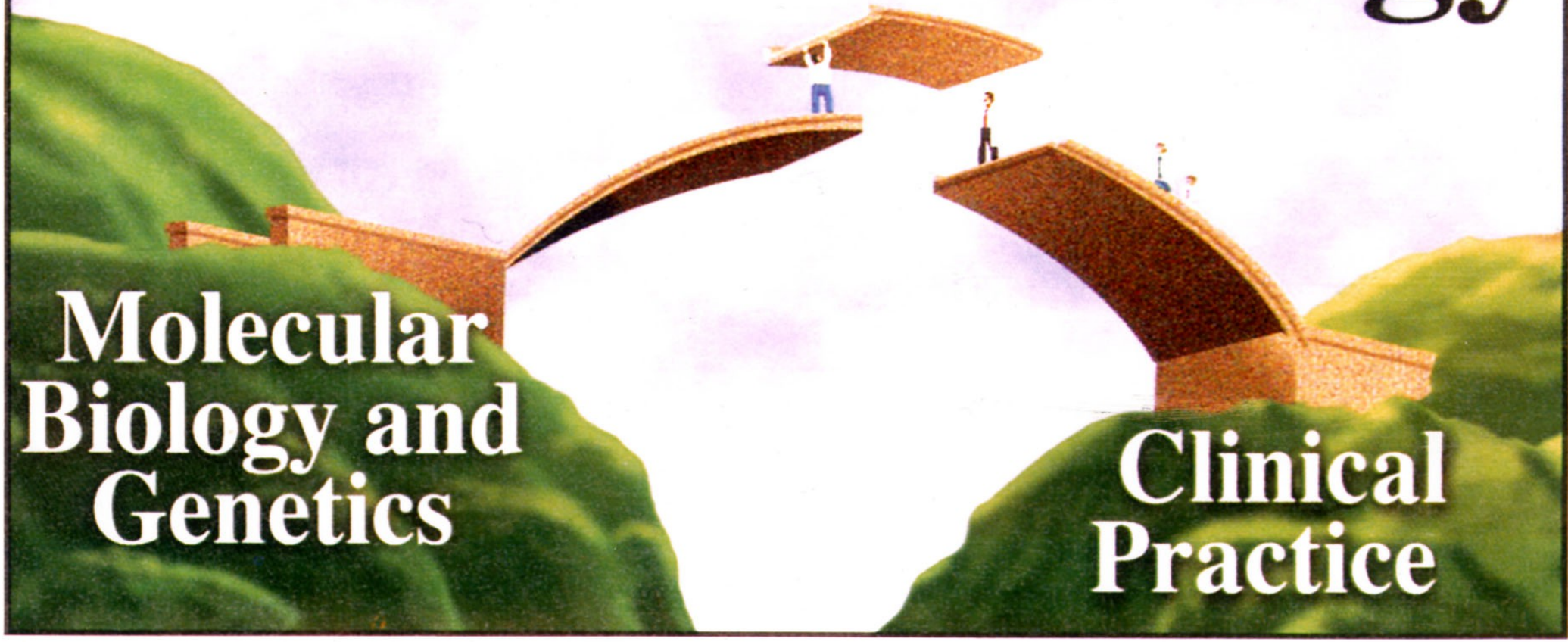
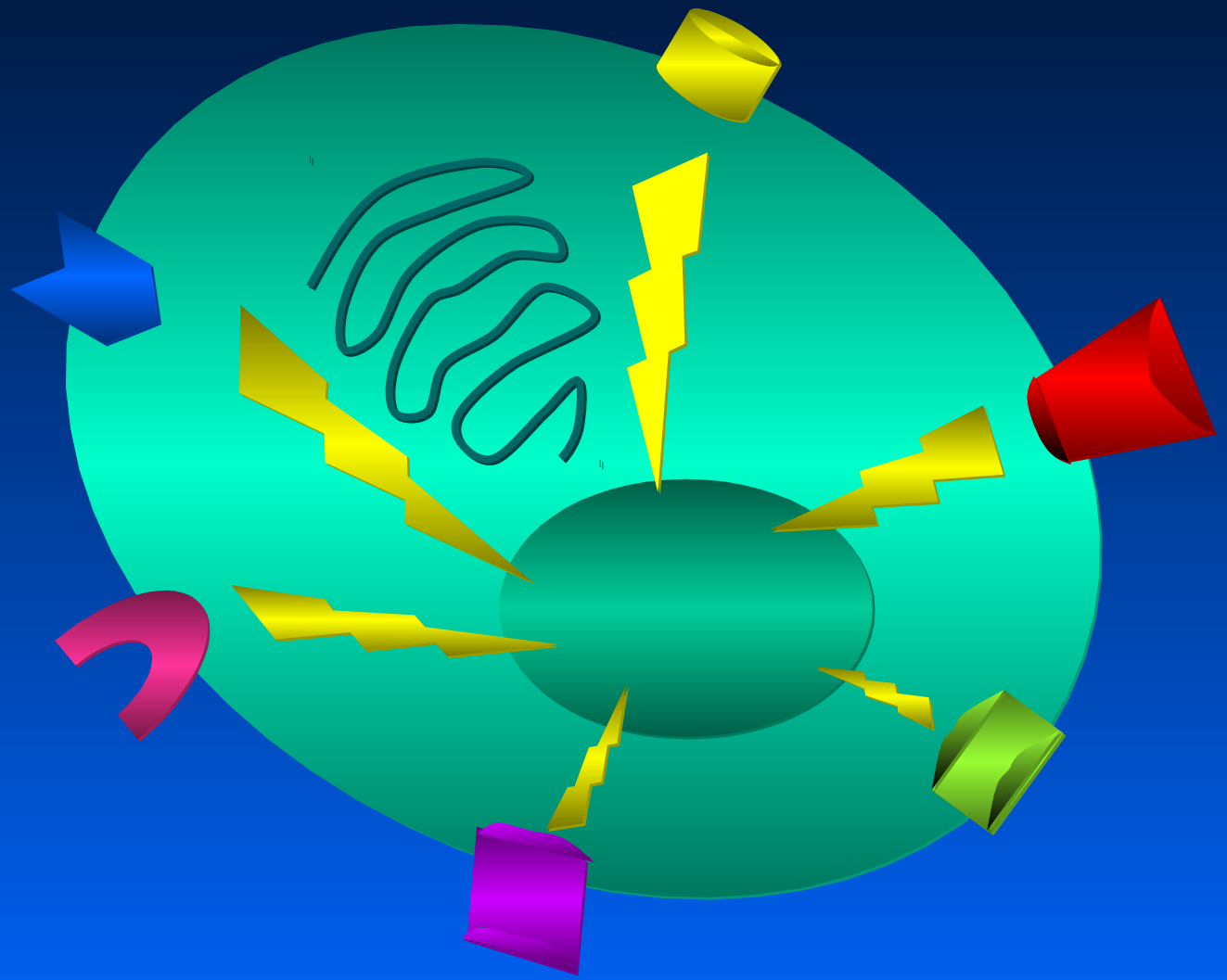
The Avidin-Biotin pretargeting system for molecular radiotherapy in cancer patients

Giovanni Paganelli - Meldola, Italy

Nuclear Oncology



Possibili bersagli per radioterapia mirata



TAA-MAb

Somatostatin-R

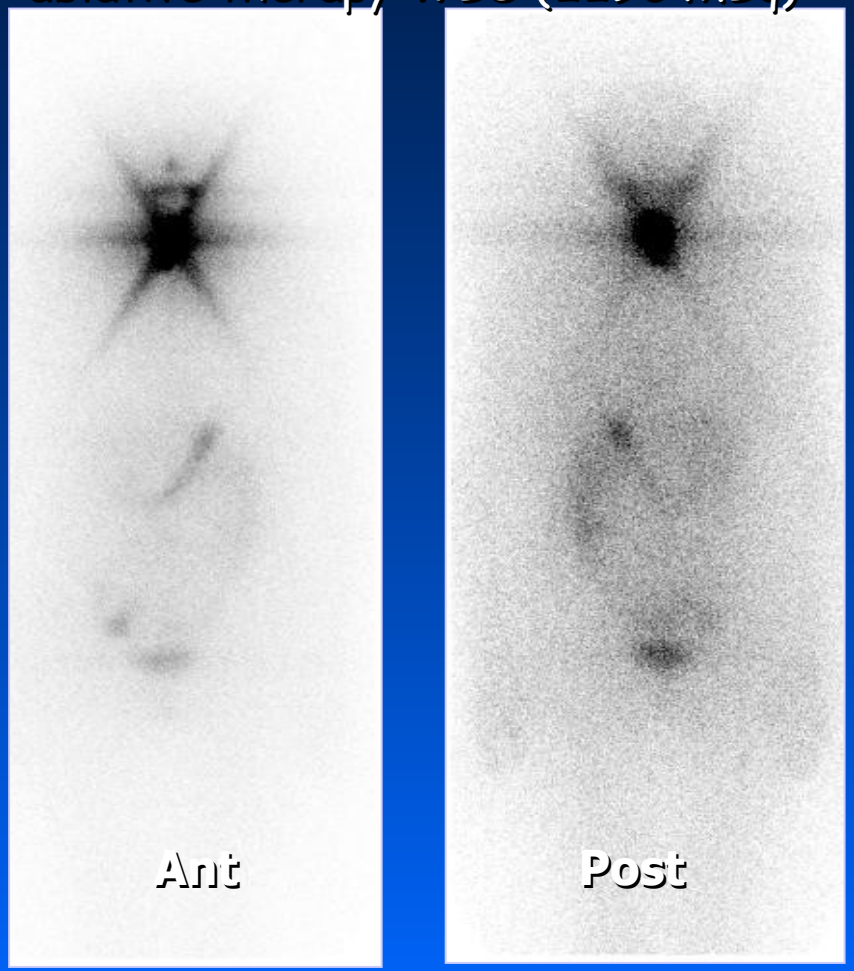
avidin

bombesin

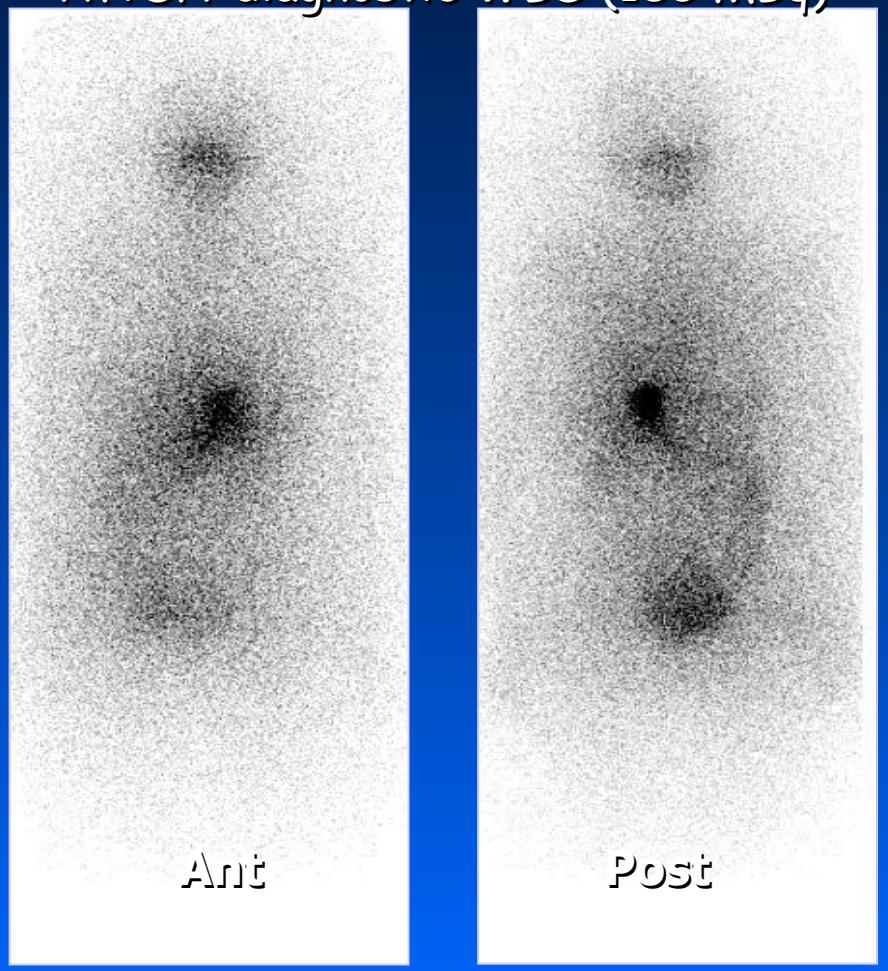
PSMA ...

The Model:
Radionuclide therapy with ^{131}I in differentiated thyroid carcinoma

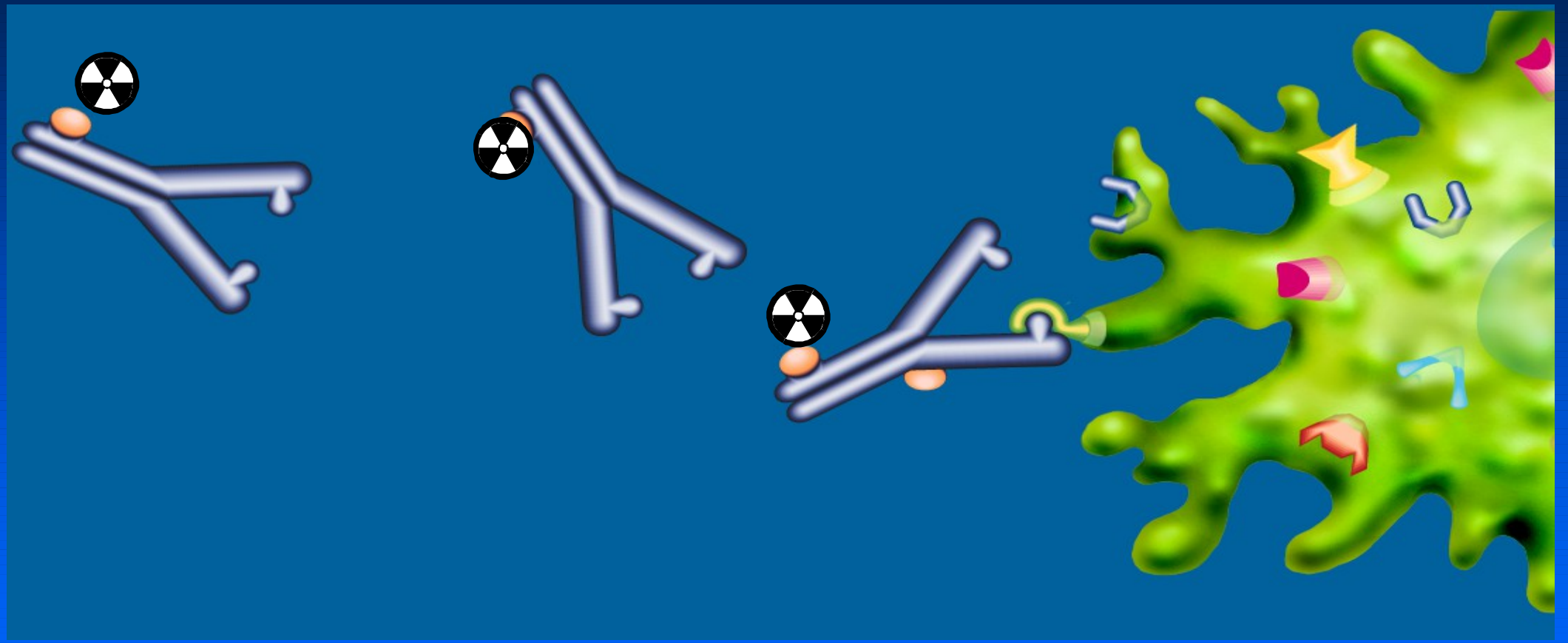
February 2002
ablative therapy WBS (2295 MBq)



August 2002
rhTSH-diagnostic WBS (185 MBq)

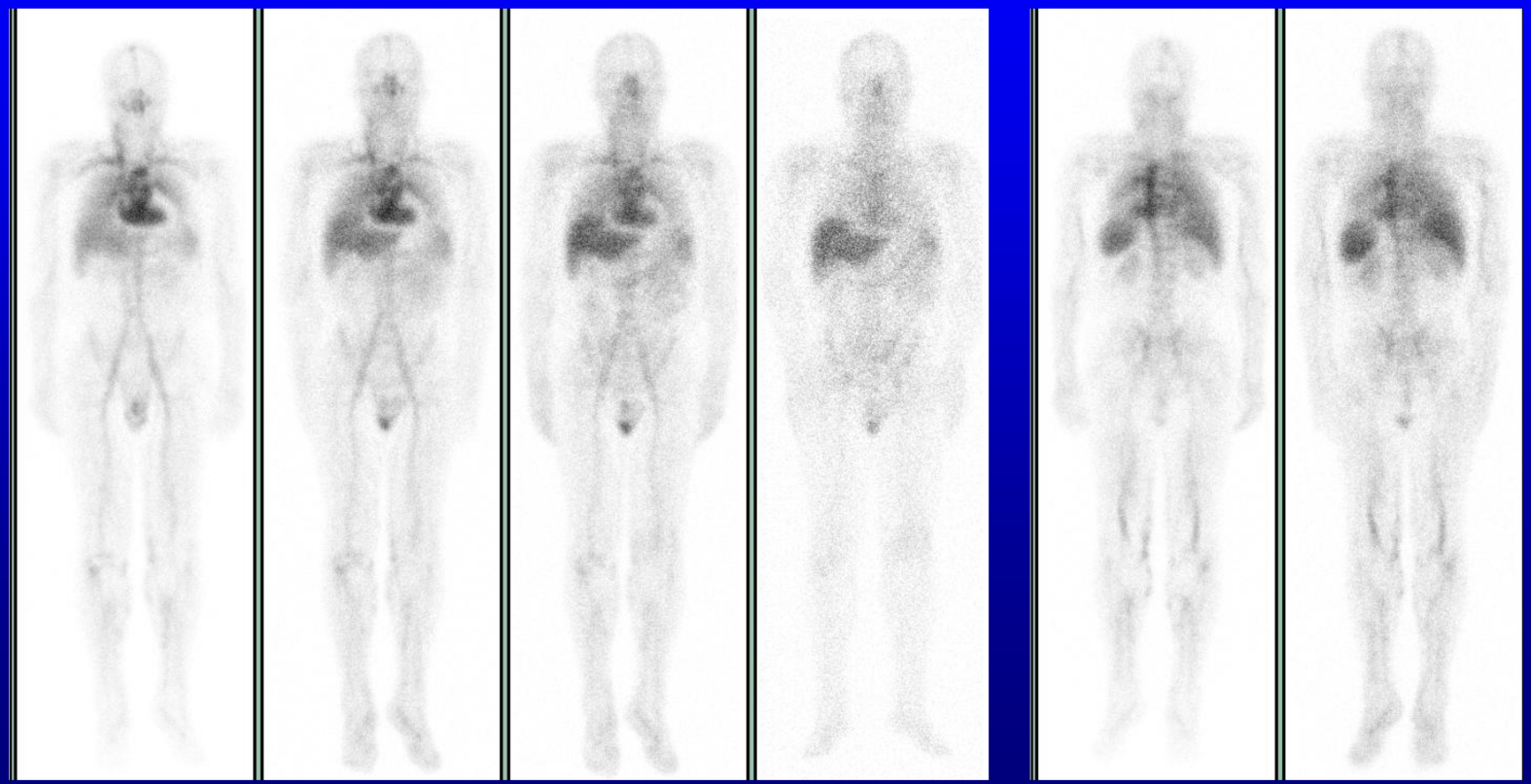


Antibody guided Tumor Targeting



Anti CD20 MoABs

Biodistribution

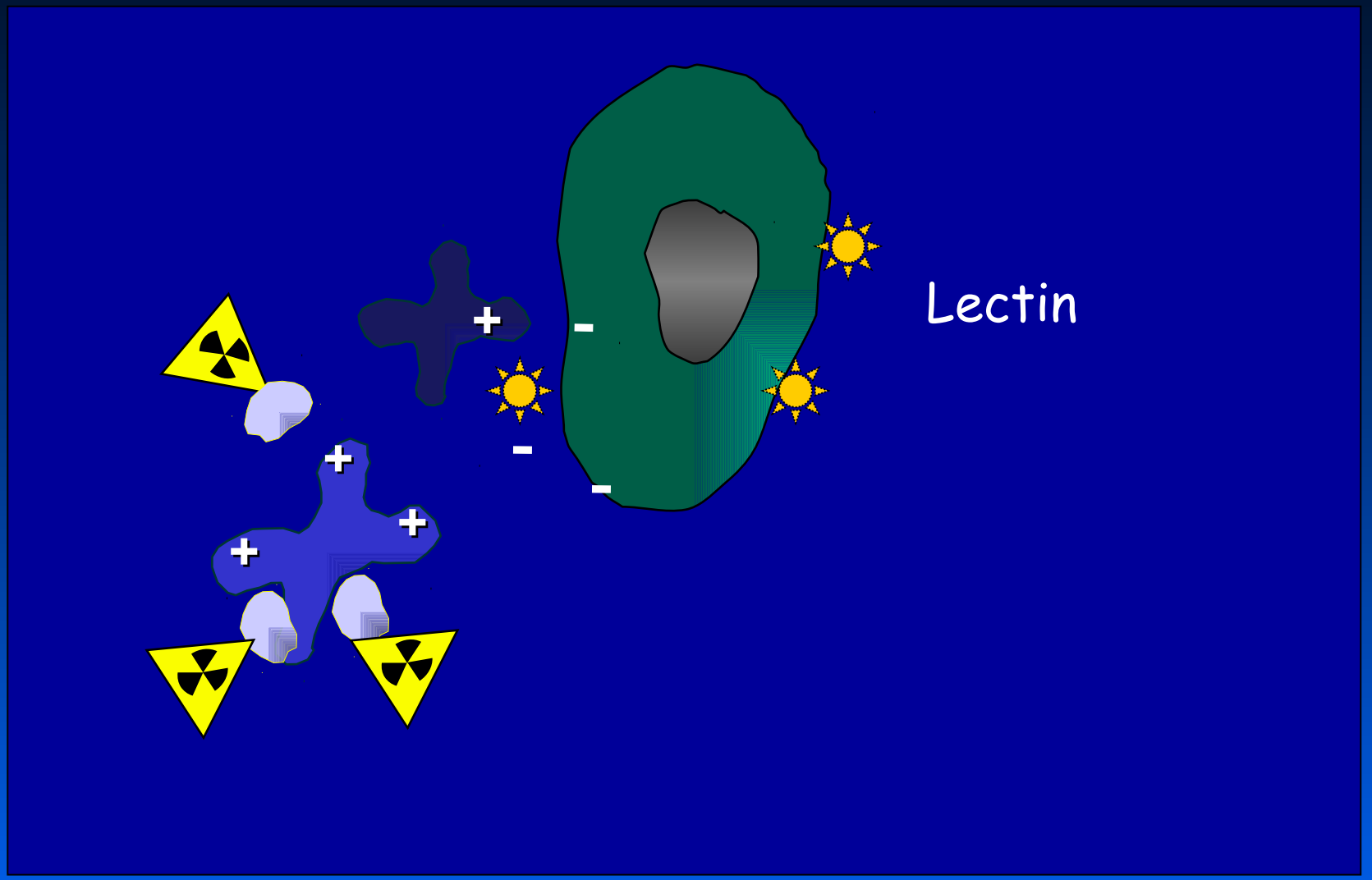


The Pretargeting

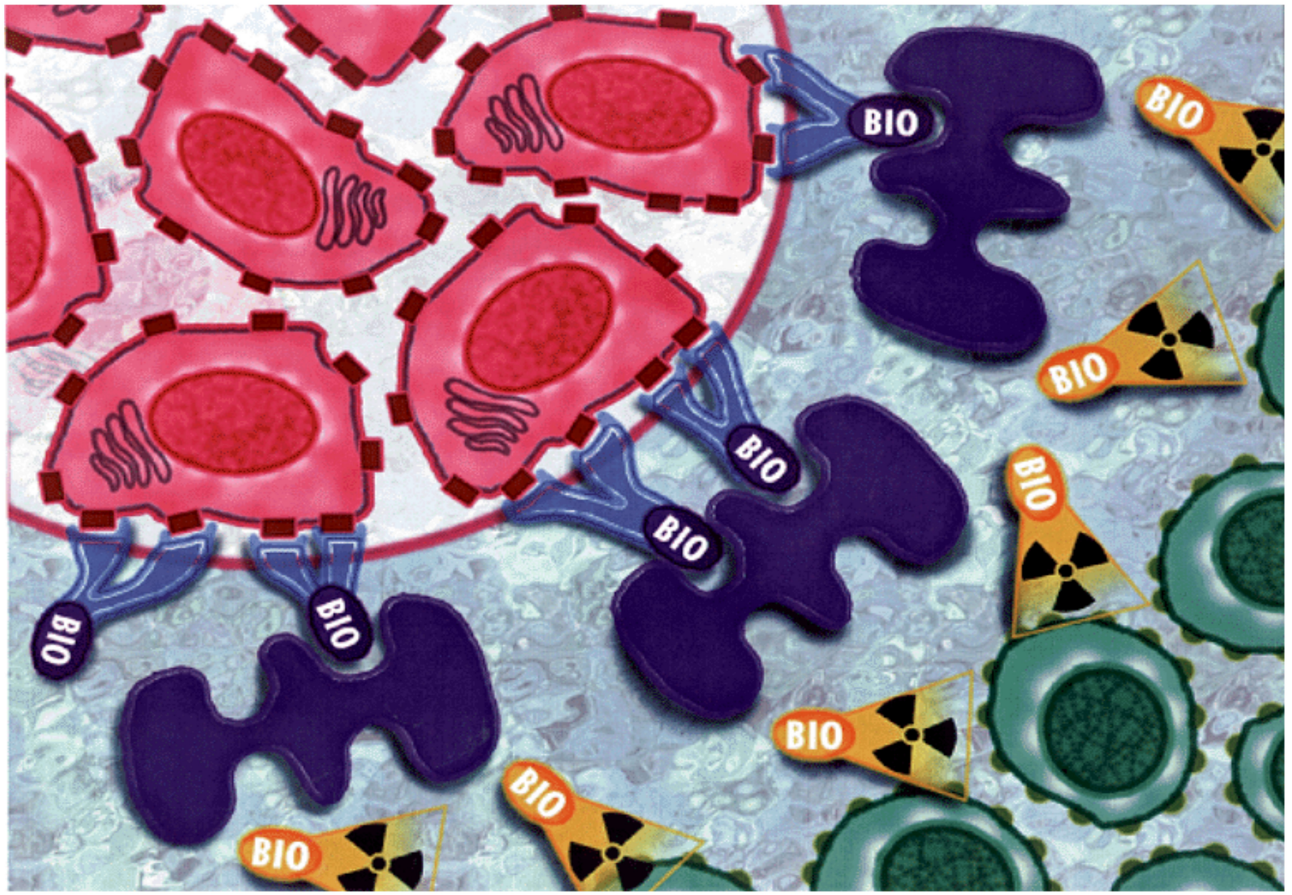
Molecular properties of avidin

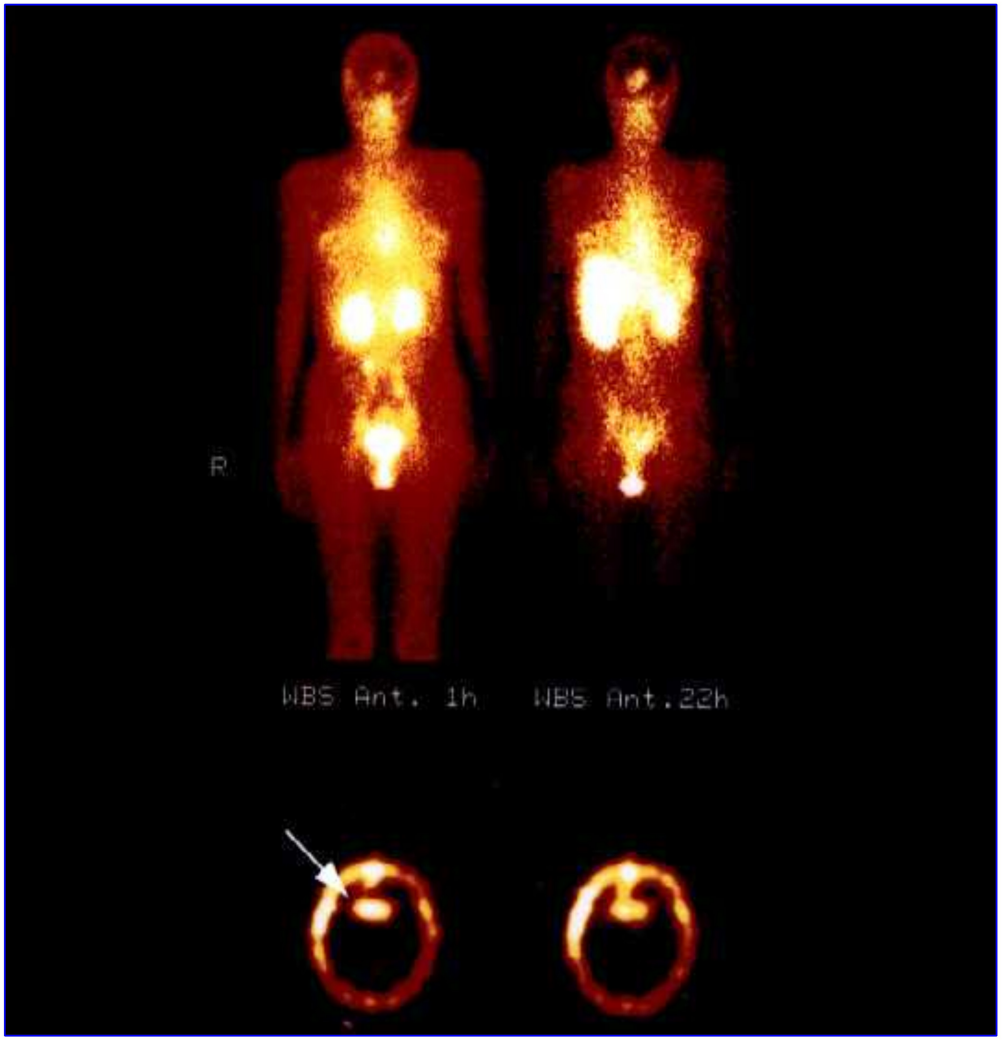
Molecular weight	~65 000
Number of subunits	4
Subunit molecular weight	~16 000
Binding sites for biotin/mole	4
K_D of the complex with biotin	~10^{-15}
Oligosaccharide units/subunit	1
Mannose/subunit	4.5
Glucosamine/subunit	3
Isoelectric point	~10.5

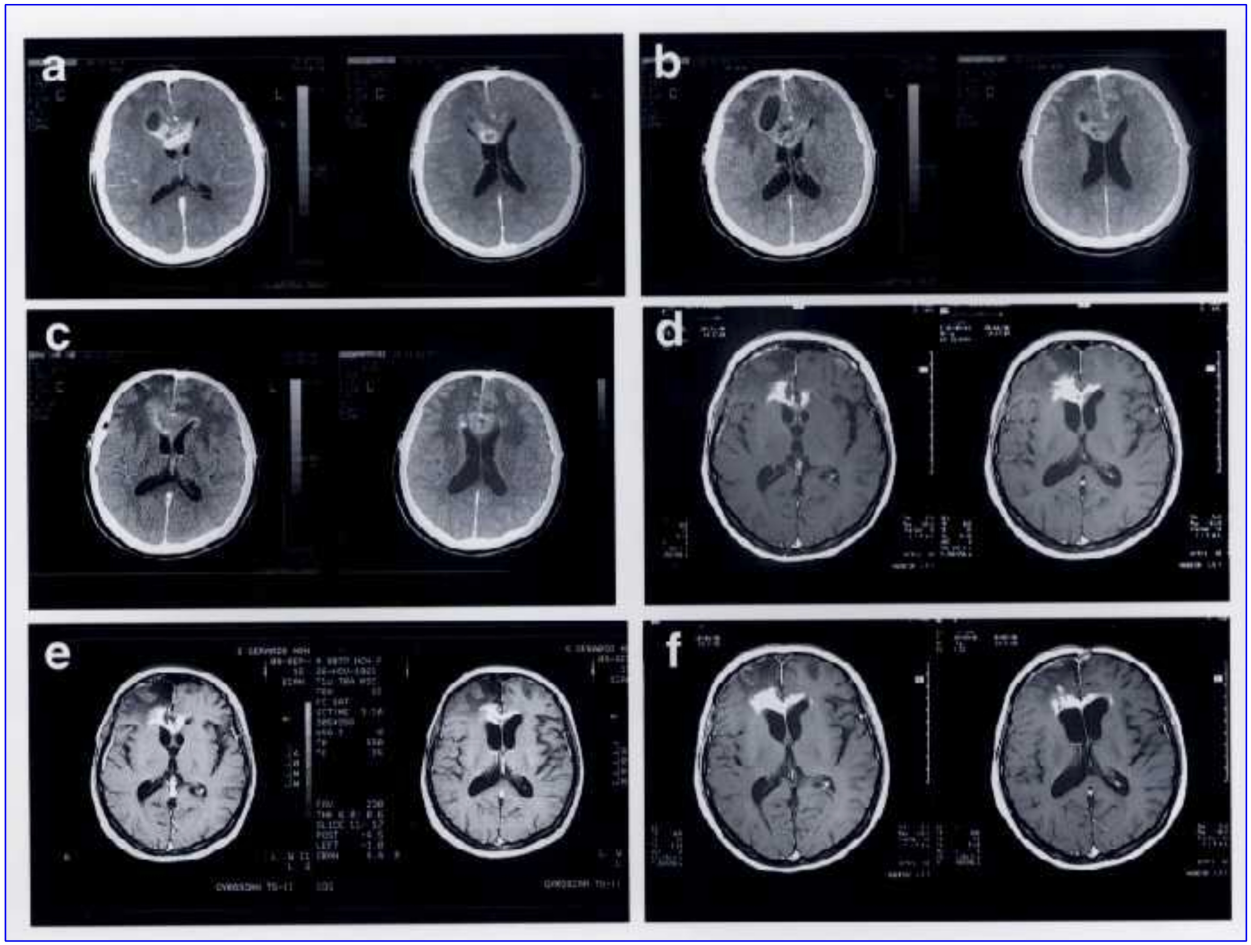
Tumor avidination



Yao - J Nat Cancer Inst, 90:25-29, 1998


BIO
BIO
BIO
BIO
BIO
BIO
BIO
BIO
BIO
BIO


R
WBS Ant. 1h
WBS Ant.22h


a
b
c
d
e
f

CLINICAL APPLICATION

Brain

Breast

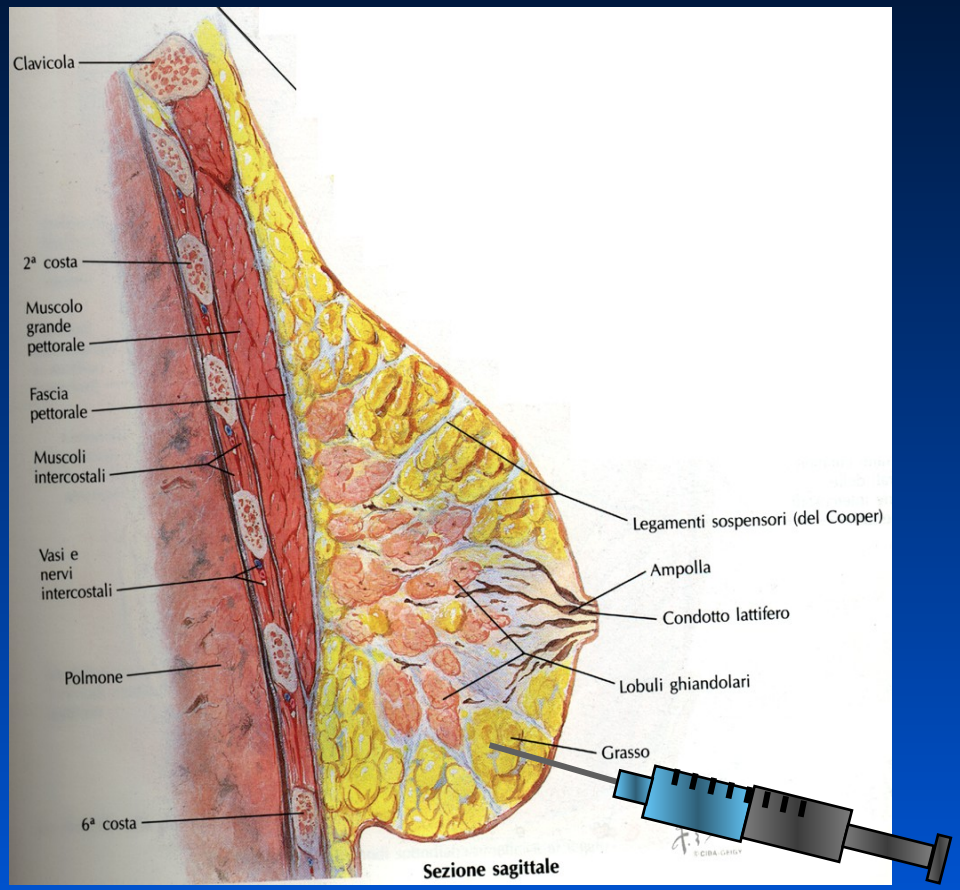
Prostate

Peritoneum

Bladder

etc…

I.A.R.T.®



Avidin

Avidin injection during surgery into the tumour bed area

Quadrantectomy + SNB + EBRT

represent the standard therapy in Early Breast Cancer

The challenge of the 21st century

Can we modify EBRT in early breast cancer?

Open problems with EBRT

- EBRT post-quadrantectomy requires 6 – 7 weeks to be completed
- EBRT may cause side effects and complications (lung – heart)
- The radiation centres are often not easy accessible

VOLUME 28 · NUMBER 35 · DECEMBER 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Benjamin D. Smith, Bruce G. Haffty, Lynn D. Wilson, Grace L. Smith, Akshar N. Patel, and Thomas A. Buchholz

From The University of Texas M. D. Anderson Cancer Center, Houston, TX; Yale University School of Medicine, New Haven, CT; and Cancer Institute of New Jersey, New Brunswick, NJ.

Submitted June 28, 2010; accepted August 23, 2010; published online ahead of print at www.jco.org on October 18, 2010.

Presented in part at the 51st Annual Meeting of the American Society for Radiation Oncology, November 1-5, 2009, Chicago, IL.

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

Corresponding author: Benjamin D. Smith, MD, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1202, Houston, TX 77030; e-mail: bsmith3@mdanderson.org.

© 2010 by American Society of Clinical Oncology

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

sites (excluding nonmelanoma skin cancers) and in situ breast cancers.

Conclusion

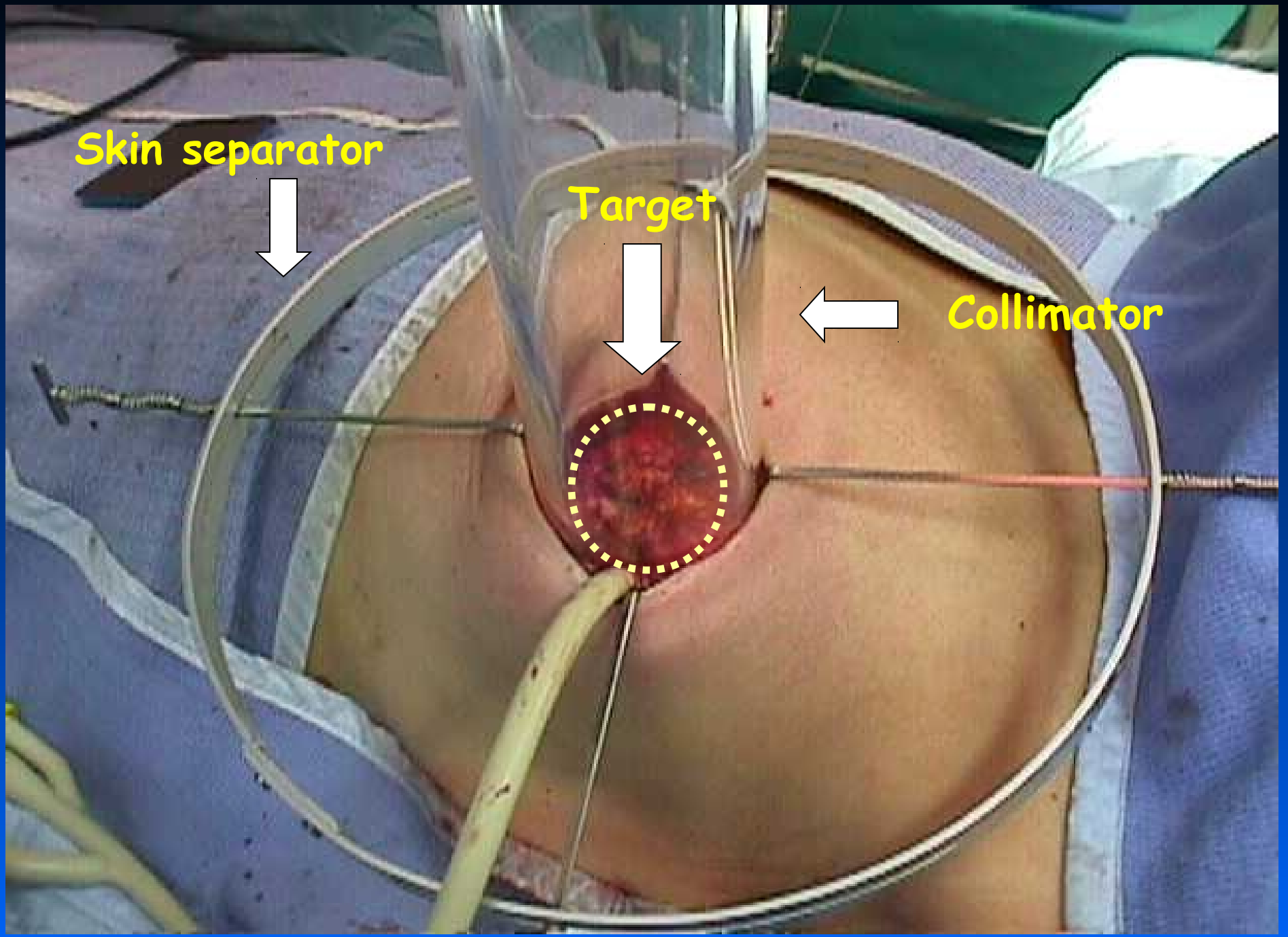
Demand for radiation therapy is expected to grow 10 times faster than supply between 2010 and 2020. Research is needed to explore strategies to enhance capacity to deliver quality radiation therapy despite increased patient loads.

Methods under investigation for accelerated radiotherapy in breast cancer

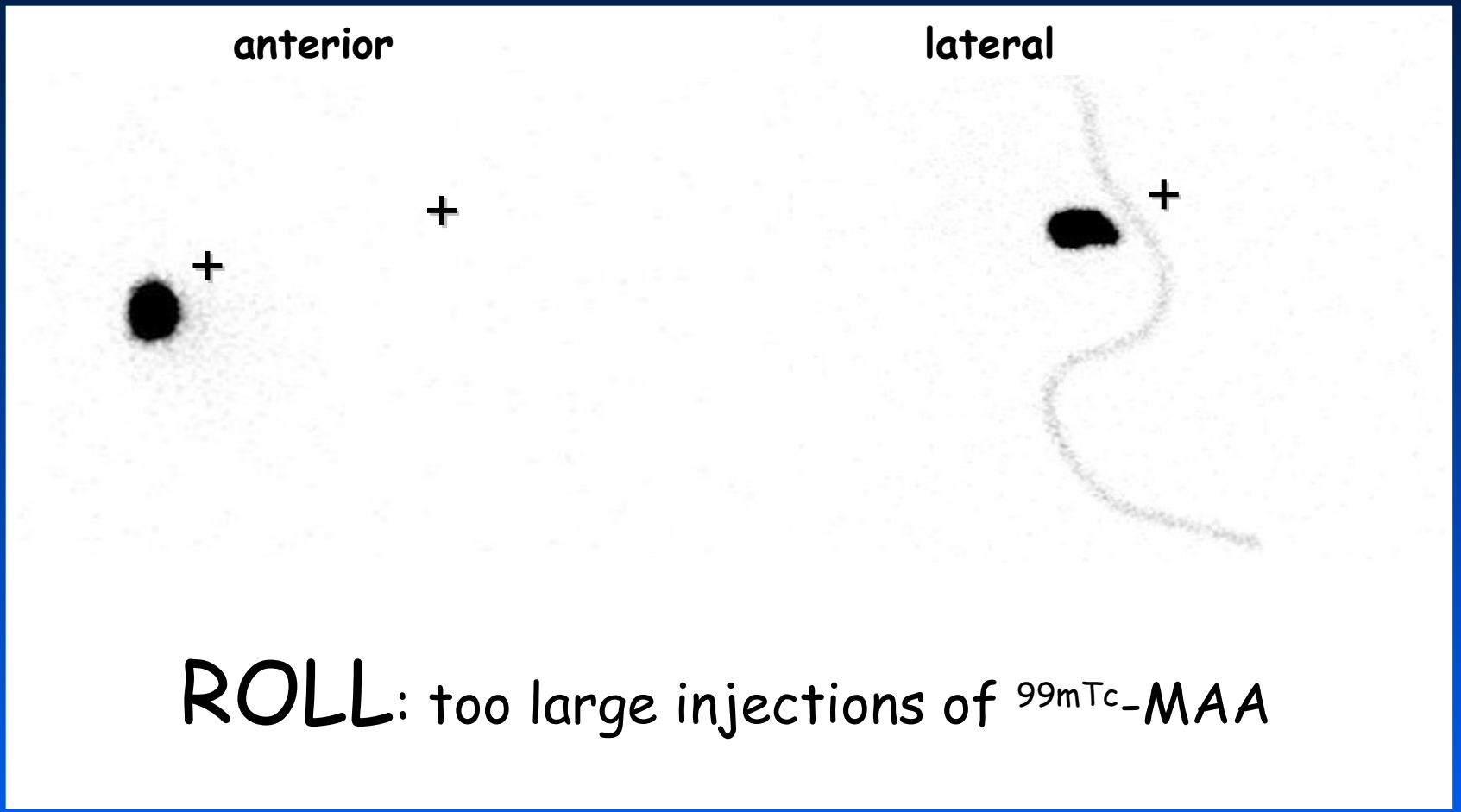
- Breast Brachitherapy
- MammoSite
- 3D Conformal EBRT
- TARGIT System
- IORT - ELIOT

Partial
breast
Irradiation
PBI

Intraoperative
Radiotherapy
IORT / ELIOT

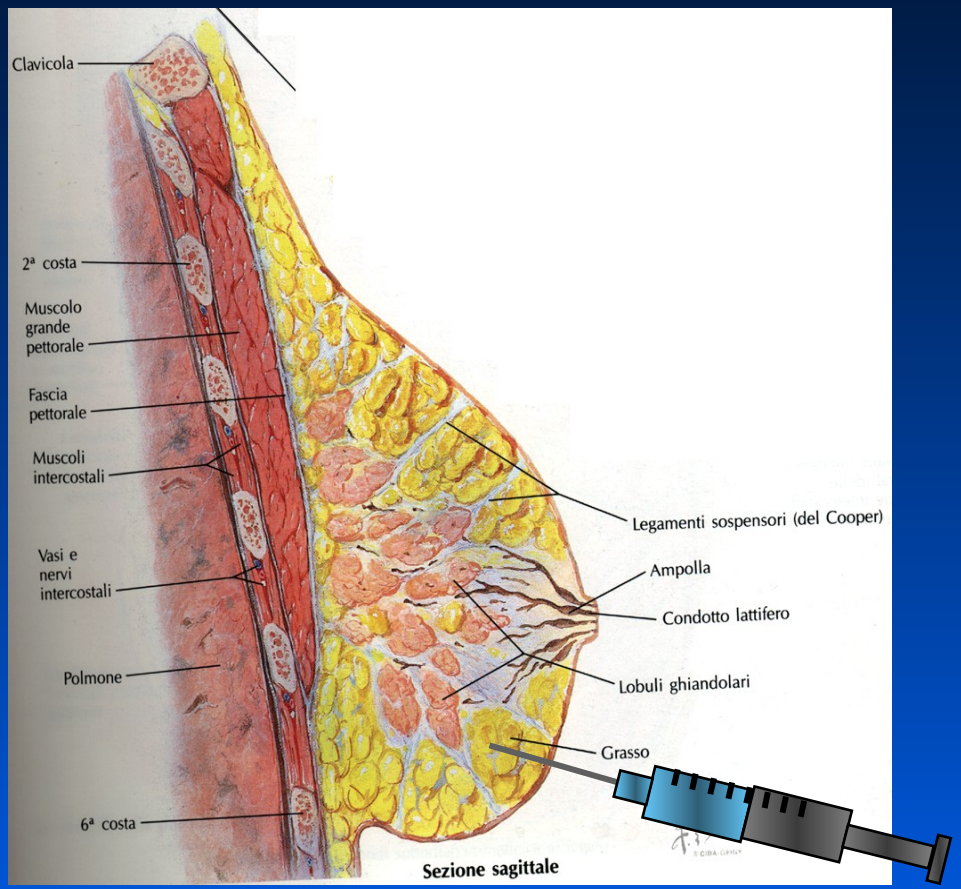

Skin separator
Target
Collimator

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



ROLL: too large injections of ^{99m}Tc-MAA

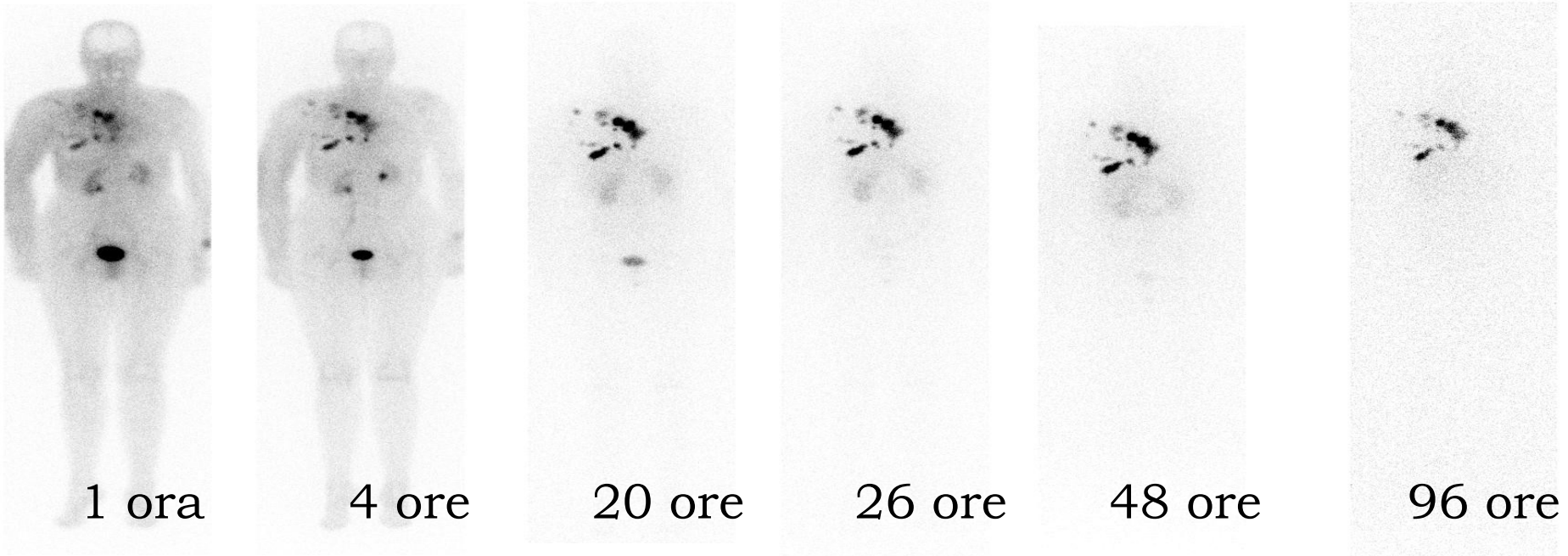
A R THE



Avidin

Avidin (Guided) Radio THerapy

"The proof of principle"



February 2004

May 2004

October 2004

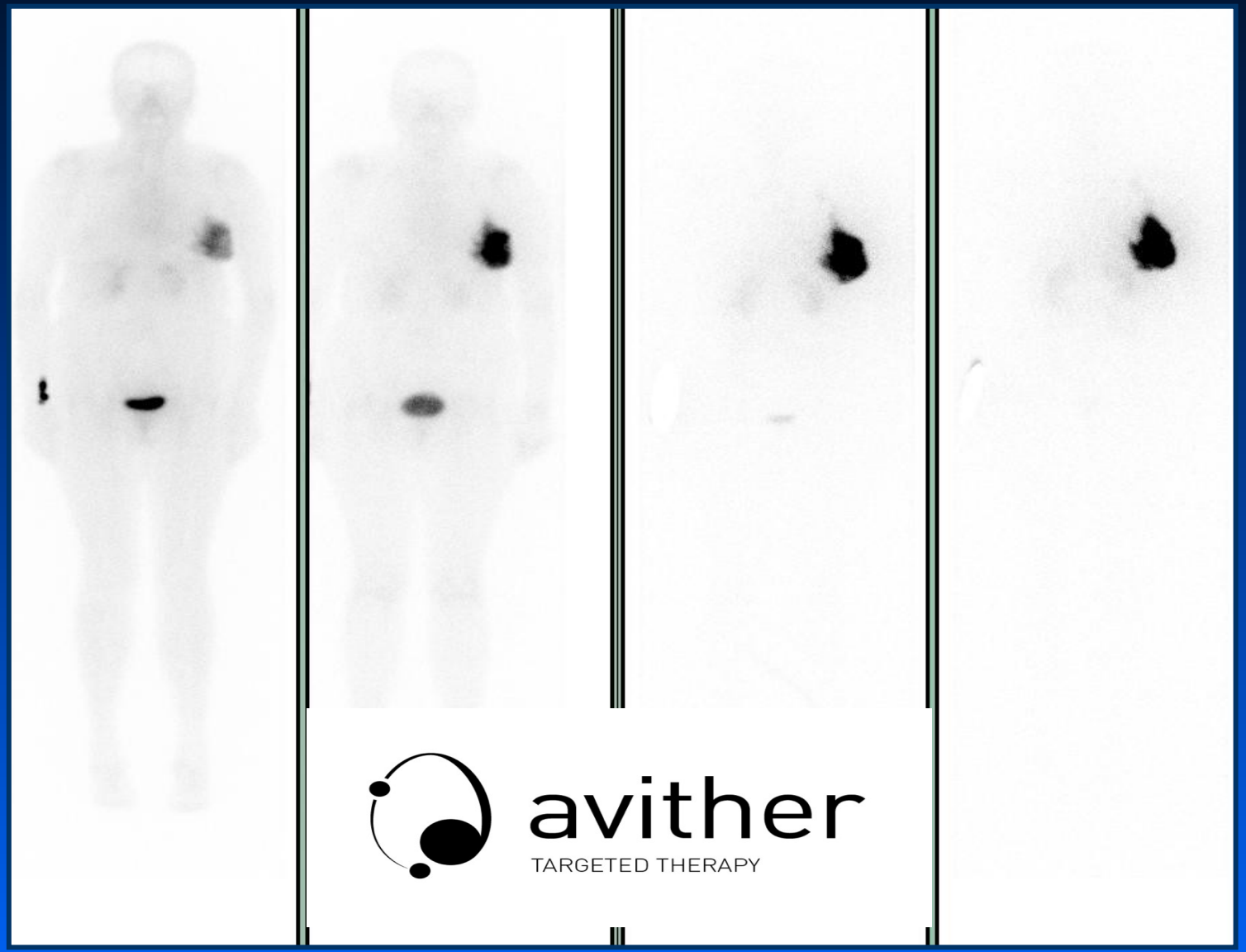
In the operative room…


15
10
5

...in the Nuclear Medicine Dept.

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

Total Body anterior view - pt no 25

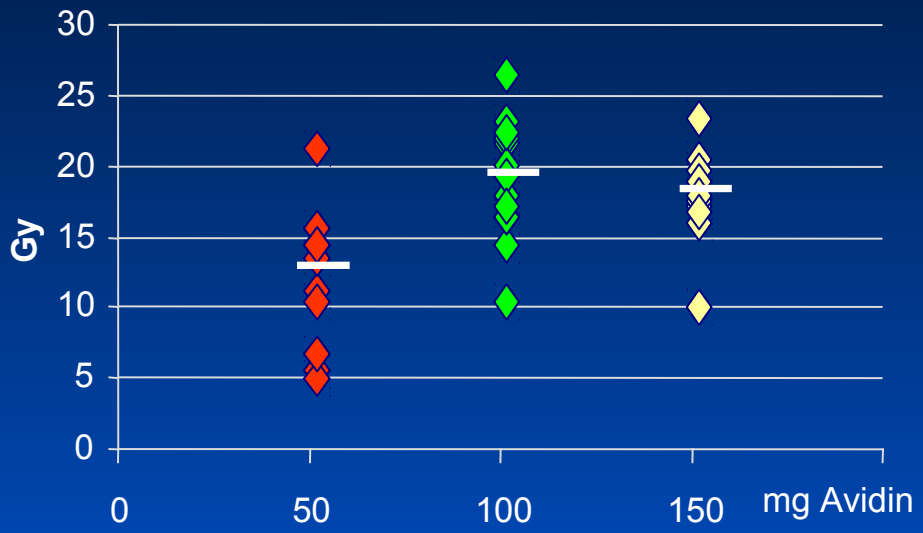


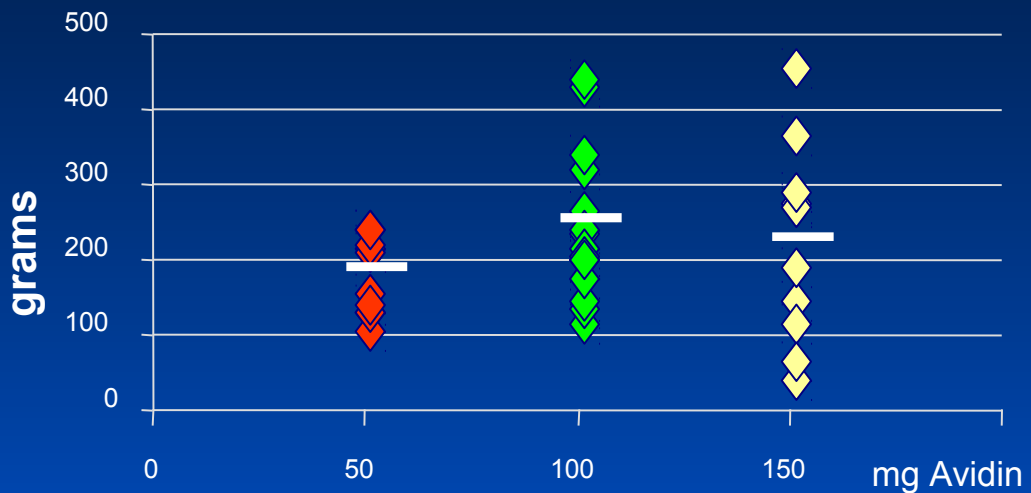
3D dosimetry in early breast cancer patients undergoing Intraoperative Avidination for Radionuclide Therapy (IART) combined with External Beam Radiation Therapy

Ferrari ME, Cremonesi M, Di Dia A, Botta F, De Cicco C, Sarnelli A, Pedicini P, Calabrese M, Orecchia R, Pedroli G, Paganelli G.

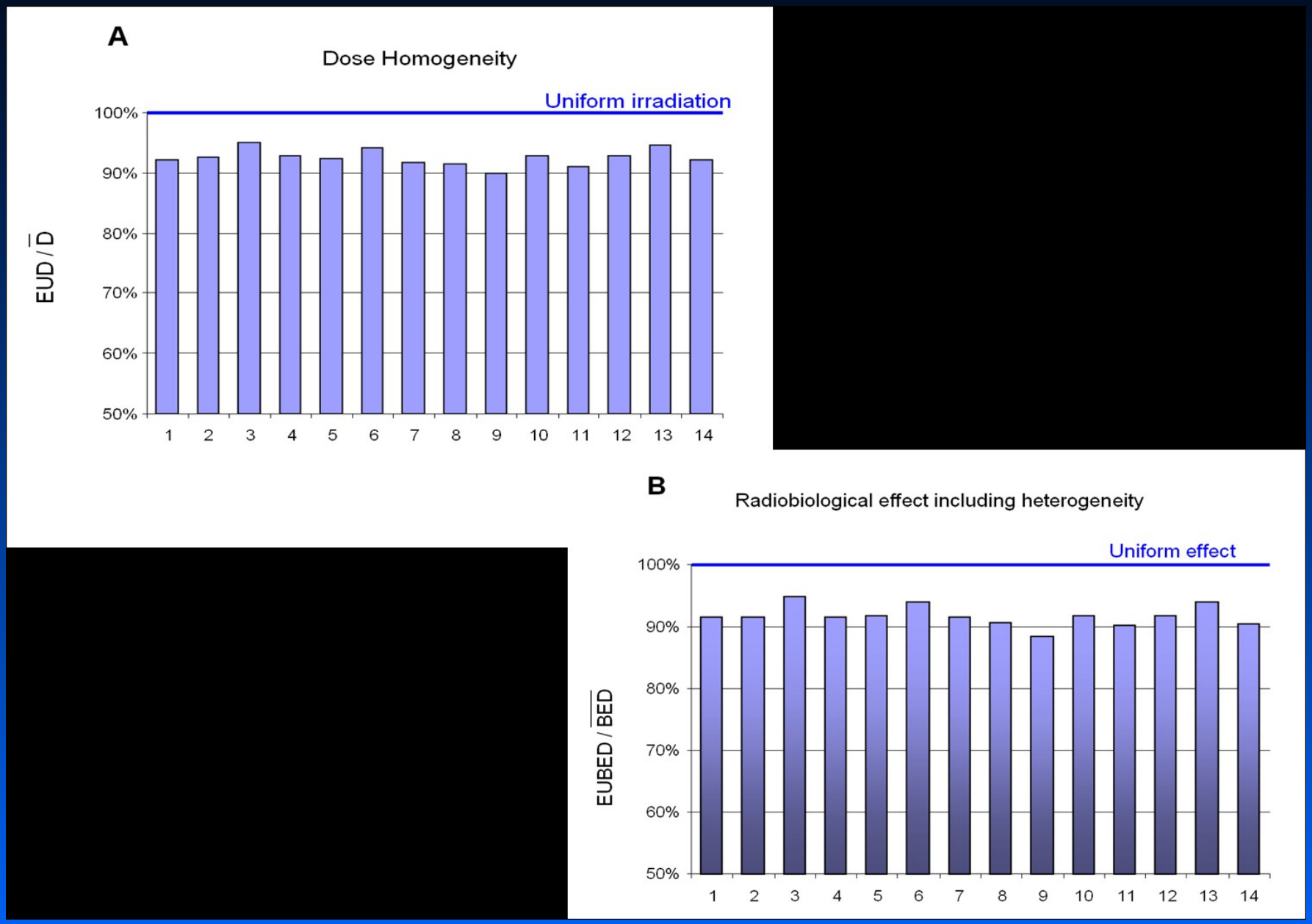
Eur J Nucl Med Mol Imaging, DOI 10.1007/s00259-012-2197-6

Mean dose (BED) and mass distribution for high uptake region in the three cohorts





	dose (Gy)	mass (g)
Cohort 100 mg	19.5 ± 4.0	254 ± 99
Cohort 50 mg	13.0 ± 5.1	188 ± 52
Cohort 150 mg	18.4 ± 3.5	230 ± 133


A
Dose Homogeneity
Uniform irradiation
100%
90%
80%
70%
60%
50%
EUD / D̄
1 2 3 4 5 6 7 8 9 10 11 12 13 14
B
Radiobiological effect including heterogeneity
Uniform effect
100%
90%
80%
70%
60%
50%
EUBED / BED
1 2 3 4 5 6 7 8 9 10 11 12 13 14

Local Toxicity post-IART® (3-4 w)

evaluated by RTOG Scale* on 34 pts

G0	G1	G2	G3	G4
pts	pts	pts	pts	pts
15	20	0	0	0

* Radiation Therapy Oncology Group, evaluation scale starting from G0 to G4


1
Pre surgery


2
Post surgery


3
3 weeks after IART


1
Pre surgery


2
Post surgery


3
3 weeks after IART


4
6 month

Conclusions

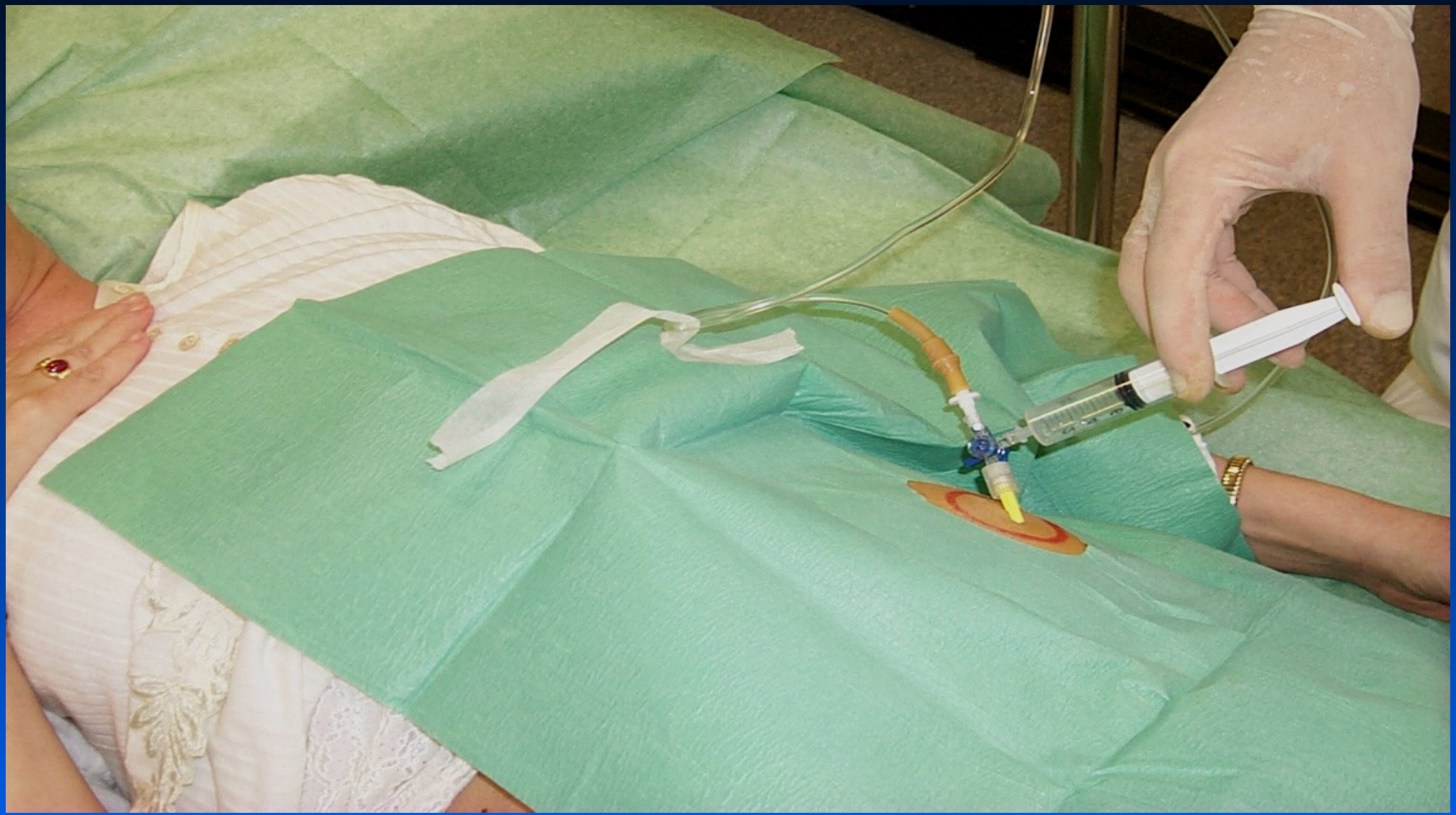
- 100 mg of avidin seems to be the optimal dose
- IART® toxicity is neglegible
- IART® + accelerated RT is feasible

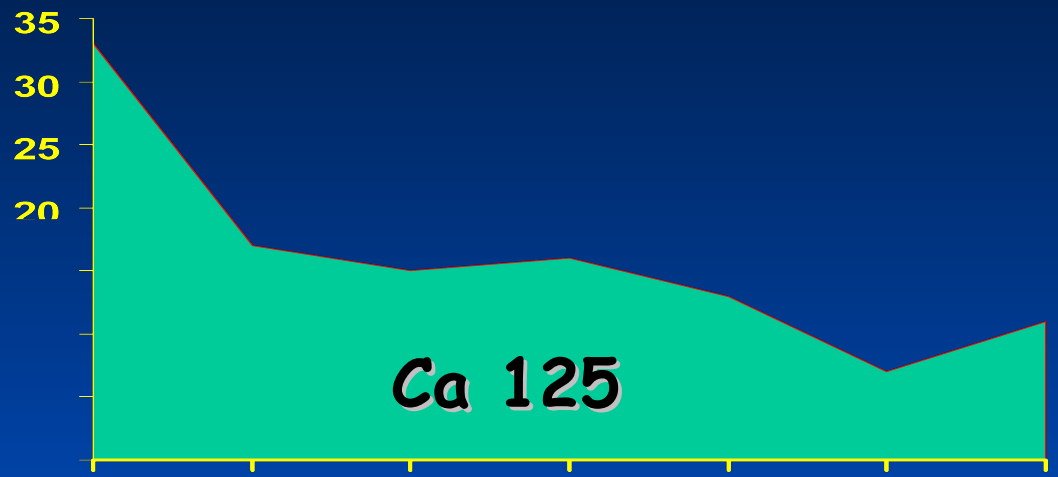
The IRST "S.A.R.A". Study Standard -vs -Accelerated- Radio-nuclide Avidinated therapy

Phase III, multicenter, randomized, clinical trial to evaluate IART with 90Y-Biotin compared to Standard RT in patients with breast cancer candidate to RT after conservative surgery

Further Applications

- Superficial bladder cancer
- Head and neck cancer
- Pancreatic cancer
- Prostate cancer
- Peritoneal carcinomatosis



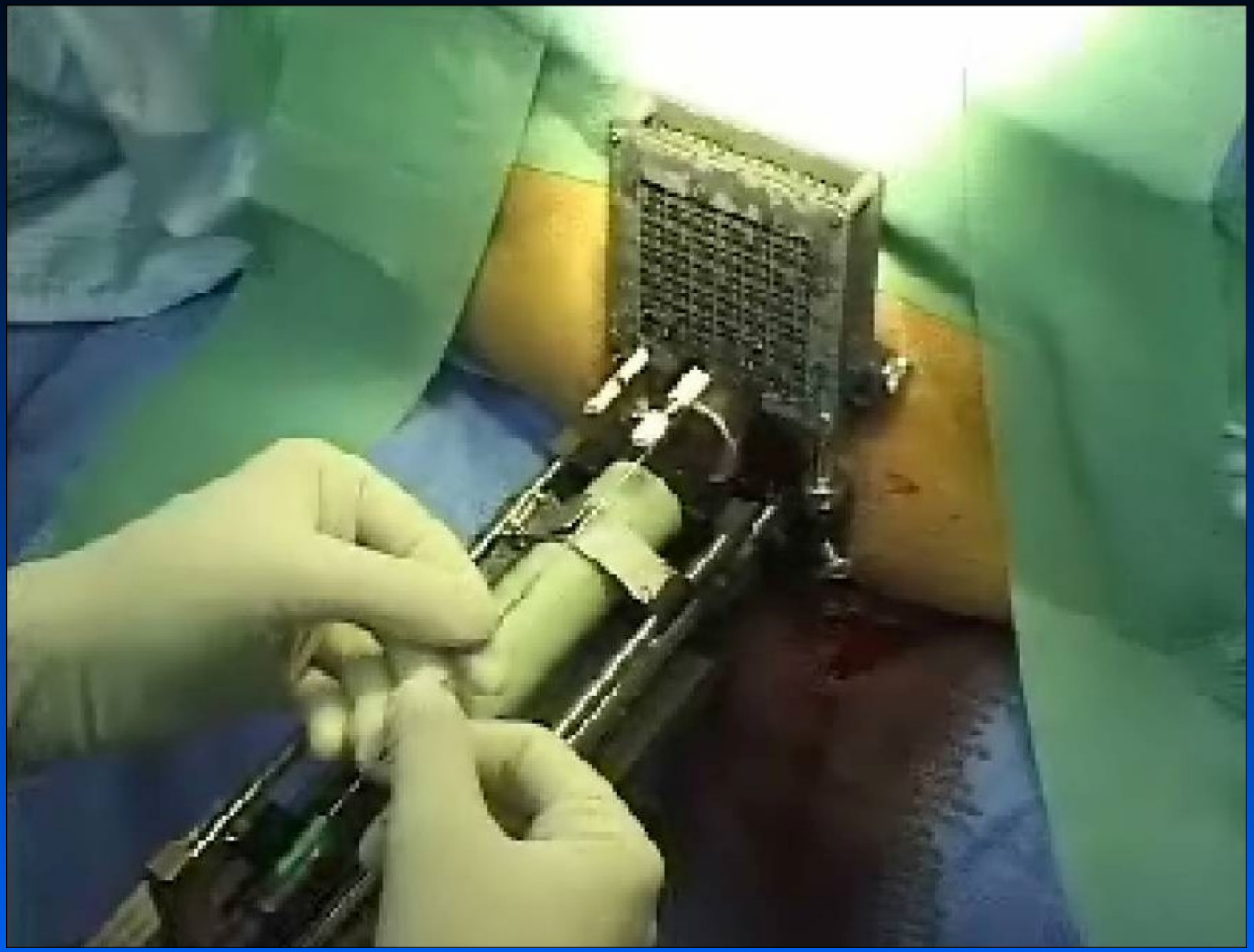


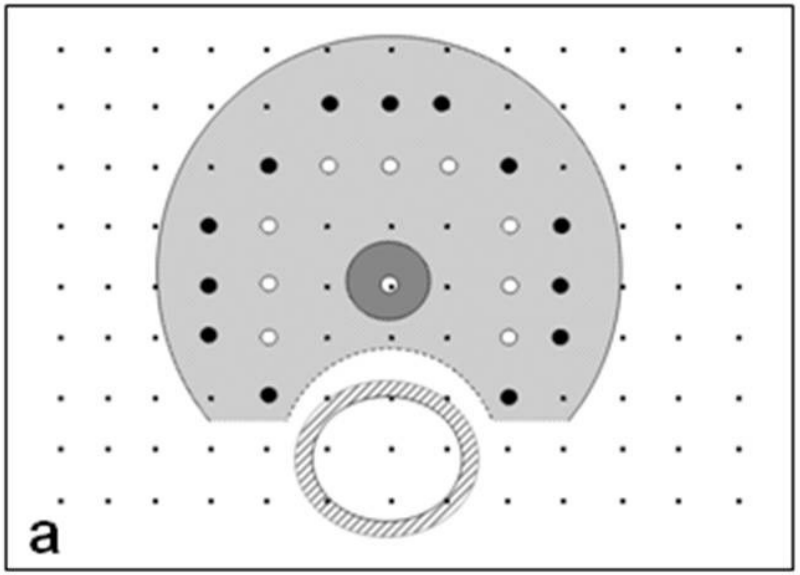
G. P. 65 aa
npl ovarica

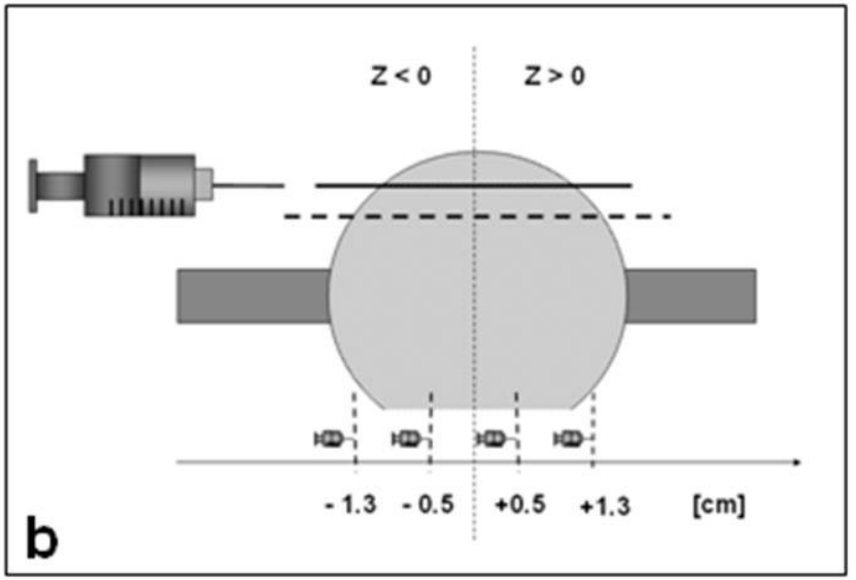
Investigation of ^{90}Y-avidin for prostate cancer brachytherapy: a dosimetric model for phase I-II clinical study

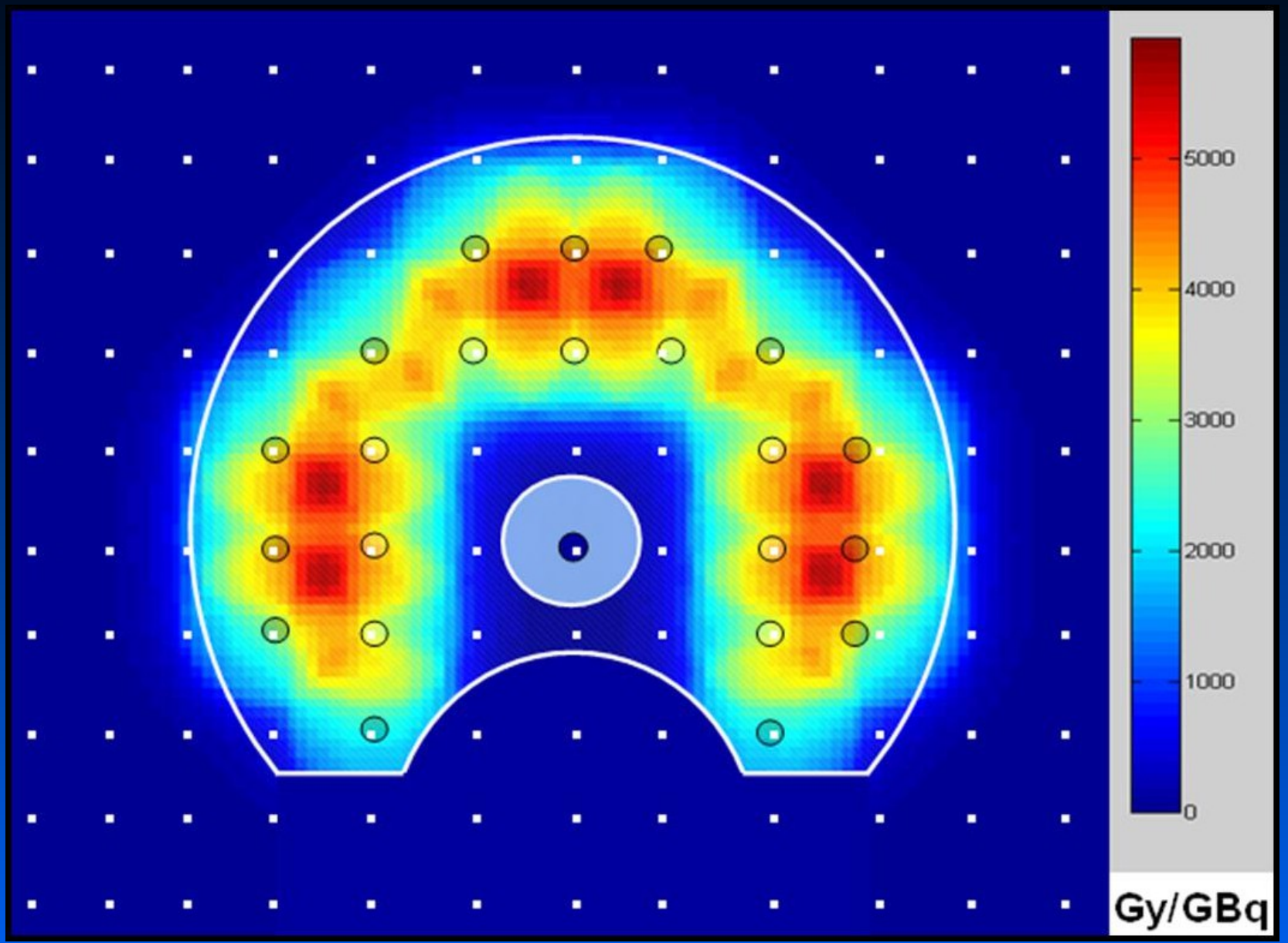
Botta F, Cremonesi M, Ferrari ME, Amato E, Guerriero F, Vavassori A, Sarnelli A, Pedroli G and Paganelli G.

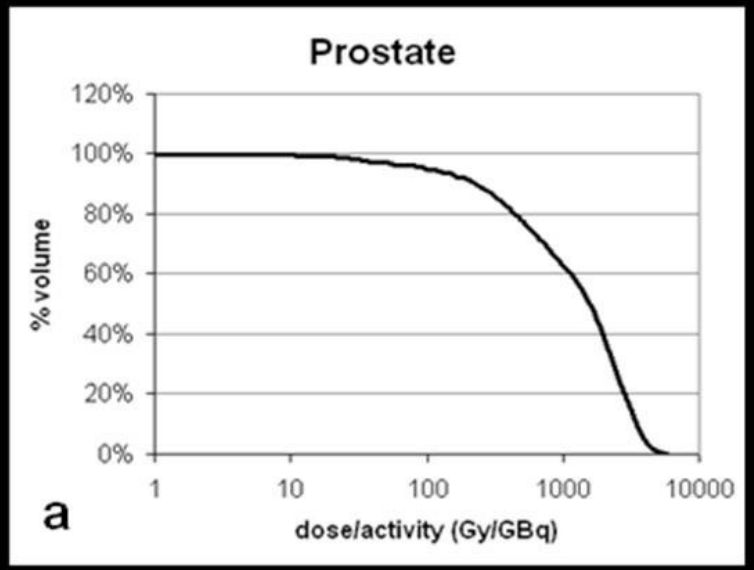
Eur J Nucl Med Mol Imaging, submitted

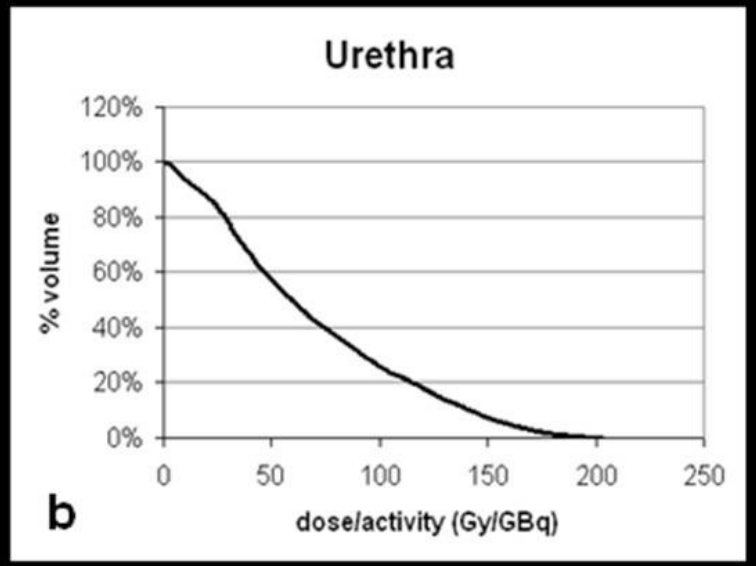


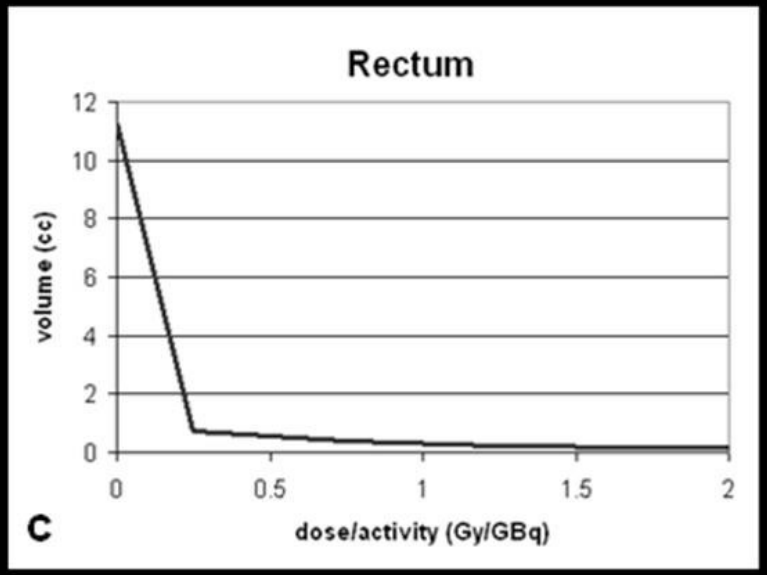

a


Z < 0
Z > 0
- 1.3
- 0.5
+0.5
+1.3
[cm]
b

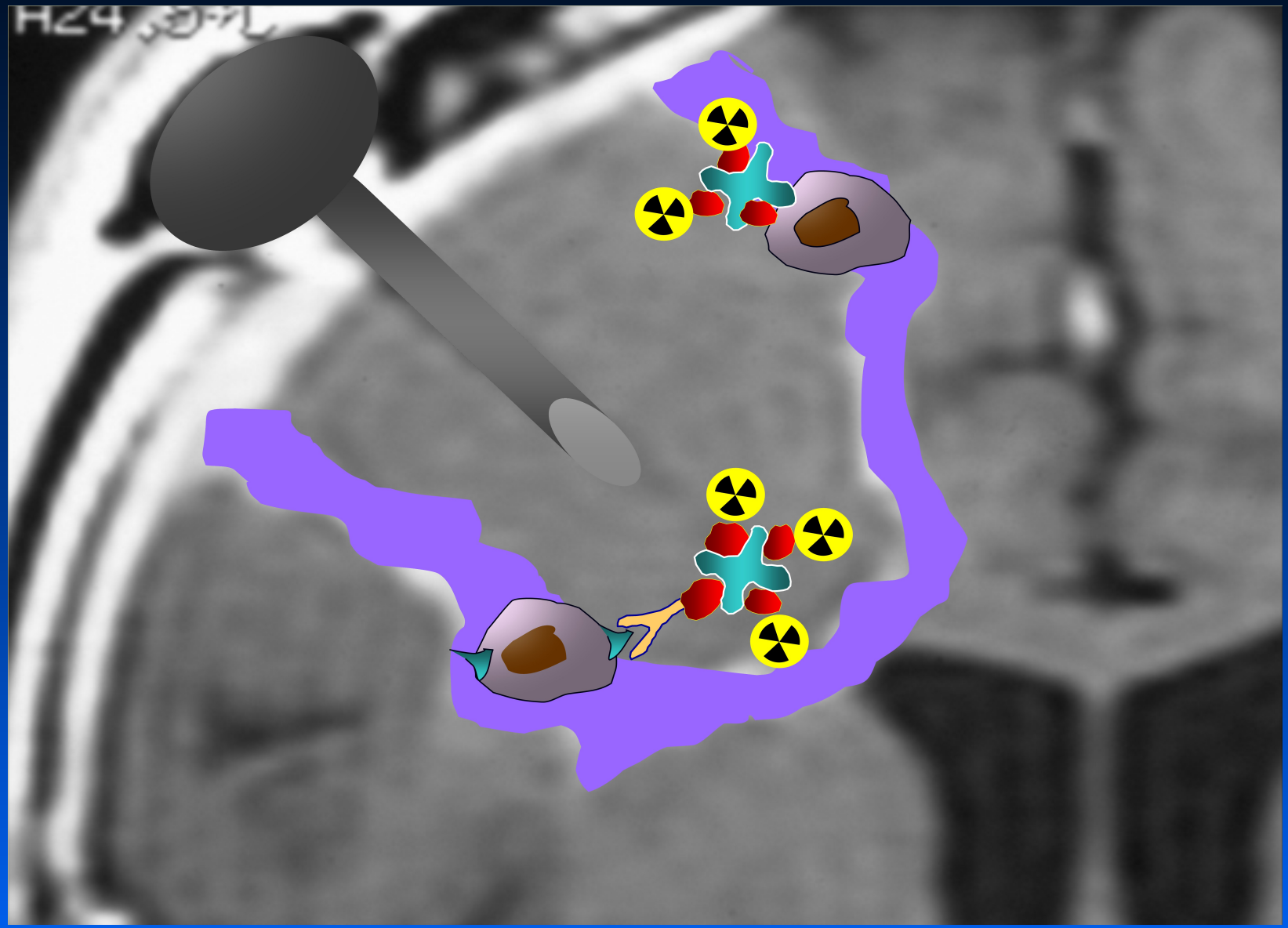

5000
4000
3000
2000
1000
0
Gy/GBq

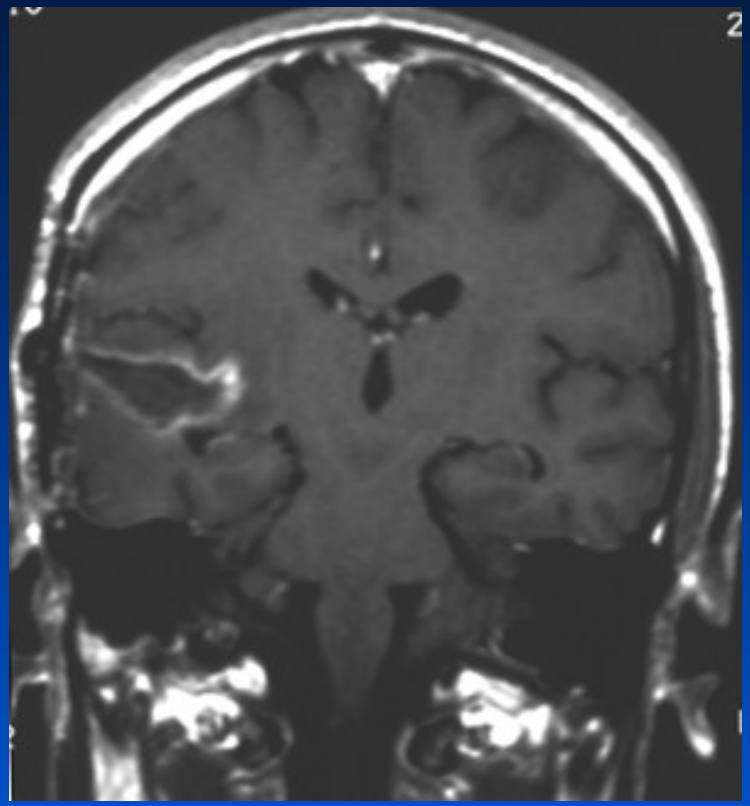

Prostate
120%
100%
80%
60%
40%
20%
0%
% volume
1
10
100
1000
10000
dose/activity (Gy/GBq)
a


Urethra
120%
100%
80%
60%
40%
20%
0%
% volume
0
50
100
150
200
250
dose/activity (Gy/GBq)
b

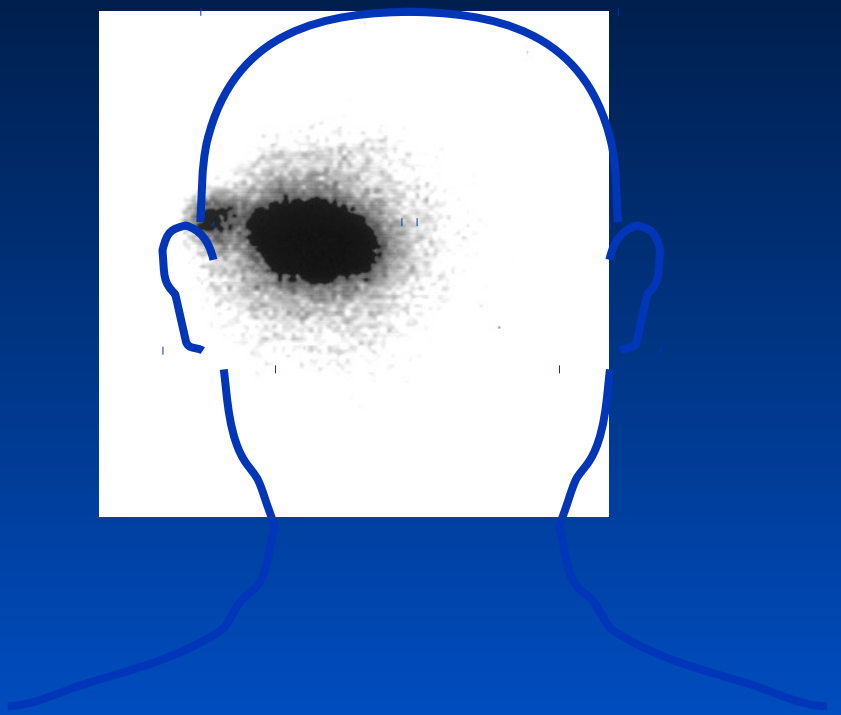

Rectum
12
10
8
6
4
2
0
volume (cc)
0
0.5
1
1.5
2
dose/activity (Gy/GBq)
c

IART in Brain Cancer





dx



15 min p.i.

Recurrent GBM PTs

Group A

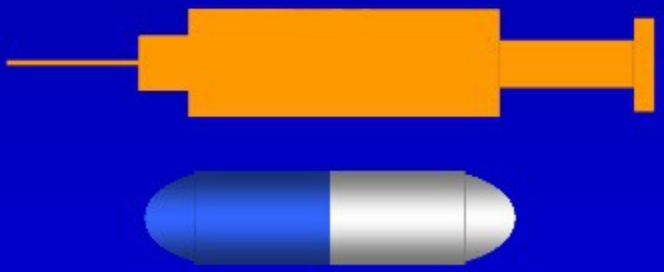
38 pts

LR-RIT

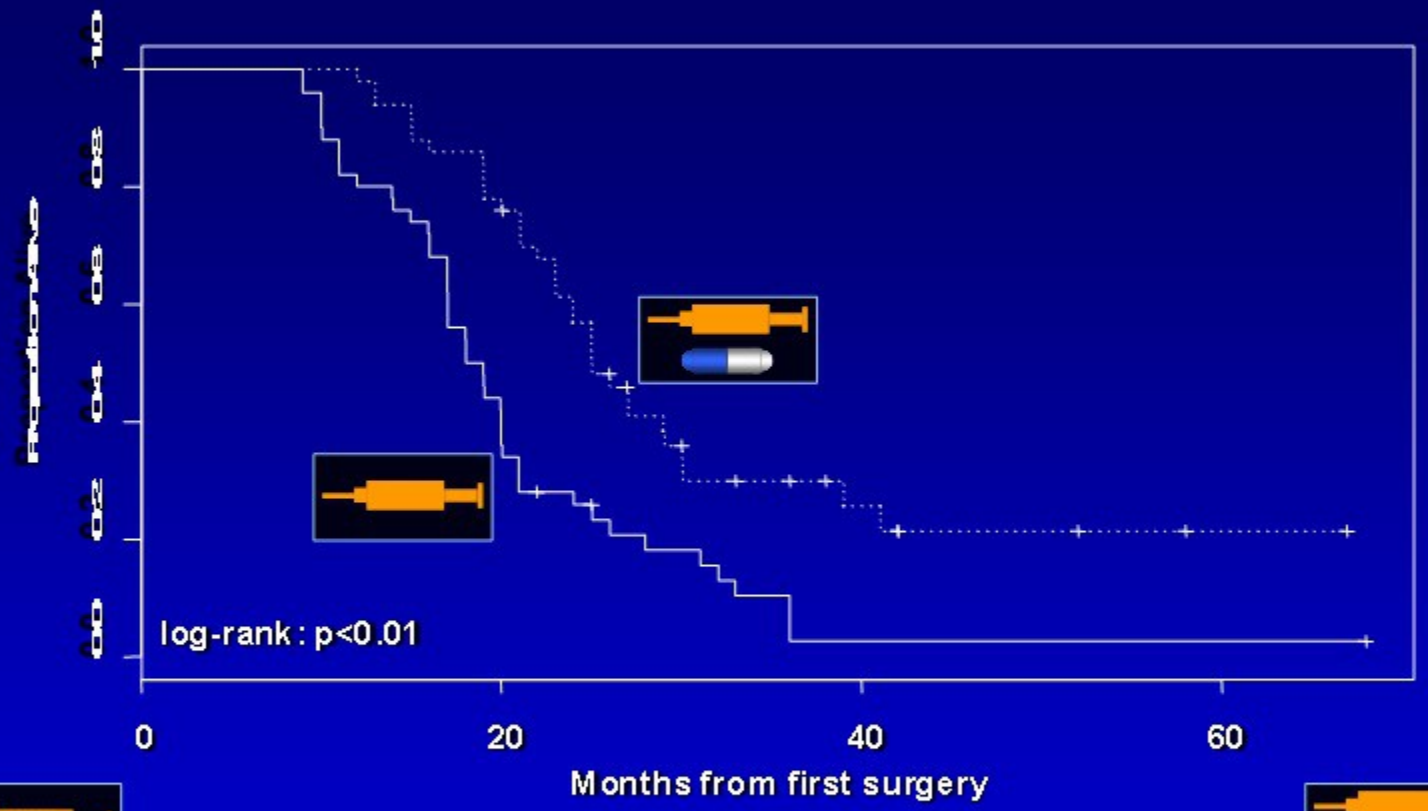
Group B

35 pts

LR-RIT + TMZ



Overall Survival and Treatment Groups



18 months
(95%CI=[17 mm, 20 mm])

25 months
(95%CI=[23 mm, 30 mm])


Thank You