Tra la radiobiologia e la clinica

Overview clinica sul ruolo della IMRT: Torace

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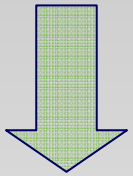
IMRT: cosa abbiamo imparato

- Migliora la conformazione della dose
- Migliora l'omogeneità (o disomogeneità) della dose



- Dose-escalation
  - Ipofrazionamento
    - Simultaneous Integrated Boost
      - Re-irradiazioni

Indicazioni nel distretto toracico

Mammella	Whole breast
	Partial breast
	Altro
Polmone	NSCLC
	Mesotelioma
	Linfomi
	Esofago
	Sarcomi
	…

L'evidenza

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journal homepage: www.elsevier.com/locate/clon

Overview

A Review of the Clinical Evidence for Intensity-modulated Radiotherapy

J. Staffurth on behalf of the Radiotherapy Development Board[1]

Cardiff University, Velindre Hospital, Whitchurch, Cardiff, UK

- **61 Studi di confronto 3D-CRT vs. IMRT, aggiornati al luglio 2009**

  MEDLINE,EMBASE, *IJROBP*, *Radiother Oncol*, ASTRO, ESTRO

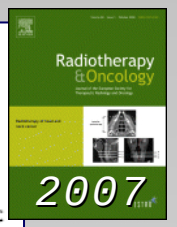
	RCTs	Pz.	Non RCTs	Pz.	On going	Pz.
Testa - collo	3	*205*	27	*1119*	6	*> 1000*
Prostata	-	-	26	*> 5000*	11	*> 4000*
Mammella	2	*664*	4	*875*	6	*> 4000*
Polmone	-	-	1	*290*	2	*n.s.*
Altro	-	-	8	*n.s.*	2	*n.s.*

Whole breast

	RCTs	Pz.	Non RCTs	Pz.	On going	Pz.
Mammella	3	1468	4	875	6	> 4000

Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy

Ellen Donovan[a], Natalie Bleakley[a], Erica Denholm[b], Phil Evans[a], Lone Gothard[c], Jane Hanson[c], Richa



A Multicenter Randomized Trial of Breast Intensity-Modulated Radiation Therapy to Reduce Acute Radiation Dermatitis

Jean-Philippe Pignol, Ivo Olivotto, Eileen Rakovitch, Sandra Gardner, Katharina Sixel, Wayne Beckham, Thi Trinh Thuc Vu, Pauline Truong, Ida Ackerman, and Lawrence Paszat

CLINICAL INVESTIGATION

RANDOMIZED CONTROLLED TRIAL OF FORWARD-PLANNED INTENSITY-MODULATED RADIOTHERAPY FOR EARLY BREAST CANCER: INTERIM RESULTS AT 2 YEARS

GILLIAN C. BARNETT, B.M., B.CH.,* JENNIFER S. WILKINSON, B.SC.,† ANNE M. MOODY, M.B., B.CHIR.,† CHARLES B. WILSON, M.D.,† NICOLA TWYMAN, M.SC.,† GORDON C. WISHART, M.D.,‡ NEIL G. BURNET, M.D.,* AND CHARLOTTE E. COLES, PH.D.†

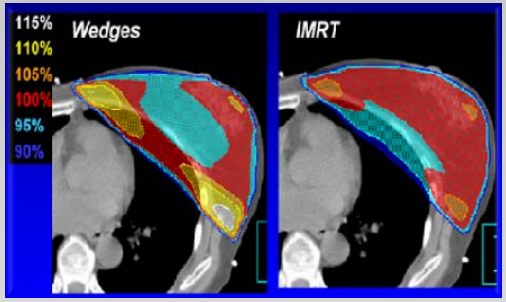
*Department of Oncology, University of Cambridge, Cambridge University Hospitals, National Health Service Foundation Trust, Cambridge, United Kingdom; †Oncology Centre, Cambridge University Hospitals, National Health Services Foundation Trust, Cambridge, United Kingdom; ‡Cambridge Breast Unit, Addenbrooke's Hospital, Cambridge, United Kingdom

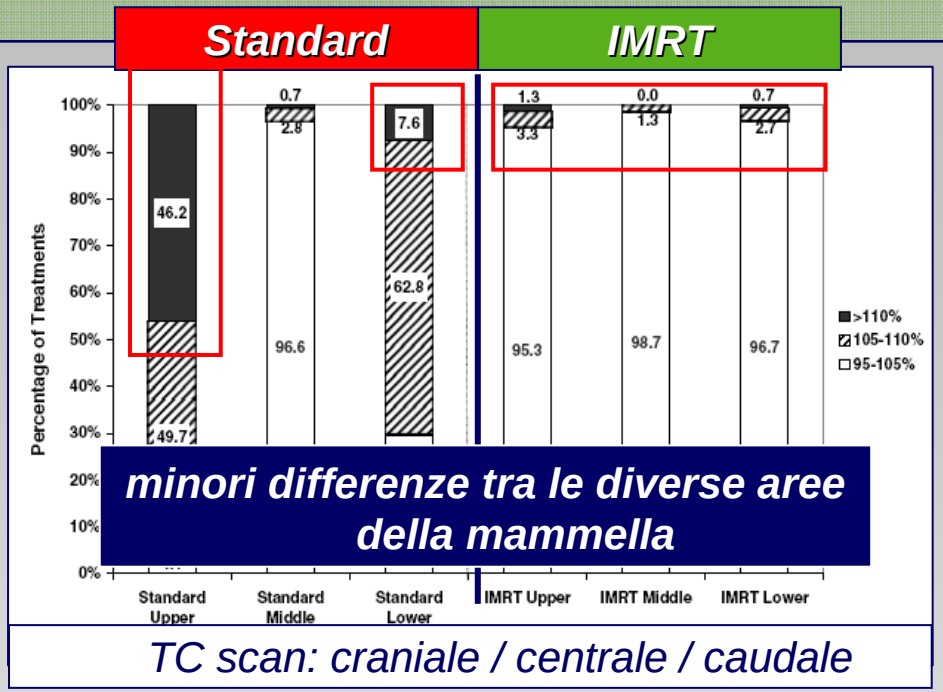
- **End-point comune: valutazione tossicità acuta/tardiva mammaria e correlazione con la tecnica utilizzata**
- **In 2 trial, planning IMRT dichiaratamente "forward"**

Whole breast

- **IMRT riduce le disomogeneità** all'interno del volume mammario

  - ***% pazienti con sovra dosaggio***





Donovan et al. 2007

  - ***Volume del sovra dosaggio***

Clinically significant maximum (median)	105.0		110.0
Sagittal dose gradient (median)	0.6		10.0
Relative volume receiving (mean)			
> 105% of the prescribed dose (V_{105})	7.7	***P<0.001***	16.9
> 107% of the prescribed dose (V_{107})	2.6		7.9
> 110% of the prescribed dose (V_{110})	0.5		2.1
> 115% of the prescribed dose (V_{115})	0.02		0.12

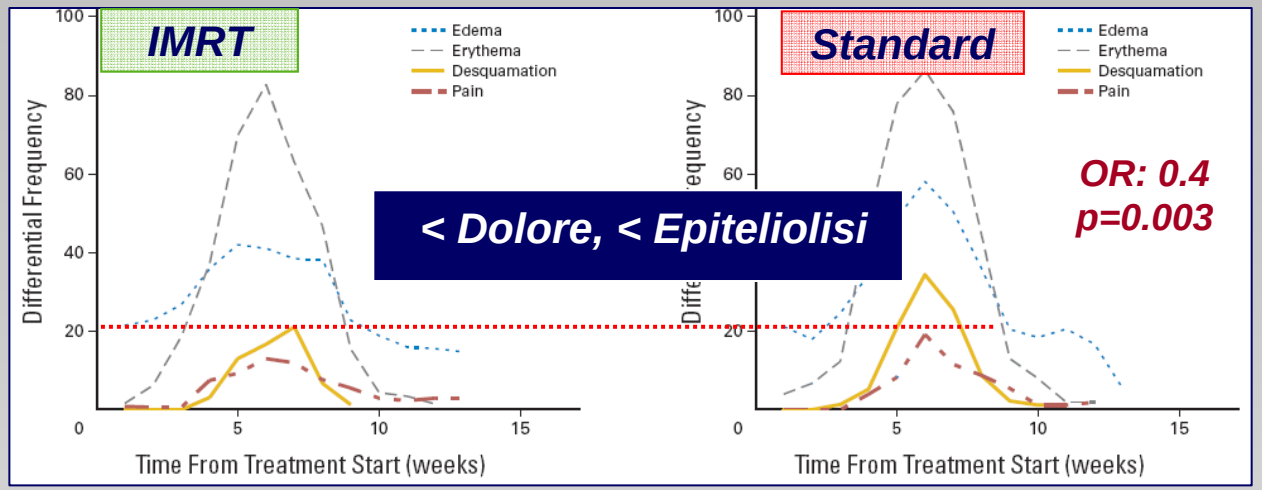
Pignol et al. 2008

Absolute volume >107% (cm^3)					
Mean	***P<0.0005***	0.54		44.5	10.5	19.8
Range		0–2		0–540	0–368.9	0–540

Barnett et al. 2011

Whole breast

- **Riduce la tossicità acuta cutanea**



Pignol et al. 2008

- **Ha un possibile impatto sulla tossicità tardiva**

Proportion of patients with any clinician-assessed breast induration (a little, quite a bit or very much) within number of assessments performed according to randomisation arm, standard 2D dosimetry or 3D intensity modulated radiotherapy (IMRT)

	Year 2 assessment		Year 5 assessment		*P*-value (from GEE)
	Standard 2D	IMRT 3D	Standard 2D	IMRT 3D	
Centre of the breast	33/122 (27%)	19/117 (16%)	37/117 (32%)	25/118 (21%)	0.02
Pectoral fold	32/119 (27%)	13/113 (12%)	34/118 (29%)	26/119 (22%)	0.006
Inframammary fold	35/121 (29%)	18/113 (16%)	28/116 (24%)	20/117 (17%)	0.009
Boost site	65/120 (54%)	44/118 (37%)	70/114 (61%)	43/115 (37%)	<0.001

Donovan et al. 2007

Whole breast

Variable	IMRT (n = 362) No toxicity	IMRT (n = 362) Any toxicity	Control (n = 365) No toxicity	Control (n = 365) Any toxicity	p
Photographic					
Shrinkage after RT	178	120	180	139	.41
Overall cosmesis	114	184	113	207	.45
Clinical					
Telangiectasia	280	49	266	76	.015
Breast edema	175	154	167	176	.24
Breast shrinkage	137	192	126	217	.19
Any induration	57	272	72	271	.23
Pigmentation	229	57	234	70	.36
Patient reported					
Breast pain	155	169	157	172	.98
Oversensitivity	188	135	202	128	.43

Barnett et al. 2011

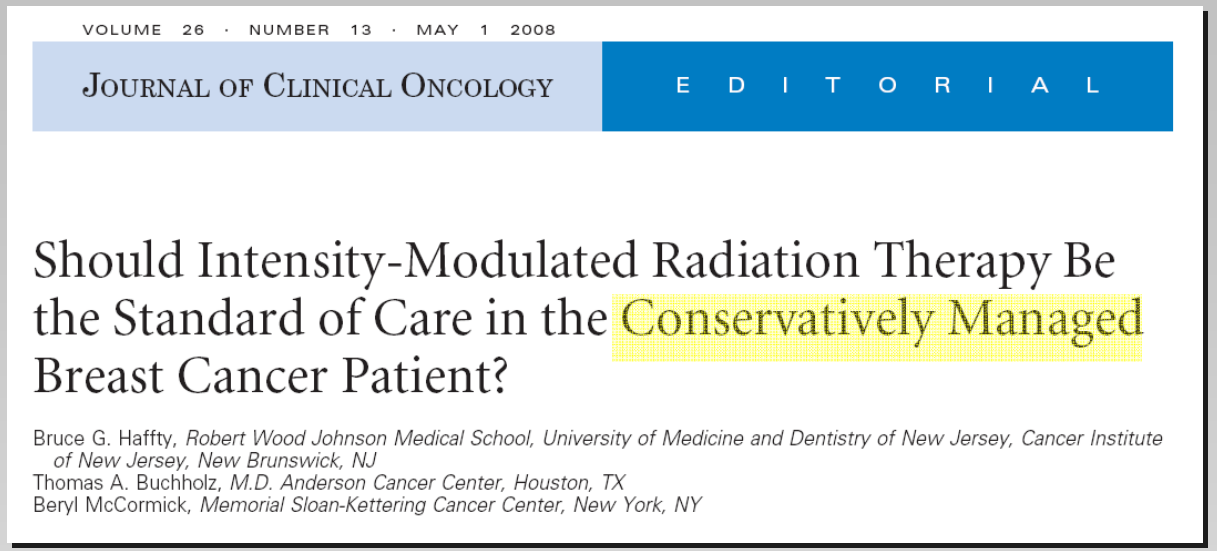
- **La scelta dell'end-point clinico può condizionare i risultati**

Variable	Surgical deficit Spearman's rho	Surgical deficit p	Surgical cosmesis Spearman's rho	Surgical cosmesis p
Pathologic tumor size	0.096	.0060	0.027	.0010
Specimen weight	0.18	< .00005	0.006	< .00005
Grade		.16		.089
Age	0.070	.042	0.029	.0003
Estrogen receptor status		.53		.64
Histologic group		.48		.60
Lymph node status		.93		.72
Body mass index		.12	0.037	.0065
Smoker status		.53		.24
Breast volume		.44		.75
Postoperative infection		.64		.13
Postoperative hematoma		.67		.091
Primary side		.077		.072

Barnett et al. 2011

- **Coesistenza di altri fattori (cosmesi post-chirurgia) sulla tossicità tardiva**

Whole breast



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E D I T O R I A L

Should Intensity-Modulated Radiation Therapy Be the Standard of Care in the Conservatively Managed Breast Cancer Patient?

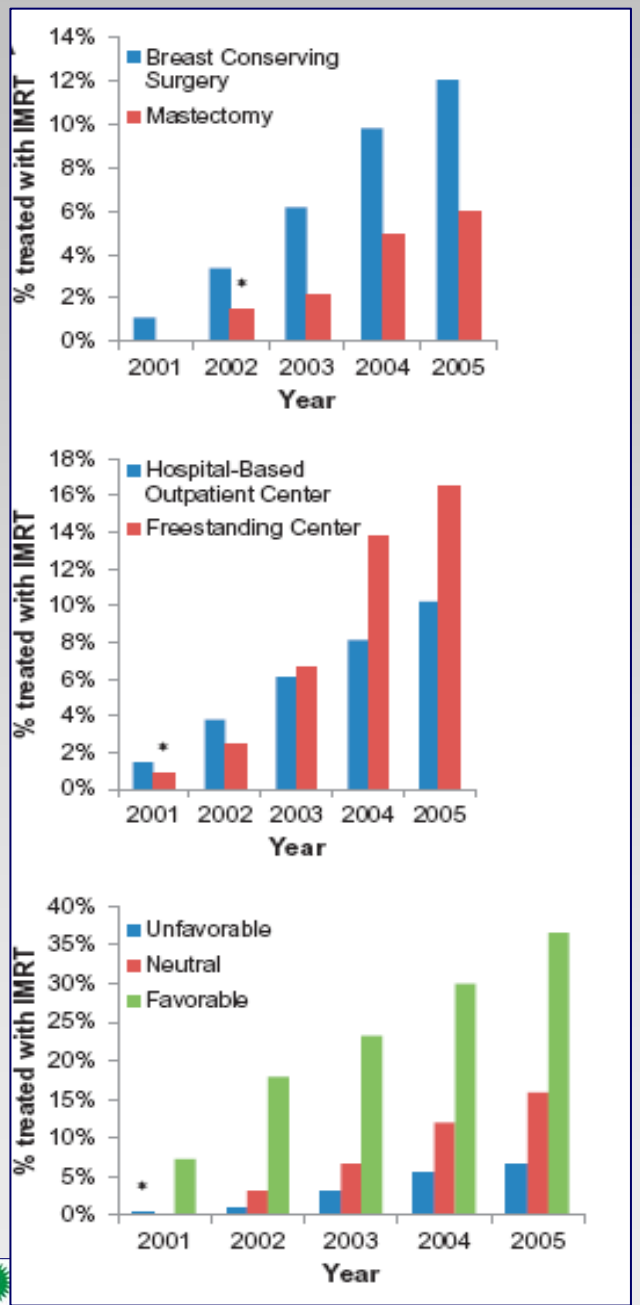
Bruce G. Haffty, *Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Cancer Institute of New Jersey, New Brunswick, NJ*
Thomas A. Buchholz, *M.D. Anderson Cancer Center, Houston, TX*
Beryl McCormick, *Memorial Sloan-Kettering Cancer Center, New York, NY*

… the primary goal of IMRT in the intact breast is to improve homogeneity of the dose distribution … in other disease sites the major benefit is in improving conformality ...

… in breast IMRT is much less complex than in other sites ...

… there are dosimetric and clinical advantages with IMRT ...

Whole breast



Adoption of Intensity-Modulated Radiation Therapy for Breast Cancer in the United States

Benjamin D. Smith, I-Wen Pan, Ya-Chen T. Shih, Grace L. Smith, Jay R. Harris, Rinaa Punglia, Lori J. Pierce, Reshma Jagsi, James A. Hayman, Sharon H. Giordano, Thomas A. Buchholz

Predictor	OR	*p*
2001	1	< 0.001
2003	7.10	< 0.001
2005	15.81	< 0.001
White	1	-
Hispanic	0.94	0.86
Black	0.60	< 0.001
Low ROs Density	1	-
✓ High ROs Density	2.32	< 0.001
Hospital-based facility	1	-
✓ Free-standing facility	1.36	< 0.001
Right breast	1	-
✓ Left breast	1.30	< 0.001

Incremento significativo se rimborso favorevole

OR = 10.87; p < 0.001

Whole breast

EDITORIAL

IMRT for Breast Cancer—Balancing Outcomes, Patient Selection, and Resource Utilization

Lisa A. Kachnic, Simon N. Powell

… does target coverage and OARs sparing provided by IMRT produce a measurable improvement in treatment outcome over 3D-CRT?...

… the current level of evidence is <u>weak</u> …the benefit observed in RCTs could likely be achieved with simple segmentation …

… the <u>true</u> value of inverse-planned IMRT will most likely be for patients with complex <u>anatomy</u>, or for <u>nodal</u> targeting …

On-going Studies

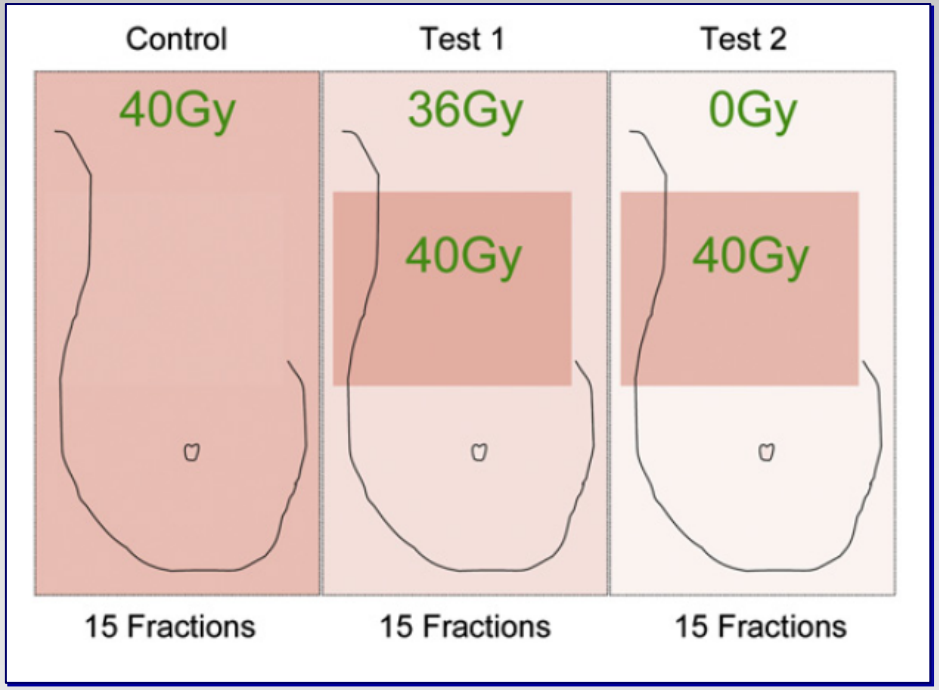
Study name	Principle research question	Number of patients	Status	Trial sponsor	Code
A clinical trial to reduce skin burn induced by breast radiotherapy using intensity-modulated radiation therapy	Phase III RCT of 2DRT versus IMRT	340	Completed	Sunnybrook Health Centre, Canada	NCT 00187343
Prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy fractions of whole breast radiotherapy in terms of late normal tissue responses and tumour control (FAST)	Phase III RCT of standardly versus hypofractionated IMRT	900	Completed	Institute of Cancer Research, UK	ISRCTN 62488883
A randomised phase II trial comparison of radiation therapy techniques in the management of node-positive breast cancer	Phase I/II RCT of 2DRT versus IMRT	Not stated	Recruiting	University of Michigan Cancer Center, USA	NCT 00581256
Randomised trial testing intensity-modulated radiotherapy and partial organ radiotherapy following breast conservation surgery for early breast cancer (IMPORT LOW)	Phase III RCT of standard radiotherapy versus partial breast IMRT	1935	Recruiting	Institute of Cancer Research, UK	ISRCTN 12852634
Randomised trial testing dose escalated intensity-modulated radiotherapy in women with higher than average local tumour recurrence risk after breast conservation therapy for early breast cancer (IMPORT HIGH)	Phase III RCT of standard IMRT versus concomitantly boosted ± dose-escalation IMRT	840	In set-up	Institute of Cancer Research, UK	ISRCTN 4743744

Staffurth, 2010

Partial breast irradiation

CANCER RESEARCH UK

In partnership with
The ROYAL MARSDEN
NHS Foundation Trust



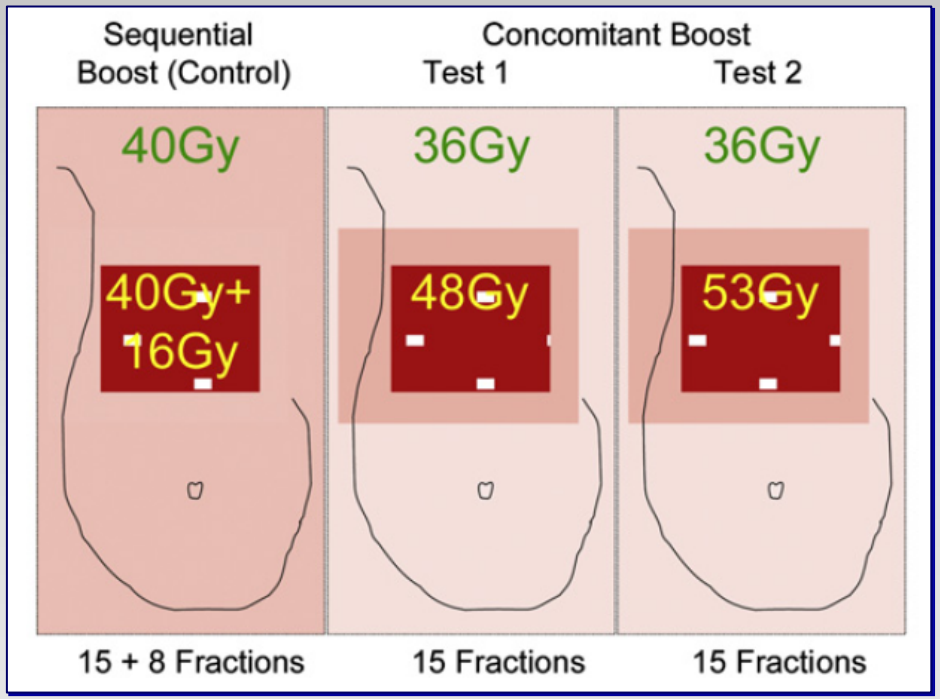
- **Open: May 2007**
- **Planned accrual: 1935 pts**
- **End point: Local control**
  - Site of relapse
  - Contralateral tumors
  - Late effects
  - QoL
  - Economic evaluation

IMPORT-LOW Trial

Dose-escalation - SIB

CANCER RESEARCH UK

In partnership with
The ROYAL MARSDEN
NHS Foundation Trust

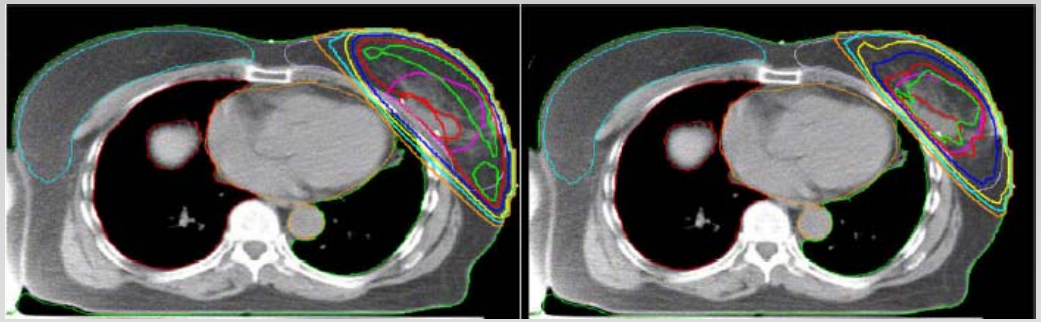


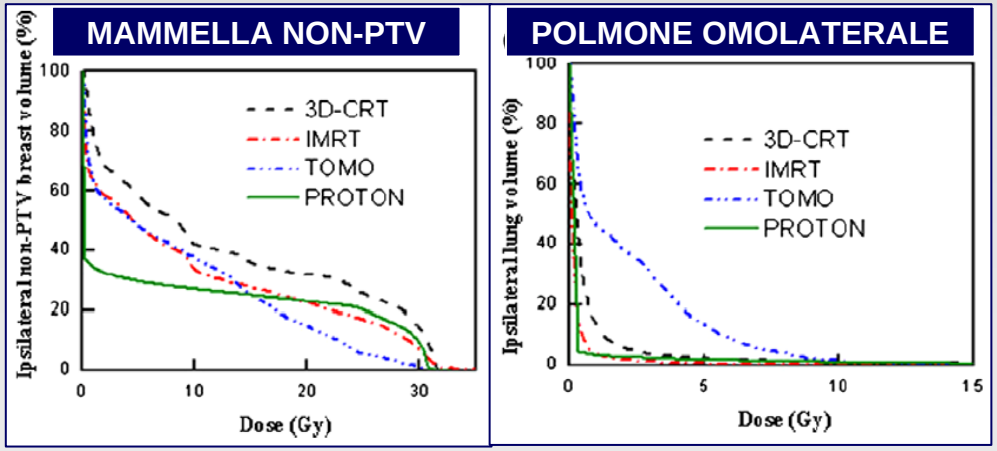
- **Open: Jan 2009**
- **Planned accrual: 840 pts**
- **End point: breast fibrosis**
  - Local control
  - Site of relapse
  - Contralateral tumors
  - Late effects

IMPORT-HIGH Trial

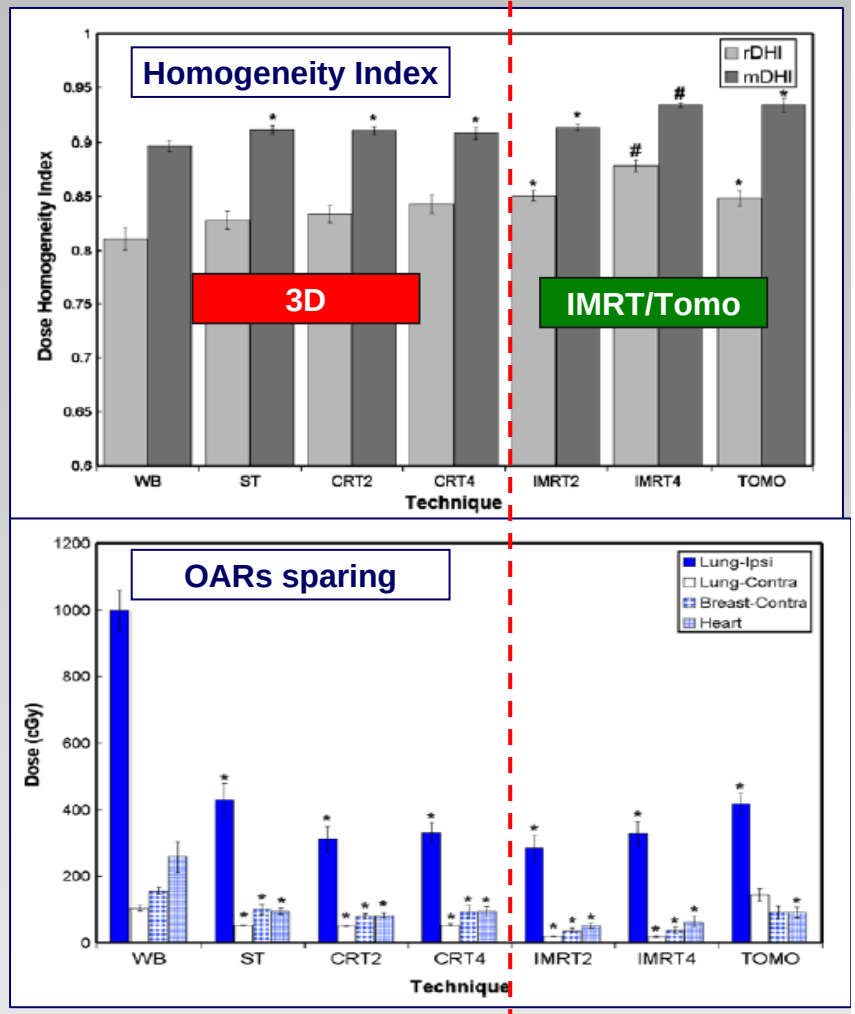
Partial breast irradiation

- Il vantaggio rispetto ai trattamenti standard è legato al gradiente
- Si guadagna in risparmio OARs, a parità di omogeneità





Moon et al. 2009



Oliver et al. 2007

Partial breast irradiation

	3D-RT (%)	IMRT (%)	Δ (%)	*t* test	Data points improved w/ IMRT (%)	Mean reduction with IMRT (%)
Mammella omolaterale						
V_{25}	60.3	56.9	3.4	<0.01	78	6
V_{50}	48.2	42.5	5.6	<0.01	91	12
V_{75}	37.4	31.2	6.3	<0.01	100	17
V_{100}	22.1	9.5	12.6	<0.01	87	57

PHYSICS CONTRIBUTION

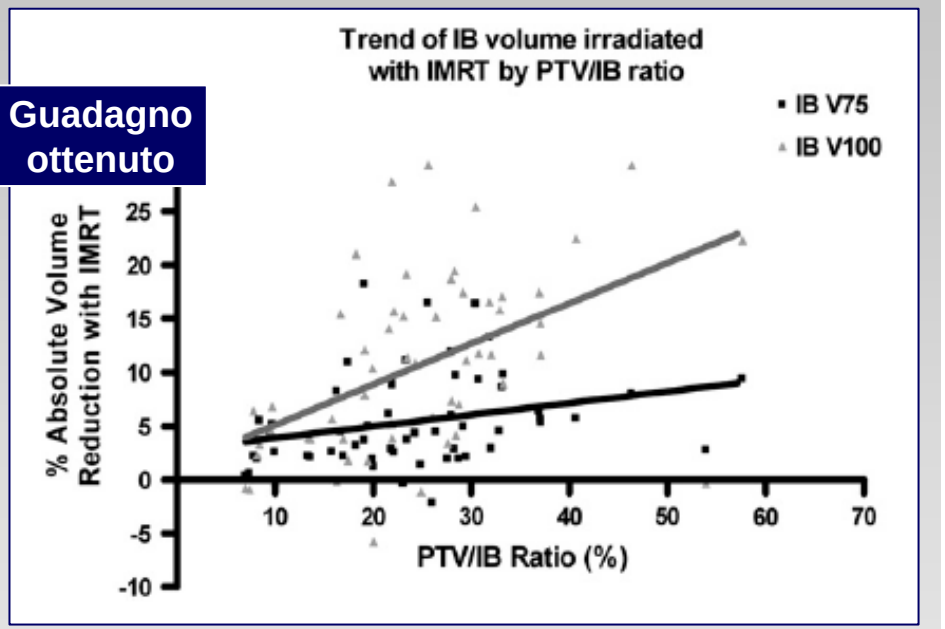
ACCELERATED PARTIAL-BREAST INTENSITY-MODULATED [illegible]ERAPY RESULTS IN IMPROVED DOSE DISTRIBUTION WHEN COMPAR[illegible]H THREE-DIMENSIONAL TREATMENT-PLANNING TECHNIQUE[illegible]

No Random

2008

KYLE E. RUSTHOVEN, M.D.,* DENNIS L. CARTER, M.D.,† KATHRYN HOWELL, M.D.,† JANE M. KERCHER, M.D.,‡ PHYLLIS HENKENBERNS, O.C.N.,† KARI L. HUNTER, C.M.D.,† AND CHARLES E. LEONARD, M.D.†

Guadagno ottenuto

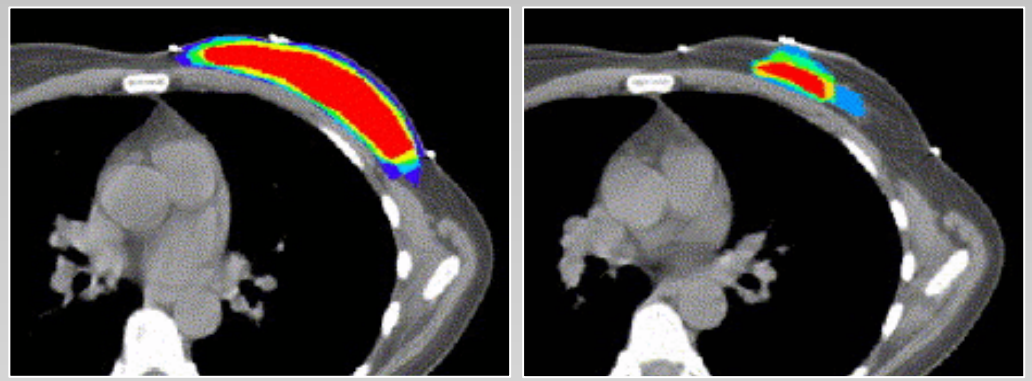


- **Specie in condizioni "sfavorevoli"**
  (elevato rapporto PTV/mammella)

- **Gli studi clinici (pochi) confermano una ridotta tossicità con PBI-IMRT**
  - Soggettiva (dolore)
    29% mild / moderate breast disconfort — *Reeder et al. IJROBP 2009 (Ph. II)*
  - Obiettiva (acuta cutanea)
    RTOG-G2: 0.8% vs. 19% — *Livi et al. IJROBP 2010 (Ph. III)*

Partial breast irradiation

- **La definizione corretta del PTV è tanto più delicata quanto maggiore è il gradiente ottenuto**



Struikmans et al 2005

- **È necessario minimizzare le inaccuratezze**

Titanium clip placement to allow accurate tumour bed localisation following breast conserving surgery – Audit on behalf of the IMPORT Trial Management Group

C.E. Coles [a], C.B. Wilson [a], J. Cumming [a], J.R. Benson [a], P. Forouhi [a], J.S. Wilkinson [a], R. Jena [b], G.C. Wishart [a,*]

[a] *Cambridge Breast Unit, Cambridge Unive*
[b] *Oncology Centre, Cambridge Universit*

CLINICAL INVESTIGATION **Breast**

CLINICAL EXPERIENCE WITH IMAGE-GUIDED RADIOTHERAPY IN AN ACCELERATED PARTIAL BREAST INTENSITY-MODULATED RADIOTHERAPY PROTOCOL

CHARLES E. LEONARD, M.D.,* MICHAEL TALLHAMER, M.S.,* TIM JOHNSON, PH.D.,* KARI HUNTER, C.M.D.,* KATHRYN HOWELL, M.D.,* JANE KERCHER, M.D.,† JODI WIDENER, M.D.,† TERESE KASKE, M.D.,‡ DEVCHAND PAUL, M.D.,§ SCOT SEDLACEK, M.D.,§ AND DENNIS L. CARTER, M.D.*

Partial breast irradiation

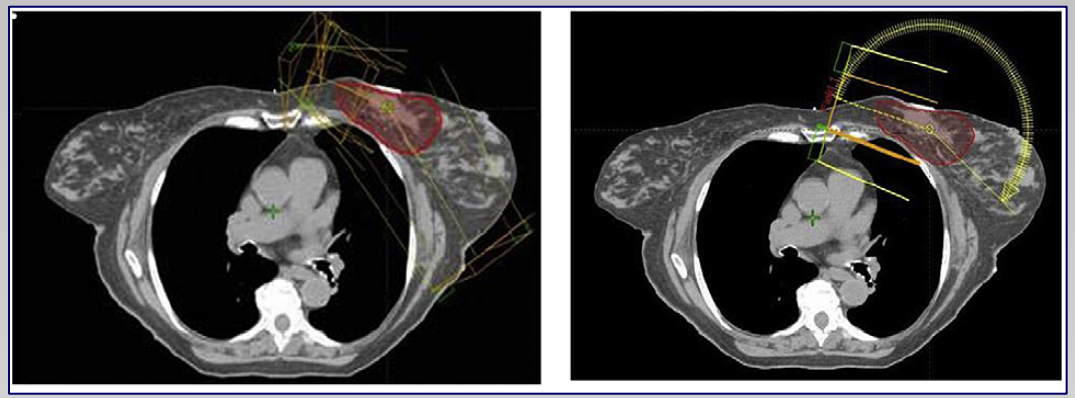
PHYSICS CONTRIBUTION

IMPACT OF VOLUMETRIC MODULATED ARC THERAPY TE… …E ON TREATMENT WITH PARTIAL BREAST IRRADIATION

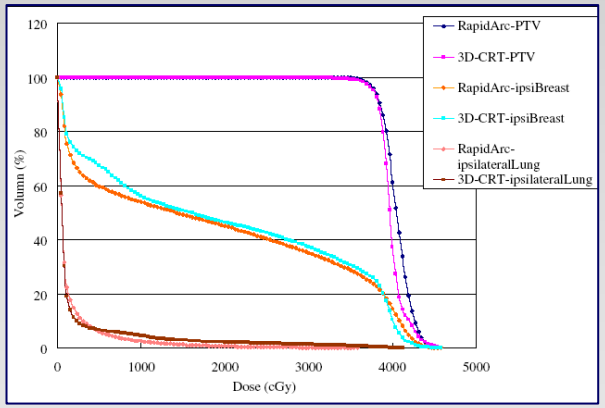
No Random

Jian-Jian Qiu, B.S.,*† Zheng Chang, Ph.D.,* Q. Jackie Wu, Ph.D.,* Sua Yoo, Ph.D.,* Janet Horton, M.D.,* and Fang-Fang Yin, Ph.D.*

- IMRT volumetrica (IGRT integrata)



- Riduzione della dose agli OARs (omolaterali)
- NON significativo incremento della dose agli OARs controlaterali



	3D-CRT	V-MAT	*p*
mean MU (*SD*)	634 (*123*)	488 (*38*)	*0.017*
mean delivery time (*SD*)	6.30 (*1.4*)	1.21 (*0.1*)	*<0.001*

- Delivery più efficiente

… the true value of inverse-planned IMRT will most likely be for patients with complex anatomy, or for nodal targeting …

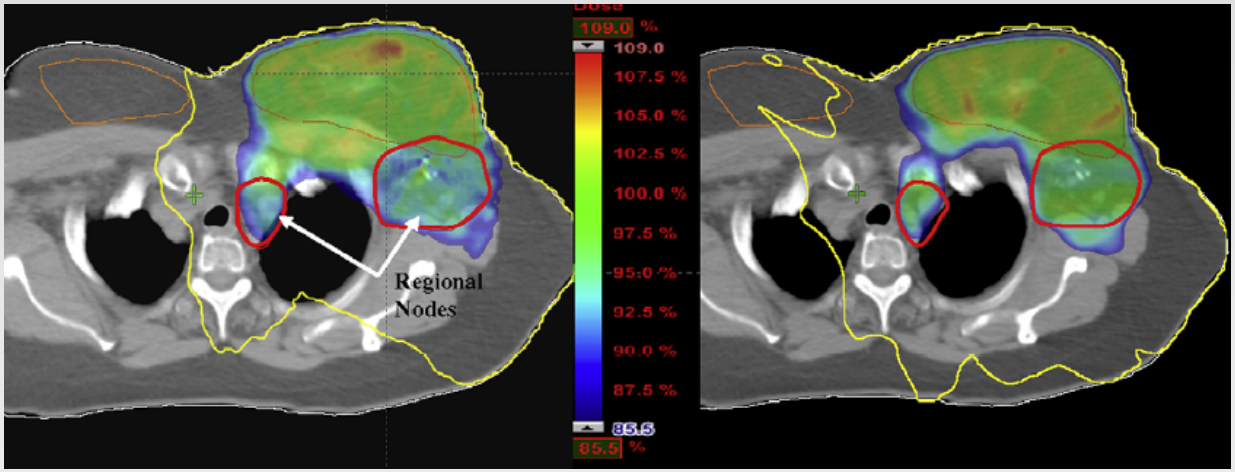
PHYSICS CONTRIBUTION

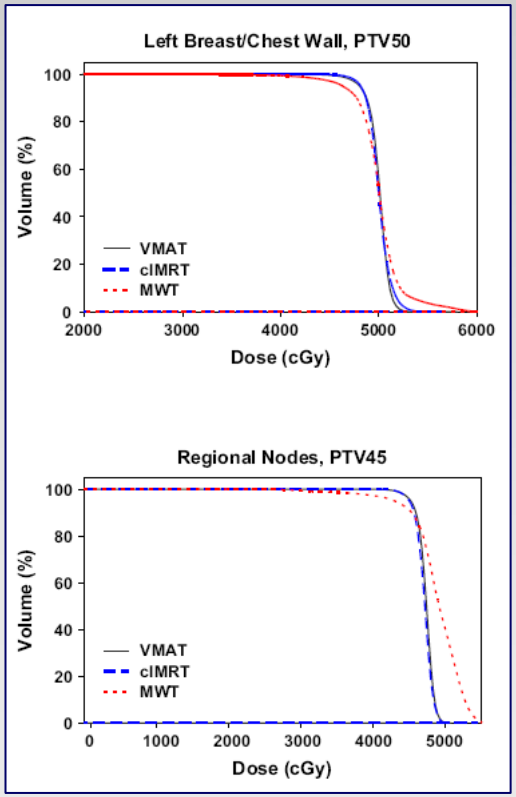
No Random

VOLUMETRIC MODULATED ARC THERAPY IMPROVES DOSIMETRY AND REDUCES TREATMENT TIME COMPARED TO CONVENTIONAL INTENSITY-MODULATED RADIOTHERAPY FOR LOCOREGIONAL RADIOTHERAPY OF LEFT-SIDED BREAST CANCER AND INTERNAL MAMMARY NODES

Carmen C. Popescu, M.S.,* Ivo A. Olivotto, M.D.,*† Wayne A. Beckham, Ph.D.,*‡ Will Ansbacher, Ph.D.,*‡ Sergei Zavgorodni, Ph.D.,‡ Richard Shaffer, F.R.C.P.,§ Elaine S. Wai, M.D.,† and Karl Otto, Ph.D.§

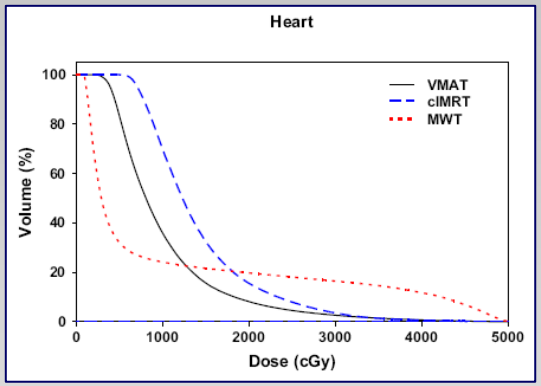
- **Nessuna differenza in omogeneità, conformità e copertura PTV rispetto a IMRT convenzionale**

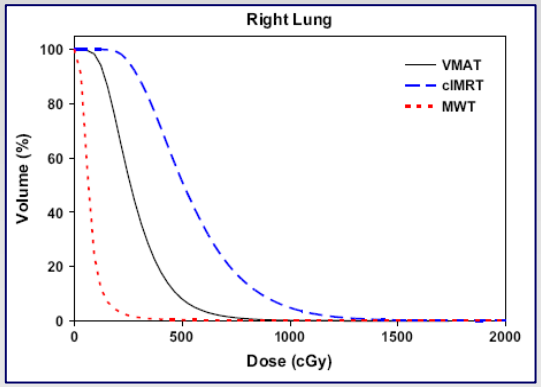


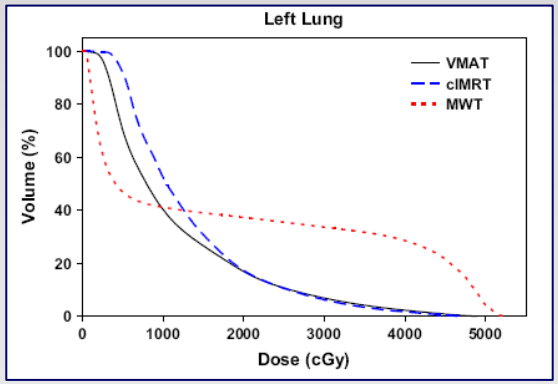


- **Significativo <u>risparmio</u> di tutti gli OARs, specie alle basse dosi**

OAR	parametro	V-MAT	IMRT	*p*
Cuore	**D media**	**10.9**	**14.1**	***<0.05***
	V45	0.3	0.1	*ns*
	V30	2.6	3.5	*ns*
	V10	**35.7**	**69.6**	***<0.05***
	V5	**83**	**00**	***<0.05***
Polmone omolaterale	**D media**	**11.6**	**13.1**	***<0.05***
	V20	16.9	17.3	*ns*
	V10	**40.3**	**52.4**	***<0.05***
	V5	**70.2**	**91.9**	***<0.05***
Polmone controlaterale	**D media**	**2.9**	**5.5**	***<0.05***
	V5	**8.1**	**51.3**	***<0.05***
Mammella controlaterale	D media	3.2	4.3	*ns*
	V5	**53.3**	**130.9**	***<0.05***

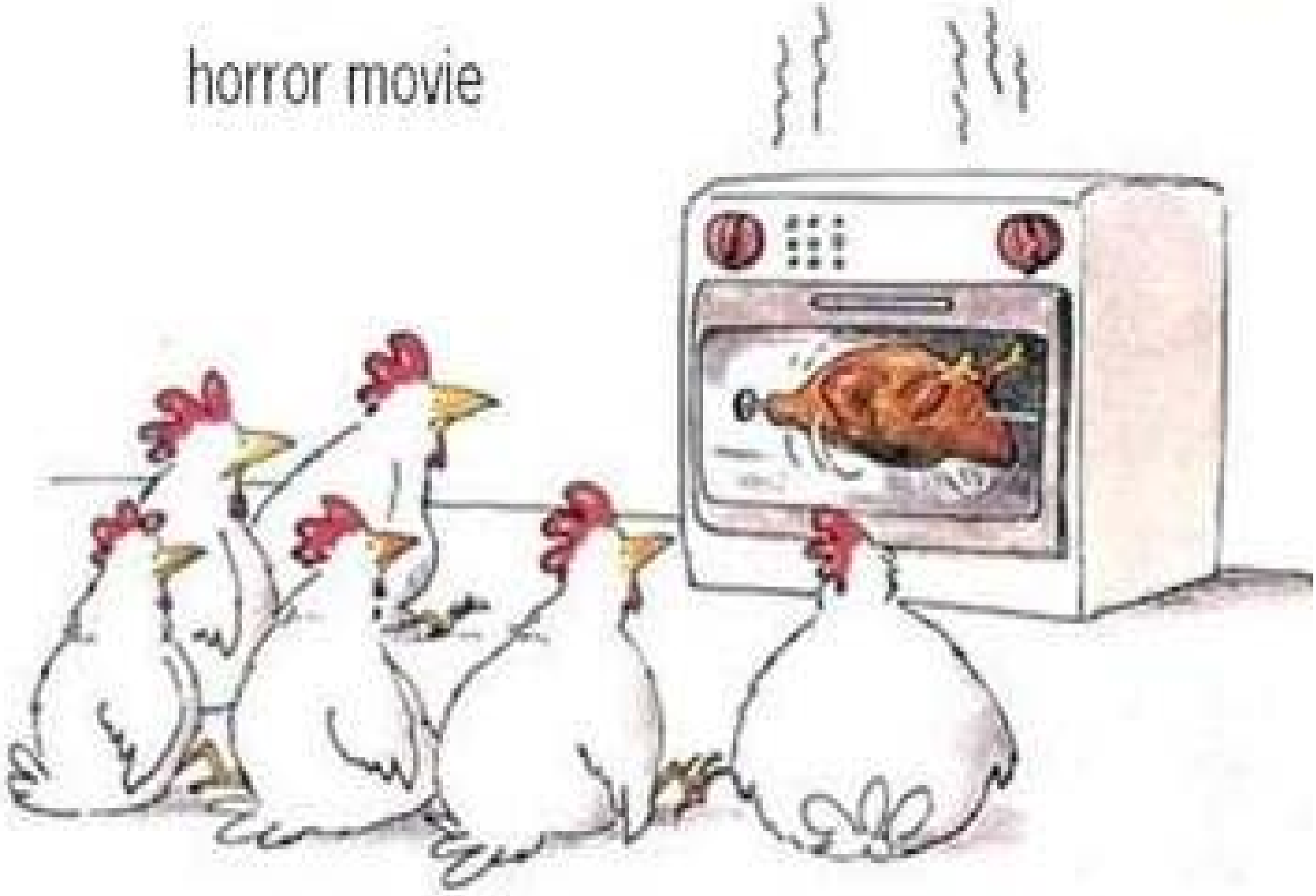






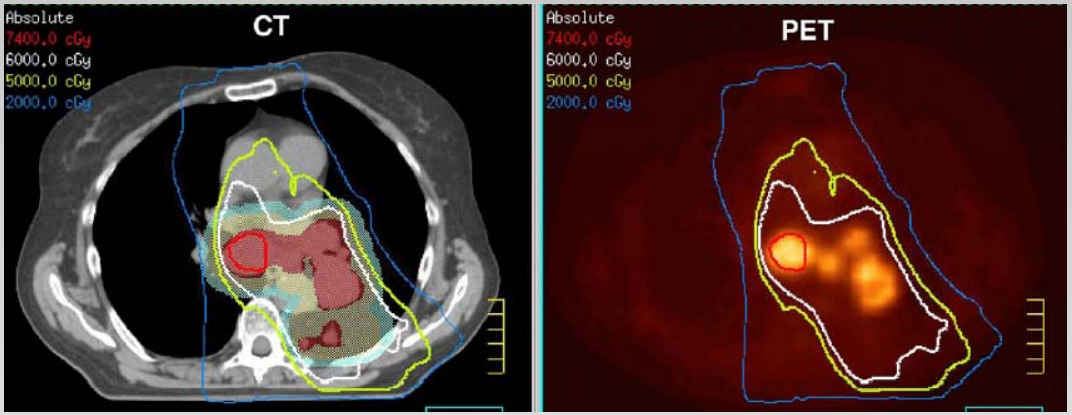
- **Impatto sul <u>delivery</u> (MU e treatment time)**

	IMRT	V-MAT
mean MU	**1254**	**862**
mean delivery time	**8.8**	**3.9**


horror movie

Polmone

- Maggiore conformazione della dose → **Dose-Escalation**
- *Dose-painting* su aree ipossiche o metabolicamente iperattive



Chang, Cox 2010

- I limiti sono sede-specifici:
  - Organ motion → Target missing
    QA dosimetrico
  - Tossicità polmonare radioindotta (basse dosi)

Polmone

- Raccomandabile l'utilizzo di apparecchiature / dispositivi / protocolli che limitino **OM < 5mm (4D-CT, Breath-hold, Gating, Tracking…)**

National Cancer Institute RRP Radiation Research Program

http://www3.cancer.gov/rrp/imrt.doc

- Se il frazionamento è convenzionale, l'organ motion incide relativamente sulla differenza tra dose pianificata e dose erogata (< 1%), in modo non significativo rispetto a quanto accade con 3D-CRT

Bortfeld et al. 2002

Chui et al. 2003

- La dose integrale e il volume polmonare irradiato a basse dosi sembrano correlati al numero di fasci utilizzato, alla tecnica IMRT (statica vs. dinamica), oltre che alle MU erogate

Chang, Cox 2010

Polmone

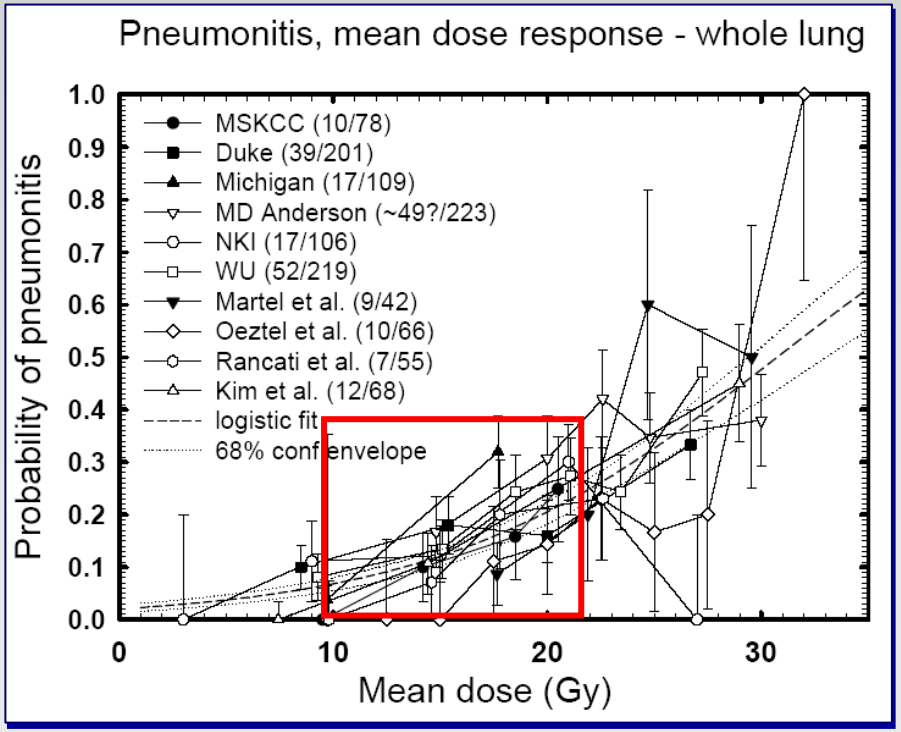
Liu et al. 2004

Table 3. Difference in lung dose and volume between 3D-CRT and IMRT plans

Statistic	V_5 (%)	V_{10} (%)	V_{20} (%)	V_{30} (%)	V_{eff} (%)	MLD (Gy)
Minimum	−25.0	−3.8	1.2	1.0	2.3	0.5
Maximum	0.7	5.8	12.0	11.9	17.7	4.4
Median	−8.0	1.6	8.0	8.9	9.0	2.0
p	0.007	0.169	0.005	0.005	0.005	0.005

Abbreviations: V_5, V_{10}, V_{20}, V_{30} = lung volume that received >5, >10, >20, >30 Gy; V_{eff} = biologically effective volume; MLD = mean lung dose.
Negative value indicates greater dose or volume treated in IMRT plans compared with 3D-CRT plans, and vise versa.

- L'incremento della irradiazione polmonare alle basse dosi (V5, V10) sembrerebbe un prezzo necessario da pagare
- Compensato dal guadagno offerto in risparmio di V20, V30, MLD
- Corrispondente ad una riduzione del 10% del rischio di polmoniti radioindotte



Courtesy of J. Bradley

Polmone

- L'impiego di metodi di delivery della dose più efficienti (minori MU)

Liu et al. 2004

- L'utilizzo di un numero limitato di fasci (i.e. < 9)

Murshed et al. 2004

- Una pianificazione IMRT statica (step & shoot)

Schwarz et al. 2005

- **Sono associate alla possibilità di contenere la dose integrale e l'esposizione di parenchima sano a basse dosi a livelli non significativamente differenti da quanto ottenibile con 3D-CRT**

- **Il beneficio in termini di dose-escalation offerto dalla IMRT è ulteriormente evidente in caso di target <u>complessi</u> (concavi e di dimensioni elevate), per i quali è ottenibile un incremento del 17% rispetto alla 3D-CRT**

PHYSICS CONTRIBUTION

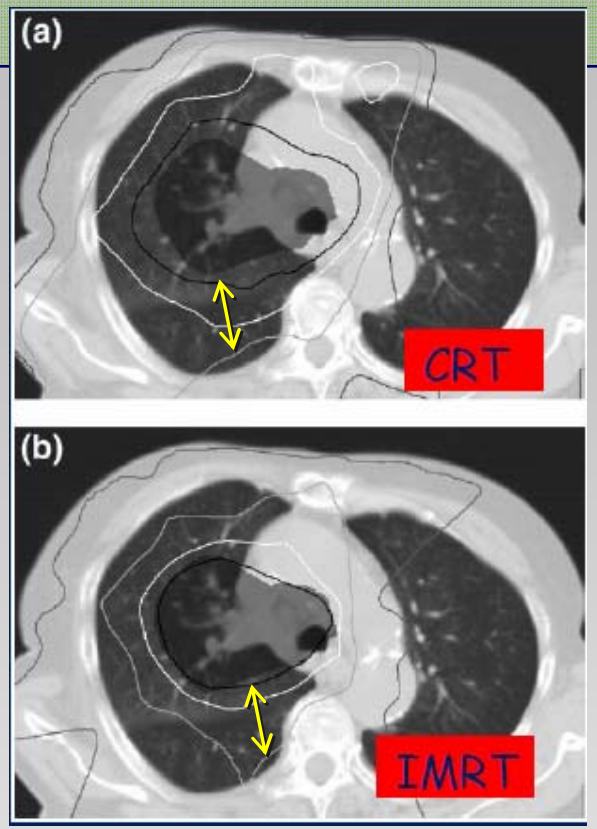
DOSE HETEROGENEITY IN THE TARGET VOLUME AND INTENSITY-MODULATED RADIOTHERAPY TO ESCALATE THE DOSE IN THE TREATMENT OF NON–SMALL-CELL LUNG CANCER

MARCO SCHWARZ, M.SC.,* MARKUS ALBER, PH.D.,† JOOS V. LEBESQUE, M.D., PH.D.,* BEN J. MIJNHEER, PH.D.,* AND EUGÈNE M. F. DAMEN, PH.D.*

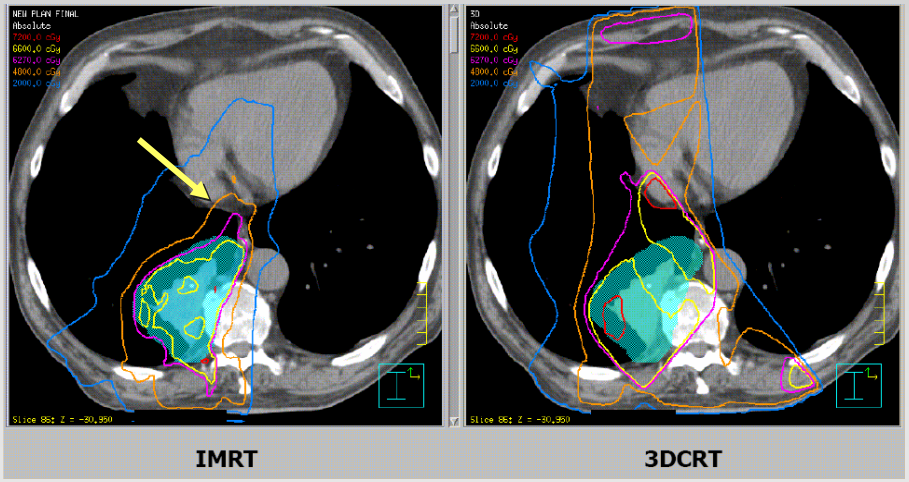
Polmone

IMRT vs. 3D-CRT: è sempre meglio?

" … maggiore conformazione della dose, maggior gradiente al di fuori del bersaglio rispetto a 3D-CRT... "



Schwarz et al. 2005



IMRT 3DCRT

Grills et al. 2003

"… il beneficio evidente nei pazienti N+ e in lesioni centrali … … IMRT può consentire, a parità di constraints, dosi 25-30% maggiori …"

Polmone

	RCTs	Pz.	Non RCTs	Pz.	On going	Pz.
Polmone	-	-	1	*290*	2	*n.s.*

No Random

CLINIC ESTIGATION Lur

INITIAL EVALUATION OF TREATMENT-RELATED PNEUMONITIS IN ADVANCED-STAGE NON–SMALL-CELL LUNG CANCER PATIENTS TREATED WITH CONCURRENT CHEMOTHERAPY AND INTENSITY-MODULATED RADIOTHERAPY

SUE S. YOM, M.D., PH.
SUSAN L. TUCKER, PH.D.,‡ CHAO
SHULIAN WANG, M.D.,‖ RADHE MOH

CLINICAL INVESTIGATION Lun

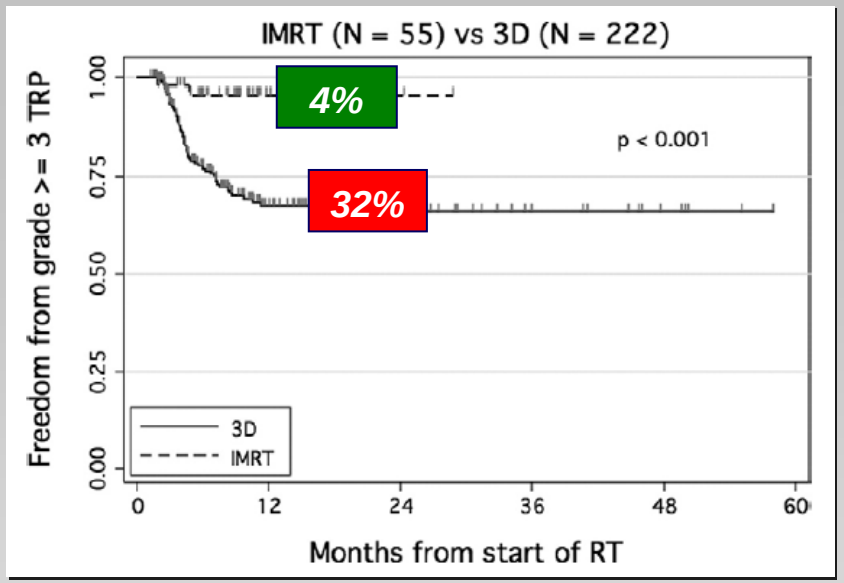
INFLUENCE OF TECHNOLOGIC ADVANCES ON OUTCOMES IN PATIENTS WITH UNRESECTABLE, LOCALLY ADVANCED NON–SMALL-CELL LUNG CANCER RECEIVING CONCOMITANT CHEMORADIOTHERAPY

ZHONGXING X. LIAO, M.D.,* RITSUKO R. KOMAKI, M.D.,* HOWARD D. THAMES, JR., PH.D.,§ HELEN H. LIU, PH.D.,† SUSAN L. TUCKER, PH.D.,‡ RADHE MOHAN, PH.D.,† MARY K. MARTEL, PH.D.,† XIONG WEI, M.D.,* KUNYU YANG, M.D.,* EDWARD S. KIM, M.D.,‖ GEORGE BLUMENSCHEIN, M.D.,‖ WAUN KI HONG, M.D.,‖ AND JAMES D. COX, M.D.*

- Confronto retrospettico tra due coorti di pazienti trattate con RT+CT
- End point primario: *treatment-related pneumonitis*

… ma anche confronto di outcome

Polmone

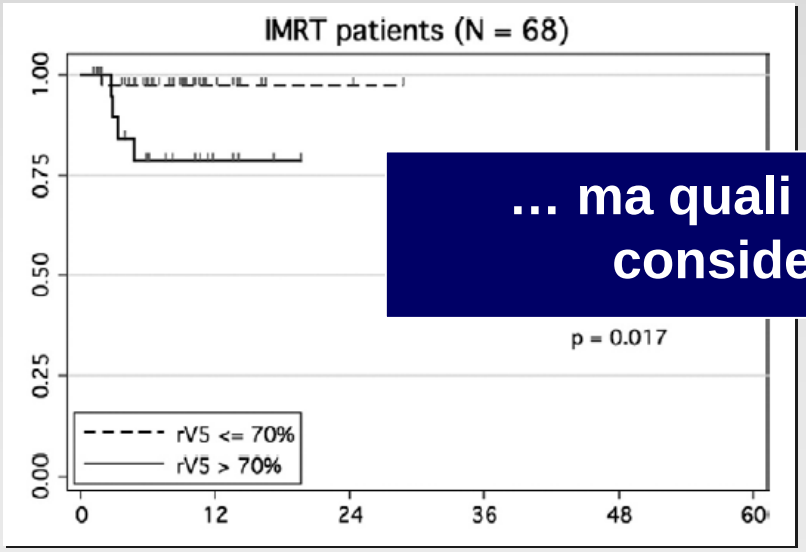


Yom et al. 2007

- **Riduzione della TRP severa**

- **Correlata alla dosimetria**

	IMRT	3D-CRT	*p*
V5	63	57	*0.011*
V10	48	49	*ns*
V20	35	38	*<0.001*
V30	29	32	*<0.001*
	19	21	*0.043*
	8	10	*0.009*
V70	<1	1	*Ns*



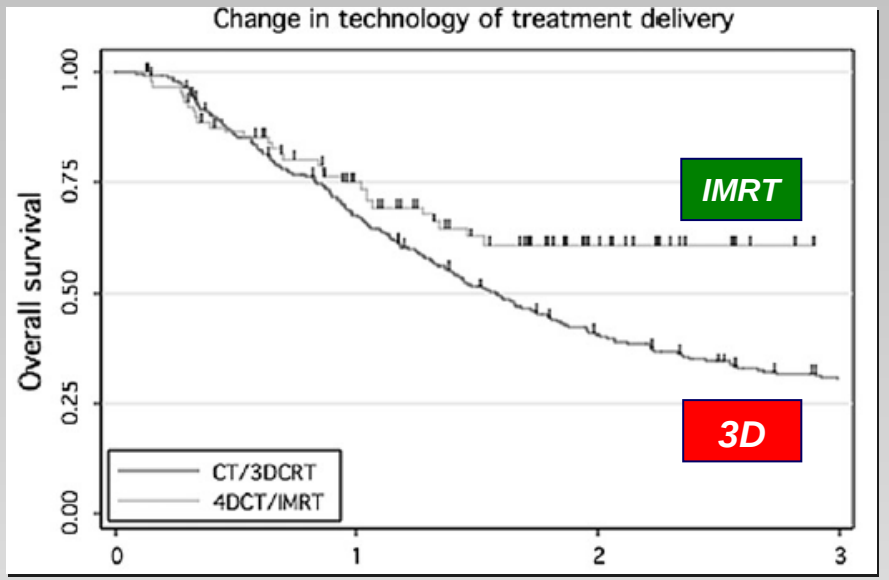
… ma quali parametri considerare ?...

Update del 2010 su 91 pazienti

- Impatto positivo della IMRT sull'outcome

	HR
Local failure	0.37
Metastasis	0.81
Death	**0.039**
Toxicity	**0.017**

Favouring IMRT



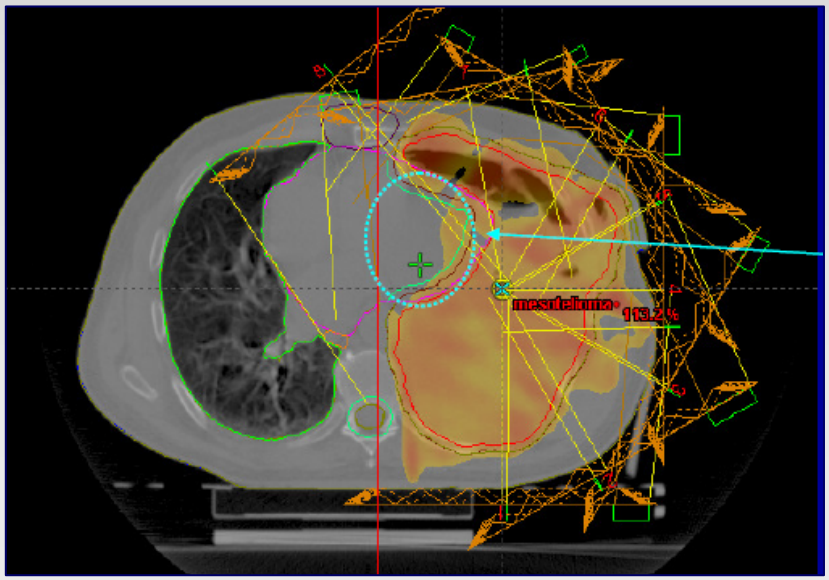
Liao et al. 2010

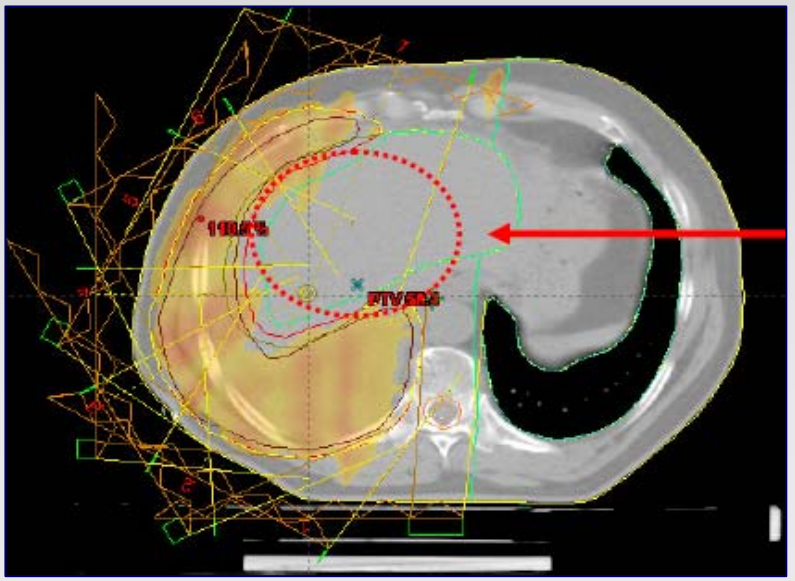
- Conferma dei risultati dosimetrici
  - IMRT superiore a 3D-CRT alle dosi considerate significative per la definizione dei constraints (V20-V30)
  - Incremento della irradiazione polmonare alle basse dosi con IMRT

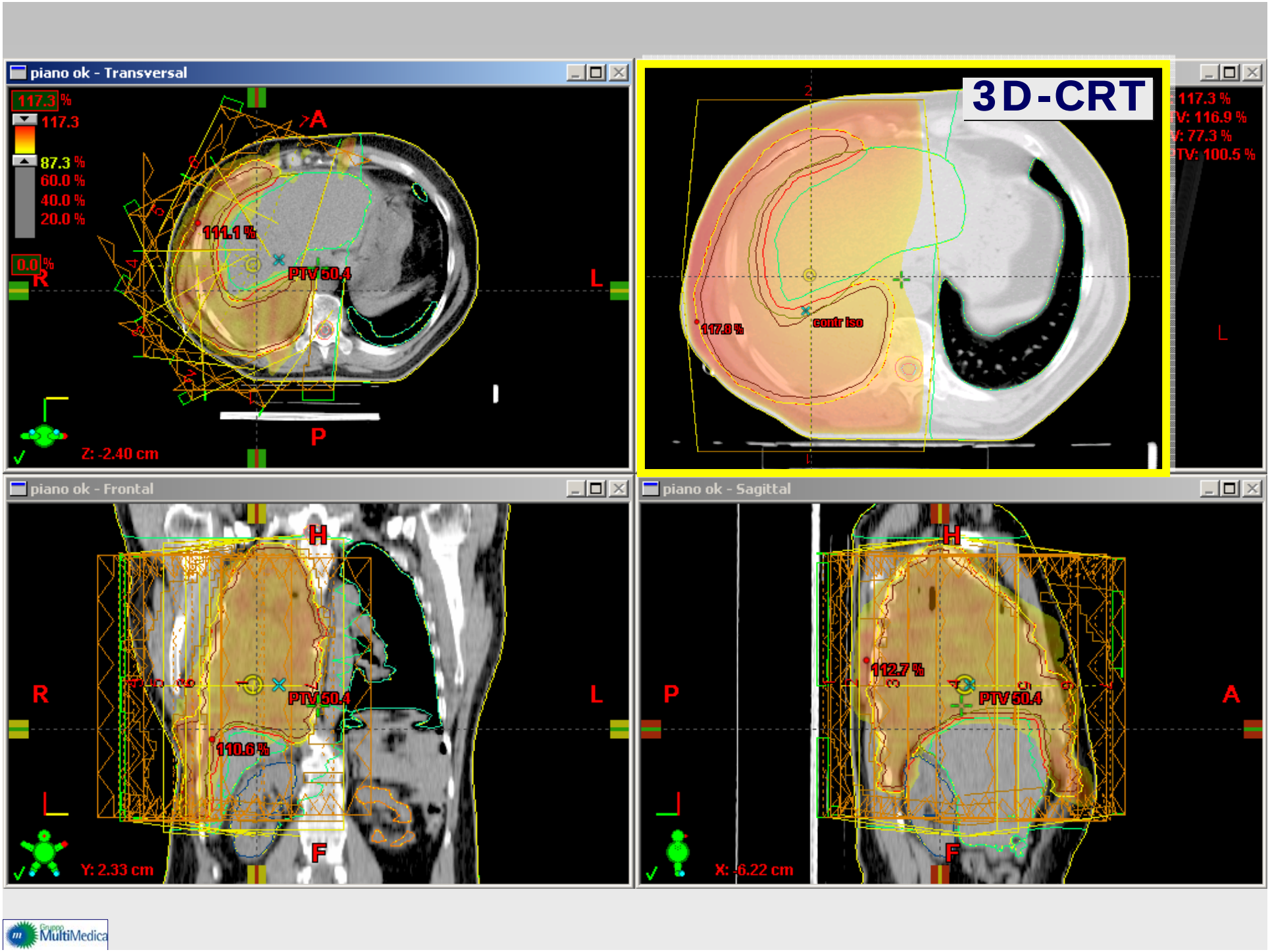
Impatto clinico?

Mesotelioma

- Si aboliscono i fasci di elettroni e le incertezze dosimetriche conseguenti
- La copertura del PTV è superiore rispetto a 3D-CRT
- È possibile ottenere un risparmio della irradiazione a livello di alcuni OARs (prevalentemente omolaterali)
- La irradiazione delle strutture sane controlaterali è incrementata






piano ok - Transversal
117.3 %
117.3
87.3 %
60.0 %
40.0 %
20.0 %
0.0 %
A
R
L
P
111.1 %
PTV 50.4
Z: -2.40 cm
3D-CRT
117.8 %
contr iso
117.3 %
V: 116.9 %
V: 77.3 %
TV: 100.5 %
piano ok - Frontal
H
R
L
F
PTV 50.4
110.6 %
Y: 2.33 cm
piano ok - Sagittal
H
P
A
F
112.7 %
PTV 50.4
X: -6.22 cm

Mesotelioma

Case	Volume of CTV (mL)	% CTV covered to 50 Gy	Volume of bCTV (mL)	% bCTV covered to 60 Gy	OAR tolerance exceeded
1	5410	93	117	96	Yes†
2	4248	98	691	99	Yes*
		96	N/A	N/A	Yes†
		94	N/A	N/A	No
5	3003	93	N/A	N/A	Yes†
	2667	95	N/A	N/A	Yes†
	4381	92	494	82	No
	4366	94	434	92	
	1581	2	348	9	

7 pazienti !

Ahamad et al. 2003

- **Buona copertura del bersaglio/i**
- **Disomogeneità**
- **Rispetto dei constraints OARs**

Target or organ	Goal dose or constraint dose
CTV	50 Gy in 25 fractions
bCTV	60 Gy in 25 fractions
Lung	<20% to receive >20 Gy
Liver	<30% to receive >30 Gy
Kidney	<20% to receive >15 Gy
Heart	<50% to receive >45 Gy
Spinal cord	<10% to receive >45 Gy
	No portion to receive >50 Gy
Esophagus	<30% to receive >55 Gy

Mesotelioma

No Random

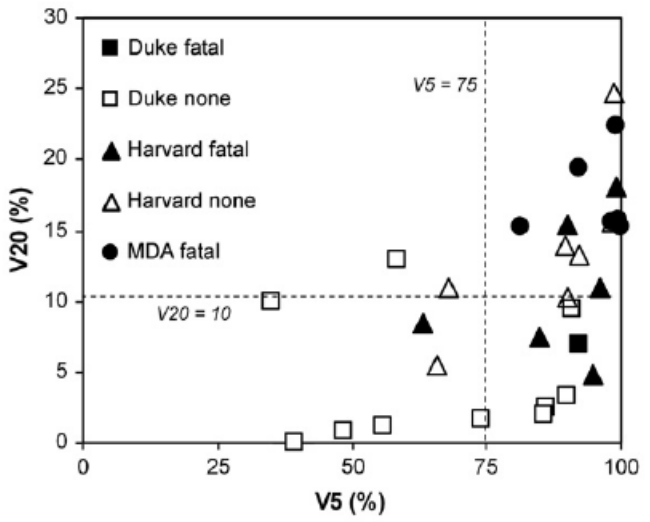
site / ference)	RT technique median dose	Timing of chemotherapy (no. of patients)	Tumor histology	No. of patients	Median survival time (months)	% local failure*	Pulmonary toxicity (no. of patients)†
Farber (15, 30)	30 Gy hemithorax + 20-25 Gy boost	Postoperative	59% E 41% B+S	120	21	9	N/R
M. D. Anderson (24, 27, 43)	45-50 Gy IMRT + 10 Gy boost	"Not Routine"	67% E 24% B 9% S	100 EPP† 63 EPP+RT	14.2	13††	38% (grade 2-3) 9.5% (fatal‡)
Dana Farber (42)	54 Gy hemithorax IMRT	Neoadjuvant (2) Intraoperative (12) Postoperative (10)	62% E 38% B 0% S	13	11‖	N/R	6 (46%, grade 5)
Duke (44)	45 Gy hemithorax/IS/nodes + 10-15 Gy boost	Neoadjuvant (2) Postoperative (10)	77% E 23% B 0% S	13	Not reached	46	**23 %** 3 (grade 2+) 1 (grade 5)
The Netherlands Cancer Institute (20)	54 Gy IMRT	None	93% E 7% B S excluded	15 EPP 12 EPP+RT	29	45¶	N/R

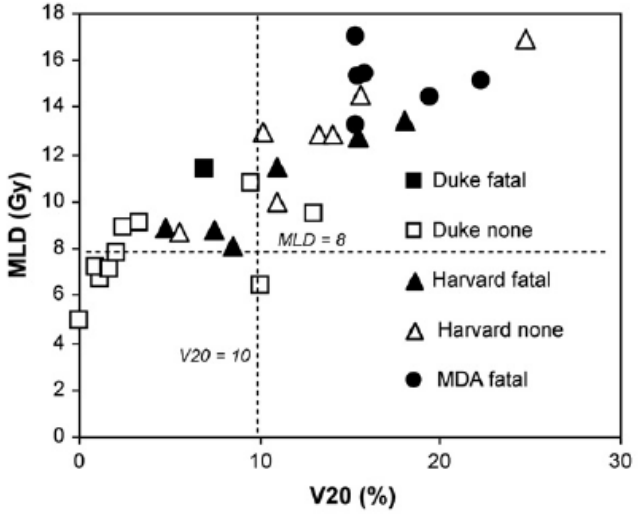
Investigator, institution	Fatality rate (%)	Median radiation dose (Gy)	With vs. without fatal pulmonary toxicity		
			MLD (Gy)	V_{20} (%)	V_5 (%)
Allen *et al.* (5), Harvard	6/13 (46)	54	15 vs. 13 ($p = 0.07$)	18 vs. 11 ($p = 0.08$)	99 vs. 90 ($p = 0.20$)
Rice *et al.* (21), MDACC	6/63 (9.5)	45	11 vs. 8 ($p = 0.003$)	11 vs. 4 ($p = <0.001$)	88 vs. 72 ($p = 0.054$)
Miles et al., DUKE	1/13 (7.7)	45	11 vs. 8 (p = NS)	7 vs. 4 (p = NS)	92 vs. 66 (p = NS)

Qual è il parametro maggiormente predittivo di tossicità polmonare?

Mesotelioma

- 13 pazienti; EEP → 40-55 Gy (+ CT)

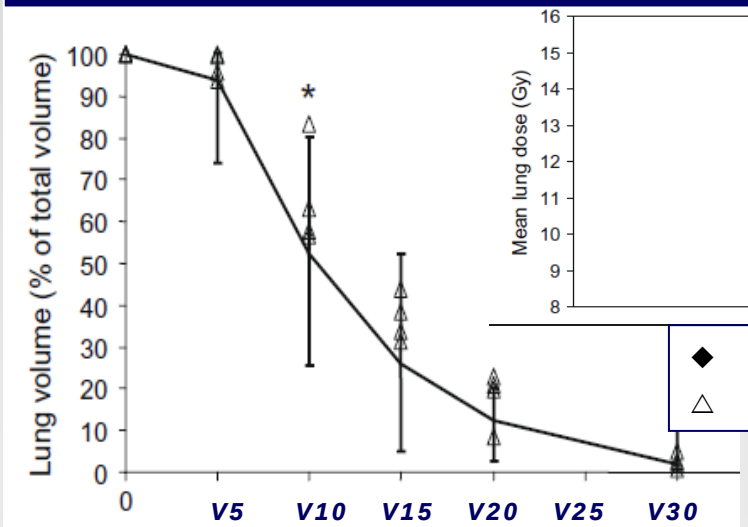




- MLD ≤ 8-10 Gy
- V20 ≤ 4-10%
- V5 ≤ 75%

Miles et al. 2008

- 26 pazienti; iCT → EEP → 50 + 10 Gy



- MLD < 12 Gy
- V20 < 15%
- V10 < 50%

Kristensen et al. 2009

Mesotelioma

REVIEW ARTICLE

Expert Opinions of the First Italian Consensus Conference on the Management of Malignant Pleural Mesothelioma

Carmine Pinto, MD, Andrea Ardizzoni, MD,† Pier Giacomo Betta, MD,‡ Francesco Facciolo, MD,§ Gianfranco Tassi, MD,¶ Sandro Tonoli, MD,‖ Maurizio Zompatori, MD,** Gabriele Alessandrini, MD,§ Stefano Maria Magrini, MD,‖ Marcello Tiseo, MD,† and Vita Mutri, MD**

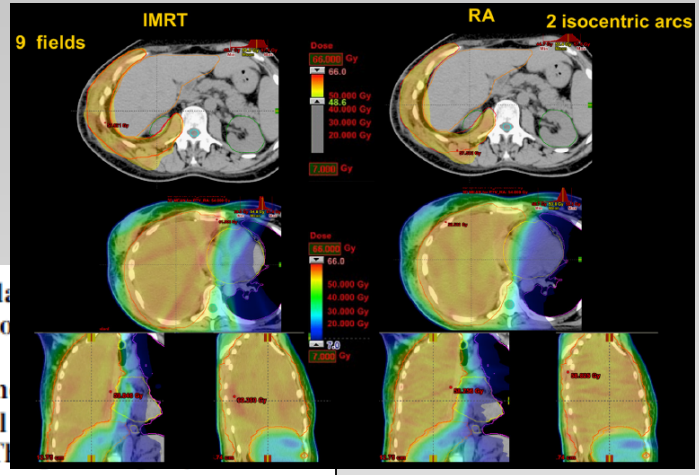
- CTV: 50–54 Gy in 25 fractions for irradiate entire surgical bed, 60 Gy to positive margins (in 25–30 fractions)
- Lung: V20 <10% (7% if possible), with mean dose ≤8.5 Gy
- Liver: V30 <30%
- Contralateral kidney: V15 <20%
- Heart: V45 <50%
- Spinal cord: V45 <10%; maximum dose <50 Gy
- Esophagus: V55 <30%
- In the absence of phase III randomized trials, the panel recommends prospective controlled studies to evaluate the efficacy and tolerability of adjuvant radiotherapy after extrapleural pneumonectomy with a minimum dose of 50 Gy.
- The use of IMRT after extrapleural pneumonectomy should nonetheless be the subject of further investigations and should be used in clinical research studies.
- Radiotherapy after radical surgery (EPP) could avoid local relapse in the majority of cases.
- The rarity of this pathology makes it desirable to share clinical protocols in Centers with an adequate clinical experience in this field.

Mesotelioma

PHYSICS CONTRIBUTION

VOLUMETRIC MODULATION ARC RADIOTHERAPY COMPARED WITH STATIC GANTRY INTENSITY-MODULATED RADIOTHERAPY FOR MALIGNANT PLEURAL MESOTHELIOMA TUMOR: A FEASIBILITY STUDY

MARTA SCORSETTI, M.D.,* MARIO BIGNARDI, M.D.,* ALESSANDRO CLIVIO, M.SC.,† LUCA COZZI, PH.D.,† ANTONELLA FOGLIATA, M.SC.,† PAOLA LATTUADA, M.SC.,* PIETRO MANCOSU, M.SC.,* PIERA NAVARRIA, M.D.,* GIORGIA NICOLINI, M.SC.,† GAETANO URSO, M.SC.,* EUGENIO VANETTI, M.SC.,† SABRINA VIGORITO, M.SC.,* AND ARMANDO SANTORO, M.D.*



Purpose: A planning study was performed to evaluate RapidArc (RA), a volumetric modul
malignant pleural mesothelioma. The benchmark was conventional fixed-field intensity-mo
(IMRT).

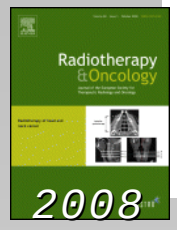
Methods and materials: The computed tomography data sets of 6 patients were included. Th
nine fixed beams were compared against double-modulated arcs with a single isocenter. All
for 15-MV photon beams. The dose prescription was 54 Gy to the planning target volume. T
for the planning target volume were a minimal dose of >95% and maximal dose of <107%. For the organs at risk, the parameters were as follows: contralateral lung, percentage of volume receiving 5 Gy (V_{5Gy}) <60%, V_{20Gy} < 10%, mean <10.0 Gy; liver, V_{30Gy} <33%, mean <31 Gy; heart, V_{45Gy} <30%, V_{50Gy} <20%, dose received by 1% of the volume ($D_{1\%}$) <60 Gy; contralateral kidney, V_{15Gy} <20%; spine, $D_{1\%}$ <45 Gy; esophagus, V_{55Gy} <30%; and spleen, V_{40Gy} <50%. The monitor units (MUs) and delivery time were scored to measure the treatment efficiency. The pretreatment portal dosimetry scored delivery to the calculation agreement with the Gamma Agreement Index.

Results: RA and IMRT provided equivalent coverage and homogeneity. Both techniques fulfilled objectives on organs at risk with a tendency of RA to improve sparing. The conformity index was 1.9 ± 0.1 for RA and IMRT. The number of MU/2Gy was 734 ± 82 for RA and 2,195 ± 317 for IMRT. The planning vs. delivery agreement revealed a Gamma Agreement Index for IMRT of 96.0% ± 2.6% and for RA of 95.7% ± 1.5%. The treatment time was 3.7 ± 0.3min for RA and 13.4 ± 0.1min for IMRT.

Conclusion: RA demonstrated compared with conventional IMRT, similar target coverage and better dose sparing to the organs at risks. The number of MUs and the time required to deliver a 2-Gy fraction were much lower for RA, allowing the possibility to incorporate this technique in the treatment options for mesothelioma patients.

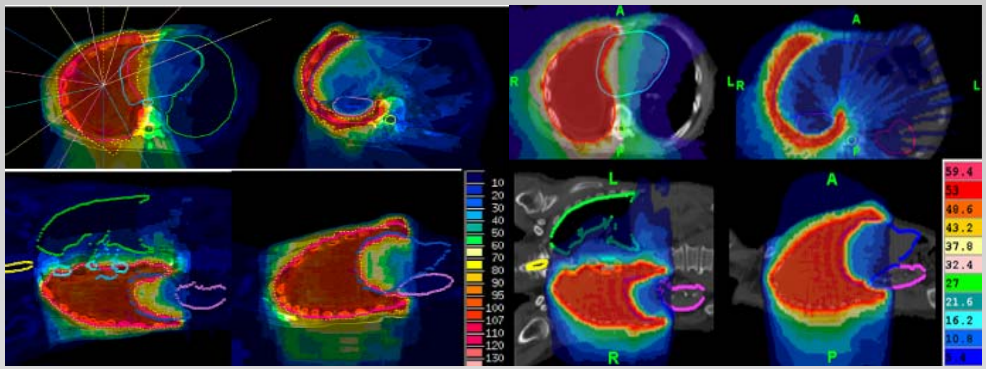
Mesotelioma

Evaluating target coverage and normal tissue sparing in the adjuvant radiotherapy of malignant pleural mesothelioma: Helical tomotherapy compared with step-and-shoot IMRT



Florian Sterzing[a,*], Gabriele Sroka-Perez[a], Kai Schubert[a], Marc W. Münter[b], Christian Thieke[b], Peter Huber[b], Jürgen Debus[a], Klaus K. Herfarth[a]

[a]Department of Radiation Oncology, University of Heidelberg, Germany, [b]Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (dkfz), Heidelberg, Germany



Purpose: To evaluate the potential of helical tomotherapy in the adjuvant treatment of malignant pleural mesothelioma and compare target homogeneity, conformity and normal tissue dose with step-and-shoot intensity-modulated radiotherapy.

Methods and materials: Ten patients with malignant pleural mesothelioma who had undergone neoadjuvant chemotherapy with cisplatin and permetrexed followed by extrapleural pneumonectomy (EPP) were treated in our department with 54 Gy to the hemithorax delivered by step-and-shoot IMRT. A planning comparison was performed by creating radiation plans for helical tomotherapy. The different plans were compared by analysing target homogeneity using the homogeneity indices HI_{max} and HI_{min} and target conformity by using the conformity index CI_{95}. To assess target coverage and normal tissue sparing TV_{90}, TV_{95} and mean and maximum doses were compared.

Results: Both modalities achieved excellent dose distributions while sparing organs at risk. Target coverage and homogeneity could be increased significantly with helical tomotherapy compared with step-and-shoot IMRT. Mean dose to the contralateral lung could be lowered beyond 5 Gy.

Conclusions: Our planning study showed that helical tomotherapy is an excellent option for the adjuvant intensity-modulated radiotherapy of MPM. It is capable of improving target coverage and homogeneity.

More sophistication…

… more room for error?

Chris Cottrill
Department of Radiotherapy
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London