



IRCC AOU SAN MARTINO IST Genova



RADIOTERAPIA DELLE STAZIONI LINFONODALI: QUALI, QUANDO E COME.....

DAVIDE BOSETTI

PRINCIPLES OF RADIATION THERAPY

Whole Breast Radiation:

Target definition includes the majority of the breast tissue, and is best done by both clinical assessment and CT-based treatment planning. A uniform dose distribution and minimal normal tissue toxicity are the goals and can be accomplished using compensators such as wedges, forward planning using segments, intensity-modulated radiation therapy (IMRT), respiratory gating, or prone positioning. The breast should receive a dose of 45-50 Gy in 1.8-2 Gy per fraction, or 42.5 Gy at 2.66 Gy per fraction. A boost to the tumor bed is recommended in patients with high-risk features (e.g., high tumor grade disease). This can be achieved with electron or photon fields. Typical dose schedules are given 5 days per week.

Chest Wall Radiation (including Scar):
The target includes the ipsilateral chest wall and any lymph node drain sites where possible. Doses should be given whether the breast has been reconstructed or not, and electron or photon fields are appropriate. CT-based treatment planning is encouraged in order to identify and avoid critical organs. Sparring of the lungs is encouraged. The use of bolus material where appropriate to ensure skin dose is adequate.

Regional Nodal Radiation:

Target delineation is best achieved by the use of CT-based treatment planning. For the paraxillary and axillary nodes, prescription depth varies based on the size of the patient. For internal mammary node identification, the internal mammary artery and vein location can be used as a surrogate for the nodal locations, which usually are not visible on imaging. Dose is 50-50.4 Gy, given as 1.8-2.0 Gy fraction size (\pm scar boost at 2 Gy per fraction to a total dose of approximately 60 Gy); all dose schedules are given 5 days per week. If internal mammary lymph nodes are clinically or pathologically positive, radiation therapy should be given to the internal mammary nodes.

Otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph node field.

Accelerated Partial Breast Irradiation (APBI):

Preliminary studies of APBI suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to whole breast RT. However, compared to whole breast RT, recent studies document that APBI low-up is limited and that APBI is not ideal to participate in clinical trials. A statement from the American Society of Radiation Oncology (ASTRO), patients who may be eligible for APBI are those who are not carriers of BRCA1/2, have a unifocal T1N0 tumor, no lymphovascular infiltrating ductal or lobular carcinoma in situ (LCIS), and no history of breast cancer in 10 fractions delivered to the ipsilateral breast. If radiation therapy is prescribed to the internal mammary nodes, it is currently under investigation.

Optimizing Delivery of Individual Therapy:

It is important to individualize delivery of radiation therapy and consider factors such as patient positioning (ie, prone vs. supine) during administration of radiation therapy.

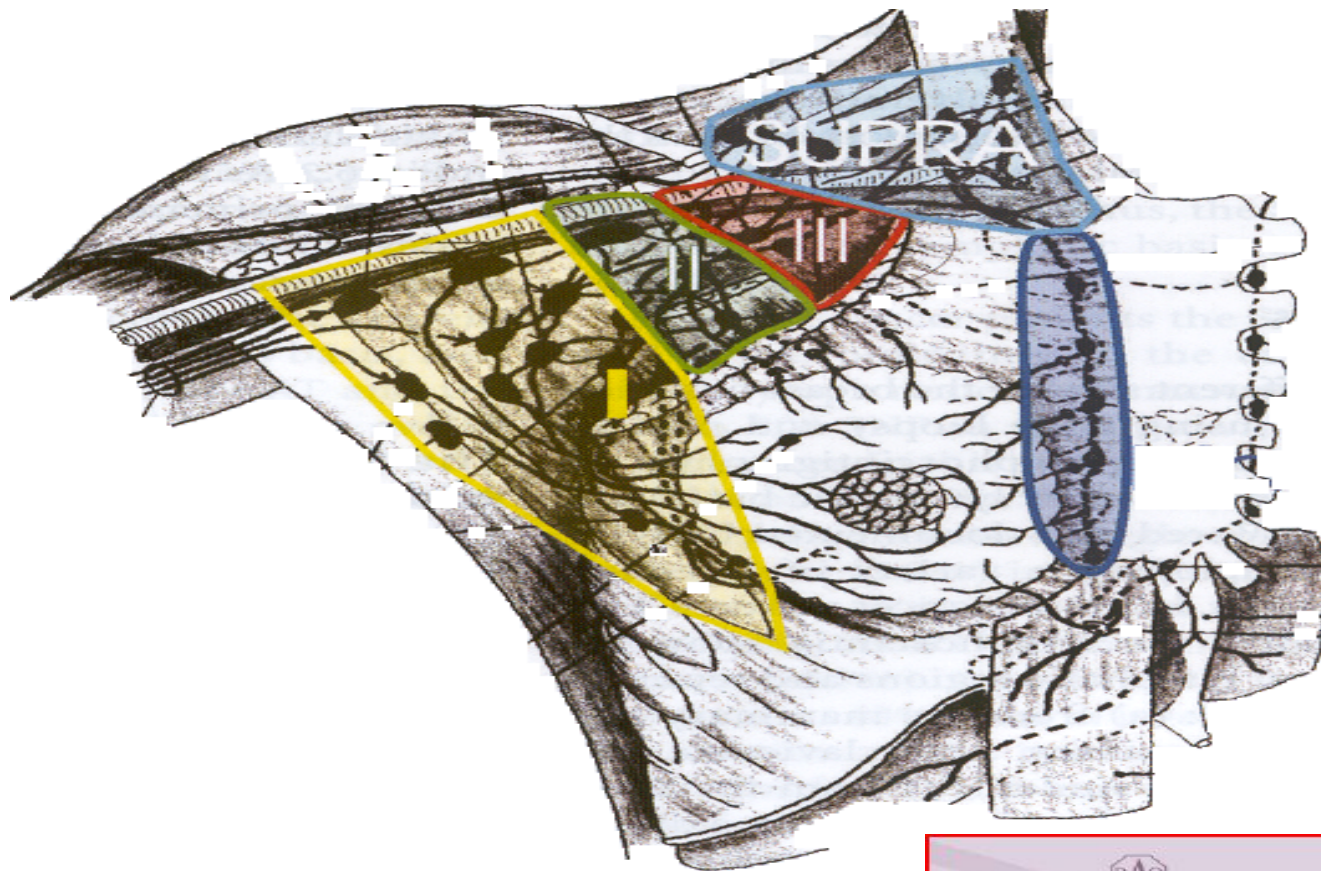
Neoadjuvant Chemotherapy:

Indications for radiation therapy and fields of treatment should be based on the worst stage pretreatment or post-treatment tumor characteristics in patients treated with neoadjuvant chemotherapy.

RADIOTERAPIA DELLE STAZIONI LINFONODALI

- **QUALI**
- **QUANDO**
- **COME**





Breast Cancer Atlas for Radiation
Therapy Planning:
Consensus Definitions

**La Radioterapia
dei Tumori
della Mammella**
Indicazioni e Criteri Guida

2019

Regional Nodal Contours: Anatomical Boundaries

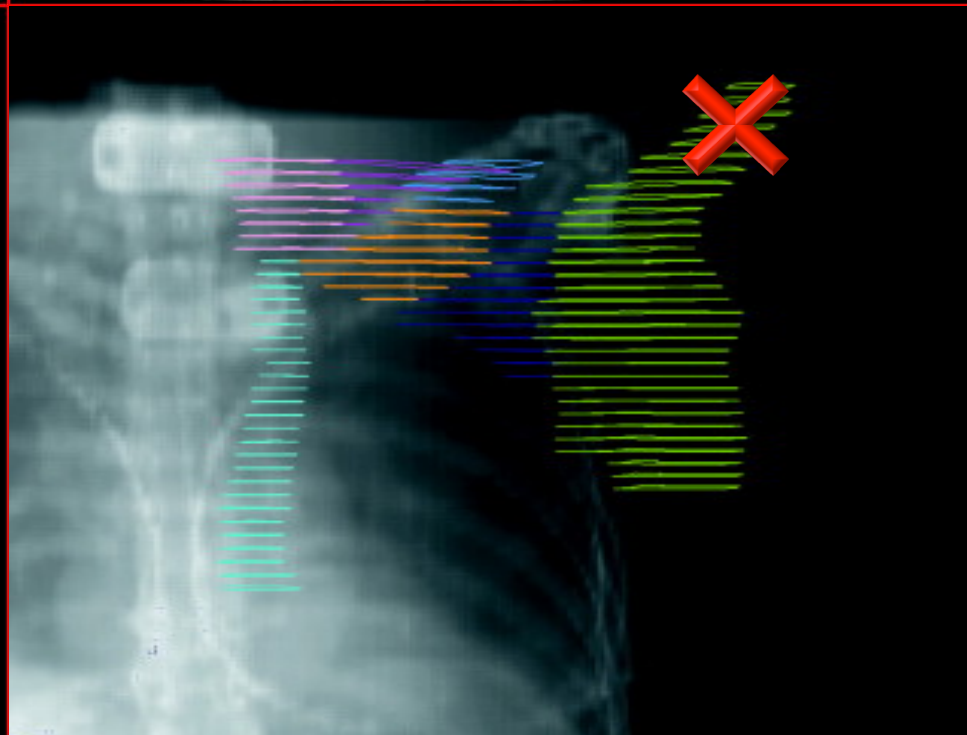
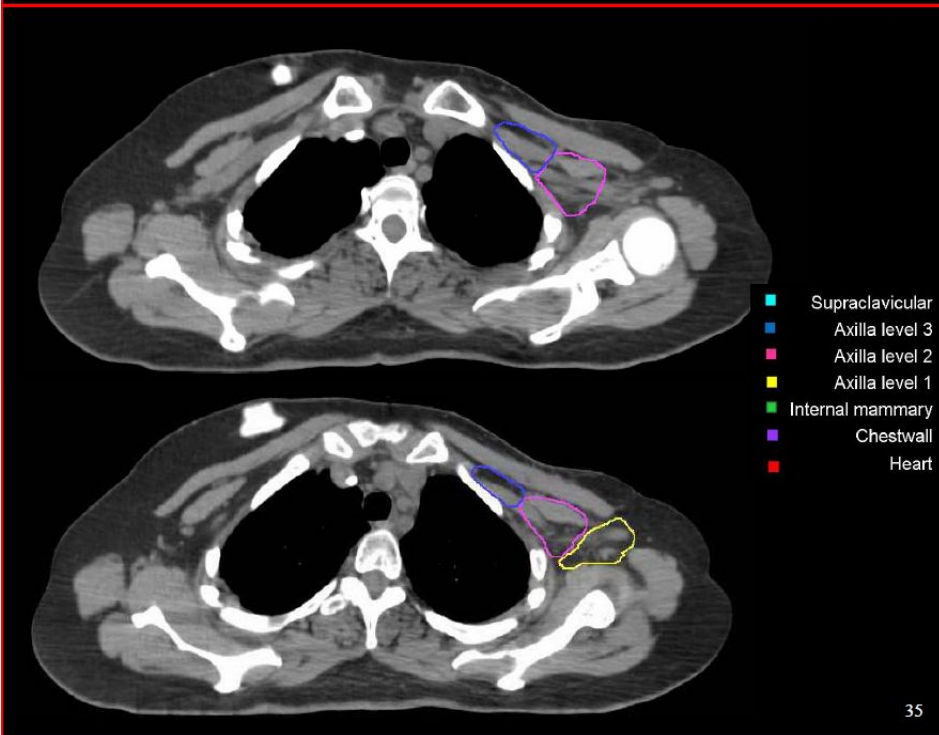
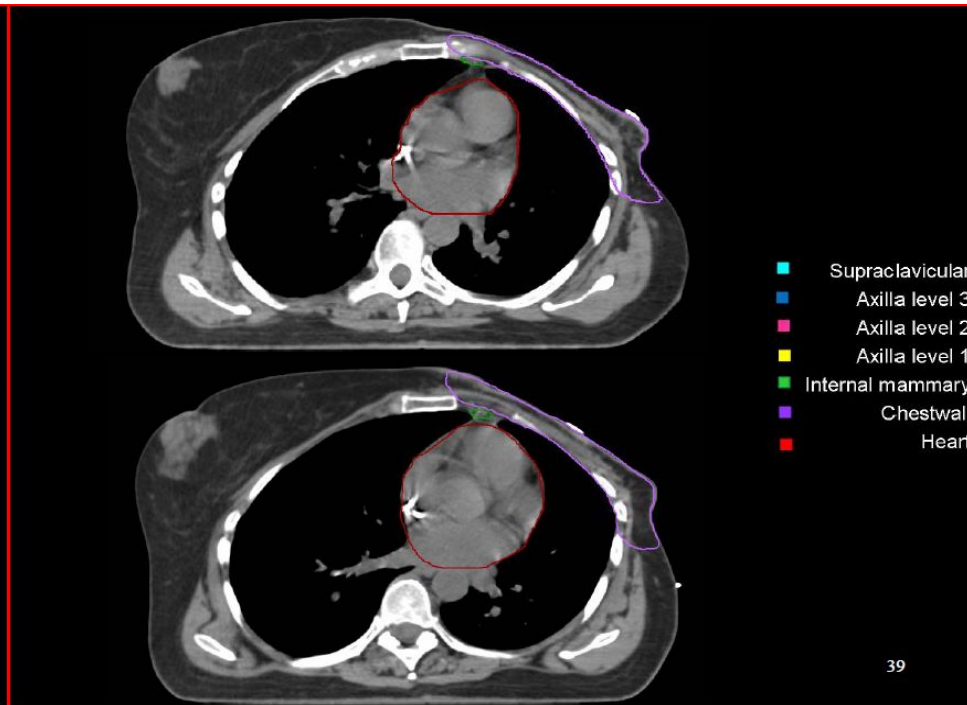
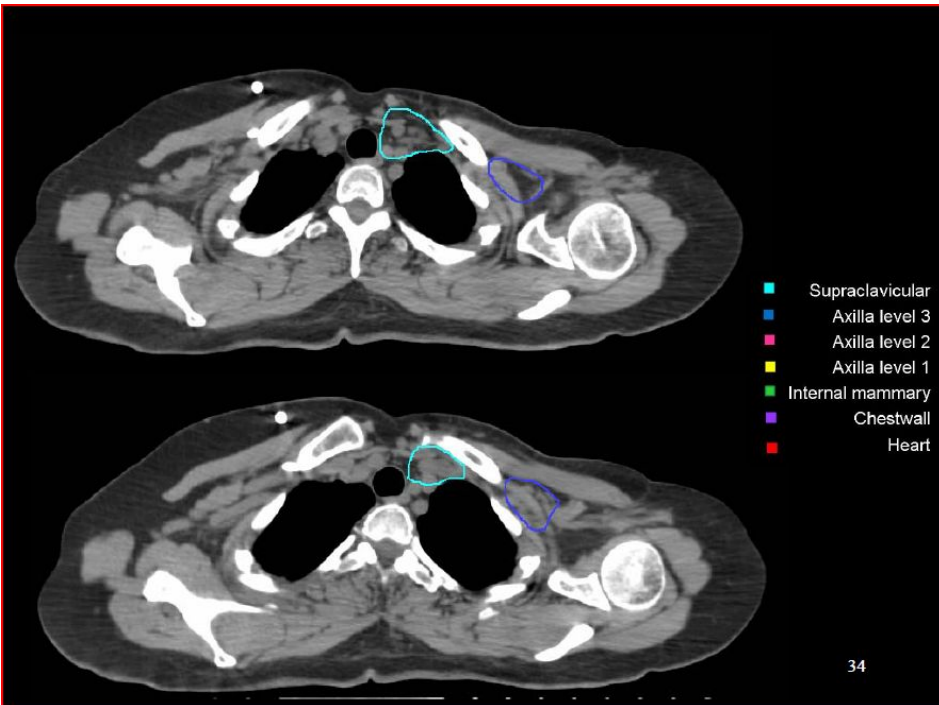
	<i>Cranial</i>	<i>Caudal</i>	<i>Anterior</i>	<i>Posterior</i>	<i>Lateral</i>	<i>Medial</i>
Supra-clavicular	Caudal to the cricoid cartilage	Junction of brachioceph.-axillary vns./caudal edge clavicle head ^a	Sternocleido mastoid (SCM) muscle (m.)	Anterior aspect of the scalene m.	<u>Cranial:</u> lateral edge of SCM m. <u>Caudal:</u> junction 1 st rib-clavicle	Excludes thyroid and trachea
Axilla-Level I	Axillary vessels cross lateral edge of Pec. Minor m.	Pectoralis (Pec.) major muscle insert into ribs ^b	Plane defined by: anterior surface of Pec. Maj. m. and Lat. Dorsi m.	Anterior surface of subscapularis m.	Medial border of lat. dorsi m.	Lateral border of Pec. minor m.
Axilla-level II	Axillary vessels cross medial edge of Pec. Minor m.	Axillary vessels cross lateral edge of Pec. Minor m. ^c	Anterior surface Pec. Minor m.	Ribs and intercostal muscles	Lateral border of Pec. Minor m.	Medial border of Pec. Minor m.
Axilla-level III	Pec. Minor m. insert on cricoid	Axillary vessels cross medial edge of Pec. Minor m. ^d	Posterior surface Pec. Major m.	Ribs and intercostal muscles	Medial border of Pec. Minor m.	Thoracic inlet
Internal mammary	Superior aspect of the medial 1 st rib.	Cranial aspect of the 4 th rib	- e.	- e.	- e.	- e.

Contouring Comments: Regional Nodal Volumes

- ^a. Supraclavicular caudal border meant to approximate the superior aspect of the breast/ chestwall field border
- ^b. Axillary level I caudal border is clinically at the base of the anterior axillary line
- ^c. Axillary level II caudal border is the same as the cranial border of level 1
- ^d. Axillary level III caudal border is the same as the cranial border of level II
- ^e. Internal Mammary lymph nodes: encompass the internal mammary/ thoracic vessels

Breast Cancer Atlas for Radiation
Therapy Planning:
Consensus Definitions



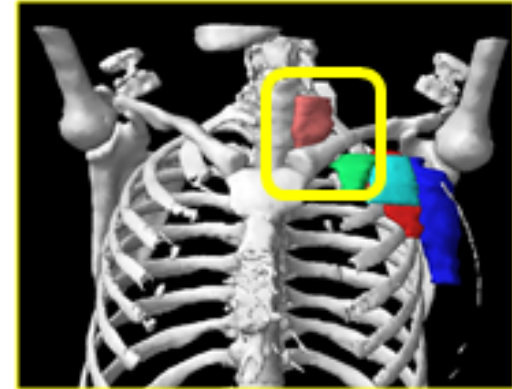


RT segue la dissezione ascellare (pre-AMAROS)

Linfonodi III livello

Linfonodi sopraclaverari

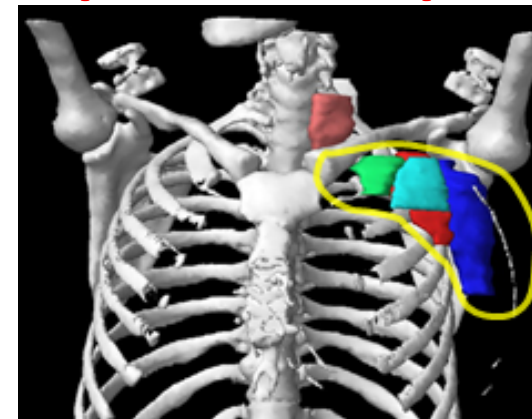
Linfonodi mammari interni
(su indicazione clinica)



RT sostituisce la dissezione ascellare, ed è stata attuata la biopsia del solo N sentinella (AMAROS)

Linfonodi I –II livello

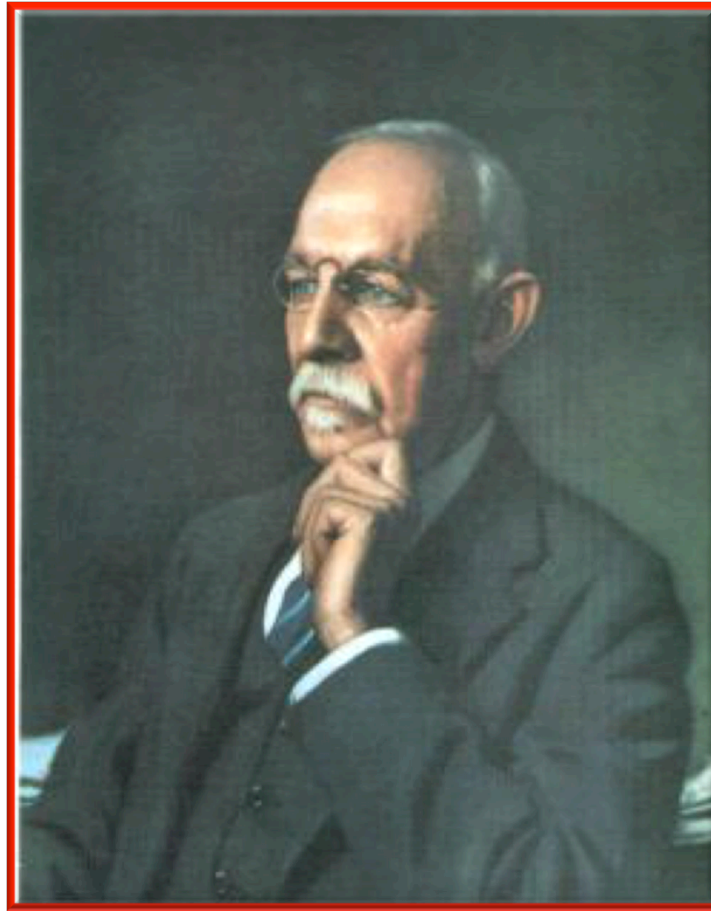
Linfonodi III livello
(opzionale)



RADIOTERAPIA DELLE STAZIONI LINFONODALI

- **QUALI**
- **QUANDO**
- **COME**





William S. Halsted
1852 - 1922

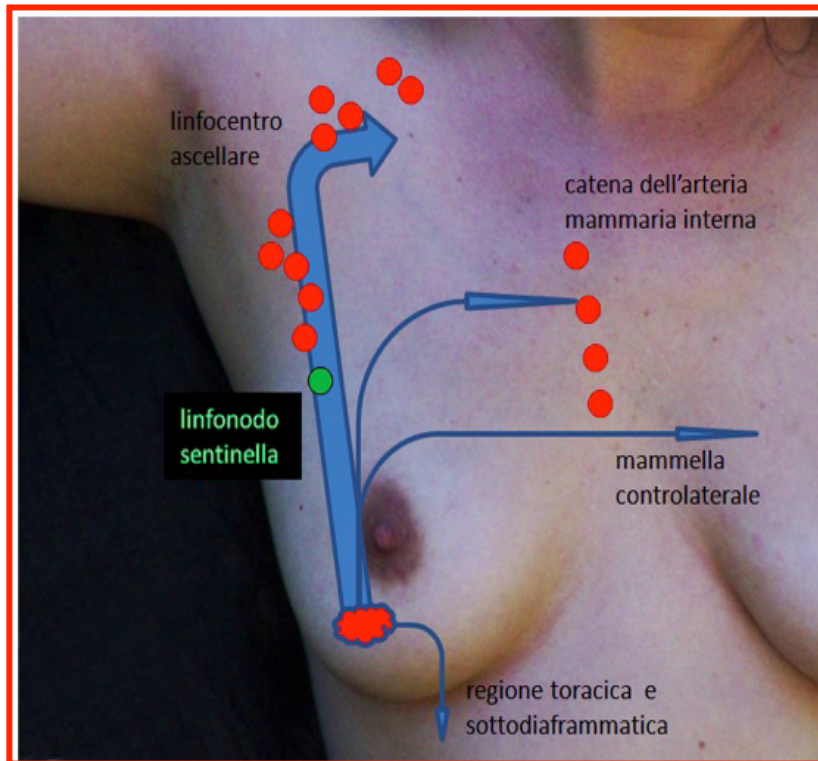
***Malattia loco-regionale a diffusione centrifuga
che segue ben determinate vie anatomiche***

TABELLA 1 Cronologia dello sviluppo dei principali concetti che hanno influito sul trattamento del tumore della mammella

1750 ca.	Ipotesi di una origine locale della malattia	Henri François Le Dran ¹¹
1750 ca.	Mastectomia con escissione in blocco della mammella e dei linfonodi ascellari palpabili	Jean-Louis Petit ⁹
1838	Origine cellulare del cancro	Johannes Müller ^d
1858	Effetto barriera dei linfonodi ascellari	Rudolph Virchow ⁵
1867	Diffusione locale della malattia in senso centrifugo	Charles H. Moore ¹³
1875	Inclusione della fascia del muscolo gran pettorale nella mastectomia	Richard von Volkmann ⁵⁰
1894	Mastectomia radicale classica	William S. Halsted, ¹⁶ Willy Meyer ¹⁷
1896	Ovariectomia bilaterale nel trattamento del tumore metastatico	George Beatson ¹⁹
1922	Radioterapia come trattamento primario del tumore mammario	Geoffrey Keynes ²²
1941	Mastectomia semplice seguita da radioterapia	Robert Mc Whirther ²³
1943	Prima stadiazione ad ampia diffusione del tumore mammario	Cushman Haagensen e Arthur Purdy Stout ⁵¹
1948	Mastectomia radicale estesa ai linfonodi della catena mammaria interna	M. Margottini ²⁴
1948	Mastectomia radicale modificata	David Howard Patey e W.H. Dyson ³¹
1950-1960	Tumorectomia semplice seguita da radioterapia loco-regionale	François Baclesse ⁴² , Sakari Mustakallio ⁵²
1961	Primo trial di chirurgia conservativa	H. Atkins e J.L. Hayward ⁵³
1966	Isolamento della proteina del recettore estrogenico	Elwood V. Jensen ²⁰
1975-1976	Primo trial di chemioterapia adiuvante	Gianni Bonadonna ⁵⁴
1980	Formulazione della <i>teoria alternativa</i> alla teoria meccanicistica di Halsted sulla diffusione dei tumori mammari	Bernard Fisher, John Devitt e George Crile ²⁹
1987	Formulazione della <i>teoria dello spettro</i> sulla diffusione dei tumori mammari	Samuel Hellman e Jay Harris ³⁰
1991	Sviluppo della biopsia del linfonodo sentinella	Armando Giuliano ⁵⁵
1994	Identificazione del gene BRCA1, seguita l'anno successivo dal BRCA2	Steven Narod ⁵⁶

Il riscontro sempre più frequente di linfonodi negativi, associato alla dimostrazione che lo svuotamento ascellare non forniva un reale vantaggio sulla sopravvivenza, ha suggerito lo sviluppo di un metodo meno invasivo per la stadiazione dell'ascella.....

Linfonodo sentinella



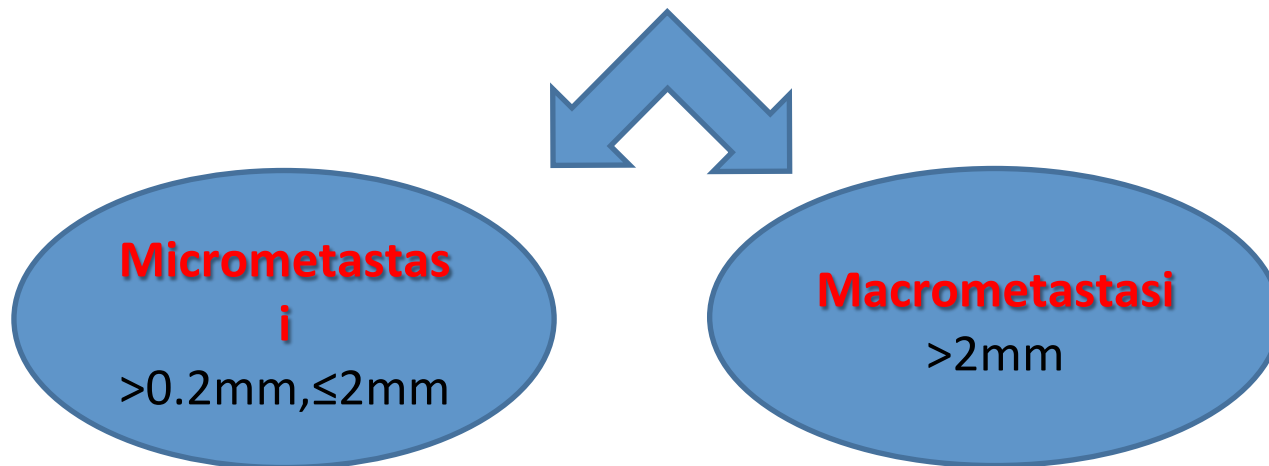
Linfonodo sentinella negativo

Linfoadenotomia

Radioterapia adiuvante stazioni linfonodali

Linfonodo sentinella positivo: *evoluzione nell'approccio terapeutico*

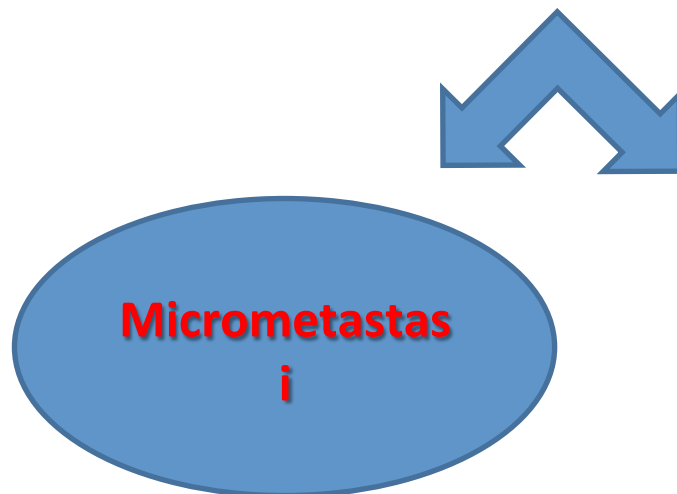
Linfoadenectomia può essere omessa??



Classificazione AJCC 2009 (settima edizione)

Linfonodo sentinella positivo: *evoluzione nell'approccio terapeutico*

Linfoadenectomia può essere omessa??

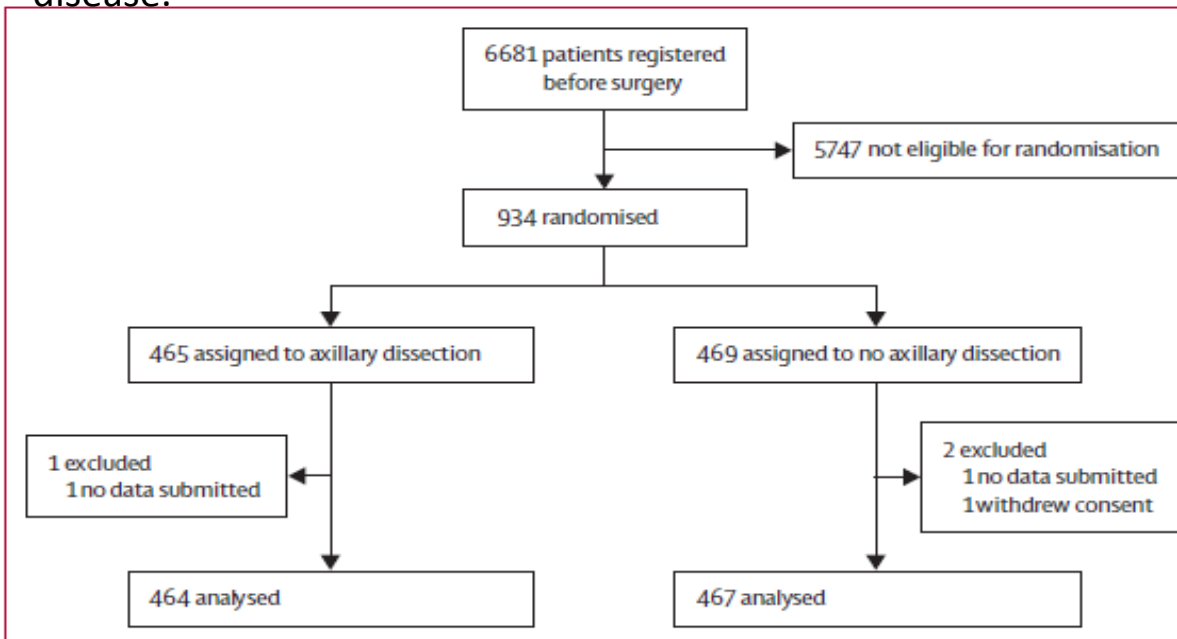


Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial



Viviana Galimberti, Bernard F Cole, Stefano Zurrada, Giuseppe Viale, Alberto Luini, Paolo Veronesi, Paola Baratella, Camelia Chifu, Manuela Sargenti, Mattia Intra, Oreste Gentilini, Mauro G Mastropasqua, Giovanni Mazzarol, Samuele Massarut, Jean-Rémi Garbay, Janez Zgajnar, Hanne Galatius, Angelo Recalcati, David Littlejohn, Monika Bamert, Marco Colleoni, Karen N Price, Meredith M Regan, Aron Goldhirsch, Alan S Coates, Richard D Gelber, Umberto Veronesi, for the International Breast Cancer Study Group Trial 23-01 investigators

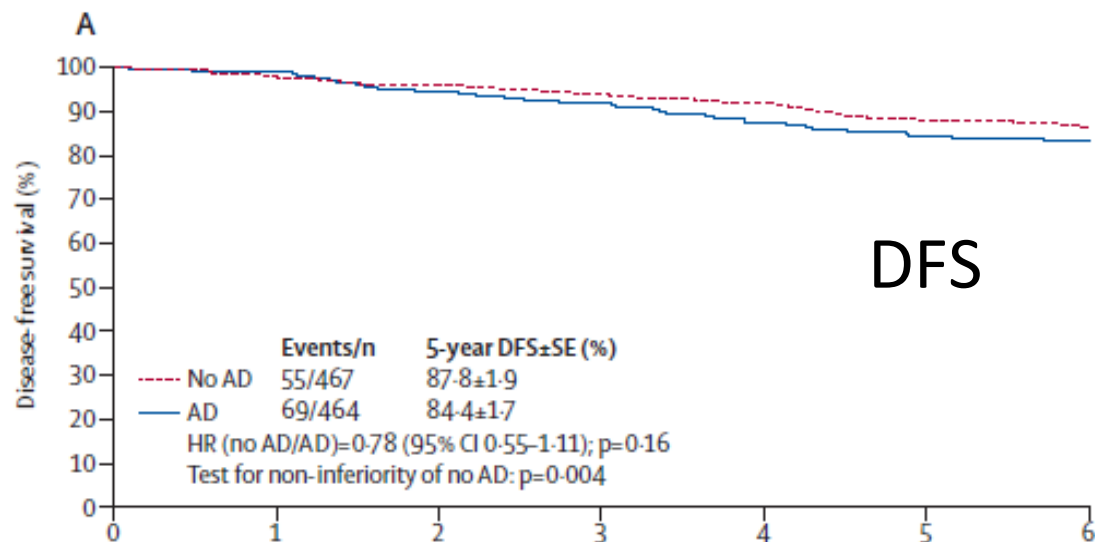
They were included in the trial and randomised if, during or following surgical treatment for breast cancer, they were found to have a tumour ≤ 5 cm in maximum diameter by pathological measurement of the surgical specimen, and one or more micrometastatic (≤ 2 mm) foci in the SNs, but no macrometastatic disease.



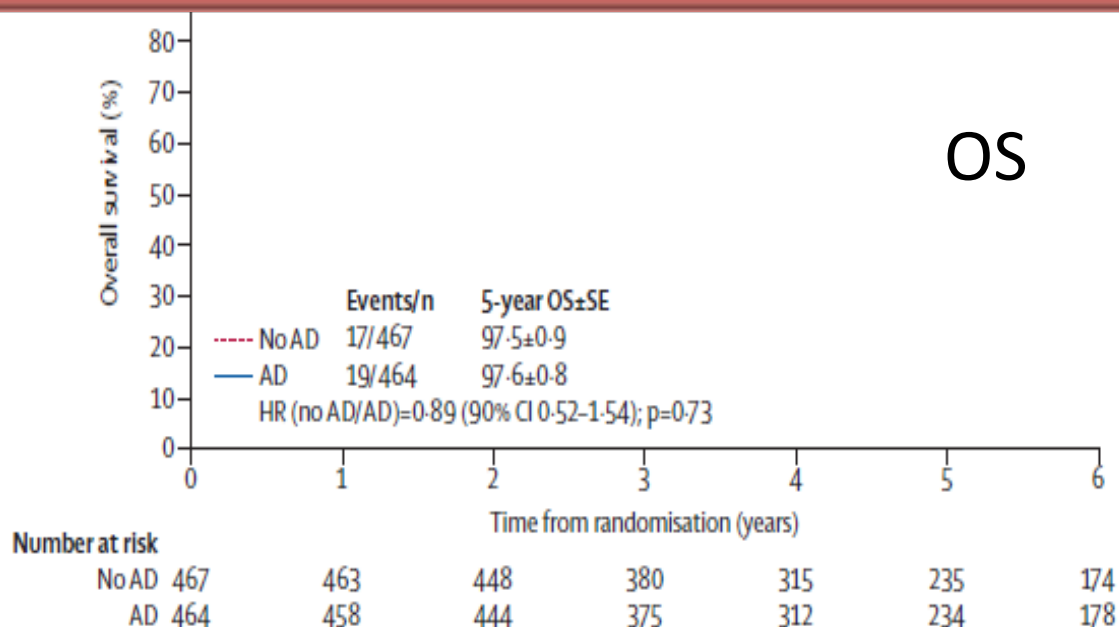
	Axillary dissection (n=464)	No axillary dissection (n=467)
Disease-free survival events*		
Total	69 (15%)	55 (12%)
Breast cancer events		
Local	10 (2%)	8 (2%)
Regional	1 (<1%)	5 (1%)
Distant	34 (7%)	25 (5%)
Contralateral breast	3 (<1%)	9 (2%)
Non-breast cancer events		
Second (non-breast) primary†	20 (4%)	6 (1%)
Death without cancer event	1 (<1%)	2 (<1%)
Deaths		
Total	19 (4%)	17 (4%)

*Includes all breast cancer events, all non-breast cancer events, and deaths with cause unknown. †Types (number) of second primaries in the group with axillary dissection were gastrointestinal (four), genitourinary (two), gynaecological (six), haematological (two), laryngeal (two), lung (one), and sarcoma (three). Types (number) in the group without axillary dissection were gastrointestinal (two), gynaecological (three), and melanoma (one).

Table 3: Disease-free survival events and deaths at 5.0 years median follow-up of intention-to-treat population



Non differenze in DFS e OS statisticamente significative in pz con micrometastasi nel linfonodo sentinella



Linfonodo sentinella positivo: *micrometastasi*

Linfoadenectomia

Radioterapia adiuvante a stazioni linfonodali

Linfonodo sentinella positivo: *evoluzione nell'approccio terapeutico*

Linfoadenectomia può essere omessa??



Macrometastasi

Radiotherapy or surgery of the axilla after a positive sentinel
node in breast cancer (EORTC 10981-22023 AMAROS):
a randomised, multicentre, open-label, phase 3
non-inferiority trial



Mila Donker, Geertjan van Tienhoven, Marieke E Straver, Philip Meijnen, Cornelis J H van de Velde, Robert E Mansel, Luigi Cataliotti, A Helen Westenberg, Jean H G Klinkenbijn, Lorenzo Orzalesi, Willem H Bouma, Huub C J van der Mijle, Gerard A P Nieuwenhuijzen, Sanne C Veltkamp, Leen Slaets, Nicole J Duez, Peter W de Graaf, Thijs van Dalen, Andreas Marinelli, Herman Rijna, Marko Snoj, Nigel J Bundred, Jos W S Merkus, Yazid Belkacemi, Patrick Petignat, Dominic A X Schinagl, Corneel Coens, Carlo G M Messina, Jan Bogaerts, Emiel J T Rutgers

Ipotesi : radioterapia ascellare offre le stesse probabilità di controllo locale e sopravvivenza – con meno effetti collaterali – rispetto alla dissezione ascellare.

Obiettivo primario: dimostrare la «non-inferiorità» in termini di **recidive ascellari**

Obiettivi secondari : confrontare **OS e DFS**; linfedema, funzionalità della spalla e QoL

	Axillary lymph node dissection (n=744)	Axillary radiotherapy (n=681)
Baseline characteristics		
Age, years	56 (48-64)	55 (48-63)
Menopausal status		
Premenopausal	283 (38%)	289 (42%)
Postmenopausal	449 (60%)	384 (56%)
Missing	12 (2%)	8 (1%)
Preoperative ultrasound axilla		
Done	440 (59%)	419 (62%)
Not done	304 (41%)	262 (38%)
Tumour on dominant side		
Yes	377 (51%)	329 (48%)
No	352 (47%)	336 (49%)
Bilateral	8 (1%)	2 (<1%)
Missing	7 (1%)	14 (2%)
Clinical tumour size		
Median (mm; IQR)	17 (13-22)	18 (13-23)
0-2 cm	612 (82%)	533 (78%)
2-5 cm	132 (18%)	143 (21%)
>5 cm	0 (0%)	1 (<1%)
Missing	0 (0%)	4 (1%)
Tumour type		
Infiltrating ductal	563 (76%)	515 (76%)
Infiltrating lobular	100 (13%)	99 (15%)
Other	81 (11%)	66 (10%)
Missing	0 (0%)	1 (<1%)
Grade		
I	179 (24%)	154 (23%)
II	356 (48%)	311 (46%)
III	192 (26%)	200 (29%)
Missing	17 (2%)	16 (2%)
Type of breast surgery		
Breast-conserving surgery	609 (82%)	557 (82%)
Mastectomy	127 (17%)	121 (18%)
Missing	8 (1%)	3 (<1%)

(Table 1 continues on next page)

	Axillary lymph node dissection (n=744)	Axillary radiotherapy (n=681)
(Continued from previous page)		
Adjuvant radiotherapy		
Breast	597 (80%)	546 (80%)
Chest wall	34 (5%)	51 (7%)
Internal mammary chain	72 (10%)	65 (10%)
Systemic treatment administered		
Any systemic treatment	666 (90%)	612 (90%)
Chemotherapy	453 (61%)	418 (61%)
Hormonal therapy	585 (79%)	525 (77%)
Immunotherapy	45 (6%)	44 (6%)
Sentinel node characteristics		
Number of sentinel nodes removed		
1	332 (45%)	293 (43%)
2	201 (27%)	217 (32%)
3	127 (17%)	105 (15%)
≥4	84 (11%)	66 (10%)
Number of positive sentinel nodes		
1	581 (78%)	512 (75%)
2	127 (17%)	134 (20%)
3	29 (4%)	27 (4%)
≥4	7 (1%)	8 (1%)
Size of the largest sentinel node metastasis		
Macrometastasis	442 (59%)	419 (62%)
Micrometastasis	215 (29%)	195 (29%)
Isolated tumour cells	87 (12%)	67 (10%)
Number of positive additional nodes (besides sentinel node)		
0	451/672 (67%)*	26/69 (38%)†
1-3	168/672 (25%)*	24/69 (35%)†
≥4	52/672 (8%)*	17/69 (25%)†
Missing	1/672 (<1%)*	2/69 (3%)†
Data are median (IQR) or number (%). Some percentages do not total 100 because of rounding. *72 patients did not have axillary lymph node dissection. †Additional metastatic lymph nodes in the axillary radiotherapy group were found in a group of patients who crossed over from axillary radiotherapy to axillary lymph node dissection and are thus not representative of the number of additional nodes in the whole group.		
Table 1: Baseline and treatment characteristics		

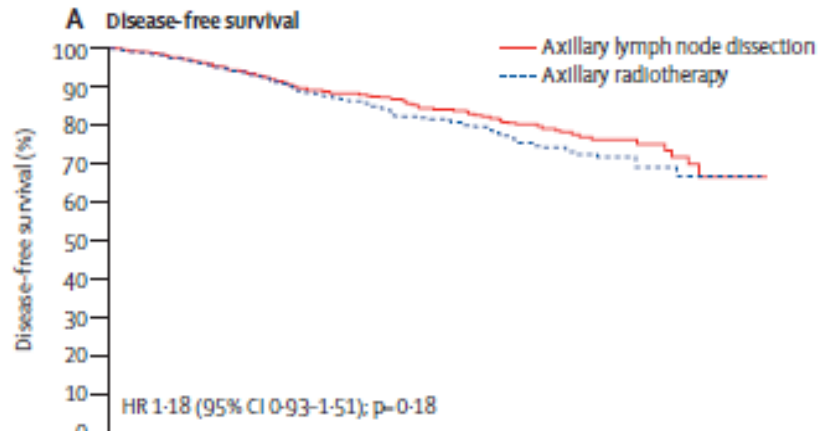
Obiettivo primario

***Sia la dissezione ascellare che la RT
ascellare offrono un ottimo livello di
controllo locoregionale***

Ma.....

Troppo pochi eventi per essere significativi

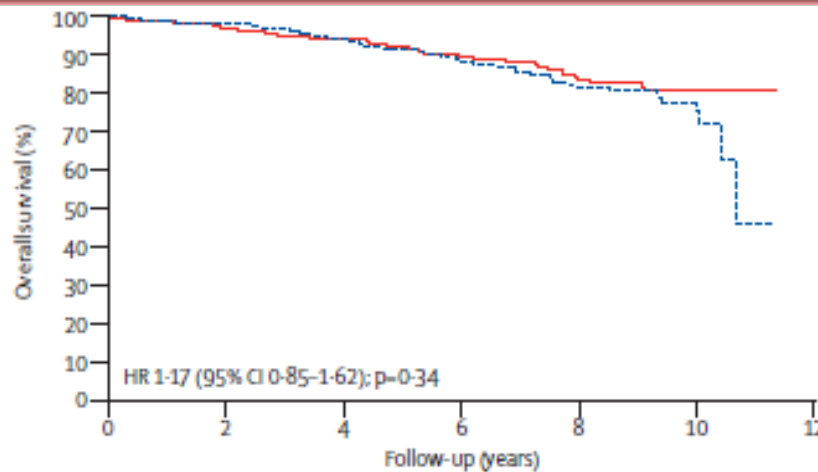
Obiettivi secondari



Disease-free survival

the five year estimates were **86.9%** for axillary lymph node dissection and **82.6%** for axillary radiotherapy (p=0.18).

Non differenze in DFS e OS con le due metodiche di trattamento nonostante un follow-up breve



Overall survival

the five year estimates were **93.3%** for the lymph node dissection and **92.5%** for axillary radiotherapy (p=0.34),

	0	2	4	6	8	10	12
Number at risk							
Axillary lymph node dissection	744	708	552	352	157	38	0
Axillary radiotherapy	681	661	505	316	151	29	0

Obiettivi secondari

	Axillary lymph node dissection	Axillary radiotherapy	p value
Clinical sign of lymphoedema in the ipsilateral arm			
Baseline	3/655 (<1%)	0/586 (0%)	0.25
1 year	11/410 (3%)	67/410 (16%)	0.0001
3 years			
5 years			
Arm circumference increase ≥10% of the ipsilateral upper or lower arm, or both			
Baseline	33/655 (5%)	24/586 (4%)	0.497
1 year	32/410 (8%)	24/410 (6%)	0.332
3 years	38/373 (10%)	22/341 (6%)	0.080
5 years	43/328 (13%)	16/286 (6%)	0.0009

Minor incidenza di linfedema statisticamente significativa nel braccio della RT

Data are n/N (%), unless otherwise specified.

Table 2: Lymphoedema

Riassumendo.....

Dissezione ascellare

N – NO RT

N + > 4 → RT delle stazioni linfonodali
(TUTTE LE LINEE GUIDA)

N + 1-3 → RT in pz con fattori prognostici
sfavorevoli quali: (G3, OR neg, Ki67, LVI nodal ratio, ECE; età...)

Biopsia N sentinella

N- → NO RT

N+ → dissezione ascellare 1-2 livello /3 se necessario, ± RT in base al n° di linfonodi positivi

N+ → non dissezione → NO RT


Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer

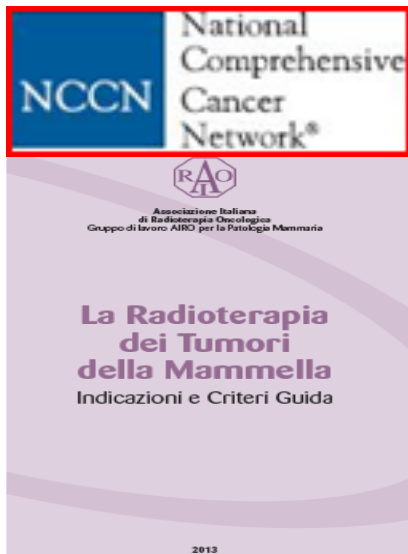
Among patients with limited sln metastatic breast cancer treated with breast conservation and systemic therapy, the use slnd alone compared with alnd did not result in inferior survival

Radioterapia post-mastectomia: Parete toracica + linfonodi

La Radioterapia dei Tumori della Mammella. Indicazioni e Criteri Guida

Tabella 1 Radioterapia post-mastectomia: indicazioni

- | | | |
|--|---|--|
| • T3N+ e nei T4 qualsiasi N.
T3N0 valutare in base ai fattori di rischio |  | <i>età inferiore a 40-45 anni, negatività recettoriale, invasione linfo-vascolare (Category 1 NCCN Guidelines)</i> |
| • Tumore esteso alla parete toracica e/o al muscolo pettorale e/o o alla cute, indipendentemente dallo stato linfonodale | | |
| • Tumore di dimensioni fino a 5 cm (T1-2) e numero di linfonodi ascellari positivi ³ 4 | | |
| • Margini positivi | | |






Radioterapia post-mastectomia: Parete toracica + linfonodi

Stadio T1-2 / N 1-3, sono stati identificati come fattori prognostici:

- **età** (<40-45 anni),
- **dimensioni tumorali** $\geq 3,5-4$ cm,
- **negatività recettoriale**



*Nonostante l'assenza di risultati di studi clinici randomizzati, si suggerisce di informare adeguatamente la paziente **sull'indicazione ad un trattamento radiante postoperatorio (category 2B NCCN).***

Effect of radiotherapy after mastectomy and axillary surgery   
on 10-year recurrence and 20-year breast cancer mortality:
meta-analysis of individual patient data for 8135 women in
22 randomised trials

EBCTCG, McGale P, Taylor C, Corra C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S.

1964-1986

Of the 1594 women with node-negative

700 (44%) → axillary dissection

870 (55%) → axillary sampling

24 (1%) → unknown extent of axillary surgery

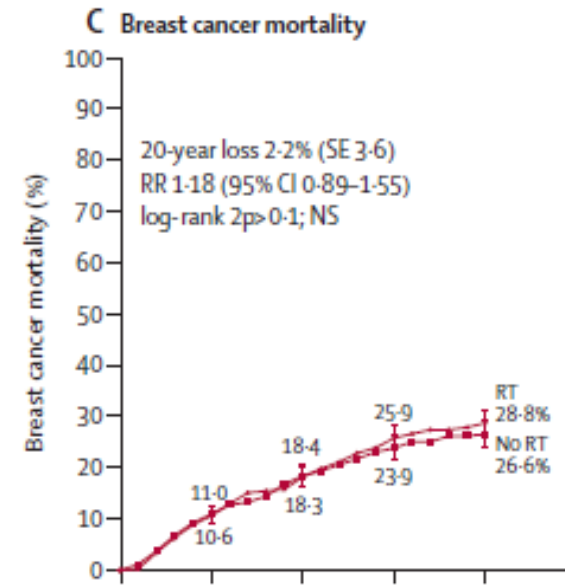
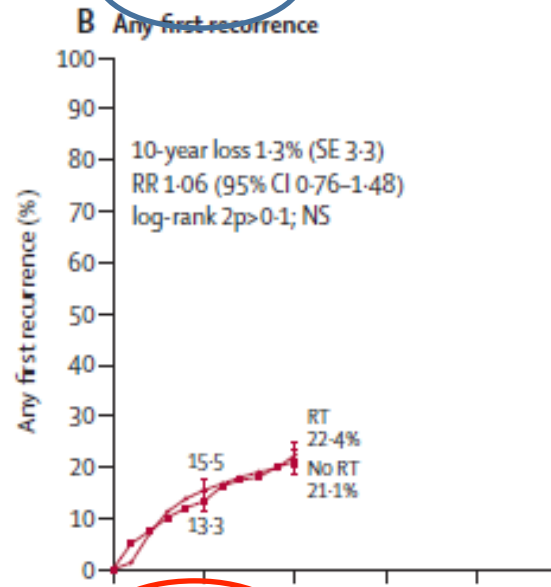
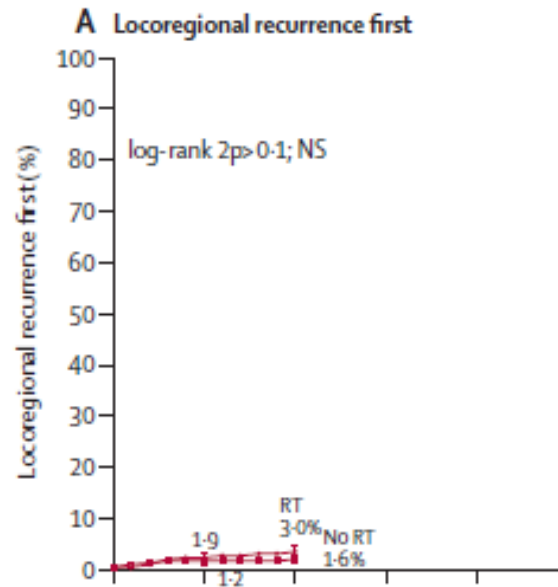
Of the 5821 women with node-positive disease,

3131 (54%) → axillary dissection

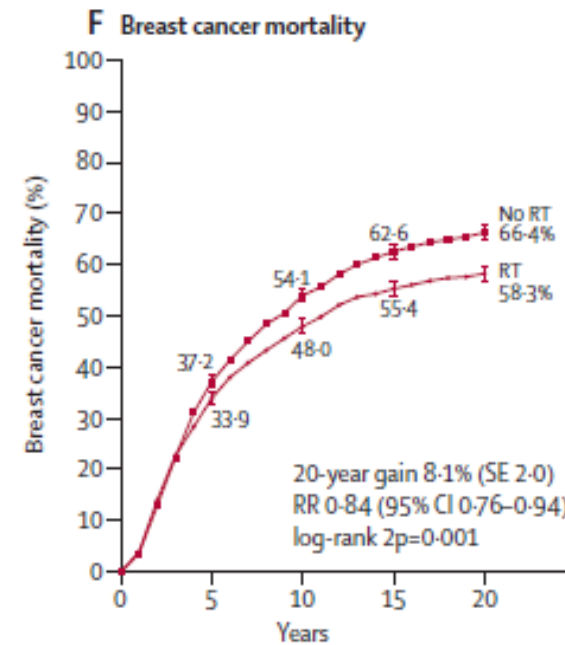
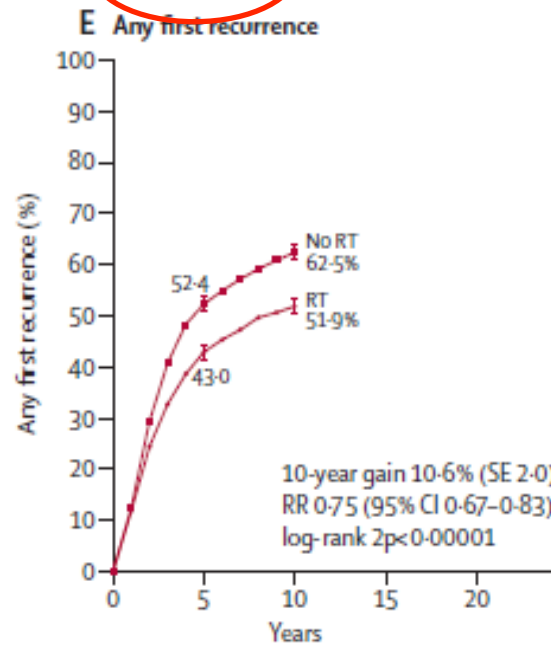
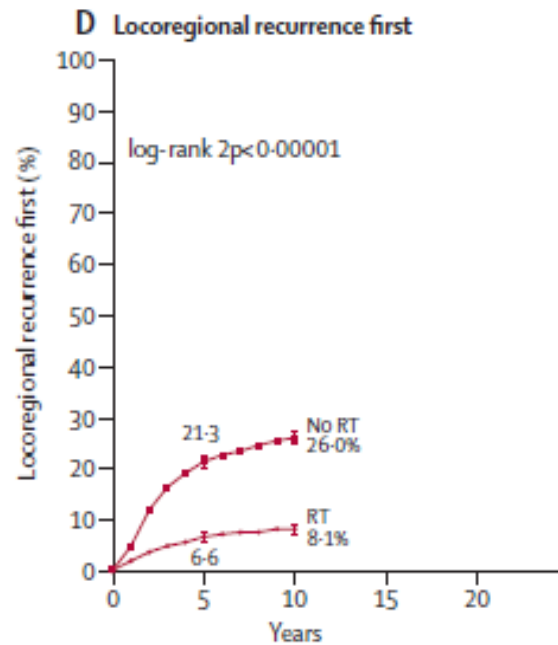
2541 (44%) → axillary sampling

149 (2%) → unknown extent of axillary surgery

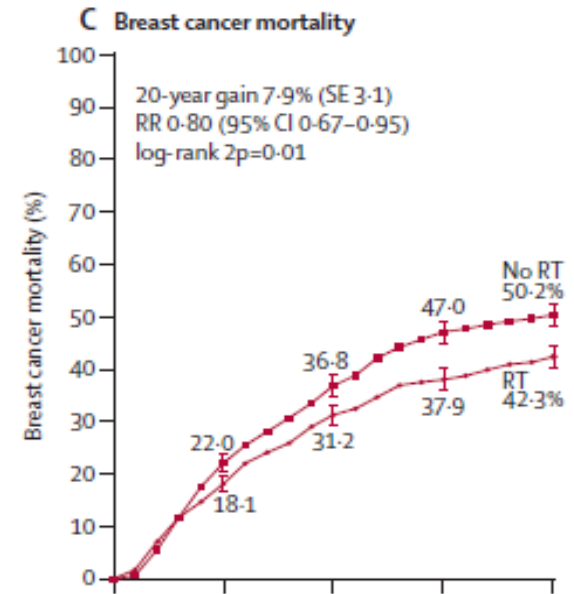
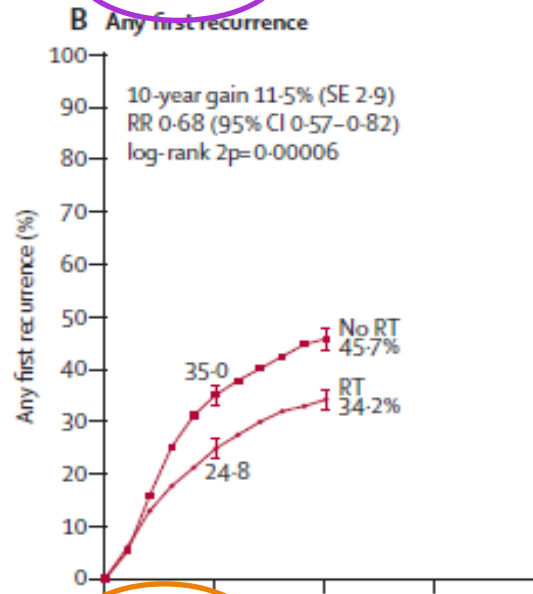
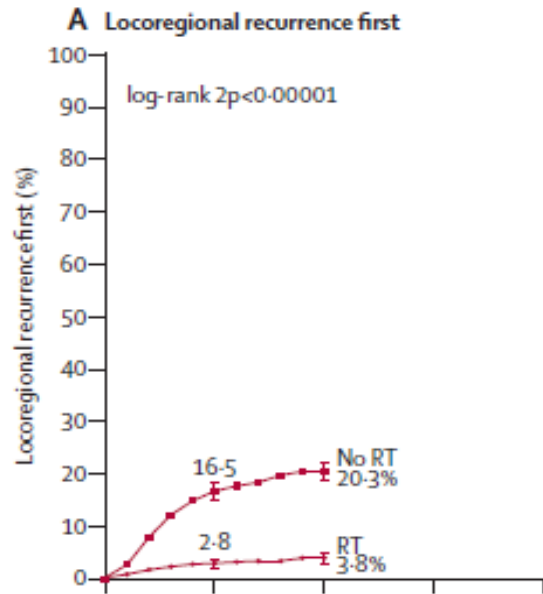
700 pN0 women with Mast+AD



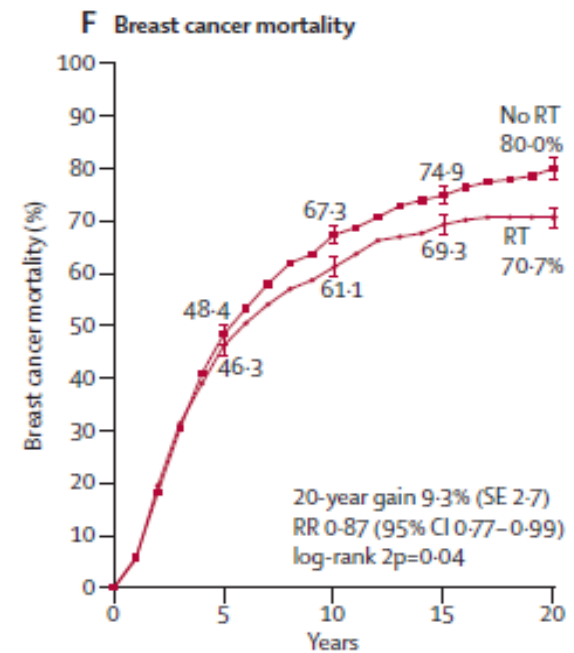
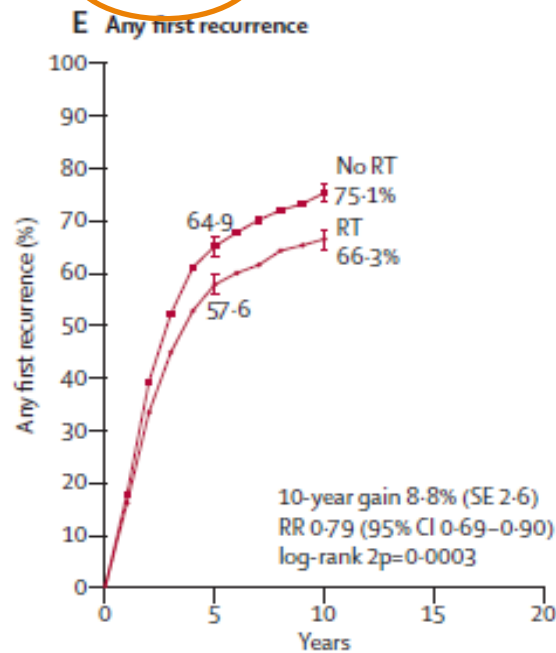
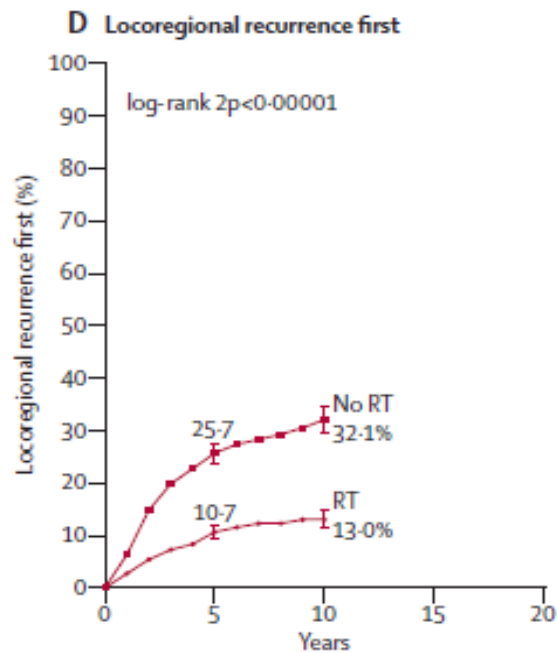
3131 pN+ women with Mast+AD



1314 pN1-3 women with Mast+AD



1772 pN4+ women with Mast+AD



1133 pN1-3 women with Mast+AD and systemic therapy

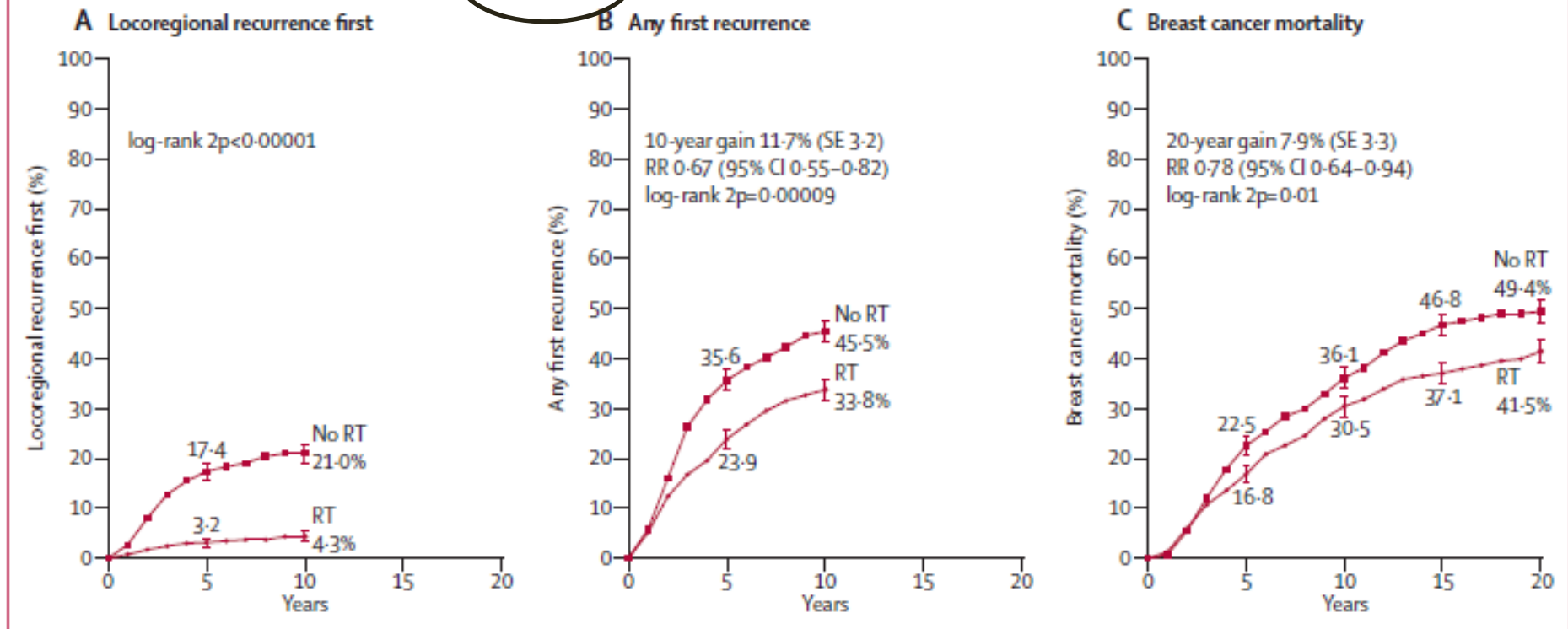


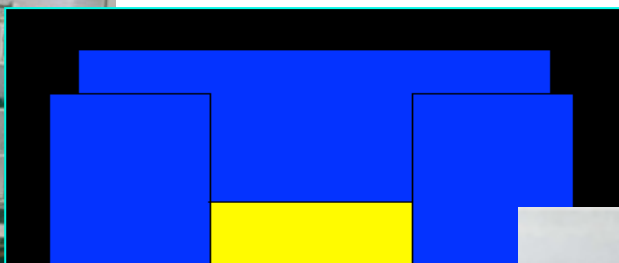
Figure 5: Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 1133 women with one to three pathologically positive nodes (pN1-3) in trials in which systemic therapy was given to both randomised treatment groups

RADIOTERAPIA DELLE STAZIONI LINFONODALI

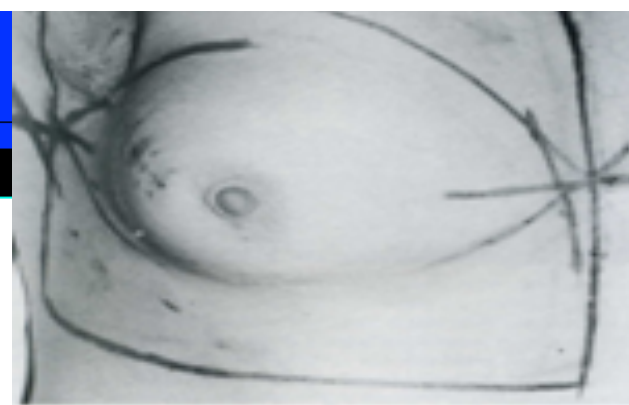
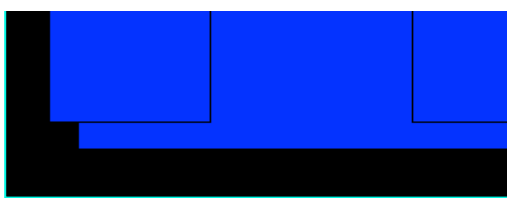
- **QUALI**
- **QUANDO**
- **COME**



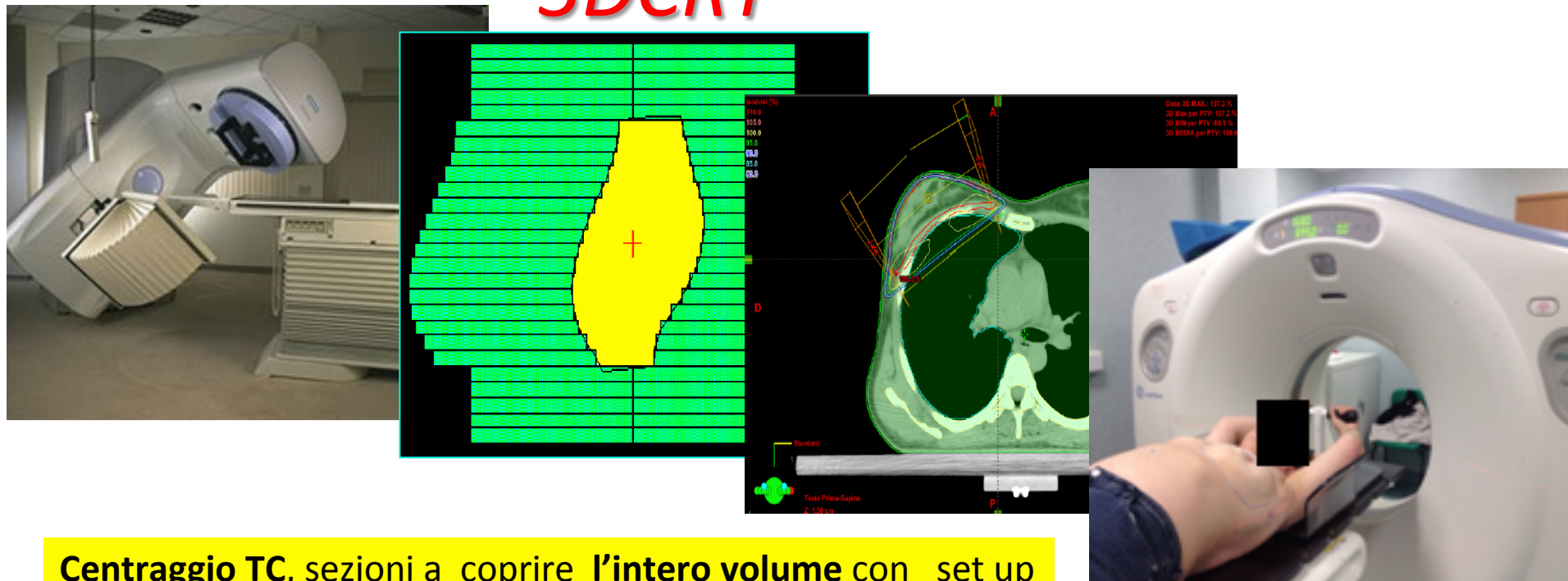
*Evoluzione tecnologica.....
Radioterapia non conformazionale*



Attualmente non più utilizzata



Evoluzione tecnologica..... 3DCRT



Centraggio TC, sezioni a coprire l'intero volume con set up accurato:

- sist. immobilizzazione,
- reperi cutanei radio-opachi,
- tatuaggi...

Identificazione dei volumi (CTV, PTV, OAR)

Pianificazione della distribuzione di dose, con TPS dedicato

Evoluzione tecnologica.....

IMRT



Wedges

115% IMRT

Non sono metodiche disponibili in tutti i centri di radioterapia

Non sono disponibili per tutti i pazienti

Presentano aspetti non completamente chiari e definiti

La scelta tra 3DCRT/IMRT viene fatta sulla singola paziente al fine di ottenere la migliore distribuzione della dose





Messaggio conclusivo



Nella scelta terapeutica di queste pazienti emerge sempre più il ruolo dell'approccio multidisciplinare al caso (chirurgo, oncologo, radioterapista.....!!!!)





Grazie per l'attenzione..... www.windowweb.it