UNIVERSITÀ degli STUDI di CATANIA

DIPARTIMENTO FISICA E ASTRONOMIA "Ettore Majorana"

Radiotherapy-induced lung cancer risk for breast cancer

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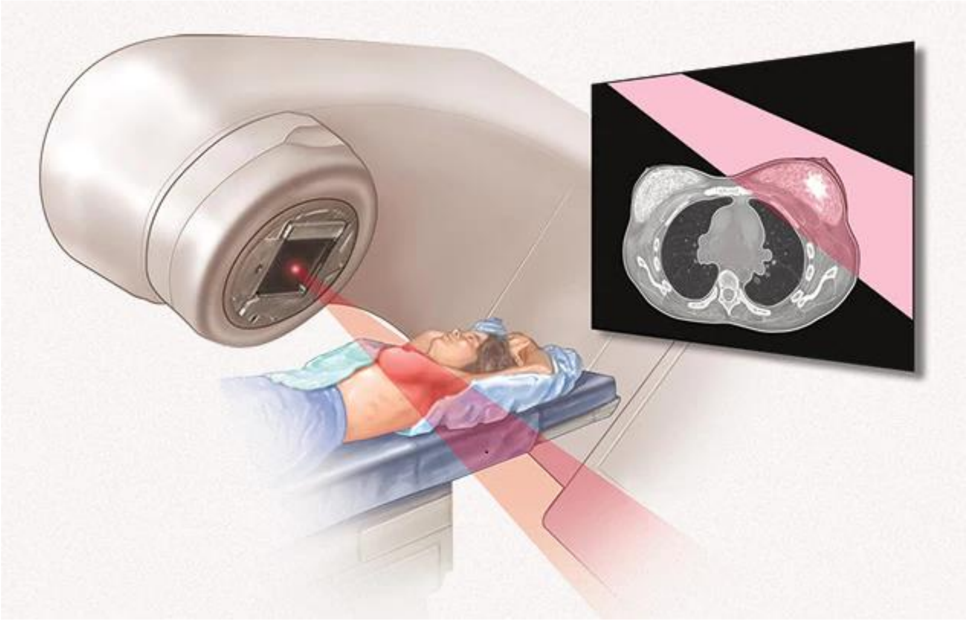
Outline:

- Breast Cancer Treatment
- The Schneider Model
- Results
- Simplified Models

Department of Medical Physics

Breast cancer treatment

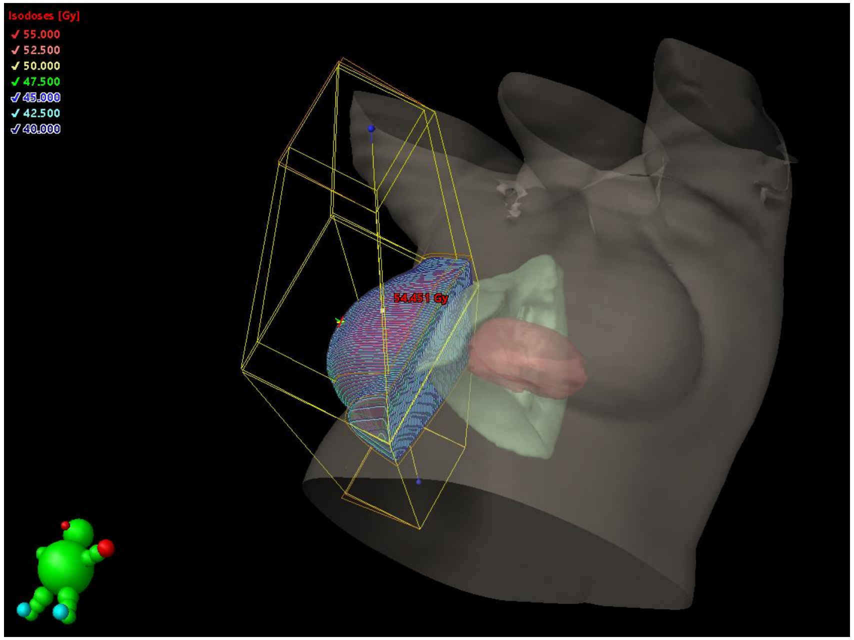


- Breast cancer is a common and prevalent neoplasm in women
- **29%** of female neoplasms
- about **50.000 diagnoses** per year (Italy)
- Conserving surgery followed by **external beam radiotherapy** is considered the "Gold Standard" for early stage of this malignant disease
- This adjuvant treatment may reduce the locoregional recurrence incidence about **20%** and breast cancer deaths about **5%** at 20 years

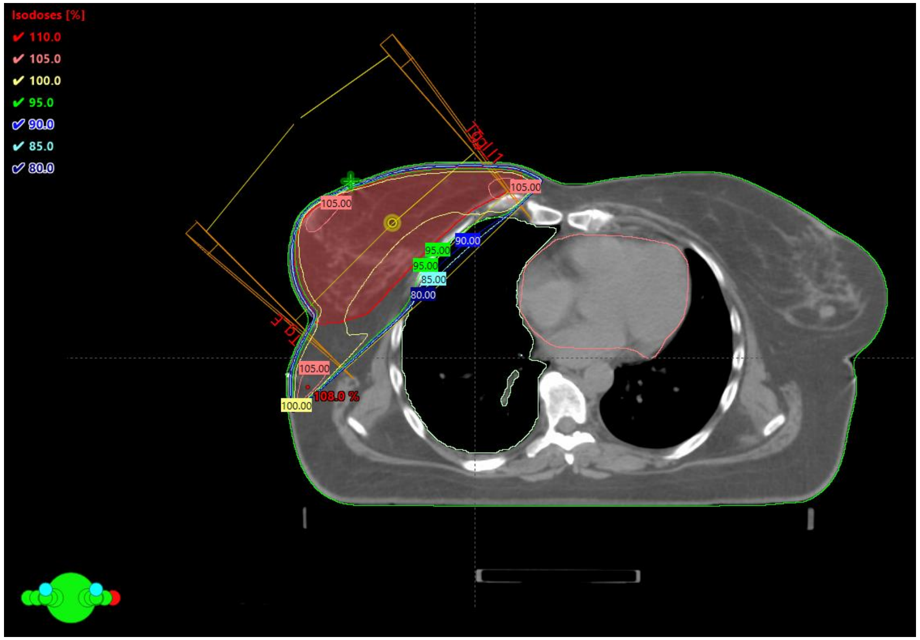
Tangential Beam 3D-CRT

3D Conformal Radiotherapy Treatment

2 tangential opposite beam (6 MV)



Transversal plane CT-scan



Organ At Risk (OAR) irradiation → Radiation-induced cancer risk

Tangential Beam 3D-CRT

Standard-Fractionated (SF) therapy ➔ **50 Gy (2 Gy x 25)**

Hypo-Fractionated (HF) therapy ➔ **42.56 Gy (2.66 Gy x 16)**

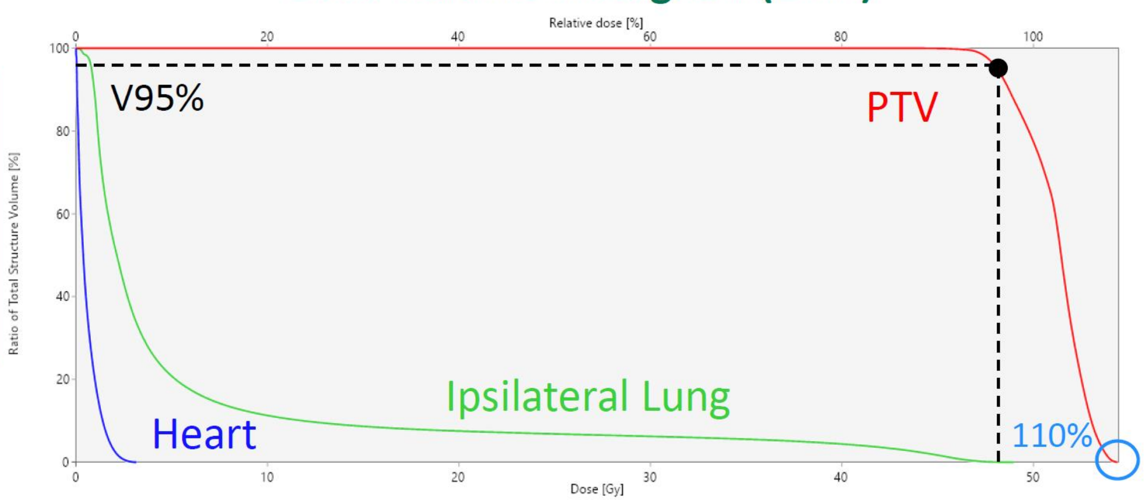
Organ At Risk (OAR) Constraints:

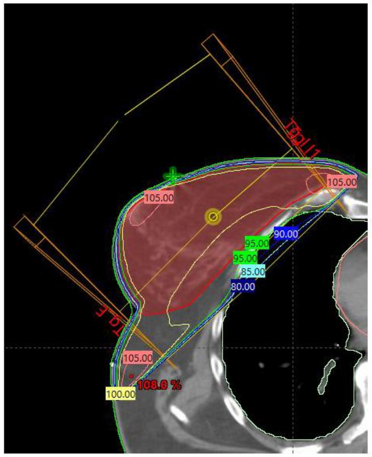
OAR	HF	SF
Ipsilateral Lung	$D_{mean} < 7$ Gy $V_4 < 40\text{-}50\%$ $V_8 < 30\text{-}35\%$ $V_{16} < 15\text{-}20\%$ $V_{20} < 10\%$	$D_{mean} < 8$ Gy $V_5 < 40\%$ $V_{20} < 15\%$
Controlateral Lung	$D_{mean} < 2$ Gy	$D_{mean} < 3$ Gy
Controlateral Breast	$D_{mean} < 3$ Gy	$D_{mean} < 4$ Gy
Heart	$D_{mean} < 3.2\text{-}4$ Gy	$D_{mean} < 5$ Gy
LAD	$D_{mean} < 15$ Gy	$D_{mean} < 17$ Gy

LAD: Left Anterior Descending coronary artery

Dose Volume Histogram (DVH)

Goals:
V95% and **110% max dose** within the Planning Treated Volume (PTV)





The Schneider Model

$$RED(D) = \frac{e^{-\alpha' D}}{\alpha' R}\left(1 - 2R + R^2 e^{\alpha' D} - (1-R)^2 e^{-\frac{\alpha' R}{1-R} D}\right)$$

Risk Equivalent Dose (RED): dose response relationship for radiation induced cancer in unit of dose

$$EAR(D, age_e, age_a) = \beta_0 RED(D) \mu(age_e, age_a)$$

Excess Absolute Risk (EAR)

Kill parameter

$$\alpha' = \alpha + \beta d_f$$

Repopulation parameter

$$0 < R < 1$$

Modifying Function μ (Life Span Study A-Bomb)

$$\mu(age_e, age_a) = e^{[\gamma_e (age_e - 30) + \gamma_a ln(\frac{age_a}{70})]}$$

Life Span Study A-Bomb

Site	β_{EAR}-Japan	β_{EAR}-UK	γ_e	γ_a
Breast	9.2(6.8;12)	8.2(6.1;11)	-0.037	1.7
Lung	7.5(5.1;10)	8.0(5.5;11)	0.002	4.23

Hodgkin's disease

$$\chi^2 = \left(EAR^{org} - \beta_{EAR}^{UK} \frac{1}{V_T} RED(D_i; \alpha, R)\right)^2$$

Hodgkin's disease

Site	$\alpha(Gy^{-1})$	α/β (Gy)	R
Breast	0.067	3	0.62
Lung	0.061	3	0.84

The Schneider Model

$$EAR(D, age_e, age_a) = \beta_0 RED(D)\mu(age_e, age_a)$$

↓

$$EAR^{org} = \frac{1}{V_T}\sum_i V(D_i)\beta_0 RED(D_i)\mu(age_e, age_a)$$

→

Organ Equivalent Dose (OED)

$$OED = \frac{1}{V_T}\sum_i V(D_i)RED(D_i)$$

↓

$$LAR = \sum_{age_e+L}^{75} EAR(OED, age_e, age_a)\frac{S(age_a)}{S(age_e)}$$

Lifetime Attributable Risk (LAR)

- **L** is **the free cancer risk time interval** of 5 years
- **$S(age_a)/S(age_e)$** is the probability of healthy female to survive from age *e* to age *a*

DVH → **OED** → **EAR** → **LAR**

OED and regional statistics

Lung differential Dose Volume Histogram (**DVH**)

$$OED = \frac{1}{V_T}\sum_i V(D_i)RED(D_i)$$

OED = 2 Gy

D = 2 Gy (uniformly distributed)

Same radiation-induced cancer risk

$$LAR = \sum_{age_e+L}^{75} EAR(OED, age_e, age_a)\frac{S(age_a)}{S(age_e)}$$

ISTAT (Sicilian women)

$$\frac{S(age_a)}{S(age_e)}$$

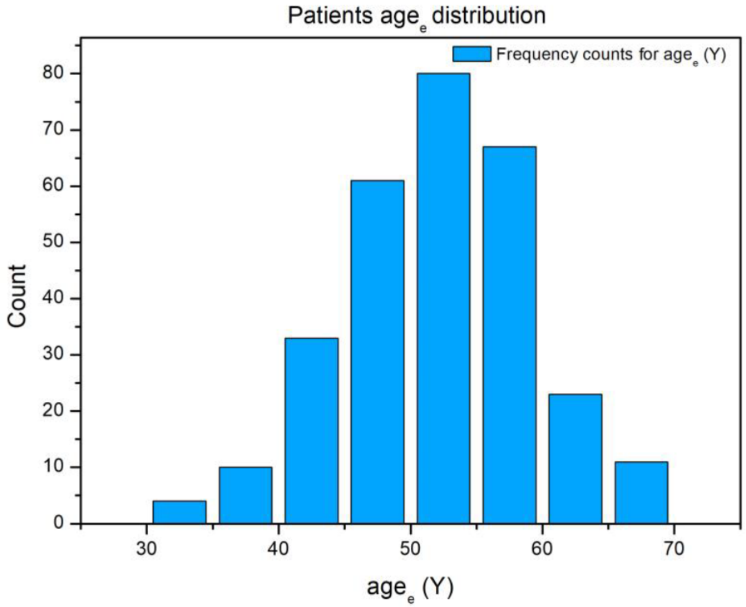
L = 5 years

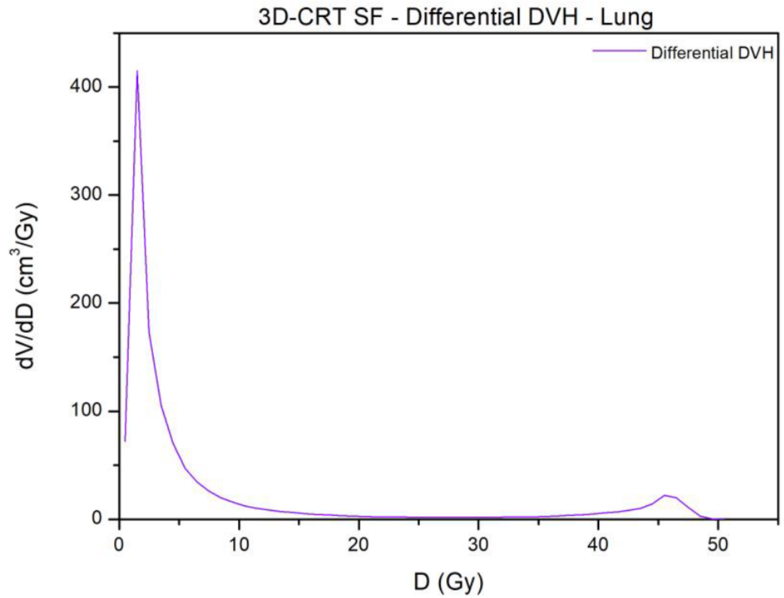
Humanitas-ICC:

age_e (Y)	$P_{5\ year}$ (%)
≤ 65	98.60%
> 65	96.34%

Statistical Sample

HUMANITAS
ISTITUTO CLINICO CATANESE





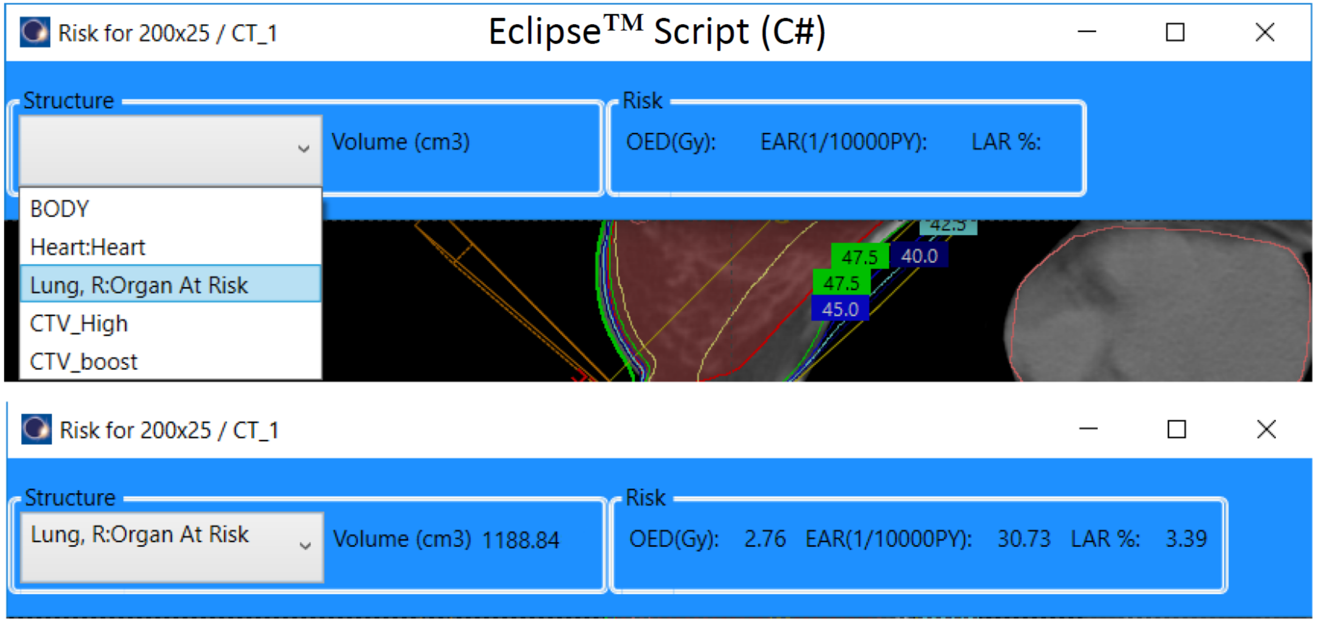
Treatment type	Number of treated women	age_e (σ_{age_e}) (Y)
3D-CRT (tot)	288	55 (7)
3D-CRT (SF and HF)	58	55 (10)

288 + 58 DVHs

Standard-Fractionated (SF) therapy → **50 Gy (2 Gy x 25)**

Hypo-Fractionated (HF) therapy → **42.56 Gy (2.66 Gy x 16)**

Results



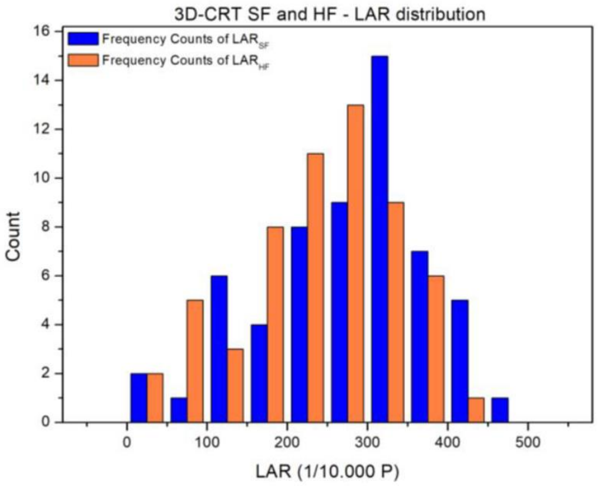
288 SF 3D-CRT treatments

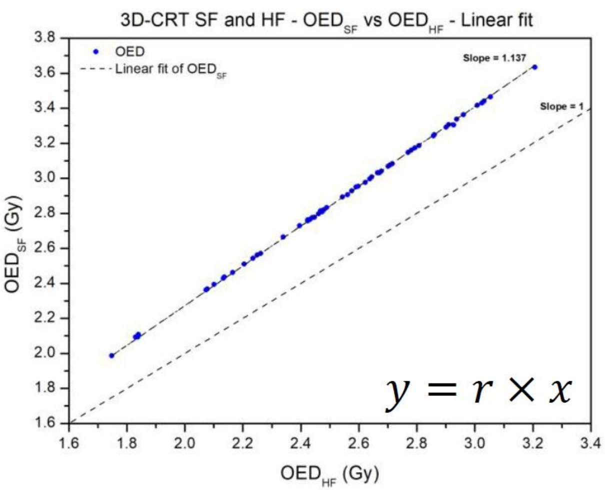
age_a (Y)	OED (σ_{OED}) (Gy)	EAR (σ_{EAR}) (1/10.000 PY)	LAR (σ_{LAR}) (1/10.000 P)
75	2.8 (0.4)	31 (5)	306 (77)

Literature data

Article	EAR (10.000 PY)	LAR (10.000 P)	age_a (Y)
Mazonakis et al.[1] SF	/	359-494	75
Mazonakis et al.[1] HF	/	316-437	75
Paganetti et al. [38]	46	275-654	70
Suzuki et al.[37]	/	275-379	75

SF and HF comparison



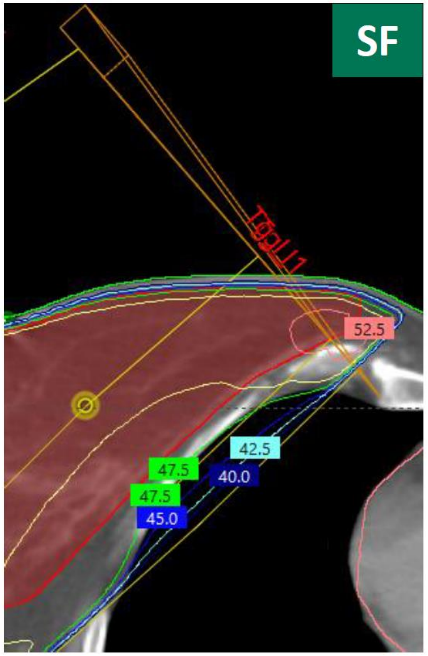


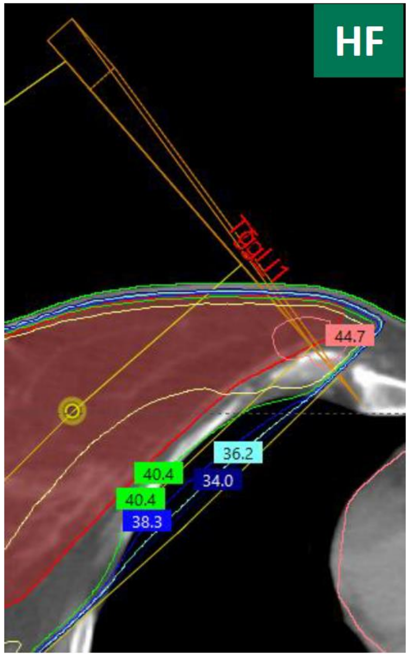
$r \pm \epsilon_d$	1.137 ± 0.001
R^2	0.99

Treatment type	OED (σ_{OED}) (Gy)	EAR (σ_{EAR}) (1/10.000 PY)	LAR (σ_{LAR}) (1/10.000 P)
3D-CRT SF	2.9 (0.4)	32 (4)	274 (104)
3D-CRT HF	2.5 (0.3)	28 (4)	241 (92)

Student's t-test between LAR_{SF} and LAR_{HF}:
P = 0.037

Null hypothesis rejected (95% C.L.)



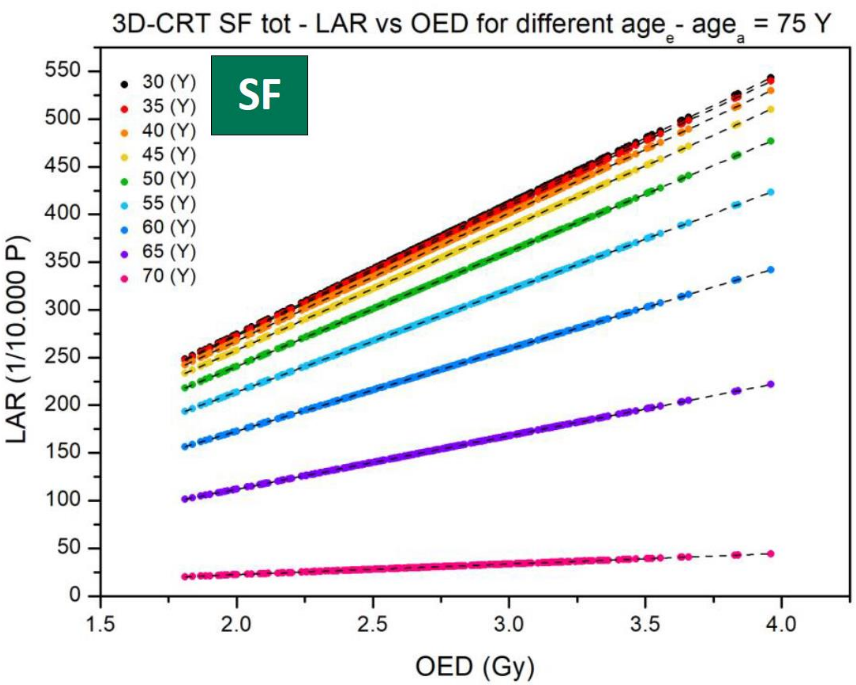


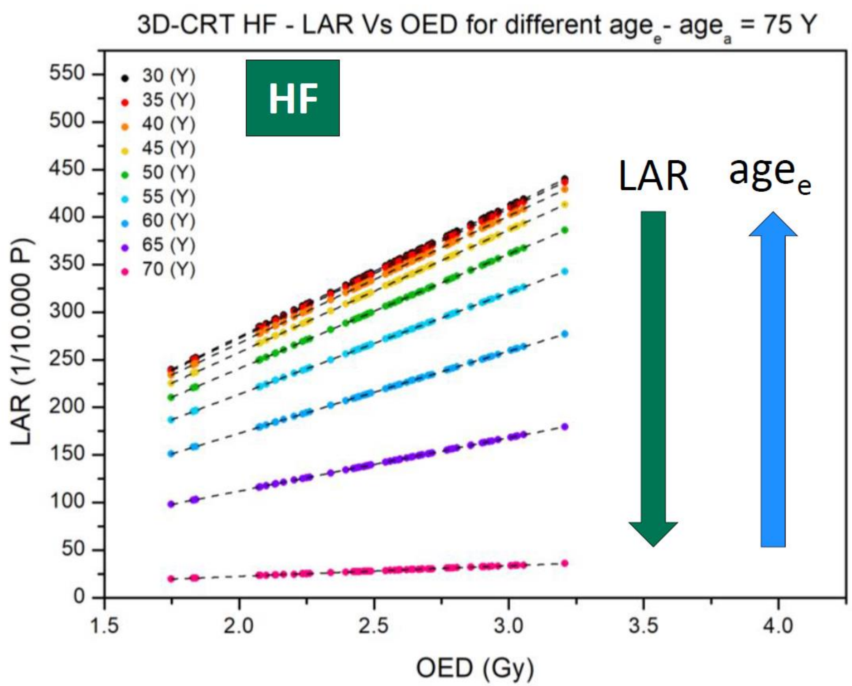
Age dependence

$$LAR = \sum_{age_e+L}^{75} EAR(OED, age_e, age_a)\frac{S(age_a)}{S(age_e)}$$

$$LAR_{(age_e)_i}^{(age_a)_{75}} = a_i \times OED$$

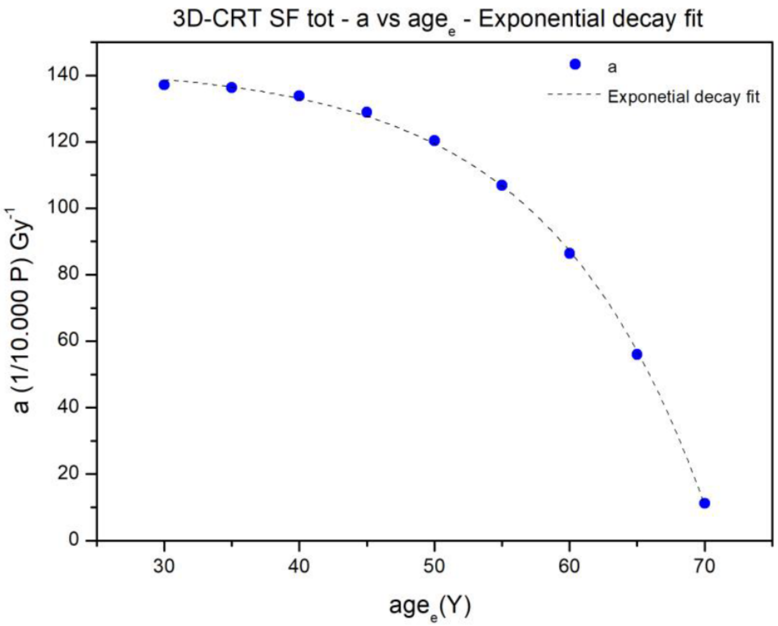
From ***i* = 30** to ***i* = 70** years in 5-year steps





Fractionation-type indipendence

The OED Simplified Model (OSM)



$A \pm \epsilon_A$ (1/10.000 P) Gy^{-1}	-0.312 ± 0.049
$B \pm \epsilon_B$ (Y)	-11.568 ± 0.293
$C \pm \epsilon_C$ (1/10.000 P) Gy^{-1}	142.928 ± 0.994
R^2	0.99

$$LAR_{(age_e)_i}^{(age_a)_{75}} = a_i \times OED$$

$$a(age_e) = A \times e^{-\frac{age_e}{B}} + C$$

OSM equation:

$$LAR = (A \times e^{-\frac{age_e}{B}} + C) \times OED$$

MSE minimization

OSM parameters:

A_{OSM} (1/10.000 P) Gy^{-1}	-0.340
B_{OSM} (Y)	-11.688
C_{OSM} (1/10.000 P) Gy^{-1}	144.557

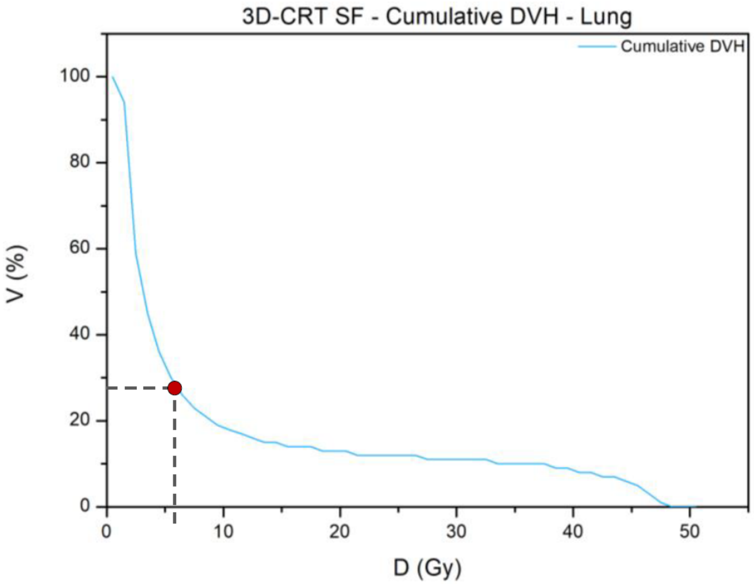
$LAR_{Schneider}$ and **LAR_{OSM}** belong to the same population with **98% C.L. (P < 0.02)**

MSE decreases by 67%
Standard deviation decreases by 46%

The Vd Simplified Model (VSM)

OED vs V_d

Evaluation performed from **d = 1** to **d = 10 Gy**

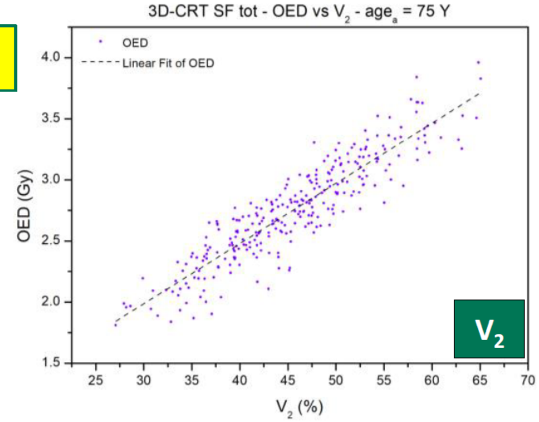


$$OED = M + N \times V_d$$

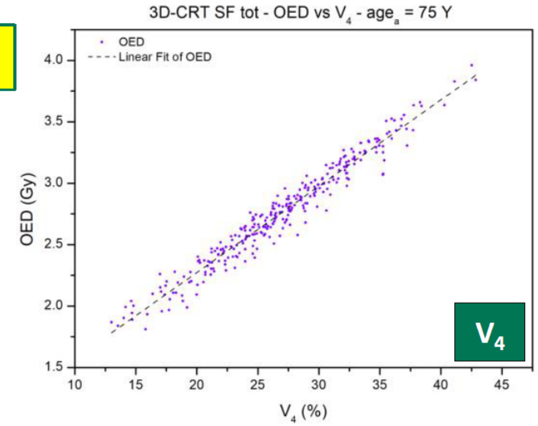
V_4 parameters:

$M \pm \epsilon_M$ (1/10.000 P) Gy^{-1}	0.866 ± 0.025
$N \pm \epsilon_N$ (Y)	0.070 ± 0.001
R^2	0.95

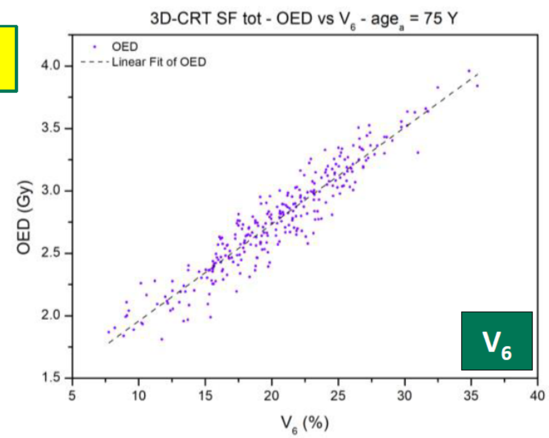
$R^2=0.83$



$R^2=0.95$



$R^2=0.89$



The V_d Simplified Model (VSM)

$$LAR^{(age_a)_{75}}_{(age_e)_i} = a_i \times OED$$

$$a(age_e) = A \times e^{-\frac{age_e}{B}} + C$$

OSM equation:

$$LAR = (A \times e^{-\frac{age_e}{B}} + C) \times OED$$

$$OED = M + N \times V_d$$

VSM equation:

$$LAR = (A \times e^{-\frac{age_e}{B}} + C) \times (M + N \times V_d)$$

A $\pm \epsilon_A$ (1/10.000 P) Gy^{-1}	-0.312 $\pm$ 0.049
B $\pm \epsilon_B$ (Y)	-11.568 $\pm$ 0.293
C $\pm \epsilon_C$ (1/10.000 P) Gy^{-1}	142.928 $\pm$ 0.994
R^2	0.99

M $\pm \epsilon_M$ (1/10.000 P) Gy^{-1}	0.866 $\pm$ 0.025
N $\pm \epsilon_N$ (Y)	0.070 $\pm$ 0.001
R^2	0.95

MSE minimization

VSM parameters (3D-CRT, V_4):

A_{VSM} (1/10.000 P) Gy^{-1}	-0.300
B_{VSM} (Y)	-11.387
C_{VSM} (1/10.000 P) Gy^{-1}	147.601
M_{VSM} (1/10.000 P) Gy^{-1}	0.830
N_{VSM} (Y)	0.069

MSE decreases by 10%
Standard deviation decreases by 6%

$LAR_{Schneider}$ and **LAR_{VSM}** belong to the same population with **98% C.L. (P < 0.02)**

Baseline increment

The **LIR** is the organ- gender- and age-dependent **Lifetime Intrinsic Risk** for developing a malignancy (e.g., lung cancer)

Integrated Cancer Registry (AOU Policlinico "G. Rodolico - San Marco")

age class (Y)	Incidence (1/100.000 PY)*
30-34	7
35-39	17
40-44	33
45-49	84
50-54	148
55-59	169
60-64	210
65-69	201
70-74	235

age_e-age_a (Y)	LIR (%) *
30-74	5.37
35-74	5.34
40-74	5.26
45-74	5.10
50-74	4.70
55-74	3.99
60-74	3.18
65-74	2.16
70-74	1.17

The patient specific **Relative-Risk (RR)** = Baseline increment

$$RR = \frac{LAR + LIR}{LIR}$$

*For Sicilian women resident in Catania

V_d Constraints

VSM equation:

$$LAR = (A \times e^{-\frac{age_e}{B}} + C) \times (M + N \times V_d)$$

$$V_d = \frac{LAR}{(A \times e^{-\frac{age_e}{B}} + C) \times N} - \frac{M}{N}$$

Organ At Risk (OAR) Constraints:

OAR	HF	SF
Ipsilateral Lung	$D_{mean} < 7$ Gy $V_4 < 40$-50% $V_8 < 30$-35% $V_{16} < 15$-20% $V_{20} < 10\%$	$D_{mean} < 8$ Gy $V_5 < 40\%$ $V_{20} < 15\%$
Controlateral Lung	$D_{mean} < 2$ Gy	$D_{mean} < 3$ Gy
Controlateral Breast	$D_{mean} < 3$ Gy	$D_{mean} < 4$ Gy
Heart	$D_{mean} < 3.2$-4 Gy	$D_{mean} < 5$ Gy
LAD	$D_{mean} < 15$ Gy	$D_{mean} < 17$ Gy

Lung cancer risk constraints*

Goals:
V95% and **110% max dose** within the Planning Treated Volume (PTV)

RR	V_{4-30}	V_{4-35}	V_{4-40}	V_{4-45}	V_{4-50}	V_{4-55}	V_{4-60}	V_{4-65}
2.0	42	43	43	44	43	41	40	43
1.9	37	37	38	38	38	35	34	37
1.8	31	32	32	33	32	30	29	32
1.7	26	26	27	27	27	25	24	26
1.6	21	21	21	22	21	20	19	21
1.5	15	15	16	16	16	14	14	15

$$RR = \frac{LAR + LIR}{LIR}$$

*For Sicilian women resident in Catania

Prospects

- Risk estimation could be extended to other breast radiation treatment techniques, i.e , Intensity Modulated Radiation Therapy (**IMRT**) and Volumetric Modulated Arc Therapy (**VMAT**)
- Contralateral Breast
- Deep Inspiration Breath Hold (**DIBH**)
- Stereotactic Body Radiation Therapy (**SBRT**)
- Stereotactic RadioSurgery (**SRS**)
- Clinical Audit

THANKS FOR YOUR ATTENTION