

Contributo della Medicina Nucleare nella cura del tumore della mammella: dalla biopsia del linfonodo sentinella alla radioterapia recettoriale.

Giovanni Paganelli

**Vice Direttore Scientifico e Direttore del Dipartimento
di Medicina Nucleare e Terapia Radiometabolica**

IRST- IRCCS



IRST IRCCS, Meldola (FC)

20 Aprile 2017, BOLOGNA



FONDAZIONE
CASSA DI RISPARMIO
IN BOLOGNA



GENUS BONONIAE
MUSEI NELLA CITTÀ



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

FESTIVAL DELLA SCIENZA MEDICA
FRA INNOVAZIONE E TRADIZIONE

DAL 20 AL 23 APRILE 2017 - BOLOGNA



Avvio attività presso sede di Meldola: **2007**
Riconoscimento IRCCS: **2012**



Mission

Favorire una stretta interconnessione tra ricerca e cura, con particolare vocazione alla ricerca traslazionale, garantendo qualità, originalità, innovazione e trasferibilità alla pratica clinica

Oncologia degenza
Oncologia Day Hospital
Radioterapia e fisica sanitaria
Medicina Nucleare
Laboratorio di Bioscienze
Radiologia – RMN 3T
Farmacia Oncologica
Biobanca

30 posti letto
6 posti letto
6 posti letto

PUBBLICI

Regione Emilia Romagna	35,00%
Azienda USL della Romagna	33,40%
Comune di Meldola	1,22%

PRIVATI

Istituto Oncologico Romagnolo	12,15%
Fondazione CR di Forlì	6,08%
Fondazione CR di Cesena	6,08%
Fondazione CR di Ravenna	3,04%
Fondazione CR Banca del Monte di Lugo	2,02%
Fondazione Banca del Monte e CR di Faenza	1,01%



MISSION: favorire una stretta interconnessione tra ricerca e cura, con particolare vocazione alla ricerca traslazionale, garantendo qualità, originalità, innovazione e trasferibilità alla pratica clinica



Sede Meldola

- Fabbrica radiofarmaci GMP
- Farmacia Oncologica Robotizzata



Casa accoglienza
San Giuseppe "Antonio Branca"



Sede Forlì

- Day Hospital oncologico
- Ambulatori oncologia



Sede Cesena

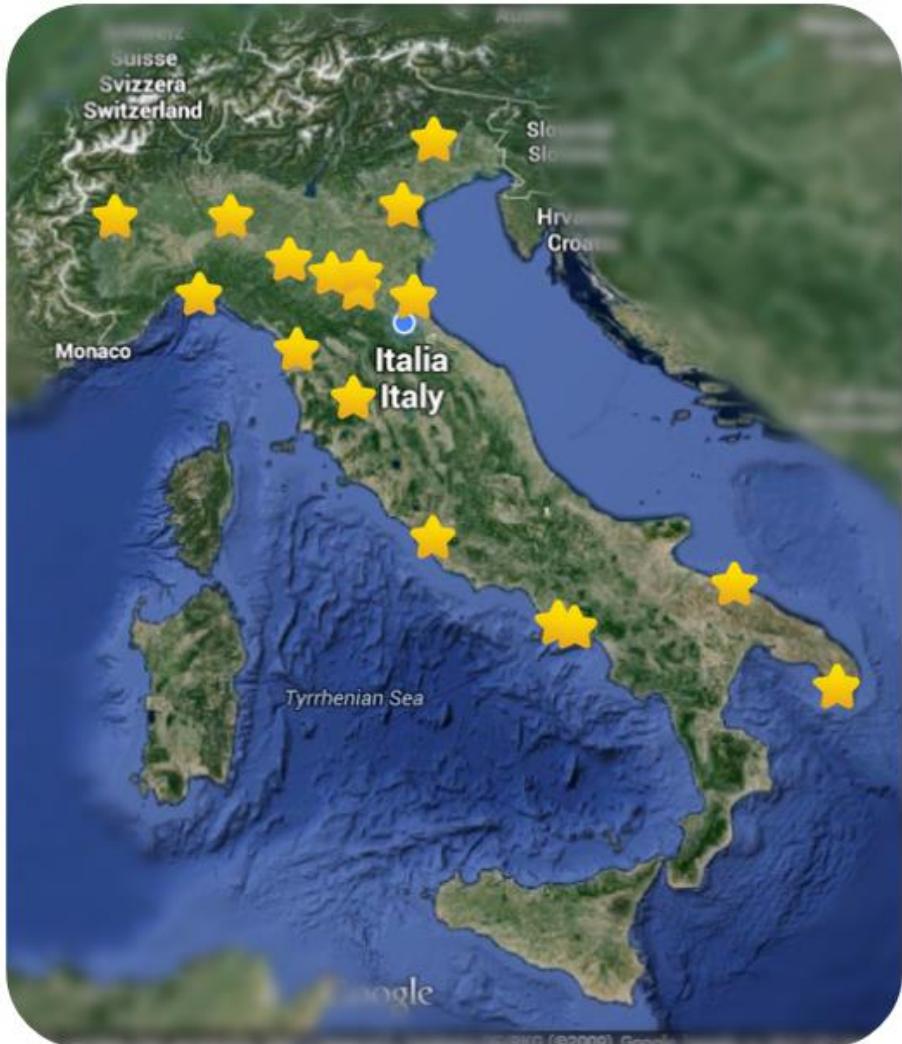
- Day Hospital oncoematologico
- Ambulatori oncoematologici



Sede Ravenna

- Radioterapia
- Fisica Sanitaria

Collaborazioni di Ricerca Nazionali ed Internazionali



Contributo della Medicina Nucleare nella cura del tumore della mammella: dalla biopsia del linfonodo sentinella alla radioterapia recettoriale.

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IRST IRCCS

Conservation Program

Phase 1

Conservation of the breast

1968-1985

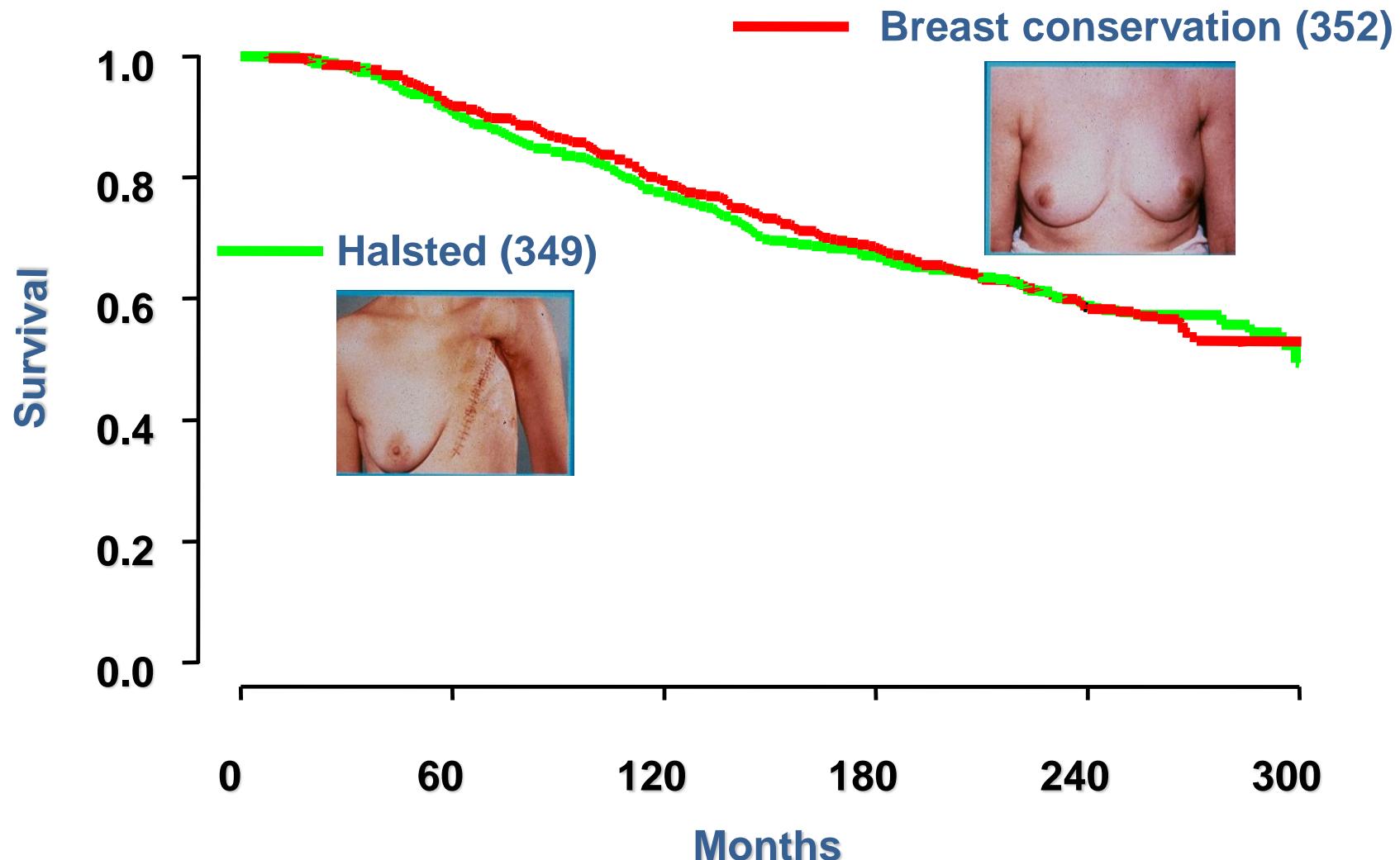
SN biopsy of axillary lymph-nodes

1995 - 2000

Phase 3

Modified Breast Irradiation: IORT and IART

2000 - ...



Phase I: Milan I study

Veronesi U, et al. N Engl J Med, 2002

Phase II: the SNB challenge

**Can lymphoscintigraphy +
radioguided SNB replace
axillary dissection?**

SN INITIAL EXPERIENCE (March '96 – September '04)

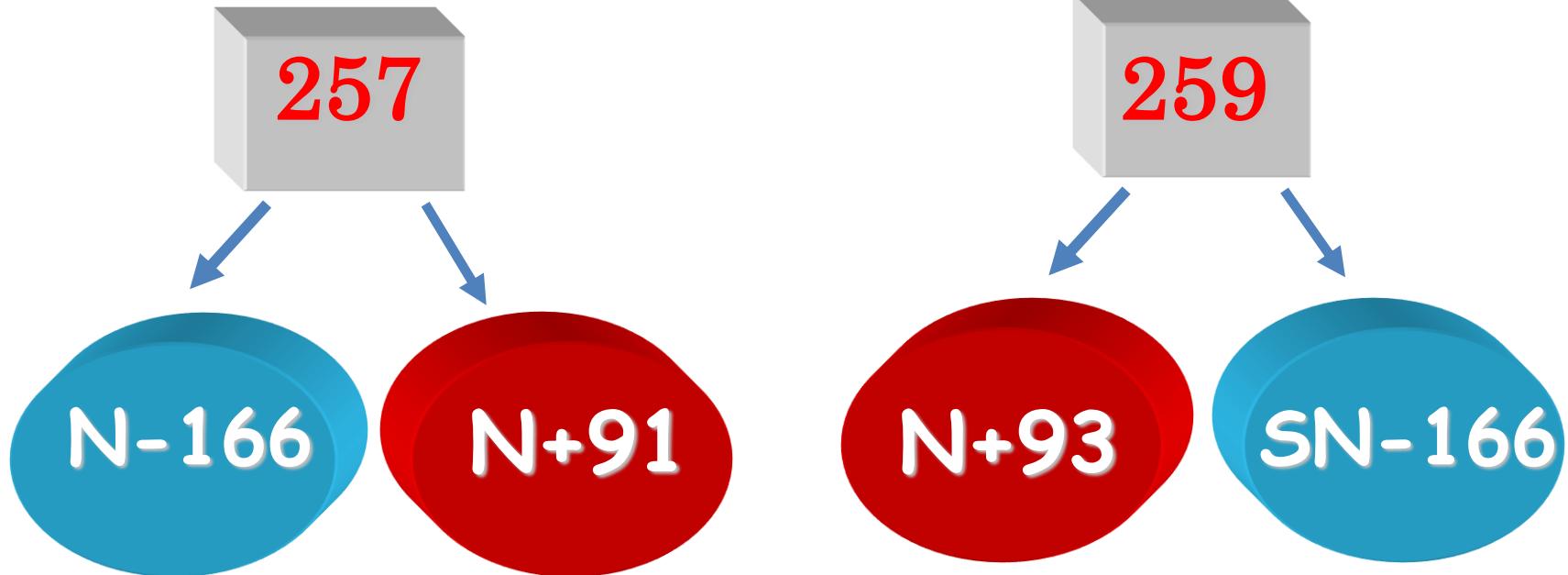
No. of cases

PILOT STUDY	371
TRIAL (185)	516
OUT-TRIAL	379
STANDARD TREATMENT	10715
– T1-2 (< 2.5 cm), N0 since January 2000	
TOTAL	11981

516 randomized cases

AXILLARY DISSECTION

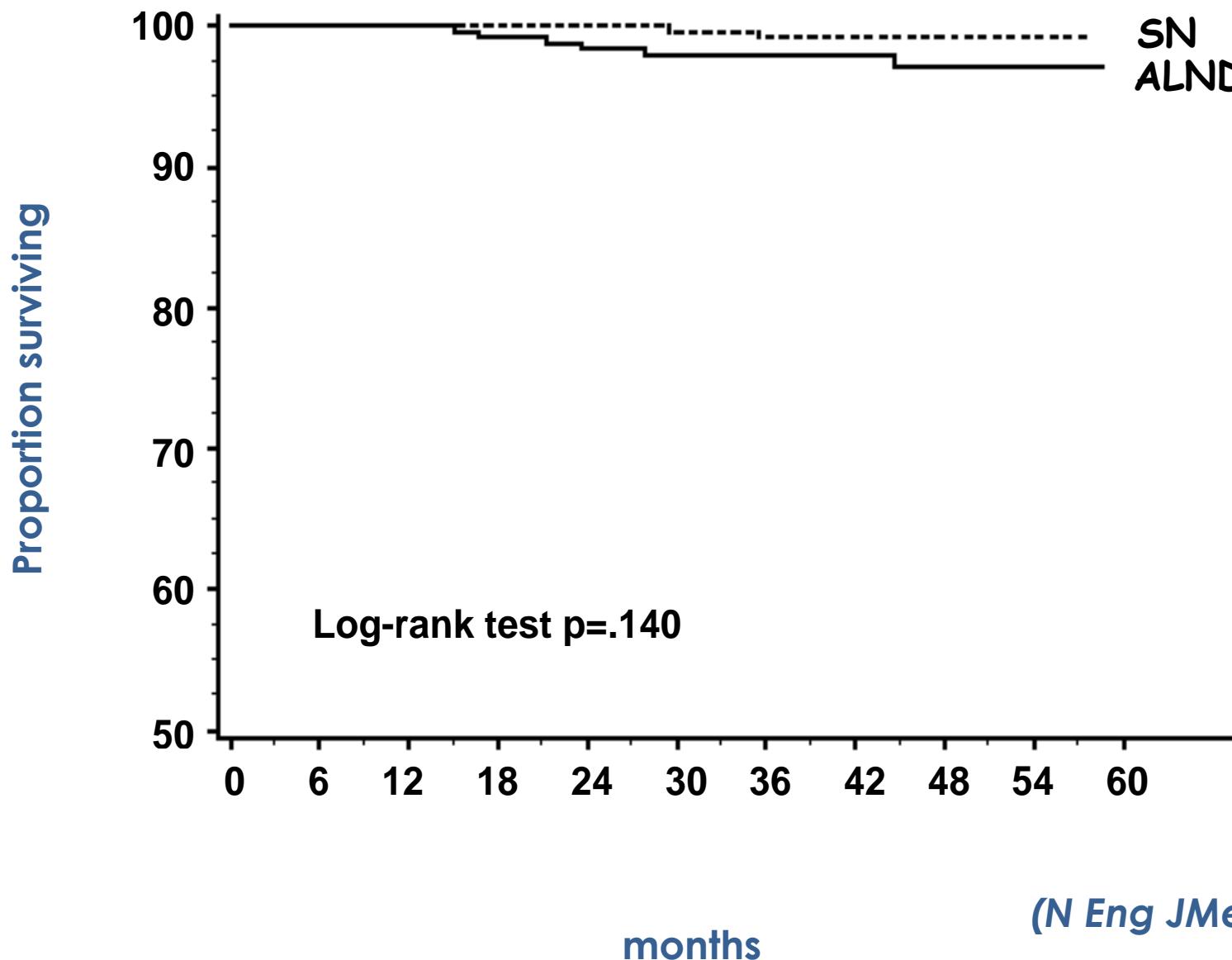
SENTINEL NODE



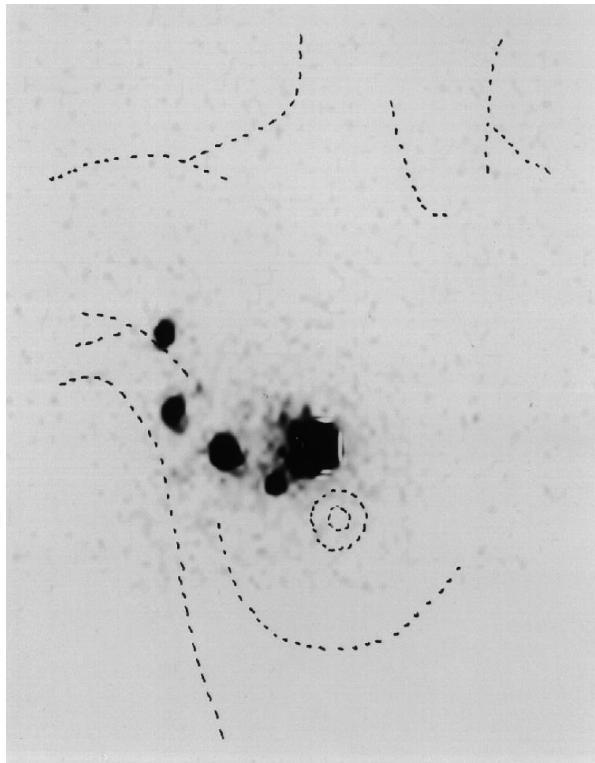
36% N+

(*N Eng JMed '03*)

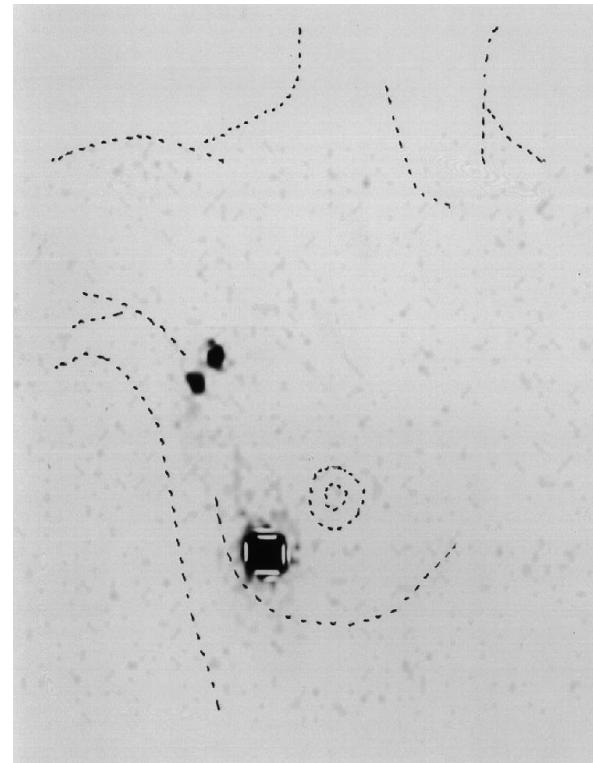
Overall survival



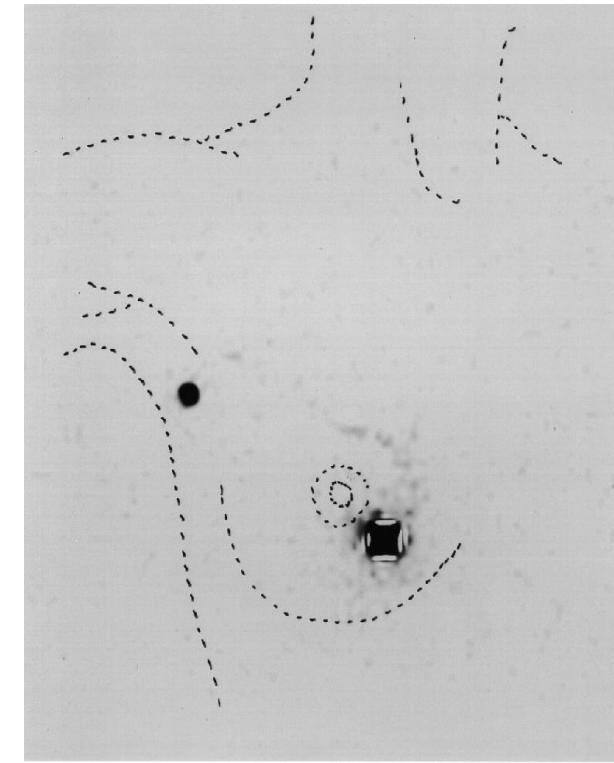
99mTc-labelled colloids (0.3 mCi/0.2ml)



< 50 nm
Sulphide



< 80 nm
Human albumin



200-1000 nm
Human albumin

**Particle size of the tracer is
important to the correct
identification of the SN**

Injection technique

Superficial lesion



subdermal

Deep lesion



peritumoral

Intratumoral
(Not for SN!)



ROLL

anterior

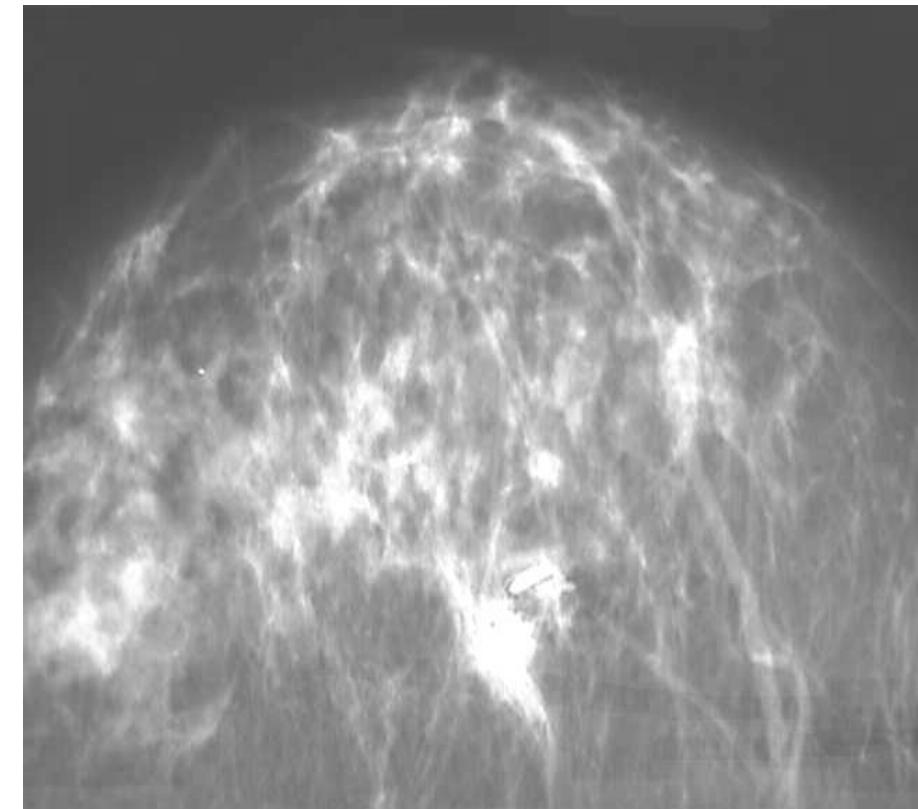
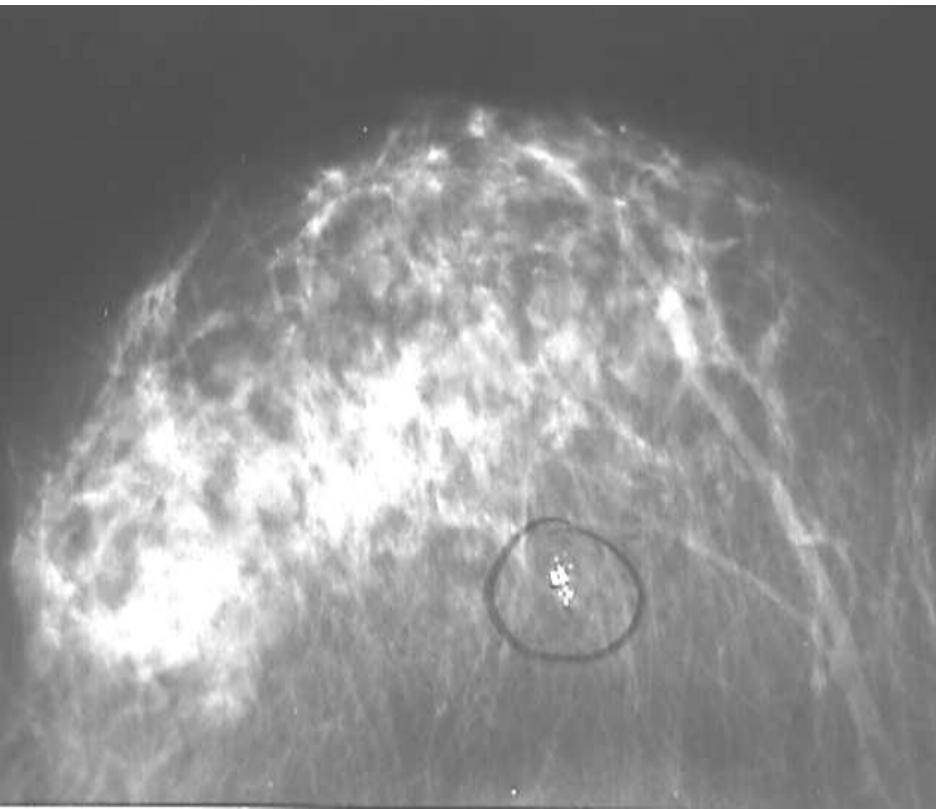
+

+

lateral

+

**Intratumoral injection: no SN identification in
30% cases**



LESIONI NON PALPABILI -MICROISTOLOGIA

E' attualmente il gold standard per la tipizzazione delle lesioni mammarie non palpabili.
In caso di esito mammografico e/o ecografico dubbio o sospetto l' iter diagnostico può continuare con il ricorso all' esame istologico.

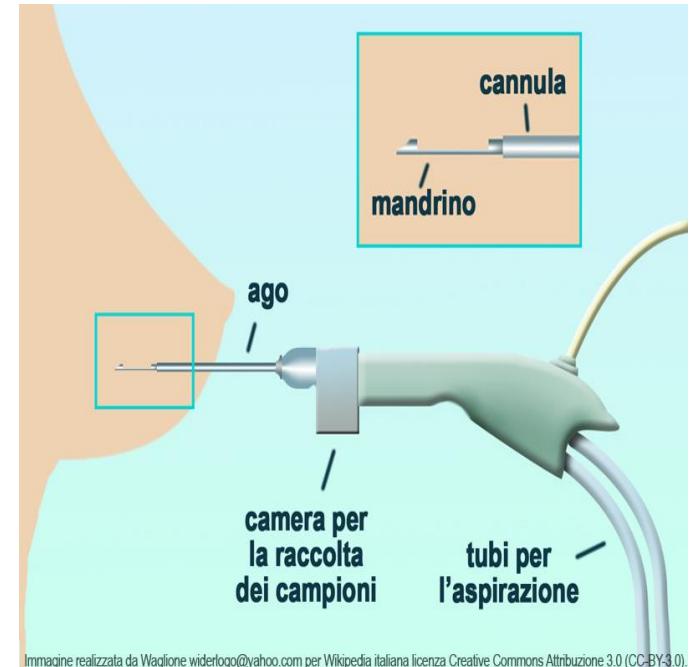


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2nd Challenge

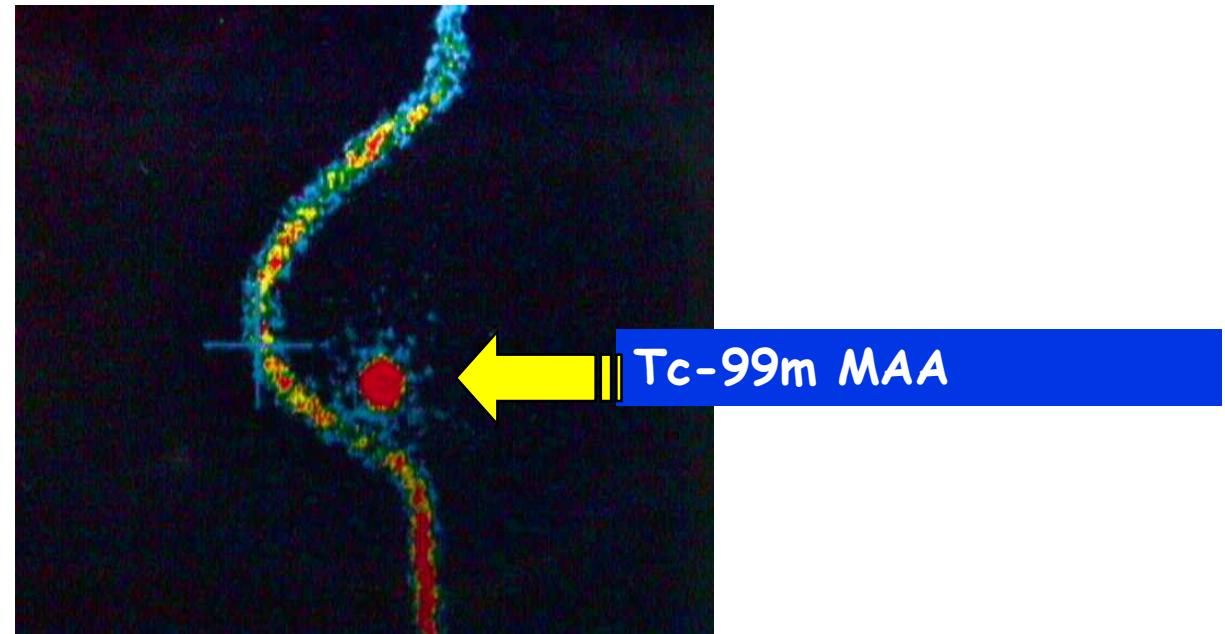
**Can nuclear medicine replace
ancor-wire or carbon injection
in non palpable breast lesions ?**

Radioguided occult lesion localisation (ROLL) in breast cancer: maximizing efficacy whilst minimizing mutilation.

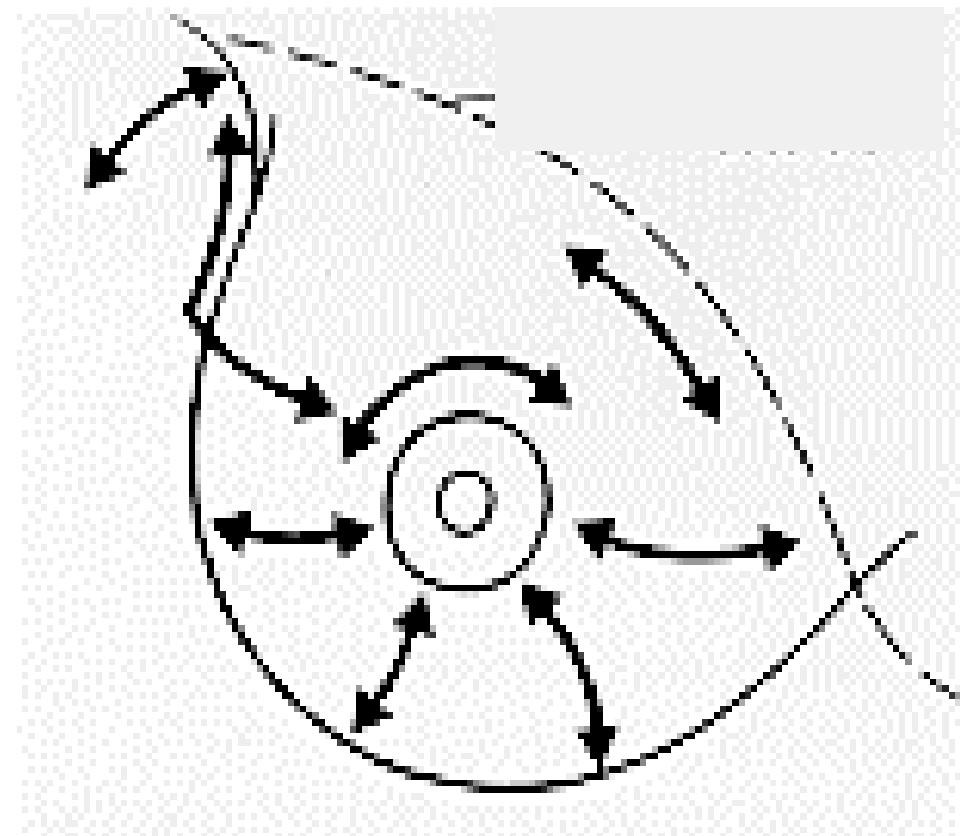
Paganelli G, Luini A, Veronesi U.

Annals of Oncology 13: 1839-1840, 2002

Pre-operative localization of non palpable lesion with Tc-99m labeled serum albumin (MAA)



The surgeon can determine the best incision to reach the lesion, independently of the site of inoculation



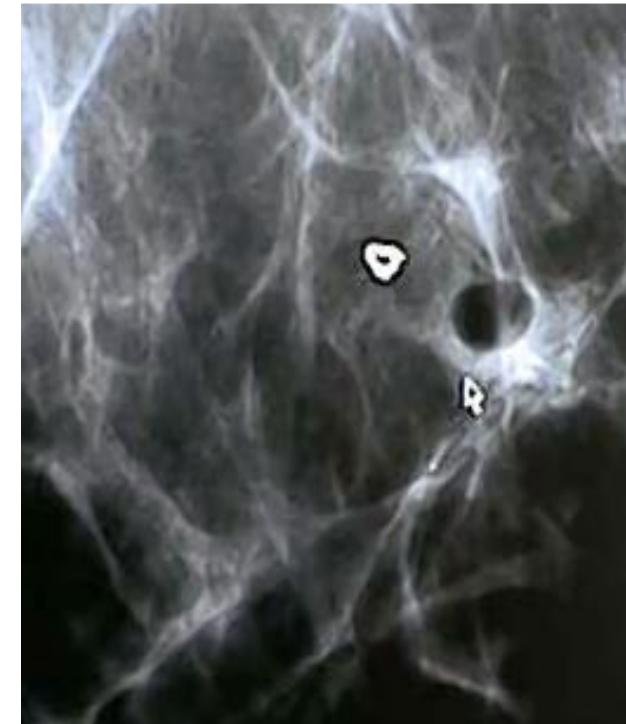
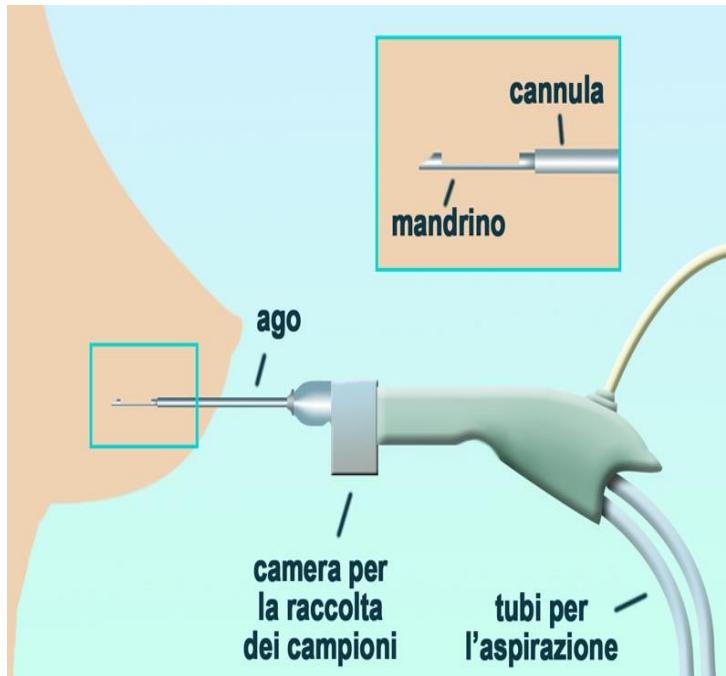
THE FUTURE

**From ROLL diagnosis to
ARTHE/IART therapy**

ARTHE

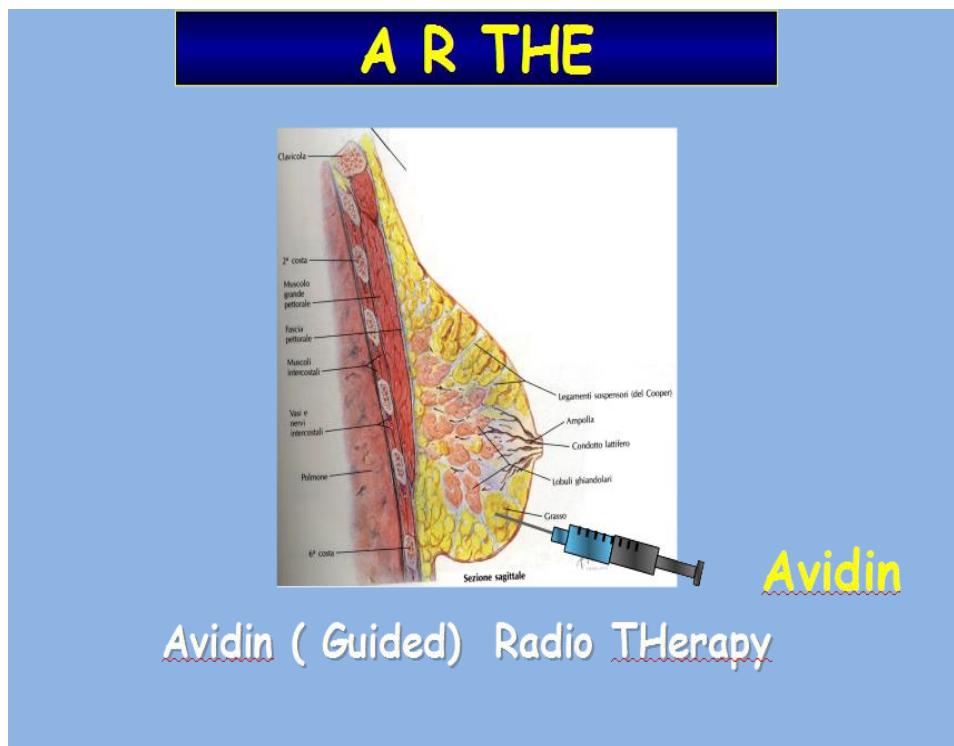
Avidination for Radionuclide Therapy

Indica una tecnica di facile esecuzione che prevede l'iniezione locale di avidina seguita da inoculo di biotina radioattiva, in grado di distruggere cellule tumorali nella piccola cavità creata dal prelievo bioptico.





Lo Studio ARTHE vuole dimostrare che il radiofarmaco **90Y Biotina** è in grado di distruggere eventuali cellule tumorali presenti nella piccola cavità biotica evitando l'intervento chirurgico per questi piccoli tumori.





**Qual è oggi la terapia
delle lesioni di maggiori
dimensioni?**

**Quadrantectomy +
SNB + EBRT***
**represent the standard
therapy in**
Early Breast Cancer

*External Beam RadioTherapy (2 months)

Open problems with EBRT

**EBRT post-quadrantectomy requires
6 – 8 weeks to be completed**

EBRT may cause side effects

**The radiation centres are often not
easy accessible**



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ORIGINAL REPORT

The Future of Radiation Oncology in the United States From 2010 to 2020: Will Supply Keep Pace With Demand?

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and Thomas A. Buchholz*

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2009, Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2835-5160/\$20.00

DOI: 10.1200/JCO.2010.31.2520

ABSTRACT

Purpose

Prior studies forecasted an incipient shortage of medical oncologists as a result of the aging US population, but the radiation oncology workforce has not been studied. Accordingly, we projected demand for radiation therapy and supply of radiation oncologists in 2010 and 2020 to determine whether a similar shortage may exist for this specialty.

Methods

Demand for radiation therapy in 2010 and 2020 was estimated by multiplying current radiation utilization rates (as calculated with Surveillance, Epidemiology, and End Results data) by population projections from the Census Bureau. Supply of radiation oncologists was projected using data from the American Board of Radiology inclusive of current radiation oncologists and active residents, accounting for variation in full-time equivalent status and expected survival by age and sex.

Results

Between 2010 and 2020, the total number of patients receiving radiation therapy during their initial treatment course is expected to increase by 22%, from 470,000 per year to 575,000 per year. In contrast, assuming that the current graduation rate of 140 residents per year remains constant, the number of full-time equivalent radiation oncologists is expected to increase by only 2%, from 3,943 to 4,022. The size of residency training classes for the years 2014 to 2019 would have to double to 280 residents per year in order for growth in supply of radiation oncologists to equal expected growth in demand.

Conclusion

Demand for radiation therapy is expected to grow 10 times faster than supply between 2010 and 2020. Research is needed to explore strategies to enhance capacity to deliver quality radiation therapy despite increased patient loads.



Table 1. Projected Estimates of Patients Receiving Radiation Therapy in 2010 and 2020

Tumor Site	No. of Patients Receiving Radiation Therapy		% Increase in Demand for Radiation Therapy From 2010 to 2020
	2010	2020	
Total	470,000	575,000	22
Breast (invasive)	103,000	119,000	15
Prostate	91,000	123,000	35
Lung	77,000	96,000	25
Oral cavity and pharynx	21,000	25,000	18
Breast (in situ)	20,000	23,000	15
Colorectum	19,000	23,000	22
Esophagus	19,000	23,000	22
Thyroid	15,000	16,000	10
CNS	12,000	14,000	16
Non-Hodgkin's lymphoma	11,000	13,000	18
Uterus	11,000	13,000	22
Larynx	9,300	12,000	24
Cervix	7,000	8,100	16
Pancreas	6,000	7,500	25
Stomach	5,300	6,800	27
Myeloma	4,700	5,800	25
Bladder	3,200	3,900	24
Hodgkin's lymphoma	3,200	3,300	6
Testis	3,000	3,000	2
Kidney	2,500	3,100	21
Melanoma	1,500	1,800	17
	4,100	4,000	4

Conclusion

Demand for radiation therapy is expected to grow 10 times faster than supply between 2010 and 2020. Research is needed to explore strategies to enhance capacity to deliver quality radiation therapy despite increased patient loads.

Women receiving Postoperative Radiotherapy according to distance to RT Center

**Distance
(Miles)**

**% who received RT after
Breast Conservative Surgery**

< 25

83

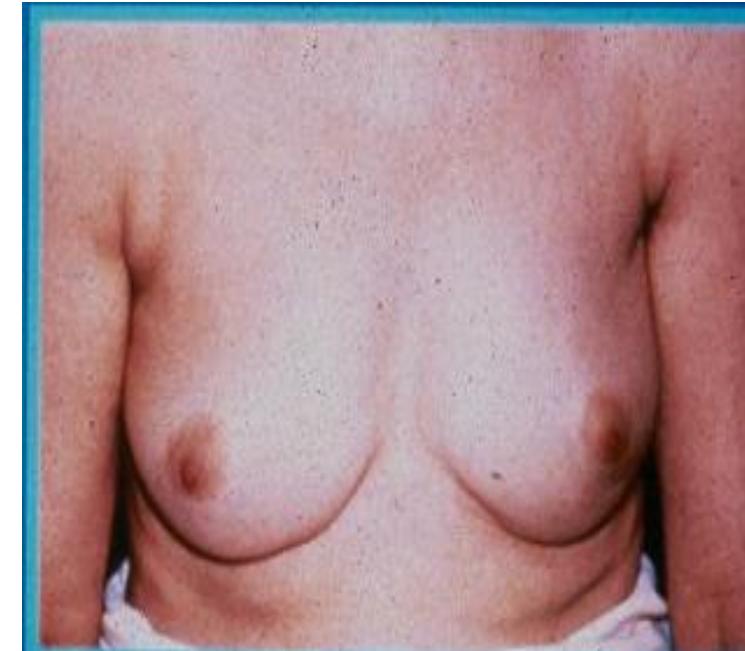
25 – 75

74

> 75

51

From WF Athas, et al., 2000



The challenge of the new century is:

Can we avoid or
modify EBRT in early breast
cancer?

- Dedicated linear accelerator for IORT



Electrons IntraOperative Therapy

- IORT represents a further step to improve the quality of life of breast cancer patients.

- There are obvious advantages in terms of overall treatment time, patients comfort, cosmetic results, quality of life.

Electrons IntraOperative Therapy

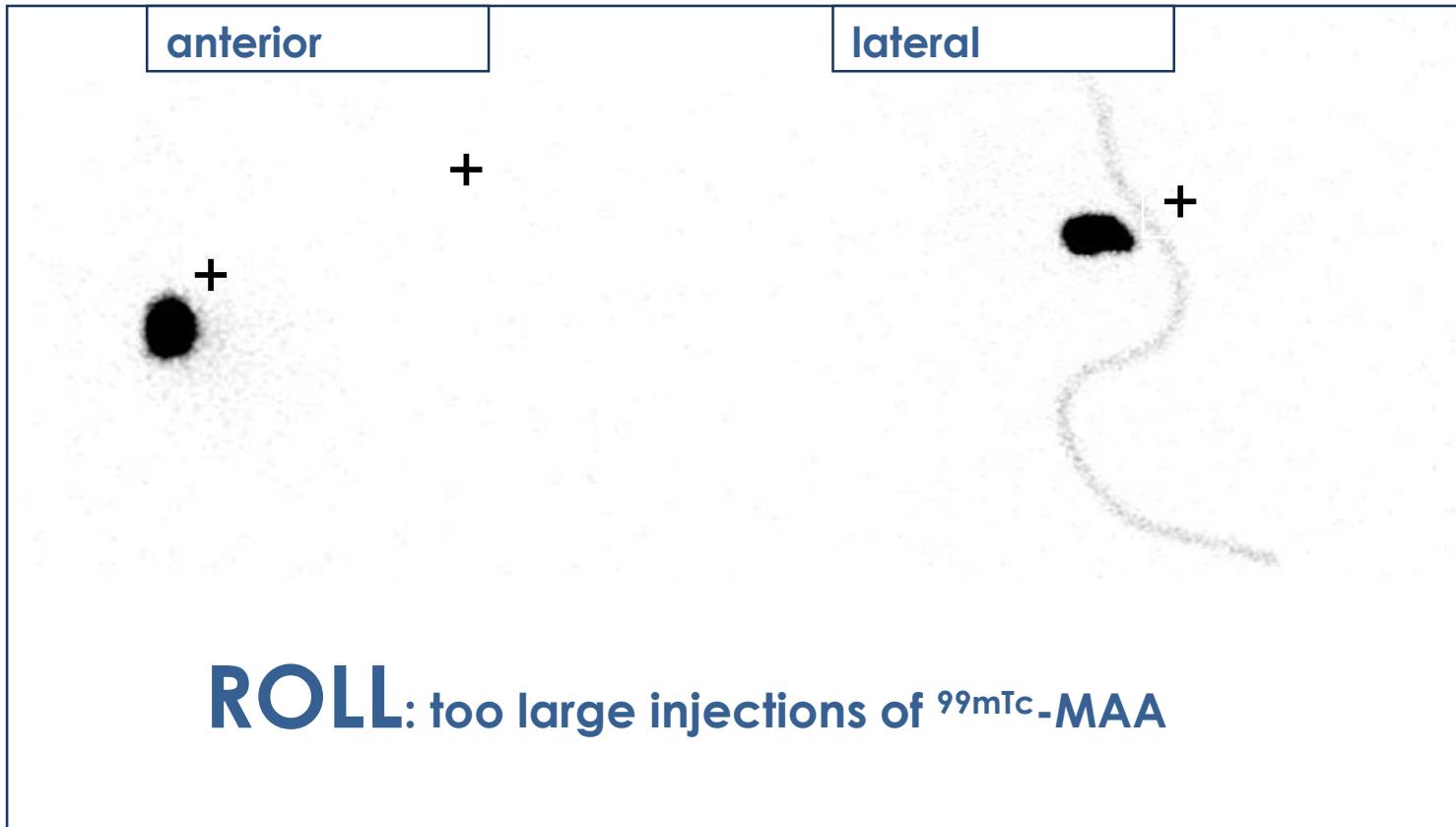
However IORT is affected by some limitations:

- Costs
- Limited targeted area

Specialized staff



Are there other methods to deliver electrons in the operated breast?

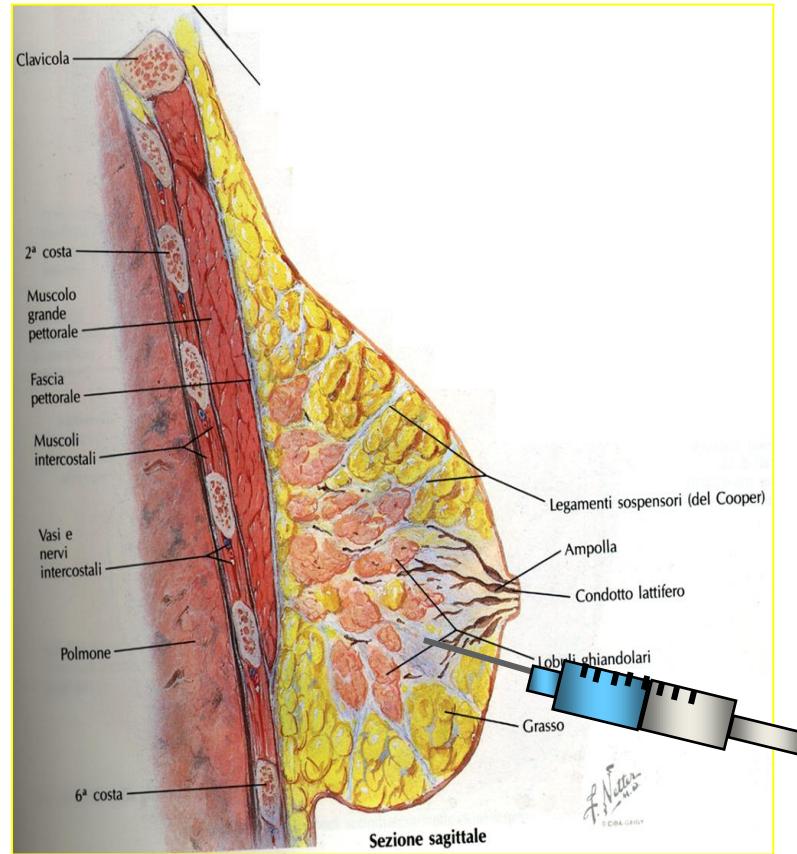


IART®

Intra-operative
Avidination *for*
Radionuclide
Therapy



I.A.R.T.



Avidin

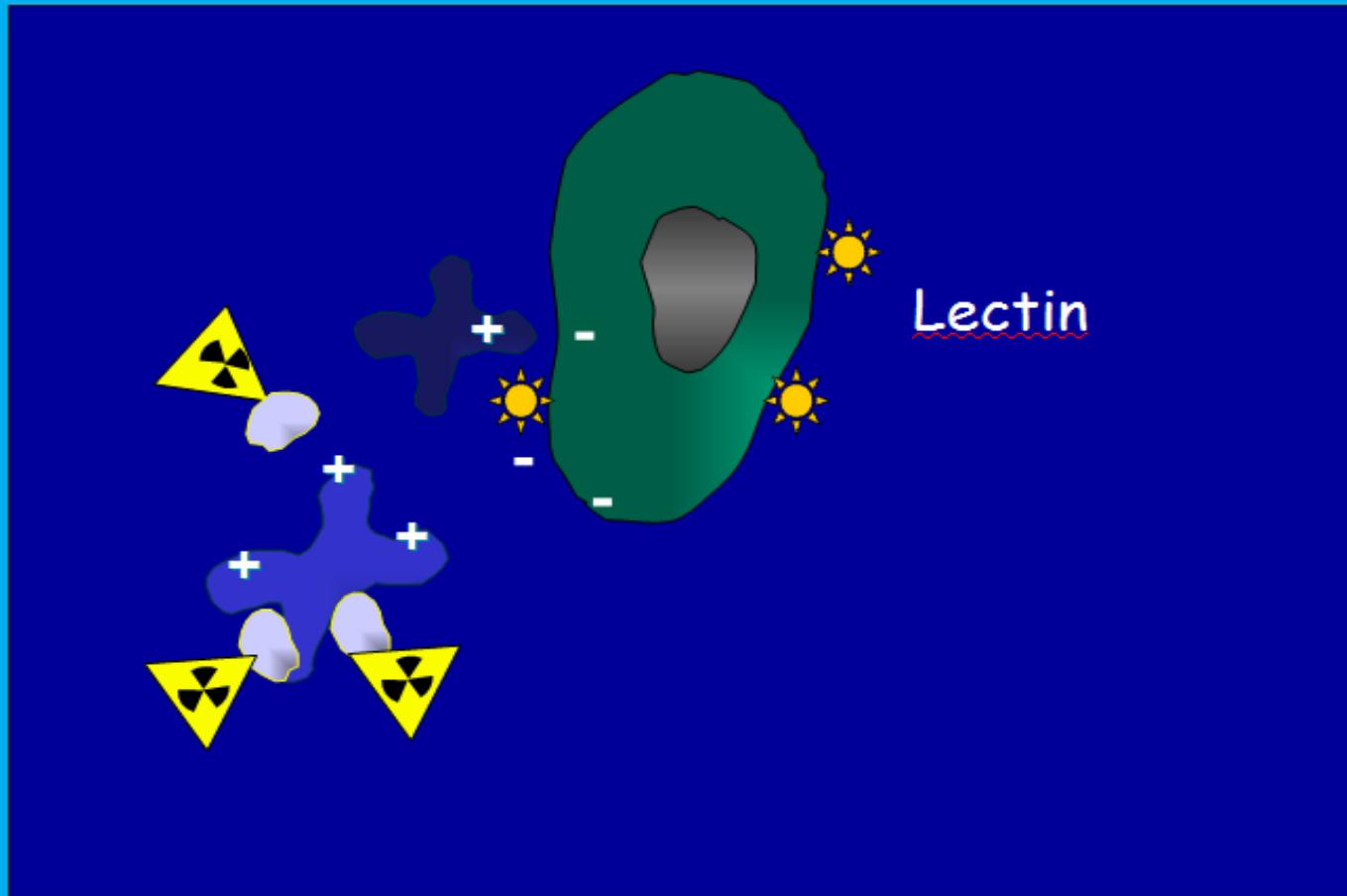
Avidin injection during surgery into the tumour bed area

Molecular properties of avidin

Avian avidin

Molecular weight	~65 000
Number of subunits	4
Subunit molecular weight	~16 000
Binding sites for biotin/mole	4
K_D of the complex with biotin	~10⁻¹⁵
Mannose/subunit	4.5
Isoelectric point	~10.5

Tumor avidination



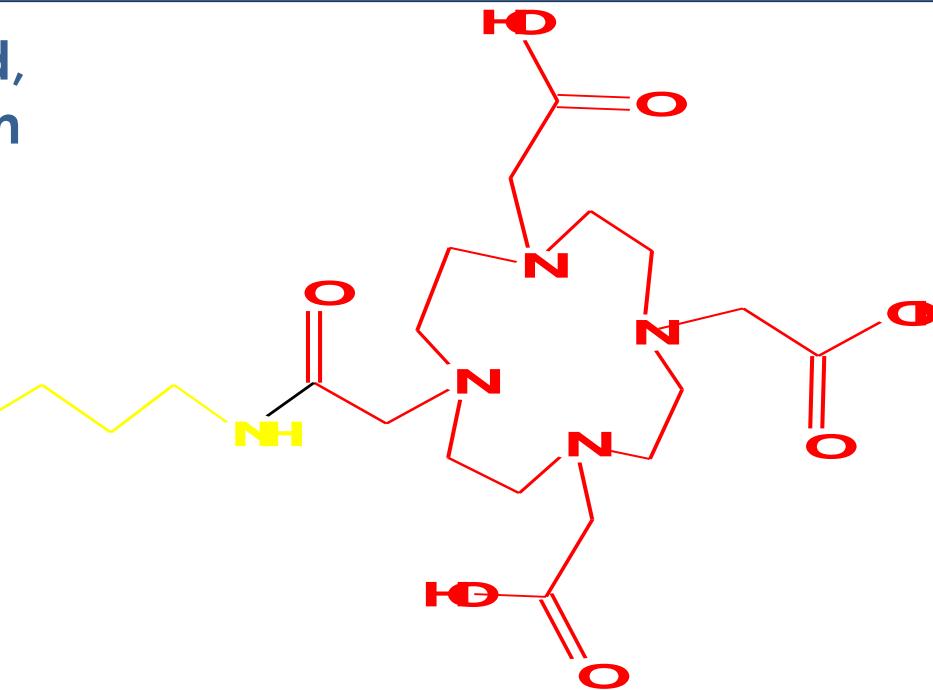
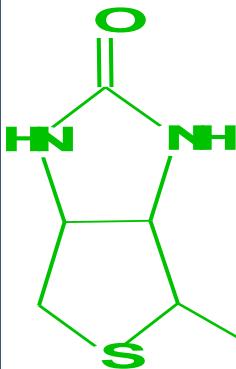


Dedicated
vial for
90Y or
177Lu-biotin



DOTA-Biotin

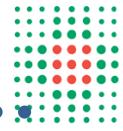
reduced amino-bond,
no substrate for serum
biotinidase



Deoxy-biotinyl-hexamethylenediamine-DOTA

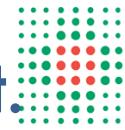
$C_{32}H_{58}N_8O_8S$

Mw = 714.918





RIPRODUZIONE VIDEO

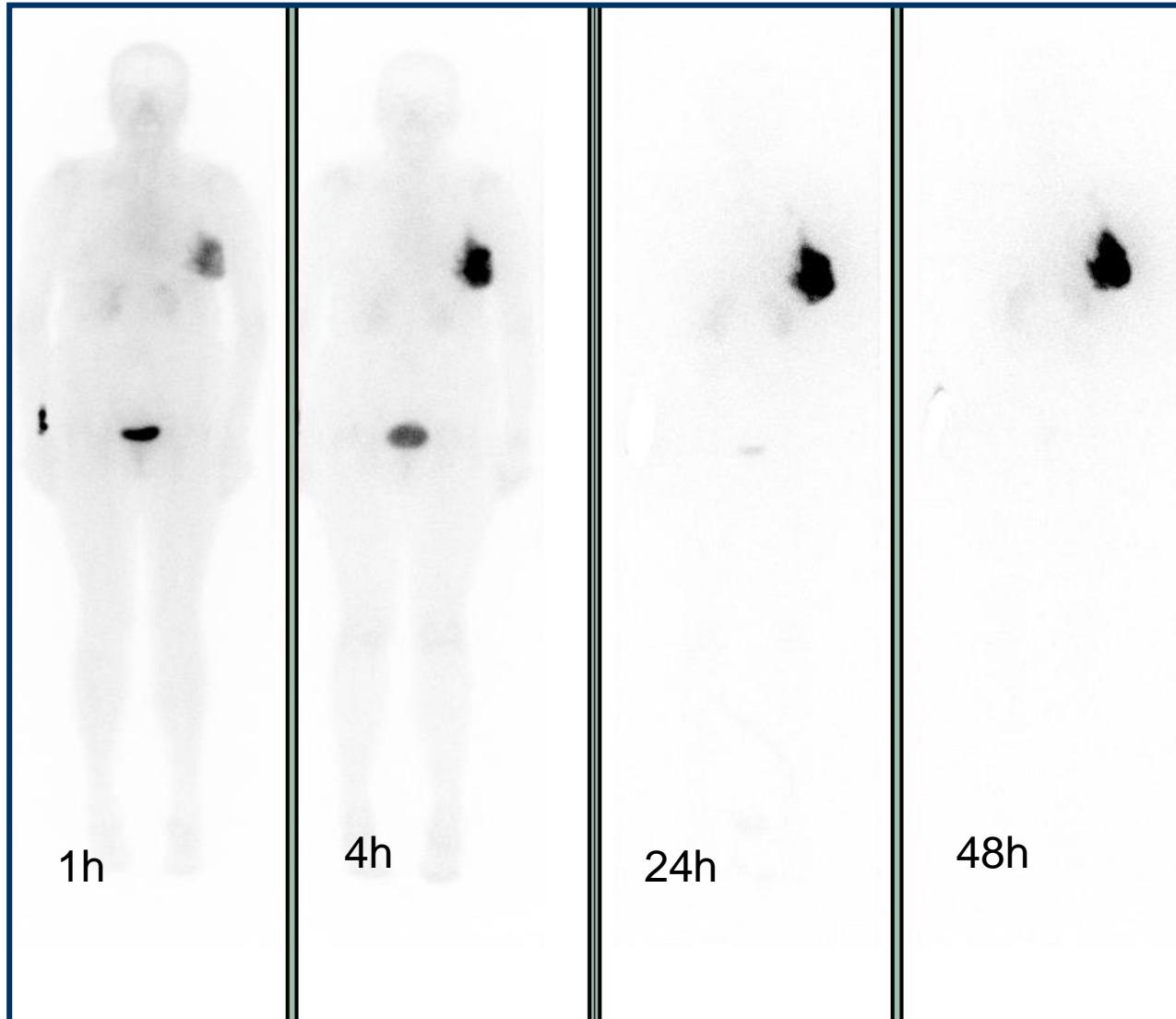


...in the Nuclear Medicine Dept.



16 to 48 hrs post-surgery ^{90}Y -Biotin i.v. injection

Total Body anterior view - pt no 25



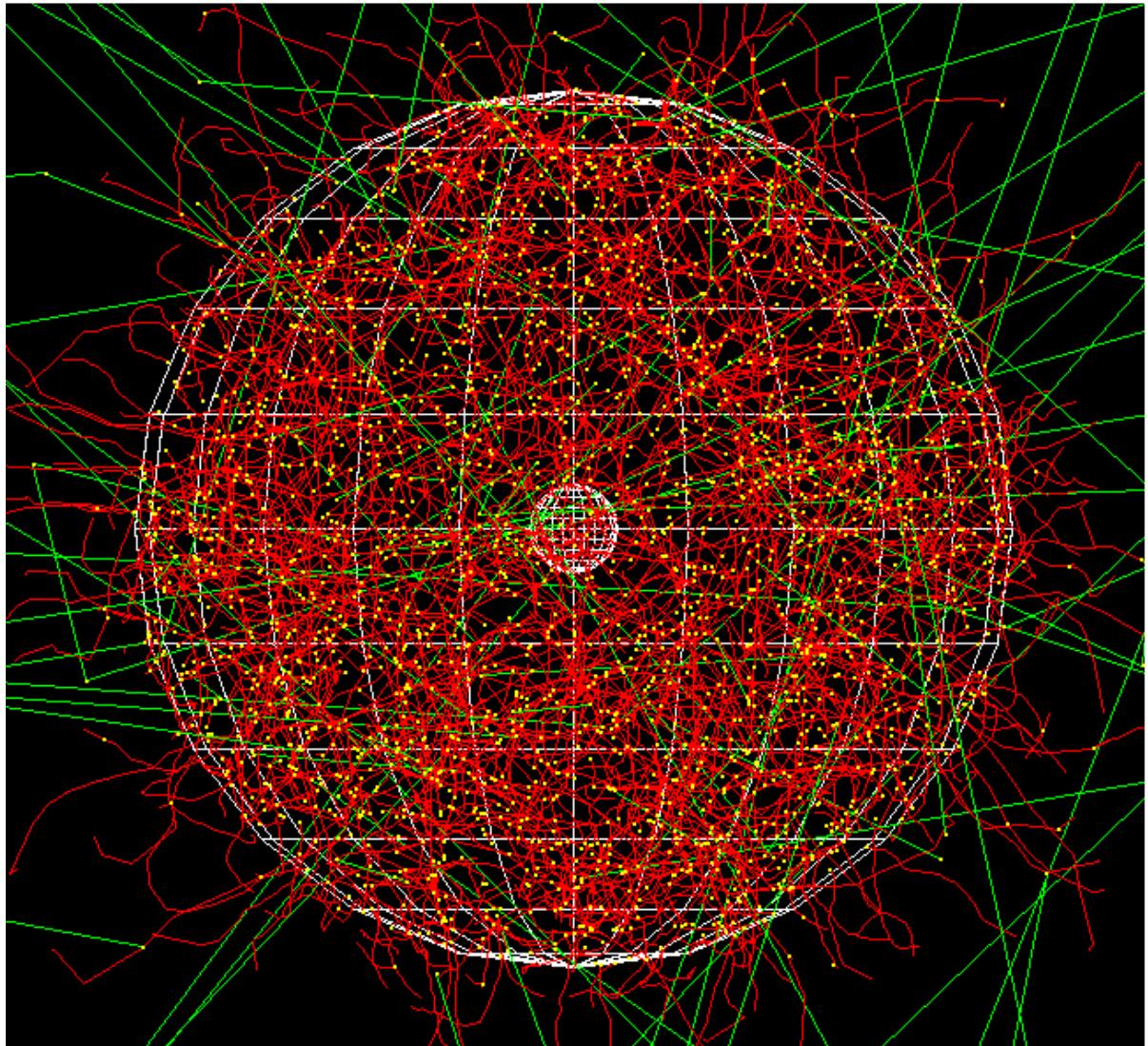
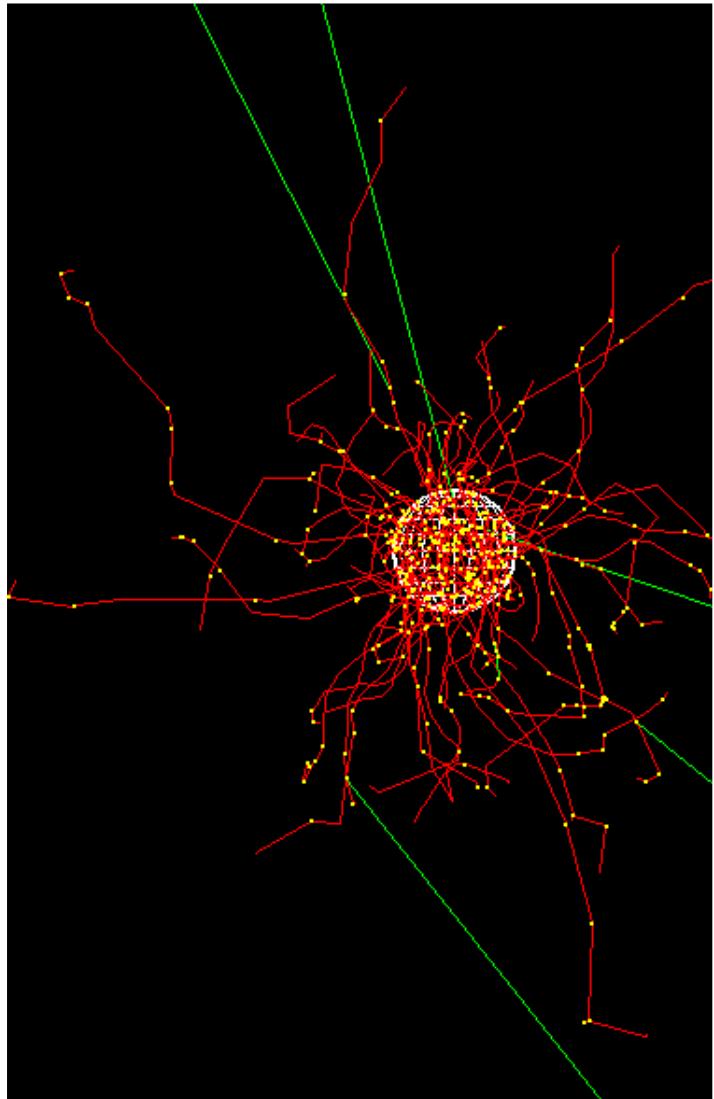
IART: ^{90}Y -biotin PET/CT





$D = 2 \text{ mm}$

$D(\text{est}) = 2 \text{ cm}$ $D(\text{int}) = 2 \text{ mm}$



IART Phase II study: summary on dosimetry

Tumour bed uptake: 8 % (4 % – 12%) of IA

Avidin injected 100 mg with dedicated syringe

Activity: 3.7 GBq of ^{90}Y -biotin

Gy

Tumour quadrant:

20 (15 – 27)



BED 23 Gy

Kidneys:

3.7 (2.2 – 5.9)



Safe !

Ur. Bladder:

5.2 (3.0 – 7.4)



EBRT – IART

The power to reduce the risk of local recurrences compared to external radiotherapy must be evaluated in a randomized trial

**CONTROLLED RANDOMIZED TRIAL
is PLANNED at IRST:**

IART vs EBRT

**in early breast cancer after
quadrantectomy**

Breast Surgery in 21st Century:

Low mutilation: QUART

High information: SNB



Better quality of life and reduced cost: IART

IART: further applications

Nipple sparing mastectomy

Superficial bladder cancer

Lung cancer and mesotelioma

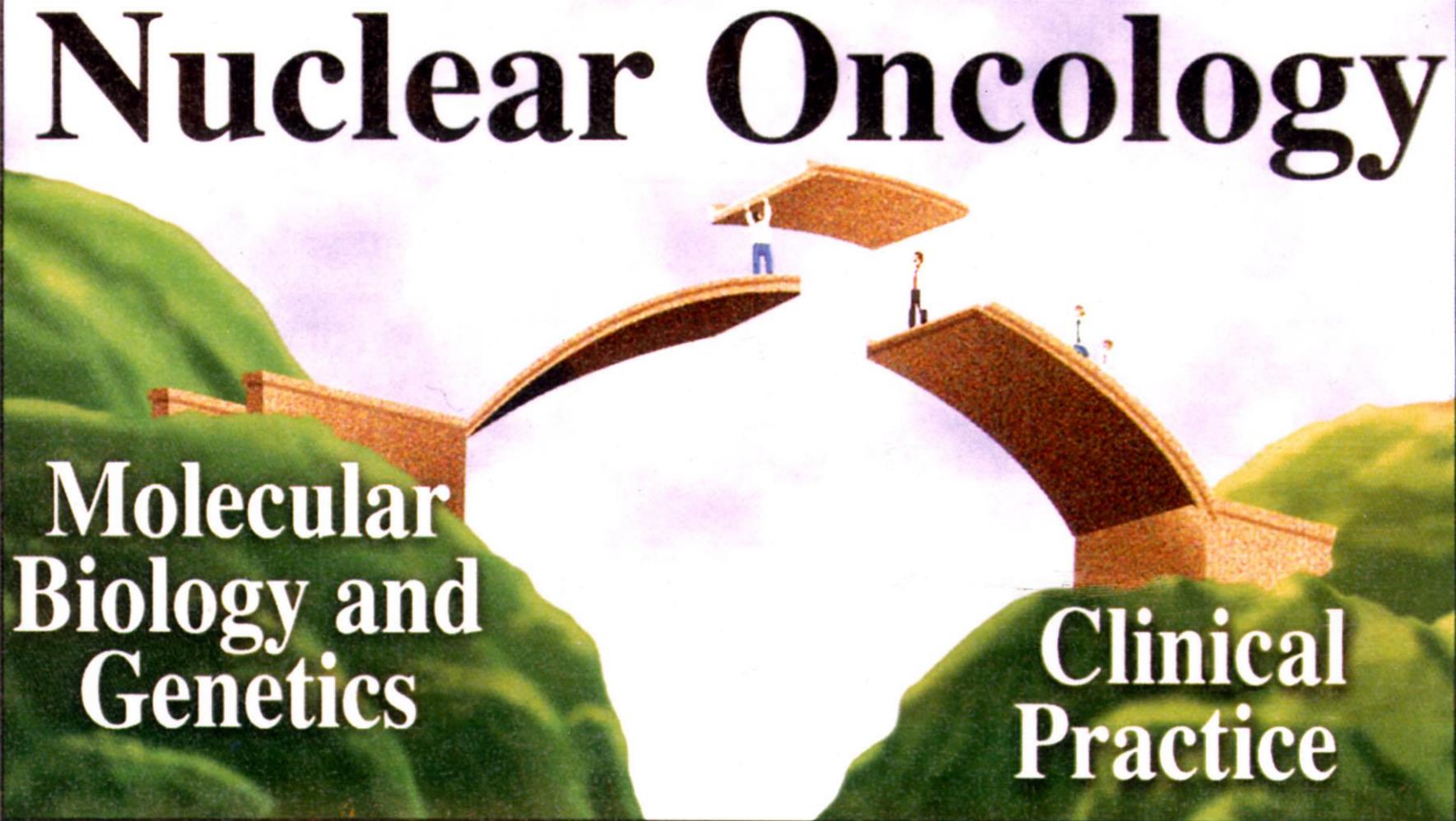
Head and neck

Prostate cancer

Ovarian cancer

Rectal and others.....

Nuclear Oncology



Molecular
Biology and
Genetics

Clinical
Practice

