Volumetric Modulated Arc Therapy (VMAT) versus Intensity Modulated Proton Therapy (IMPT) for left sided breast cancer: Dosimetric and Normal Tissue Complication Probability (NTCP) evaluation of a hypofractionated regimen (HypoRT)

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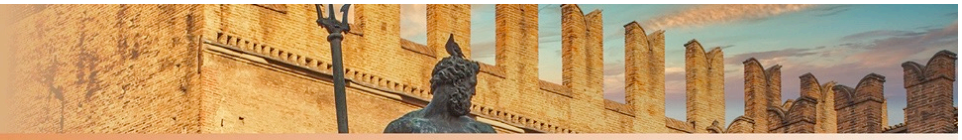

DICHIARAZIONE

Relatore: Carlotta Giandini

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
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SUMMARY

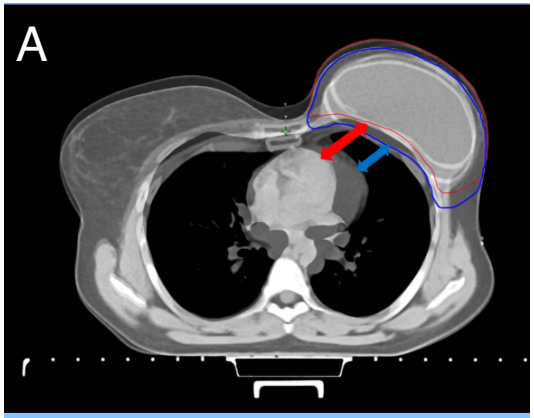
- **INTRODUCTION**
- **AIMS**
- **MATERIALS AND METHODS**
- **RESULTS**
- **DISCUSSION**
- **CONCLUSIONS**

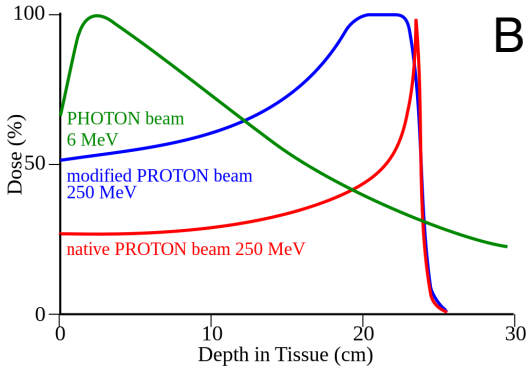
INTRODUCTION

- Thoracic acute OARs toxicities and risk of secondary cancer for breast cancer (BC) radiotherapy (RT)
- OARs sparing is still a concern, especially for left-sided BC (LSBC)

POSSIBLE SOLUTIONS?

1. Dose optimisation by reducing physiological organ motion → Deep Inspiration Breath Hold (DIBH): patient inspiring to a specified pre-acquired threshold and then holding that level of inspiration while radiation is delivered → Favorable anatomical condition in the chest area, by increasing the space between the target volume and the heart (A)
2. Dose optimisation with Proton Therapy (PT) → Bragg peak (B) → Ballistic target accuracy → OARs sparing





AIMS

- To compare clinically significant OARs dose metrics and target dose distribution between Volumetric Modulated Arc Therapy (VMAT) and Intensity Modulated Proton Therapy (IMPT) rival plans in the setting of left-sided breast cancer (LSBC) patients employing DIBH with a hypofractionated regimen.
- To evaluate median differences between VMAT and IMPT treatments in terms of Normal Tissue Complication Probability (NTCP) for selected clinical endpoints

MATERIALS AND METHODS

- Population: 22 LSBC patients (any TNM stage, any systemic therapy, any surgery)
- Timing: Aprile 2022 – Luglio 2022
- SimCT: 3 mm scan, 2 scans per patient both in free breathing and DIBH
- Rival planning on DIBH scan: Volumetric Modulated Arc Therapy (VMAT) versus Intensity Modulated Proton Therapy (IMPT) with a costant Relative Biological Effectiveness (RBE) of 1.1.
- Prescribed dose: 40.05-42.4 Gy in 15-16 fxs with a tumor bed boost when needed

➢ Dosimetric Evaluation: D99%, D98%, D95%, D50%, D2% , D1%, Dmax, Dmean, Dmin extracted from DVH

➢ NTCP evaluation: 10 models with clinically relevant acute and late toxicities

➢ Statistical analysis: Paired, 2-tailed Wilcoxon signed rank test to compare dosimetry and NTCP of rival plans → Δ**NTCP PH-PT**, defined as the NTCP for photons minus NTCP for protons for every selected clinical endpoint

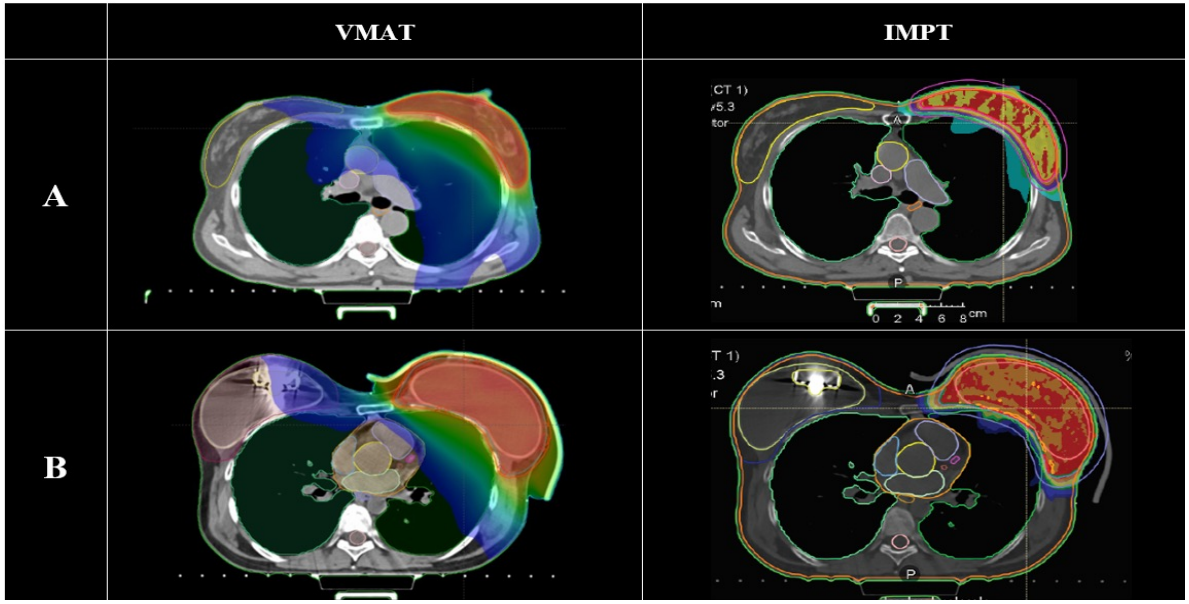
PARAMETERS	Patients (n)
CTV - T	
Breast	13
Chest wall with prosthesis	3
Chest wall with expander	5
Chest wall only	1
CTV- N	
CLN	8
IMN	1
No	13
RT SCHEDULE	
42.4 Gy_{RBE} /16 fx	8
40.05 Gy_{RBE} /15 fx	14
TUMOR BED BOOST	
SIB (48 Gy_{RBE} /15 fx)	5
SEQ (16 Gy_{RBE} /8 fx)	2
No	15

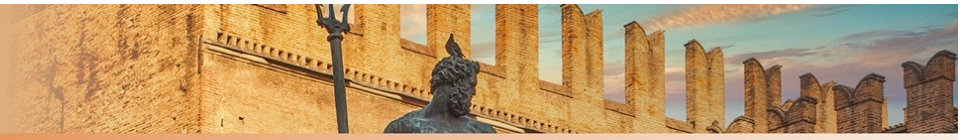
Abbreviations = n: number of patients; CTV-T: primary Clinical Target Volume; CTV – N: nodal Clinical Target Volume; CLN: Sovra and Infraclavicular Lymph nodes; IMN: Internal Mammary Chain Modes; SIB: Simultaneous Integrated Boost; SEQ: Sequential Boost; fx: fractions

RESULTS

- Primary CTV consisted of the breast gland in 13 patients (59%) and the chest wall, with or without reconstruction, in 9 patients (41%)
- V95% was always equal or higher than 95% of the target volume for every CTV

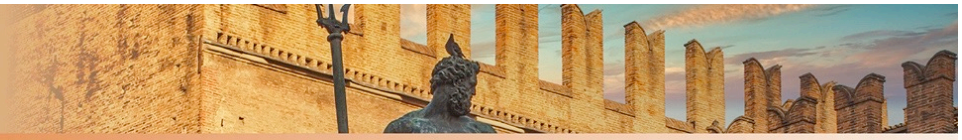
Figure 1. Example of dose distribution in VMAT versus IMPT plans for intact breast (A) versus reconstructed chest wall (B) irradiation





OAR	VMAT – PH median (range)	IMPT – PT median (range)	Pvalue
HEART			
D2 % (GyRBE)	10,11 (5,83 - 12,68)	0,84 (0,04 - 10,99)	<0,0001
D98 % (GyRBE)	1,26 (0,22-2,01)	0,00 (0,00 - 0,00)	<0,0001
Dmax (GyRBE)	22,32 (11,26 - 31,00)	13,89 (6,71 - 33,67)	<0,0001
Dmean (GyRBE)	3,43 (1,99 - 4,58)	0,07 (0,01 - 1,00)	<0,0001
Dmin (GyRBE)	0,87 (0,16 - 1,66)	0,00 (0,00 - 0,06)	<0,0001
LUNG LEFT			
D2 % (GyRBE)	31,00 (27,05 - 35,37)	20,39 (12,95 - 30,05)	<0,0001
D98 % (GyRBE)	0,78 (0,26 - 2,50)	0,00 (0,00 - 0,01)	<0,0001
Dmax (GyRBE)	40,47 (37,59 - 51,32)	39,98 (32,85 - 45,78)	0.0119
Dmean (GyRBE)	8,68 (5,15 - 11,87)	2,20 (0,92 - 9,10)	<0,0001
Dmin (GyRBE)	0,44 (0,11 - 1,27)	0,00 (0,00 - 0,90)	0.0005
V20 GyRBE (%)	9,35 (4,90 - 16,50)	2,24 (0,48 - 15,72)	<0,0001
LUNG RIGHT			
D2 % (GyRBE)	8,74 (5,33 - 15,02)	0,03 (0,00 - 5,52)	<0,0001
D98 % (GyRBE)	0,47 (0,12 - 1,20)	0,00 (0,00 - 0,00)	<0,0001
Dmax (GyRBE)	17,46 (9,18 - 39,04)	2,13 (0,01 - 41,17)	<0,0001
Dmean (GyRBE)	2,82 (1,78 - 4,72)	0,01 (0,00 - 0,45)	<0,0001
Dmin (GyRBE)	0,18 (0,06 - 0,52)	0,00 (0,00 - 0,01)	<0,0001
OESOPHAGUS - NO NRT			
D2 % (GyRBE)	5,72 (3,76 - 11,71)	0,00 (0,00 - 0,28)	0.0002
D98 % (GyRBE)	0,34 (0,22 - 1,39)	0,00 (0,00 - 0,00)	0.0002
Dmax (GyRBE)	6,51 (4,39 - 15,10)	0,04 (0,00 - 0,98)	0.0002
Dmean (GyRBE)	2,32 (1,61 - 4,40)	0,00 (0,00 - 0,02)	0.0002
Dmin (GyRBE)	0,25 (0,18 - 1,30)	0,00 (0,00 - 0,00)	0.0002
OESOPHAGUS - NRT			
D2 % (GyRBE)	38,51 (14,47 - 39,64)	31,01 (0,21 - 39,20)	0.0039
D98 % (GyRBE)	1,16 (0,16 - 1,96)	0,00 (0,00 - 0,00)	0.0039
Dmax (GyRBE)	40,63 (16,09 - 41,19)	39,76 (0,60 - 40,85)	0.0195
Dmean (GyRBE)	8,85 (4,85 - 13,29)	4,00 (0,02 - 8,56)	0.0039
Dmin (GyRBE)	1,07 (0,14 - 1,78)	0,00 (0,00 - 0,00)	0.0039
V35 GyRBE (%)	4,90 (0,00 - 12,30)	0,64 (0,00 - 8,45)	0.0078

CONTRALATERAL BREAST			
D2 % (GyRBE)	7,04 (3,49 - 11,33)	0,40 (0,02 - 2,25)	<0,0001
D98 % (GyRBE)	0,92 (0,48 - 1,41)	0,00 (0,00 - 0,00)	<0,0001
Dmax (GyRBE)	12,18 (6,32 - 27,71)	2,24 (0,18 - 11,84)	<0,0001
Dmean (GyRBE)	2,55 (1,36 - 2,89)	0,04 (0,00 - 0,18)	<0,0001
Dmin (GyRBE)	0,61 (0,36 - 0,99)	0,00 (0,00 - 0,01)	<0,0001
THYROID			
D2 % (GyRBE)	40,86 (40,57 - 41,36)	39,67 (29,26 - 40,34)	0.0078
D98 % (GyRBE)	9,00 (5,36 - 12,22)	0,31 (0,16 - 0,58)	0.0078
Dmax (GyRBE)	41,75 (40,99 - 42,82)	40,79 (40,29 - 41,18)	0.0078
Dmean (GyRBE)	24,30 (21,01 - 26,30)	17,32 (16,31 - 18,40)	0.0078
Dmin (GyRBE)	7,51 (3,50 - 9,12)	0,24 (0,12 - 1,31)	0.0078
V20 GyRBE (cm3)	5,03 (2,59 - 12,12)	4,43 (2,75 - 10,37)	0.0781
LADCA			
D2 % (GyRBE)	11,04 (5,39 - 16,56)	3,30 (0,14 - 15,16)	0.0001
D98 % (GyRBE)	3,32 (0,72 - 6,12)	0,00 (0,00 - 0,05)	<0,0001
Dmax (GyRBE)	13,52 (5,95 - 19,00)	6,32 (0,37 - 19,26)	0.0001
Dmean (GyRBE)	6,57 (3,94 - 11,20)	0,67 (0,02 - 6,17)	<0,0001
Dmin (GyRBE)	2,93 (0,61 - 5,66)	0,00 (0,00 - 0,03)	<0,0001
VENTRICLE LEFT			
D2 % (GyRBE)	6,10 (4,10 - 11,15)	0,34 (0,02 - 11,24)	<0,0001
D98 % (GyRBE)	1,67 (0,26 - 2,58)	0,00 (0,00 - 0,00)	<0,0001
Dmax (GyRBE)	13,51 (6,38 - 23,55)	8,08 (0,32 - 29,70)	0.0005
Dmean (GyRBE)	2,95 (1,13 - 4,78)	0,04 (0,00 - 1,04)	<0,0001
Dmin (GyRBE)	1,34 (0,19 - 2,16)	0,00 (0,00 - 0,01)	<0,0001
V5 GyRBE (%)	4,33 (0,60 - 38,60)	0,07 (0,00 - 6,73)	<0,0001
V23 GyRBE (%)	0,00 (0,00 -0,00)	0,00 (0,00 - 0,11)	>0,05



CLINICAL ENDPOINT	PTS (N)	VMAT - PH MEDIAN % (RANGE)	IMPT - PT MEDIAN % (RANGE)	ΔNTCP PH – PT (%)	PVALUE
ACUTE TOXICITIES					
RADIATION DERMATITIS	22	11,25 (7,36-52,06)	43,27 (37,49-86,45)	33.3	<0,0001
RADIATION PNEUMONITIS	22	4,97 (3,38-7,04)	2,51 (2,22-5,30)	-2.26	<0,0001
ACUTE ESOPHAGITIS	9	4,07 (3,32-5,65)	3,41 (3,32-4,75)	-0,37	0,0078
LATE TOXICITIES					
LUNG FIBROSIS	22	3,30 (2,27-5,07)	1,63 (1,26-4,04)	-1,80	<0,0001
BREAST FIBROSIS	13	24,19 (13,46-28,50)	20,59 (12,74-26,49)	-1,97	0,0024
NO BOOST	6	13,95 (13,46 - 14,34)	12,81 (12,74 - 12,81)	-1,16	0,0313
BOOST	7	24,99 (24,19 - 28,50)	22,29 (20,59 - 26,49)	-2,82	0,0313
HYPOTYROIDISM	8	37,07 (12,96-46,78)	39,47 (17,71-46,12)	2,32	0,0781
EAR OF ACE AT AGE 80					
NO CARDIAC RISK FACTOR					
AGE 40-49	22	0,70 (0,30-1,00)	0,20 (0,2-0,3)	-0,65	<0,0001
AGE 50-59		0,60 (0,30-0,90)	0,10 (0,10-0,30)	-0,60	<0,0001
AGE 60-69		0,50 (0,30-0,80)	0,10 (0,10-0,30)	-0,50	<0,0001
AGE 70-79		0,30 (0,10-0,40)	0,10 (0,10-0,10)	-0,25	<0,0001
≥1 CARDIAC RISK FACTOR					
AGE 40-49	22	1,10 (0,60-1,70)	0,30 (0,30-0,60)	-1,10	<0,0001
AGE 50-59		1,10 (0,50-1,70)	0,30 (0,30-0,50)	-1,10	<0,0001
AGE 60-69		1,00 (0,50-1,40)	0,20 (0,20-0,50)	-0,90	<0,0001
AGE 70-79		0,80 (0,40-1,20)	0,20 (0,20-0,40)	-0,80	<0,0001

CLINICAL ENDPOINT	PTS (N)	VMAT - PH MEDIAN % (RANGE)	IMPT - PT MEDIAN % (RANGE)	ΔNTCP PH – PT (%)	PVALUE
EAR OF SECONDARY IPSILATERAL LUNG CANCER AT AGE 80 (EVER SMOKERS)					
AGE 30-39	22	11,14 (6,61-15,23)	2,82 (1,18-11,68)	-7,41	<0,0001
AGE 40-49	22	11,02 (6,54-15,07)	2,79 (1,17-11,55)	-7,33	<0,0001
AGE 50-59	22	10,23 (6,08-14,00)	2,59 (1,08-10,73)	-6,81	<0,0001
AGE 60-69	22	8,82 (5,24-12,06)	2,23 (0,93-9,25)	-5,87	<0,0001
AGE 70-79	22	5,52 (3,28-7,55)	1,40 (0,59-5,79)	-3,67	<0,0001
EAR OF SECONDARY CONTRALATERAL LUNG CANCER AT AGE 80 (EVER SMOKERS)					
AGE 30-39	22	3,62 (2,28 - 6,05)	0,01(0,00 - 0,58)	-3,46	<0,0001
AGE 40-49	22	3,58 (2,25 - 5,99)	0,01 (0,00 - 0,57)	-3,42	<0,0001
AGE 50-59	22	3,33 (2,09 - 5,56)	0,01 (0,00 - 0,53)	-3,18	<0,0001
AGE 60-69	22	2,87 (1,80 - 4,79)	0,01 (0,00 - 0,46)	-2,74	<0,0001
AGE 70-79	22	1,80 (1,13 - 3,00)	0,01 (0,00 - 0,29)	-1,71	<0,0001
EAR OF SECONDARY OESOPHAGEAL CANCER AT AGE 80 *					
AGE 30-39	9	0,21 (0,12-0,32)	0,10 (0,00-0,21)	-0,11	0,0039
AGE 40-49	9	0,21 (0,12-0,32)	0,10 (0,00-0,21)	-0,11	0,0039
AGE 50-59	9	0,19 (0,11 - 0,29)	0,09 (0,00 - 0,19)	-0,10	0,0039
AGE 60-69	9	0,18 (0,10 - 0,27)	0,08 (0,00 - 0,17)	-0,10	0,0039
AGE 70-79	9	0,13 (0,07 - 0,20)	0,06 (0,00 - 0,13)	-0,07	0,0039
EAR OF SECONDARY CONTRALATERAL BREAST CANCER	19	1,09 (0,63-1,96)	0,02 (0,00-0,08)	-1,01	<0,0001

DISCUSSION

- IMPT showed a statistically significant reduction for almost all OARs dose metrics considered in this study as expected from literature
- Results of NTCP evaluation are aligned with literature

Limits Of This Study:

- Small sample
- Lack of powerful evidence and external validation of the majority of NTCP models applied
- Most NTCP are photon-based and some (radiation pneumonitis, acute oesophageal toxicity and lung fibrosis) are based on predominately different cancer population
- No established NTCP models for glenohumeral joint toxicity → possible need of delivery in the arm-down position → advantage of IMPT beam geometry (en face fields)
- Use of DIBH for PT is under debate

CONCLUSIONS

- NTCP models are efficient tools to predict the risk of toxicity and subsequently to choose the best RT treatment strategy in breast cancer patients.
- Clinical validation in a bigger dataset of patients is warranted to confirm these results.
- Given the present limited access to proton centers, a composite score for breast cancer patients based on NTCP evaluation of clinically relevant endpoints in rival VMAT e IMPT plans, could be a useful tool for patient selection and to optimize resources in RT wards globally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