Associazione Italiana Radioterapia Oncologica
Lazio Abruzzo Molise

Cenni di patogenesi e strumenti di valutazione

Antonella Ciabattoni

UOC Radioterapia Ospedale S. Filippo Neri, ASL RM1

ASL ROMA E

REGIONE LAZIO

Associazione Italiana
Radioterapia Oncologica
Gruppo Interregionale
Lazio/Abruzzo/Molise

Le terapie di supporto in Radioterapia:

Verso una Guida Pratica

Lunedì 4 Dicembre 2017
Centro Studi Cardello
Via del Cardello 24 – Roma

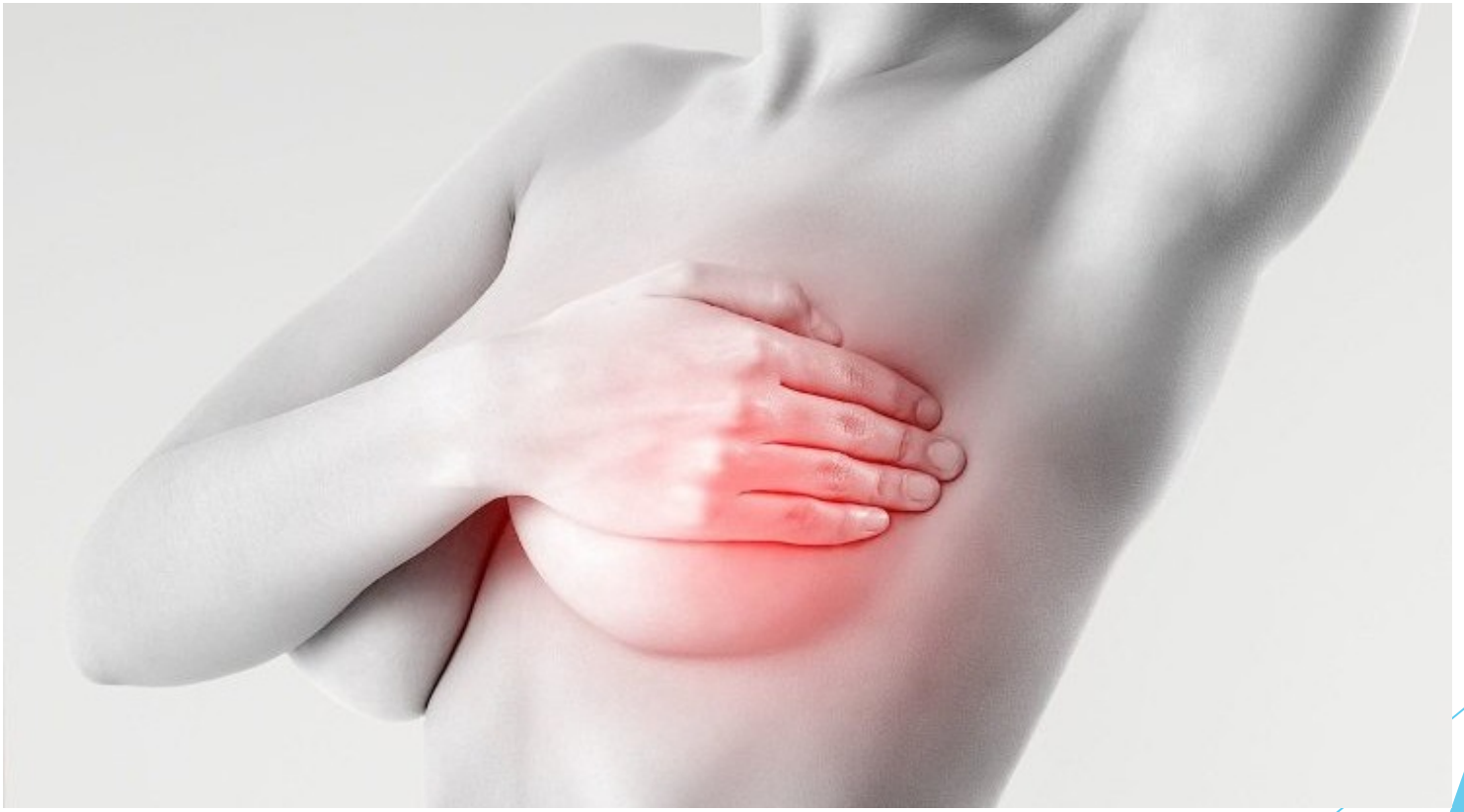
MAMMELLA – CUTE E LINFEDEMA
Presidi di prevenzione e trattamento delle tossicità

Dott.ssa Laura Verna

Ospedale San Pietro
FATEBENEFRATELLI

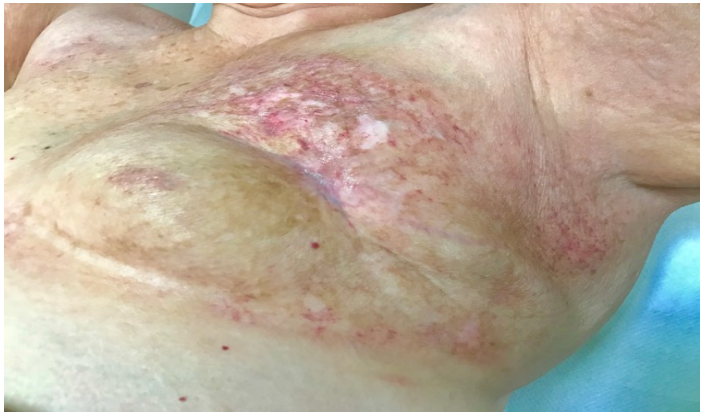
TOSSICITA’ CUTANEA

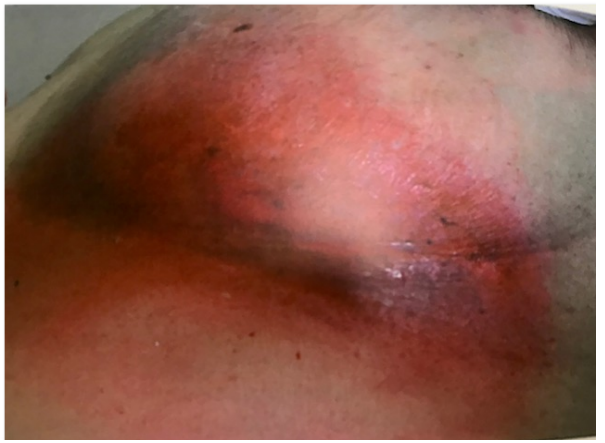
La tossicita' cutanea e' l'effetto collaterale piu' comune nelle pz affette da neoplasia mammaria sottoposte a radioterapia

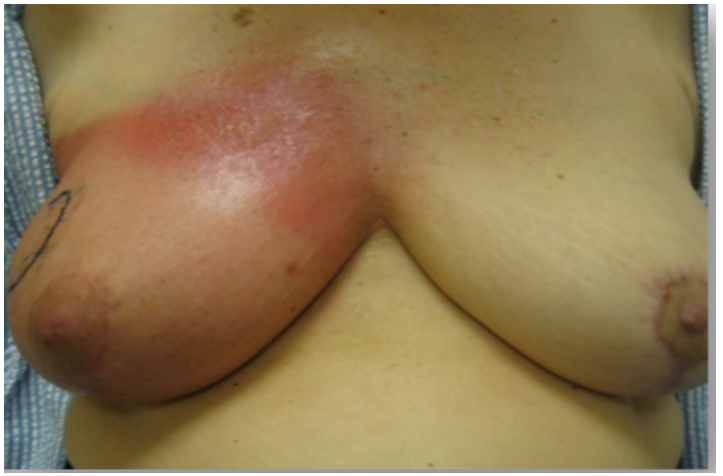


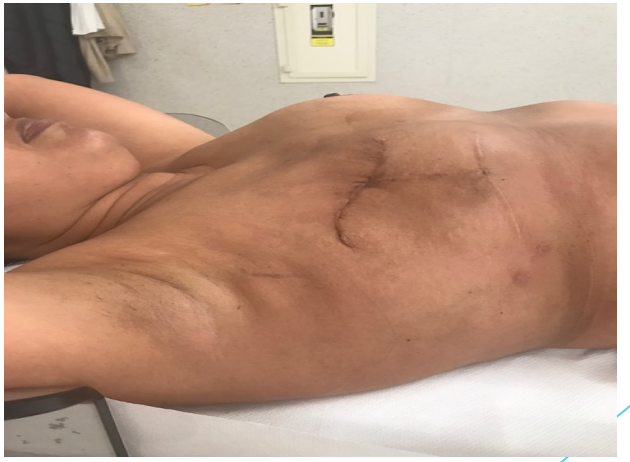
TOSSICITA’ CUTANEA

Nonostante il progredire della tecnologia, piu' della meta' delle pz sottoposte a RT sulla mammella andranno incontro a diversi gradi di tossicita' cutanea.







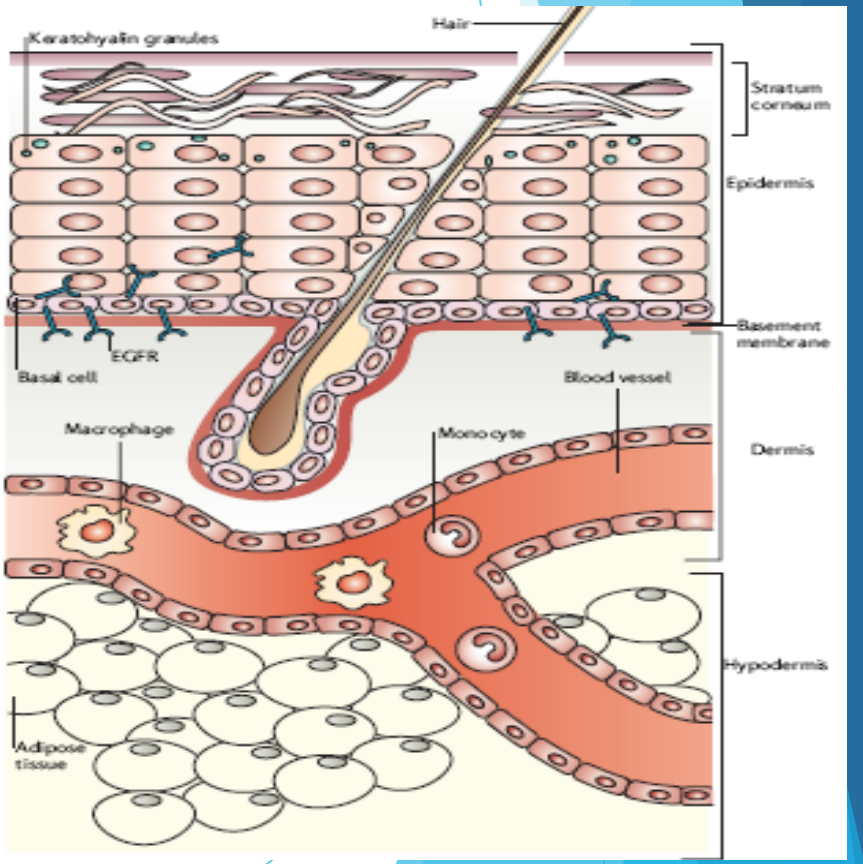


Ospedale San Pietro
FATEBENEFRATELLI

TOSSICITA' CUTANEA

Le reazioni cutanee da radioterapia sono il risultato combinato di risposta infiammatoria + danno alle cellule attivamente proliferanti

- Le radiazioni ionizzanti alterano le capacità mitotiche delle cellule staminali dello strato basale prevenendo il processo di ripopolamento cellulare
- La perdita delle cellule basali inizia al raggiungimento di una dose totale pari a **20-25 Gy**
- La deplezione massima di queste cellule si ottiene a **50 Gy**



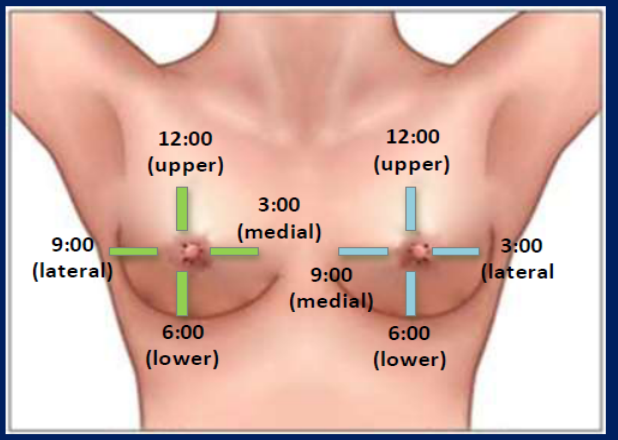
Ospedale San Pietro
FATEBENEFRATELLI

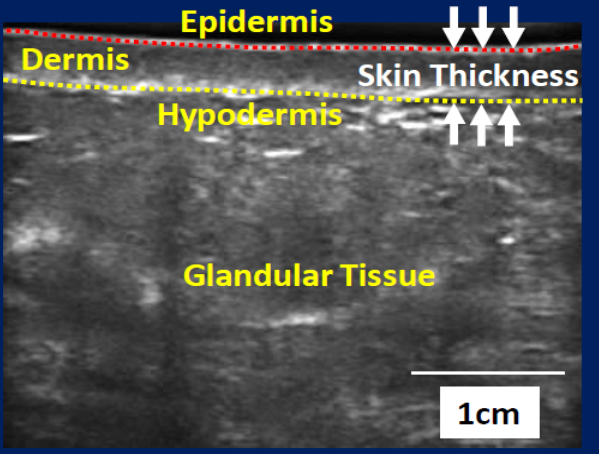
TOSSICITA' CUTANEA

Ultrasound Tissue Characterization

Clinical Scanner: SonixTouch

Frequency: 10 MHz

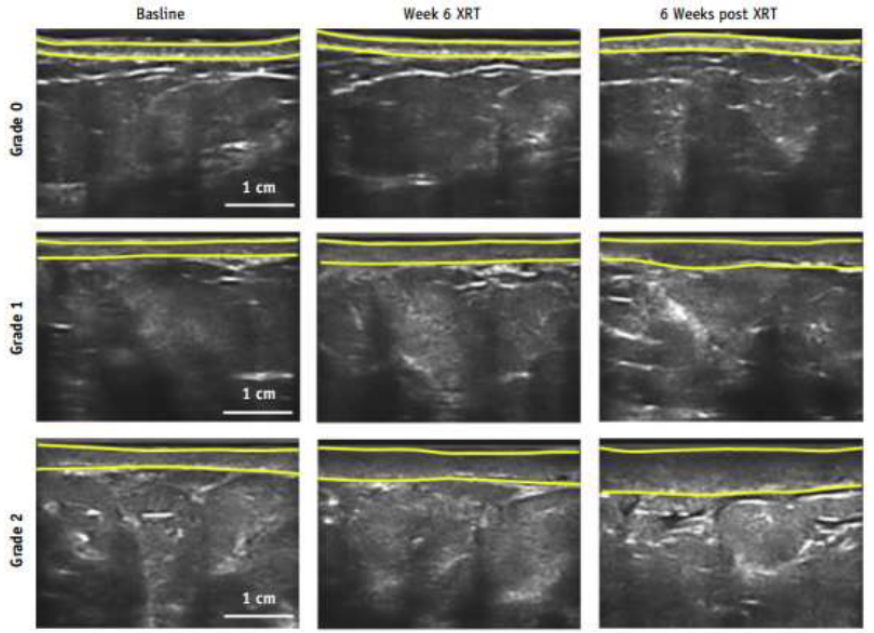




Ospedale San Pietro
FATEBENEFRATELLI

TOSSICITA' CUTANEA

Skin Thickening and Radiation

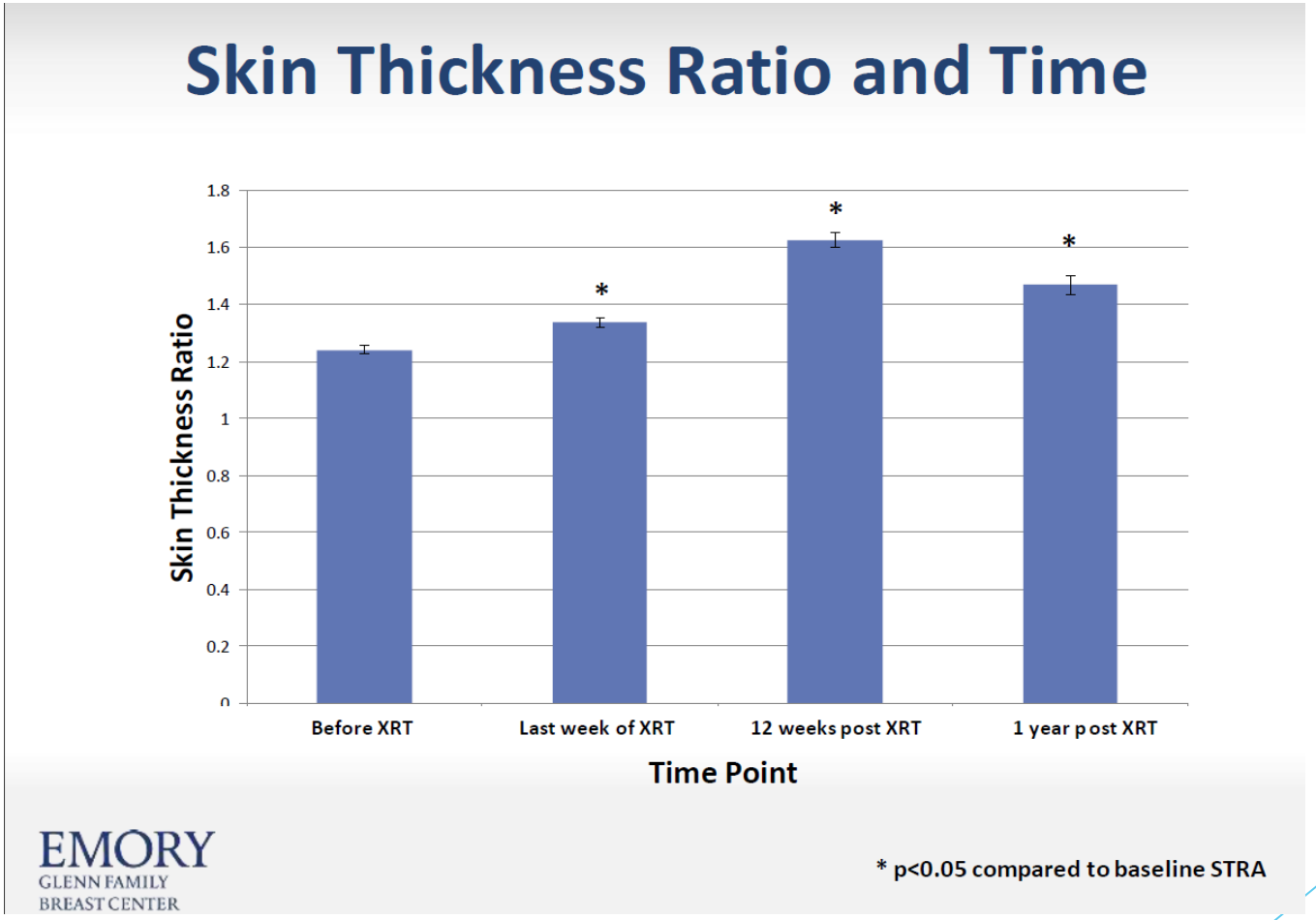


EMORY
GLENN FAMILY
BREAST CENTER
WINSHIP CANCER INSTITUTE

Torres et al. *International Journal of Radiation Oncology, Biology, Physics* 2016

Ospedale San Pietro
FATEBENEFRATELLI

TOSSICITA' CUTANEA



Ospedale San Pietro
FATEBENEFRATELLI

FATTORI DI RISCHIO

PAZIENTE-CORRELATI
Età
Alterazione del circolo linfatico
Volume irradiato
Infezioni della ferita chirurgica e del letto operatorio
Livello di igiene locale
Fototipo
Comorbidità (ipertensione, diabete, malattie del collagene)
Suscettibilità genetica

TRATTAMENTO-CORRELATI
Dose totale / Frazionamento
Durata del trattamento
”Target Volume” (> sensibilità per volumi >20 cm3 , > sensibilità a livello di pliche cutanee, ascelle e inguini)
Tipologia di radiazione (elettroni/fotoni)
Bolus
Chemioterapia pregressa o concomitante (Radiation Recall)
Ormonoterapia

TOSSICITA' CUTANEA

Hypofractionation: Quality of Life

Michigan Radiation Oncology Quality Consortium

- **2309 evaluable patients (578 received HF).**
- **Outcomes worse with CF vs. HF**
  - Moist desquamation, 28.5% vs 6.6%, P < .001
  - Grade 2 dermatitis, 62.6% vs 27.4%, P < .001)
  - Self-reported pain (moderate/severe pain, 41.1% vs 24.2%, P = .003)
  - Burning/stinging bother (often/always, 38.7% vs 15.7%, P = .002).
  - Hurting bother (33.5% vs 16.0%, P = .001)
  - Swelling bother (29.6% vs 15.7%, P = .03)
  - Fatigue (29.7% vs 18.9%, P = .02)

MROQC
Michigan Radiation Oncology Quality Consortium

Jagsi et al JAMA Oncol 2015.

PENN RADIATION ONCOLOGY

Penn Medicine

Ospedale San Pietro
FATEBENEFRATELLI

TOSSICITA' CUTANEA

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 2), pp: 3059-3063

Research Paper

Dosimetric evaluation of the skin-sparing effects of 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy for left breast cancer

In Young Jo[1], Shin-Wook Kim[2], Seok Hyun Son[2]

[1]Department of Radiation Oncology, Samsung Medical Center, Seoul, Korea

[2]Department of Radiation Oncology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Correspondence to: Seok Hyun Son, **email:** sonshyun@catholic.ac.kr

Keywords: *breast cancer, 3-dimensioanl conformal radiotherapy, intensity-modulated radiotherapy, radiation-related dermatitis, skin-sparing*

Received: *August 19, 2016* ***Accepted:*** *December 01, 2016* ***Published:*** *December 09, 2016*

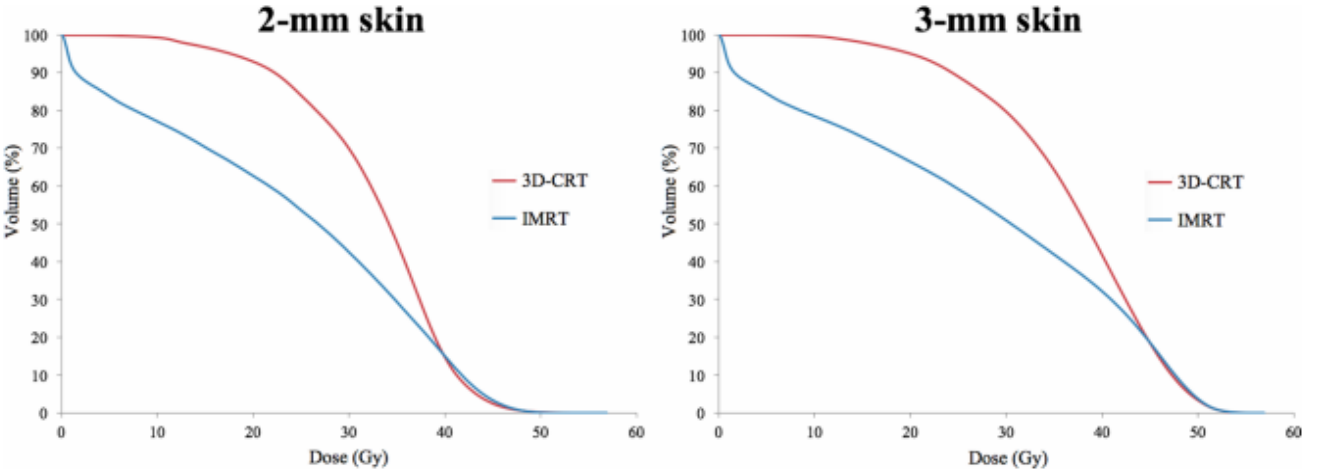


Figure 2: Comparison of dose-volumetric histograms for 2-mm skin and 3-mm skin between 3D-CRT and IMRT.

Ospedale San Pietro FATEBENEFRATELLI

EFFETTI ACUTI e TARDIVI

Effetti acuti:

- durante ed entro 6 settimane dalla fine della radioterapia
- attesi, frequenti, reversibili

Effetti tardivi:

- latenza di 6 mesi
- occasionali, progressivi, irreversibili

Radiotherapy-related skin reactions

Acute skin reactions associated with radiotherapy can be distressing and can lead to treatment interruption. Anticipating, assessing and managing the problem according to best evidence can make a big difference.

This grandround was first presented by Lena Sharp, from the Stockholm-Gotland Regional Cancer Centre, in Stockholm, as a live webcast for the European School of Oncology, in collaboration with the European Oncology Nursing Society. It is edited by Susan Mayor. The webcast of this and other educational sessions can be accessed at e-eso.net.

EJC, June 2016

Evaluation Tools???

Clinical Journal of Oncology Nursing • Volume 15, Number 5 2011 481-492

Putting Evidence Into Practice:

Table 2. Clinical Measurement Tools for Radiodermatitis

TOOL	DESCRIPTION	BENEFITS AND/OR LIMITATIONS
Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria (1985) (Cox et al., 1995)	Assesses intensity or severity of reaction Ordinal scale 0–4	No reliability or validity data published Observation of physical changes Does not address symptoms or patient perspective Commonly used in clinical trials
Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer toxicity criteria (Cox et al., 1995)	Assesses late complications Ordinal scale 1–4 Acute: less than 90 days after first treatment Late: after day 90 Also assesses fibrosis, induration, skin contracture, and necrosis	No reliability or validity data published Observation of physical changes Does not address symptoms or patient perspective
Common Terminology Criteria for Adverse Events [v.4.03] (version 2.0 incorporated into Oncology Nursing Society *Radiation Therapy Patient Care Record* for Radiation Dermatitis by Site Group) (Catlin-Huth et al., 2002)	Adverse events reporting tool Severity scale Rash: dermatitis associated with radiation Ordinal scale 0–5 Grades of desquamation	No reliability or validity data published Observation of physical changes Does not address symptoms or patient perspective
Skin Toxicity Assessment Tool (known as STAT) (Berthelet et al., 2004)	Three areas of assessment Patient and treatment factors affecting incidence and intensity of radiodermatitis Objective scoring of grades of desquamation Patient symptoms	Preliminary reliability and validity results reported (Berthelet et al., 2004) Easy to use in the clinical setting Quickly administered
Radiation-Induced Skin Reaction Assessment Scale (known as RISRAS) (Noble-Adams, 1999a, 1999b)	Weighted categories (e.g., moist desquamation weighted higher than dry desquamation) for overall score that incorporates effect on patient Symptom scale (e.g., tenderness, itching, burning, warmth, effect on activity) Observer assessment (e.g., erythema, dry desquama-	Nursing assessment tool Objective observer assessment and patient's perspective of symptoms Reliability and validity scores have been reported. Has not been widely used in practice research

LENT SOMA EORTC-RTOG

1995

RTOG/EORTC and LENT-SOMA classification of late skin and subcutaneous side effects

Scoring system	Grade 1	Grade 2	Grade 3	Grade 4
RTOG				
Skin	Slight atrophy, pigmentation change, and slight hair loss	Atrophic patches, moderate telangiectasia, and total hair loss	Marked atrophy and gross telangiectasia	Ulceration
Subcutaneous tissue	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate asymptomatic fibrosis and slight loss of field contracture (<10% linear reduction)	Severe induration and loss of field contracture (>10% linear reduction)	Necrosis
LENT-SOMA				
Subjective measures				
Scaliness/roughness	Present and asymptomatic	Symptomatic	Requires constant attention	
Sensation	Hypersensitivity and pruritus	Intermittent pain	Persistent pain	Debilitating dysfunction
Objective measures				
Edema	Present and asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Alopecia (scalp)	Thinning	Patchy and permanent	Total and permanent	
Pigmentation change	Transitory and slight	Permanent and marked		
Ulcer/necrosis	Epidermal only	Dermal	Subcutaneous	Bone exposed
Telangiectasia	Minor	Moderate (<50%)	Gross (≥50%)	
Fibrosis/scar	Present and asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Atrophy/contraction (depression)	Present and asymptomatic	Symptomatic (<10%)	Secondary dysfunction (10–30%)	Total dysfunction (≥30%)

RTOG = Radiation Therapy Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; LENT-SOMA = Late Effects Normal Tissue Task Force-Subjective, Objective, Management and Analytic.

NCI CTCAE v. 4.03

Acute RT Toxicity *CTCAE*

34 tools!!!

Table 1 Dermatitis radiation according to the Common Terminology Criteria for Adverse Events v4.03 (CTCAE)

Grade	Description
1	Faint erythema or dry desquamation
2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
4	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
5	Death

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

STAT Skin Toxic

Integrates both the the patients and the assessors,

Pre
Tox

Five Cardinal Signs of Infiammation

Eric Berthelet, MD,§*
Winkle Kwan, MBBS,§ V*

TABLE 2B. Interobserver Reliability, Subjective Indicators

	Agreement	Confidence Interval	κ
Burning	79%	71%–86%	0.49
Itching	82%	74%–89%	0.68
Pulling	77%	68%–84%	0.58
Tenderness	72%	63%–79%	0.55
Other	92%	86%–96%	0.38

The percent agreements for the subjective indicators represent the proportion of exact agreement when each symptom is scored using a scale of 0–5.

- Area (cm x cm)

Dry Desquamation
- Area (cm x cm)

Moist Desquamation
- Area (cm x cm)

TABLE 2A. Interobserver Reliability, Objective Indicators

	Agreement	Confidence Interval	κ
Intact skin	83%	75%–89%	0.59
Erythema	65%	56%–73%	0.46
Dry desquamation	88%	81%–93%	0.47
Moist desquamation	95%	89%–98%	0.81
Exudate	97%	92%–99%	0.74

The percent agreements for the subjective indicators represent the proportion of exact agreement when each symptom is scored using a scale of 0–5.

im;
al;

RISRAS
Radiation Induced Skin Reaction Assessment Scale

Integrates both the subjective complaints of the patients and the objective findings of the assessors,

4 CLINICAL PHOTOGRA… DIFFERENT… EXPERTS
- NURSES
- DOCTORS
- RADIOGR… S

Radiation-Induced Skin Reaction Assessment Scale (RISRAS)
(Bewertungsskala für strahleninduzierte Hautreaktionen)

Erythema (E)	**0** (Normal skin)	**1** (Dusky pink)	**2** (Dull red)	**3** (Brilliant red)
Dry Desquamation (DD)	**0** (Normal skin)	**1** (<25%)	**2** (>25-50)	**3** (>50-75)
Moist Desquamation (MD)	**0** (Normal skin)	**1,5** (<25%)	**3,0** (>25-50)	**4,5** (>50-75)
Necrosis	**0** (Normal skin)	**2,5** (<25%)	**5,0** (>25-50)	**7,5** (>50-75)

Nobel-Adams R 1999 Radiation-induced reactions 3; evaluating the RISRAS. British Journal of Nursing 8(19):1305-1312

EFFETTI ACUTI: come si manifestano

timing	effetto	patogenesi	caratteristiche
• Tra la II e la IV settimana di terapia	**Secchezza**	Distruzione delle ghiandole sebacee	• Molto frequenti • Di scarsa rilevanza clinica in quanto rapidamente reversibili
	Epilazione	Danno dei follicoli piliferi	
	Iperpigmentazione	Stimolazione dei melanociti	
	Eritema/ Edema	Reazione infiammatoria citochino-mediata	
• Dopo la III settimana di terapia	**Epiteliolisi cutanea secca**	Depauperamento delle cellule staminali dello strato basale	
• Tra la IV e la V settimana di terapia	**Epiteliolisi cutanea umida**	Scomparsa completa delle cellule staminali dello strato basale	• Più rara • Associata a secrezione sierosa • Può esporre a complicazioni di natura infettiva

EFFETTI TARDIVI: come si manifestano

timing	effetto	patogenesi	note cliniche	caratteristiche
• Dopo 90 gg dal termine del trattamento	**Atrofia di cute ed annessi**	Depauperamento fibroblasti dermici e riassorbimento fibre collagene		• Questi quattro fenomeni sono irreversibili !!
	Fibrosi	Proliferazione dei fibroblasti rimanenti per azione del TBF-beta con deposizione di tessuto fibroso denso	La fibrosi radio-indotta è caratterizzata da indurimento, edema ed aumento di spessore del derma	
	Discromie	Estremamente variabile: stimolazione/ deplezione dei melanociti		
• A partire da 6 mesi dal termine del trattamento	**Teleangectasie**	Alterazione dei piccoli vasi con perdita delle cellule endoteliali.	Aree di cute distrofica con vasi sottili e dilatati. Le alterazioni del microcircolo possono provocare ischemia e successiva necrosi	

GESTIONE DELLA TOSSICITA' CUTANEA

Si fonda su due aspetti importanti:

- **PREVENZIONE**: con interventi da effettuarsi prima , durante e dopo il trattamento radiante

- **TRATTAMENTO**: con interventi da effettuarsi in base al grado di tossicità

GESTIONE DELLA TOSSICITA' CUTANEA

PREVENZIONE

- Mantenere una buona igiene della cute. Lavarsi con acqua e asciugarsi tamponando. E' preferibile usare detergenti a pH neutro
- Idratare la cute con creme emollienti
- Immediatamente prima della seduta di radioterapia, la cute deve essere detersa e non devono essere applicate creme idratanti, gel, emulsioni o medicazioni
- Usare indumenti di seta, lino o cotone. Evitare indumenti in fibre sintetiche che riducono la dispersione di calore
- Evitare la depilazione o l'uso di lamette. Radersi con rasoio elettrico
- Evitare soluzioni alcooliche (deodoranti, profumi) e l'uso del borotalco
- Non esporre la parte irradiata a raggi diretti del sole o lampade UV (dopo la RT per almeno 6-12 mesi)
- Non sottoporre la pelle irradiata a temperature molto fredde o molto calde (es.impacchi di ghiaccio, borse di acqua calda)
- Evitare di fare il bagno nelle piscine contenenti disinfettanti a base di cloro che possono aumentare la secchezza della pelle

TOSSICITA’ CUTANEA

Nonostante nella pratica clinica siano stati utilizzati da decenni i prodotti piu' diversi, la review della letteratura “evidence based”in merito e' davvero molto limitata

Ospedale San Pietro
FATEBENEFRATELLI

GESTIONE della TOSSICITA' CUTANEA:
PREVENZIONE

Un "detergente delicato" secondo il Cancer research UK e la BC Cancer Agency è:

– Senza profumo
– Con pH compreso tra 5 e 6
– Senza lanolina
– Senza surfactanti

Ospedale San Pietro
FATEBENEFRATELLI

DETERGENTE

- Deterge delicatamente, riducendo la secchezza cutanea (Coco Glucoside e Glyceryl Oleate)
- Idrata la pelle in profondità (Glicerina e Acido Lattico)
- Contrasta bruciore, pizzicore e prurito (Aloe barbadensis gel)

DEODORANTE

- Contiene **Trietil Citrato** e **Acido Tannico**
- controlla la sudorazione senza alterare il pH dell'epidermide e assicura un'azione deodorante e protettiva

- Permette una detersione delicata grazie alla sua formulazione ricca di agenti lavanti di origine vegetale
- L' uso quotidiano favorisce il ripristino della naturale funzione barriera della cute svolgendo una profonda azione idratante e lenitiva
- Può essere utilizzato anche sulle mucose

- idratante, lenitivo, protettivo, antiossidante, antiradicali liberi
- contiene un solo tensioattivo (non ionico) di esclusiva origine vegetale, delicato e ad altissima tollerabilità, non irritante, associato all'olio VEA (vitamina E acetato allo stato puro) in percentuale elevata con effetto idratante, protettivo e lenitivo del prurito.

Ospedale San Pietro
FATEBENEFRATELLI

GESTIONE DELLA TOSSICITA' CUTANEA:

PRINCIPI ATTIVI PIU' STUDIATI ED UTILIZZATI

CALENDULA: Attivita' antinfiammatoria, antisettica, cicatrizzante, rifrescante, emolliente.

VOLUME 22 · NUMBER 8 · APRIL 15 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Randomized Trial of *Calendula Officinalis* Compared With Trolamine for the Prevention of Acute Dermatitis During Irradiation for Breast Cancer

P. Pommier, F. Gomez, M.P. Sunyach, A. D'Hombres, C. Carrie, and X. Montbarbon

From the Department of Radiation Oncology and the Department of Biostatistics, Centre Léon Bérard, Lyon, France.

Submitted July 10, 2003; accepted January 26, 2004.

Supported by a grant from the Department of Research and Development, Boiron Ltd, France.

Role of the funding source: The sponsors of this study had no role in the collection, analysis, or interpretation of data, nor in the writing of the report or the decision to submit the article for publication.

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

Address reprint requests to Xavier Montbarbon, MD, Department of Radia-

A B S T R A C T

Purpose
The effectiveness of nonsteroid topical agents for the prevention of acute dermatitis during adjuvant radiotherapy for breast carcinoma has not been demonstrated. The goal of this study was to compare the effectiveness of calendula (Pommade au Calendula par Digestion; Boiron Ltd, Levallois-Perret, France) with that of trolamine (Biafine; Genmedix Ltd, France), which is considered in many institutions to be the reference topical agent.

Patients and Methods
Between July 1999 and June 2001, 254 patients who had been operated on for breast cancer and who were to receive postoperative radiation therapy were randomly allocated to application of either trolamine (128 patients) or calendula (126 patients) on the irradiated fields after each session. The primary end point was the occurrence of acute dermatitis of grade 2 or higher. Prognostic factors, including treatment modalities and patient characteristics, were also investigated. Secondary end points were the occurrence of pain, the quantity of topical agent used, and patient satisfaction.

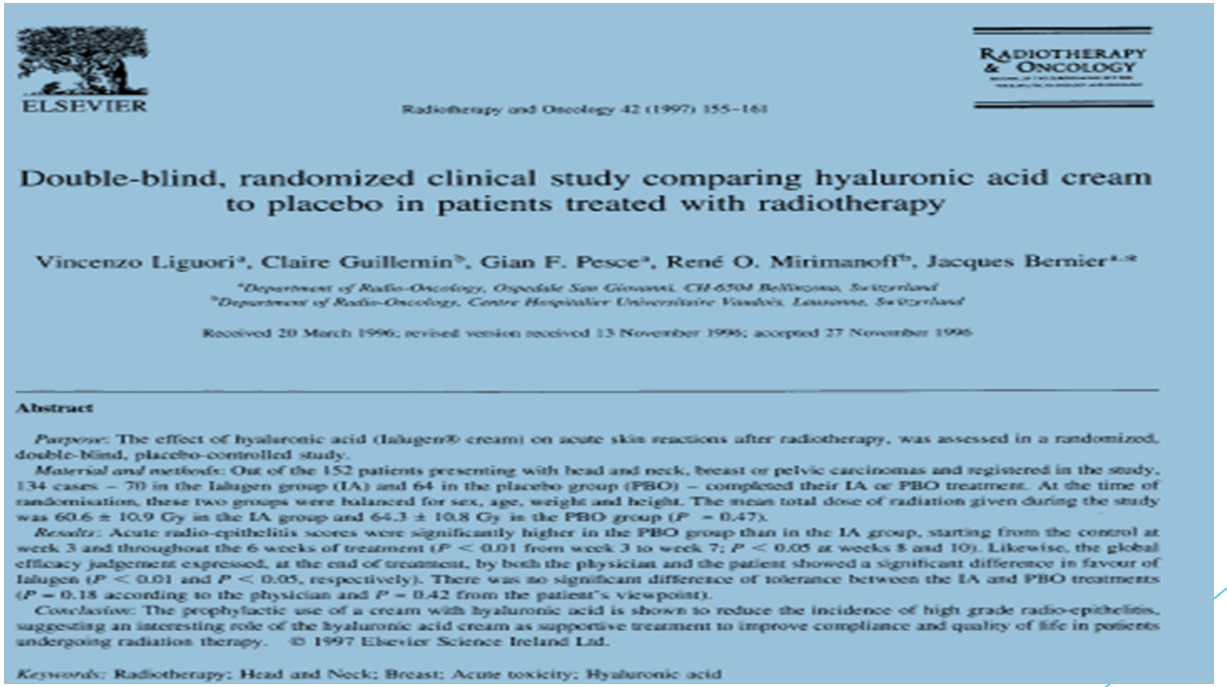
Results
The occurrence of acute dermatitis of grade 2 or higher was significantly lower (41% *v* 63%; $P < .001$) with the use of calendula than with trolamine. Moreover, patients receiving calendula had less frequent interruption of radiotherapy and significantly reduced radiation-induced pain. Calendula was considered to be

Ospedale San Pietro
FATEBENEFRATELLI

GESTIONE DELLA TOSSICITA' CUTANEA:

PRINCIPI ATTIVI PIU' STUDIATI ED UTILIZZATI

- ACIDO IALURONICO: Attivita' lenitiva ed idratante, stimola la produzione di collagene e di elastina. Favorisce la normale idratazione dei tessuti e la rimarginazione delle ferite.



ELSEVIER

Radiotherapy and Oncology 42 (1997) 155–161

RADIOTHERAPY & ONCOLOGY

Double-blind, randomized clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy

Vincenzo Liguori[a], Claire Guillemin[b], Gian F. Pesce[a], René O. Mirimanoff[b], Jacques Bernier[a,*]

[a]Department of Radio-Oncology, Ospedale San Giovanni, CH-6504 Bellinzona, Switzerland
[b]Department of Radio-Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Received 20 March 1996; revised version received 13 November 1996; accepted 27 November 1996

Abstract

Purpose: The effect of hyaluronic acid (Ialugen® cream) on acute skin reactions after radiotherapy, was assessed in a randomized, double-blind, placebo-controlled study.

Material and methods: Out of the 152 patients presenting with head and neck, breast or pelvic carcinomas and registered in the study, 134 cases – 70 in the Ialugen group (IA) and 64 in the placebo group (PBO) – completed their IA or PBO treatment. At the time of randomisation, these two groups were balanced for sex, age, weight and height. The mean total dose of radiation given during the study was 60.6 ± 10.9 Gy in the IA group and 64.3 ± 10.8 Gy in the PBO group ($P = 0.47$).

Results: Acute radio-epithelitis scores were significantly higher in the PBO group than in the IA group, starting from the control at week 3 and throughout the 6 weeks of treatment ($P < 0.01$ from week 3 to week 7; $P < 0.05$ at weeks 8 and 10). Likewise, the global efficacy judgement expressed, at the end of treatment, by both the physician and the patient showed a significant difference in favour of Ialugen ($P < 0.01$ and $P < 0.05$, respectively). There was no significant difference of tolerance between the IA and PBO treatments ($P = 0.18$ according to the physician and $P = 0.42$ from the patient's viewpoint).

Conclusion: The prophylactic use of a cream with hyaluronic acid is shown to reduce the incidence of high grade radio-epithelitis, suggesting an interesting role of the hyaluronic acid cream as supportive treatment to improve compliance and quality of life in patients undergoing radiation therapy. © 1997 Elsevier Science Ireland Ltd.

Keywords: Radiotherapy; Head and Neck; Breast; Acute toxicity; Hyaluronic acid

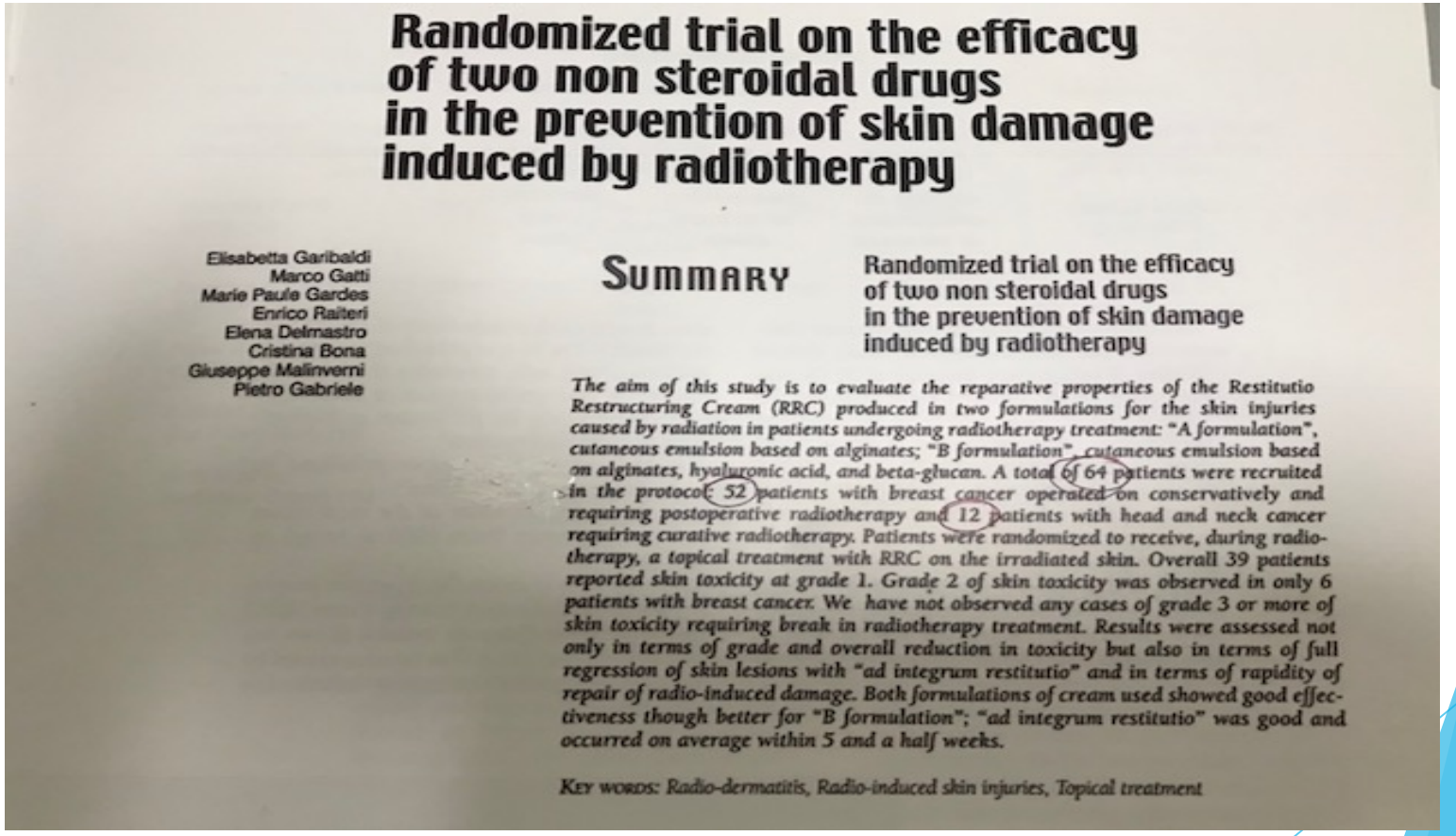
GESTIONE DELLA TOSSICITA' CUTANEA:

PRINCIPI ATTIVI PIU' STUDIATI ED UTILIZZATI

- ALGINATI e ACIDO ALGINICO : Polisaccaridi idrofilici estratti da un alga marina bruna (classe Phaeophyta). Proprieta' di ritenzione idrica , capacita' di passare allo stato semisolido(gelatinizzarsi)per garantire la giusta umidità e temperatura ideale per la cicatrizzazione.
- Beta-GLUCANI: Non viene sintetizzato dall'organismo umanoe viene pertanto riconosciuto come non-self dal sistema immunitario.
  Ha capacità di stimolare l'immunità naturale; stimola la rigenerazione cutanea e promuove la guarigione delle ferite.
- VERBASCOSIDE :azione antinfiammatoria allevia il dolore e prurito.
  Studi hanno dimostrato efficacia simile a quella del cortisone

GESTIONE DELLA TOSSICITA' CUTANEA

Journal of Plastic Dermatology 2009



Randomized trial on the efficacy of two non steroidal drugs in the prevention of skin damage induced by radiotherapy

Elisabetta Garibaldi
Marco Gatti
Marie Paule Gardes
Enrico Raiteri
Elena Delmastro
Cristina Bona
Giuseppe Malinverni
Pietro Gabriele

SUMMARY

Randomized trial on the efficacy of two non steroidal drugs in the prevention of skin damage induced by radiotherapy

The aim of this study is to evaluate the reparative properties of the Restitutio Restructuring Cream (RRC) produced in two formulations for the skin injuries caused by radiation in patients undergoing radiotherapy treatment: "A formulation", cutaneous emulsion based on alginates; "B formulation", cutaneous emulsion based on alginates, hyaluronic acid, and beta-glucan. A total of 64 patients were recruited in the protocol: 52 patients with breast cancer operated on conservatively and requiring postoperative radiotherapy and 12 patients with head and neck cancer requiring curative radiotherapy. Patients were randomized to receive, during radiotherapy, a topical treatment with RRC on the irradiated skin. Overall 39 patients reported skin toxicity at grade 1. Grade 2 of skin toxicity was observed in only 6 patients with breast cancer. We have not observed any cases of grade 3 or more of skin toxicity requiring break in radiotherapy treatment. Results were assessed not only in terms of grade and overall reduction in toxicity but also in terms of full regression of skin lesions with "ad integrum restitutio" and in terms of rapidity of repair of radio-induced damage. Both formulations of cream used showed good effectiveness though better for "B formulation"; "ad integrum restitutio" was good and occurred on average within 5 and a half weeks.

KEY WORDS: Radio-dermatitis, Radio-induced skin injuries, Topical treatment

Ospedale San Pietro
FATEBENEFRATELLI

- **Alginati**
- **BETA-Glucano** **DISPOSITIVO MEDICO**
- **Acido Ialuronico**:

- **Acido Ialuronico 0.2%**
- **Calendula Officinalis 2%**: **DISPOSITIVO MEDICO**
- **BETA-Glucano 0.05%**

- **Calendula Officinalis** **DISPOSITIVO MEDICO**

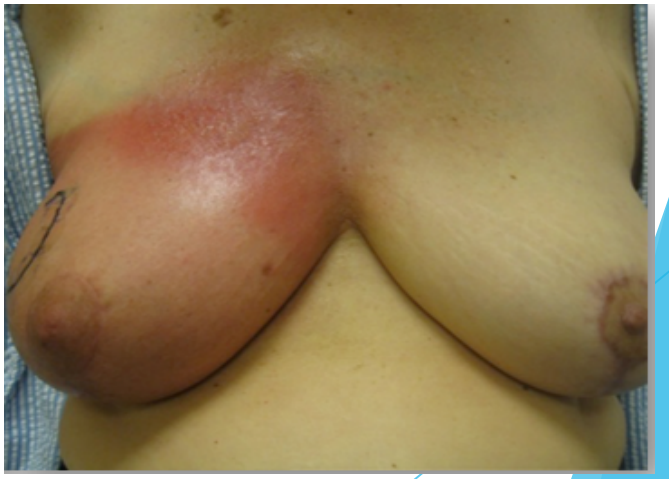
Ospedale San Pietro
FATEBENEFRATELLI

GESTIONE DELLA TOSSICITA' CUTANEA

TRATTAMENTO

TOSSICITA' G1 – G2

- **Buona igiene della cute:**
  Bioclin olio detergente®, Prodea Olio®, VEA detergente®
- **Idratare la cute:** Neoviderm®, Fairest RT®, Verbaderm pomata®
- **In caso di prurito ed in assenza di lesioni:** (creme steroidee) Flubason®, Eumovate®
- **Corretta gestione dell'essudato:** Hyalosilver®, Cicatridina spray® Streptosil ® (Sulfatiazolo+Neomicina)



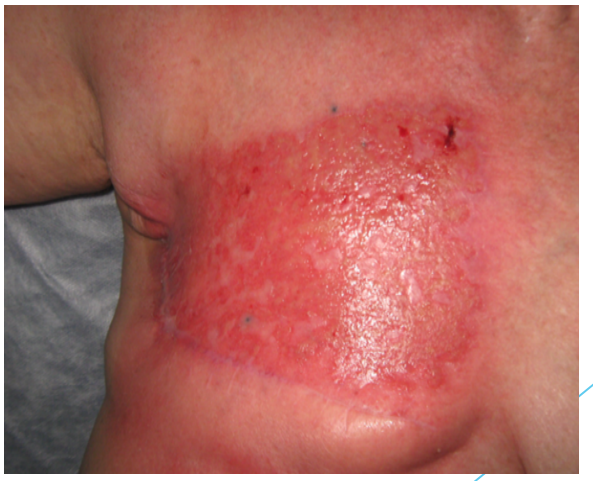
Ospedale San Pietro
FATEBENEFRATELLI

GESTIONE DELLA TOSSICITA' CUTANEA

TRATTAMENTO

TOSSICITA' G3 – G4

- Detergere con Sol.Fisiologica e H2O2 (10 VOL 3%)
- Toccature con eosina → Rubrosin®
- Trattare le infezioni con antimicrobici topici a base di Ag o antibiotici sistemici
- Corretta gestione dell'essudato con medicazioni a base di idrocolloide e/o alginato di calcio
- Gestione dell'emorragia con medicazioni a base di alginato di calcio



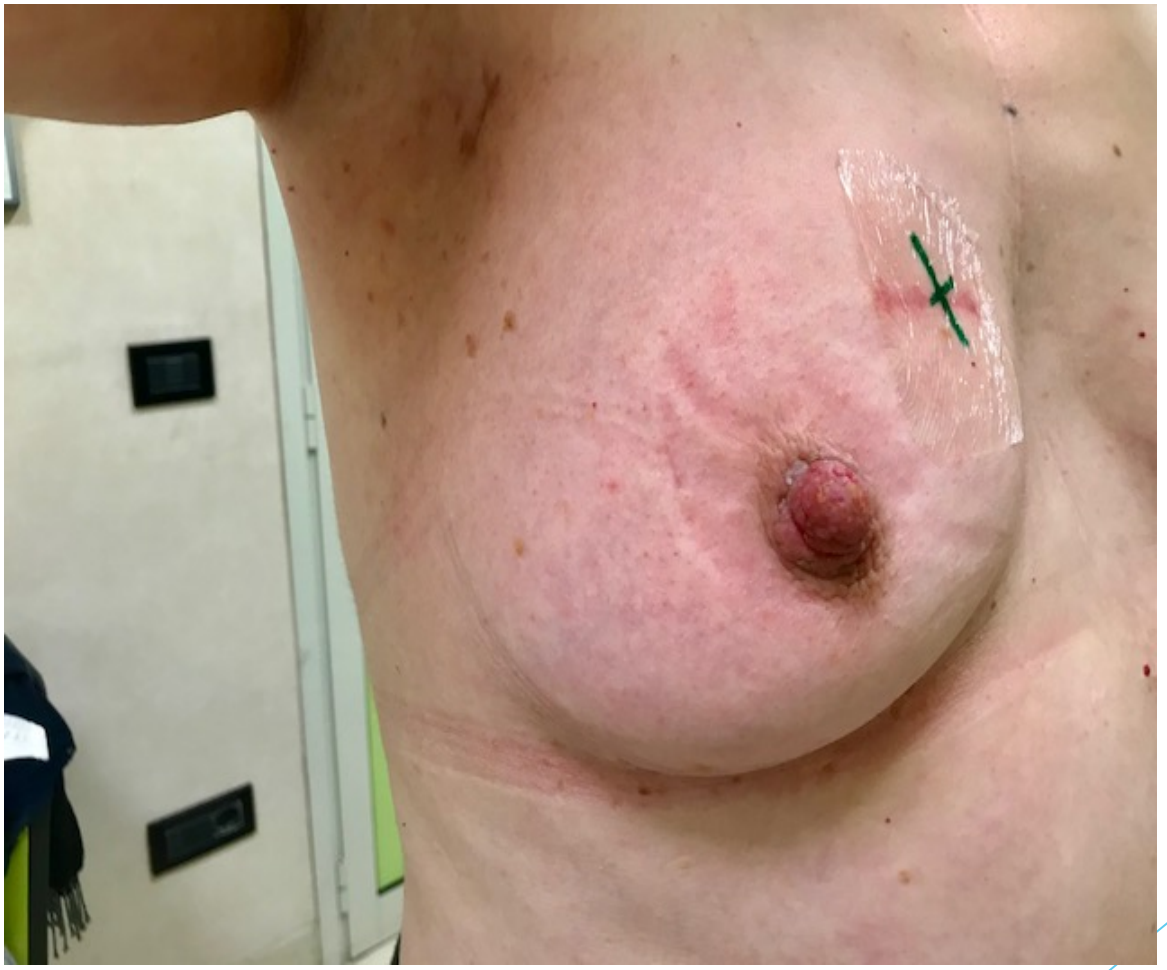
Ospedale San Pietro
FATEBENEFRATELLI

TOSSICITA’ CUTANEA:

A fronte di una letteratura basata sulle evidenze molto limitata....
ESPERIENZA E PRATICA CLINICA medica ed infermieristica

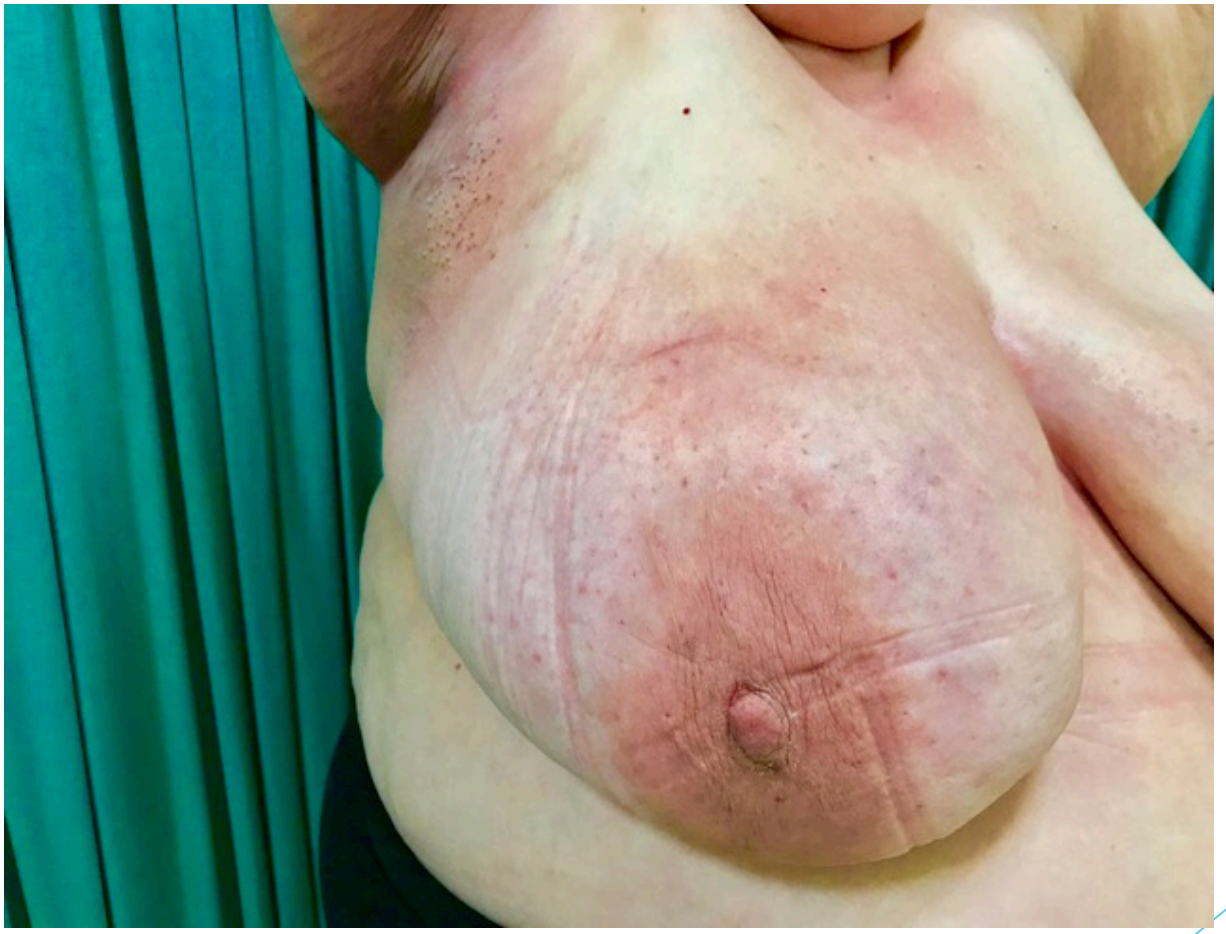
Ospedale San Pietro
FATEBENEFRATELLI

TOSSICITA' CUTANEA:
Esperienza clinica



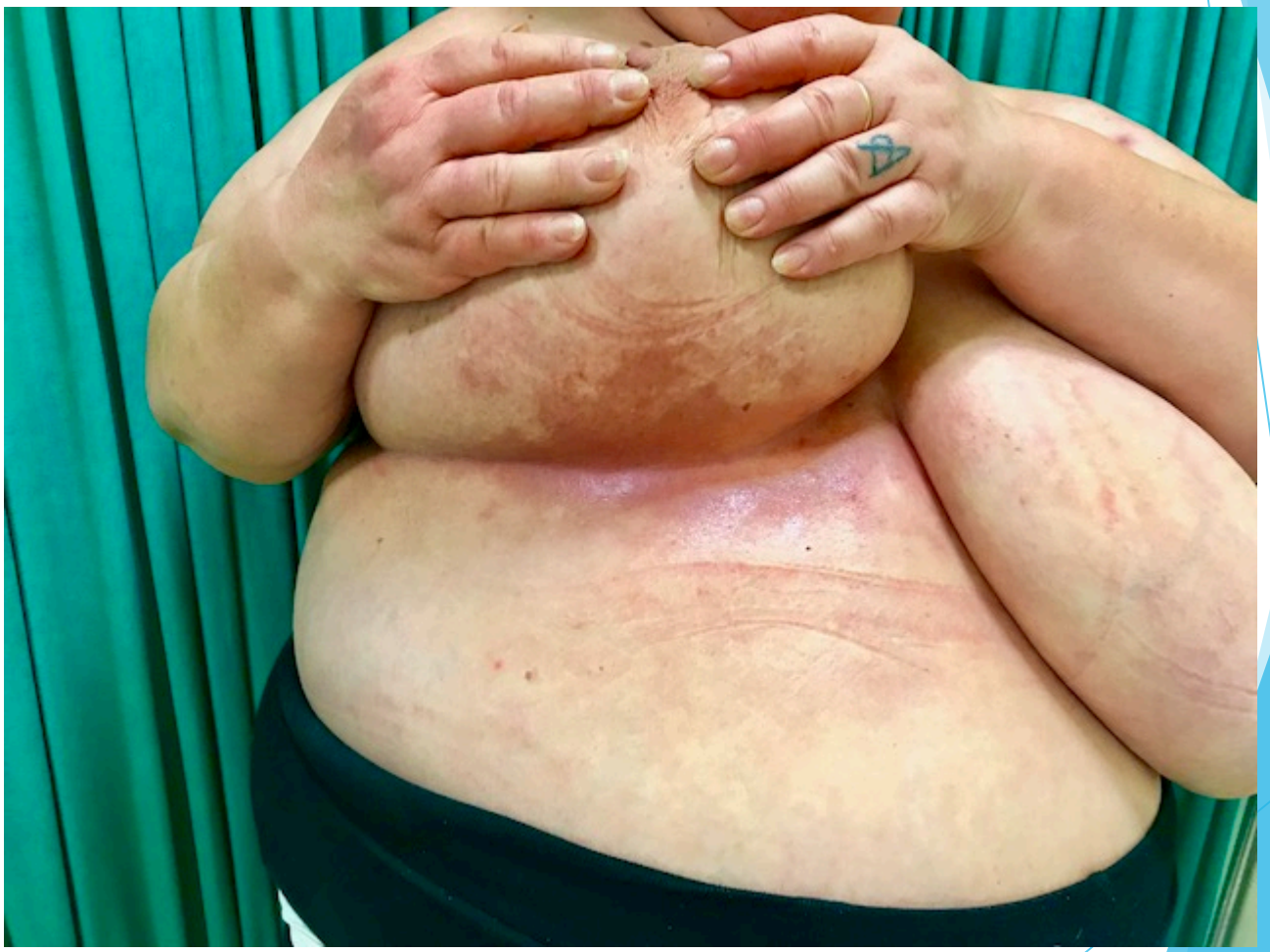
Ospedale San Pietro
FATEBENEFRATELLI

TOSSICITA' CUTANEA:
Esperienza clinica

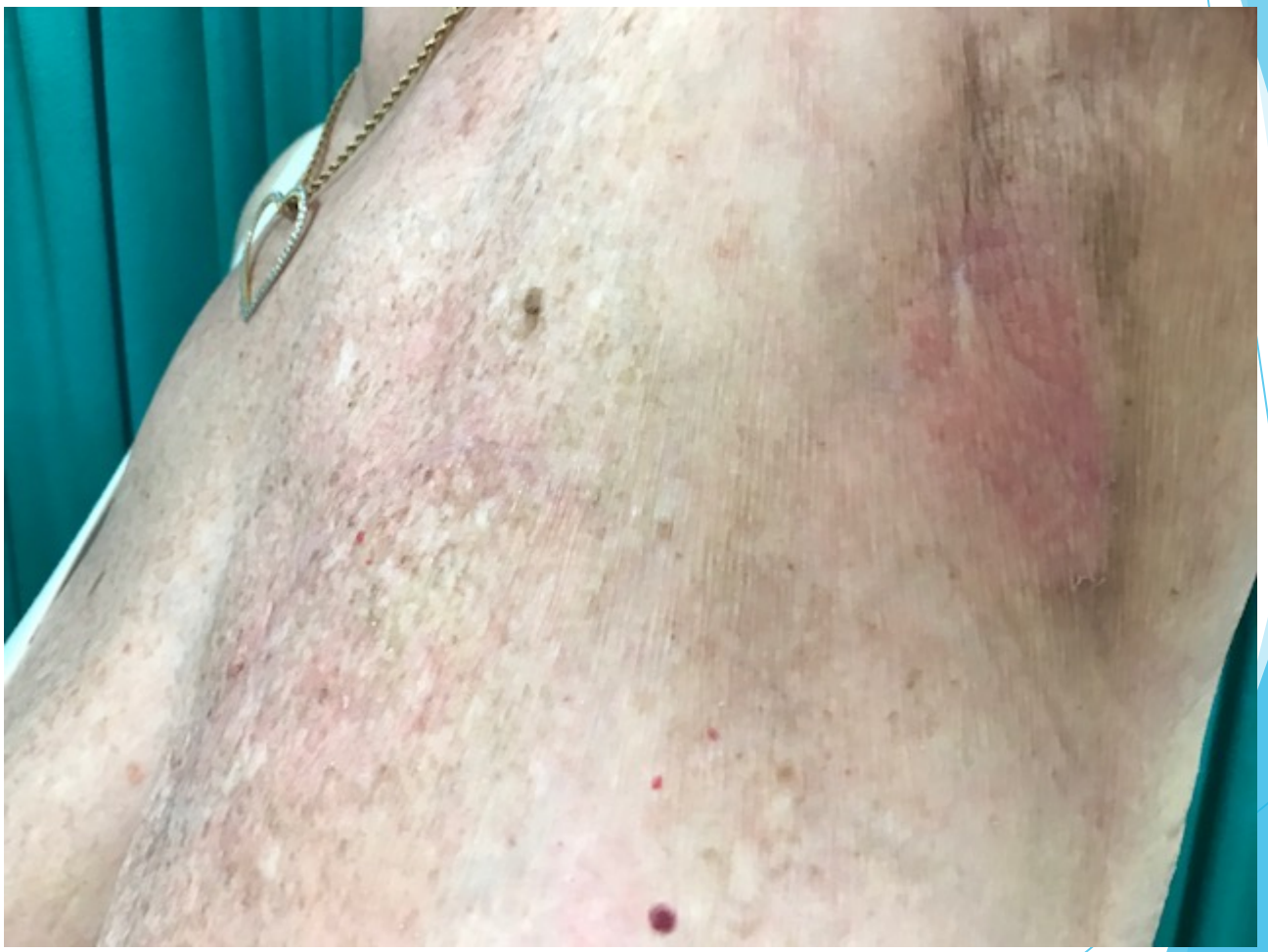


Ospedale San Pietro
FATEBENEFRATELLI

TOSSICITA' CUTANEA:
Esperienza clinica



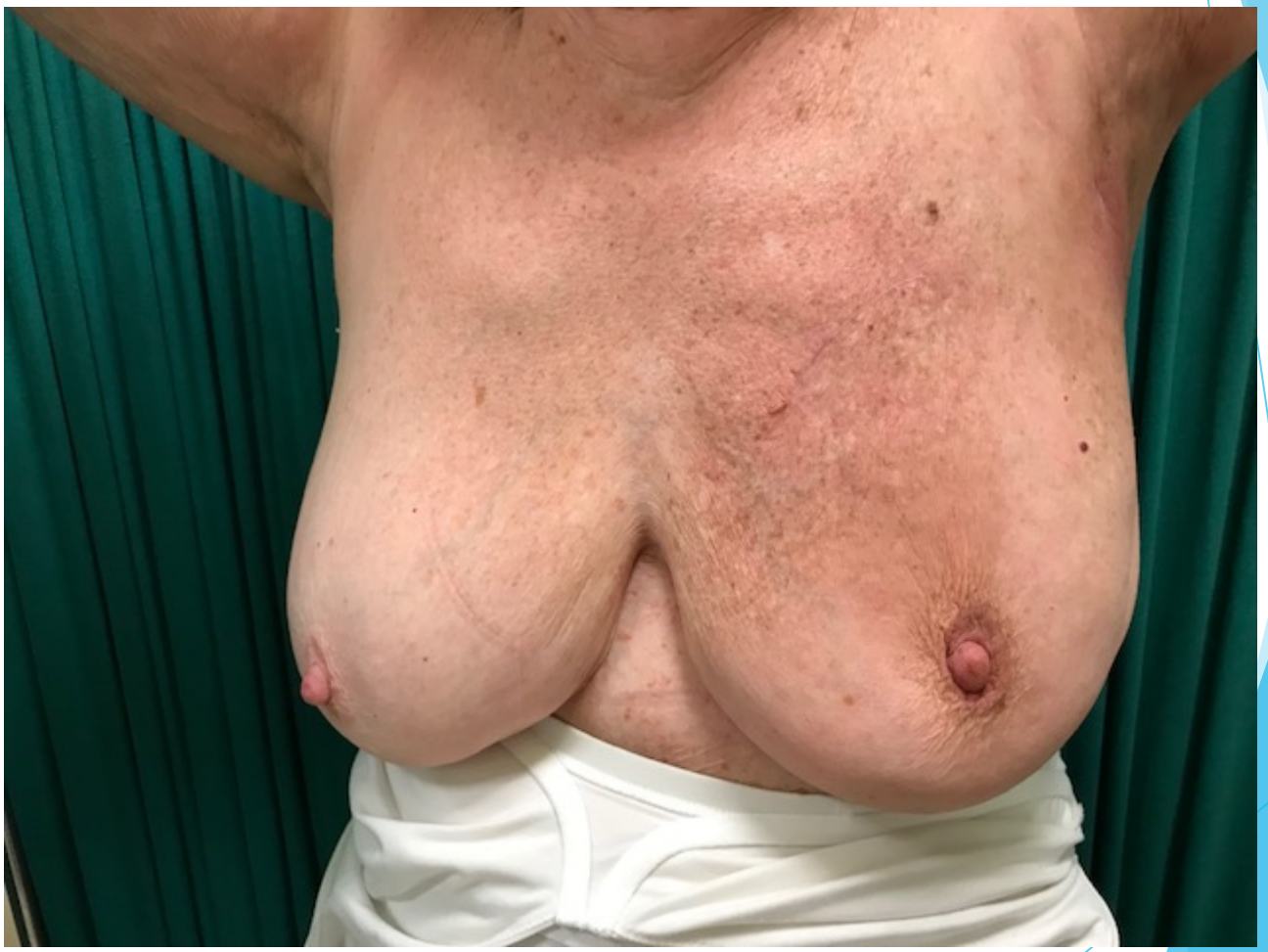
TOSSICITA' CUTANEA:
Esperienza clinica



Ospedale San Pietro
FATEBENEFRATELLI

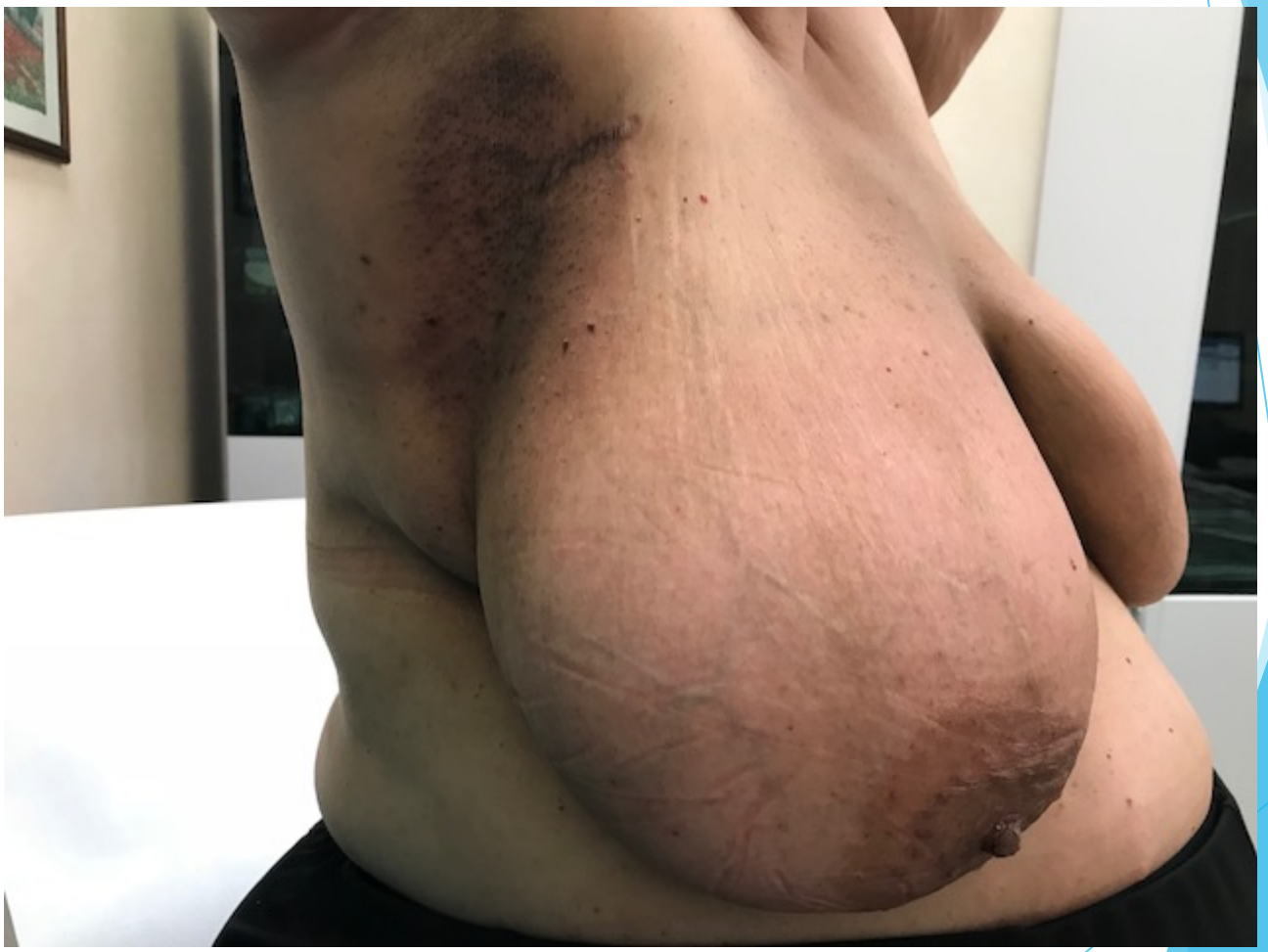
TOSSICITA' CUTANEA:

Esperienza clinica



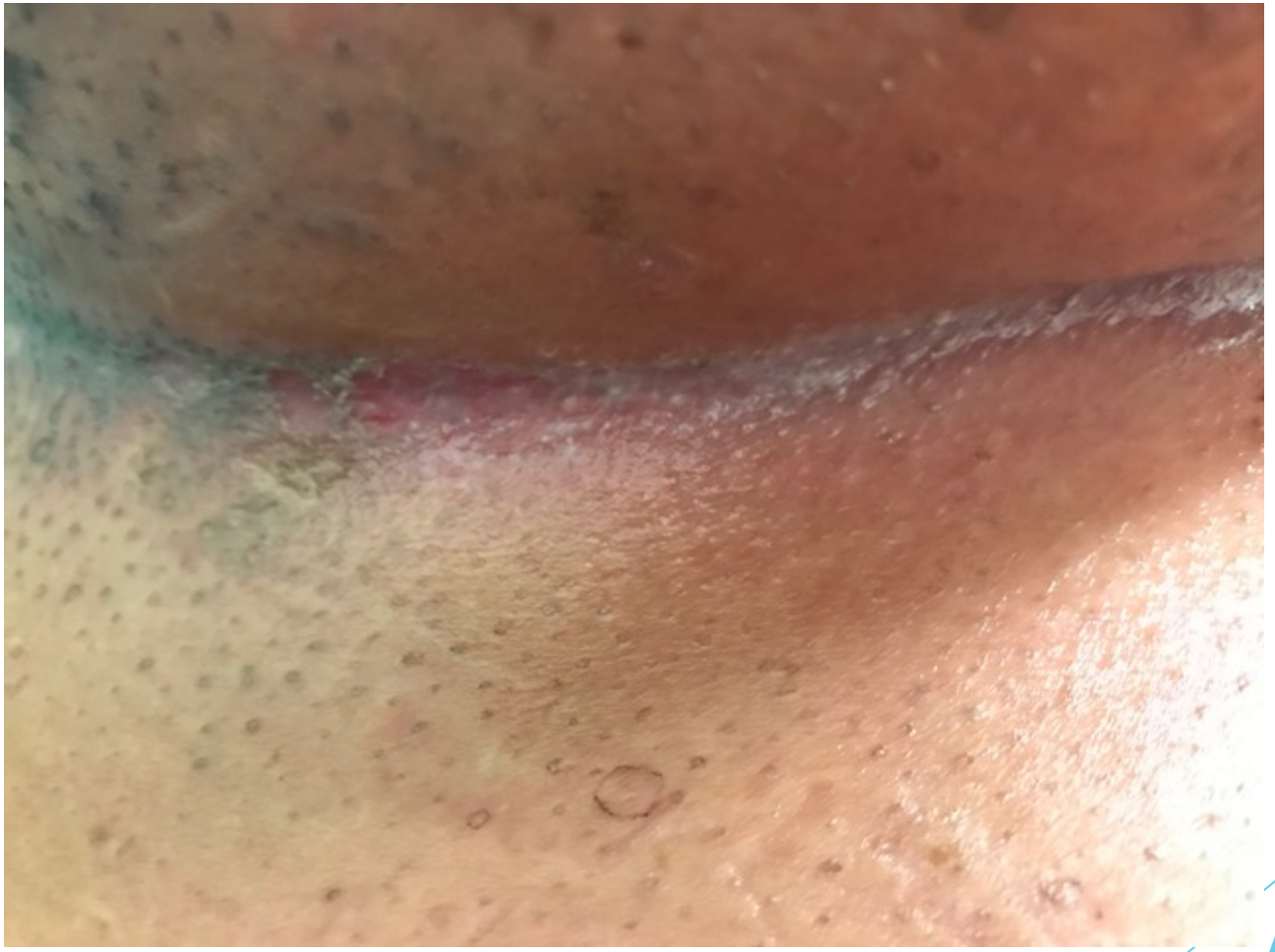
Ospedale San Pietro
FATEBENEFRATELLI

TOSSICITA' CUTANEA:
Esperienza clinica



Ospedale San Pietro
FATEBENEFRATELLI

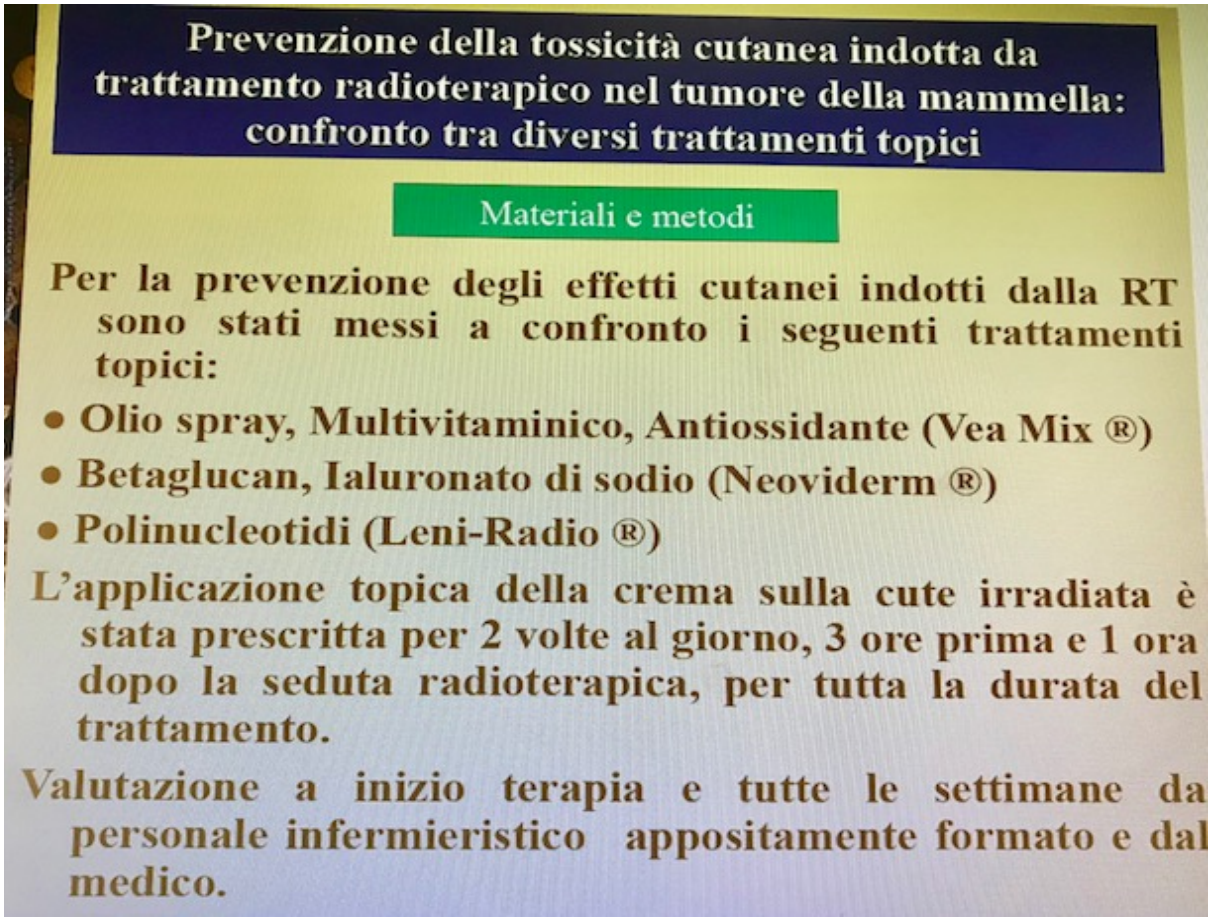
TOSSICITA' CUTANEA:
Esperienza clinica



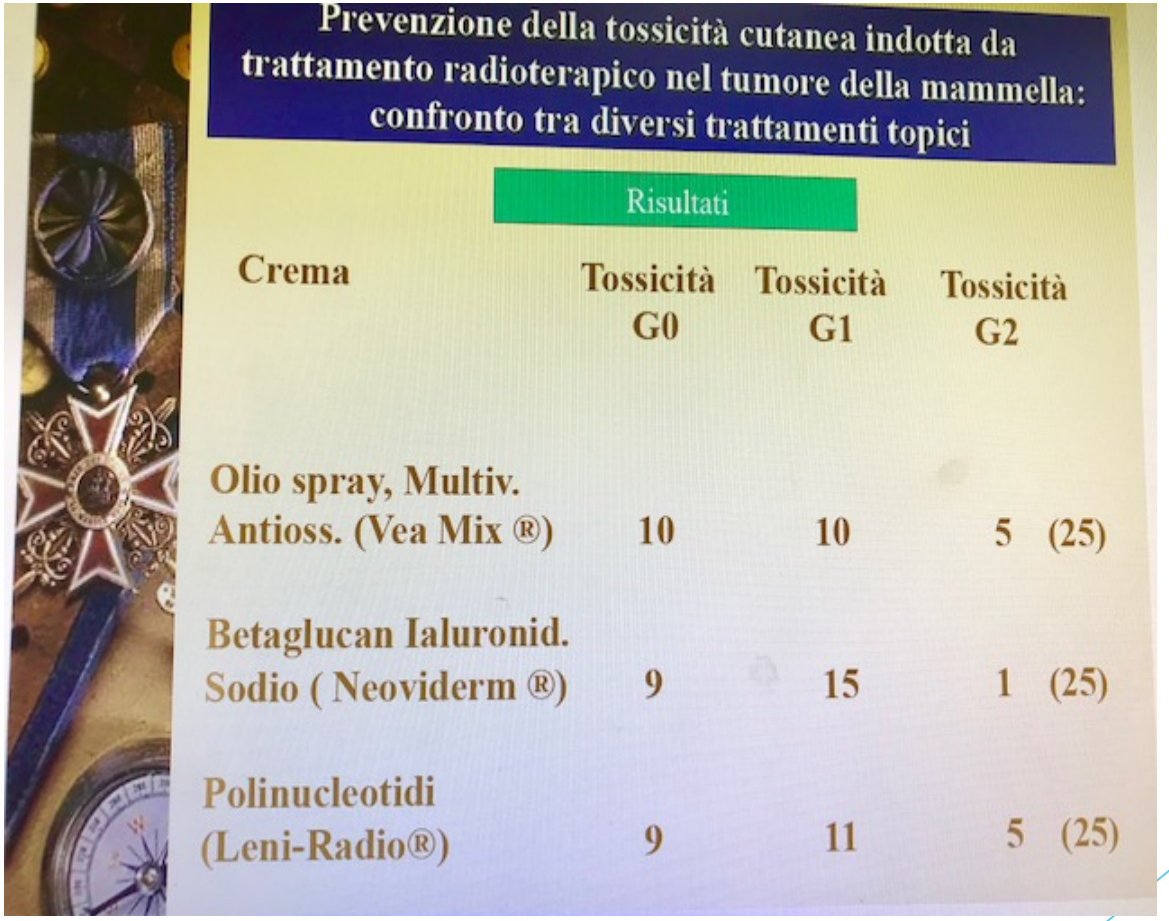
Ospedale San Pietro
FATEBENEFRATELLI

TOSSICITA’ CUTANEA

TOSSICITA' CUTANEA



TOSSICITA' CUTANEA



Prevenzione della tossicità cutanea indotta da trattamento radioterapico nel tumore della mammella: confronto tra diversi trattamenti topici

Risultati

Crema	Tossicità G0	Tossicità G1	Tossicità G2
Olio spray, Multiv. Antioss. (Vea Mix ®)	10	10	5 (25)
Betaglucan Ialuronid. Sodio (Neoviderm ®)	9	15	1 (25)
Polinucleotidi (Leni-Radio®)	9	11	5 (25)

TOSSICITA’ CUTANEA

Ospedale San Pietro
FATEBENEFRATELLI

TOSSICITA' CUTANEA

In epoca di crisi..."Last but not least"....

I COSTI !!!!!!

Ospedale San Pietro
FATEBENEFRATELLI

LINFEDEMA

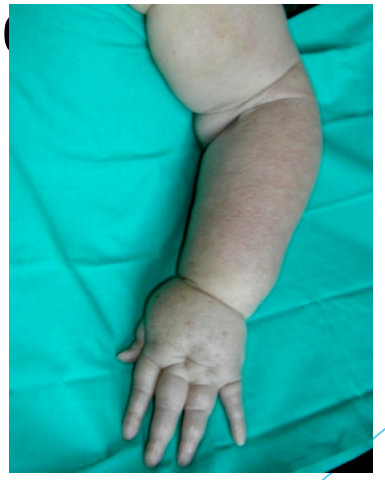
Accumulation of abnormal amount of protein rich fluid in the interstitium due to compromised lymphatic system

Highest incidence is observed following breast cancer surgery with radiotherapy

How big is the problem…..

About 15-20% of patients with breast cancer will experience lymphedema…

Lacova & Yoder, 20



I would have done almost anything to not be suffering with lymphedema.

I fear lymphedema more than recurrence

...lymphedema almost immediately after surgery, ... It has ruined my life. I feel like a freak. I'd almost rather I had died.

Lymphedema became a part of our lives as it strangled the mobility and quality of life from [my wife] and consequently from me. ... it eventually took over and was the worst part of [my wife's] illness

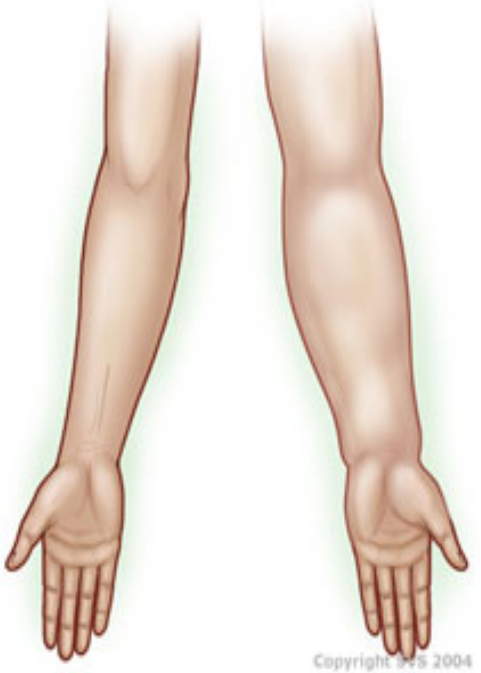
"Army of Women " 970 pts surveyed

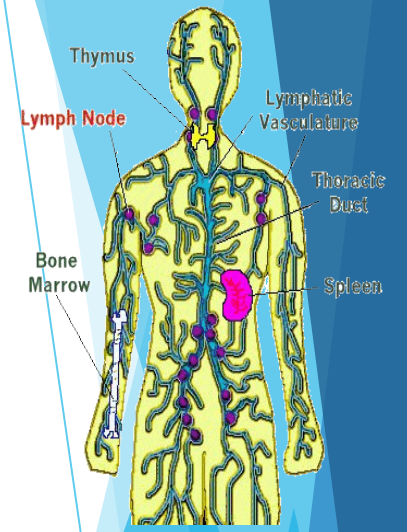
Courtesy Alice Ho, MD

What is lymphedema?

Abnormal accumulation of high-protein concentrated fluid (*interstitial*), usually in the arms or legs.

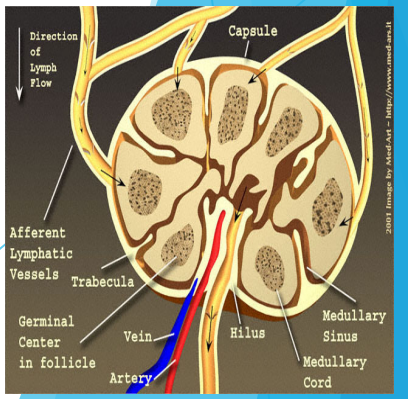
Dell & Doll, 2006





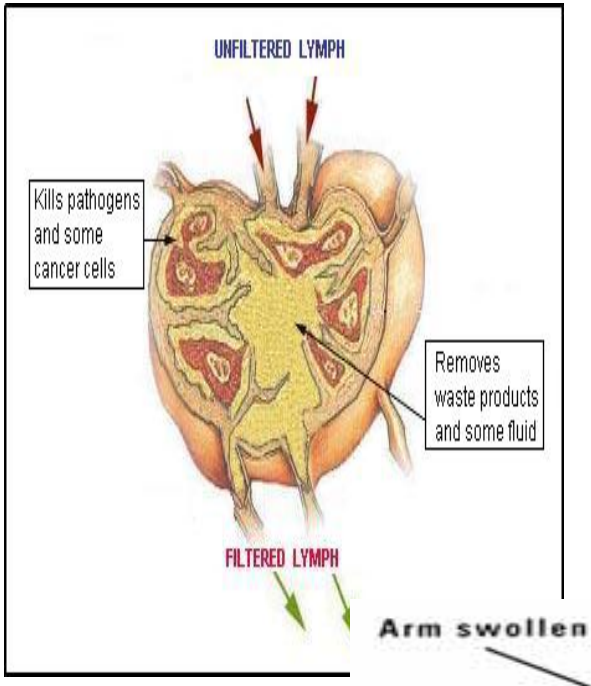
- Lymph vessels are similar to veins, but with thinner walls to allow larger proteins to permeate through

- Lymph vessels usually do not have a large basement membrane, which allows large molecules to enter that cannot be reabsorbed readily by the venous system



Lymphedema: Pathogenesis

- Once this *interstitial* fluid is absorbed, it moves through the lymphatic vessels and is considered lymph fluid
- As lymph fluid moves through the lymphatic system, it passes through Lymph Nodes that filter harmful substances



Lymphedema occurs when there is an interruption or obstruction of the lymphatic system that causes an accumulation of fluid in the limb

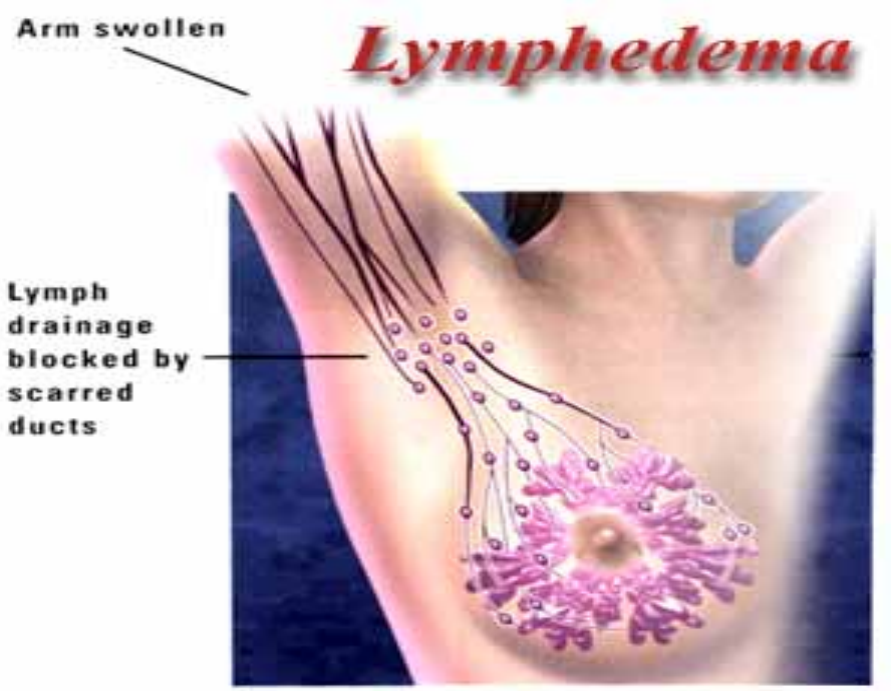


Image Source: Be a Survivor, By Vladmir Lange, M.D.

LINFEDEMA: Definizione

- **Lymphedema measurement**
  - Lymphedema defined as difference in arm circumference on the treated side:
    - **≥ 2cm on at least 2 visits**, when measured 15cm above or 10cm below the olecranon process.
  - Additional cases added per evaluation by a Physical Medicine and Rehabilitation specialist

LINFEDEMA: Definizione

Lymphedema Measurement

Diagnostic Criteria for Breast Cancer-Related Lymphedema

No universal standard definition

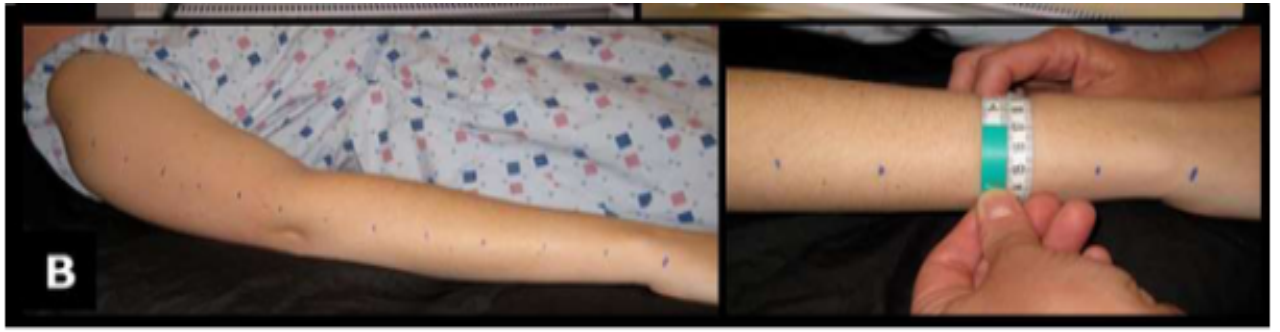
- **Absolute Circumference change >2 cm at 1 or 2 points**
- **Absolute volume change >200 mL**
- **Absolute volume difference >10%**
- **Relative volume change: >10%**
- **Bioimpedance Spectroscopy:**

  L-Dex score >10 or change of 10 from baseline

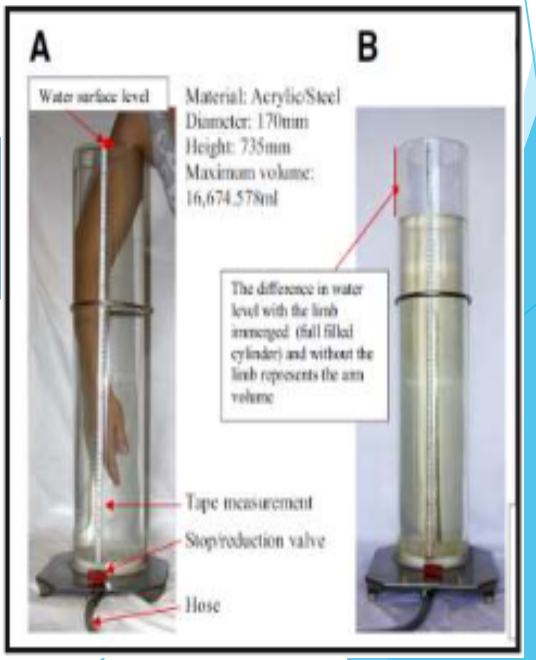
(Ancukiewicz et al 2012).

LINFEDEMA: Come si misura

- **MISURA della CIRCONFERENZA**: poca affidabilità



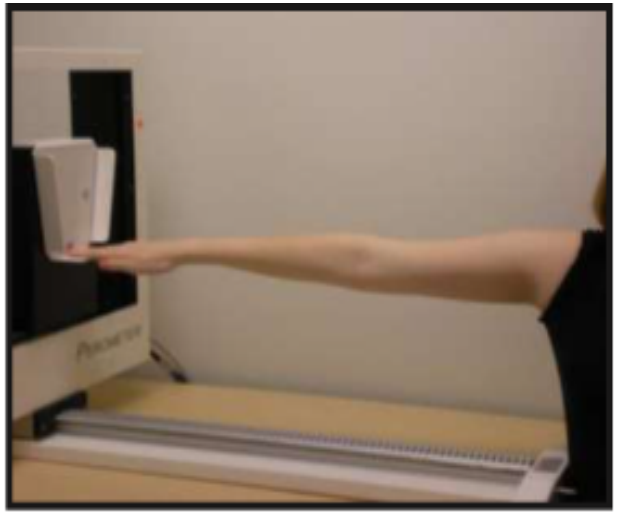
- **WATER DISPLACEMENT** : poco igienico



Ospedale San Pietro
FATEBENEFRATELLI

LINFEDEMA: Come si misura

- **PEROMETRO**: valutazione del volume a infrarossi



- **BIOIMPEDENZOMETRIA**: capacità di una corrente elettrica di passare attraverso il braccio per determinare la quantità di fluido extracellulare

Ospedale San Pietro
FATEBENEFRATELLI

Lymphedema: Imaging Diagnosis

Table 1 The role of imaging modalities in the management and planning of lymphoedema surgery

Modality	Benefits and indications
Doppler ultrasound	Mapping lymph node anatomy
Duplex ultrasound	Mapping lymph node anatomy; identificat for planning vascularised transfer
Computed tomography (CT)	Mapping lymph node anatomy
Computed tomographic angiography (CTA)	Mapping lymph node anatomy; identification of lymph node v for planning vascularized transfer
Magnetic resonance imaging (MRI)	Diagnosis of lymphoedema; mapping lymph node anatomy
Magnetic resonance angiography (MRA)	Mapping lymph node anatomy; mapping lymph node anatomy lymph node vascular anatomy for planning vascularized transfe
Magnetic resonance lymphangiography (MRL)	Diagnosis of lymphoedema; measurements and identificati vessel diameter and course
Indocyanine green (ICG) immunofluorescence	Identification of lymphatic vessel anatomy ar planning; intraoperative guidance
Lymphocyntigraphy	Useful for intraoperative guidance for 'reverse

Lymphedema: Clinical Diagnosis

A QUALITY OF LIFE MEASURE FOR LIMB LYMPHOEDEMA (LYMQOL)

Journal of Lymphoedema, 2010, Vol 5, No 1

Vaughan Keeley, Sue Crooks, Jane Locke, Debbie Veigas, Katie Riches, Rachel Hilliam

A specific quality of life scale in upper limb lymphedema : the ULL-27 questionnaire

R. Launois[1-2] ; A.C. Mègnigbêto[1-2] ; K. Pocquet[3] ; F. Alliot[4]

pisi, MH Witte, CL Witte (Ed) Progress in Lymphology XVIII International Congress of Lymphology – Sept. 2001. Genoa (Italy)
Lymphology 35 (Suppl): 1-760, 2002: 181-187

Physical Therapy
Journal of the American Physical Therapy Association

PTJ

Lymphoedema Functioning, Disability and Health Questionnaire (Lymph-ICF): Reliability and Validity
Nele Devoogdt, Marijke Van Kampen, Inge Geraerts, Tina Coremans and Marie-Rose Christiaens
PHYS THER. 2011; 91:944-957.
Originally published online April 14, 2011
doi: 10.2522/ptj.20100087

NIH Public Access
Author Manuscript
J Lymphoedema. Author manuscript; available in PMC 2010 June 8.

Published in final edited form as:
J Lymphoedema. 2007 October ; 2(2): 12–21.

SELF-REPORTED MANAGEMENT OF BREAST CANCER-RELATED LYMPHOEDEMA

Announcing: A New Lymphedema-Specific Outcor

Lymphology 48 (2015) 128-138

VALIDATION OF THE LYMPH
A CONDITION-SPECI
FOR PERSONS

J. W

CoxHealth Outpatient Rehabilitation (JW) a
Springfield, Missouri, USA

Patient Name _____

Listed below are symptoms or problems many individuals with lymphedema report. Please indicate to what extent these problems associated with your lymphedema have affected you in the past 2 weeks. If both limbs are swollen, compare symptoms in the swollen limbs to any non-swollen limbs.
Circle the number which best describes your symptom level.

I. Physical Concerns

1. The amount of pain associated with my lymphedema is:
2. The amount of limb heaviness associated with my lymphedema is:
3. The amount of skin tightness associated with my lymphedema is:
4. In comparison to my unaffected limb, the size of my swollen limb seems:
5. In comparison to my unaffected limb, the skin texture of my swollen limb feels:
6. Lymphedema affects movement of my swollen limb:
7. The strength in my swollen limb compared with the unaffected limb is:
8. How often have you become ill with an infection in your swollen limb requiring oral antibiotics or hospitalization in the past 2 YEARS?

II. Psychosocial Concerns

9. Lymphedema affects my body image (i.e. "How I think I look."):
hedema affects my socializing with others:
hedema affects my intimate relations:
hedema "gets me down" (i.e. I have feelings of depression, frustration, or anger due to the lymphedema.):

III. Functional Concerns

13. Lymphedema affects my ability to perform duties at home:
14. Lymphedema affects my ability to perform duties at work (if applicable):
15. Lymphedema affects my performance of preferred recreational activities:
16. Lymphedema affects the proper fit of clothing/shoes:
17. Lymphedema affects my sleep:
18. I must rely on others for help due to my lymphedema:

Circle of Hope
Lymphedema Foundation, Inc.

National Lymphedema Network:
www.lymphnet.org.

LINFEDEMA: Fattori di Rischio

- Tipo di chirurgia
- Terapia radiante
- Elevato BMI (Body Mass Index)
- Linfadenectomia ascellare (numero LNF correlato??)

Clinical Impact of the Randomized Trials

Before the Randomized Trials:

98% of patients with ≥4+ LN (Ceiley et al 2005)

40% of patients with 1-3 LN+ (Ceiley et al 2005)

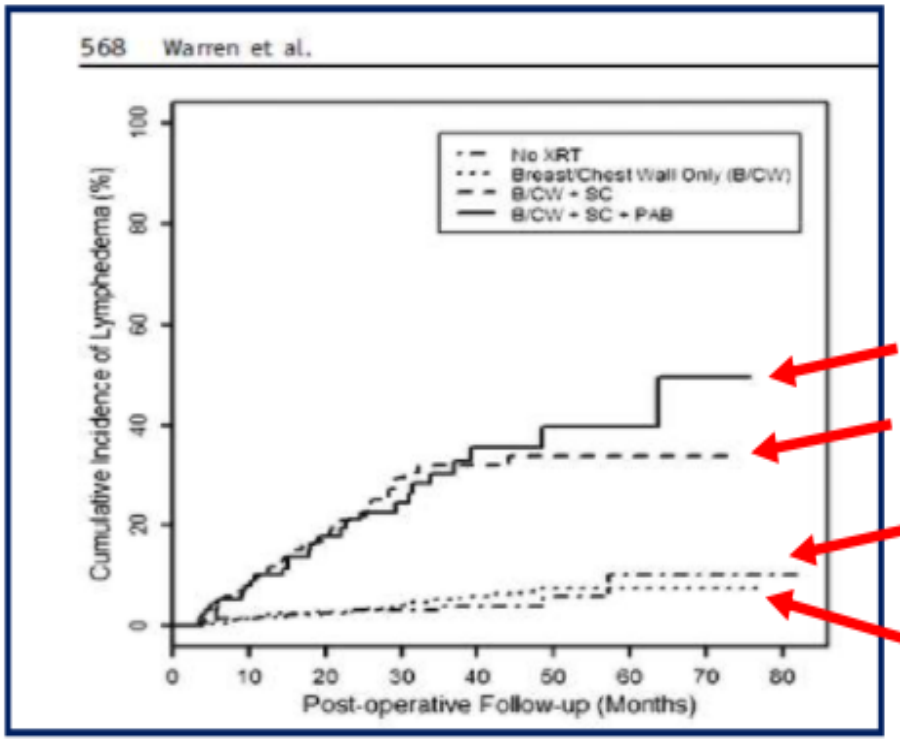
After the Randomized Trials:

Patients with 1-3 LN positive

Patients with high risk negative LN's

LINFEDEMA: Studi clinici

- Z0011
- AMAROS
- MA.20
- EORTC



Supraclavicular + axilla

Supraclavicular RT

Chest wall only radiation

No radiation at all

#ASTRO17

2017 ANNUAL MEETING | SAN DIEGO CONVENTION CENTER | SAN DIEGO

Ospedale San Pietro
FATEBENEFRATELLI

AMAROS (Lymph Nodes pos)

Phase III: positive SLN + RT vs ALND

- 4,823 patients

p<.0001

- Assessment of Lymphedema:

  Arm circumference at 15 cm above and 15 cm below medial epicondyle

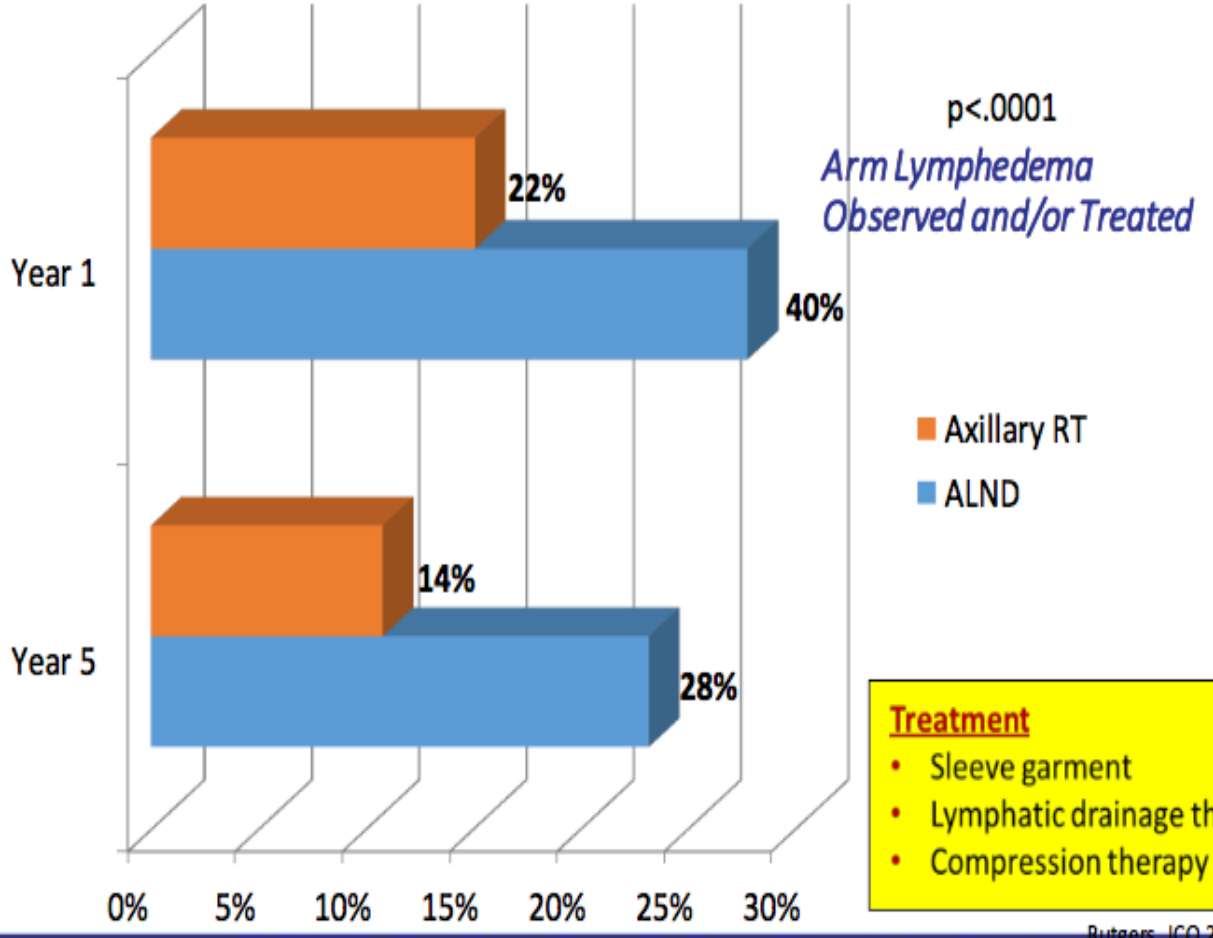
- Measurements at baseline, 1, 3, 5 and 10 years

- **Lymphedema definition: an increase in arm circumference of at least 10%**
  - No integration of the baseline
  - Not based on arm volume

Rutgers, JCO 2013

AMAROS (Lymph Nodes pos)

Phase III: SLN + RT vs ALND



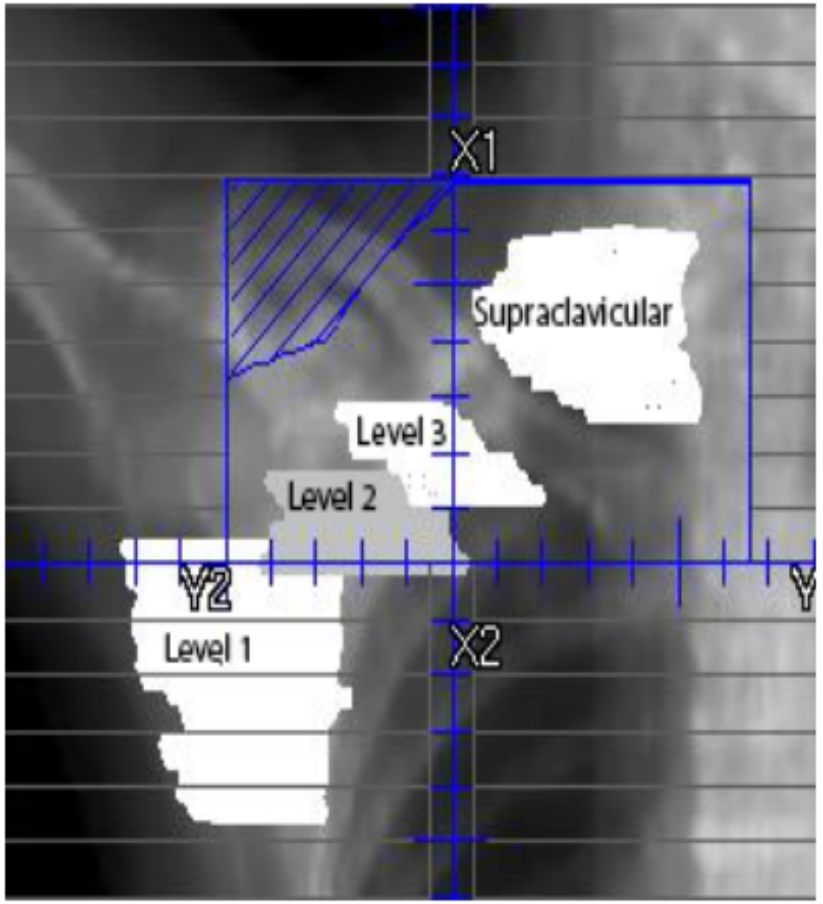
Treatment

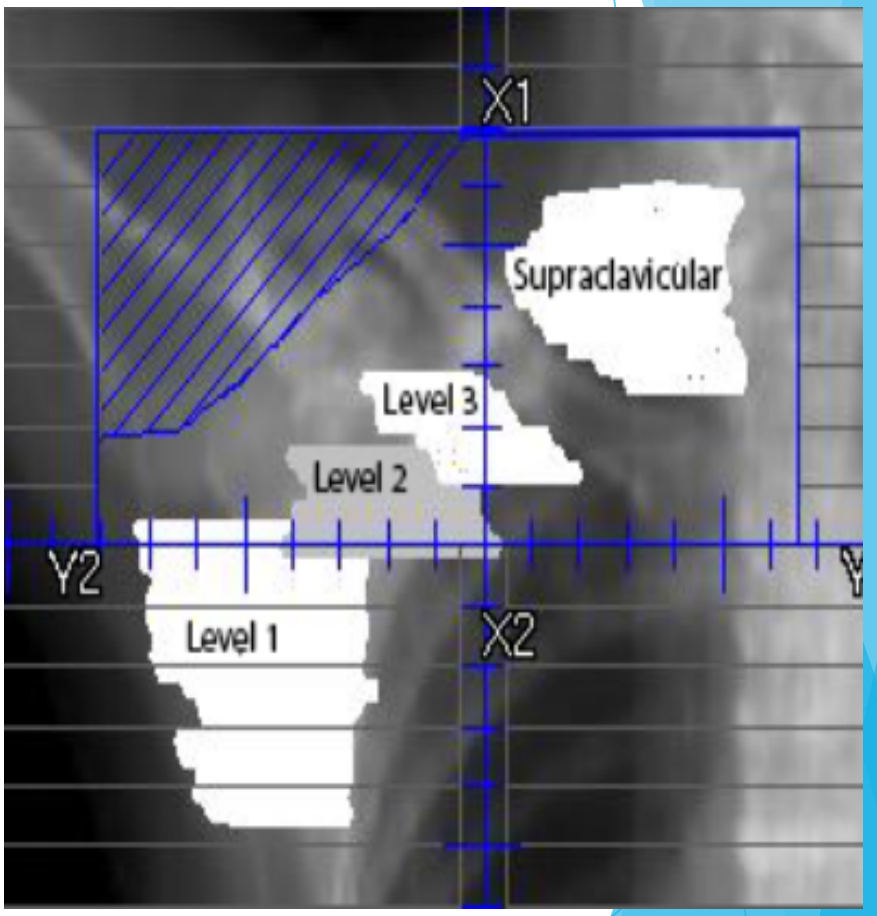
- Sleeve garment
- Lymphatic drainage therapy
- Compression therapy

Rutgers, JCO 2013

Ospedale San Pietro
FATEBENEFRATELLI

RT Field





Ospedale San Pietro
FATEBENEFRATELLI

Radiation Therapy Risk Factors for Development of Lymphedema in Patients Treated With Regional Lymph Node Irradiation for Breast Cancer

Ravi A. Chandra, MD, PhD,* Cynthia L. Miller, BS,† Melissa N. Skolny, MHSA,‡ Laura E.G. Warren, MD, EdM,* Nora Horick, MS,§ Lauren S. Jammallo, BS,‡ Betro T. Sadek, MD,‡ Mina N. Shenouda, MD,‡ Jean O'Toole, PT, MPH,‖ Michelle C. Specht, MD,¶ and Alphonse G. Taghian, MD, PhD†

2015

Table 3 Cumulative incidence of lymphedema at 24 months by type of regional radiation therapy

Location	Cumulative incidence (%) of lymphedema (95% confidence interval)
SC only	22.27 (15.13-32.07)
SC plus PAB	20.98 (11.30-37.03)
SC field lateral border	
<1/3 humeral head	19.50 (9.10-38.94)
1/3-2/3 humeral head	18.48 (8.05-39.19)
>2/3 humeral head	23.69 (15.83-34.56)

Abbreviations: PAB = posterior axillary boost; SC = supraclavicular.

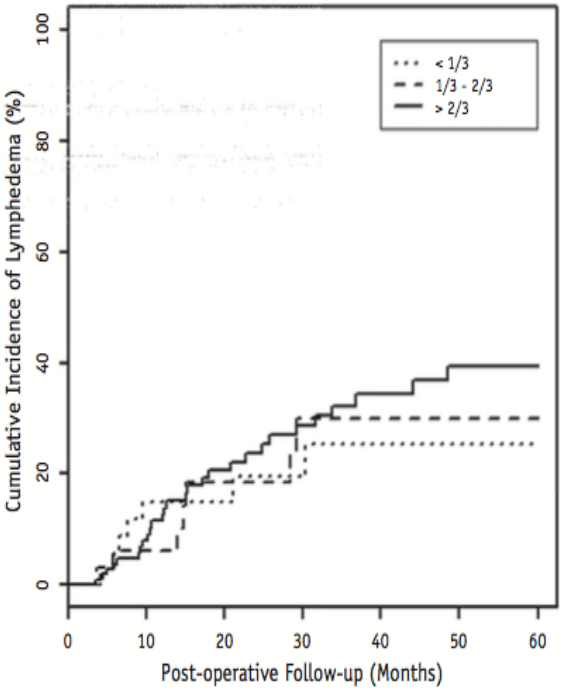


Fig. 1. Cumulative incidence of lymphedema stratified by lateral border (relative to humeral head) of the supraclavicular field.

Ospedale San Pietro
FATEBENEFRATELLI

Immediate Implant Reconstruction Is Associated With a Reduced Risk of Lymphedema Compared to Mastectomy Alone

A Prospective Cohort Study

Ann of Surg 2016

Cynthia L. Miller, BS, Amy S. Colwell, MD,† Nora Horick, MS,‡ Melissa N. Skolny, MSHA,* Lauren S. Jammallo, BS,* Jean A. O'Toole, MPH, PT,§ Mina N. Shenouda, MD,* Betro T. Sadek, MD,* Meyha N. Swaroop, BS,* Chantal M. Ferguson, BS,* Barbara L. Smith, MD, PhD,¶ Michelle C. Specht, MD,¶ and Alphonse G. Taghian, MD, PhD**

- 2005-2013
616 pts (891 mastectomies)

-prospectively screened for lymphedema with pre-op measurements
- Median FU 22.2 months

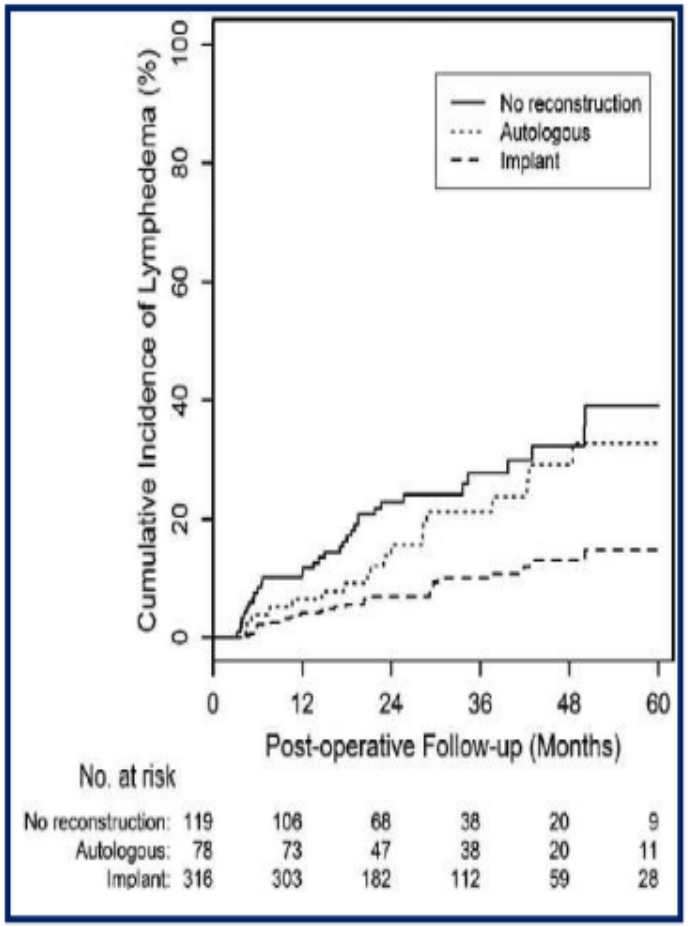
65% immediate implant
11% immediate autologous
24% no reconstruction

TABLE 3. Two-year Cumulative Incidence of Lymphedema (≥10% WAC) Overall and by Type of Immediate Breast Reconstruction

	N	2-yr Cumulative Incidence	95% CI
Entire cohort	891	10.58%	8.41%–13.27%
Immediate reconstruction	681	5.13%	3.50%–7.49%
Implant	580	4.08%	2.59%–6.41%
Autologous	101	9.89%	4.98%–19.13%
No reconstruction	210	26.66%	20.38%–34.43%

Reconstruction and Lymphedema

Lymphedema incidence (≥10%) by type of immediate breast reconstruction



Multivariate analysis of immediate breast reconstruction and lymphedema risk (≥10%)

	HR (95%)	P
BMI	3.4 (2.2 – 5.2)	<0.0001
ALND	7.5 (3.5 – 16.3)	<0.0001
# of LN dissected	1.03 (1.0 – 1.05)	0.03
Immediate Implant vs No reconstruction	0.35 (0.2 – 0.6)	<0.0001
Autologous vs No reconstruction	0.7 (0.4 – 1.2)	0.21

Stages of Lymphedema

Brunner Classification

Latency Stage Stage 0 *(pts at risk)*	Transport Capacity is reduced No visible edema Subjective complaints of heaviness, achiness
Stage 1 Reversible lymphedema	Accumulation of protein-rich edema Pitting <20% increase Reduces w/elevation (no fibrosis)
Stage 2 Spontaneously Irreversible Lymphedema	Accumulation of protein-rich edema Pitting becomes progressively difficult Fibrosis 20-40% increase
Stage 3 Lymphostatic Elephantiasis	Accumulation of protein-rich edema Fibrosis, sclerosis, skin changes, papillomas, hyperkeratosis (elephantiasis) > 40% increase

Evaluation Tools???

PREVENZIONE

NON CHIRURGICA

- FISIOTERAPIA (compreso il drenaggio linfatico manuale, il massaggio del tessuto cicatriziale, esercizi della spalla)

CHIRURGICA

- MAPPATURA INVERSA DELL'ASCELLA : alcuni studi hanno mostrato la possibilità di identificare e risparmiare il drenaggio linfatico del braccio nelle pazienti sottoposte a ALND o SLNB
- PROCEDURA LYMPHA (Lymphatic Microsurgical Preventing Healing Approach): è una anastomosi venosa-linfatica da eseguire al momento dell'ALND. I linfatici del braccio sono identificati iniettando una tintura blu nel braccio e il tessuto nodale viene rimosso come parte di un ALND. Successivamente, i linfatici del braccio precedentemente identificati sono anastomizzati ai rami della vena ascellare

LINFEDEMA: stadio subclinico

Stadio I: **linfedema SUBCLINICO**

- Non è clinicamente / visivamente evidente ma è misurabile oggettivamente.
- La pz riferisce dolenzia, pesantezza dell'arto e intorpidimento. Il fluido è ricco di proteine.
- Volume dell'arto aumentato del 3-5% rispetto al basale

TERAPIA

- Manicotto elastico (standard o personalizzato), 20-30 mmHg con **uso diurno** fino alla scomparsa del gonfiore

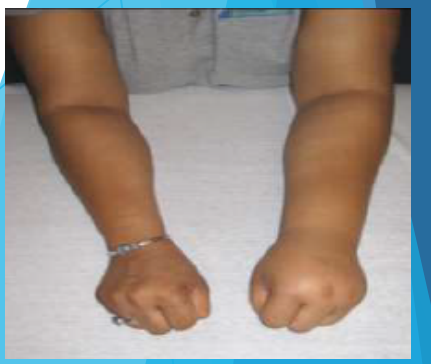
LINFEDEMA : stadio lieve e moderato

Stadio II: **linfedema LIEVE**

- Gonfiore clinicamente / visivamente evidente all'ispezione con oscuramento dell' architettura anatomica. La paziente riferisce pesantezza dell' arto, dolore, gonfiore e intorpidimento. Accumulo di fluido ricco di proteine. Il gonfiore si attenua con l'innalzamento dell'arto.
- Volume dell'arto aumentato del 5-8% rispetto al basale

Stadio III: **linfedema MODERATO**

- Alterazione visivamente apprezzabile dal normale contorno anatomico. La sola elevazione dell'arto raramente riduce il gonfiore del tessuto, poiché è presente fibrosi tissutale.
- Volume dell'arto >8% rispetto al basale



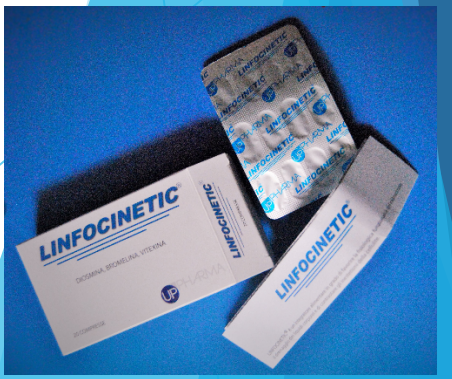
Ospedale San Pietro
FATEBENEFRATELLI

TRATTAMENTO (stadio lieve e moderato)

- Manicotto elastico (standard o personalizzato), 20-30 mmHg con uso continuo e regolare
- Terapia decongestionante: è un programma a due fasi che consiste in una fase di trattamento e una fase di mantenimento. La fase di trattamento dura 2-4 settimane nella durata e si compone di quattro componenti: cura della pelle e delle unghie, drenaggio linfatico manuale, compressione bendaggio ed esercizio fisico
- Agenti farmacologici → Linfadren® (Diosmina, Cumarina, Arbutina)

  → Linfocinetic® (Bromelina, Diosmina, Vitexina)

- Perdita di peso



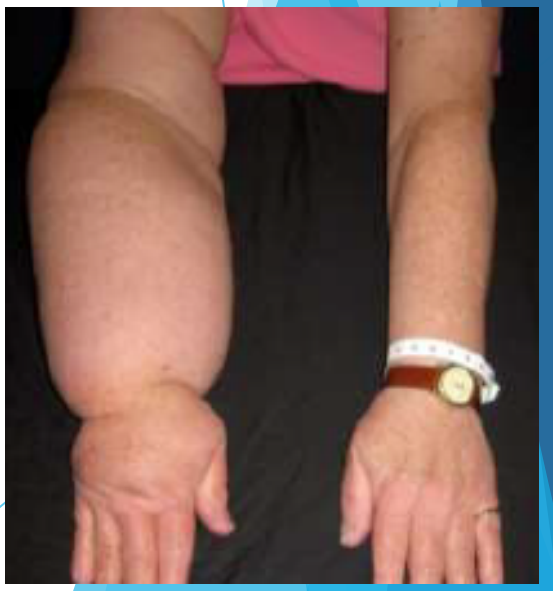
LINFEDEMA : Stadio severo e terminale

Stadio IV: **linfedema SEVERO**

- Obliterazione delle pieghe della pelle; deviazione evidente del normale contorno anatomico; elefantiasi linfostatica caratterizzata da marcata fibrosi tissutale e da cambiamenti della pelle, come ipercheratosi e crescita eccessiva verrucosa
- Volume dell'arto >8% rispetto al basale che limita le normali attività quotidiane

Stadio V: **END-STAGE**

- Quadro di linfangiosarcoma
- Interferisce con le attività della vita quotidiana



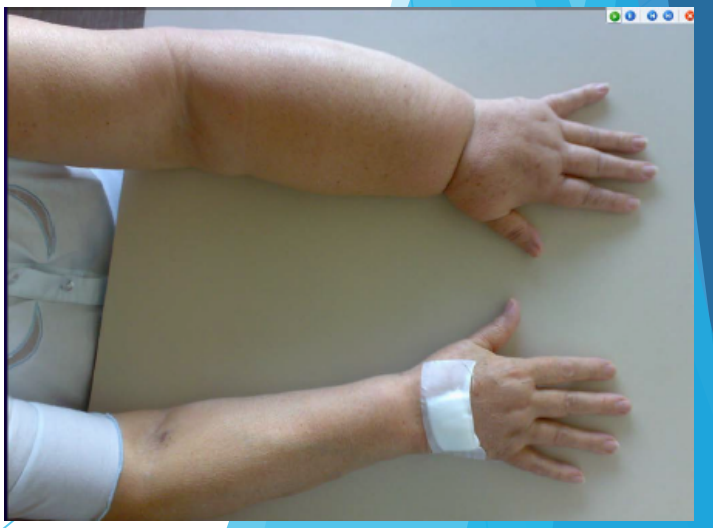
Ospedale San Pietro
FATEBENEFRATELLI

TRATTAMENTO (stadio avanzato)

CHIRURGICO

- ESCISSIONE: escissione radicale del tessuto sottocutaneo e l'innesto cutaneo per chiudere il difetto. Questi interventi chirurgici non affrontano la disfunzione linfatica sottostante, hanno lo scopo di ottimizzare il comfort della paziente e migliorare l'aspetto fisico attraverso la rimozione della pelle e dei tessuti ridondanti

- MICROCHIRURGIA LINFATICA: sono state descritte molte tecniche ricostruttive tra cui l'anastomosi linfatica (LVA) e il trasferimento linfonodale (LNT)



Ospedale San Pietro
FATEBENEFRATELLI

CONCLUSIONI

- Il malato oncologico ha una più lunga prospettiva di vita rispetto al passato e necessita di un approccio multidisciplinare che tenga conto del suo benessere psico-fisico tanto quanto dell'andamento della sua malattia

- L'alterazione della propria immagine corporea è uno dei fattori che interferisce maggiormente , in senso negativo, con la qualità di vita

- Prioritario diventa il controllo dermo-cosmetologico dei segni e sintomi cutanei che il paziente oncologico subisce dai trattamenti chemio e radioterapici

Grazie per l'attenzione !