



# Irradiazione Mammaria Ipofrazionata: valutazione di appropriatezza, efficacia ed efficienza.

## Contra

*Luigia Nardone*



UNIVERSITÀ  
CATTOLICA  
del Sacro Cuore

# Appropriatezza

L'idea di **appropriatezza** in Sanità è nata da un editoriale del British Medical Journal :

“Appropriateness: the next frontier”

- per orientare le scelte di amministratori e clinici
- per risolvere la crescente crisi finanziaria della sanità

# Appropriatezza

- Nel 2004 la Società Italiana per la Qualità dell'Assistenza Sanitaria in una dichiarazione programmatica ha elencato i dodici principi per il miglioramento della Sanità
- Appropriatezza ed efficacia sono definiti come mezzi necessari per realizzare interventi clinici e organizzativi secondo il metodo scientifico
- Efficienza è determinata dalla ottimizzazione delle risorse

## **Carta di Portonovo**

### *Principi della Qualità*

- 1. *Centralità della persona*
- 2. *Etica ed Equità*
- 3. *Condivisione, Coerenza e Uniformità*
- 4. *Valutazione*
- 5. *Leadership: apertura, trasparenza e collaborazione*
- 6. **Efficacia e appropriatezza**
- 7. *Sicurezza*
- 8. **Efficienza**
- 9. *Integrazione e continuità assistenziale*
- 10. *Informazione, comunicazione e partecipazione*
- 11. *Innovazione e creatività*
- 12. *Competenza e formazione*

# Appropriatezza

Un intervento sanitario è **appropriato** quando:

a parità di “resa” clinica (efficacia), è in grado di ottimizzare l’impiego delle risorse (efficienza).

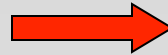
- Appropriatezza **metodologica**
  - *formulazione della diagnosi e correttezza dell’intervento terapeutico*
- Appropriatezza **scientifica**
  - *conoscenze scientifiche su cui si basano le decisioni*
- Appropriatezza **organizzativa**
  - *utilizzo del miglior contesto per erogare la prestazione*
- Appropriatezza **economica**
  - *valutazione di una procedura perché sia non solo adeguata alla situazione patologica ma non faccia spendere troppo*

**“ Riferire ogni azione clinica e organizzativa ai dati e al metodo scientifico ”**

# Appropriatezza metodologica e scientifica

## “intervento giusto al paziente giusto”

- Dei pazienti



Età  
Stadio di T e di N  
Dimensione mammaria  
Radiosensibilità individuale

- Del tumore



Fattori prognostici e predittivi  
Indici di aggressività biologica

- Dei trattamenti



Razionale radiobiologico  
Frazionamento, Boost  
Terapie sistemiche

# Età

**I DATI SONO INSUFFICIENTI**

**PER PAZIENTI SOTTO I 50 ANNI !**

## NOTA

*Smith BD IJROBP 81,1, 2011*

- Il rischio di RL decresce con l'età <40 (elevato) >70 (molto basso)
- Il rischio di RL decresce con l'età <40 (elevato) >70 (molto basso)
- Solo lo Studio Canadese ha stratificato x età (305 pz), senza report per il sottogruppo
- Solo lo Studio Canadese ha stratificato x età (305 pz), senza report per il sottogruppo
- Tra 70% e 79% pazienti >50 anni

# Radiosensitività

**QUANTEC: VISION PAPER**

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S145-S150, 2010

## **BIOMARKERS AND SURROGATE ENDPOINTS FOR NORMAL-TISSUE EFFECTS OF RADIATION THERAPY: THE IMPORTANCE OF DOSE-VOLUME EFFECTS**

SØREN M. BENTZEN, PH.D., D.Sc.,<sup>\*†</sup> MATTHEW PARLIAMENT, M.D.,<sup>‡</sup> JOSEPH O. DEASY, PH.D.,<sup>§</sup>  
ADAM DICKER, M.D., PH.D.,<sup>†¶</sup> WALTER J. CURRAN, M.D.,<sup>¶||</sup> JACQUELINE P. WILLIAMS, PH.D.,<sup>\*\*</sup>  
AND BARRY S. ROSENSTEIN, PH.D.<sup>††</sup>

### **VARIABILITA' BIOLOGICA**

Determinanti biologici di rischio di tossicità sui tessuti normali variabili individualmente e responsabili di effetti patogenetici .

# BIOMARKERS PREDITTIVI e di RISPOSTA

- **Citochine e fattori di crescita**

- Trasforming Growth Factor -  $\beta$ 1 (TGF- $\beta$ 1)

- Profibrotico a “basse dosi”

- Trasforming Growth Factor -  $\beta$ 1 (TGF- $\beta$ 1)

- Profibrotico a “basse dosi”

- **Inteleukina 1 $\alpha$  (IL-1 $\alpha$ ) e IL-6**

- Proinfiammatorie

- **Variazioni genetiche**

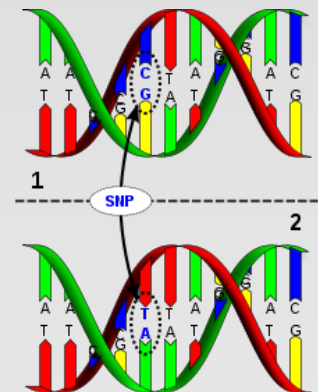
- Mutazioni gene ATM

- Iperradiosensibilità a “basse dosi”

- Polimorfismi a singolo nucleotide (SNPs)

X-Ray Cross Complementing (XRCC)

**XRCC1 e XRCC3 Sono associati alla aumentata radiosensibilità nel BC e differente capacità riparativa**





**CLINICAL INVESTIGATION**

**Breast**

**ASSOCIATION BETWEEN GENETIC POLYMORPHISMS IN THE XRCC1, XRCC3, XPD, GSTM1, GSTT1, MSH2, MLH1, MSH3, AND MGMT GENES AND RADIOSENSITIVITY IN BREAST CANCER PATIENTS**

MONICA MANGONI, M.D., PH.D.,\* SIMONETTA BISANZI, M.Sc.,† FRANCESCA CAROZZI, PH.D.,†

CRISTINA SANI, M.Sc.,† GIAMPAOLO BITTI, M.D.,\* LORENZO LIVI, M.D.,\*

EMANUELA BARLETTA, M.D., PH.D.,‡ ADELE SENIORI COSTANTINI, M.D.,§ AND GIUSEPPE GORINI, M.D.§

\*Clinical Physiopathology Department, Radiotherapy Unit, University of Florence, Italy; †Analytical and Biomolecular Cytology Unit, Cancer Prevention and Research Institute (ISPO), Florence, Italy; ‡Department of Experimental Pathology and Oncology, University of Florence, Florence, Italy; §Occupational and Environmental Epidemiology Unit, Cancer Prevention and Research Institute (ISPO), Florence, Italy

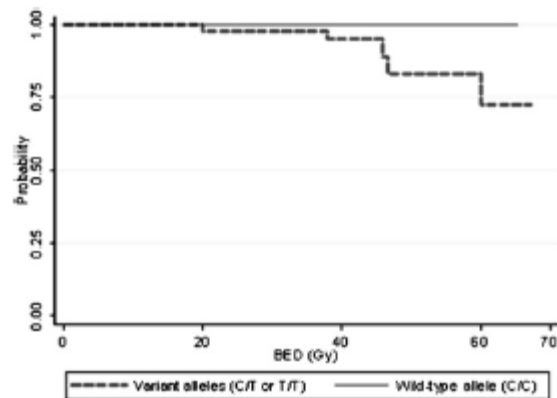


Fig. 1. Probability of not developing severe acute skin reactions (Grade  $\geq 2c$ ) after radiotherapy among carriers of the wild-type allele (C/C) and of the variant alleles (C/T or T/T), genetic polymorphism XRCC3-Thr241Met. Breast cancer patients treated with radiotherapy only ( $n = 61$ ). BED = biologically effective radiation dose.

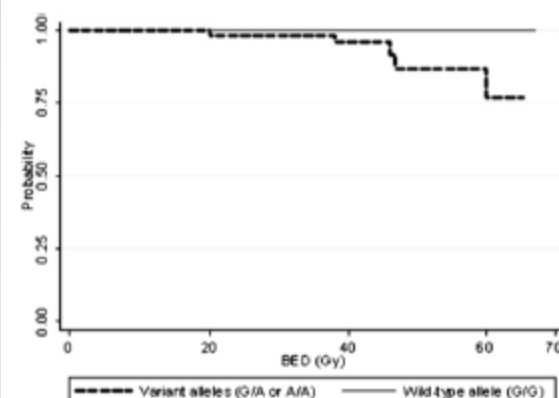
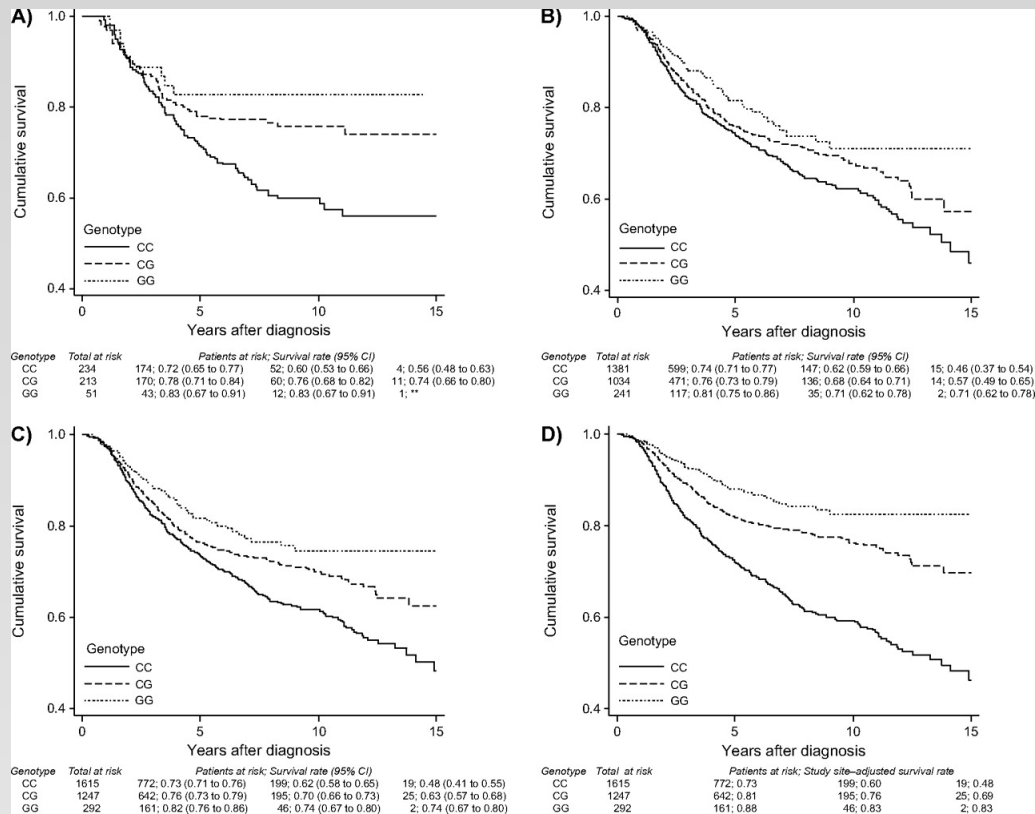


Fig. 3. Probability of not developing severe acute skin reactions (Grade  $\geq 2c$ ) after radiotherapy among carriers of the wild-type allele (G/G) and of the variant alleles (G/A or A/A), genetic polymorphism MSH3-Ala1045Thr. Breast cancer patients treated with radiotherapy only ( $n = 61$ ). BED = biologically effective radiation dose.

# Association Between a Germline *OCA2* Polymorphism at Chromosome 15q13.1 and Estrogen Receptor–Negative Breast Cancer Survival

Elizabeth M. Azzato, Jonathan Tyrer, Peter A. Fasching, Matthias W. Beckmann, Arif B. Ekici, Rüdiger Schulz-Wendtland, Stig E. Bojesen, Børge G. Nordestgaard, Henrik Flyger, Roger L. Milne, José Ignacio Arias, Primitiva Menéndez, Javier Benítez, Jenny Chang-Claude, Rebecca Hein, Shan Wang-Gohrke, Heli Nevanlinna, Tuomas Heikkinen, Kristiina Aittomäki, Carl Blomqvist, Sara Margolin, Arto Mannermaa, Veli-Matti Kosma, Vesa Kataja, The Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer, Jonathan Beesley, Xiaqing Chen, Georgia Chenevix-Trench, Fergus J. Couch, Janet E. Olson, Zachary S. Fredericksen, Xianshu Wang, Graham G. Giles, Gianluca Severi, Laura Baglietto, Melissa C. Southey, Peter Devilee, Rob A. E. M. Tollenaar, Caroline Seynaeve, Montserrat García-Closas, Jolanta Lissowska, Mark E. Sherman, Kelly L. Bolton, Per Hall, Kamila Czene, Angela Cox, Ian W. Brock, Graeme C. Elliott, Malcolm W. R. Reed, David Greenberg, Hoda Anton-Culver, Argyrios Ziogas, Manjeet Humphreys, Douglas F. Easton, Neil E. Caporaso, Paul D. P. Pharoah

Manuscript received July 29, 2009; revised February 1, 2010; accepted February 15, 2010.



Cumulative overall survival among patients with estrogen receptor (ER)–negative breast cancer by genotype of the single-nucleotide polymorphism rs4778137.



# Analysis of Gene Expression Using Gene Sets Discriminates Cancer Patients with and without Late Radiation Toxicity

J. Peter Svensson<sup>1,2</sup>, Lukas J. A. Stalpers<sup>3</sup>, Rebecca E. E. Esveldt-van Lange<sup>1</sup>, Nicolaas A. P. Franken<sup>3</sup>, Jaap Haveman<sup>3</sup>, Binie Klein<sup>1</sup>, Ingela Turesson<sup>2</sup>, Harry Vrieling<sup>1</sup>, Micheline Giphart-Gassler<sup>1\*</sup>

<sup>1</sup>Department of Radiation Oncology, Academic Hospital, and Clinical Immunology, Academic Hospital, <sup>2</sup>Department of Radiation Oncology, Academic Hospital, <sup>3</sup>Department of Radiation Oncology, Academic Hospital, c Medical Center, University of Amsterdam,

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ALEX

**VARIABILITA' BIOLOGICA**  
nella radioresponsività potrebbe in futuro  
**guidare la scelta terapeutica**

Mitigare il rischio in soggetti ad alto rischio  
Intensificare la terapia in soggetti a basso  
rischio

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**ASSOCIATION BETWEEN GENETIC POLYMORPHISMS IN THE XRCC1, XRCC3, XPD, GSTM1, GSTT1, MSH2, MLH1, MSH3, AND MGMT GENES AND RADIOSENSITIVITY IN BREAST CANCER PATIENTS**

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# Caratteristiche del tumore

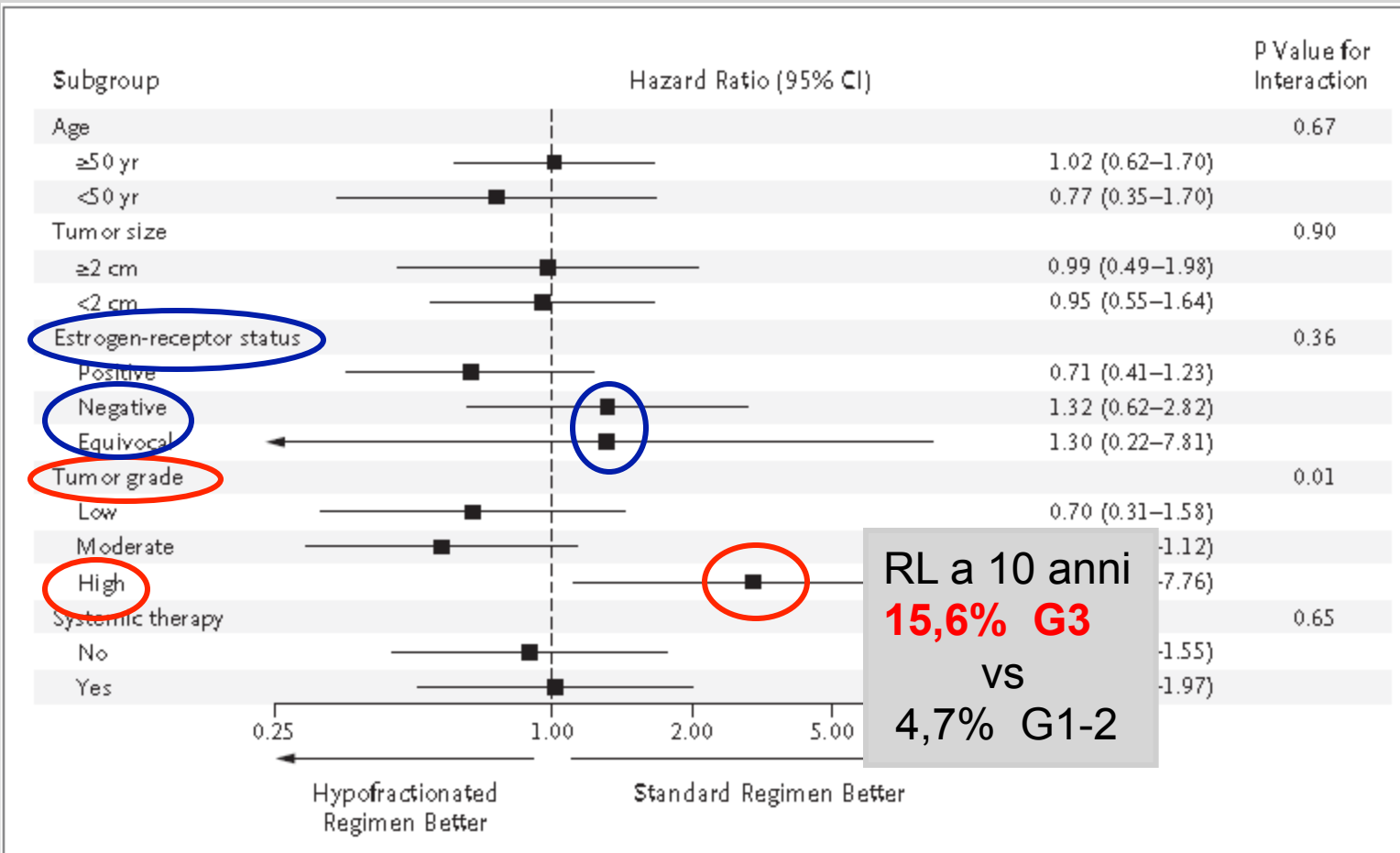
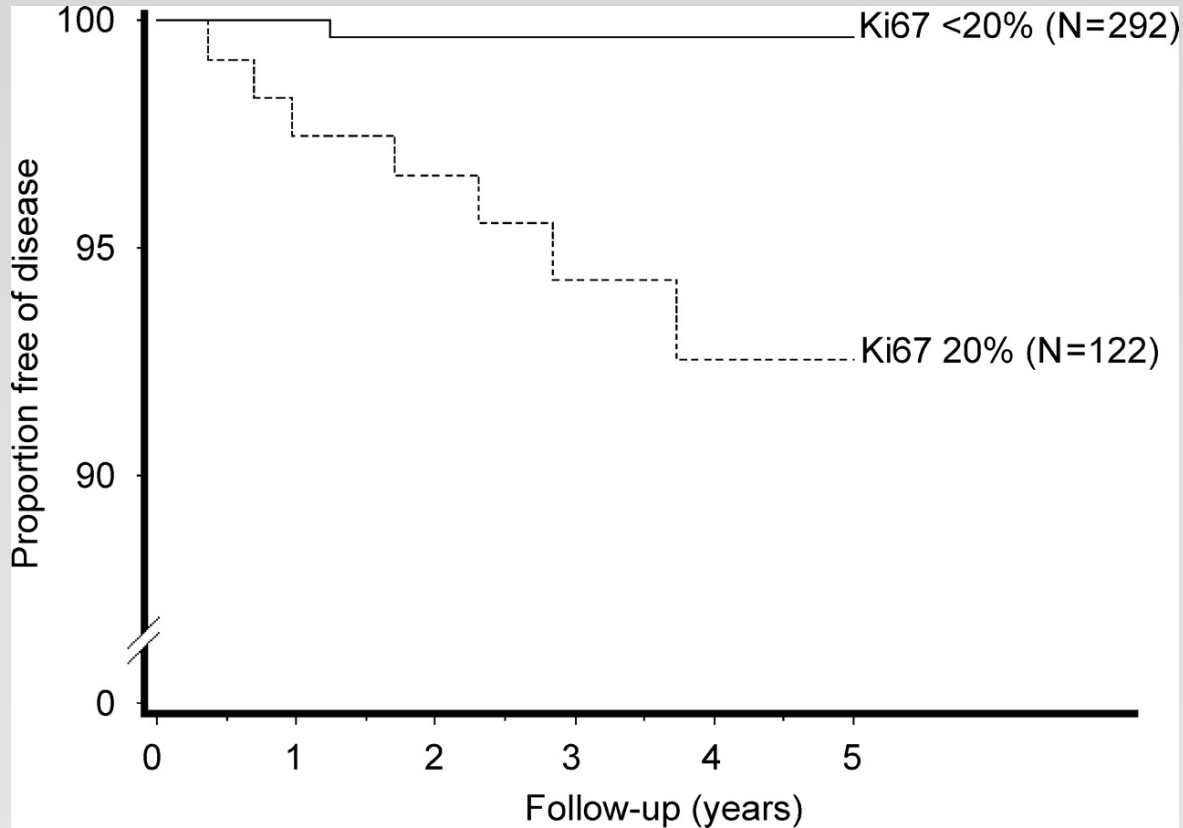


Figure 2. Hazard Ratios for Ipsilateral Recurrence of Breast Cancer in Subgroups of Patients.

# La biologia del tumore

**Kaplan–Meier plots of disease-free survival comparing elevated Ki-67 ( $\geq 20\%$ ) versus low Ki-67 ( $<20\%$ ) for pT1mic, pT1a, pT1b node-negative breast cancer.**



## Age, Breast Cancer Subtype Approximation, and Local Recurrence After Breast-Conserving Therapy

Nils D. Arvold, Alphonse G. Taghian, Andrzej Niemierko, Rita F. Abi Raad, Meera Sreedhara, Paul L. Nguyen, Jennifer R. Bellon, Julia S. Wong, Barbara L. Smith, and Jay R. Harris

### Patients and Methods

We studied 1,434 consecutive patients with invasive BC who received BCT from December 1997 to July 2006. Ninety-one percent received adjuvant systemic therapy; no patients received trastuzumab.

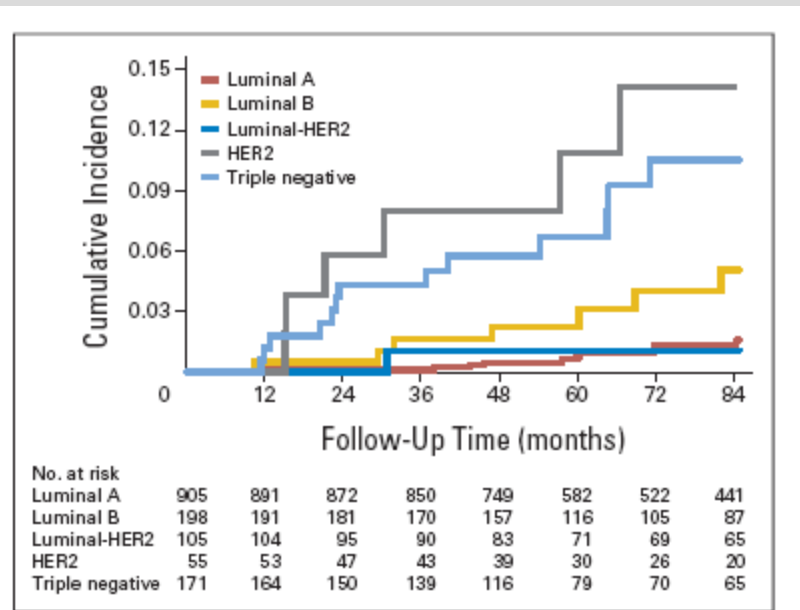


Fig 2. Unadjusted cumulative incidence of local recurrence by breast cancer subtype on the basis of competing risks analysis. HER2, human epidermal growth factor receptor 2.

Variabilità RL secondo fattori prognostici

# Variabilità RL secondo fattori prognostici

VOLUME 28 • NUMBER 10 • APRIL 1 2010

JOURNAL OF CLINICAL ONCOLOGY

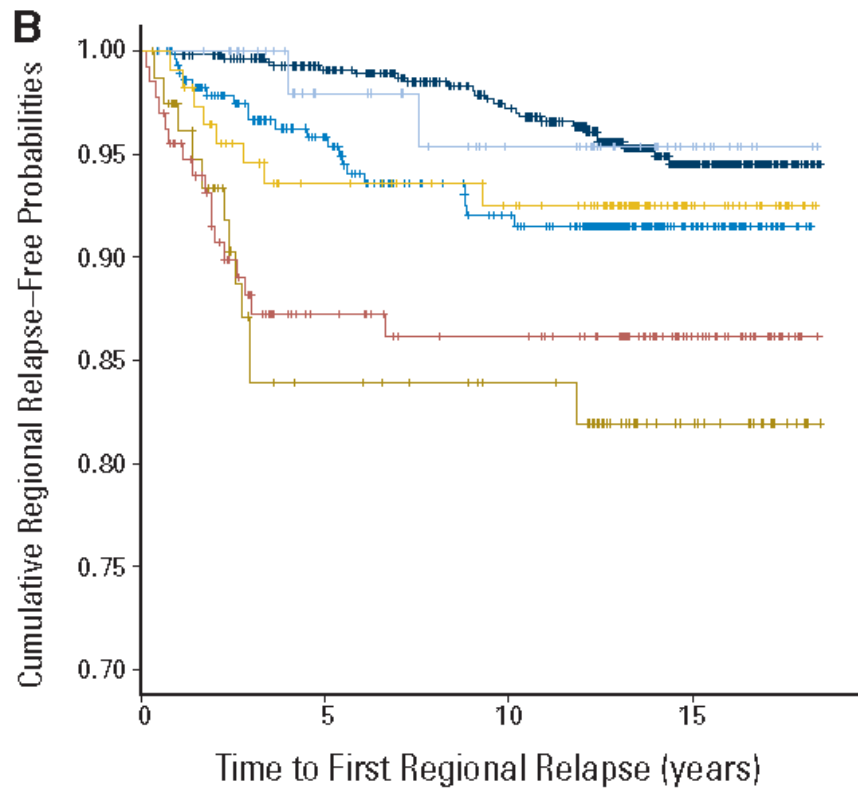
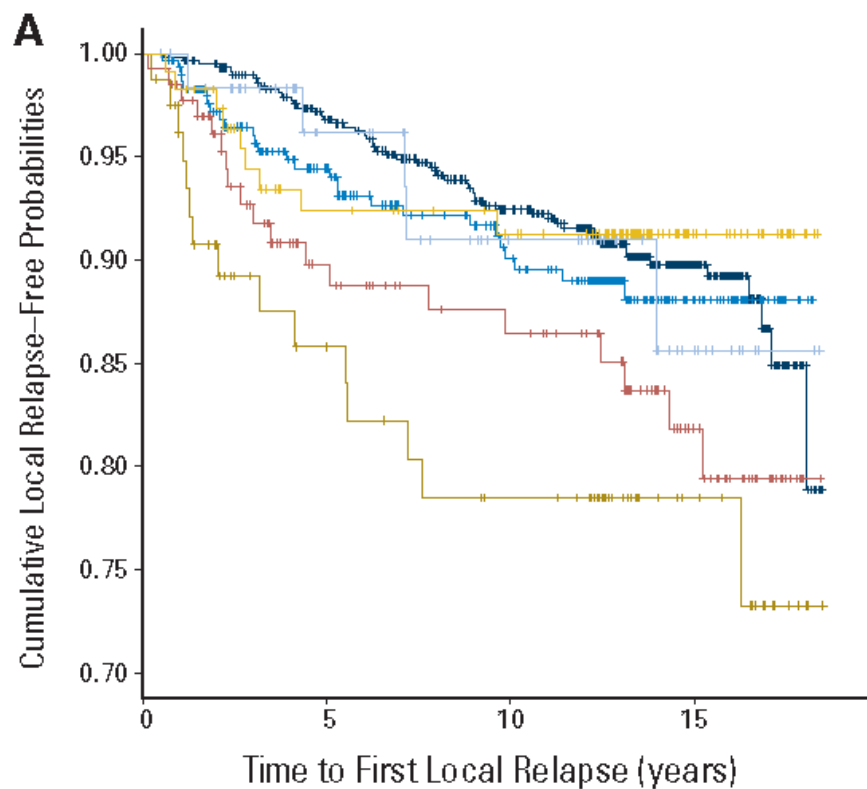
ORIGINAL REPORT

## Breast Cancer Subtypes and the Risk of Local and Regional Relapse

*K. David Voduc, Maggie C.U. Cheang, Scott Tyldesley, Karen Gelmon, Torsten O. Nielsen, and Hagen Kennecke*

### Sottotipi biomolecolari

LUMINAL A	—	TRIPLE NEG	—
LUMINAL B	—	BASAL	—
LUMINAL HER2	—	HER2 +3	—



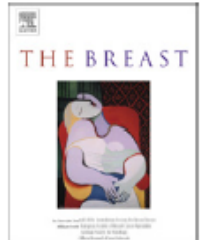
# .....il trattamento giusto

- Frazionamento
- Boost
- Tecnica RT
- Associazione con terapie sistemiche



Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

# The Breast

journal homepage: [www.elsevier.com/brst](http://www.elsevier.com/brst)

Original article

## Pushing the limits of hypofractionation for adjuvant whole breast radiotherapy

John Yarnold <sup>a,\*</sup>, Joanne Haviland <sup>b</sup>

**Schema of the UK FAST trial testing two dose levels of a 5-fraction regimen delivered as one fraction per week versus 50 Gy in 25 fractions over 5 weeks to the whole breast after local tumour excision of early breast cancer.**

Group	Total dose (Gy)	Fraction size (Gy)	Number of fractions	Fractions per week
Control	50.0	2.0	25	5
Test 1 <sup>a</sup>	30.0	6.0	5	1
Test 2 <sup>b</sup>	28.5	5.7	5	1

<sup>a</sup> Iso-effective with Control if  $\alpha/\beta = 4.0$  Gy.

<sup>b</sup> Iso-effective with Control if  $\alpha/\beta = 3.0$  Gy.



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Età ≥50 anni

T&lt;3cm N0

No boost

No chemioterapia

Phase III randomised trial

First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015)

## Fractionation schedule

	50 Gy, N = 239 (%)	30 Gy, N = 248 (%)	28.5 Gy, N = 242 (%)
--	--------------------------	--------------------------	----------------------------

No change	189 (79.1)	160 (64.5)	184 (76.0)
Mild change	46 (19.2)	65 (26.2)	49 (20.2)
Marked change	4 (1.7)	23 (9.3)	9 (3.7)

50 Gy end	Risk ratio for 28.5 Gy vs 50 Gy (95% CI), p-value for trend	Risk ratio for 30 Gy vs 28.5 Gy (95% CI), p-value for trend
	1, p = 0.26	1, p = 0.002
	1.07 (0.75–1.54)	1.37 (1.00–1.90)
	2.25 (0.70–7.18)	2.70 (1.28–5.67)

Relapses, second primary cancers and deaths by

**35.5%**

Total

50 Gy 30 Gy 28.5 Gy

Other cause<sup>a</sup> 4“In conclusion, a **5-fraction schedule** of whole breast radiotherapy delivered in once-3 6 **13**entified that **is fully fractionated****e in breast**

annual clinical

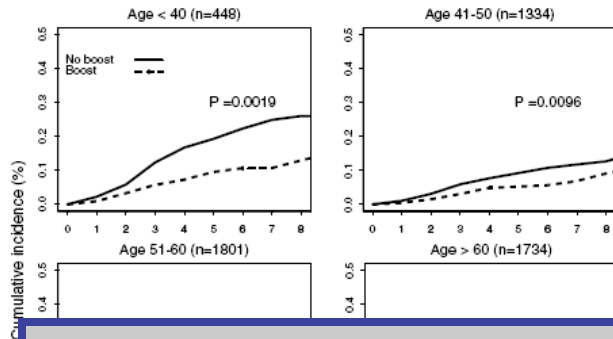
assessments of a range of adverse effects in the breast recorded at a median of **3.1 years.**”<sup>a</sup> Deaths from other causes included 4 cardiac-related events, 2 of which were in patients who received left-sided radiotherapy.

Breast cancer	2	2	6	10
Other cause <sup>a</sup>	4	3	6	13

<sup>a</sup> Deaths from other causes included 4 cardiac-related events, 2 of which were in patients who received left-sided radiotherapy.

# Boost

N. Antonini et al. / Radiotherapy and Oncology 82 (2007) 265–271



La somministrazione del boost riduce globalmente il tasso di recidiva locale di un fattore di 2 ( $p < 0.0001$ )

**BOOST SI – BOOST NO?  
SECONDO QUALI CRITERI**

	42.5 Gy/13F	41.0 Gy/13F	40 Gy/13F	42.5 Gy/10F
Experimental arm A	42.5 Gy/13F	41.0 Gy/13F	40 Gy/13F	42.5 Gy/10F
Experimental arm B	39 Gy/13F	39 Gy/13F	N/A	N/A
Mean age (years)	54.5	57.2	57.4	Not reported
Node + (%)	32.7	28.8	22.8	0
Mastectomy (%)	0	15	8	0
Boost (%)	74.5	60.6	42.6	0
Chemotherapy (%)	15.9	33.3	22.2	11
Regional RT (%)	20.6	14.2	7.3	0

# Irradiazione di N

Canada (18, 19, 21)  
N = 1,234

RMH/GOC (17, 20)  
N = 1,410

START A (10)  
N = 2,236

START B (16)  
N = 2,215

n

%

n

%

n

%

n

%

**SCARSITA' di POPOLAZIONE e BREVE  
FOLLOW-UP PER DATI SICURI di  
EFFICACIA e TOSSICITA'  
per RACCOMANDARE  
IPOFRAZIONAMENTO su N**

•T3-4 trattati con MR

•Tra 26% e 60% N+ : 21%, 14% e 7% irradiati su N

# Tossicità cutanea e sottocutanea tardiva e cosmesi

Canada (18, 19, 21)      RMH/GOC (17, 20)      START A (10)      START B (16)

**“NO COMMENT”**

**“Peso” della Chirurgia non confrontabile per tecniche e ricostruzione oncoplastica**

**Radioterapia “desueta”**

RMH/GOC	19,31	5, 10	50/25	60.4	46.6	6.4	9.8
			42.9/13	54.3	42.0	11.2	15.6
			39/13	69.7	43.9	3.9	6.6
START A	29,34	5	50/25	59.0		1.0*	
			41.6/13	58.1		1.09*	
			39/13	65.9		0.69*	
START B	30,34	5	50/25	58.8		1.0*	
			40/15	64.5		0.83*	
Canadian	28,35	5, 10	50/25	79.2	71.3		
			42.5/16	77.9	69.8		

# Frazionamento e mortalità cardiaca

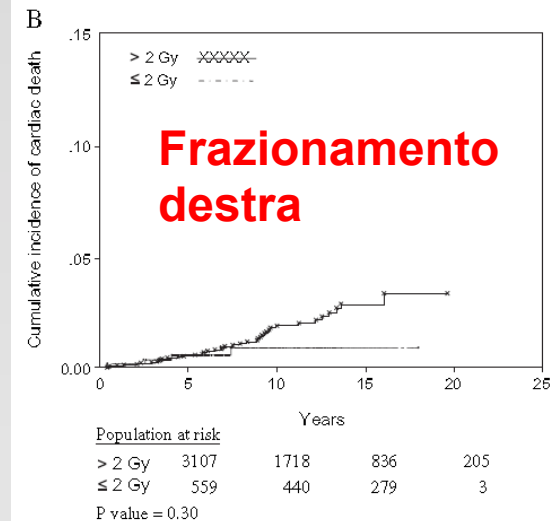
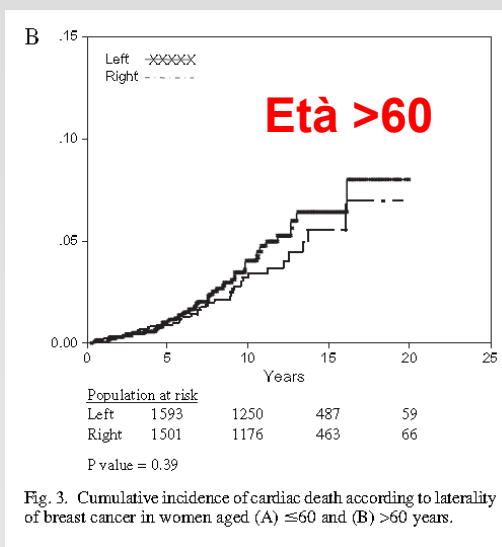
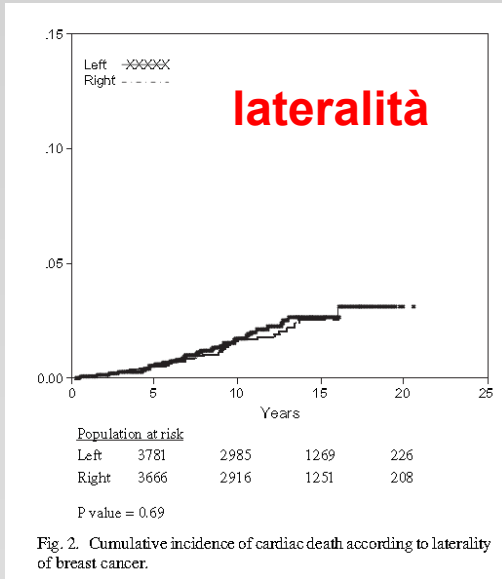


Fig. 4. Cumulative incidence of cardiac death according to fraction size in women with (A) left-sided and (B) right-sided breast cancer.

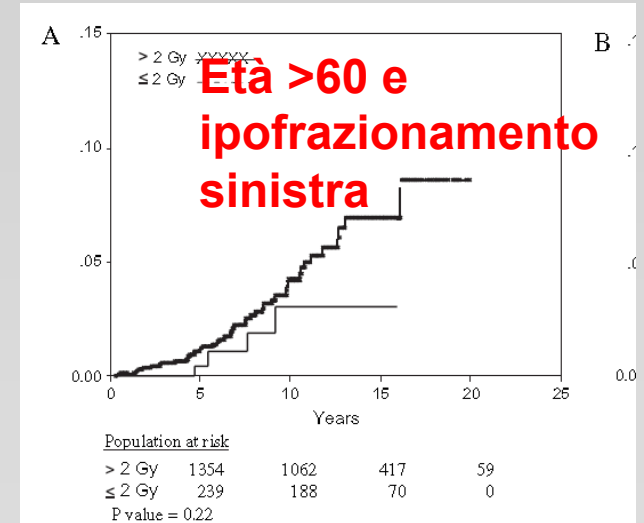


Fig. 5. Cumulative incidence of cardiac death according to fraction size in women  $>60$  years with (A) left-sided

F-up medio 7,9 (0.3-20.5)

Rischio Relativo a 10 anni per età  $>60$  e frazioni  $>2$  Gy

**1.22**

## RADIATION-RELATED HEART DISEASE: CURRENT KNOWLEDGE AND FUTURE PROSPECTS

SARAH C. DARBY, PH.D.,\* DAVID J. CUTTER, F.R.C.R.,\* MARJAN BOERMA, PH.D.,†

Mortalità correlata a malattia cardiaca

Standard 1,5%

**Ipofrazionamento 1,9%**

*“Mantenere il volume e la dose cardiaca ai livelli minori possibili”*

QUALE TOSSICITA' CARDIACA DOPO PIU' LUNGO F-UP?



Contents lists available at SciVerse ScienceDirect

# Radiotherapy and Oncology

journal homepage: [www.thegreenjournal.com](http://www.thegreenjournal.com)



## Editorial

### Radiation-induced heart morbidity after adjuvant radiotherapy of early breast cancer – Is it still an issue?

Birgitte Offersen\*, Inger Høiris, Marie Overgaard

**RACE STUDY**  
**(Danish e Swedish case-control study)**  
**In corso**

“There  
risk of

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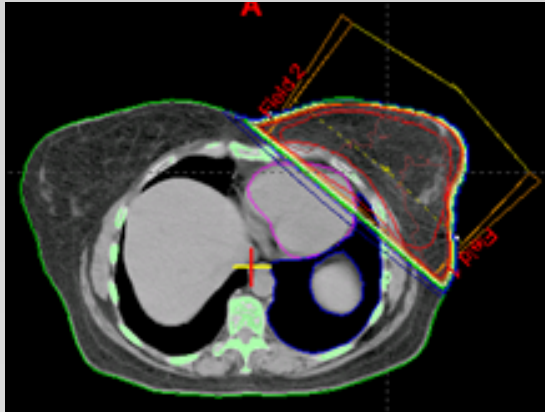
apy and the

**elineation** of  
for breast  
of the patients  
y.....

....there are still patients with unfavourable anatomy combined with a tumour bed just in front of the heart who receive a high dose to the heart. “



# Dimensione mammaria



Solo 14%-16% in START trials

	Canada (18, 19, 21)	RMH/GOC (17, 20)	START A (10)	START B (16)
Energy	Co-60, 4 MV or 6 MV	6 MV*	6 MV*	6 MV*
Wedges	Yes	Yes	Yes	Yes
Inhomogeneity cCorrections		GOC only	Variable	Variable
Planning	2D	2D RMH 3D GOC	2D or 3D	2D or 3D
Central Axis Dose Homogeneity	7% to +7%	5% to +7%	5% to +5%	5% to +5%
Separation	≤ 25 cm			

- Scelta della tecnica RT ottimale

# Dimensione mammaria e tossicità

Breast radiotherapy



Scelta della tecnica RT ottimale

236-240

Preferibile utilizzo di **IMRT** per migliorare omogeneità di dose, ridurre Hot Spot e tossicità

**Active Breath Hold**

**IMRT Posizione prona**

John R. Yarnold

# Terapie sistemiche: chemio

Ca

**DIVERSI SCHEMI CT  
SOTTOGRUPPI TROPPO PICCOLI  
FOLLOW-UP TROPPO BREVI**

**MANCANZA di DATI PER  
CT CONCOMITANTE  
CT NEO-ADIUVANTE**

Canadian RMH/GOC



CMF o altro

Nessuna paziente ha ricevuto Trastuzumab

# Terapie sistemiche: ormonoterapia

DONNE IN POST MENOPAUSA  
OGGI ASSUMONO I.A.

Ta

Non riportato se concomitante o sequenziale alla RT

Scarso uso di Inibitori Aromatasi

# Shorter fractionation schedules in breast cancer radiotherapy: Clinical and economic implications

Mariella Mannino, John R. Yarnold\*



45 (2009) 730-731

The Breast 19 (2010) 192–197

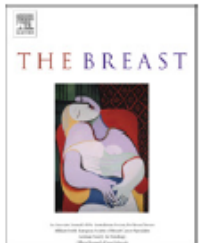


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The Breast

journal homepage: [www.elsevier.com/brst](http://www.elsevier.com/brst)



Original article

## Hypofractionated breast radiotherapy: Financial and economic consequences

Yolande Lievens\*

*Department of Radiation Oncology, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium*

# Appropriatezza organizzativa ed economica

## Elementi che incidono sui costi totali

### – **Attività del centro**

- Costi del personale
- Costi e Ammortamento macchine e Volume di lavoro
- Tipologia di pazienti
- Expertise

### – **Complessità del trattamento**

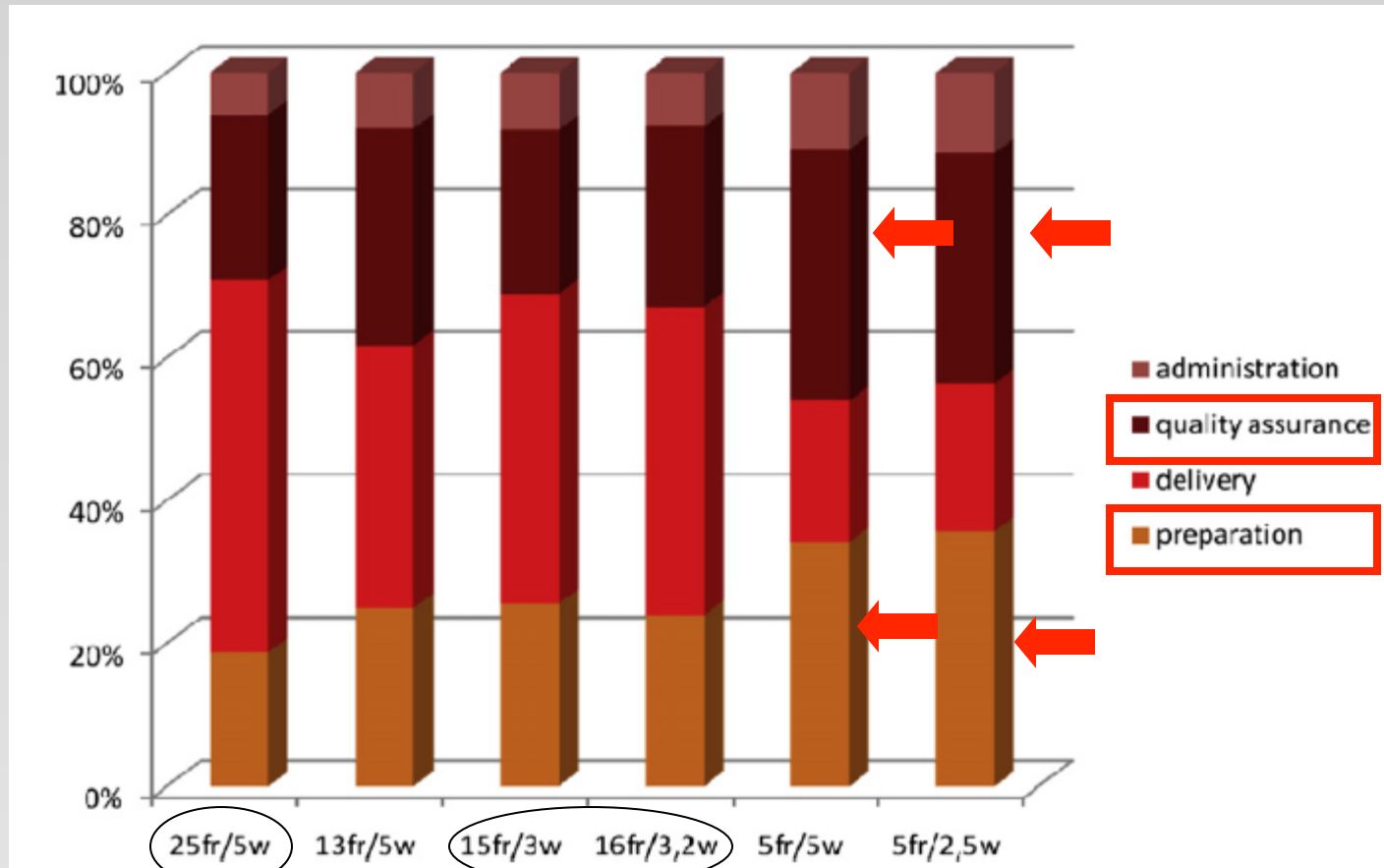
- Treatment planning
- Numero campi - Numero di frazioni
- IMRT – IGRT...
- Tempo di occupazione per ciascun operatore (medico tecnico fisico..) per ogni procedura
- Costi diretti (materiale di consumo)

### – **Organizzazione ospedaliera strutturale e amministrativa**

### – **Organizzazione SSN, Assicurazioni**

### – **Costi del paziente e familiari**

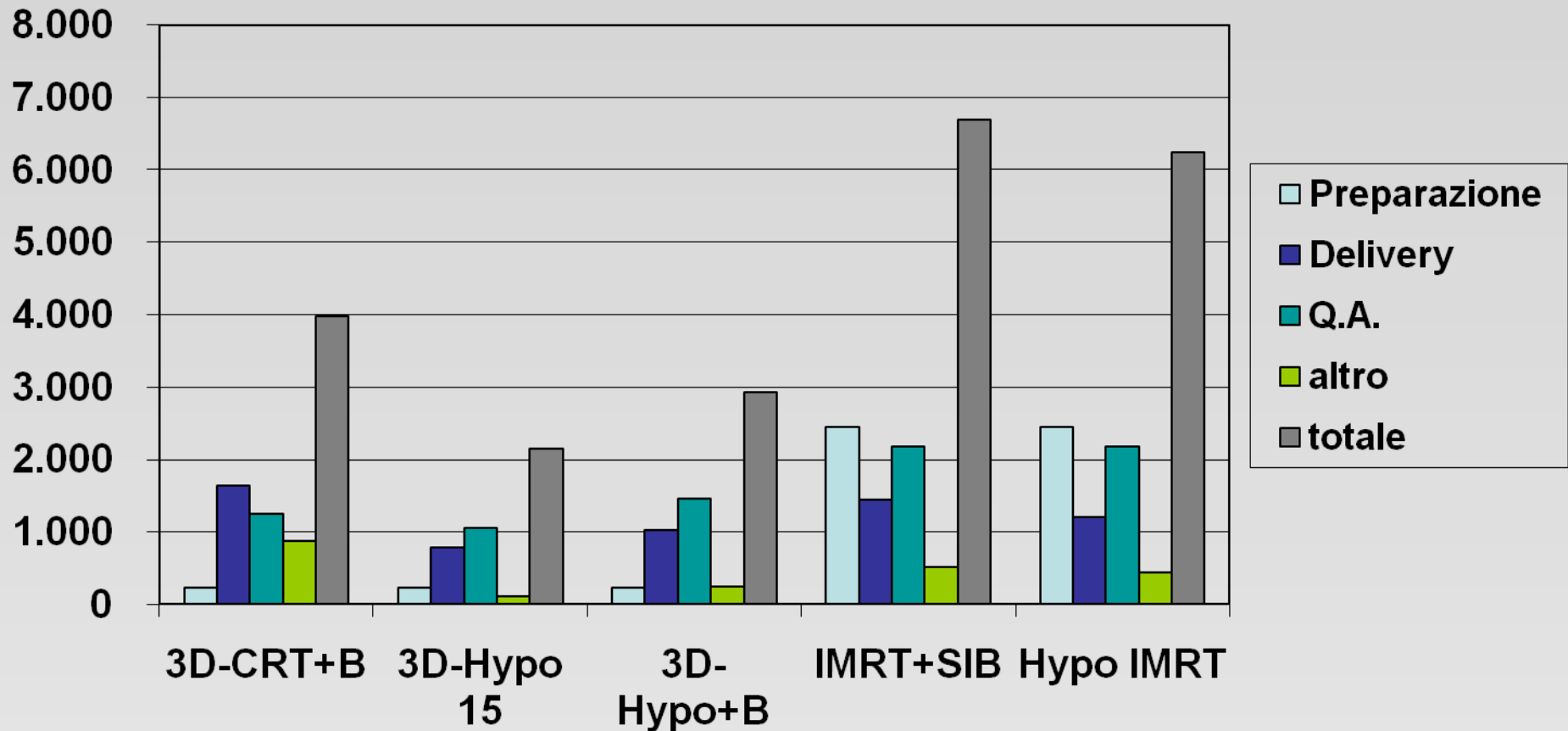
# Valutazioni economiche



Distribuzione proporzionale dei costi correlati al trattamento

# Valutazioni economiche

Ipotesi di stima dei ricavi secondo diverse modalità tecniche



**Il totale dei ricavi cambia con la complessità del prodotto**



# In sintesi

L'ipofrazionamento Whole Breast ha alcune  
**“aree oscure”**

- **Selezione delle pazienti**
  - T, N, Grading, fattori biologici, radiosensibilità, “large breast”
- **Scelta del trattamento**
  - ipofrazionamento ideale, boost, RT linfonodale (?)
- **Effetti collaterali tardivi**
  - Tossicità cardiaca
- **Interpretazione radiobiologica**
  - Razionale radiobiologico,  $\alpha/\beta$  ratio, BED
- **Organizzazione sanitaria**
  - Tecnologia e economia sanitaria
  - Costi sociali e nuovi studi e assicurazioni

# Conclusioni

- ***Efficacia e appropriatezza sono gli strumenti per raggiungere l'efficienza***

**NECESSITA' di PIU' LUNGO FU<sub>p</sub> ?**

**o**

**NECESSITA' di NUOVI TRIALS?**

**CON SOTTOGRUPPI PREDETERMINATI  
PER DIVERSI FATTORI di RISCHIO**

**NUOVE TECNICHE RADIOTERAPICHE  
e VALIDAZIONI RADIOBIOLOGICHE e BIOGENETICHE**

QUA' SE FA QUELO CHE SE SA



MA SE SA QUELO CHE SE FA





	Canada (18, 19, 21)	RMH/GOC (17, 20)	START A (10)	START B (16)
Energy	Co-60, 4 MV or 6 MV	6 MV*	6 MV*	6 MV*
Wedges	Yes	Yes	Yes	Yes
Inhomogeneity cCorrections		GOC only	Variable	Variable
Planning	2D	2D RMH 3D GOC	2D or 3D	2D or 3D
Central Axis Dose Homogeneity	7% to +7%	5% to +7%	5% to +5%	5% to +5%
Separation	≤ 25 cm			
Percent receiving boost	0%	75%†	61%	39%
Boost dose		14 Gy, 7 fr	10 Gy, 5 fr	10 Gy, 5 fr
Boost modality		Electrons	Electrons	Electrons
Percent receiving regional nodal irradiation	0%	21%	14%	7%
Target for nodal irradiation		SCV ± Ax	SCV ± Ax	SCV ± Ax
Use of PAS		Yes		
Dose to regional nodes		Same as breast	Same as breast	Same as breast

	Canada (18, 19, 21) N = 1,234		RMH/GOC (17, 20) N = 1,410		START A (10) N = 2,236		START B (16) N = 2,215	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Treated with breast-conserving surgery	1,234	100%	1,410	100%	1,900	85%	2,038	92%
Age ≥50 years	929	75%	987	70%	1,727	77%	1,758	79%
pT1 2	1,234	100%	1,324	94%	Majority		Majority	
pN0	1,234	100%	564	40%	1,547	69%	1,635	74%
Chemotherapy not used	1,098	89%	1,214	86%	1,443	65%	1,724	78%
Central axis inhomogeneity 7% to +7%	1,234	100%	1,410	100%	2,236	100%	2,215	100%
High tumor grade	233	19%			629	28%	509	23%





# .....il paziente giusto

## Selezione pazienti

- Dimensione di T
- Stato di N
- Grading
- Large breast
- Caratteristiche biologiche del tumore

# Selezione pazienti :

## Canadian trial vs START trials

Selected characteristics of randomized trials of breast hypofractionation.

	RMH/GOC	START A	START B	Canadian
Site	UK	UK	UK	Canada
Years accrual	1986–98	1998–2002	1999–2001	1993–96
Standard arm	50 Gy/25F	50 Gy/25F	50 Gy/25F	50 Gy/25F
Experimental arm A	42.9 Gy/13F	41.6 Gy/13F	40 Gy/15F	42.5 Gy/16F
Experimental arm B	39 Gy/13F	39 Gy/13F	N/A	N/A
Mean age (years)	54.5	57.2	57.4	Not reported
Node + (%)	32.7	28.8	22.8	0
Mastectomy (%)	0	15	8	0
Tumor size $\geq$ T2 (%)	42.5 <sup>a</sup>	48.6	35.9	20
Boost (%)	74.5	60.6	42.6	0
Chemotherapy (%)	13.9	35.5	22.2	11
Regional RT (%)	20.6	14.2	7.3	0

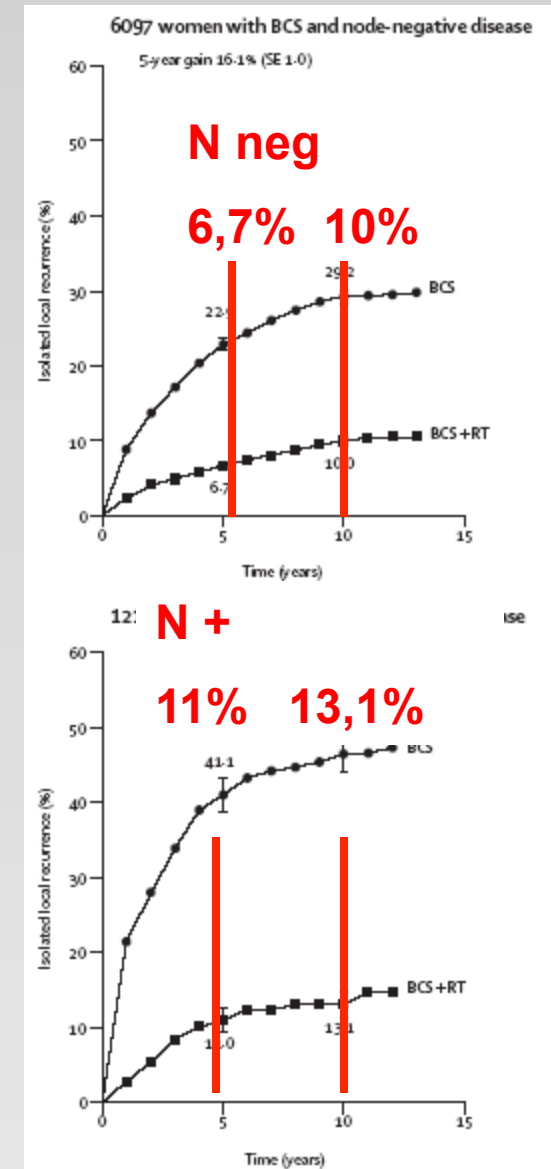
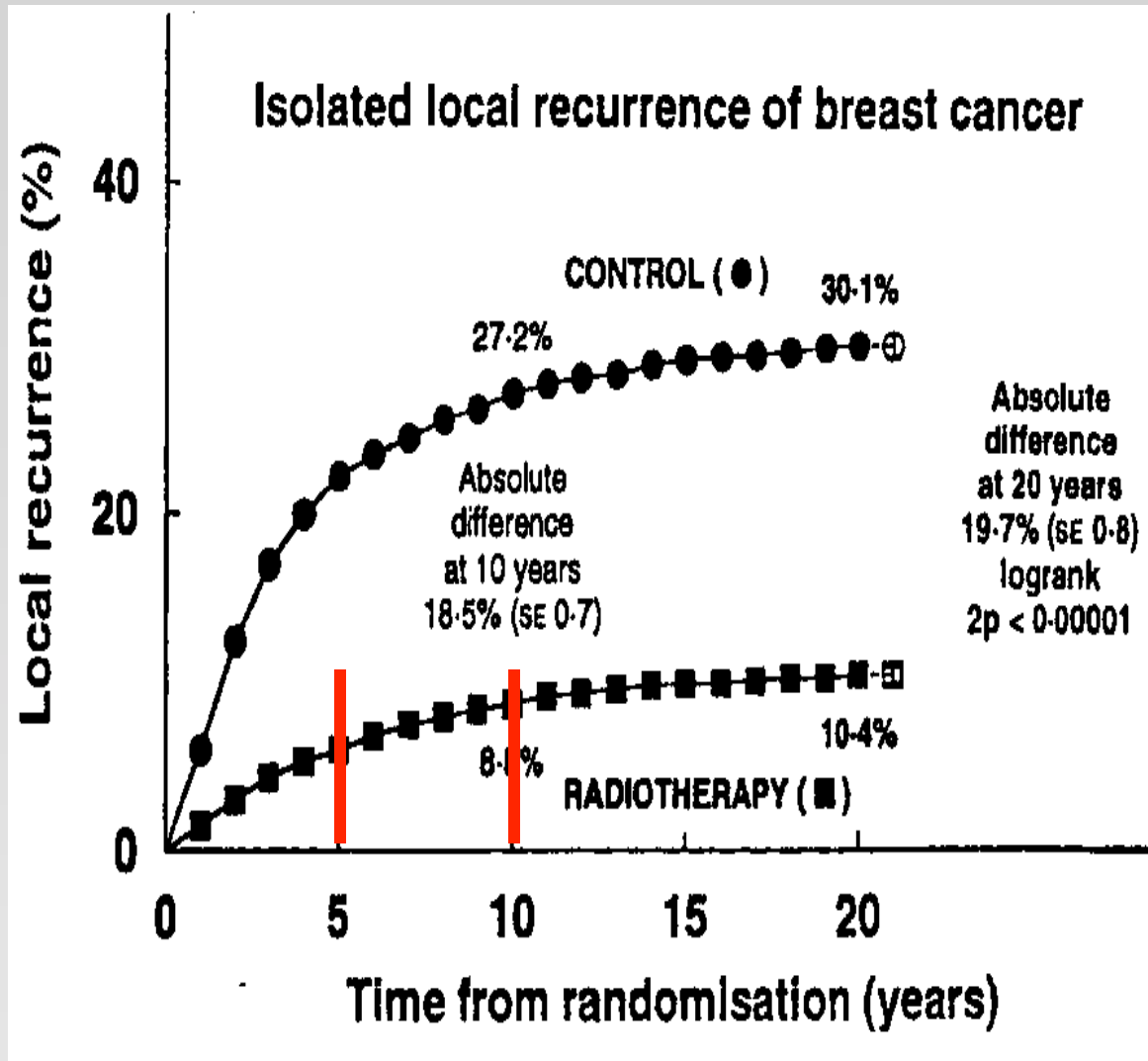
# Selezione pazienti :

## Canadian trial vs START trials

- Tumori  $\leq 2$  cm pT1
- pN 0
- G 1-3
- NO boost
- NO RT su N
- Terapie sistemiche
  - Ormonoterapia consentita
  - chemioterapia 11%
- NO “large breasts”

- Tumori  $< 5$  cm pT1-3
- pN0-1 (28.8% e 22.8%)
- G3 20% e 22%
- NO boost (40% e 55%)
- Boost (60% e 43%)
- RT su N 14% e 7%
- Terapie sistemiche
  - OT 54% e 74%
  - CT 11% e 7%
  - CT+OT 25% e 14%
- “Large breasts” 14% e 16%

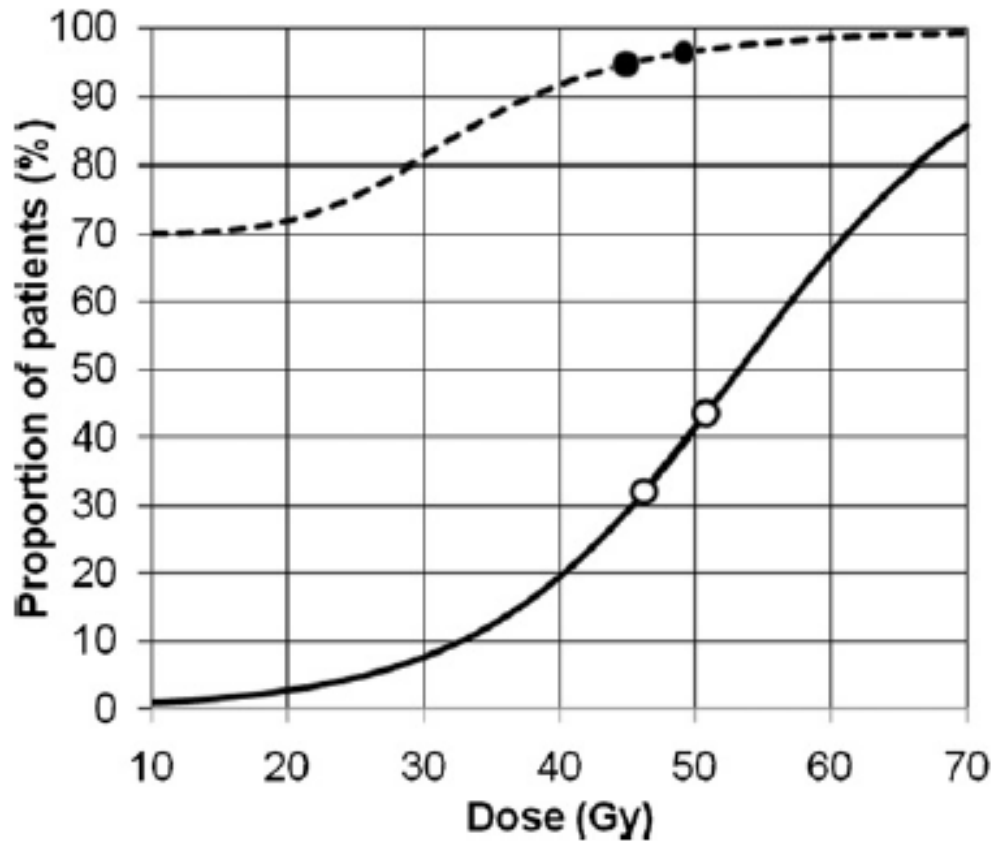
# Incidenza recidiva locale



Rates of Local recurrence in the altered fractionation trials.

	Total dose (Gy)/fraction	5 yr local recurrence (%)	10 yr local recurrence (%)	
RMH/GOC	50/25		12.1	T1-2 N0(1)
	39/13		14.8	
	42.9/13		9.6	
START A	50/25	3.6		?
	39/13	5.2		
	41.6/13	3.5		
START B	50/25	3.3		
	40/15	2.2		
Canadian	50/25	3.2	6.7	T1 N0
	42.5/16	2.8	6.2	

# DOSE ESCALATION HAS A MUCH GREATER EFFECT ON NORMAL TISSUE RESPONSES THAN ON TUMOR CONTROL AFTER WHOLE-BREAST RADIOTHERAPY



# Effetti collaterali

## START B

Incidence of ischaemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis according to fractionation schedule

	Fractionation schedule		Total n=2215
	50 Gy n=1105	40 Gy n=1110	
<b>Ischaemic heart disease*</b>			
Reported	19 (1.7)	15 (1.3)	34 (1.5)
Confirmed [left-sided] <sup>†‡</sup>	12 (1.1) [4]	7 (0.6) [3]	19 (0.9) [7]
<b>Symptomatic rib fracture<sup>§</sup></b>			
Reported	17 (1.5)	16 (1.4)	33 (1.5)
Confirmed <sup>†</sup>	2 (0.2)	2 (0.2)	4 (0.2)
<b>Symptomatic lung fibrosis</b>			
Reported	15 (1.4)	16 (1.4)	31 (1.4)
Confirmed <sup>†</sup>	1 (0.1)	3 (0.3)	4 (0.2)

# BED

Comparison of various fractionation schedules according to Biologically Equivalent Doses (BED).<sup>a</sup>

Dose/fractions	Normal tissue $\alpha/\beta_{3.4}$	Tumor control $\alpha/\beta_4$	Acute skin toxicity $\alpha/\beta_{10}$
50 Gy/25	79.4	75	60
42.9 Gy/13	84.5	78.3	57.1
41.6 Gy/13	80.8	74.9	54.9
42.5 Gy/16	75.7	70.7	53.8
39 Gy/13	73.4	68.3	50.7
40 Gy/15	71.4	66.7	50.7
45 Gy/25	68.8	65.3	53.1
37.5 Gy/16	63.4	59.5	46.3

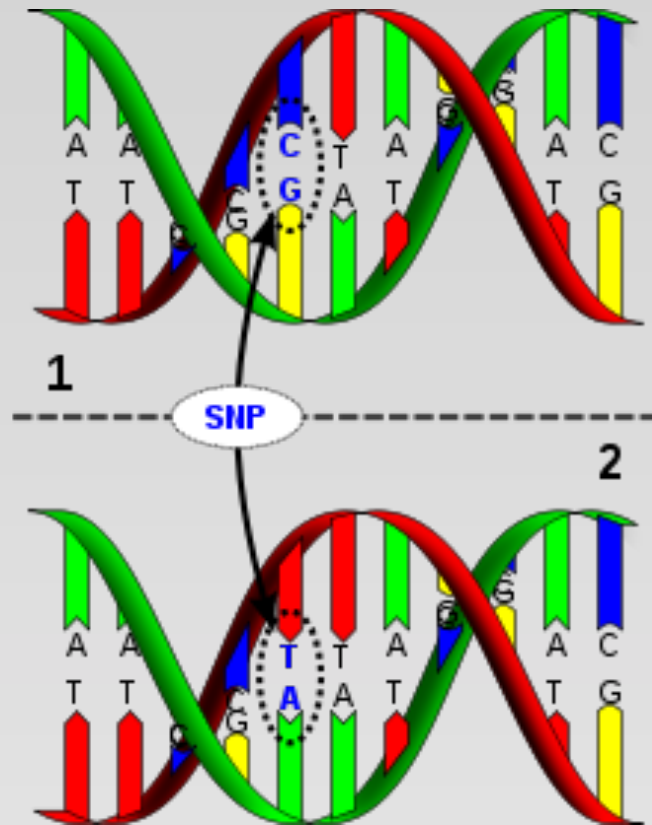
**Si riduce la tossicità acuta a svantaggio del controllo tumorale ?**



Rates of Local recurrence in the altered fractionation trials.

	Total dose (Gy)/fraction	5 yr local recurrence (%)	10 yr local recurrence (%)
RMH/GOC	50/25		12.1
	39/13		14.8
	42.9/13		9.6
START A	50/25	3.6	
	39/13	5.2	
	41.6/13	3.5	?
START B	50/25	3.3	
	40/15	2.2	
Canadian	50/25	3.2	6.7
	42.5/16	2.8	6.2

# Polimorfismo a singolo nucleotide



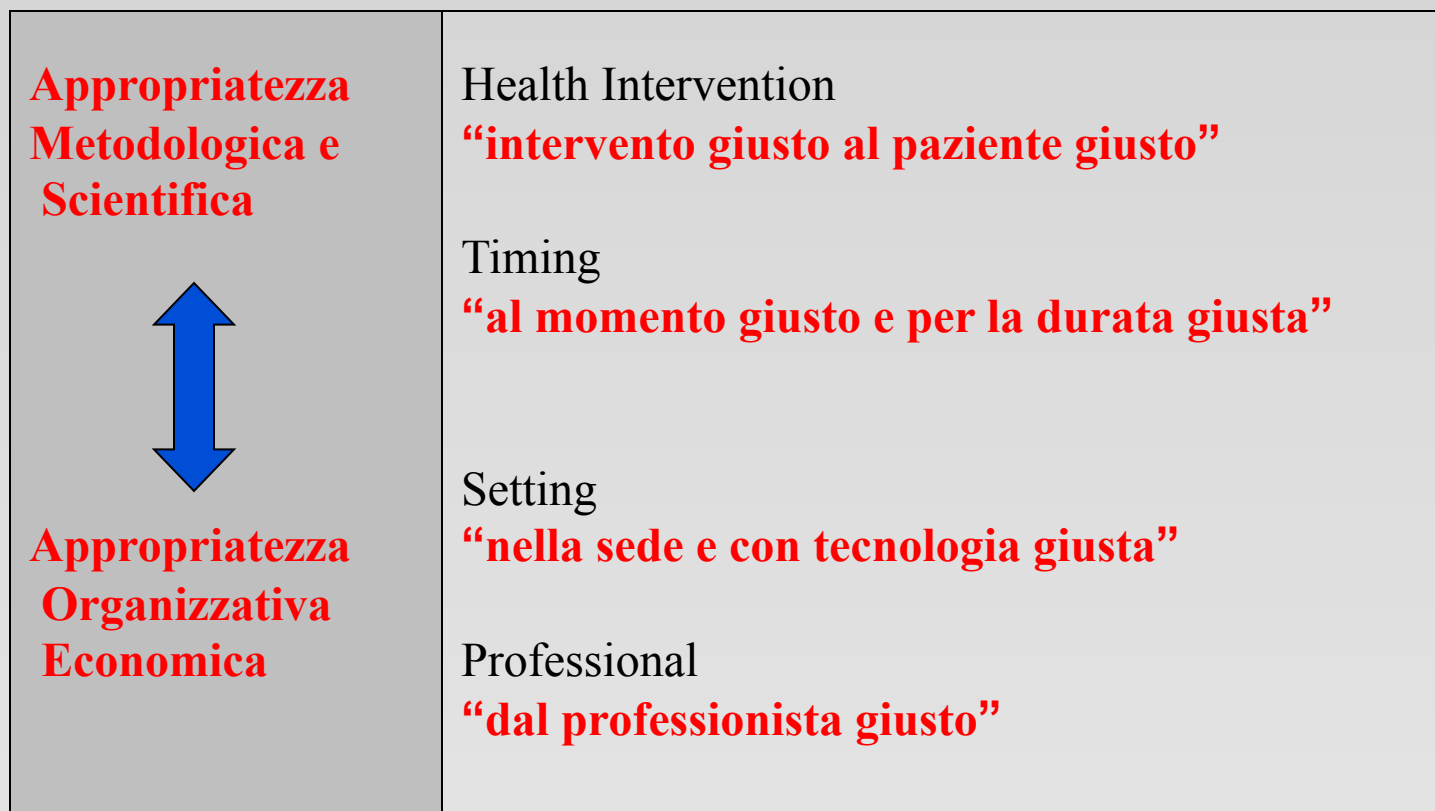
- E' il più comune tipo di variazione genetica
- Numerosi SNPs sono stati identificati e caratterizzati,
- Sono candidati come potenziali predittori di variazioni nella funzione biologica
- Ci sono geni interessati nella riparazione del DNA e nella risposta alla radiazione
- Ricerca delle varianti genetiche che modulano la radiosensibilità individuale

## X-Ray Cross Complementing (XRCC)

**XRCC1 e XRCC3 Sono associati alla aumentata radiosensibilità nel BC e differente capacità riparativa**

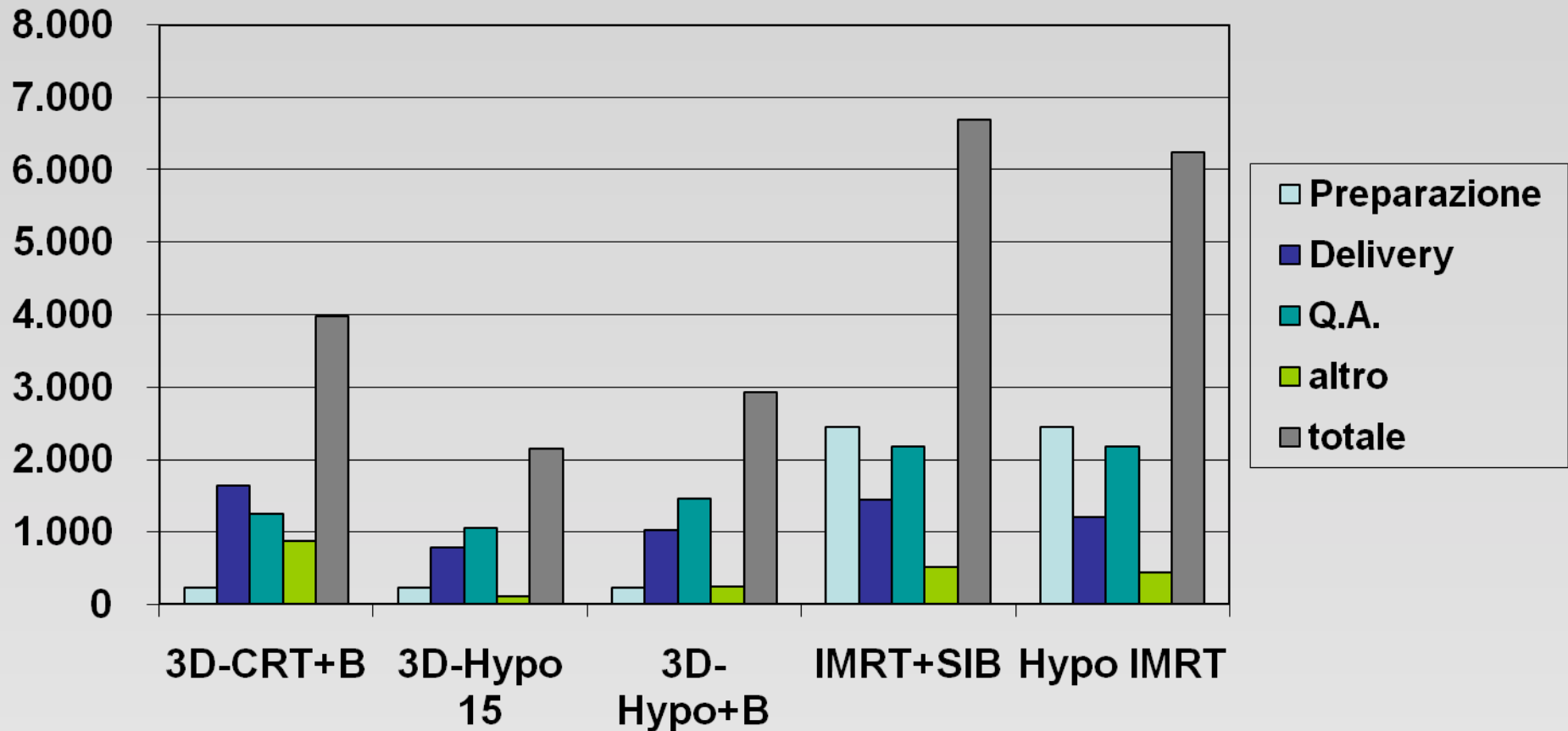
DNA molecule 1 differs from DNA molecule 2 at a single base-pair location (a C/T polymorphism).

# Appropriatezza



# Valutazioni economiche

Ipotesi di stima dei ricavi secondo diverse modalità tecniche



**Il totale dei ricavi cambia con la complessità del prodotto**