OSPEDALE SAN RAFFAELE

ORDINE INTERPROVINCIALE DEI CHIMICI E DEI FISICI DELLA LOMBARDIA

LA FISICA SANITARIA AL SERVIZIO DELLE DONNE

Nuove frontiere per il trattamento radioterapico della mammella

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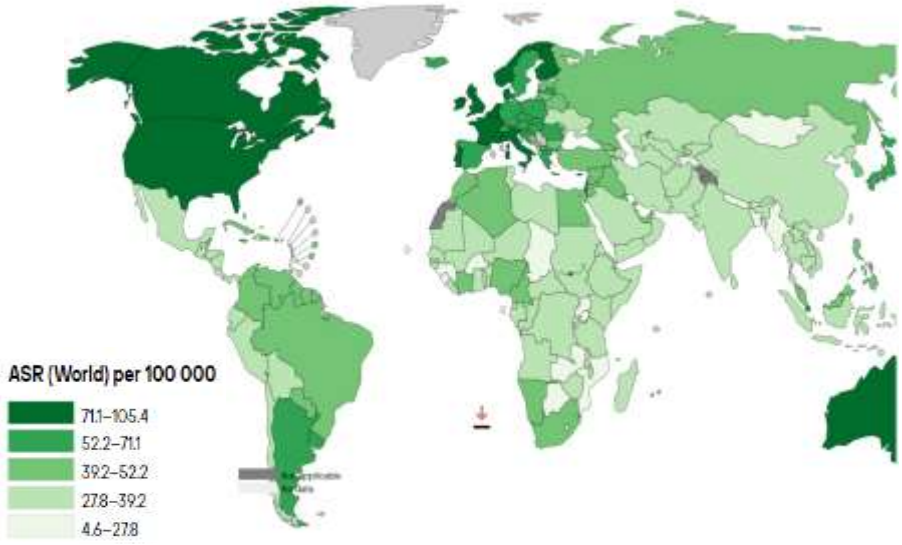
Breast Cancer (BC)

According to World Health Organization

- 670 000 deaths globally in 2022.
- Breast cancer was the most common cancer in women in 157 countries out of 185 in 2022.
- BC occurs in every country in the world.
- Approximately 0.5–1% of breast cancers occur in men.

In 2023, the Italian Association of Medical Oncology estimated **55.900 new diagnosis** of BC in Italy



Age-Standardized Rate Incidence, both sexes, in 2022

BC treatment → Surgery / Chemotherapy / Radiotherapy / Immunotherapy → **Personalized treatment**

Breast Cancer (BC)

Dose Scheduling

Contouring (CTV/OAR)

- CTV/OAR AI-based autocontouring
- AI- Deep learning model for CTV autocontouring
- Probabilistic CTV map

Optimization Planning

- ViTAT technique assessment
- KB- model (for Vitat technique)
- Intervaribility and trasferibility of KB models

RT Delivery

Followup

Toxicity prediction

- Cardiotoxicity
- Acute and long term moderate skin effects
- Pulmonary effect

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Dose Scheduling

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50 Gy/25 fr
(5 weeks)

Historical standard

2002–2013	42.5 Gy in 16 fractions	Canadian Trial (Whelan et al.)	First demonstration of equivalence between moderate hypofractionation and conventional fractionation
2008	41.6 Gy in 13 fractions and 40 Gy in 15 fractions	START-A and START-B	Equivalent tumor control with reduced toxicity compared with 50 Gy in 25 fractions

~ 2013 — **40 Gy /15 fr (3 weeks) (with/ out SIB 48 Gy)**

10-year START follow-up. Established moderate hypofractionation as the new standard of care

~ 2020 — **APBI 30 Gy /5 fr (1 weeks) [~ 195 pts]**

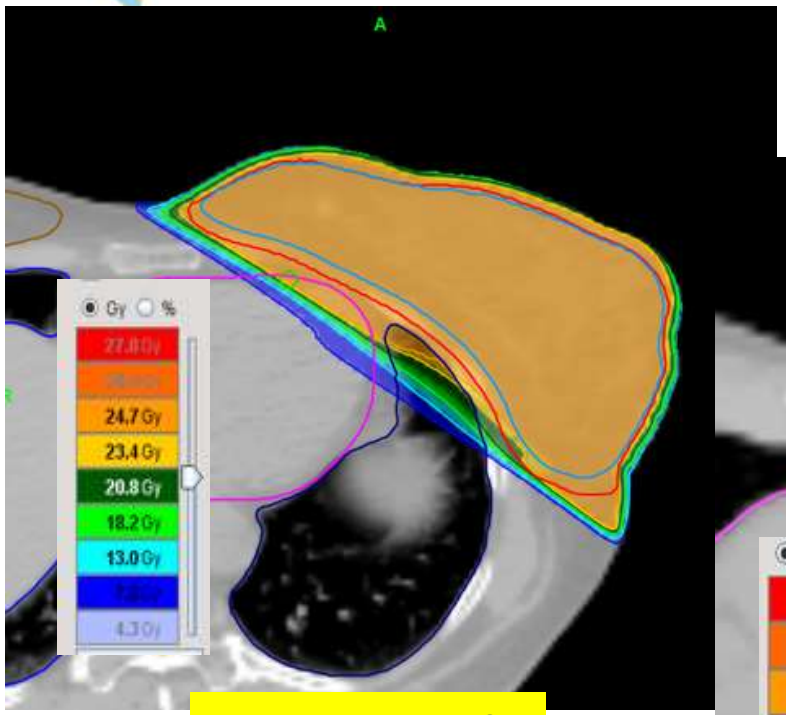
APBI Florence Trial


Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial
THE LANCET ONCOLOGY

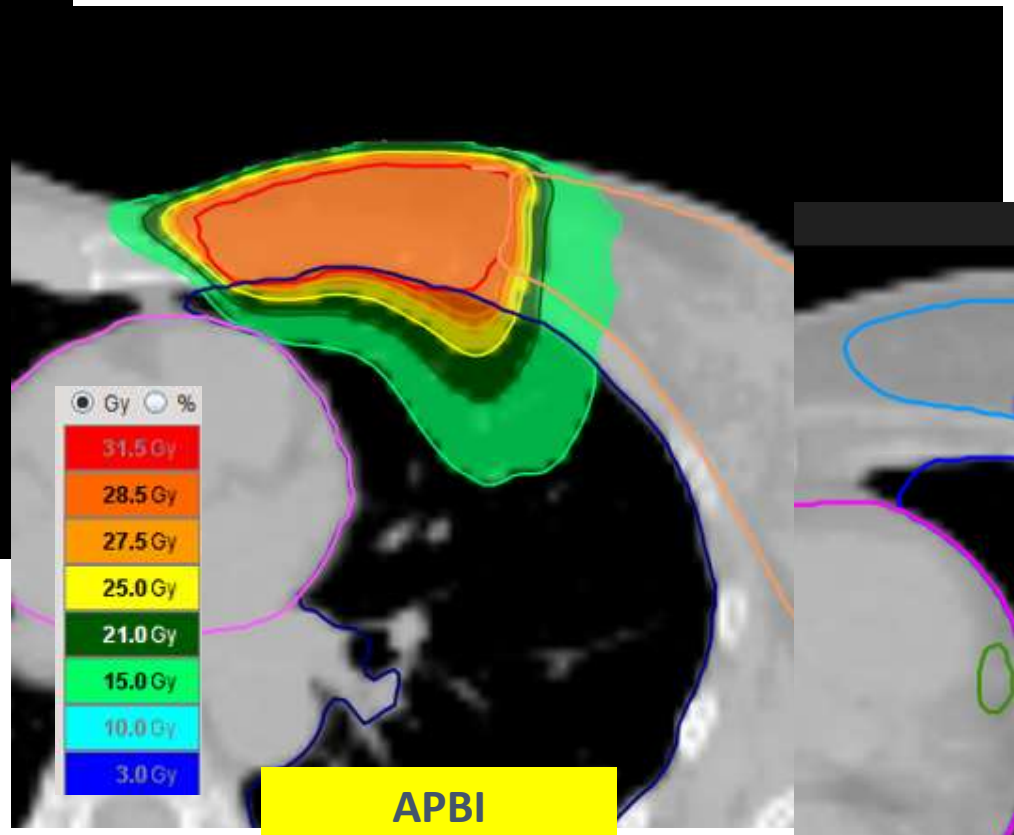
~ 2020 — **26 Gy /5 fr (1 weeks) (with SIB) [~ 149 pts]**

FAST-Forward Trial non-inferior to 40 Gy in 15 fractions; adopted as a standard option in many centers worldwide

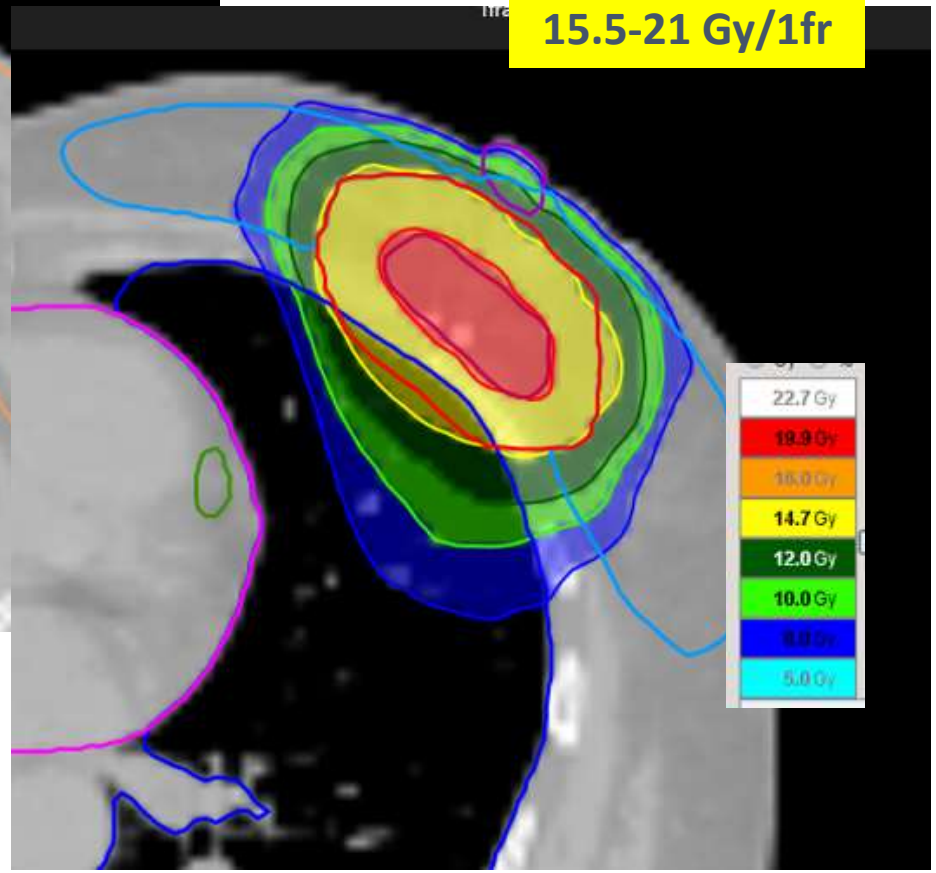
~ 2025 — **APBI: 15,5 Gy-21 Gy/ 1 fr [~ 13 pts]**



Fast Forward
26 Gy/5fr



APBI
30 Gy/5fr



APBI
15.5-21 Gy/1fr

2025 Notification submitted to the Ethics Committee ➡ Approved

2 bracci
- 15,5 Gy (21 Gy)/1
- 30 Gy/5

Inclusion Criteria

1) Patients aged ≥40 years (Fertile women using contraception methods initiated during oncological treatment)
2) Stage pTis-T2, up to 3 cm in the greatest diameter
3) Luminal A and Luminal B HER2-negative histological subtypes
4) Negative surgical margins (≥ 0.2 cm)
5) Negative lymph nodes
6) Clinical M0
7) PS (ECOG) ≤2 10)
8) No prior thoracic radiotherapy

2025 Notification submitted to the Ethics Committee → Approved

Primary Objective: demonstrate the **non-inferiority** of local control (ipsilateral breast tumor recurrence - IBTR) compared to the department's standard APBI treatment (30 Gy in 5 fractions).

Time point 5 years

Efficacy:

- ……
-Distant Metastases-Free Survival (DMFS)
-Disease-Free Survival (local, regional, distant, DFS)
-Breast Cancer Specific Survival (BCSS)
-Overall Survival (OS)
-Cosmesis

Time point 5 years

Secondary Objectives: incidence of acute and late side effects:

- Acute toxicity: grade ≥3 (1 – 3 month)

Time point 1 and 3 m

- Late toxicity: RTOG/EORTC (for skin) and CTCAE v 5.0 (for other toxicities).

Time point 5 y

> 1000


Radiotherapy and Oncology

Original Article

Skin dose-volume predictors of moderate-severe late side effects after whole breast radiotherapy

> 100


CLINICAL INVESTIGATION

Pulmonary Function and Lung Fibrosis up to 12 Years After Breast Cancer Radiotherapy

> 800


Radiotherapy and Oncology

Original Article

Density and volume of cardiac calcifications detected on planning CT predicts cardiotoxicity after hypo-fractionated whole breast Radiotherapy

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Toxicity Predictivity

BC Toxicity : Skin Toxicity

Severe late toxicities affect **about or less** than **5%** of patients. Acute reactions can predispose to long-term tissue changes such as fibrosis.

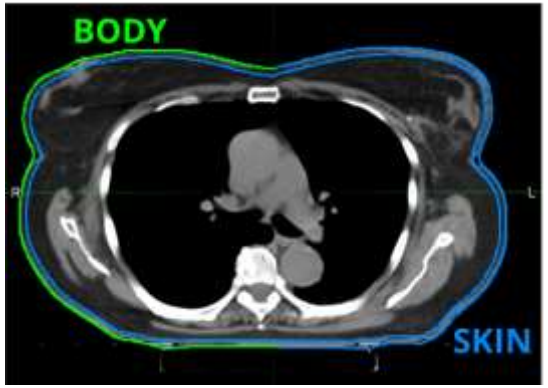
They can significantly impact quality of life, especially when patients develop fibrosis or persistent pain.

- Skin & breast (S/B) toxicities are variegated and may have different patterns…interplay with surgery

- **Acute:** desquamation, erythema, oedema,….
- **Late:** Fibrosis, telengectasia, atrophia, pain, breast induration, fat necrosis,….**highly impacting QoL**

- Reported risk factors: breast dimension, selected drucgs, psoriasis, diabetes, hypertension, smoking
- Dosimetry factors: total dose, dose fractionation, treated volume (WB vs WB+boost, PBI vs WB)

- **Association between acute and late tox !**



Skin, defined as the first 5 mm body layers:
tissue alteration measured in the epidermis, dermis, and hypodermis.

BC Toxicity: Moderate –Severe Late Skin Effects

Data Set
(retrospective monocentric)

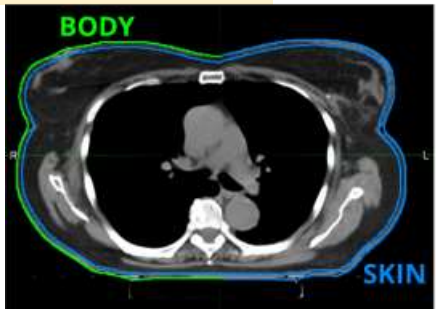
N=1066 (2009-2017)
3DCRT (TF), 40Gy/15fr
whole breast, no boost

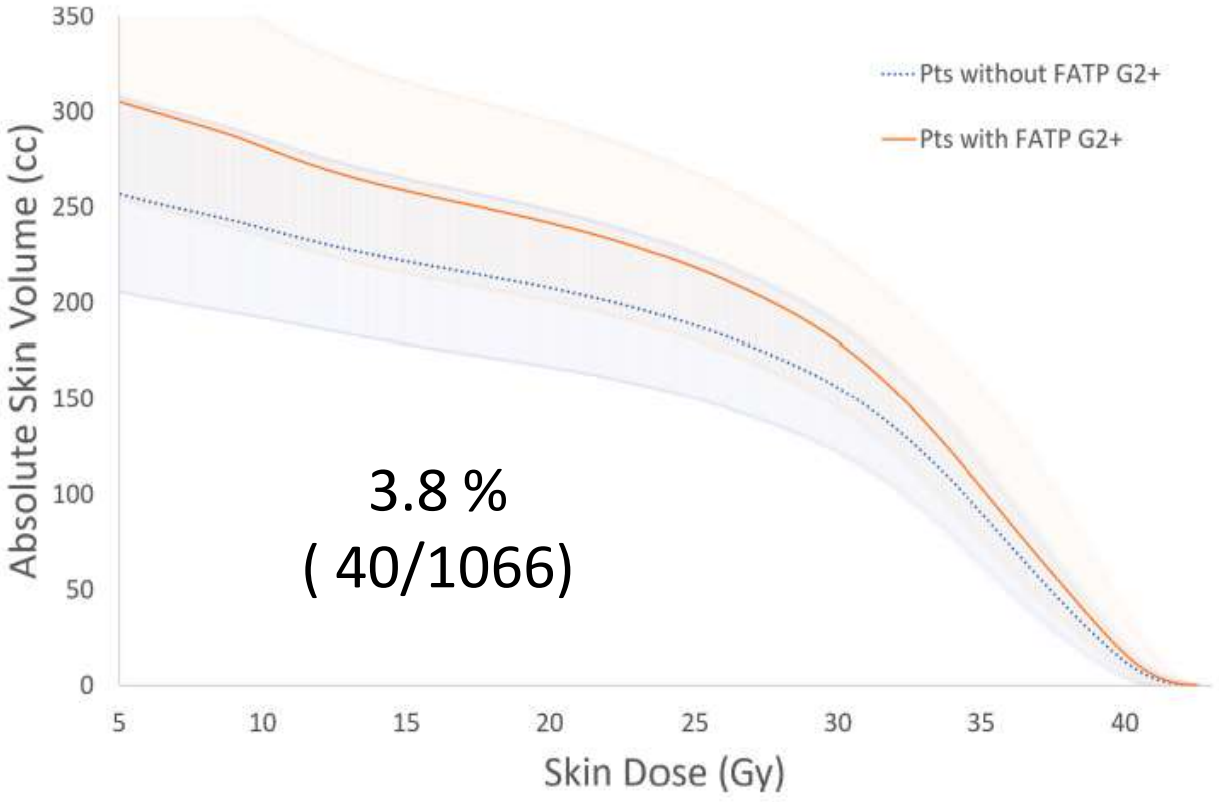
End Point

Moderate –severe late side effects
Fibrosis-Atrophy-Telangiectasia-Pain (FATP G ≥ 2)
Within 42 months after RT end

Skin Structure

The outer CT body contour's 5 mm inner isotropic expansion.





3.8 %
(40/1066)

Multifactorial Model for FATP G2+

PR = 0.28 – AUC = 0.75 ± 0.04 – HL p = 0.88

Variable	Coeff.	Std. Err.	P > z	OR
Aromatase Inhibitor	−0.79	0.270	0.040	0.453
Cosmesis	1.98	0.432	0.000	7.253
V20 Gy	0.017	0.003	0.000	1.017
V42 Gy	0.082	0.044	0.05	1.086
Constant	−7.042	0.854	0.000	

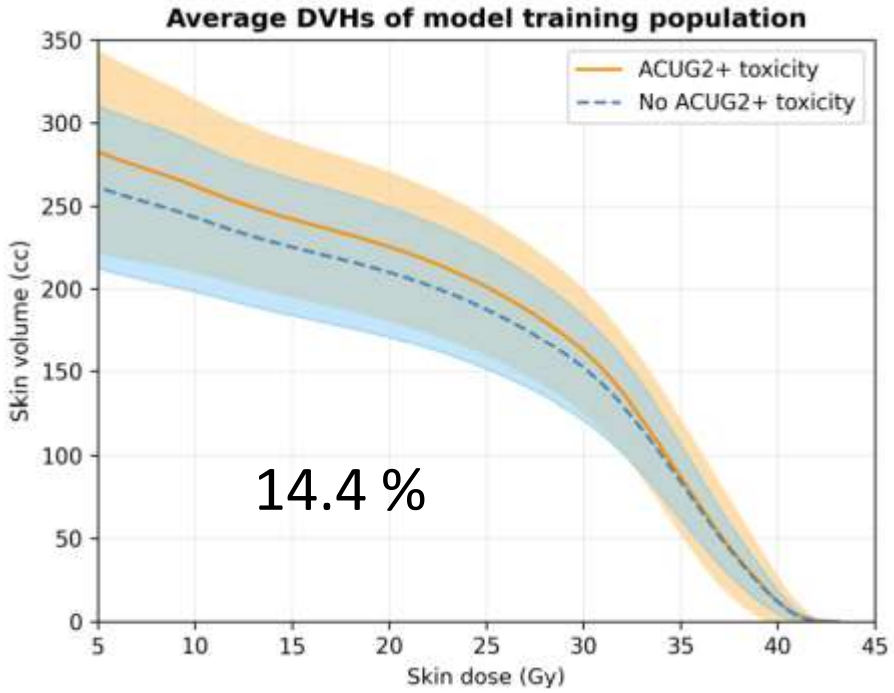
[Cicchetti et al, Radiotherapy and Oncology 2024]

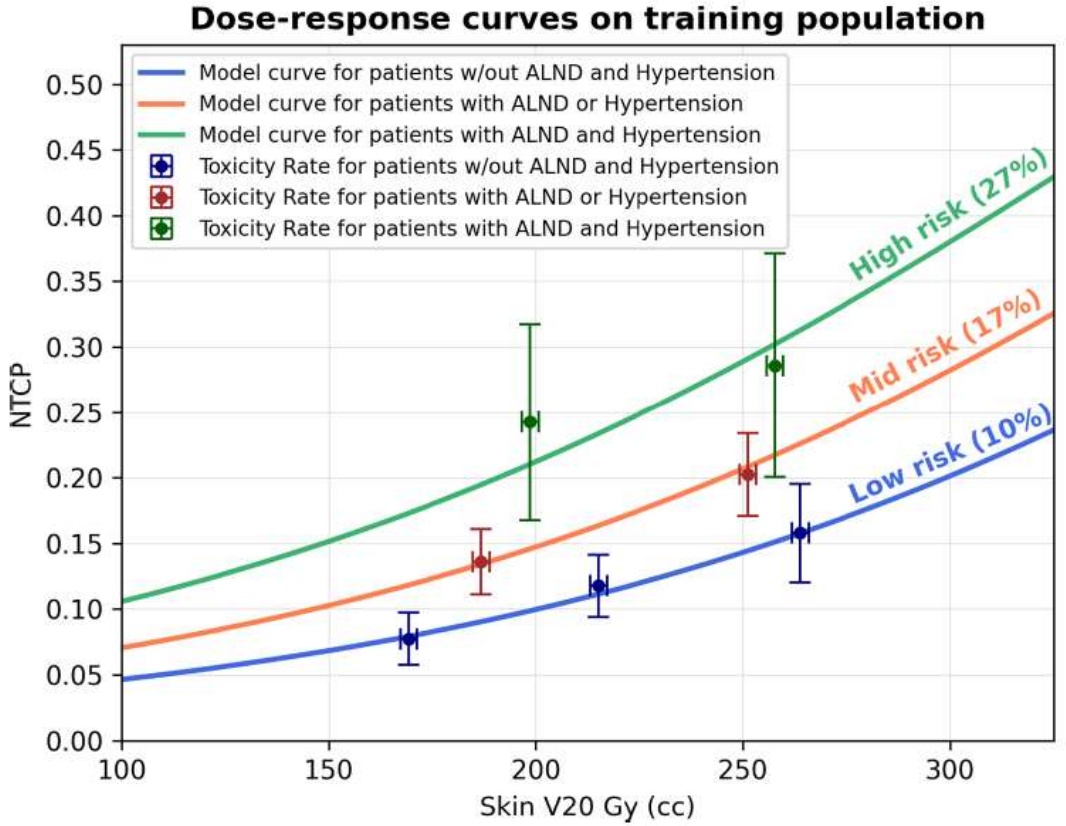
BC Toxicity: Acute Skin Effects

Data Set (Training cohort)

N=1570 (2009-2017)
40Gy/15fr ; whole breast, no boost
878 training (2009-2017) : 3DCRT
692 validation (2017 -2021): 404 static ; 288 arc

Variable	Coefficient	Std err	z-score	P > |z|	OR	95 % CI
V20 Gy	0.008	0.002	3.476	0.0005	1.008	1.004 to 1.01
ALND	0.458	0.229	1.998	0.0457	1.580	1.01 to 2.48
Hypertension	0.430	0.199	2.165	0.030	1.538	1.04 to 2.27



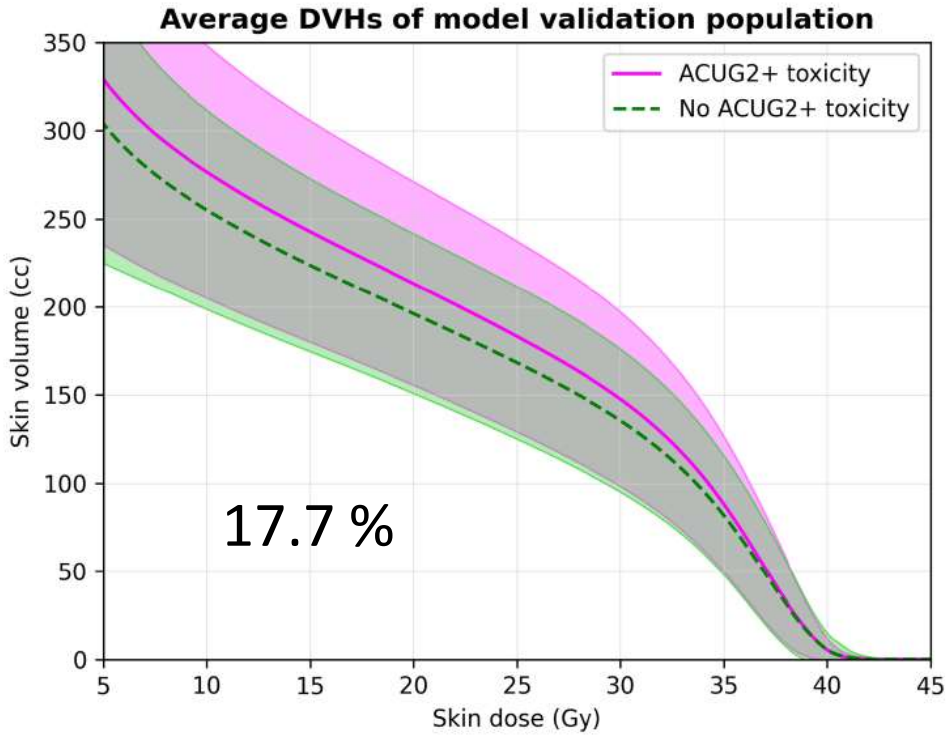


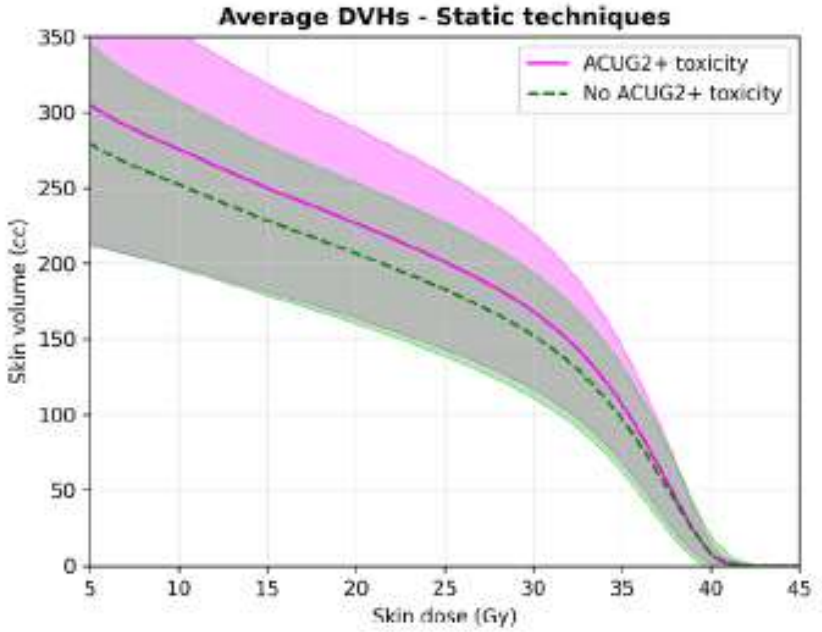
[Vincenzi et al, Radiotherapy and Oncology 2025]

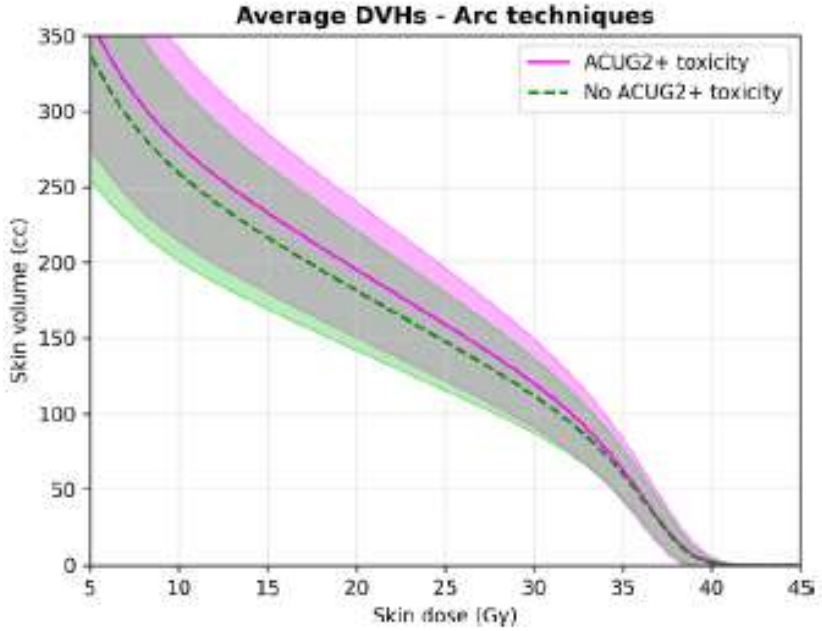
BC Toxicity: Acute Skin Effects

Data Set (Validation cohort)

N=1570 (2009-2017)
40Gy/15fr ; whole breast, no boost
692 validation (2017 -2021): 404 static ; 288 arc







V20 confirmed as predictor parameter

Hormonal therapy with aromatase inhibitors was a protective factor.

[Vincenzi et al, Radiotherapy and Oncology 2025]

BC Toxicity: Pulmonary Toxicity

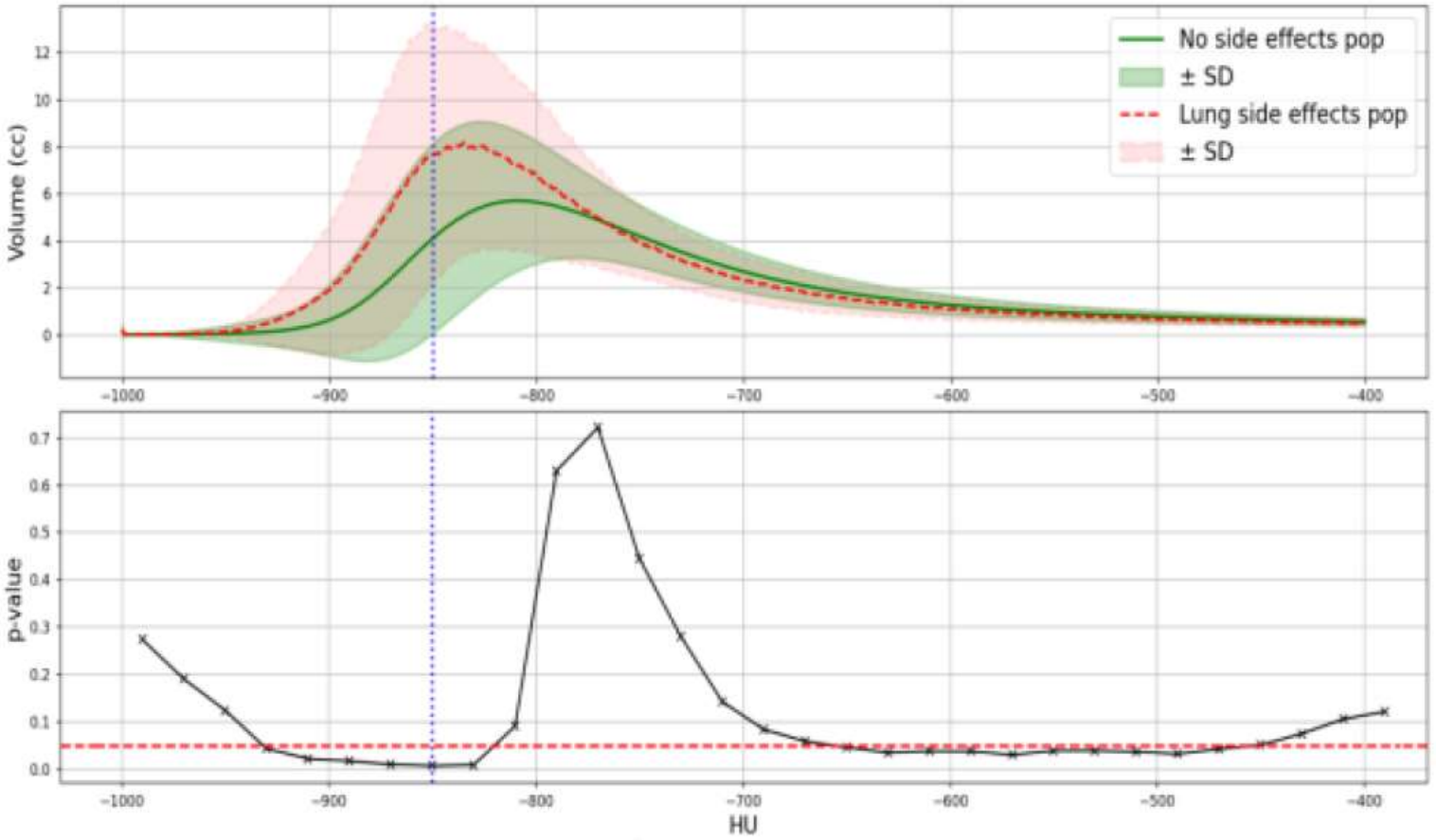
Data Set

N=1172
40Gy/15fr ;
whole breast, 3dCRT

End Point

Radiation-induced pulmonary events
- Dosimetric , Clinical and CT-based densitometric predictors (for heart and lung)

At 6.5 year (followup)
18 pts moderate/severe pulmonary events

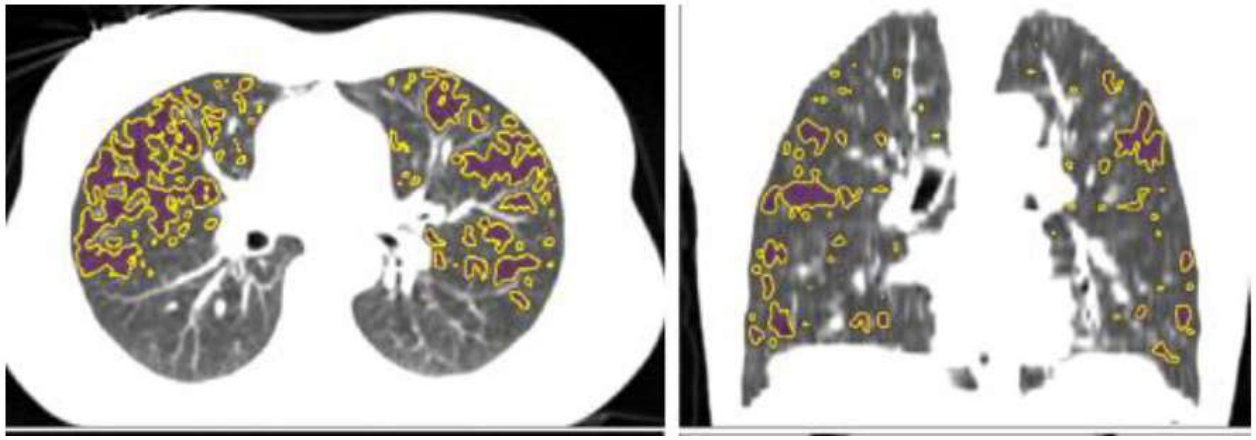


- Lower lung HU (≤850)
- Higher V850,
- larger lung volume
- cardiac calcification were associated with increased risk.

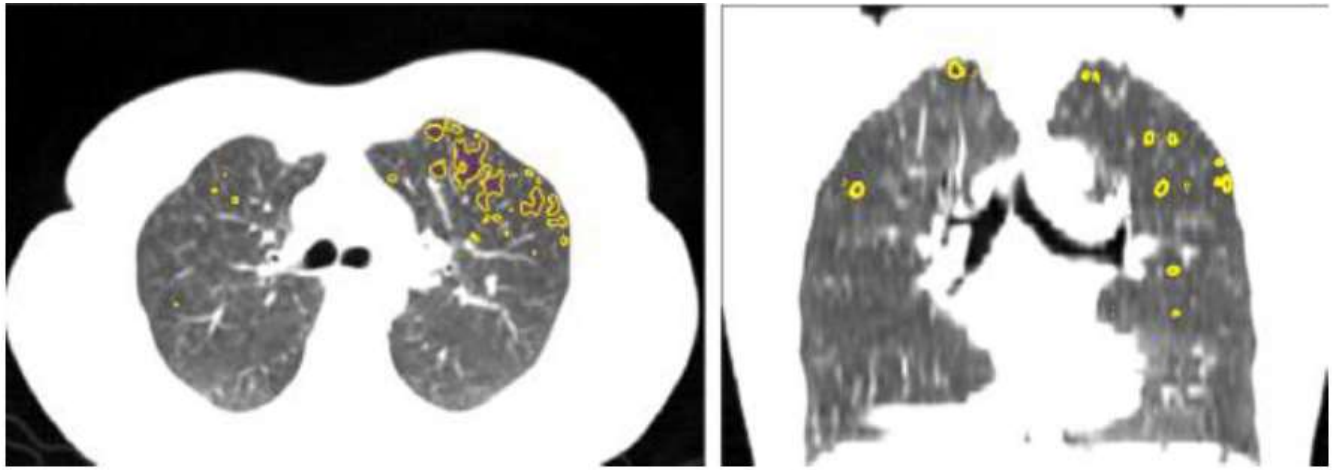
[Fois et al, Cancers 2026]

BC Toxicity: Pulmonary Toxicity

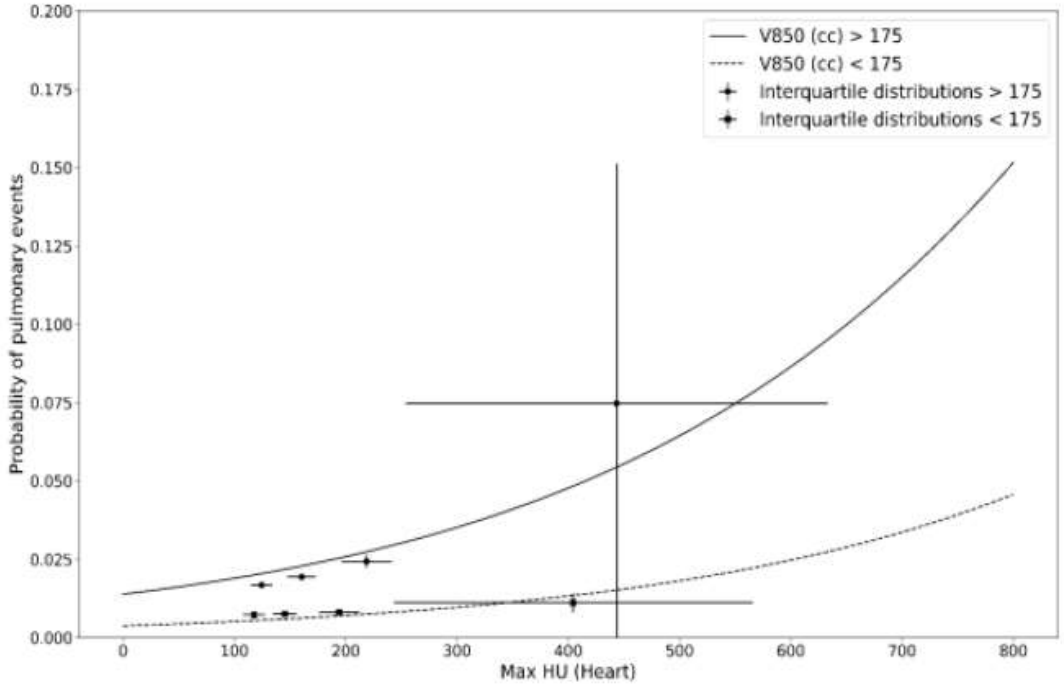
V850 region of a patient with pulmonary event



V850 region of a patient without pulmonary event



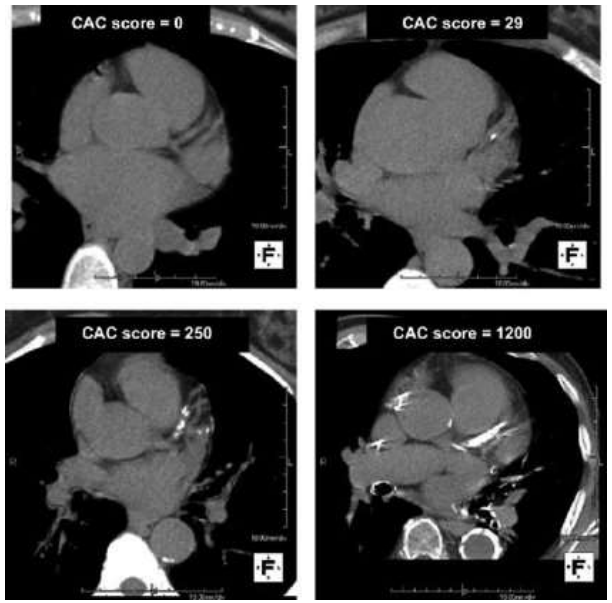
- The best model combined **V850 >175 cc** with **Max_HU_Heart** (AUC = 0.68). V850 >175 cc identified a 4-fold higher risk, consistent with air trapping/emphysema.

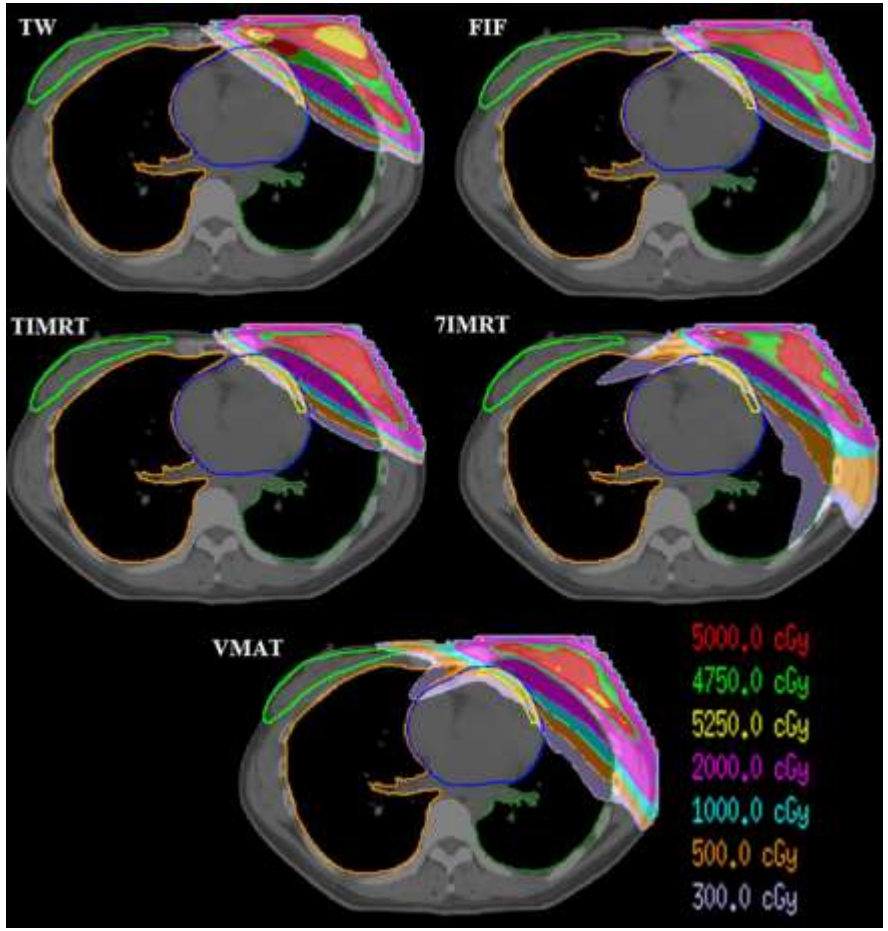


[Fois et al, Cancers 2026]

BC Toxicity : Cardiac Toxicity

- Cardiac toxicity after breast RT, still a relevant issue
- Evidence of linear relationship with mean heart dose, MHD
- Evidence of clinical risk factors…anthracycline, chronic kidney disease, smoking, age…
- Possible role of cardiac substructures; emerging evidence of Cardiac Artery Calcification associated with cardiac events in breast ca pts
- Increased attention during the last 10-15 years….improvement in RT planning and delivery techniques





BC Toxicity : Cardiac Toxicity

‘Calcified Lesion’ within the heart

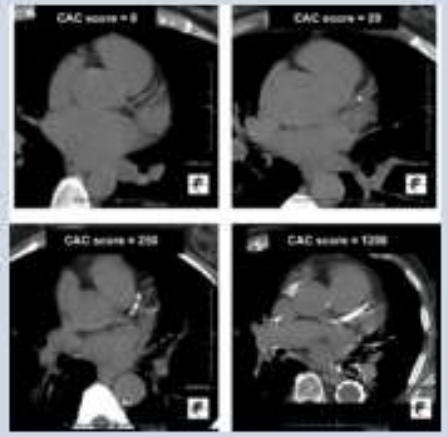
>130 HU pixels and area ≥1mm² or ≥4 adjacent pixels

[Agatson 1990; Neves 2017]

Data set

N=1091 (2009-2017)
3DCRT (FIF), 40Gy/15fr
whole breast, no boost

Mediano Fup: 6.5 y
29 cardiac events



Agatson score (AS):

weighted sum of the calcified lesion area, where a lesion is made of contiguous pixels with HU >130 HU and min 1mm2

- $w_{pixel} = 1$ if $130\,HU \leq Pixel \leq 199\,HU$
- $w_{pixel} = 2$ if $200\,HU \leq Pixel \leq 299\,HU$
- $w_{pixel} = 3$ if $300\,HU \leq Pixel \leq 399\,HU$
- $w_{pixel} = 4$ if $Pixel \geq 400\,HU$

extract:
Volume of CAC (Cardiac Calcification)
Heart Max HU
Agatson Score

✓ Test the **association** between **CAC scores** and **cardiac events**

✓ Assess **interplay** with dosimetry/clinical **predictors**

[Belardo et al, Radiotherapy and Oncology 2025]

BC Toxicity : Cardiac Toxicity

Variable	p-value	Odds ratio	CI at 95%
Laterality	0.1556	1.6748	[0.8163; 3.4364]
Age	0.0001*	1.0682	[1.0325; 1.1050]
Chemotherapy	0.9899	0.9639	[0.4432; 2.0964]
Anthracyclines	0.3593	0.5894	[0.2051; 1.6942]
Concomitant CT/RT	0.1627	2.6571	[0.6048; 11.6728]
Monoclonal therapy	0.6414	0.6853	[0.1616; 2.9066]
Hormonal therapy	0.7706	0.9194	[0.3941; 2.1451]
Smoking	0.8095	1.0640	[0.4561; 2.4821]
Obesity	0.0515	1.9319	[0.9379; 3.9794]
Diabetes	0.4481	1.3597	[0.5527; 3.3453]
Hypertension	0.0615	1.8217	[0.9104; 3.6451]
MHD	0.4955	0.9735	[0.7274; 1.3031]
1 Gy cutoff MHD	0.0468*	2.1662	[0.9936. 4.7226]
Agatson score	0.0046*	1.0015	[1.0010; 1.0020]
Volume score	0.0036*	1.0009	[1.0006; 1.0013]
MAX HU score	0.0001*	1.0034	[1.0019; 1.0048]

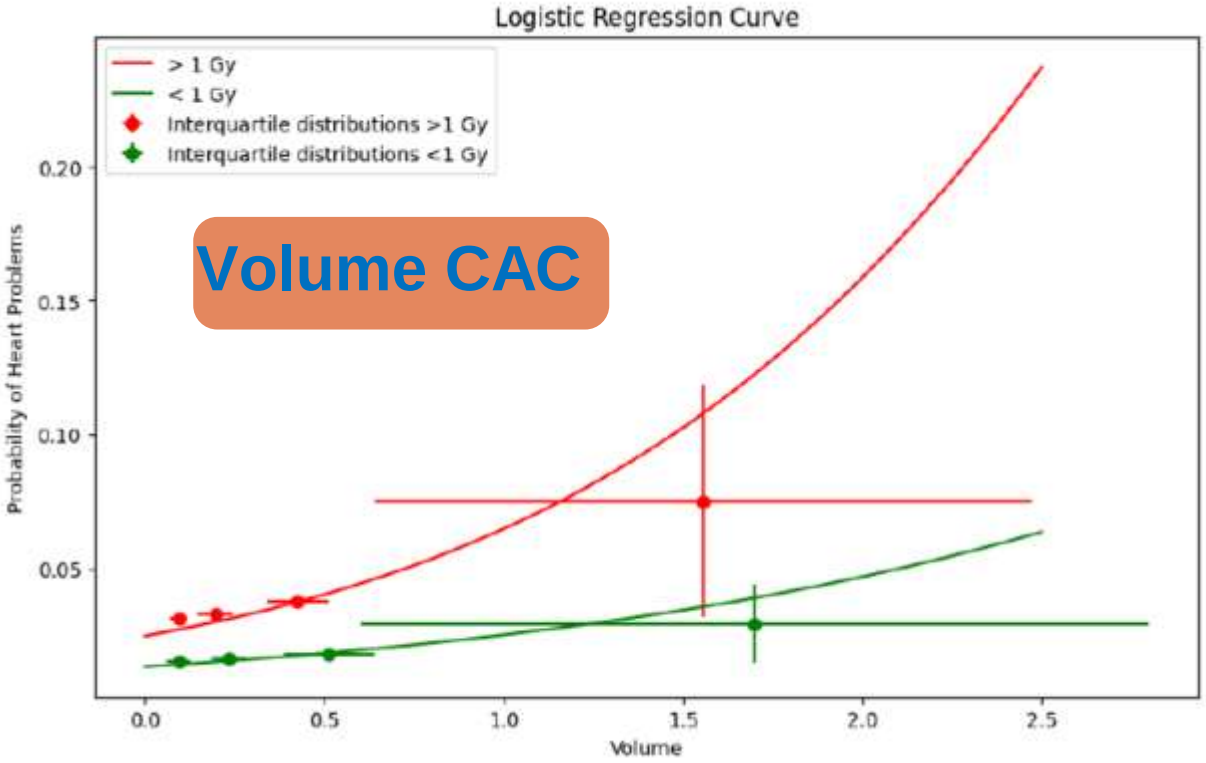
	Model p-value: <0.0001 ROC p-value: <0.0001 AUC [95% CI]: 0.770 [0.744, 0.795]		Model p-value: <0.0001 ROC p-value: <0.0001 AUC [95% CI]: 0.771 [0.745, 0.796]		Model p-value: <0.0001 ROC p-value: <0.0001 AUC [95% CI]: 0.753 [0.726, 0,778]	
	Volume score		**Agatson score**		**Maximum HU score**	
	p-value	**Odds [95% CI]**	**p-value**	**Odds [95% CI]**	**p-value**	**Odds [95% CI]**
Age	0.0343	1.0406 [1.003, 1.0797]	0.0337	1.0408 [1.0031, 1.0800]	0.0158	1.0455 [1.0084, 1.0839]
MHD >1Gy	0.0093	3.3086 [1.343, 8.1493]	0.0123	3.1338 [1.2811, 7.6660]	0.0202	2.8082 [1.1747, 6.7132]
CAC Score	<0.0001	1.0005 [1.001, 1.002]	<0.0001	1.0013 [1.0008, 1.0019]	0.0004	1.0029 [1.0013, 1.0045]

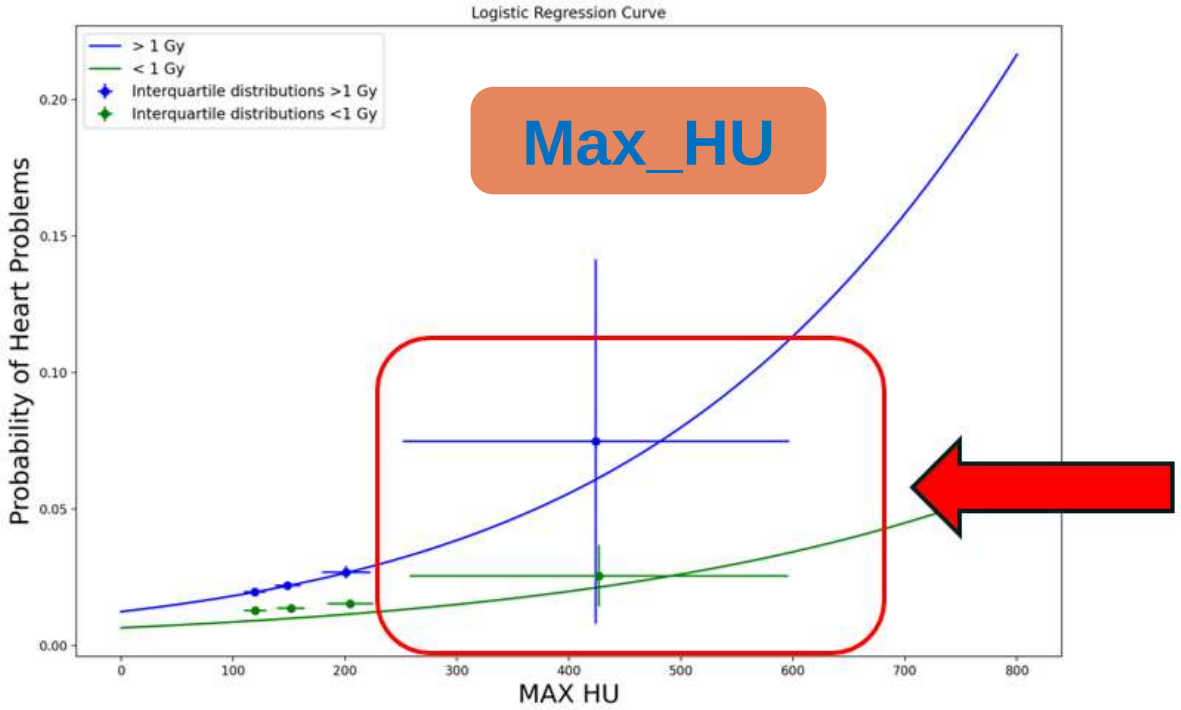
- ✓ Similar performances for the three different scores
- ✓ CAC score is always the major predictor

[Belardo et al, Radiotherapy and Oncology 2025]

BC Toxicity : Cardiac Toxicity

Risk of Cardiac events vs CAC score, for MHD > or < 1 Gy
(@ fixed median age)





The independent role of MHD>1Gy suggests that the max cost-benefit in reducing the risk should be through DIBH for left pts with “severe” CAC score (ex: Max_HU>200-250)

[Belardo et al, Radiotherapy and Oncology 2025]

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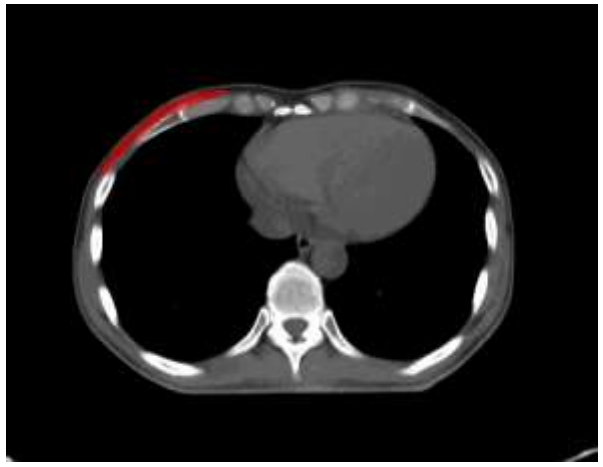
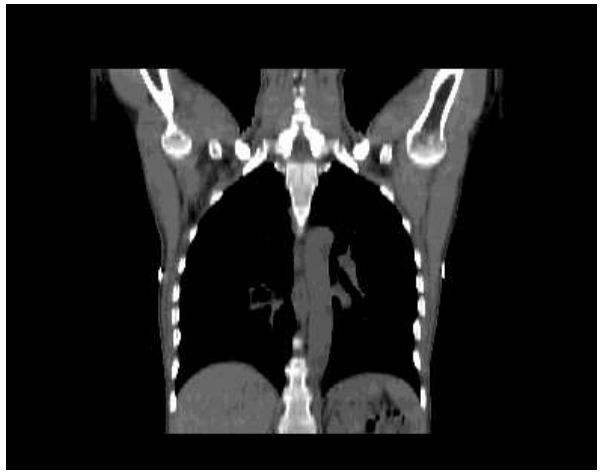
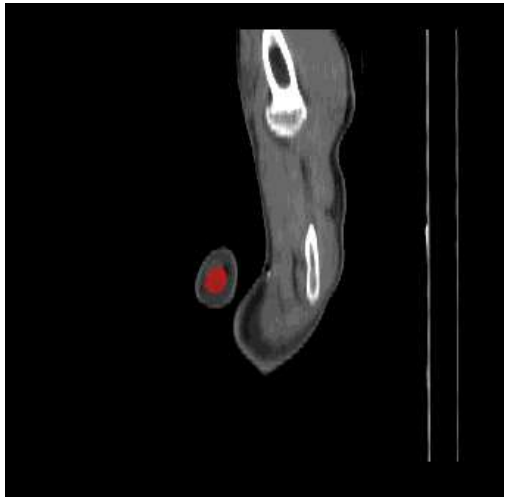
CTV /OAR Contouring

BC: CTV & OAR Autocontouring

- Manual delineation is labor-intensive and a highly time-consuming task ≈ 15-30 min
- Inter-observer Variability (IOV): Subjective nature leads to significant differences between observers, affecting treatment consistency
- Intra-observer variability: same observer shows inconsistencies at different time points

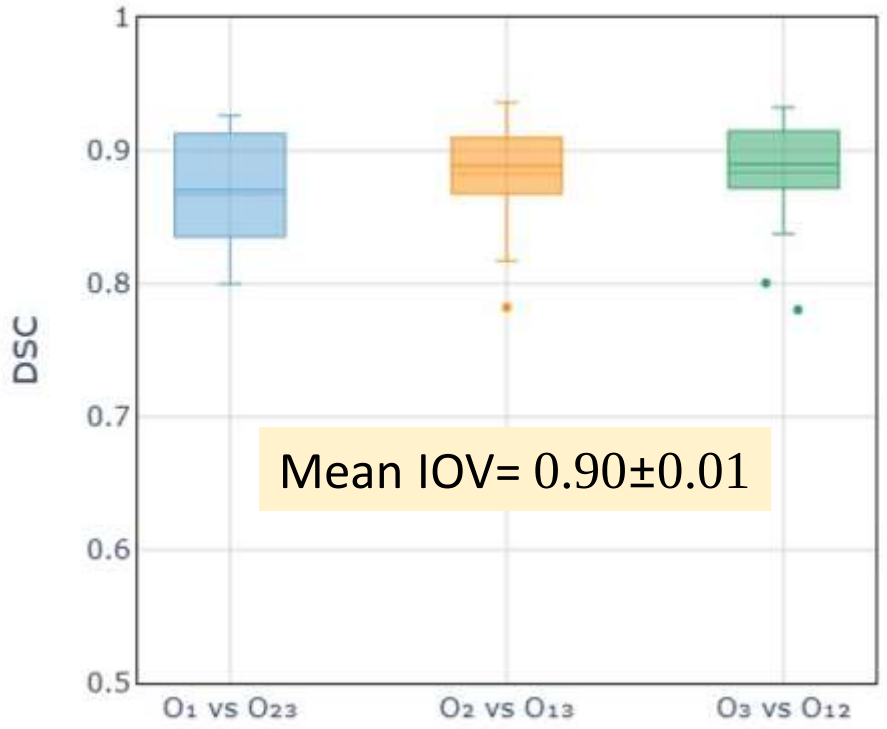






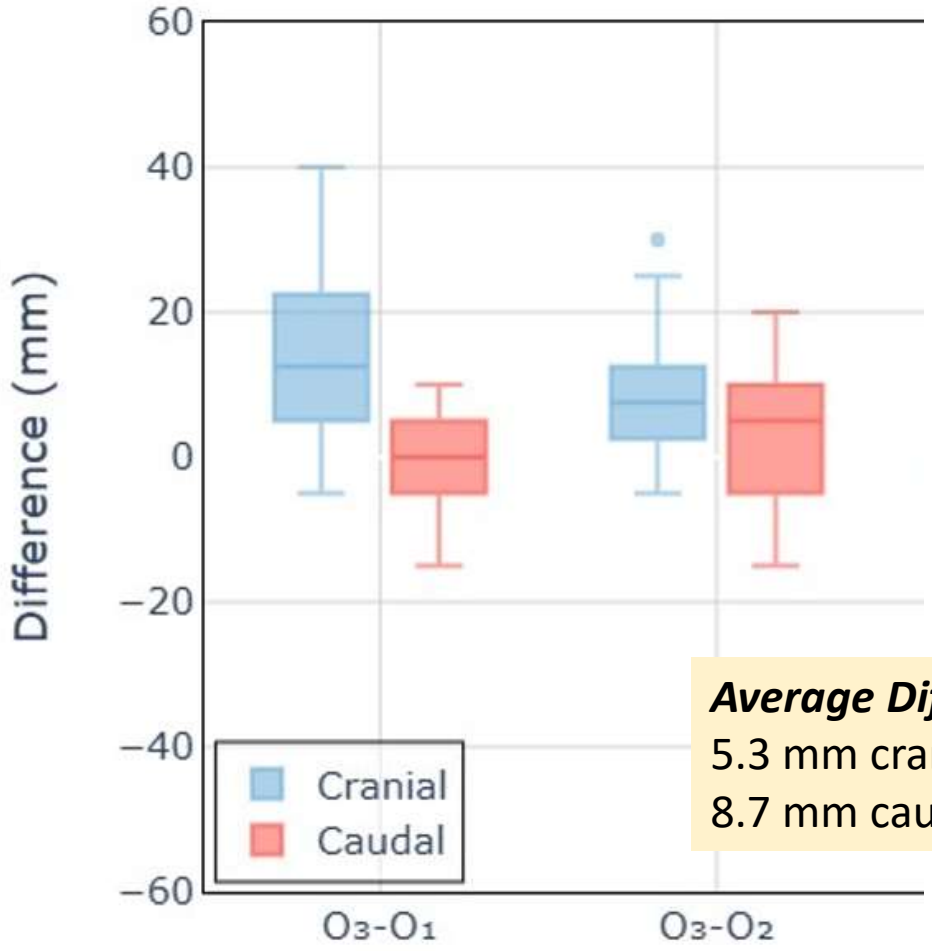
BC: CTV & OAR Autocontouring

- 40 BC pts
  - 20 BC dx
  - 20 BC sx
- 3 Expert Observer



Mean IOV= 0.90±0.01

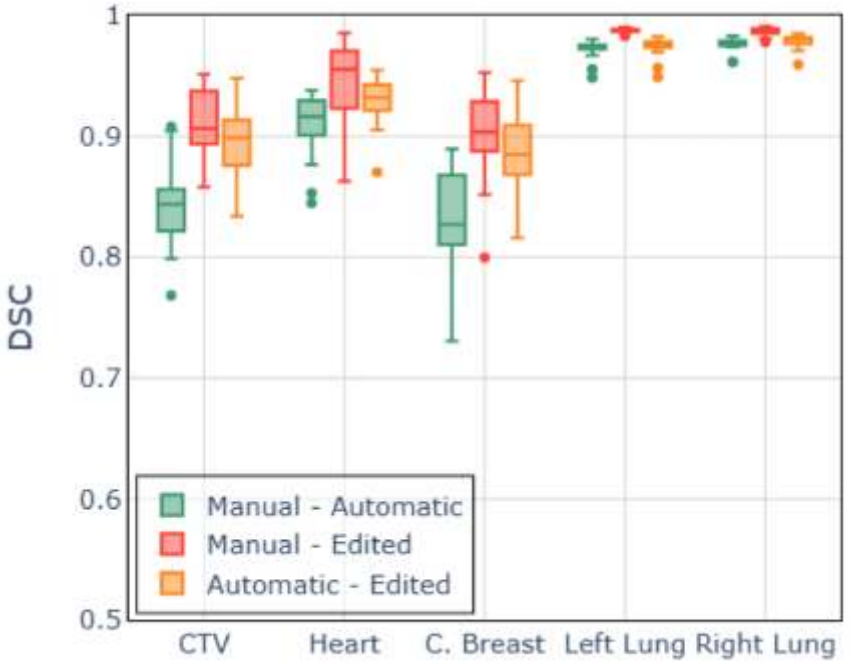
No significant differences for the three expert observers

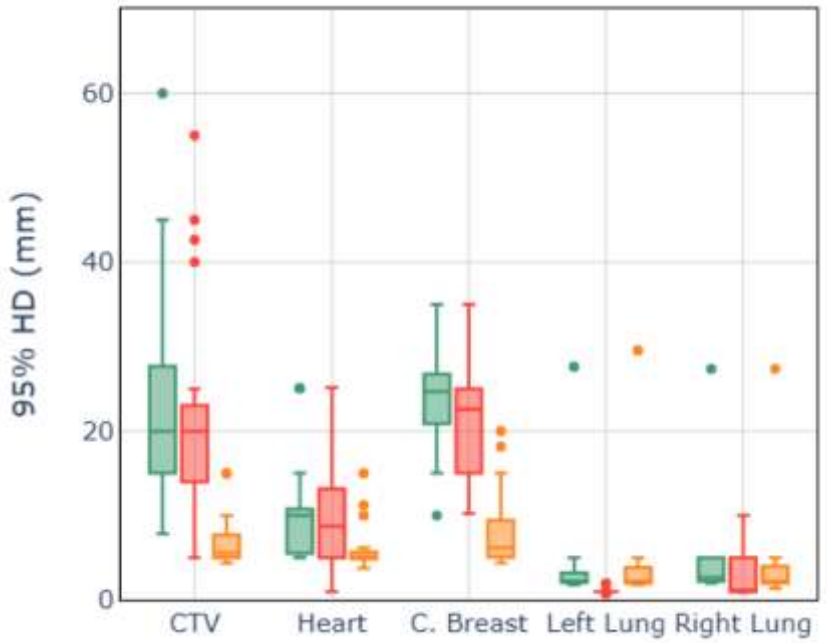


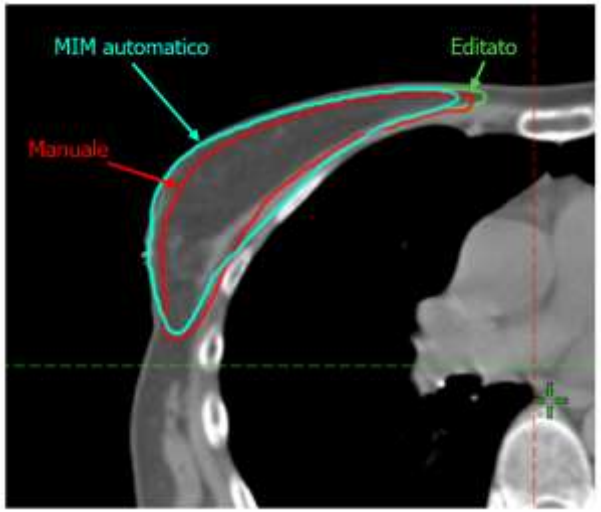
Average Difference
5.3 mm cranial direction
8.7 mm caudal direction

[Maddaloni et al, Physica Medica, submitted]

BC: CTV & OAR Autocontouring







- ✓ Automatic segmentation of the heart and contralateral breast achieved good agreement with manual contours - > dosimetric confirmation
- ✓ For the breast CTV, discrepancies between manual and automatic contours were significantly greater than IOV ($p < 0.05$), indicating lower consistency -> editing time longer than manual contouring
- ✓ Commercial AI-based segmentation tools may reliably replace manual contouring just for select OARs

[Maddaloni et al, Physica Medica, submitted]

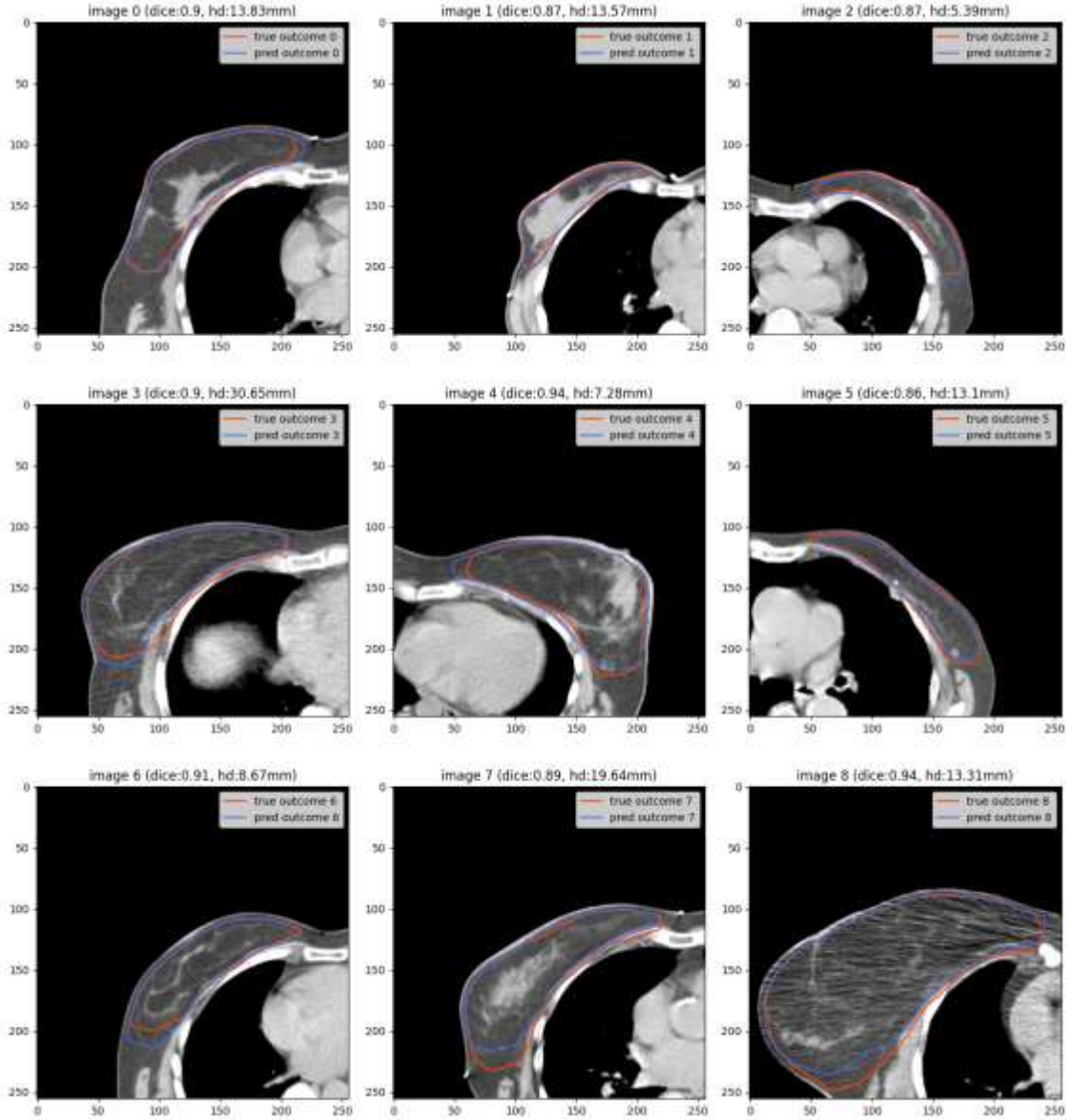
BC: Deep Learning CTV Contouring

Training & Internal Validation

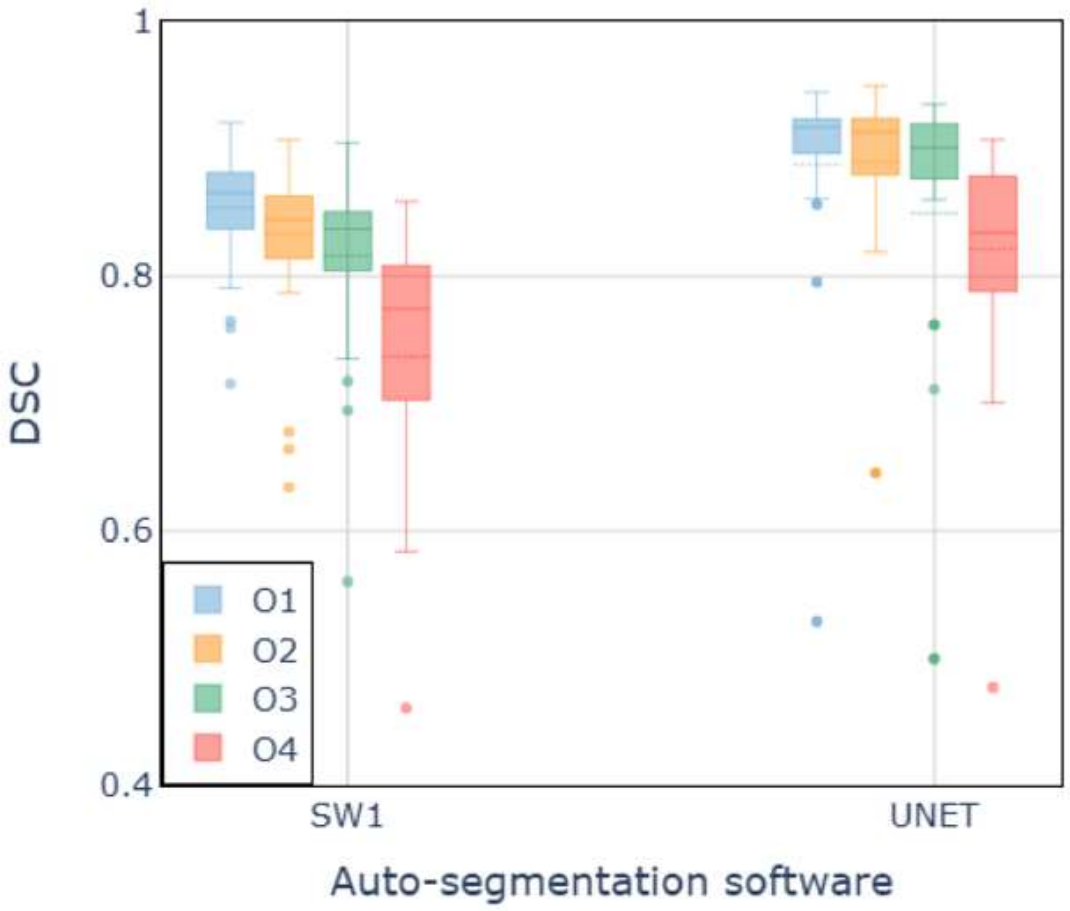
3D Unet trained on OSR data (n=861 pts)
- 450 Right BC
- 411 Left BC

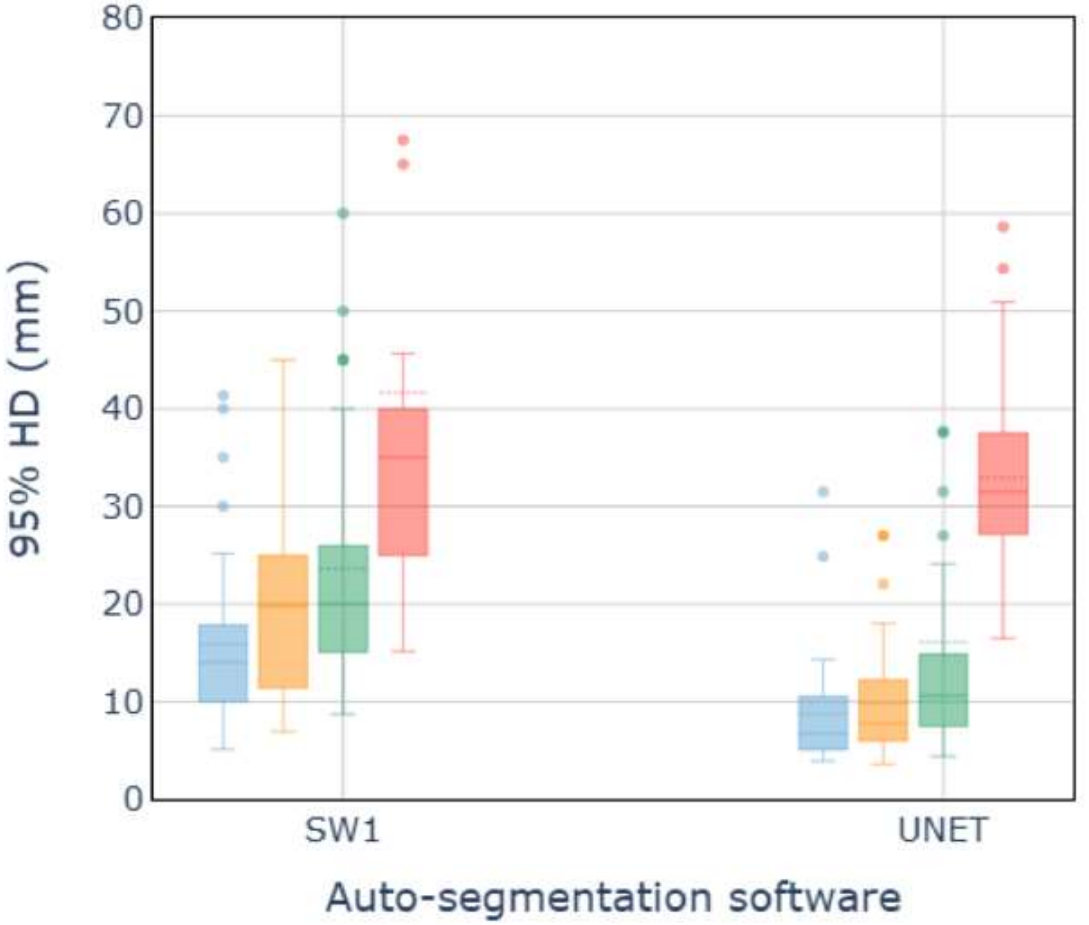
- The model well matches the clinicians' contours on the chest and skin side.
- It is more uncertain on the lateral and cranio-caudal side (different strategies followed by clinicians).
- Larger prediction along the cranio-caudal axis in both directions. Clinical contours are cleanly cut from one slice to the next one, while prediction is smoothly closed.

Validation performance reach inter observer variabilities values



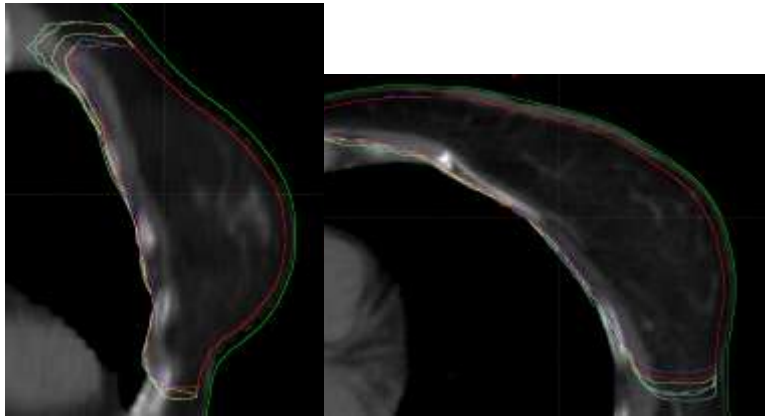
[Ubeira-Gabellini et al, Phiro 2025]





U-net : accordo migliore con CTV manuale

BC: Probabilistic CTV map



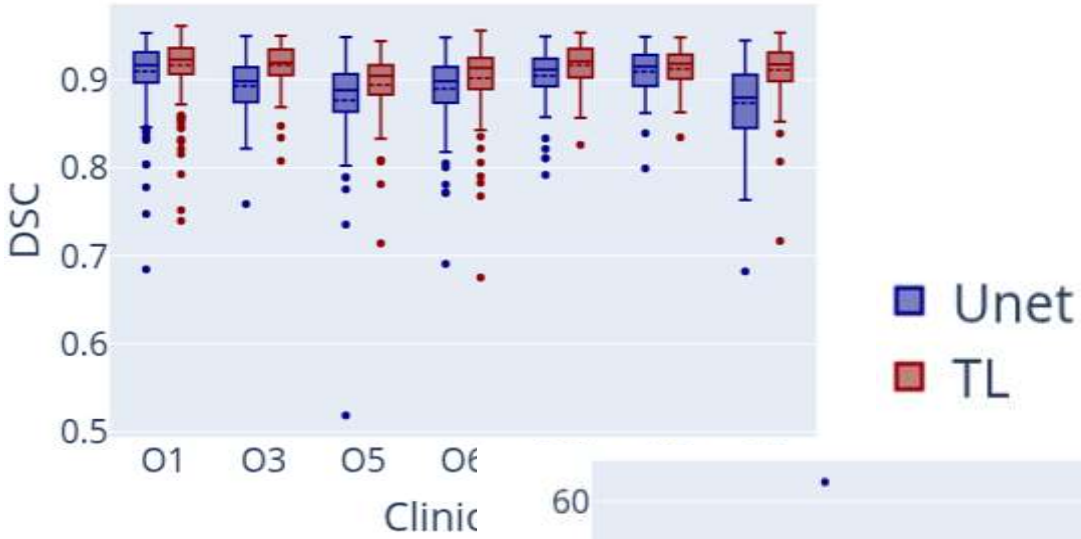
Data Set

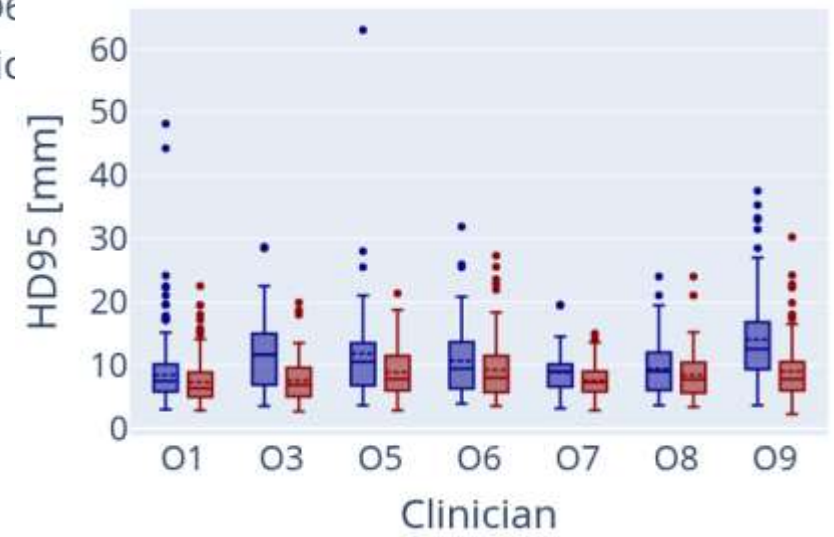
- ❑ **Dataset A (Training/Validation):**
- 861 patients treated 2017-2021 | 450 right-side, 411 left-side BC | Used for training of global 3D-Unet
- ❑ **Dataset B (Extended Training /Validation):**
- 100 additional patients post-2021 (54 left, 46 right) | Used to enlarge clinician label numbers
- ❑ **Dataset A + B:** Mean age 61±13 years (range 28-88) | Clinicians with <23 cases excluded (107 patients removed)

- ❑ **Dataset C (Test Set):**
- 40 patients (2022+) | Each contoured by 3 expert clinicians (O1, O2, O3) + 1 resident (O4*)

Transfer Learning

- Fine-tuned 200 additional epochs on individual clinician datasets (>70 cases each)
- Seven TL models: O1, O3, O5, O6, O7, O8, O9 produced 3D prediction of CTV



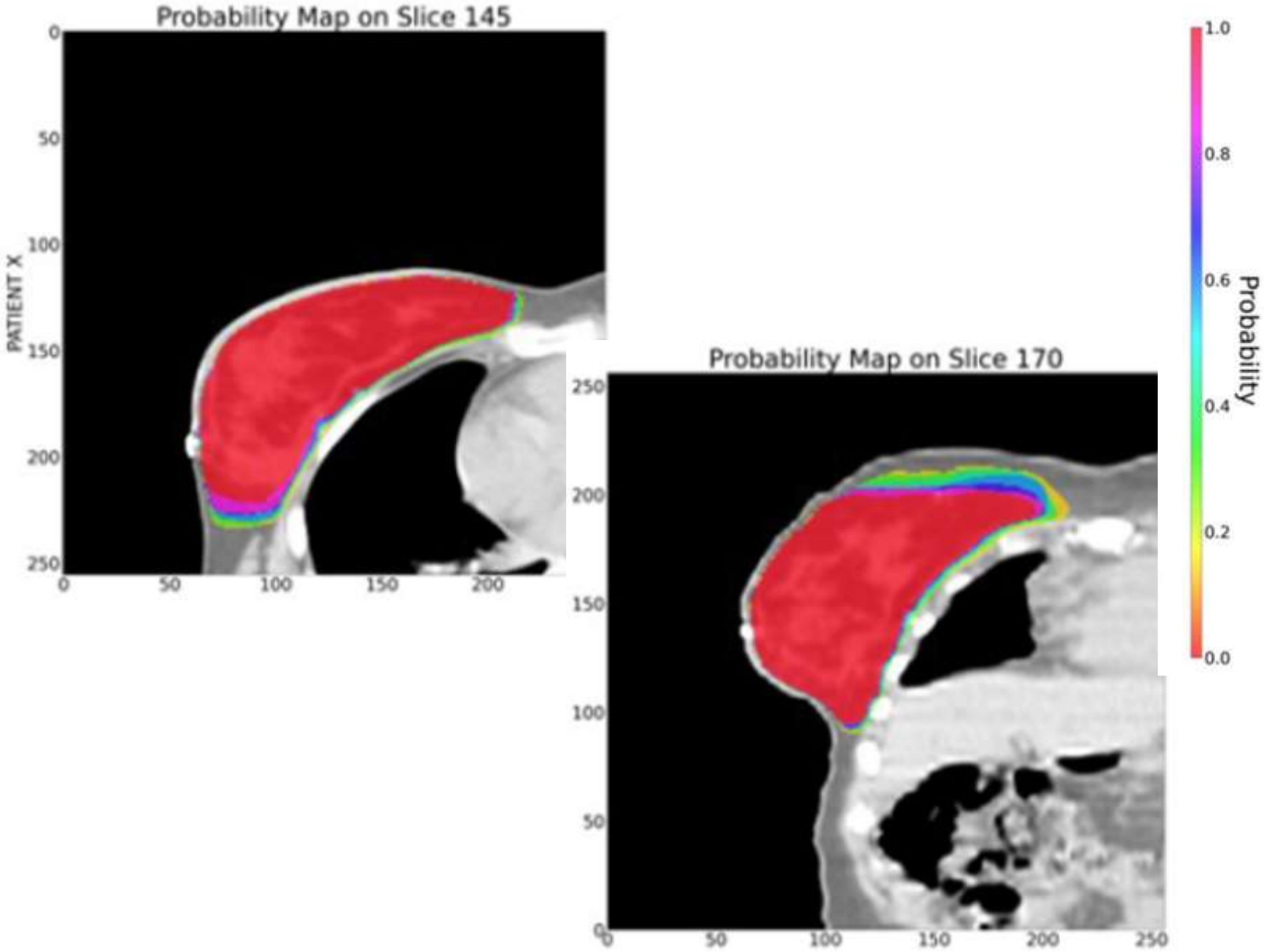


TL models statistically outperform baseline UNet for ALL 7 clinicians across similarity metrics (p<0.05, Wilcoxon test)

BC: Probabilistic CTV map

Probabilistic Map Generation

- Seven binary 3D predictions averaged per patient CT
- Seven iso-probability levels: 14%, 29%, 43%, 57%, 71%, 86%, 100%
- 100% = intersection of all 7 models (most restrictive)
- 14% = union (broadest, at least 1 model agreement)



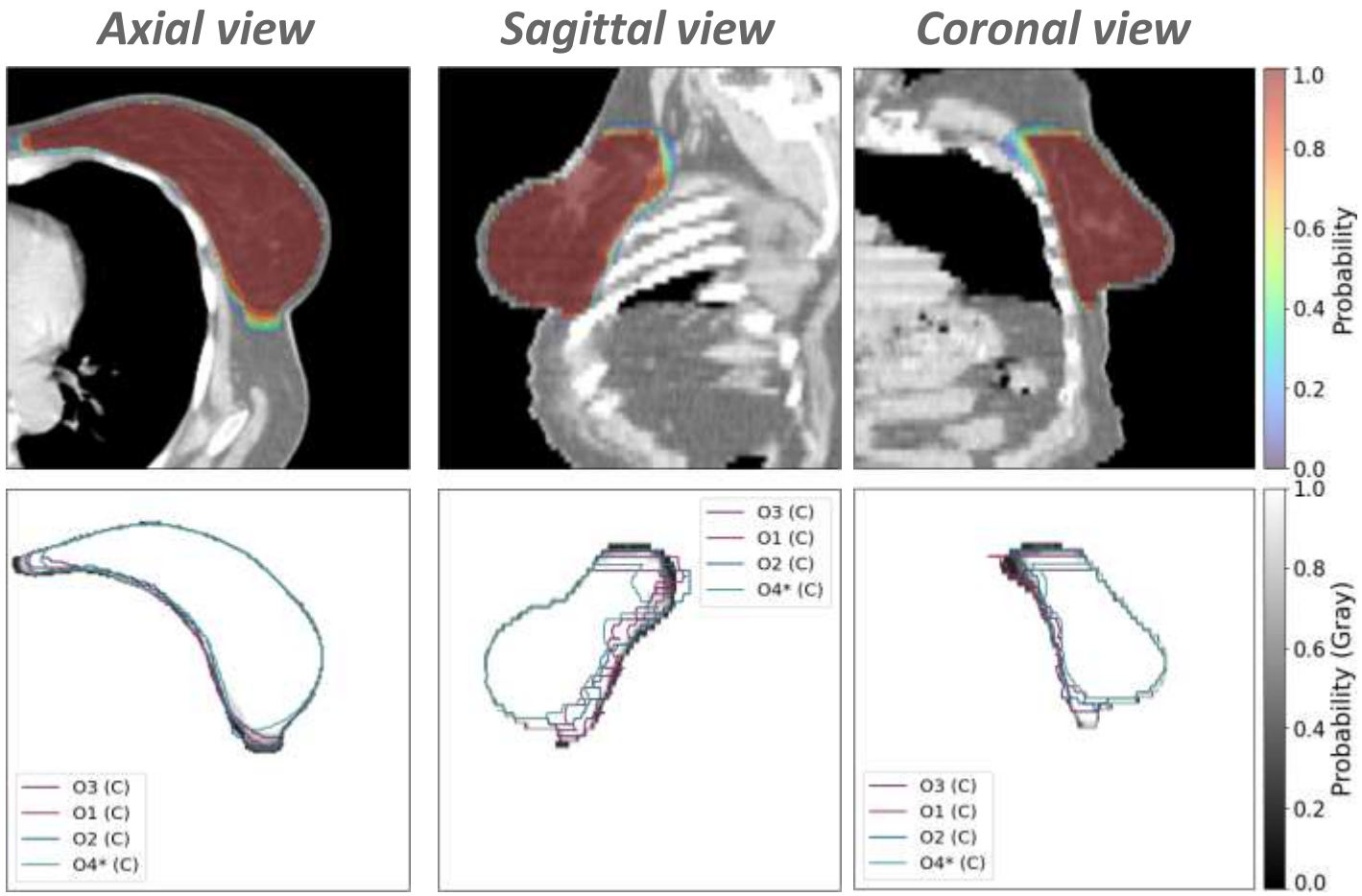
BC: Probabilistic CTV map

Validation

40 pts (20 dx, 20 sx)
3 Expert Observer
1 Resident

3D segmentation masks of the iso-probabilities are compared with masks of the 4 clinicians.

- All expert contours fall within the 14%–100% band, in line with training data distributions
- Model consistently conservative (iso-probabilities larger)
- Variability largest at cranial-caudal and lateral borders (consistent with known IOV)
- Resident contours deviate markedly from the iso-probabilities: systematically tighter delineations in cranial-caudal axis
- Clearly identified as outlier vs. expert clinicians: it demonstrates model sensitivity to contouring expertise level



OSPEDALE SAN RAFFAELE

OCF

Planning Optimization

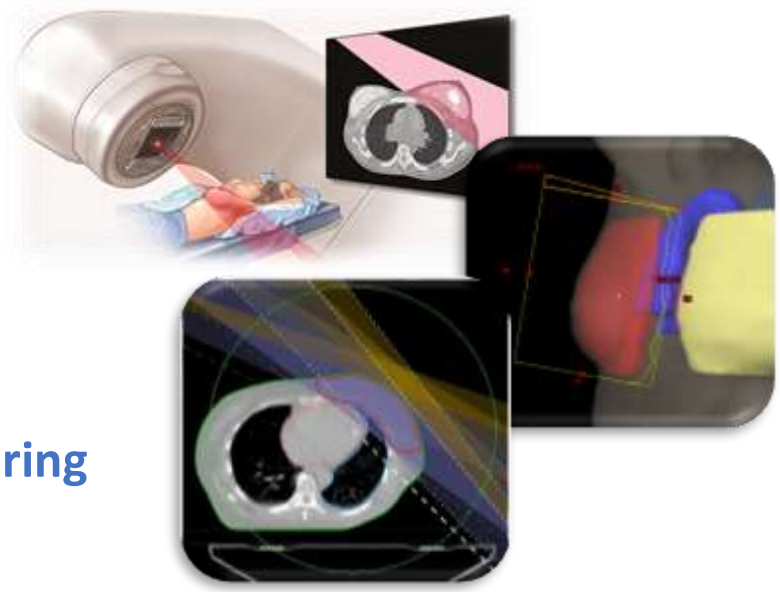
Whole-breast irradiation – Delivery Techniques

Static techniques (3DCRT & IMRT):

- 3DCRT Tangential Fields (TF) irradiation
- IMRT Static Field
- IMRT Tomo Direct (TD) irradiation

↓ Conformity

↑ OAR low-dose sparing

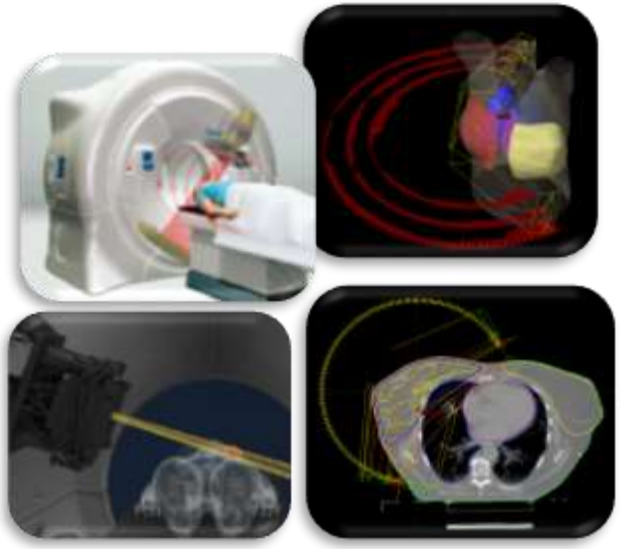


Rotational techniques:

- Volumetric RapdiArc (RA) irradiation
- TomoHelical (TH) irradiation

↑ Conformity

↓ OAR low-dose sparing

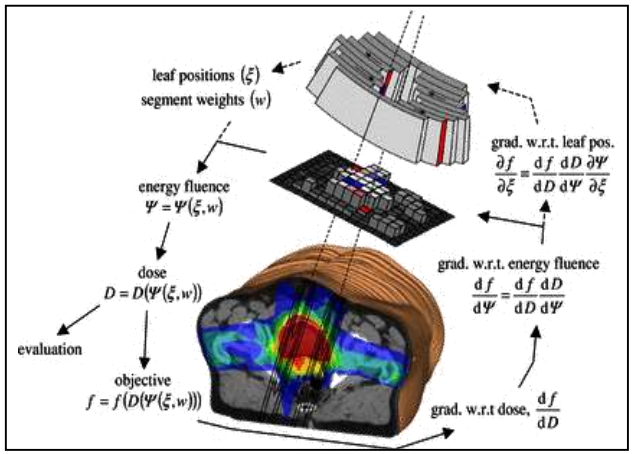


BC: Planning Optimization

Auto-plan scenario: motivations

→ IMRT planning is based on the inverse problem optimization:

- not single physical solution which fulfils the ideal objectives
- multi-objective problem with conflicting objectives
- trial-and-error procedure



→ IMRT planning optimization results:

- **time consuming**
- **planner depending**
- **Institution depending**
- **risk of clinically relevant sub-optimal plans**

BC: Planning Optimization

- Developing and validating an arc-technique mimicking Tangential Field **ViTAT (Virtual Tangential Arc Technique)**,
- Implementation of Plan automation using Varian RP
- Challenges and potentials of multi-Institute KB plan prediction & automation; The MIKAPOCo project ...in short
- MIKAPOCo for breast: KB models transferability for tangential fields
- Benchmark MIKAPOCo model and potentials for large-scale implementation

MIKAPOCo* project

M*ulti-I*nstitutional **K*nowledge-**b*ased **A*pproach in **P*lanning **O*ptimization for the **Co*mmunity*

Improving the quality of Radiotherapy by multi-Institution Knowledge-Based planning optimization models
AIRC IG-23150

BC: Planning Optimization

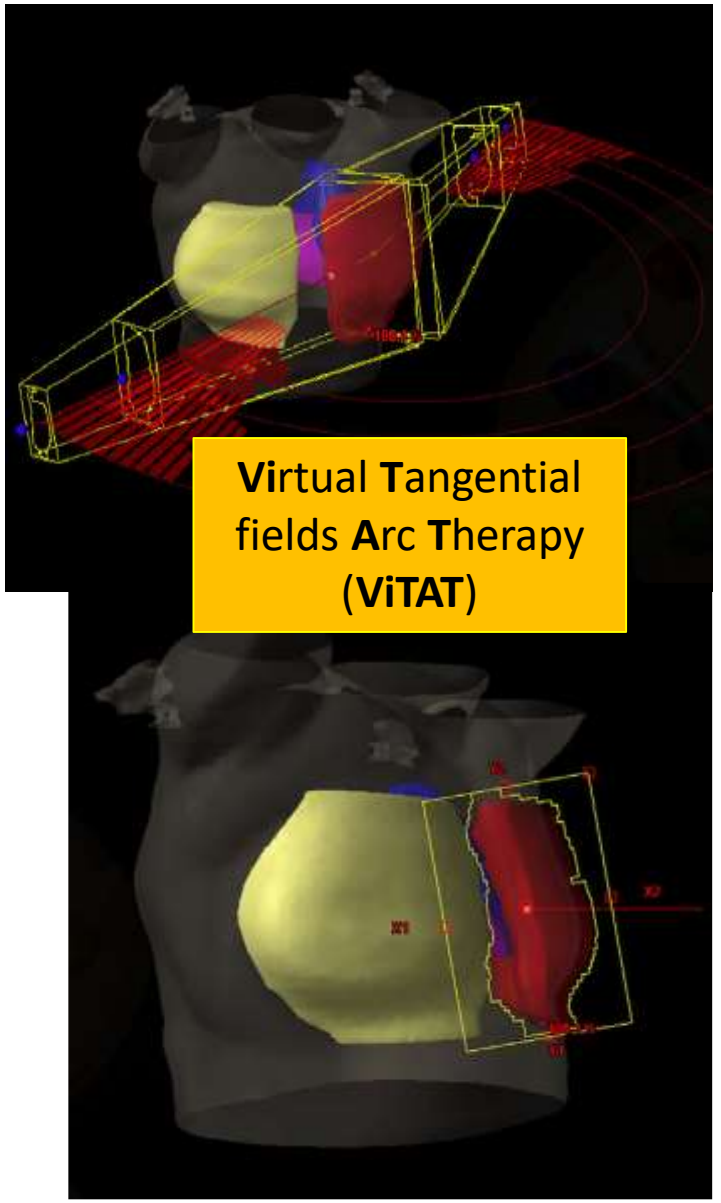
Automating tangential-field (TF) breast RT

- Taking historical patient's data, plans optimized by manual Field-in-Field technique

- Developing and validating an arc-technique mimicking TF (ViTAT)
  - 4 arcs, fully blocked apart the first 20°
  - Gantry start and stop based on the past experience, permitting automatic field setting (through template)

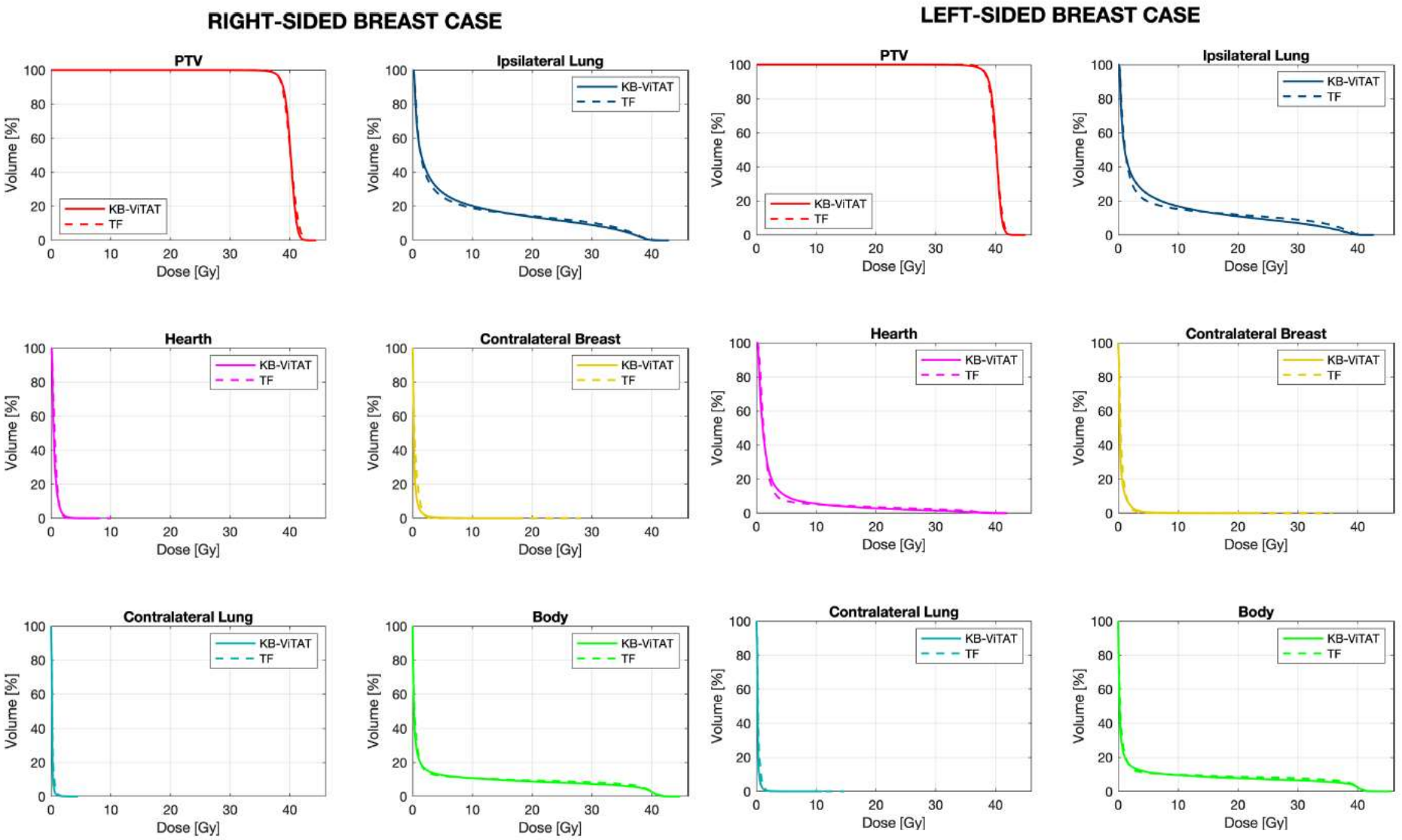
- Developing automatic Knowledge Based models (one for right and one for left) obtained by linking dose cubes to «fake» arcs

- Generating and fine-tuning an optimal template for each side to mimic/improve TF performances for both OARs and PTVs



[Esposito et al, Phys Med 2020; Castriconi et al. Front Oncol 2021]

BC: Planning Optimization



- PTV & omolateral OARs: minor differences and no significant differences for Dmean
- Reduced dose to controlateral OARs
- Reduced Integral dose
- Time for automatic optimization and calculation: 12 min

RP Plan prediction models of TF may translate into a feasible, highly efficient automatic technique for plan optimization and delivery !

Fully automated procedure in clinical use since 2021

KB approach Pros & Cons

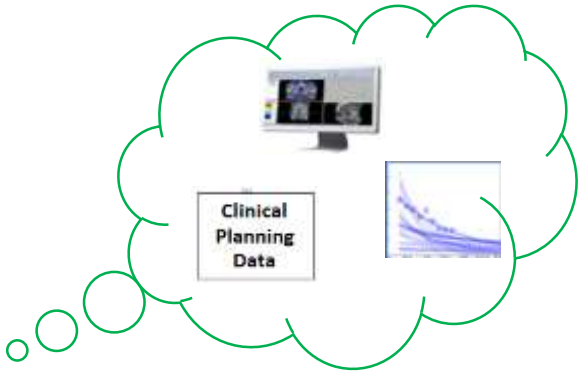
→ What about Institutes experiences?

✓ **Improving plan quality and efficiency**

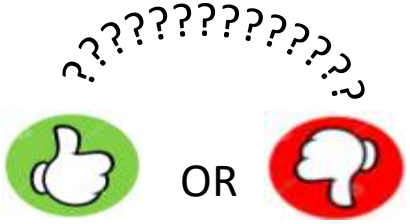
(reduce sub-optimal plans, inter-planner variability, planning time, Trial QA/audit….)

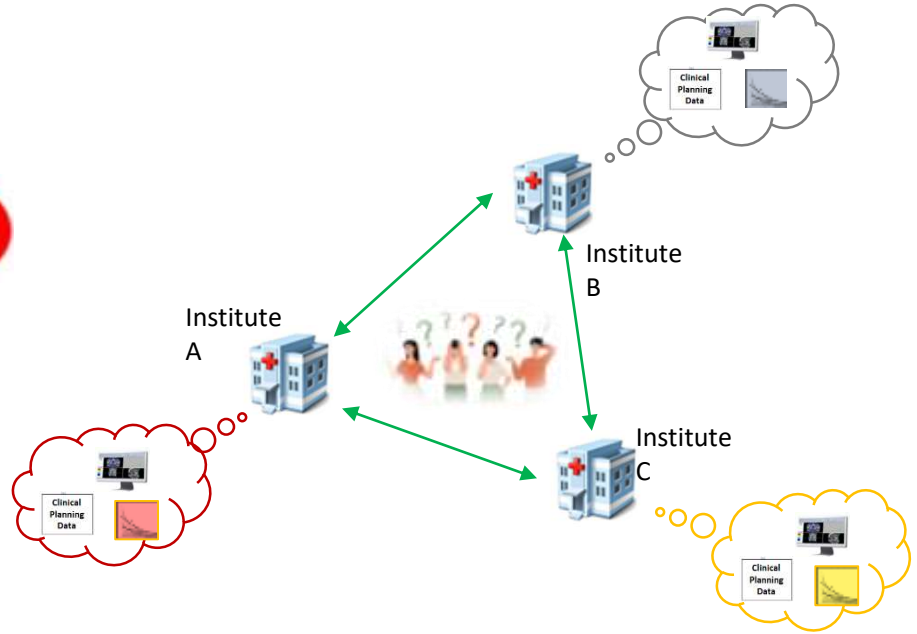
Single Institute experience

Institute A



→ What about multi-Institutes experiences?





CHALLENGES

(?) Inter-Institute protocols variability (dose, fractionation, technique ...)

(?) Inter-Institute CTV/PTV/OARs definition and contouring variability

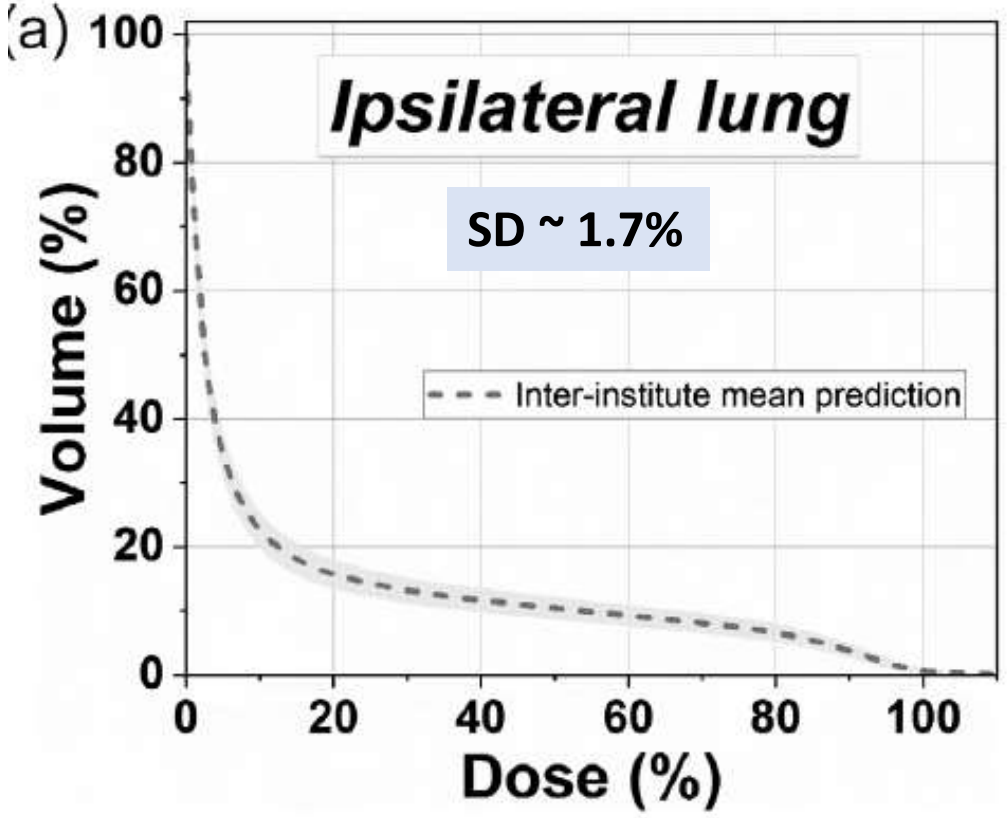
(?) Variability in KB methodology/implementation

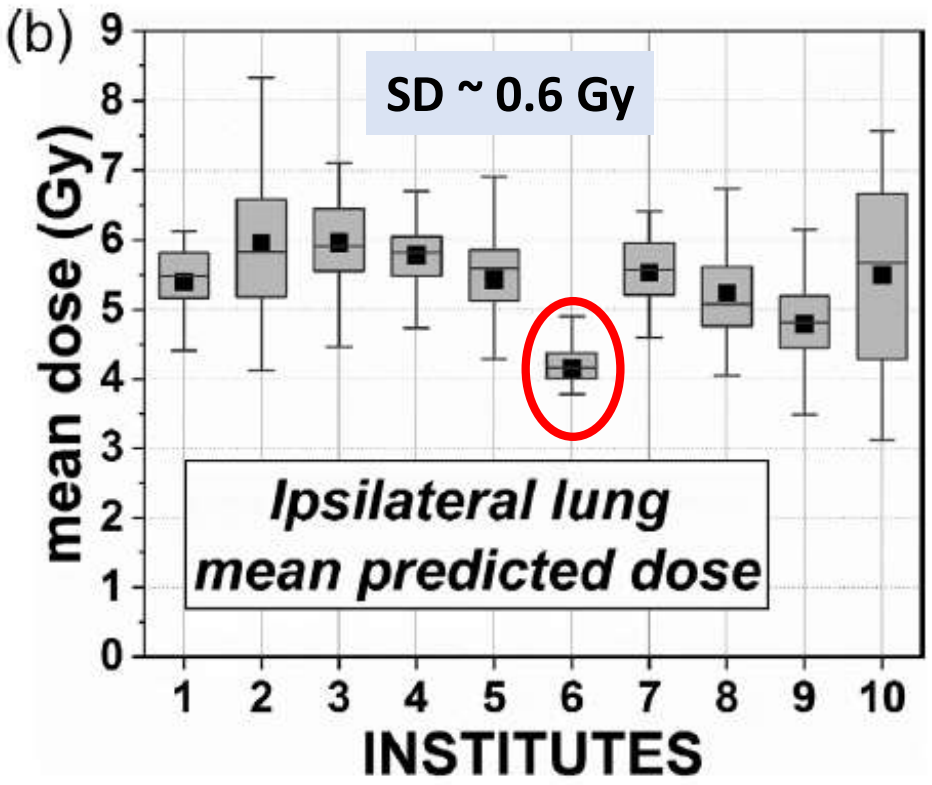
(?) Inter-changeability/esportability of KB models from an institute to another

(?) Pooling multi-insitution data to generate models incorporating «variability» ….benchmarking

BC Planning Optimization: Inter-Institute variability

Right Breast

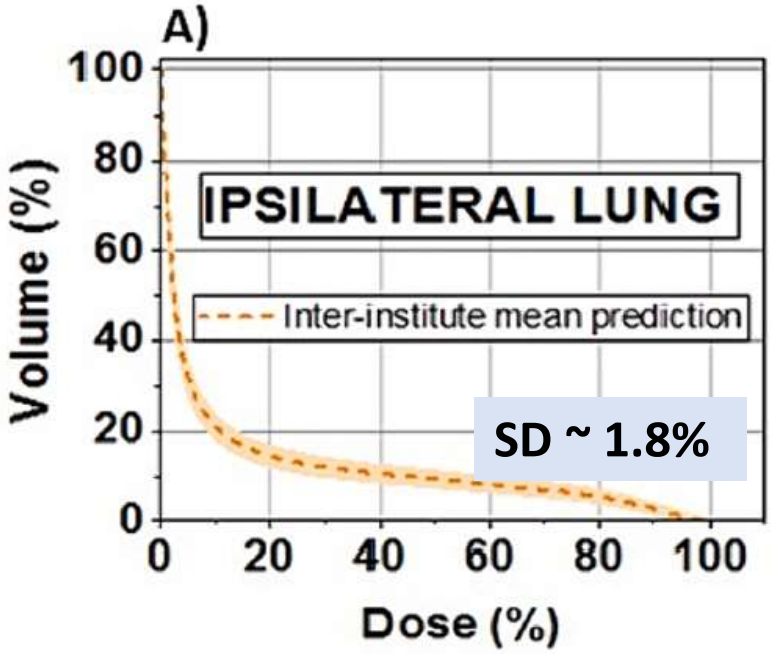


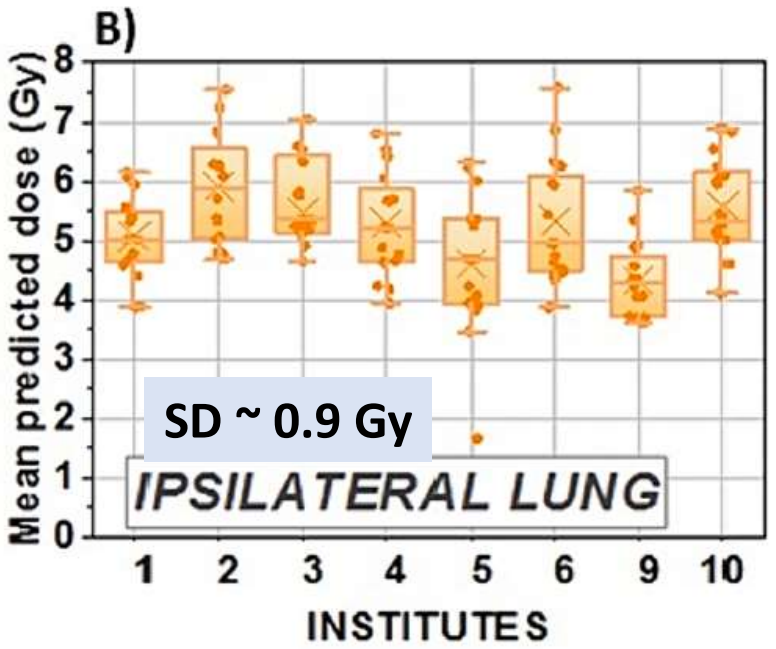


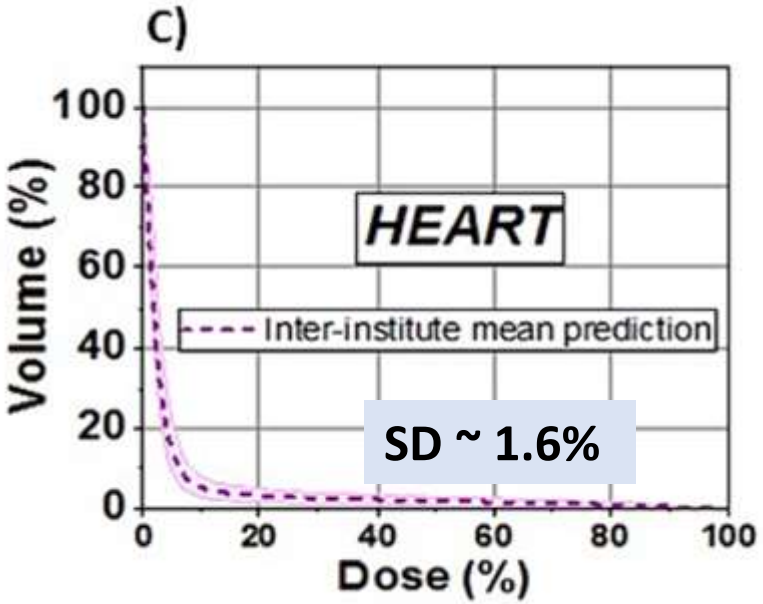
- Limited inter-institute variability of plan prediction
- The overall inter-institute variability for ipsilateral lung dose prediction was < 2%
- Inst 6 showed the lowest mean dose prediction value (no overlap between PTV and lung)

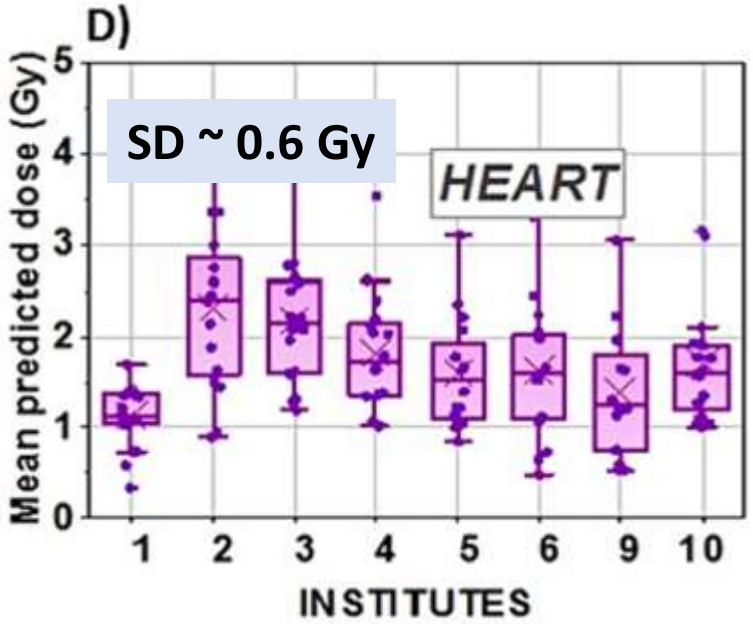
[Tudda et al, R&O 2022]

BC Planning Optimization: Inter-Institute variability









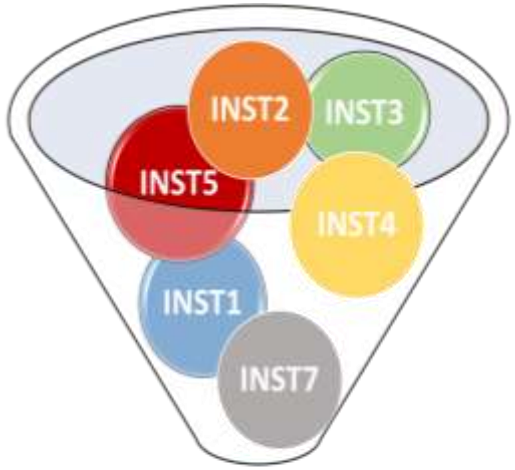
Left Breast

Low inter-institutional variability of 2% for plan prediction.

[Castriconi et al Phys Med 2024]

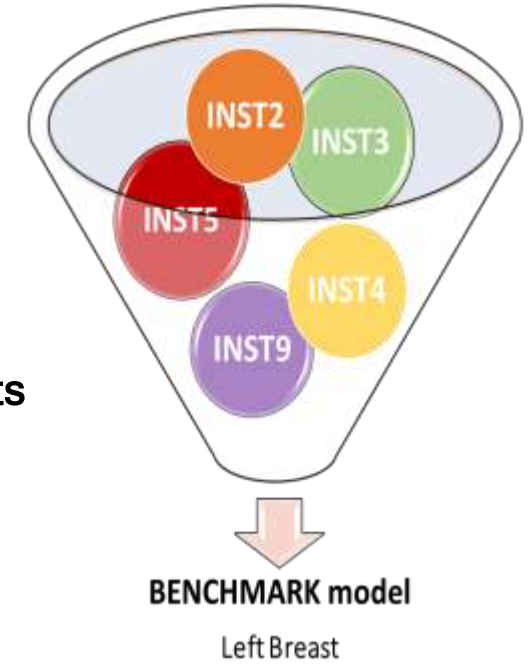
BC Planning Optimization: Building Benchmark models

- Pooling transferable models: asked the centers participating to the previous phase to join, on volountary basis in merging data in building big «bechmark» models
- Resulting models will be more generalizable and usable by the community
- 6 and 5 Institutes (with transferable models) joined the project
- Benchmark models were generated, tuned, validated and performances were compared against the single institute models in an independent set of patients



Right Breast

6 institutes, 456 pts

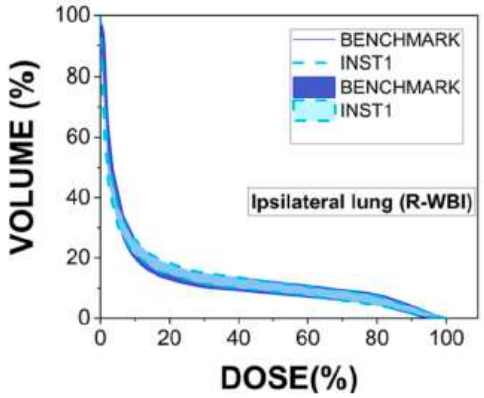


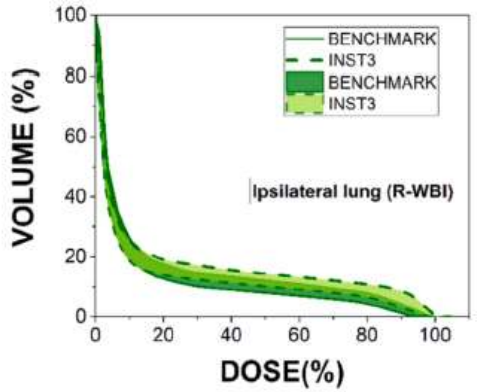
Left Breast

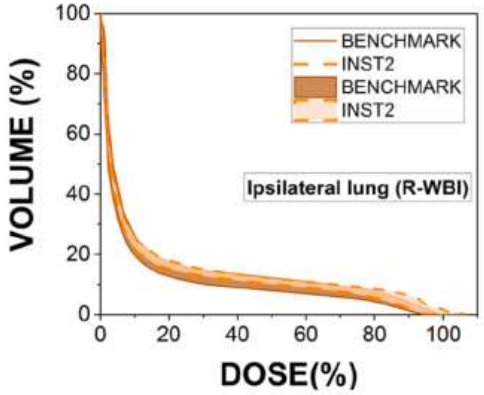
5 institutes, 393 pts

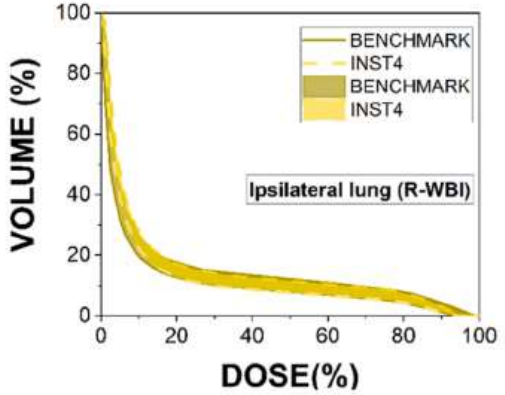
[Tudda et al , Physica Medica 2025]

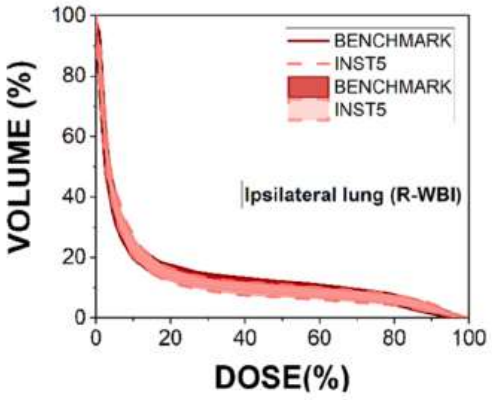
BC Planning : Benchmark Right Breast model

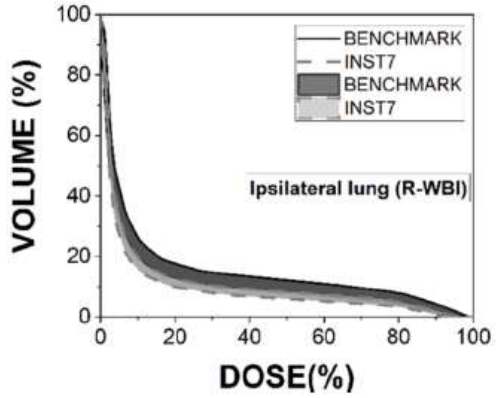




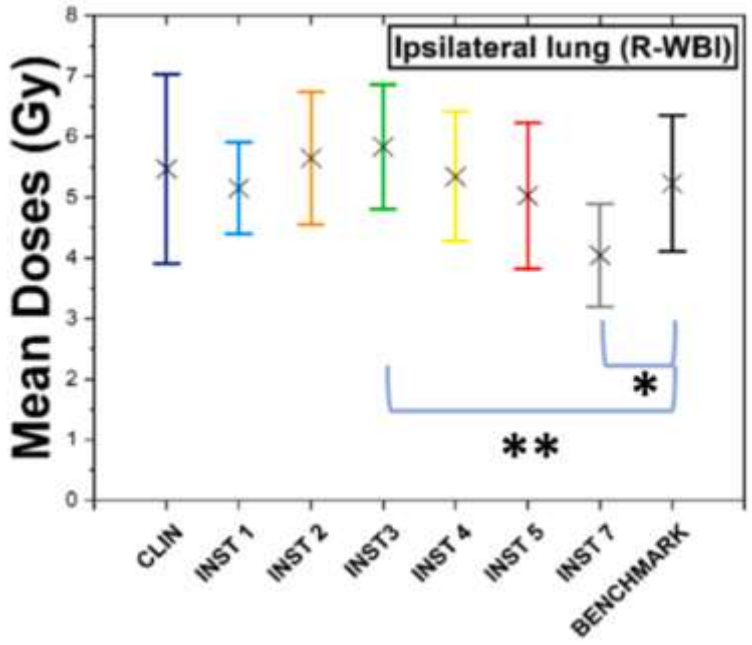






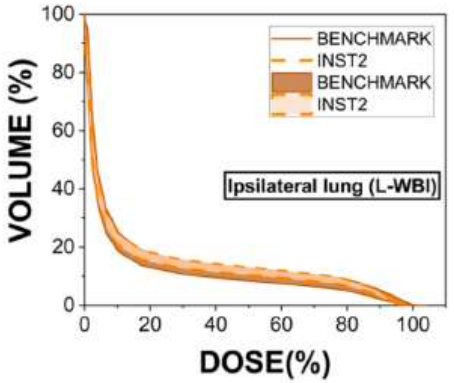


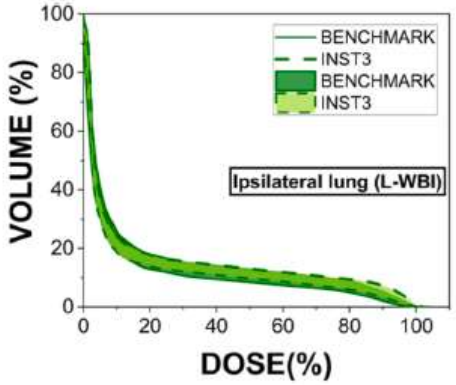
Right Breast
30 new Pts

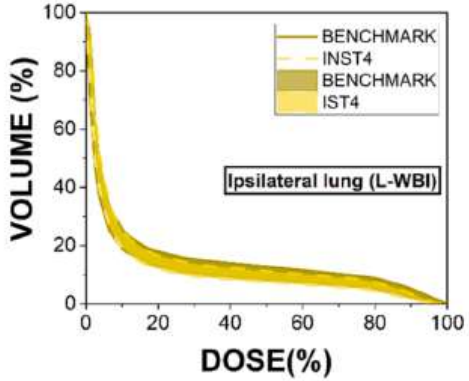


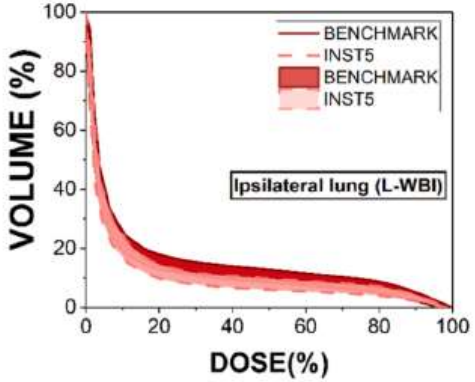
- ✓ Good overlap between prediction bands (Benchmark vs Single – Institute model)
- ✓ The KB-benchmark model predicts slightly lower lung Dmean when compared to KB-institution models, except for INST7

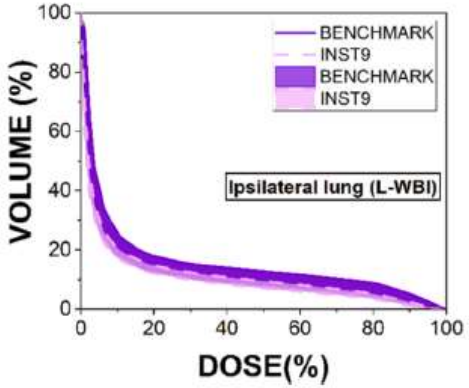
BC Planning : Benchmark Left Breast model

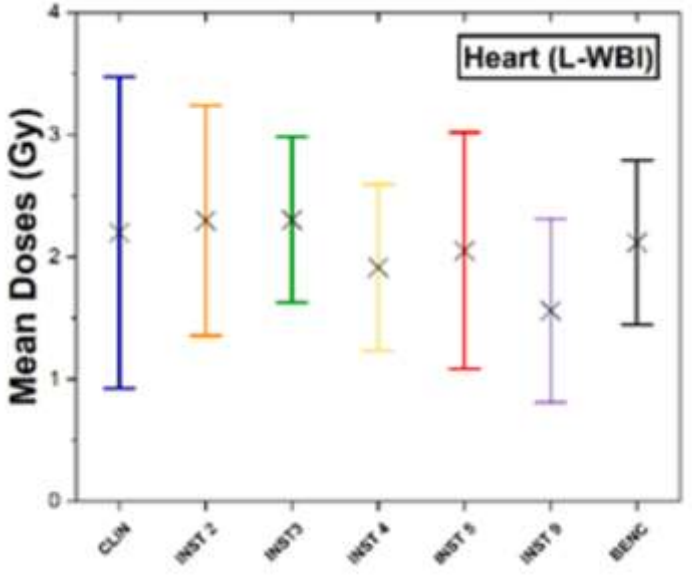


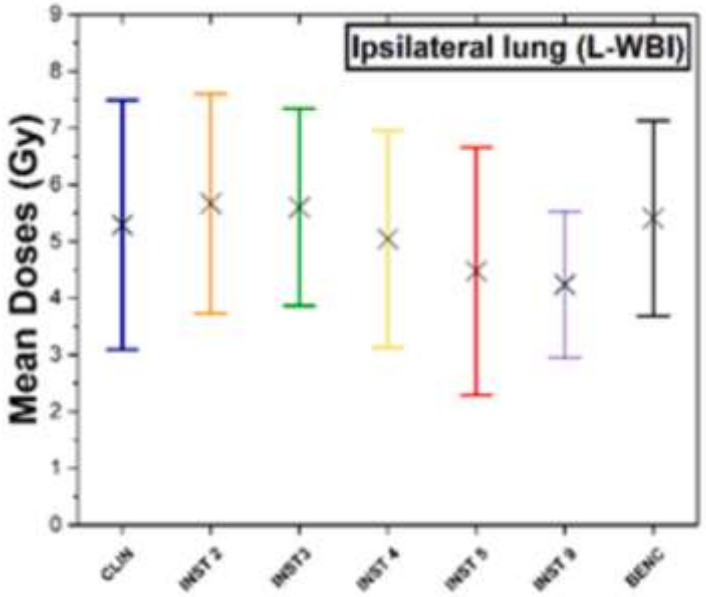












Left Breast
25 new Pts

- ✓ Excellent similarity between KB-benchmark and KB-institution model predictions

Ringraziamenti

- Dr.ssa Roberta Castriconi
- Dr.ssa Alessia Tudda
- Dr.ssa Mariagiulia Ubeira
- ..... tutte le donne del SFS e della RT di OSR