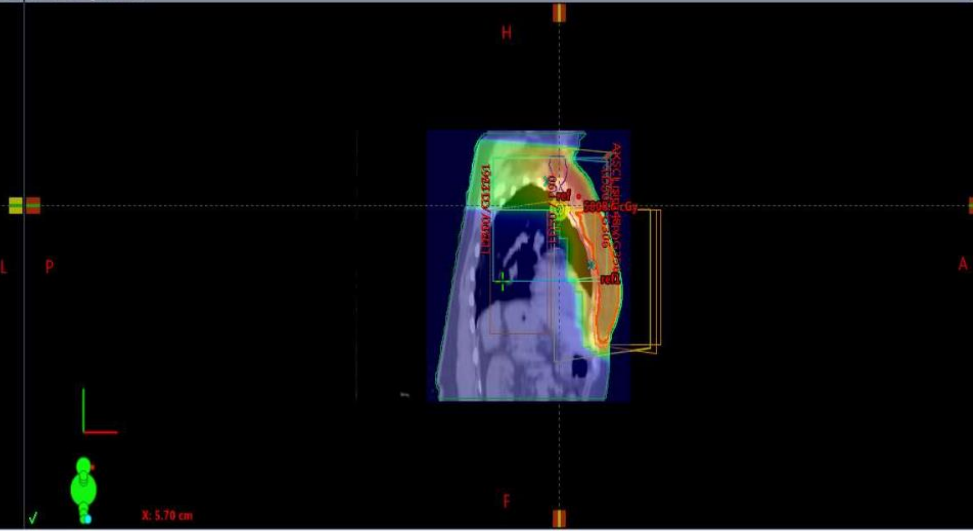




Plan Sum - Frontal - CT_1



Plan Sum - Sagittal - CT_1



After neoadjuvant systemic therapy, radiotherapy is indicated based on the tumor stage **before** the application of this therapy, regardless of the tumor's response to the applied therapy, as follows (Level of evidence A, Recommendation category II):

✓ In stages I and II of the disease:

When there is residual disease in axillary lymph nodes (ypN+) or if cN1 and ypN0, adjuvant breast radiotherapy is recommended with optional radiotherapy to the axilla, supraclavicular region, and the internal mammary artery region.




Conventional fractionation

- Daily dose of 1.8-2 Gy per fraction,
- 5 days a week
- Postoperative radiotherapy – TD 45-50.4 Gy in 23-28 fractions
- Radical radiotherapy – TD 70 Gy in 35 fractions



Hypofractionation

- More than 2.6 Gy per fraction
- 5 days a week
- Total tumor dose of 40-42.5 Gy in 15-16 fractions
- Ultra hypofractionated regimen 26 or 27 Gy in 5 fractions

- 
- Shortening of treatment from 6-7 to 3-4 weeks
 - Cheaper treatment

- Better availability
- Shorter waiting lists

- Equivalent efficiency compared to standard fractionation mode

Original Article

ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer



Orit Kaidar-Person^{a,*}, Birgitte Vrou Offersen^{b,1}, Sandra Hol^c, Meritxell Arenas^d, Cynthia Aristei^e, Celine Bourcier^f, Maria Joao Cardoso^g, Boon Chua^h, Charlotte E. Colesⁱ, Tine Engberg Damsgaard^j, Dorota Gabrys^k, Reshma Jaggi^l, Rachel Jimenez^m, Anna M. Kirbyⁿ, Carine Kirkove^o, Youlia Kirova^p, Vassilis Kouloulis^q, Tanja Marinko^r, Icro Meattini^s, Ingvil Mjaaland^t, Gustavo Nader Marta^{u,v}, Petra Witt Nystrom^w, Elzbieta Senkus^x, Tanja Skyttä^y, Tove F. Tvedskov^z, Karolien Verhoeven^{aa}, Philip Poortmans^{ab}

^a Oncology Institute, Radiation Oncology Unit, Rambam Medical Center, Haifa, Israel; ^b Department of Experimental Clinical Oncology, Danish Center for Particle Therapy, Department of Oncology, Aarhus University Hospital, Denmark; ^c Department of Radiation Oncology, Institute Verbeeten, Tilburg, the Netherlands; ^d Department of Radiation Oncology, Hospital Universitari Sant Joan de Reus, University Rovira i Virgili, Spain; ^e Radiation Oncology Section, Department of Surgical and Biomedical Science, University of Perugia and Perugia General Hospital, Italy; ^f Department of Radiation Oncology, ICM – Val d'Aurelle, INSERM U1194, ICRM; Montpellier University, Montpellier, France; ^g Breast Unit, Champalimaud Foundation, and Nova Medical School, Lisbon, Portugal; ^h Faculty of Medicine, The University of New South Wales, UNSW Sydney, NSW, Australia; ⁱ Cambridge University, Department of Oncology, United Kingdom; ^j Department of Plastic and Breast Surgery, Aarhus University Hospital, Denmark; ^k Department of Radiation Oncology, Maria Skłodowska Curie Memorial Cancer Centre, Gliwice, Poland; ^l Department of Radiation Oncology, University of Michigan, Ann Arbor, USA; ^m Department of Radiation Oncology, Massachusetts General Hospital, Boston, USA; ⁿ Department of Radiotherapy, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, UK; ^o Department of Radiation Oncology, University Hospital St-Luc, Brussels, Belgium; ^p Department of Radiation Oncology, Institut Curie, Paris, France; ^q National and Kapodistrian University of Athens, Medical School, 2nd Dpt of Radiology, Radiotherapy Unit, Athens, Greece; ^r Department of Radiation Oncology, Institute of Oncology Ljubljana, Slovenia; ^s Department of Biomedical, Experimental, and Clinical Sciences, University of Florence, Italy, Radiation Oncology Unit – Oncology Department, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; ^t Department of Oncology & Radiotherapy, Stavanger University Hospital, Norway; ^u Department of Radiation Oncology, Hospital Sirio-Libanês, São Paulo, Brazil; ^v Department of Radiology and Oncology, Division of Radiation Oncology, Instituto do Câncer do Estado de São Paulo (ICESP), Faculdade de Medicina da Universidade de São Paulo, Brazil; ^w The Skandion Clinic, Uppsala, Sweden and Danish Center for Particle Therapy, Aarhus, Denmark; ^x Department of Oncology & Radiotherapy, Medical University of Gdańsk, Poland; ^y Department of Oncology, Tampere University Hospital, Finland; ^z Dept. of Breast Surgery, Herlev Hospital, Copenhagen, Denmark; ^{aa} GROW School for Oncology and Developmental Biology, Department of Radiation Oncology, Maastricht University Medical Centre, Netherlands; ^{ab} Department of Radiation Oncology, Institut Curie, and Paris Sciences & Lettres University, Paris, France.

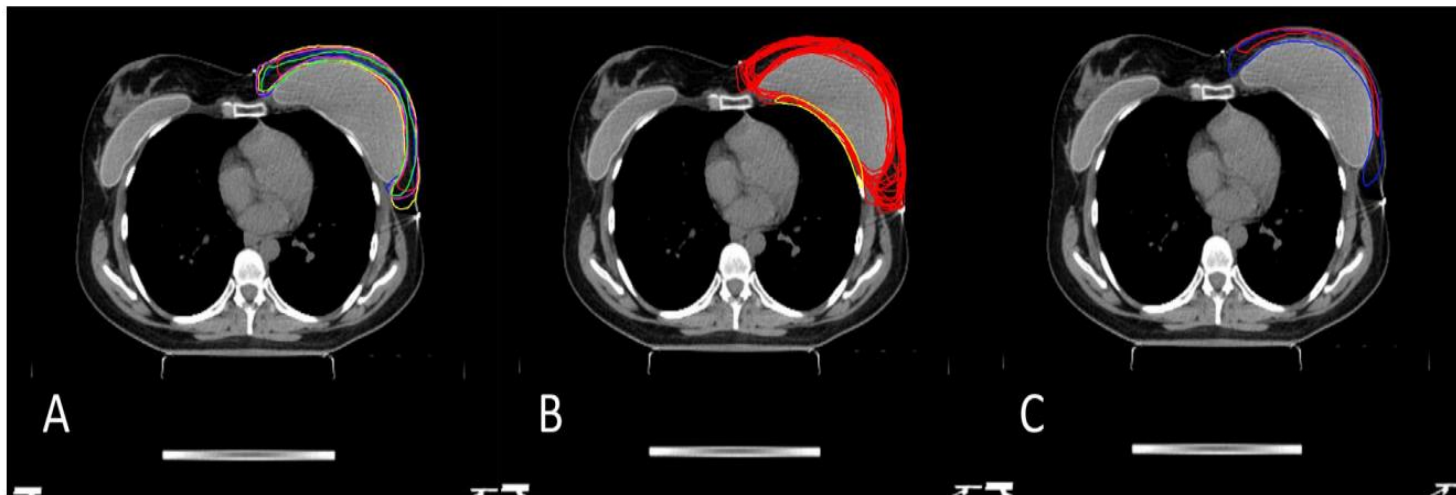


Fig. 1. CTV contouring of case with immediate breast reconstruction left using an implant. (A) by writers of guideline of DBCG RT Recon Trial ($n = 5$); (B) by other radiation oncologists ($n = 18$); (C) by breast cancer surgeons ($n = 2$).

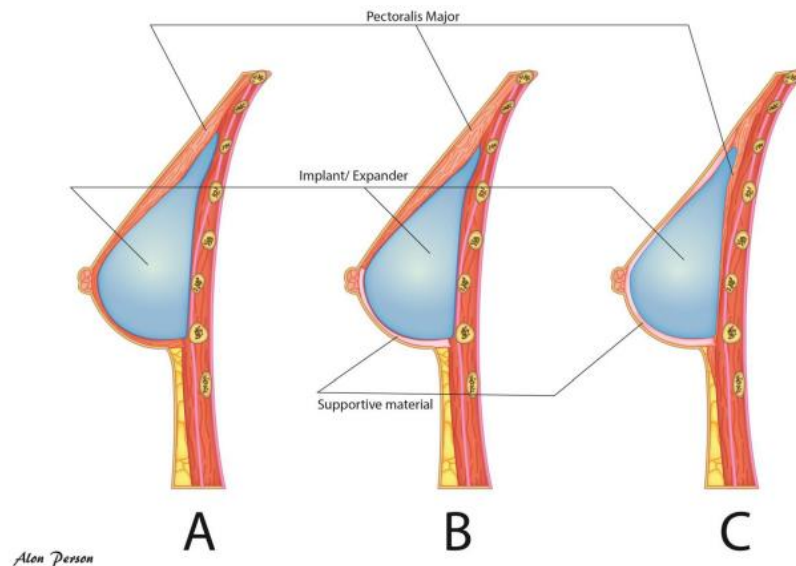


Fig. 3. Implant positioning. (A) retropectoral with full coverage by the pectoral muscle; (B) retro-pectoral with partial coverage by the pectoral muscle and supportive material in the lower part; (C) pre-pectoral with full coverage by supportive material.



Fig. 4a. CTvp_chestwall with only a ventral part (red) in cases for whom only the subcutaneous lymphatic plexus should be irradiated. Pectoral muscles (yellow) and implant (green).

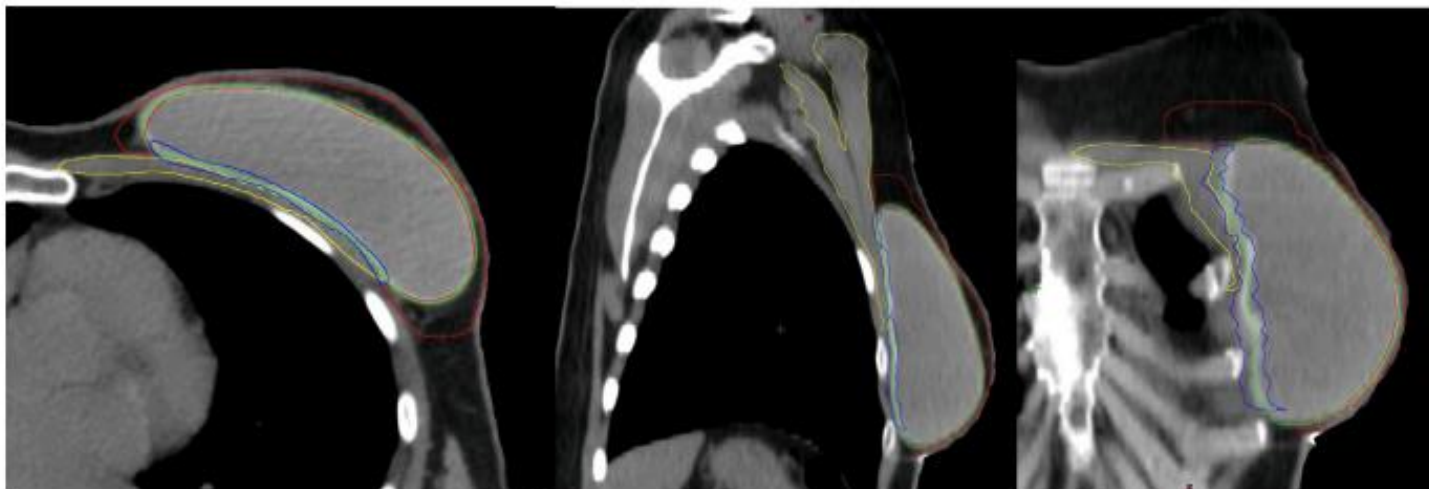
Indications for including a volume posterior to the implant in the CTVp_chestwall.

Partial inclusion in retro-pectoral implant positioning: in case of the presence of adverse factors and/or if the tumour was localised in areas within the breast close to the dorsal fascia that was not covered by the initial position of the major pectoral muscle: separate volume (blue volume in Fig. 4B)

Complete inclusion in pre-pectoral implant positioning: in case of the presence of adverse factors (blue in Fig. 4C)

Adverse prognostic tumour characteristics include:

- Large primary breast cancer (pT3) treated by mastectomy and IBR-i
- Locally advanced breast cancer (LABC) with non-pathological complete response to primary systemic therapy
- Invasion of the major pectoral muscle and/or the chest wall



PRINCIPLES OF RADIATION THERAPY

Accelerated Partial Breast Irradiation (APBI)/Partial Breast Irradiation (PBI)

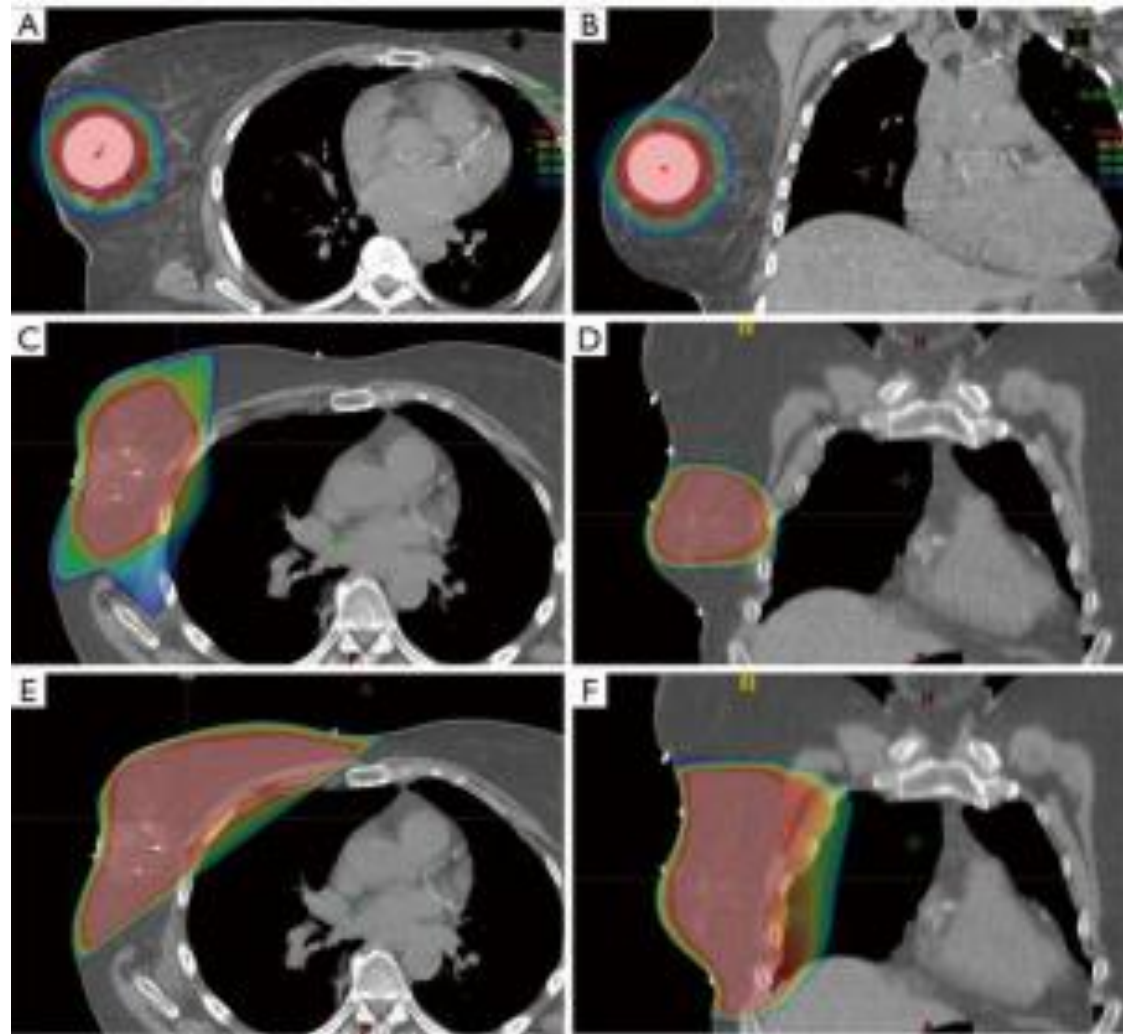
- APBI/PBI offers comparable local control to WBRT in selected patients with low-risk early-stage breast cancer. However, the optimal external beam-APBI/PBI technique/fractionation for minimizing long-term cosmesis effects has not been determined.
 - Patients are encouraged to participate in clinical trials.
 - The NCCN Panel recommends APBI/PBI for any patient with no *BRCA* 1/2 mutations meeting the criteria outlined in the 2016 ASTRO consensus statement for guidance on APBI/PBI use.

According to the 2016 ASTRO criteria, patients aged ≥50 years are "suitable" for APBI/PBI if they have:

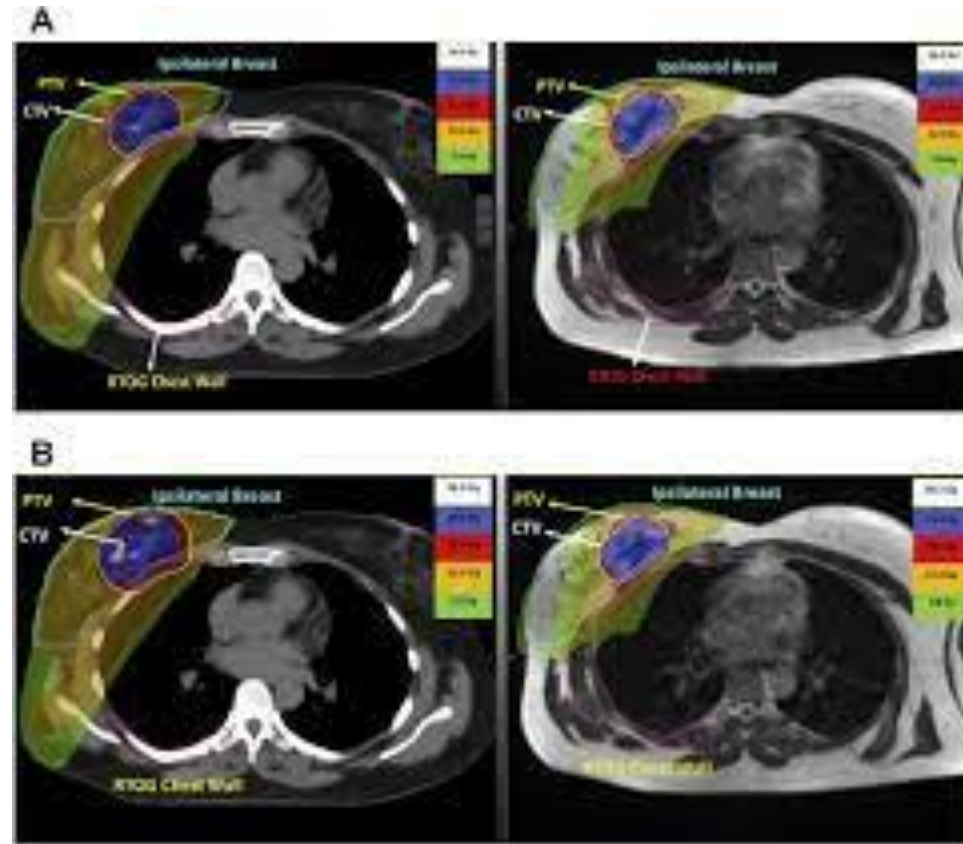
 - ◊ Invasive ductal carcinoma measuring ≤2 cm (pT1 disease) with negative margin widths of ≥2 mm, no LVI, and ER-positive tumors or
 - ◊ Low/intermediate nuclear grade, screening-detected DCIS measuring size ≤2.5 cm with negative margin widths of ≥3 mm.

• RT dosing:

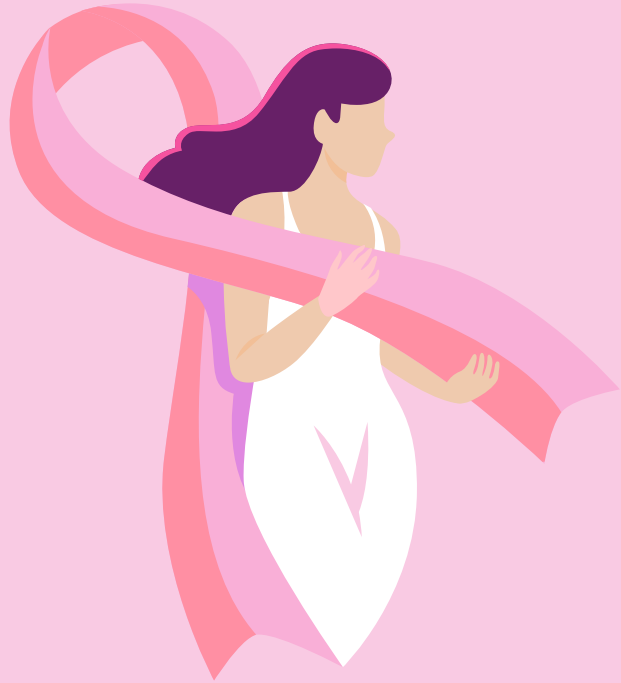
Regimen	Method	Reference
30 Gy/5 fractions QOD (preferred)	External beam RT (EBRT)^e	Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. <i>Eur J Cancer</i> 2015;51:451-463. Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-Florence Trial. <i>J Clin Oncol</i> 2020;38:4175-4183.
40 Gy/15 fractions	EBRT	Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. <i>Lancet</i> 2017;390:1048-1060.
34 Gy/10 fractions BID	Balloon/Interstitial	Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. <i>Lancet</i> 2019;394:2155-2164.
38.5 Gy/10 fractions BID	EBRT	Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. <i>Lancet</i> 2019;394:2165-2172.



Accelerated partial breast irradiation can be implemented using the previously described external beam radiotherapy techniques, typically employing 4-5 non-coplanar fields. The tumor bed is defined based on postoperative changes, seromas, or surgical clips if placed. The clinical target volume encompasses the tumor bed with a 15 mm margin, with an additional 10 mm margin to account for potential interfractional shifts.

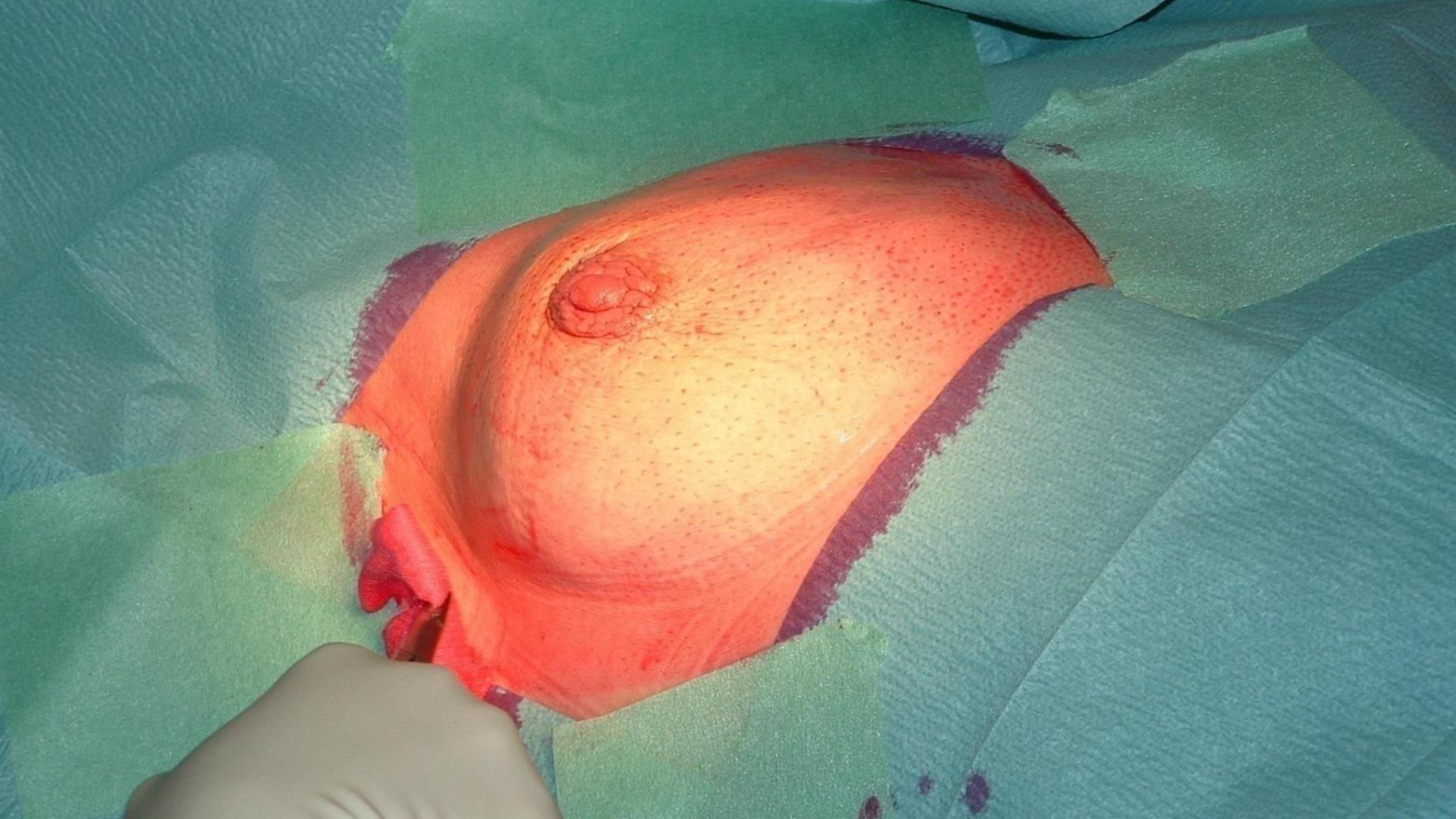


No	OARs	Parameters	Endpoints
1	Lung	V20≤30% Dmean ≤ 20 Gy	Symptomatic pneumonitis
2	Heart	Dmean < 26 Gy V25 < 10%	Pericarditis Long term cardiac mortality
3	Spinal Cord	Dmax = 50 Gy	Myelopathy
4	Esophagus	Dmean < 34 Gy	Grade ≥ 3 acute esophagitis

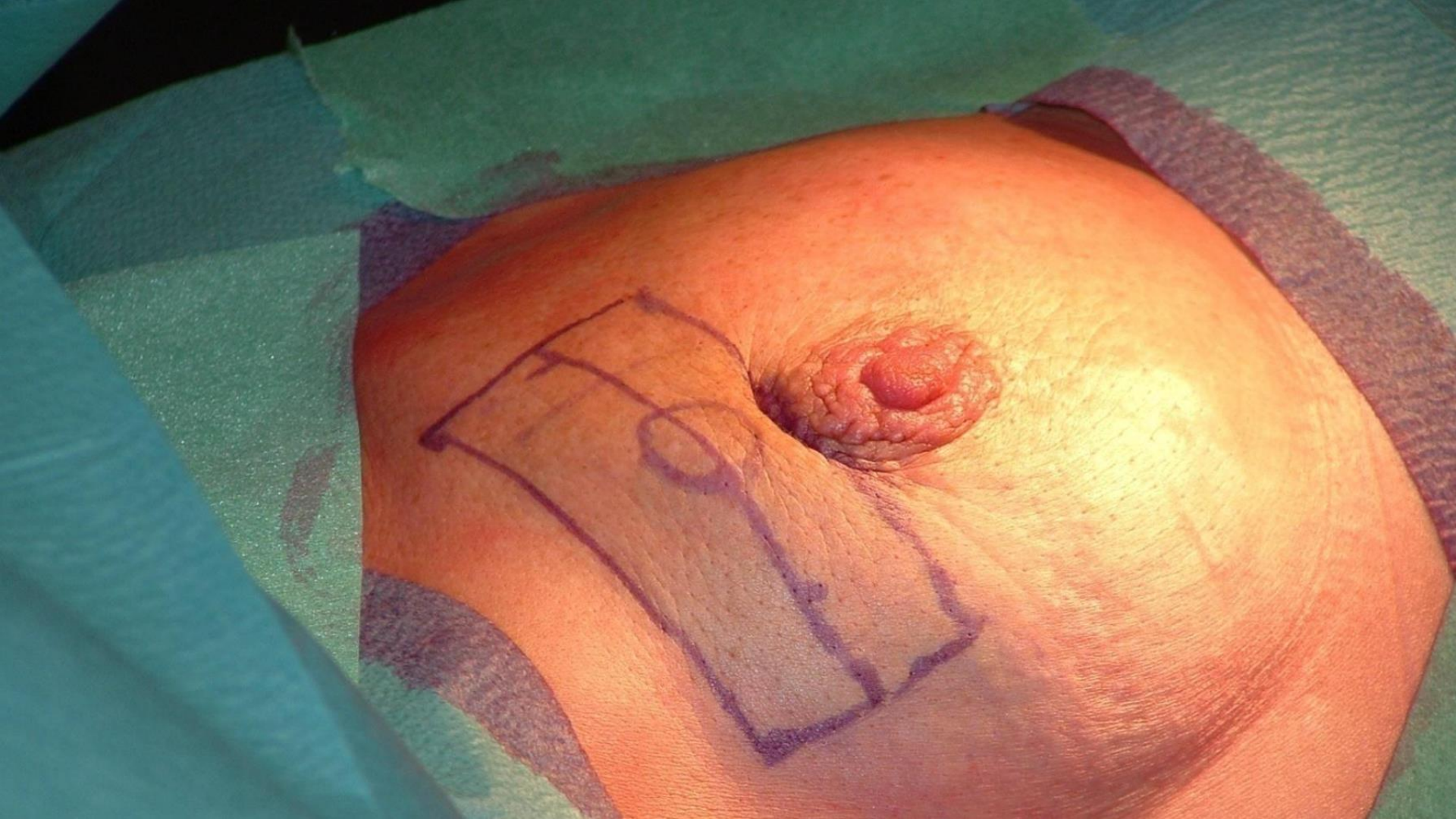


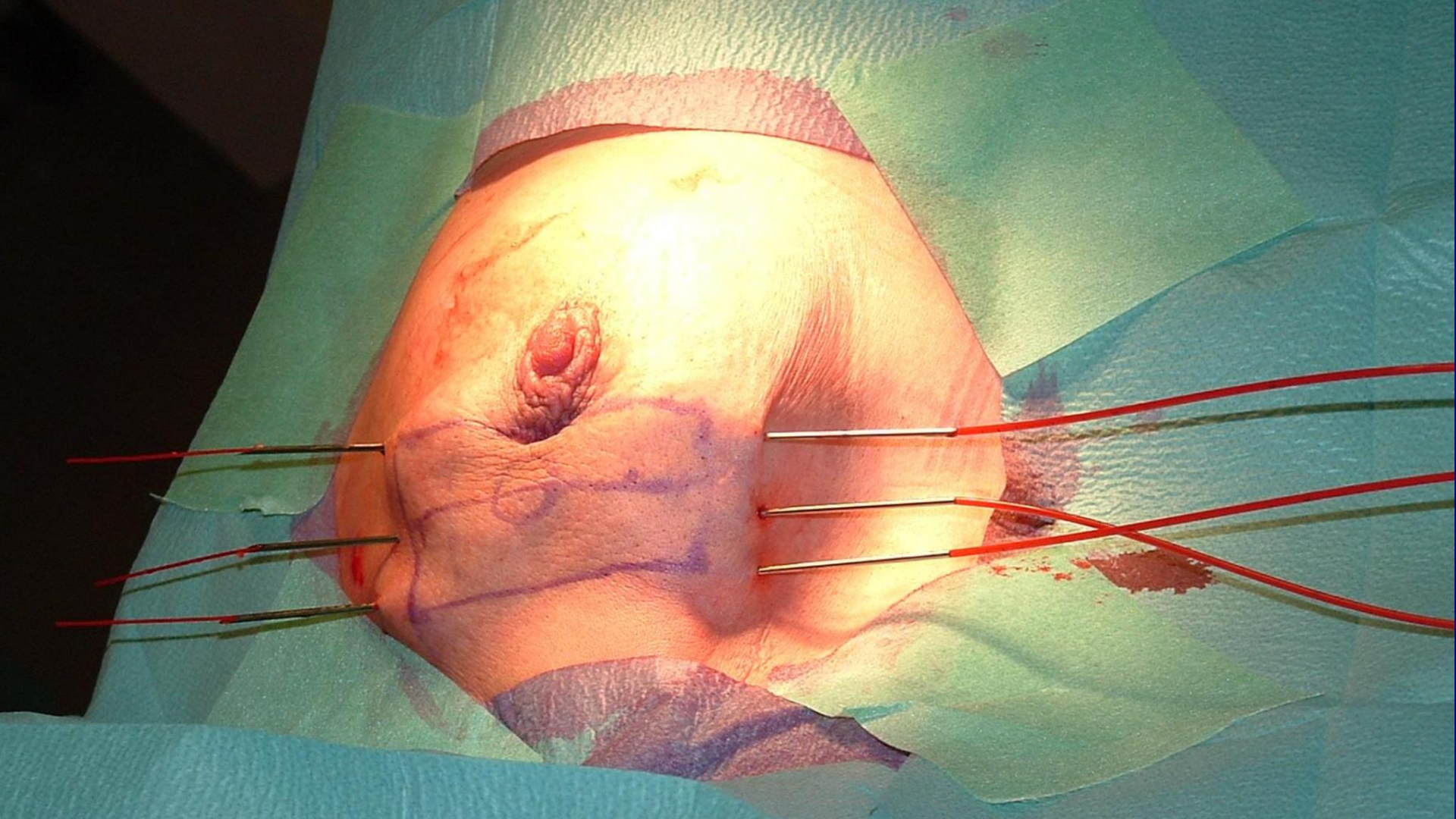
Brachytherapy

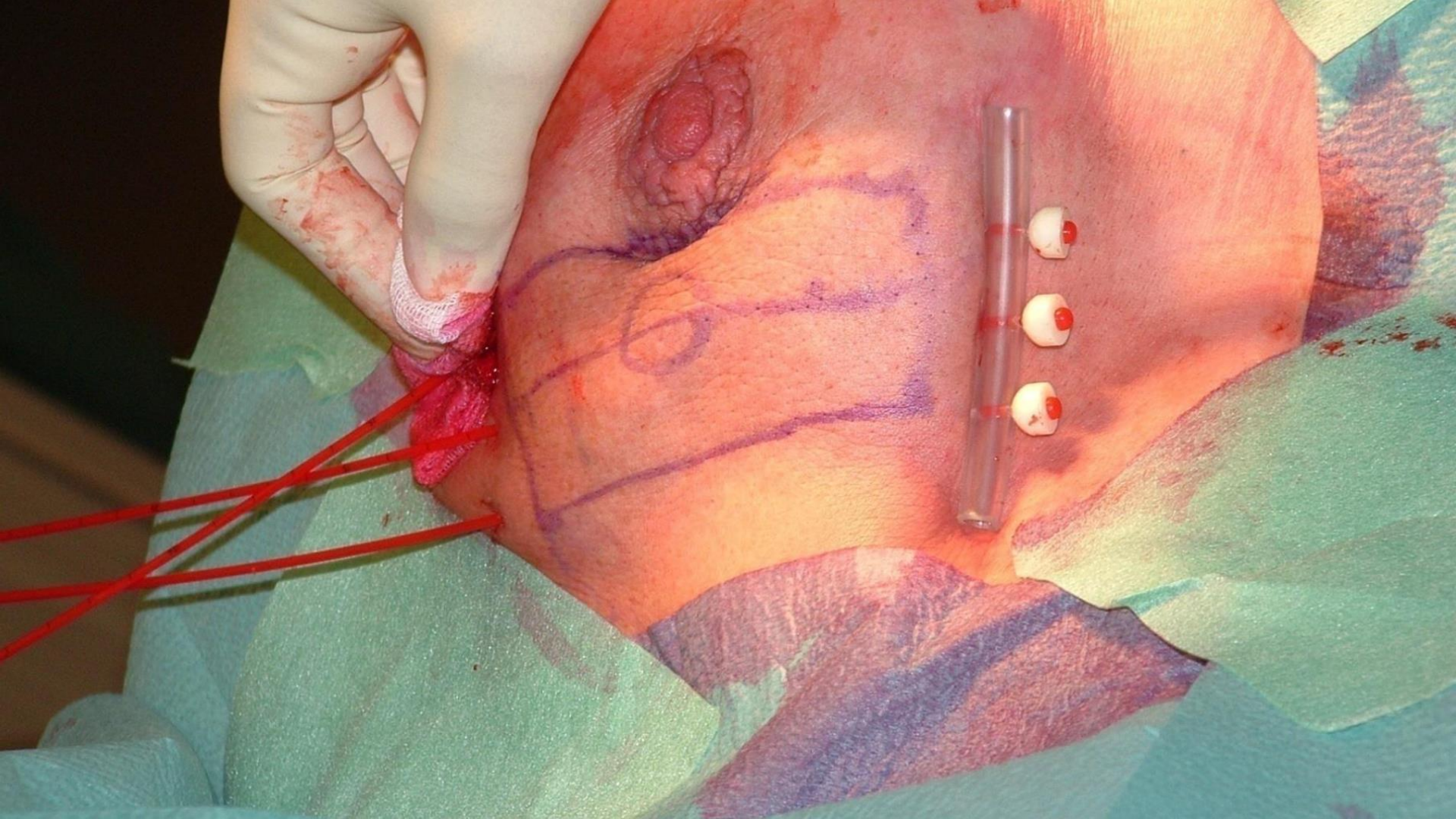


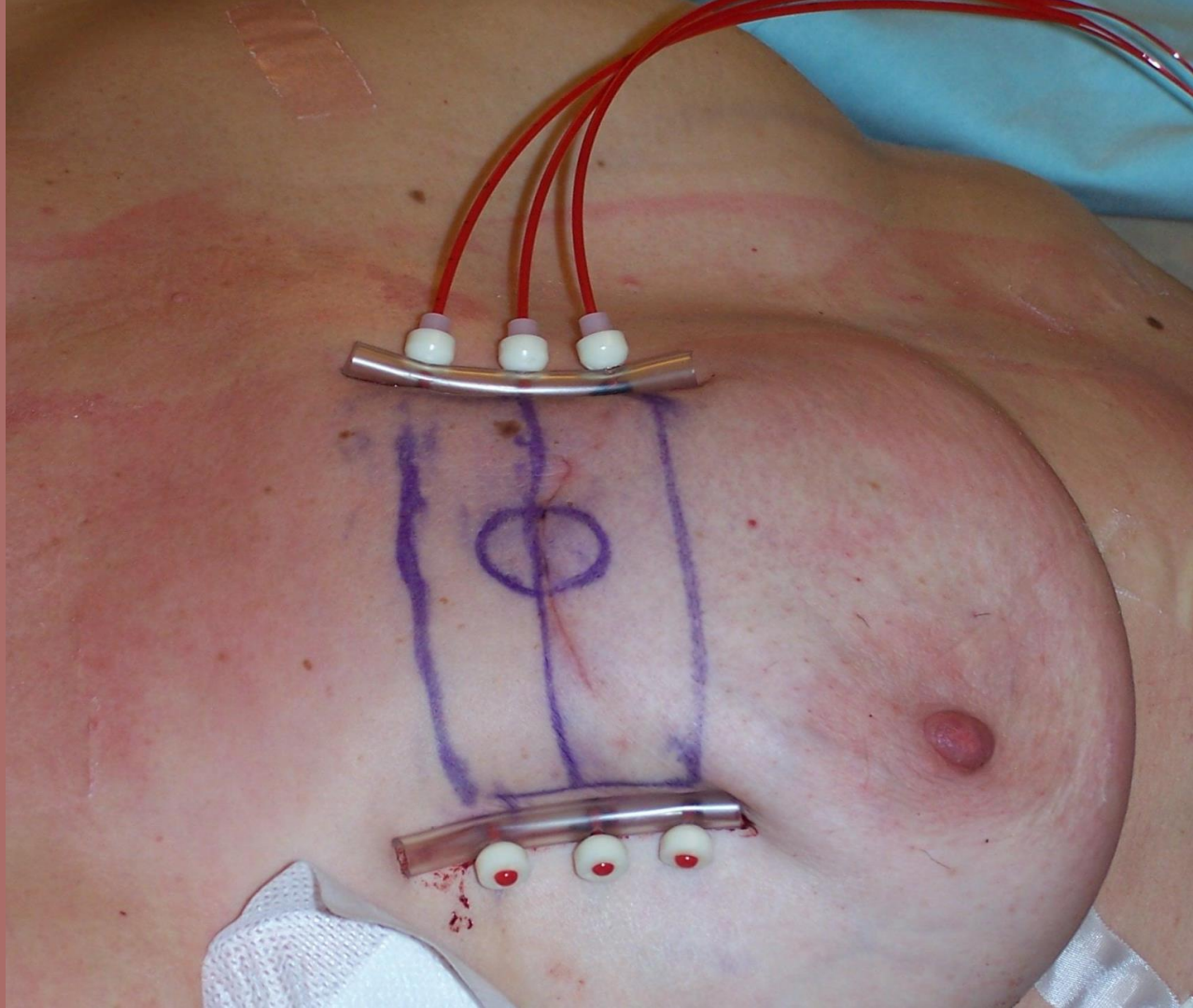


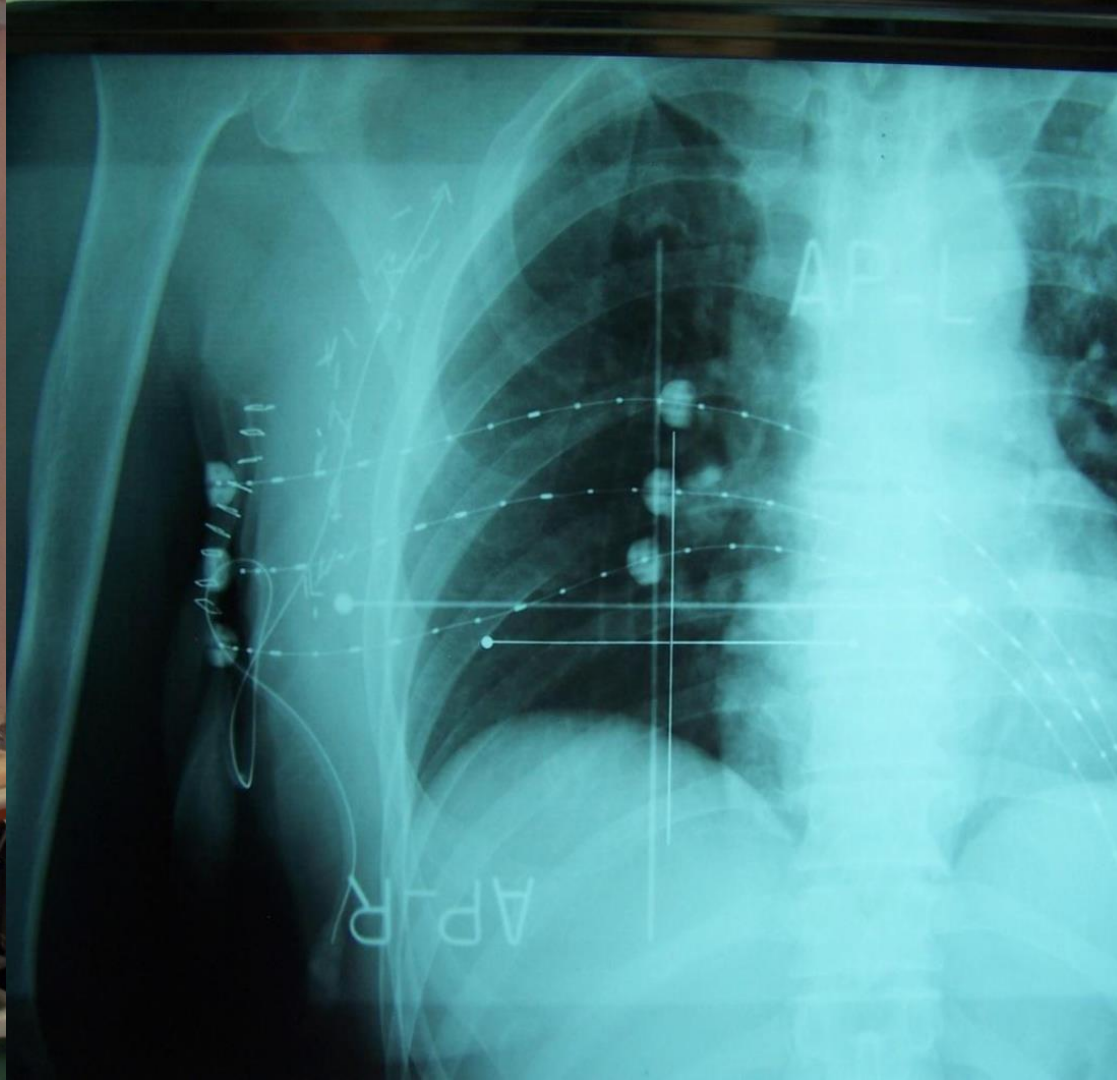


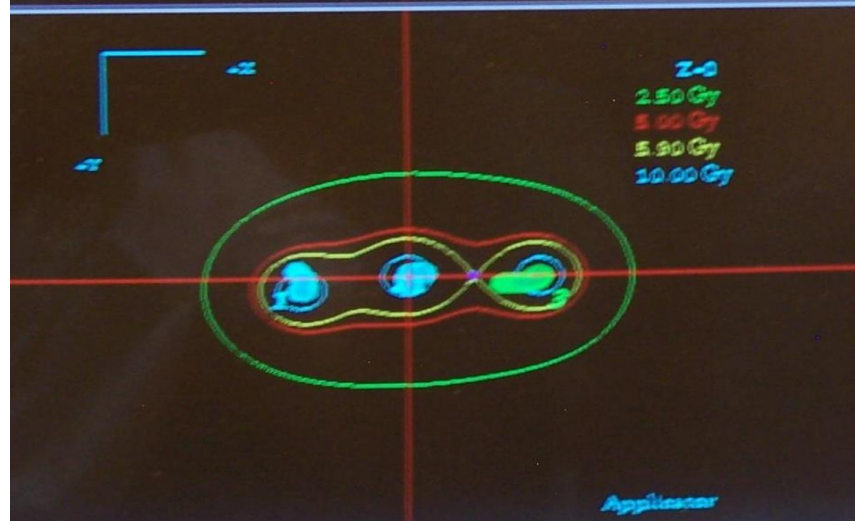
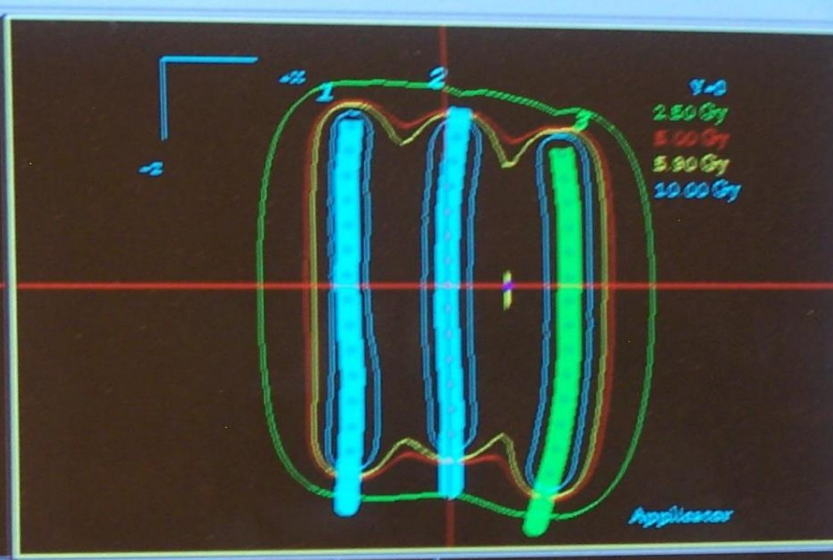
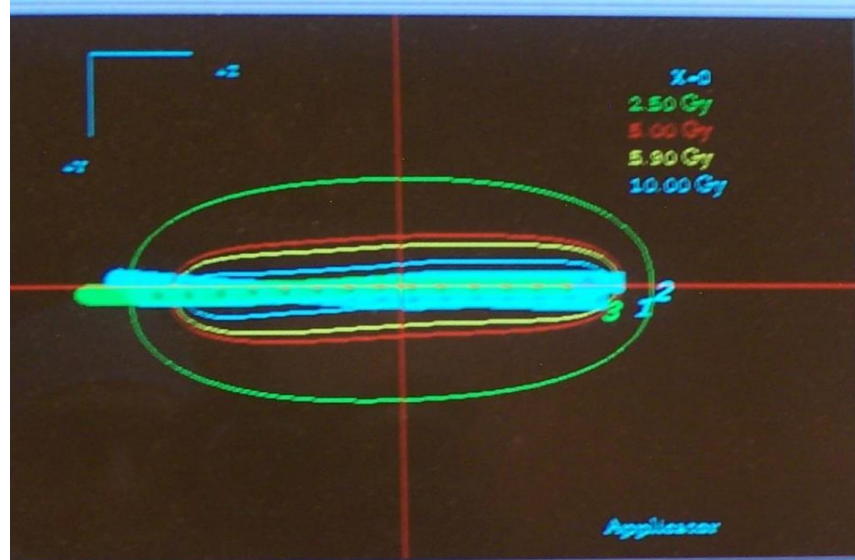










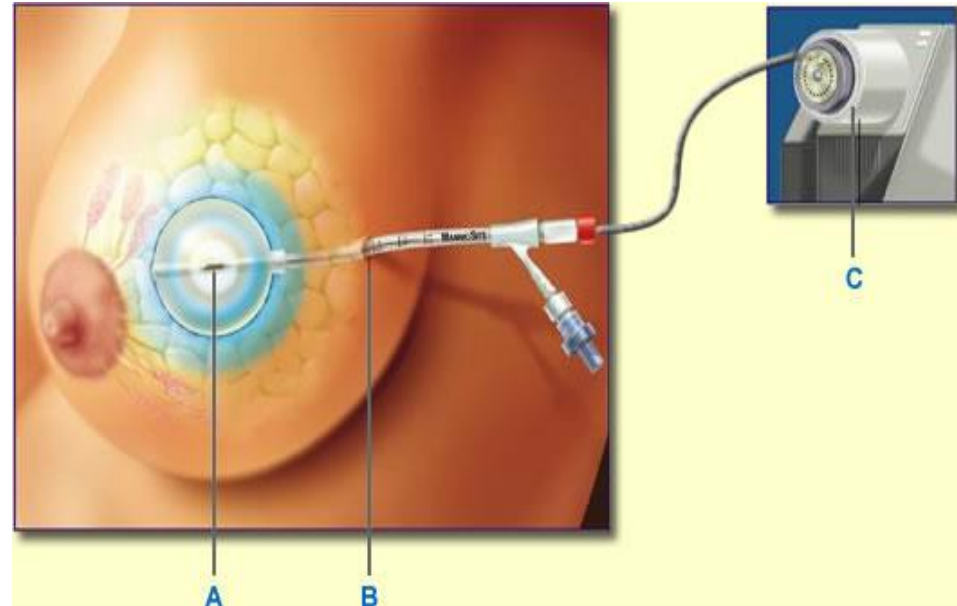


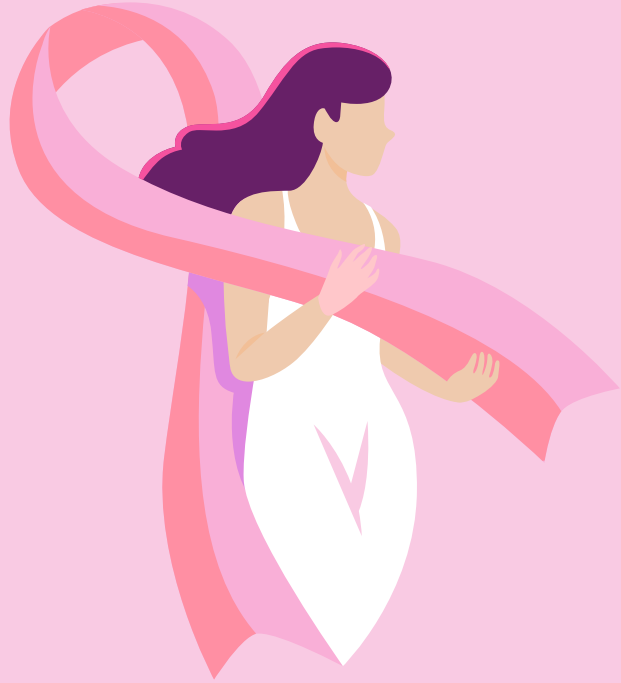


Interstitial brachytherapy of breast - MAMOSITE

The balloon applicator is intraoperatively placed in the resection cavity immediately after lumpectomy.

Radiation: The radiation source is HDR Ir-192U, which is brought to the center of the balloon.





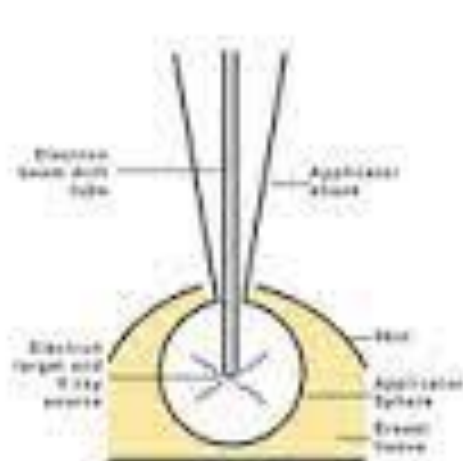
Intraoperative radiotherapy - IORT

IORT

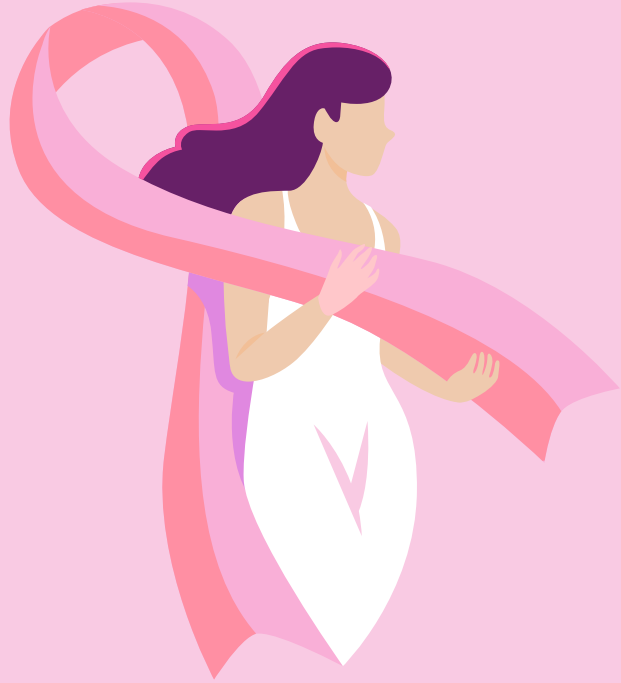
- Intraoperative Radiotherapy (IORT) involves delivering a radiation dose in a single fraction directly to the tumor bed during the surgical procedure, before tumor cells have the opportunity to proliferate postoperatively. The tissue is vascularized, increasing the efficiency of radiotherapy. Additionally, radiation therapy is administered with direct visualization of the tumor bed during the surgical intervention.
- IORT reduces unwanted radiation complications on the skin, heart, and lungs, eliminating the possibility that the patient may not complete the recommended radiation treatment for various reasons.
- The drawback of IORT is that the definitive pathological findings are available after the procedure, making it challenging to accurately define resection margins—a limitation that has been actively addressed in recent years through technological advancements.

- The system generates low-energy photons (30-50 kVp) with a rapid dose fall-off in tissue, and as such, it does not require special protection in the room (operating room) where the procedure is performed. The entire treatment lasts between 20 and 45 minutes, depending on the size of the surgical cavity, the diameter of the applicator, and the prescribed dose.
- The Phase III TARGIT study (which included approximately 2000 patients from 28 centers) demonstrated no statistically significant differences in the rate of local relapse and radiation toxicity. It represents Level I evidence for the application of IORT.
- IORT can be conducted using electrons, and various commercially available systems exist, but they require specific conditions for IORT application.





- Precise localization of the tumor bed and targeted delivery of a high radiation dose (20-25 Gy in one fraction)
- Minimal exposure to surrounding healthy structures
- Possibility of dose escalation (significantly higher than achievable with external beam radiotherapy)
- Potential for re-irradiation, especially in recurrent cancers
IORT can be used independently or in combination with external beam RT.
- In addition to early breast cancers, IORT can be performed in most intra-abdominal tumors, recurrent colorectal cancers, gynecological cancers, soft tissue tumors, as well as malignant tumors of the head and neck and pediatric tumors.



Palliative radiotherapy

Palliative radiotherapy

- Palliative radiotherapy for the primary tumor and re-irradiation of local/regional recurrence
- Palliative radiotherapy of bone metastasis
- Palliative radiotherapy of brain metastasis

Palliative radiotherapy for the primary tumor and re-irradiation of local/regional recurrence

- Palliative radiotherapy for the primary breast tumor represents an effective method in the treatment of pain, ulceration, and bleeding.
- Recommended fractionation regimens are: 20 Gy/5 fractions, 30 Gy/10 fractions, 40 Gy/20 fractions, 39 Gy/13 fractions.
- Prior adjuvant radiotherapy to the same breast does not significantly increase radiation toxicity and should not be a contraindication for conducting palliative radiotherapy.
- In the case of locoregional recurrence, appropriate surgical resection is indicated whenever possible.
- The use of radiotherapeutic retreatment is possible, although data on acute and chronic adverse effects vary among published studies.

- The NRG Oncology/RTOG 1014 Phase II clinical trial has shown that, in the case of local recurrence, breast-conserving surgery followed by partial breast re-irradiation can be an effective alternative to mastectomy in patients with cancer in the ipsilateral breast and clinically negative lymph nodes (N0) after initial breast-conserving surgery followed by postoperative radiotherapy.
- The definitive decision on the application of radiotherapeutic retreatment, as well as the fractionation regimen, must take into account the previously administered dose and late toxicity of healthy tissue (considering both the previous and planned doses).

Palliative radiotherapy of bone metastasis

- Radiotherapy provides effective palliation for painful bone metastases with a low rate of adverse effects. Pain reduction with palliative radiotherapy occurs in 50-80% of patients.
- Numerous prospective randomized studies have shown that, in the treatment of painful bone metastases, a similar effect is achieved with a single fraction compared to a prolonged course of radiotherapy for previously untreated bone metastases.
- When palliative radiotherapy is applied as retreatment, preference should be given to Stereotactic Body Radiotherapy (SBRT), especially for metastatic lesions in the spine.
- The total dose and fractionation regimen depend on the patient's overall condition, the extent of disease dissemination, and the clinical benefit of the applied treatment modality.
- Recommended fractionation regimens are: Total Dose (TD) 30 Gy in 10 fractions TD 20 Gy in 8 fractions TD 16 Gy in 4 fractions TD 8 Gy in 1

Palliative radiotherapy of brain metastasis

- The use of radiotherapy following neurosurgical treatment improves overall survival (OS) and symptom control compared to radiotherapy alone.
- NCCTG N107C/CEC-3 and JCOG0504 – randomized Phase III clinical studies have shown that postoperative whole brain radiotherapy (WBRT) compared to stereotactic radiosurgery (SRS) results in equivalent or better local disease control in the SRS group, with a lower risk of cognitive impairment but no difference in OS.
- When neurosurgical resection is not possible, it is recommended to consider the possibility of conducting SRS depending on patient characteristics, tumor features, and clinical benefit.
- The total volume of lesions is a consideration, rather than the total number of lesions, and this volume is 30 cm² – in such cases, stereotactic radiotherapy/radiosurgery is the treatment of choice.
- The use of WBRT is indicated for patients with a larger number/volume of lesions in the CNS when stereotactic radiotherapy/radiosurgery is not recommended.
- The most commonly applied fractionation regimens are: Total Dose (TD) 30 Gy in 10 fractions, TD 20 Gy in 5 fractions.
- The ACSO-SNO-ASTRO guideline recommends sparing the hippocampus, implying a lower risk of cognitive function impairment in selected patients.

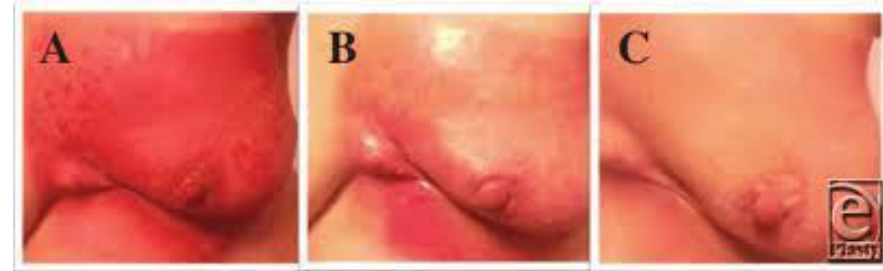
Indication for SBRT and SRS

- Metastases in the CNS
- Retreatment of previously irradiated metastases in the spinal cord and CNS
- Solitary metastases in the spinal cord - several studies have examined the use of hypofractionated radiotherapy and radiotherapy doses delivered in a single fraction in the treatment of uncomplicated bone metastases. Yamada and colleagues demonstrated that, with the use of radiotherapy for spinal metastatic lesions in non-operatively treated patients, the three-year local disease control is 98%.
- Metastases in the lungs - in metastatic breast cancer, isolated lung or pleural metastases can be found in 15-24% of patients. Time to disease progression, the number of metastases, and the possibility of resection are positive prognostic factors. In a multi-institutional Phase I/II study, the one-year local disease control with SBRT was 100%, and the two-

- Liver metastases - approximately half of patients with breast cancer show disease progression in the liver, and in about 35% of cases, it occurs as the first metastatic lesion. Local ablative therapy for liver metastases is not the first choice in treatment due to the presence of disease in other organs. Data on the use of SBRT in the treatment of breast cancer liver metastases are limited. In multi-institutional studies investigating the use of SBRT in the treatment of liver metastases, where breast cancer is one of the entities studied, one-year local disease control was shown to be 87%, with a one-year overall survival of 84% and an acceptable level of toxicity.
- The use of SBRT is recommended in cases where patients are not candidates for surgical treatment due to comorbidities or when metastases are unresectable due to their location. In cases of indolent disease and a favorable biological tumor profile, SBRT is recommended for treating 1-5 lesions with a diameter of ≤ 5 cm.
- Recommended doses and fractionation regimens are as follows (Level of Evidence B, Recommendation Category II): 48-60 Gy in 3-4 fractions, 25-70 Gy in 3-6 fractions, 30-45 Gy in 3 fractions, 14-30 Gy in a single

Adverse effects of radiotherapy

- Complications of RT can occur during the actual application of RT or some time after the completion of RT.
- During the administration of RT, the most common occurrence is **radiation dermatitis** of the irradiated skin region, presenting as erythema, hyperpigmentation with dry desquamation, and less frequently, moist desquamation. All these changes are mild and transient. Complications that arise later, some time after the completion of RT treatment, may affect the skin and soft tissues of the irradiated region (fibrosis, hyperpigmentation, and telangiectasias) or lead to the development of arm lymphedema, radiation pneumonitis, cardiac toxicity, and damage to the brachial plexus.
- **Arm lymphedema** is usually associated with the extent of axillary surgery, and the use of RT further increases the risk. Axillary dissection and RT of the axillary region can each individually carry a risk of lymphedema of less than 10%. However, this risk increases to 40% when a complete axillary dissection of all three levels of the axilla is combined with RT of the entire axillary region.



Adverse effects of radiotherapy

- **Pneumonitis and pulmonary fibrosis** are associated with an increase in lung volume within the radiation field, as well as the use of hormone therapy (HT). Analyses have shown that when RT is applied with only tangential fields to the breast region, pneumonitis occurs in 0.2% of cases, while this percentage increases to 1.4% if regional lymphatic radiation is included. The addition of adjuvant HT further increases the incidence of pneumonitis to 3.3%, and if adjuvant HT is given concurrently with RT, pneumonitis occurs in 8.8% of cases.
- **Cardiac toxicity** can manifest as pericarditis, pancarditis, cardiomyopathy, and coronary artery disease with ischemic heart disease. Previous studies have shown increased cardiovascular-related mortality in patients who underwent postoperative RT. However, new RT techniques and CT-based planning have enabled individualized RT planning for each patient, minimizing radiation to critical organs such as the heart and lungs.
- **Damage to the brachial plexus** can occur during radiation of the supraclavicular and axillary regions. Brachial plexopathy is a rare complication if a standard total tumor dose is given with conventional fractionation regimens. This type of damage was more associated with older radiation techniques, where the dose to the brachial plexus exceeded 130% of the prescribed dose.

Absolute contraindications	Relative contraindications
ATM zygots	Previous RT of chest wall/breast
Pregnancy?	Connective tissue disease affecting the skin (SLE, Scleroderma)
	Genetic predisposition to the development of breast cancer.
	Li Fraumeni sy
	Pregnancy?