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RADIOTERAPIA NELLE PAZIENTI ANZIANE

Paolo Rovea,Marina Guenzi,Laura Lozza,Alessandra Huscher,Maria Rosa Laporta,Giuse Gambaro,Claudia Fillini,Marco Gatti

Rapporter : Giuseppina Gambaro

Lancet Oncol 2012

Review

Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA)

Laura Biganzoli, Hans Wildiers, Catherine Oakman, Lorenza Marotti, Sibylle Loibl, Ian Kunkler, Malcolm Reed, Stefano Ciatto, Adri C Voogd, Etienne Brain, Bruno Cutuli, Catherine Terret, Margot Gosney, Matti Aapro, Riccardo Audisio

As the mean age of the global population increases, breast cancer in older individuals will be increasingly encountered in clinical practice. Management decisions should not be based on age alone. Establishing recommendations for management of older individuals with breast cancer is challenging because of very limited level 1 evidence in this heterogeneous population. In 2007, the International Society of Geriatric Oncology (SIOG) created a task force to provide evidence-based recommendations for the management of breast cancer in elderly individuals. In 2010, a multidisciplinary SIOG and European Society of Breast Cancer Specialists (EUSOMA) task force gathered to expand and update the 2007 recommendations. The recommendations were expanded to include geriatric assessment, competing causes of mortality, ductal carcinoma in situ, drug safety and compliance, patient preferences, barriers to treatment, and male breast cancer. Recommendations were updated for screening, primary endocrine therapy, surgery, radiotherapy, neoadjuvant and adjuvant systemic therapy, and metastatic breast cancer.

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Sandro Pitigliani Medical Oncology Unit, Istituto Toscano Tumori, Hospital of Prato, Prato, Italy (L Biganzoli MD, C Oakman MD); Department of General Medical Oncology, University Hospitals, Leuven, Belgium (H Wildiers MD); EUSOMA, Florence, Italy (L Marotti BSc); German Breast Group, University of Frankfurt, [illegible]

- Aumento età media della popolazione

  - Aumento numero donne anziane affette da carcinoma mammella

    - Limitati dati con livello evidenza 1 per questa eterogenea popolazione.

Lancet Oncol 2012

- 2007 SIOG (International Society of Geriatric Oncology) crea una task force per fornire raccomandazioni EBM per il trattamento delle donne anziane affette da carcinoma della mammella

- 2011 Task force SIOG ed EUSOMA composta da:
  oncologi medici
  radioterapisti oncologi
  chirurghi
  medici geriatri
  radiologi
  epidemiologi

- 2012 pubblicazione update e ampliamento raccomandazioni

Search strategy and selection criteria

Medline was the primary information source for this task force. A search of PubMed was done for English language articles published from 2007 to June, 2010, for the updated sections, and from 1990 to June, 2010, for the new sections. The search terms used were "breast neoplasms", "aged", "aged 80 and over", "frail elderly", "survival", "geriatric assessment", "mammography", "radiography", "mastectomy", "segmental", "lymph node excision", "sentinel lymph node biopsy", "radiotherapy", "neoadjuvant", "adjuvant", "secondary", "chemotherapy", "tamoxifen", "aromatase inhibitors", "pharmacology", "communication barriers", "communication", "information", and "male". Additional publications considered important by the task force were included. Randomised control trials, meta-analysis, retrospective studies, cohort studies, and reviews were included. Meeting abstracts from key international conferences were also included. The taskforce meeting was held July 1–2, 2010. Recommendations were initially prepared in small working groups and consensus was reached by whole group discussion. Publications and abstracts from key international meetings held between July, 2010, and manuscript finalisation in October, 2011, which were relevant to the topic were included by task-force members during manuscript preparation. Final consensus was reached by email refinements.

Lancet Oncol 2012

Raccomandazioni SIOG/EUSOMA

Age alone should not dictate any aspect of management for older individuals with breast cancer. All decisions should consider :

- physiological age
- estimated life expectancy
- potential risks vs absolute benefi ts
- treatment tolerance,
- patient preference
- potential barriers to treatment

Lancet Oncol 2012

TRATTAMENTO DEL CA MAMMELLA NELLE DONNE ANZIANE

Rischio di progressione e morte causata dal tumore

Rischio invalidità e morte per altre comorbidità

Effetti collaterali dei trattamenti (reversibili o irreversibili)

RISCHIO DI UNDERTREATMENT

Numerosi studi retrospettivi hanno dimostrato un tendenza al minore trattamento nelle donne anziane rispetto alle giovani in relazione a CHIRURGIA , RADIOTERAPIA, ORMONOTERAPIA e CHEMIOTERAPIA anche dopo aggiustamento per razza , istruzione , stadio,caratteristiche biologiche.

- **Discriminazione per l'età in se**
- **Gestione delle comorbidità e difficoltà relazionali**
- **Paura della tossicità dei trattamenti**
- **Minor risorse economiche e sociali delle anziane**

Giordano JCO 2005, Lancet 2012

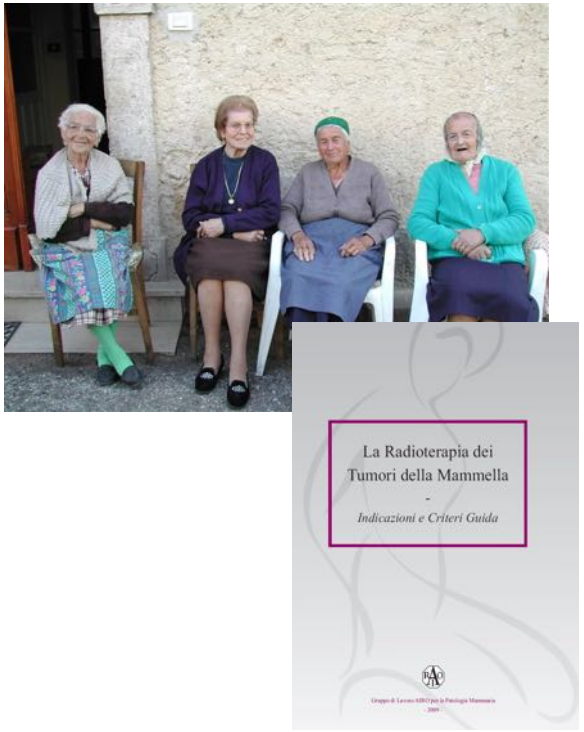
TRIAL CLINICI : SCARSA RAPPRESENTAZIONE

L'età avanzata è uno dei principali fattori che limita l'arruolamento di pazienti nei trial clinici.

Le donne anziane sono disponibili a partecipare ai trial clinici al pari delle donne più giovani, mentre gli oncologi sono riluttanti ad arruolare gli anziani, principalmente per paura della tossicità, della scarsa compliance e delle limitazioni logistiche/economiche/sociali.

Simon JCO 2004, Lewis JCO 2003 Kemeny JCO 2003

Cap. 4 - Tumore mammario nella donna anziana



4.1 Epidemiologia
4.2 Diagnosi e screening
4.3 Trattamento
- 4.3.1 Chirurgia
- 4.3.2 Radioterapia
- 4.3.3 Terapie sistemiche adiuvanti

Problematiche

Cosa si intende per anziana?
Importanza delle comorbidità!

corretto approccio diagnostico e terapeutico
- prescindere dall'età anagrafica,
- derivare da valutazione multidisciplinare
- (oncologica, internisticogeriatrica,sociale e psicologica)

DEFINIZIONE DI ANZIANA

- anziana “giovane” 65-75 anni
- anziana “vero” 76-85 anni
- “grande” anziana >85 anni

Raccomandazioni SIOG/EUSOMA

	2007 recommendations (SIOG)	Current recommendations (SIOG/EUSOMA)
General recommendations for all aspects of management	--	All management decisions for an older individual with breast cancer should consider: Physiological age Life expectancy Potential risks vs absolute benefits Treatment tolerance Patient preference Potential barriers to treatment
Competing causes of mortality	--	Relative breast-cancer survival is the preferred way to describe the outcome of older patients with breast cancer Assessment of comorbidity and function can predict likelihood of dying from non-breast cancer causes
Geriatric assessment	--	Collaborative geriatric and oncology management can optimise care General health and functional status can be captured in a multidomain geriatric assessment; however, it is unclear which elderly patients are most likely to benefit and which method is best A screening assessment is a reasonable first step in identifying patients that may benefit from an extended CGA Active intervention for CGA-identified reversible geriatric domains can reduce morbidity and mortality, and improve quality of life Serial geriatric assessment can identify incident deterioration, for which intervention might improve outcomes

Raccomandazioni SIOG/EUSOMA

Ductal carcinoma in situ (DCIS)	There are no strong data available for treatment of older women with DCIS Healthy older women with localised DCIS should be considered for BCS and postoperative radiotherapy

Ductal carcinoma in situ

Variability in study design and selection criteria makes the occurrence of ductal carcinoma in situ (DCIS) in elderly women difficult to assess. A French survey done in 2003–04 reported that 13·4% of women treated for DCIS were 70 years or older.[25] DCIS in elderly patients was mammographically detected in 83·8%, compared with 91·6% in younger women (p<0·0001).[25]

There is little outcome data for elderly women treated for DCIS. A meta-analysis confirmed significant benefit from adjuvant radiotherapy plus breast-conserving surgery (BCS) over BCS alone in women older than 50 years (10-year local recurrence rate [LRR] 10·8% *vs* 27·8%, respectively), without specific data in women older than 70 years.[26] However, the proportional benefit in reduced breast events in the adjuvant radiotherapy group increased significantly with age in 10-year cohorts including 60–69 years and 70 years or older (p=0·02). Despite lower LRR with radiotherapy, randomised trials have not shown a survival benefit from radiotherapy. Therefore, in older women, lower LRR should be weighed against harms of treatment and competing causes of mortality.

Correa ,2010

Raccomandazioni SIOG/EUSOMA

Surgery	Patients 70 years or older should be offered the same surgery as younger patients Standard of care is BCS plus WBRT, or mastectomy with or without postoperative radiotherapy Mastectomy is indicated for large or multifocal tumours not amenable to conservative excision, patients who are not fit for WBRT, and patients who prefer mastectomy to BCS plus WBRT ALND is indicated for clinically positive or highly suspected nodes, since nodal status can affect adjuvant therapy SLNB is a safe alternative to primary ALND in patients with clinically node negative disease. Need for ALND after positive SLNB is controversial	Patients 70 years or older should be offered the same surgery as younger patients Standard of care is BCS plus WBRT, or mastectomy with or without postoperative radiotherapy Mastectomy is indicated for large or multifocal tumours not amenable to conservative excision, patients who are not fit for WBRT, and patients who prefer mastectomy to BCS plus WBRT; ALND is indicated for clinically positive or highly suspected nodes In clinically node negative disease, axillary staging by SLNB with completion ALND for tumour-positive SLNB remains the standard of care. Omission of SLNB and completion ALND might be reasonable in some older patients (see text)

An alternative to completion ALND for SLN-positive disease is axillary irradiation, which is being investigated in the AMAROS trial. An early observation indicates that lack of knowledge of the extent of nodal involvement in the axillary irradiation group did not substantially affect administration of adjuvant systemic therapy, suggesting that axillary radiotherapy might be a reasonable option for older patients with positive SLN, avoiding the morbidity of ALND.[31]

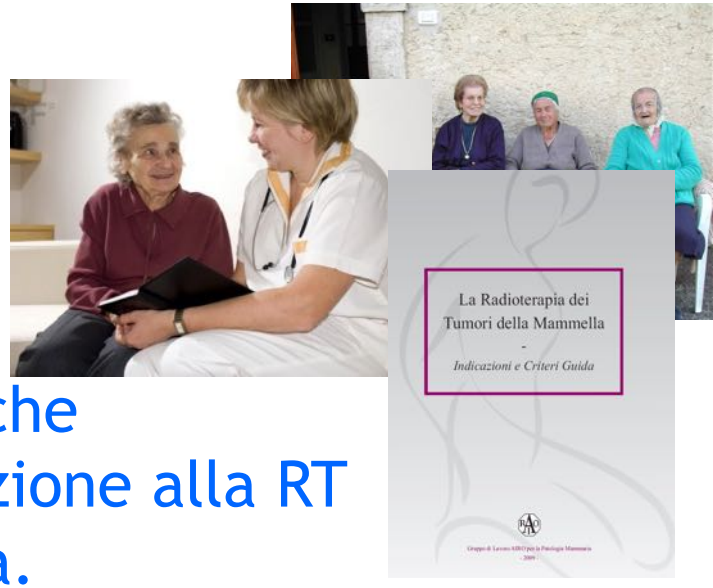
Thus, axillary staging by SLNB with completion ALND for SLN-positive disease remains the standard of care for elderly patients with clinically node-negative breast cancer. Further studies are needed before omission of completion ALND becomes standard of care. Omission of SLNB and completion ALND might be reasonable in some elderly patients, since ALND did not affect breast-cancer mortality and subsequent symptomatic axillary disease is rare.

JCO,2010

Raccomandazioni SIOG/EUSOMA

	2007 recommendations (SIOG)	Current recommendations (SIOG/EUSOMA)
Radiotherapy	WBRT after BCS, with a boost to the tumour bed, should be considered in all elderly patients since it decreases risk of local relapse (there is no evidence for an overall survival advantage in analyses restricted to elderly patients) Post-mastectomy chest-wall radiation should be considered for elderly patients with at least four nodes or a pT3/4 tumour The role of omission of postoperative WBRT, partial breast irradiation, and hypofractionation are undefined	WBRT after BCS, with a boost to the tumour bed, should be considered in all elderly patients since it decreases risk of local relapse. There is no subgroup of fit older patients in whom post-BCS WBRT can be systematically omitted (see text) Post-mastectomy chest-wall radiation should be considered for elderly patients with at least four nodes or a pT3/4 tumour Hypofractionated radiation schedules offer similar local-regional control and adverse effects as standard WBRT The evidence for PBI in older patients is not sufficiently robust to recommend it as standard therapy (see text)

Lancet 2012



Problematiche

A parità di stadiazione e di caratteristiche cliniche e anatomopatologiche l'indicazione alla RT è analoga alle pz delle altre fasce d'età.

RT ben tollerata
principale inconveniente del trattamento radiante post-operatorio rimane il tempo (e il disagio) legati al suo completamento.

considerare
ipofrazionamenti
APBI

→ Per ridurre il disagio

1- SI PUO' OMETTERE LA RADIOTERAPIA DOPO CHIRURGIA CONSERVATIVA?

Opinione controversa nelle pazienti anziane .
Molti trial randomizzati valutanti la RT escludono le pazienti con più di 70 anni.

STUDI RANDOMIZZATI BCS +RT IN DONNE ANZIANE BASSO RISCHIO (pT1-2,RE+,PR+)

TABLE 5

Randomized studies of postoperative radiotherapy after breast-sparing surgery in older women with favorable risk factors

Author	n	Fu	Stadium	Age	Treatment		DFS/BCSS		Overall survival		Local recurrence rate	
Fyles (21)	769	5 years	pT1pN0 ER + PR positive	50–59: 25% 60–69: 30% >70:44%	Breast-sparing surgery		DFS p = 0.004		n. s.		p<0.001	
					Tam	Tam + RT	+ RT 91%	– RT 84%	+ RT 93%	– RT 93%	+ RT 0.6%	– RT 7.7%
Hughes (e18)	636	10 years	pT1pN0 ER+PR positive	70–74: 44% ≥ 75: 56%	Breast-sparing surgery		BCSS n. s.		n. s.		p = 0.015	
					Tam	Tam + RT	+ RT 98%	– RT 96%	+ RT 63%	– RT 61%	+ RT 2%	– RT 9%
Pötter (e19)	869	4.5 years	pT1–2 pN0 ER+PR positive	50–59: 28% 60–69: 36% >79: 35%	Breast-sparing surgery		DFS p = 0.0021		n. s.		p = 0.0001	
					TAM/An	AM/An + RT	+ RT 97.9%	– RT 93.9%	+ RT 97.7%	– RT 96.2%	+ RT 0.5%	– RT 5.1%

Fu, Duration of follow-up DFS, disease-free survival; BCSS, breast cancer-specific survival; n. s., non-significant; Tam, tamoxifen; RT, radiotherapy; An, anastrozole; ER, estrogen receptor; PR, progesterone receptor

In tutti e tre gli studi la percentuale di Recidive Locali è più alta senza Radioterapia .
Nelle donne >70 anni (56%>75 anni) Hughes e coll.non evidenziano differenza di sopravvivenza e considerano il TAM sufficiente.
Gli altri due studi evidenziano una significativa riduzione nella «desease-free survival» senza Radioterapia.

Sautter-Bihi,Dtsch Arztzebl Int 2011

Health Technology Assessment 2011; Vol. 15: No. 12
ISSN 1366-5278

A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial

LJ Williams, IH Kunkler, CC King, W Jack and M van der Pol

Donne > 65 anni T1-2N0M0 : BCS +Ormonoterapia con o senza WBRT

RT ben tollerata anche dalle «oldest» senza alterare la qualità di vita e la sola età non può essere considerata il parametro principale per raccomandare o no la RT. Inoltre non va sottovalutato lo stato psicologico e la qualità di vita nel caso di recidiva

CONCLUSIONE

Non vi è sottogruppo di pazienti anziane «fit» nelle quali la WBRT possa essere sistematicamente omessa.
Tuttavia in assenza di benefici di sopravvivenza tale posizione va valutata in rapporto alle possibilità di accesso giornaliero e la preferenza della paziente in base al rischio di recidiva.

2 - IPOFRAZIONAMENTO

E’ possibile ridurre il numero di sedute di Radioterapia per le pazienti anziane ?

Published as: *Lancet Oncol*. 2008 April 01; 9(4): 331–341.

The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

Published as: *Lancet*. 2008 March 29; 371(9618): 1098–1107.

The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 1, pp. 59–68, 2011

0360-3016/$ – see front matter
doi:10.1016/j.ijrobp.2010.04.042

CLINICAL INVESTIGATION **Breast**

FRACTIONATION FOR WHOLE BREAST IRRADIATION: AN AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) EVIDENCE-BASED GUIDELINE

BENJAMIN D. SMITH, M.D.,* SOREN M. BENTZEN, PH.D., D.SC.,† CANDACE R. CORREA, M.D.,‡ CAROL A. HAHN, M.D.,§ PATRICIA H. HARDENBERGH, M.D.,¶ GEOFFREY S. IBBOTT, PH.D.,‖ BERYL MCCORMICK, M.D., FACR.,# JULIE R. MCQUEEN, CHES., RHED.,** LORI J. PIERCE, M.D.,†† SIMON N. POWELL, M.D., PH.D.,# ABRAM RECHT, M.D.,§§ ALPHONSE G. TAGHIAN, M.D., PH.D.,¶¶ FRANK A. VICINI, M.D., FACR.,‖‖ JULIA R. WHITE, M.D.,## AND BRUCE G. HAFFTY, M.D.***

*Department of Radiation Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX; †Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI; ‡Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; §Department of Radiation Oncology, Duke University Medical Center, Durham, NC; ¶Shaw Regional Cancer Center, Vail, CO; ‖Department of Radiation Physics, University of Texas M. D. Anderson Cancer Center, Houston, TX; #Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; **Oncology Patient Navigator, Duke Raleigh Cancer Center, Durham, NC; ††Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; §§Department of Radiation Oncology, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA; ¶¶Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA; ‖‖Department of Radiation Oncology, Beaumont Cancer Institute, Royal Oak, MI; ##Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI; and ***Department of Radiation Oncology, Cancer Institute of New Jersey, New Brunswick, NJ

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Jean-Philippe Pignol, M.D., Mark N. Levine, M.D., Jim A. Julian, Ph.D., Robert MacKenzie, M.D., Sameer Parpia, M.Sc., Wendy Shelley, M.D., Laval Grimard, M.D., Julie Bowen, M.D., Himu Lukka, M.D., Francisco Perera, M.D., Anthony Fyles, M.D., Ken Schneider, M.D., Sunil Gulavita, M.D., and Carolyn Freeman, M.D.

Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial

J Roger Owen, Anita Ashton, Judith M Bliss, Janis Homewood, Caroline Harper, Jane Hanson, Joanne Haviland, Soren M Bentzen, John R Yarnold

Studies of hypofractionation versus standard fractionation WBRT

	Inclusion criteria	Treatment: hypofractionation versus WBRT	Local recurrence rate	Comment
Bentzen et al; START A (2008)[37]	BCS or mastectomy	39 Gy in 13 fractions over 5 weeks versus 41·6 Gy in 13 fractions over 5 weeks versus 50 Gy in 25 fractions over 5 weeks	5·2% (5 year) 3·5% (5 year) 3·6% (5 year)	..
Bentzen et al; START B (2008)[38]	BCS or mastectomy	40 Gy in 15 fractions over 3 weeks versus 50 Gy in 25 fractions over 5 weeks	2·2% (5 year) 3·3% (5 year)	Better breast cosmesis with hypofractionation
Whelan et al; Canadian trial (2010)[39]	BCS, TI–2N0M0, clear resection margins	42·5 Gy in 16 fractions over 3 weeks versus 50 Gy in 25 fractions over 5 weeks	6·2% (10 year) 6·7% (10 year)	No significant difference in breast cosmesis and late cardiotoxicity between treatment groups

WBRT=whole-breast radiotherapy. BCS=breast-conserving surgery.

Controllo locale equivalente al frazionamento standard

Non maggiore tossicità

PARTIAL BREAST IRRADIATION

Solo nello studio randomizzato TARGIT–A sono ben rappresentate le donne anziane con percentuali di recidive locali do 0,95% e 1.2% rispettivamente con PBI e WBRT.

ELIOT : riporta 2.3% recidive dopo 36 mesi FW mediano

Non sufficiente evidenza nelle pazienti anziane da raccomandarne il trattamento come standard therapy.
Ragionevole indicazione per le pazienti anziane con difficoltà al trattamento standard,raccomandato consenso informato.