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BOLOGNA, 5-6 maggio 2010

Sovradiagnosi e SOVRATRATTAMENTO dai dati disponibili

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Sovradiagnosi e sovratrattamento : dai dati disponibili !!!

BMC Women's Health

BioMed Central

Commentary

The overdiagnosis nightmare: a time for caution

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Abstract

Overdiagnosis (and overtreatment) of cancers not bound to become symptomatic during lifetime is an unavoidable drawback of mammography screening. The magnitude of overdiagnosis has been

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ORIGINAL PAPER

Estimates of overdiagnosis of invasive breast cancer assoc with screening mammography

Stephen Morrell · Alexandra Barratt · Les Irwig · Kirsten Howard · Corné Biesheuvel · Bruce Armstrong

Received: 5 March 2009 / Accepted: 20 October 2009 / Published online: 6 November 2009

Abstract

Purpose To estimate the extent of overdiagnosis of invasive breast cancer associated with screening in New South Wales, Australia, a population with a well-established mammography screening program which has achieved full geographic coverage.

Methods We calculated overdiagnosis as the observed annual incidence of invasive breast cancer in NSW in 1999–2001 (a screened population) minus the expected annual incidence in this population at the same time, as a percentage of the expected incidence. We estimated expected incidence without screening in 1999–2001 from the incidence of invasive breast cancer in: (1) women in unscreened age groups (interpolation method); and (2) women in all age groups prior to the implementation of screening (extrapolation method). We then adjusted these estimates for trends in

major risk factors for breast cancer t
with the introduction of mammogra
ing obesity, use of hormone replacen
nulliparity. Finally, we adjusted fo
estimates of expected incidence in l
compared with the observed incid
calculate overdiagnosis of breast c
screening.

Results Overdiagnosis of invasive b
69 year NSW women was estimated
the interpolation and extrapolation m

Conclusion Overdiagnosis of in
attributable to mammography scr
substantial. Our estimates are simi
from other screening programmes.
greater attention in research and
health policy making.

Keywords Breast cancer incidenc
Mammography screening · Overdia

This is original work. Earlier iterations of it have been presented at research gatherings and symposia.

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Introduction

The incidence of breast cancer (dc
(DCIS) and invasive breast cancer)
over the past 20 years [1, 2], in para
of screening mammography. While
well accepted as a consequence of
ing [3], overdiagnosis of invasive
controversial and more counterint
plausible that overdiagnosis of invas
occur through extension of the "l
screening which is the tendency of
aggressive or even inconsequentia

Open A

BMJ

Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends

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doi:10.1136/bmj.b2587

ABSTRACT

Objective To estimate the extent of overdia
detection of cancers that will not cause dea
symptoms) in publicly organised screening

Design Systematic review of published tren
incidence of breast cancer before and after
introduction of mammography screening.

Data sources PubMed (April 2007), referen

RESEARCH

Review

Overdiagnosis and overtreatment of breast cancer

Estimates of overdiagnosis from two trials of mammographic screening for breast cancer

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Breast Cancer Research 2005, **7**:258-265 (DOI 10.1186/bcr1354)

Abstract

Randomised controlled trials have shown that the policy of mammographic screening confers a substantial and significant reduction in breast cancer mortality. This has often been accompanied, however, by an increase in breast cancer incidence, particularly during the early years of a screening programme, which has led to concerns about overdiagnosis, that is to say, the diagnosis of disease that, if left undetected and therefore untreated, would not become symptomatic. We used incidence data from two randomised controlled trials of mammographic screening, the Swedish Two-county Trial and the Gothenburg Trial, to establish the timing and magnitude of any excess incidence of invasive disease and ductal carcinoma *in situ* (DCIS) in the study groups, to ascertain whether the excess incidence of DCIS reported early in a screening trial is balanced by a later deficit in invasive disease and provide explicit estimates of the rate of 'real' and non-progressive 'overdiagnosed' tumours from the study groups of the trials. We used a multistate model for overdiagnosis and used Markov Chain Monte Carlo methods to estimate the parameters. After taking into account the effect of lead time, we estimated that less than 5% of cases diagnosed at prevalence screen and less than 1% of cases diagnosed at incidence screens are being overdiagnosed. Overall, we estimate overdiagnosis to be around 1% of all cases diagnosed in screened populations. These estimates are, however, subject to considerable uncertainty. Our results suggest that overdiagnosis in mammography screening is a minor phenomenon, but further studies with very large numbers are required for more precise estimation.

Introduction

Randomised controlled trials have shown that the policy of mammographic screening confers a substantial and significant reduction in breast cancer mortality [1-3]. There is continuing interest in the human costs associated with the mortality benefit, in particular, whether overdiagnosis occurs in breast cancer screening and, if so, its magnitude [4,5]. In this context, overdiagnosis means the diagnosis of cancer as a result of screening, usually histologically confirmed, that would not have arisen clinically during the lifetime of the host had screening not taken place.

When a mammographic screening programme is initiated, usually a large increase in breast cancer incidence is observed in the early years of the programme, and a relatively small increase later [4,6]. This in itself is not sufficient to imply overdiagnosis, for the following reasons:

1. In most parts of the world, breast cancer incidence was increasing prior to the epoch of mammography. Thus at least part of any excess incidence observed in the screening epoch is probably due to an existing increasing trend in incidence.
2. In addition, the early diagnosis of cancers due to lead time may exacerbate the underlying temporal increase by bringing forward in time future higher rates of disease.
3. In relation to this, screening also causes an artificial increase in age-specific incidence. With two years lead time on average, we would observe age 52 incidence at age 50, and so on.
4. There will be a substantial excess in incidence in the first few years of the programme due to the prevalence screen: large numbers of asymptomatic tumours in the prevalence pool will have their diagnosis date brought forward to the time of the prevalence screen.

Review

Overdiagnosis and overtreatment of breast cancer

Overdiagnosis in randomised controlled trials of breast cancer screening

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Breast Cancer Research 2005, **7**:230-234 (DOI 10.1186/bcr1314)

Abstract

Data from randomised controlled trials of mammographic screening can be used to determine the extent of any overdiagnosis, as soon as either a time equivalent to the lead-time has elapsed after the final screen, or the control arm has been offered screening. This paper reviews those randomised trials for which breast cancer incidence data are available. In recent trials in which the control group has not been offered screening, an excess incidence of breast cancer remains after many years of follow-up. In those trials in which the control arm has been offered screening, although there is a possible shift from invasive to *in situ* disease, there is no evidence of overdiagnosis as a result of incident screens.

Introduction

Overdiagnosis in mammographic screening is taken here to mean the diagnosis of invasive or *in situ* breast cancer that, in the absence of screening, would not have presented clinically during the woman's lifetime.

In studying overdiagnosis, randomised controlled trials have the advantage that data on the incidence of breast cancer in the intervention and control arms are usually available in detail at an individual level. Overdiagnosis of both ductal carcinoma *in situ* (DCIS) and invasive cancer may occur; however, it is not easy to determine to what extent an excess of DCIS is due to stage-shifting from invasive disease, although estimates can be made where sufficiently detailed information is available [1]. Most trials have provided relatively little information on the treatment of breast cancer cases, so that the extent of overtreatment is difficult to quantify.

Overdiagnosis can be studied in randomised controlled trials by comparing the cumulative incidence of breast cancer in the intervention and control arms at different times from date of entry or randomisation. While screening is continuing in the intervention arm of a trial, incidence in that arm will be increased because of the advancement of diagnosis by the lead-time in screen-detected cancers, as well as by any overdiagnosis. This 'prevalence peak' will be followed by a corresponding decrease once screening ceases. Overdiagnosis can therefore be estimated only after a time equivalent to the lead-time has elapsed following the final screen. In several trials, women in the control arm have subsequently been offered screening. Once this has occurred, only overdiagnosis due to incident, not prevalent, screens would be observable, because women in both arms of the trial would be subject to any overdiagnosis occurring at prevalent screens.

The extent of any overdiagnosis in trials of breast screening may be affected by the 'intensity' of screening (one or two views, modalities employed, screening frequency and recall policy), and by the uptake of screening in the intervention arm. It may also depend on the age range of women included in the trial, both because of variation in the natural history of the disease with age and because of increased mortality from other causes in older women during the 'lead-time' before a screen-detected cancer would have presented clinically. The extent to which overdiagnosis is observed will also depend on the extent of 'contamination' in the control arm by opportunistic screening.

Method

This review considers those randomised trials that include screening by mammography (with or without clinical examination). There are eight randomised controlled trials of mammography that have so far completed and reported mortality results, and for which data on breast cancer

SOVRATRATTAMENTO

SOVRADIAGNOSI

Lesioni che non si sarebbero mai rilevate clinicamente (o **per assenza di evolutività** , o per una una lenta progressione o per decesso per altre cause) se la paziente non avesse partecipato allo screening

SOVRATRATTAMENTO

SOVRADIAGNOSI

In cosa si traduce l'overdiagnosi e cosa si intende per sovratrattamento e per chi

Per la donna ?

Per il chirurgo

per l'epidemiologo ?

È evidente che il concetto di **sovradiagnosi** è più un **concetto epidemiologico**, che si misura sulla popolazione invitata a screening, e **non un concetto clinico che si può misurare sul singolo individuo.**

Quando viene fatta una diagnosi di tumore della mammella in fase iniziale **non è possibile mai astenersi da qualsiasi terapia** in quanto non si sa, in quel specifico caso, quale sarà la sua evoluzione clinica.

L'introduzione di terapie sempre meno aggressive e una **corretta valutazione biologica della neoplasia** potrebbe consentire comunque di **evitare trattamenti eccessivi** per alcuni tumori che forse non sarebbero mai comparsi clinicamente, se non diagnosticati nella fase preclinica grazie allo screening.

N° 48 - 2006 ● ATTUALITÀ IN SENOLOGIA

A CURA DI E. PACI, M. ROSSELLI DEL TURCO

- Sovratrattamento quantitativo
- Sovratrattamento qualitativo

"FALSI ALLARMI"

Necessità di approfondimenti diagnostici, anche invasivi (FNA, Core Biopsy)
Impatto fisico, ma soprattutto psicologico

FALSI POSITIVI

Necessità di un intervento chirurgico

SOVRATRATTAMENTO QUANTITATIVO

La lesione benigna diagnosticata e operata in corso di screening rappresenta un esempio perfetto di sovrattrattamento quantitativo , tuttavia anche dai dati GISMA ciò è vero solo per quel 50 % circa di lesioni benigne non evolutive (che andavano diagnosticate in maniera non invasiva)

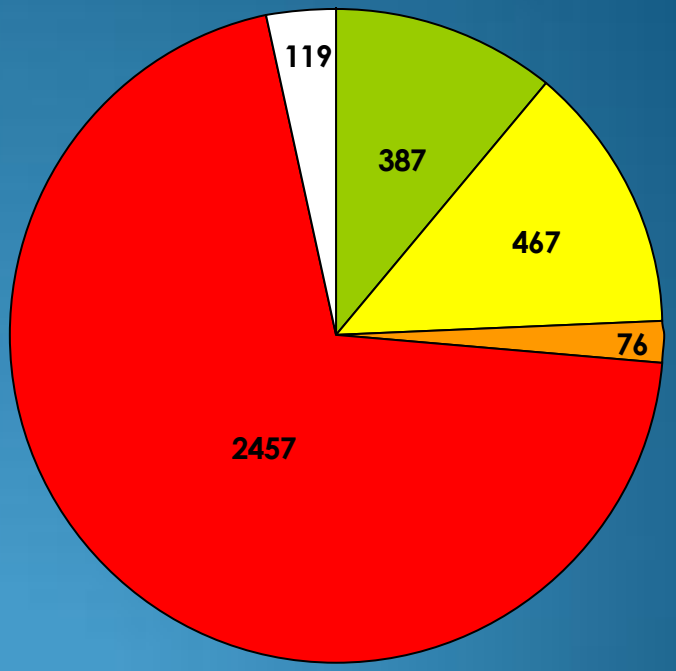
Problematiche
“indecisione “anatomo-patologo
Pressing chirurgo
Spauracchio medico-legale

Escissione chirurgica

Diagnosi istopatologica definitiva

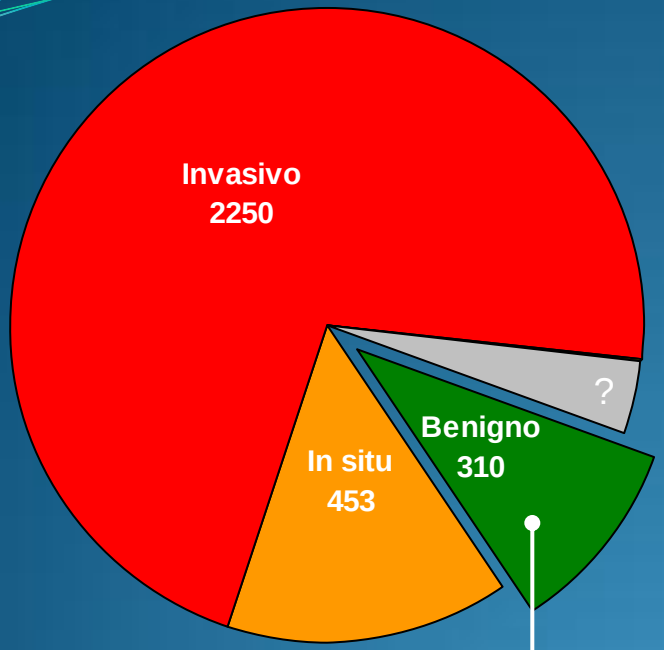
Dati: SQTM Screening Italia 2008

	N.	%
Benigno	387	11.0
In situ	467	13.3
Microinvasivo	76	2.2
Invasivo	2457	70.1
Ignoto	119	3.4
Totale	3506	100

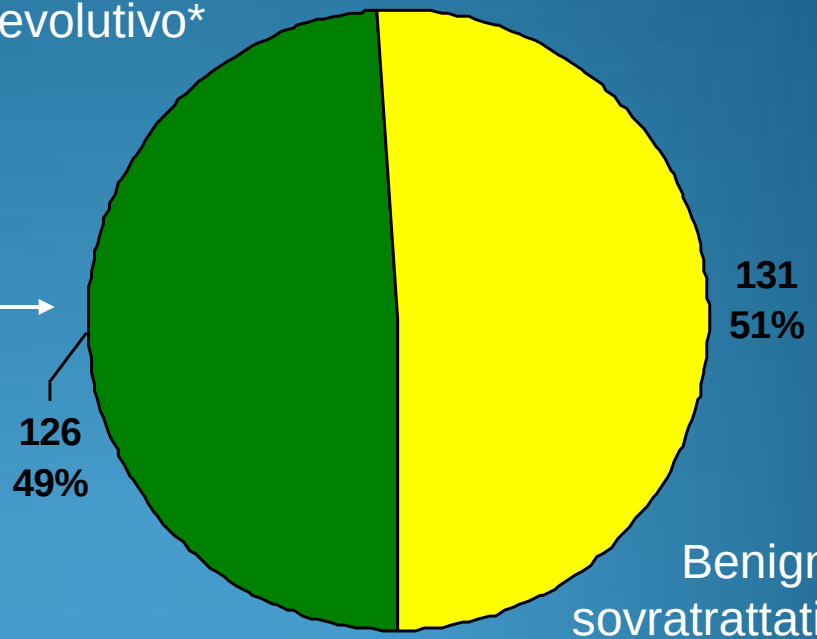


GISMa/ONS 2009

Diagnosi istologica delle lesioni di screening – Italia GISMa 2007



Benigni a rischio evolutivo*



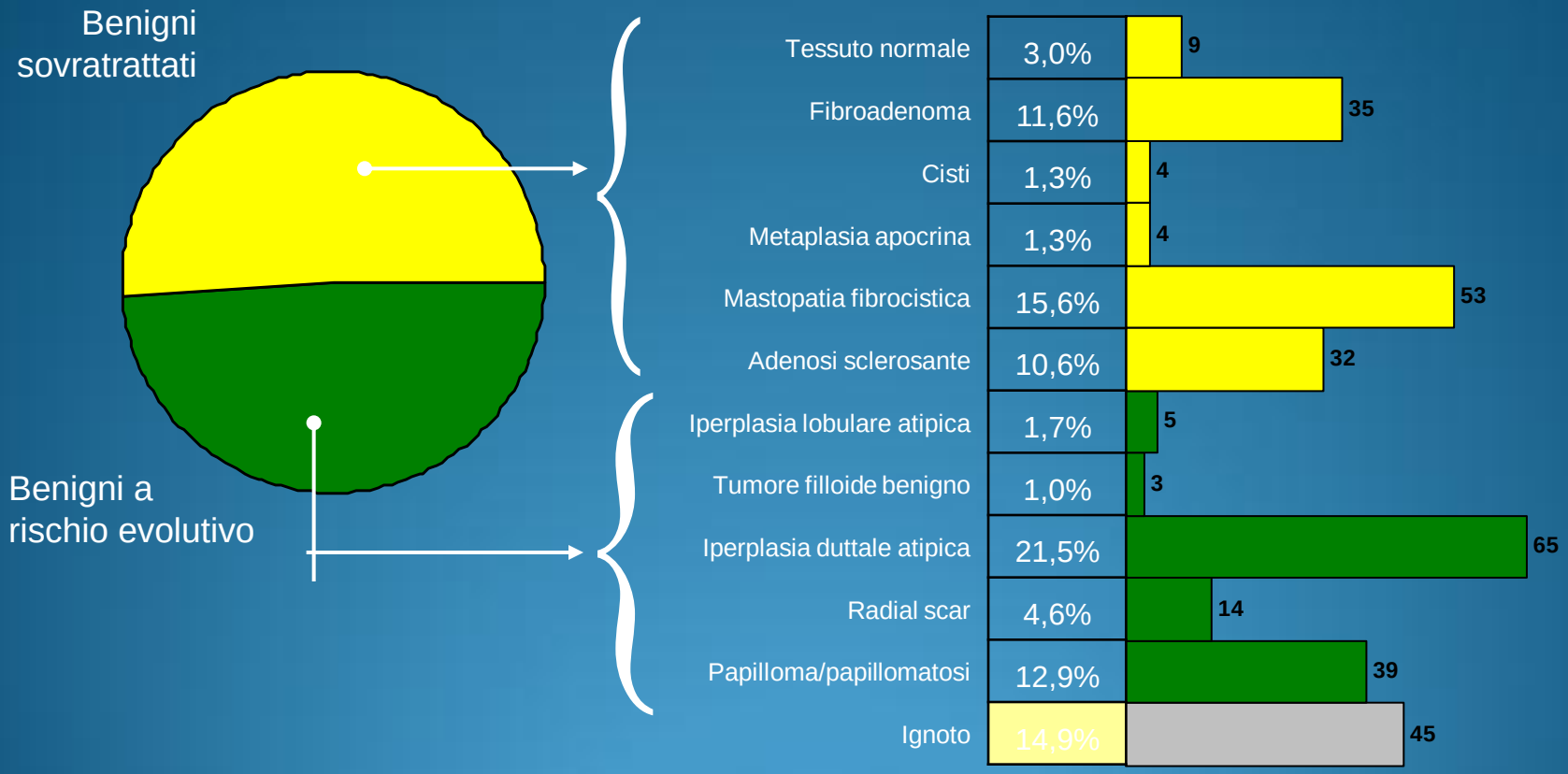
Benigni sovratrattati*

B/M = 0.11

* La somma non fa 310 perché sono state escluse le lesioni sincrone

Dati: SQTM Italia Screening 2007

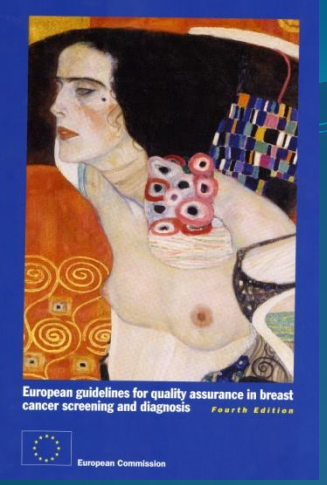
Tipo istologico delle lesioni benigne - Italia GISMa 2007



Dati: SQTM Italia Screening 2007

Diagnosi preoperatoria nei benigni - Italia 2007

	U/R1	U/R2	U/R3	U/R4	U/R5
C/B1	1		1		
C/B2	1	2	3		
C/B3	5	17	80	12	4
C/B4	16	14	47	21	4
C/B5	1	1	1	2	1



B3. Lesion of uncertain malignant potential

This category mainly consists of lesions which **may provide benign histology on CB**, but either are known to

- show **heterogeneity** or
- to have an **increased risk (albeit low) of associated malignancy.**

sovradiagnosi ⟵ sottodiagnosi

LIN (regrouping ALH and LCIS) should be classified as B3: this process does not necessarily have the same management implications as a diagnosis of DCIS but surgical diagnostic excision might be considered.

Surgical excision is not mandatory when flat epithelial atypia is found as the most advanced lesion on vacuum-assisted core biopsy performed for low radiological risk calcifications

Columnar cell lesions associated with breast calcifications on vacuum-assisted core biopsies: clinical, radiographic, and histological correlations

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Sovratrattamento per falsi positivi

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journal homepage: www.ejconline.com

Screen-detected breast lesions with malignant needle core biopsy diagnoses and no malignancy identified in subsequent surgical excision specimens (potential false-positive diagnosis)

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Screen-detected breast lesions
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ABSTRACT

Although breast needle core biopsy (NCB) is now a standard diagnostic procedure in the triple assessment of screen-detected breast lesions, data on the false-positive diagnoses of malignancy (malignant NCB 'B5' with normal/benign surgery) are lacking. In this study, we have studied a large series of NCBs (101,440) to assess the causes and pitfalls resulting in false-positive NCB diagnoses and to evaluate their impact on patients' management in the screening service. Our results showed that of 40,395 malignant NCBs reported during the period of this study, 174 NCBs are considered as false-positives (0.43%; (95% confidence interval [CI] = 0.37–0.49%)). However, on review, 165 cases (95%) were found to be the result of true removal of the whole lesion in the core with subsequent negative excision biopsy samples (true-positive NCBs). This may reflect sampling of small screen detected lesions and the use of larger core biopsies at assessment. The remaining 9 cases were considered as true false-positive cores, giving a false-positive rate of 0.02% (95% CI = 0.01–0.04%). Analysis of these 9 cases showed that 8 cases, originally diagnosed as DCIS, were classified as borderline lesions or lesions of uncertain malignant potential after surgical excision. The classification and management of such borderline lesions remains controversial and diagnostic surgical excision is usually the optimum management. One case was the result of pathological misinterpretation of fat necrosis as invasive carcinoma. This was the only case that resulted in a significant over-management of the patient. In conclusion, our results showed that the true false-positive rate of NCB is extremely rare. Significant over-management of screen-detected breast lesions as a result of false-positive NCB may be considered almost nil.

REPORTING, RECORDING AND AUDITING B5 CORE BIOPSIES WITH NORMAL/BENIGN SURGERY

NHSBSP Good Practice Guide No 9
November 2007

- Therefore, the total number of false-positive NCBs included in this study was 174 cases giving a false-positive rate of 0.4% (95% confidence interval [CI] = 0.37–0.49%).

- True false-positive NCB (lesions on the NCB did not justify the inclusion in the B5 category); this was identified in 9 cases; 8 were reported as B5a and 1 as B5b. All these 9 cases were subjected to external review and the NCBs were re-diagnosed as follows:
  - Eight cases were down-graded from B5a (DCIS) to either B3 or B4 as follow
  - One case was misinterpreted on histology and was diagnosed as fat necrosis

Sovratrattamento quantitativo

- Diffusione diagnosi preop (non -operatoria"!!)
- Affinamento tecniche (evoluz.tec. VACB)
- Esperienza operatori (rad/anapat/chir)

Limiti :

-interpretazione anatomo-patologica x les. border line

- impossibilità/ difficoltà nell'identificazione del potenziale evolutivo delle lesioni di basso grado

Sovratrattamento quantitativo

Lesioni neoplastiche non evolutive, indolenti, o a potenziale maligno limitato

- DCIS a basso grado

- Carcinomi infiltranti di piccole dimensioni, scoperti dallo screening, non palpabili, G1,TUBULARI, in over 65 anni, o con importanti comorbidità.

Review

Overdiagnosis and overtreatment of breast cancer

Progression of ductal carcinoma *in situ*: the pathological perspective

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The latter studies, which are biased towards lower-grade lesions, show that, untreated, up to 50% of DCIS lesions progress to invasive disease, and that the time for progression may be up to four decades Saunders ME et al, Cancer 2005Collins LC, Cancer 2005

Taken together, these studies suggest that whilst progression to invasive disease is more rapid in high-grade DCIS, all grades have significant potential to progress.

The challenge is to define better ways of quantifying the risk of progression for individual lesions in order to better tailor treatment decisions.

Jones JL, BCR 2006

Identificazione potenziale evolutivo DCIS

Barnes and colleagues [20] have recently reported the independent prognostic value of HER4 expression in DCIS.

Barnes NLP et al, Clin CancerRes 2005

Whether HER4 expression can contribute to the recognition of a subgroup of DCIS with better prognosis remains to be established and will require larger long-term studies and, in particular, greater numbers of lower grade lesions.

Jones JL, BCR 2006

Identificazione potenziale evolutivo DCIS

ORIGINAL ARTICLE

2009

Prognostic Significance of Oncogenic Markers in Ductal Carcinoma In Situ of the Breast: A Clinicopathologic Study

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Modern Pathology (2006) 19, 617–621

www.modernpathology.org

The Prognostic Significance of Multiple Morphologic Features and Biologic Markers in Ductal Carcinoma In Situ of the Breast

A Study of a Large Cohort of Patients Treated with Surgery Alone

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Gordon F. Schwartz, M.D., M.B.A.[3]
Shanth A. Goonewardene, M.D.[1]
Albert J. Kovatich, M.S.[4]
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Terry Hyslop, Ph.D.[5]
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BACKGROUND. A number of conventional histopathologic features have been associated with recurrence of ductal carcinoma in situ (DCIS) after surgery alone and are included in the Van Nuys Pathologic Classification and Prognostic Index. To the authors' knowledge, very little is known regarding the prognostic significance of the many biologic markers that have been studied in DCIS in the past decade.

METHODS. Clinical and pathologic data were analyzed from 151 patients who underwent wide local excision alone for DCIS that was diagnosed by mammography or as an incidental finding between 1982 and 2000. Using local disease recurrence as an endpoint, the authors sought to determine the prognostic significance of a large number of histopathologic parameters as well as biologic markers (estrogen receptor [ER], progesterone receptor [PR], p53, HER-2/*neu*, Ki-67, p21, and bcl-2), as determined by immunohistochemical staining of contemporary or archival tissue.

RESULTS. With a median follow-up of 65 months, 42 recurrences were reported to occur between 11 months and 97 months after definitive surgery. In a univariate

Ductal carcinoma *in situ* with basal-like phenotype: a possible precursor to invasive basal-like breast cancer

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Basal-like carcinomas have recently been identified in gene expression profiling studies as a subtype of invasive breast cancer. These lesions are estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative (triple negative), and typically express basal cytokeratins, epidermal growth factor receptor (EGFR), and/or c-kit. As poorly differentiated invasive ductal carcinomas, they presumably have a ductal carcinoma *in situ* (DCIS) precursor with similar cytologic and immunophenotypic features. However, the frequency and even the existence of a DCIS lesion with an immunophenotype analogous to that of invasive basal-like carcinomas have not been previously evaluated. We studied 66 cases of high nuclear grade DCIS using antibodies to ER, PR, HER2, three basal cytokeratins, EGFR, and c-kit to determine the frequency of the triple negative phenotype, and to determine the relationship between the triple negative phenotype and expression of basal cytokeratins and other biomarkers characteristically expressed by invasive basal-like carcinomas. Four cases (6%) exhibited the triple negative phenotype; the remaining cases showed other combinations of ER, PR, and HER2 expression (nontriple negative). Basal cytokeratins, EGFR, or both were expressed by all four triple negative lesions, but by only 21 of 51 (42%) nontriple negative cases ($P=0.04$). We conclude that a small proportion of high-grade ductal carcinomas *in situ* exhibit an ER-negative/PR-negative/HER2-negative (triple negative) phenotype, and these lesions more commonly show expression of basal cytokeratins and/or EGFR than nontriple negative high-grade DCIS. Given that invasive breast cancers typically share immunophenotypic features with the ductal carcinoma *in situ* from which they arise, our findings raise the possibility that the triple-negative, basal cytokeratin and/or EGFR-positive DCIS lesions we identified represent a precursor lesion to invasive basal-like carcinomas.

Modern Pathology (2006) **19**, 617–621. doi:10.1038/modpathol.3800570; published online 10 March 2006

Keywords: breast cancer; basal-like carcinoma; ductal carcinoma *in situ*

Recent gene expression profiling studies have identified a subtype of breast cancer known as basal-like carcinomas.[1–4] These lesions constitute about 15% of invasive breast cancers, are characterized by lack of expression of estrogen receptor (ER) and progesterone receptor (PR), and absence of HER2 protein overexpression (the so-called 'triple negative' phenotype), and have a poor prognosis.[5–8] Basal-like carcinomas typically exhibit expression of one or more of the basal cytokeratins (such as CK5/6, CK14, and CK17), epidermal growth factor receptor (EGFR), and/or c-kit.[5–8] These tumors are often seen in women with BRCA1 mutations, but also occur among sporadic breast cancers.[4–7,9] In expression array studies, the majority of triple negative invasive breast cancers cluster with basal-like carcinoma.[4–7,10]

Basal-like carcinomas are poorly differentiated invasive ductal carcinomas,[4,5,7] and presumably have a ductal carcinoma *in situ* (DCIS) precursor with similar cytologic and immunophenotypic features. However, the frequency and even the existence of a distinctive DCIS lesion with an immunophenotype similar to that of basal-like carcinoma has not been previously identified.

To address this issue, we studied 66 cases of high nuclear grade DCIS to determine the frequency of the triple negative phenotype, and to determine the relationship between the triple negative phenotype and expression of basal cytokeratins and other biomarkers characteristically expressed by invasive basal-like carcinomas.

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e of HER4 Expression Predicts Recurrence of Ductal oma *In situ* of the Breast

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l tyrosine kinase receptor HER2 (*c-erbB2/neu*) is ith resistance to hormone therapy and poor nvasive breast cancer, whereas HER4 expression ith endocrine responsiveness. Patterns of tyrosine or coexpression may aid prediction of recurrence gery for ductal carcinoma *in situ* (DCIS). Women ergone surgery for pure DCIS were studied. Out of tumors, 39 had recurred and 90 had not recurred of follow-up. Primary tumors were compared for 3, and HER4, estrogen receptor, and Ki67 by chemistry. HER2 was expressed in 58%, HER3 in R4 in 63% of nonrecurrent DCIS, compared with sion in 82% ($P = 0.008$), HER3 expression in 71% d HER4 expression in 36% ($P = 0.004$) in DCIS ently recurred. Dually expressing HER2/4 DCIS ely to be estrogen receptor positive than HER2-ng DCIS (73% versus 53%; $P = 0.05$). HER2 vas associated with a higher percentage and sion a significantly lower percentage of prolifer-cells (median, 13.8% versus 8.4%; $P = 0.001$). of HER2 with HER4 was associated with reduced mpared with HER2-only positive DCIS ($P = 0.003$). ion remained significant when analyzing only high DCIS ($P = 0.015$). Low nuclear grade, low rate and presence of HER4 expression were predictors of nonrecurrence. Potentially, HER4 ay identify women who could avoid radiotherapy onserving surgery for DCIS.

CTION

idence of the preinvasive breast cancer ductal *situ* (DCIS) has increased by over five times because of the introduction of national screening programs in the 1980s (1), and now accounts for 25% of all screen-detected breast cancers (2). After breast-conserving surgery and radiotherapy, between 12% and 20% of cases recur by 10 years (3) depending on margin status. This 6-fold increase in the number of DCIS cases necessitates accurate prediction of recurrence risk. Clinicopathologic risk factors for the recurrence of DCIS have been identified, including involved or close (<1 mm) surgical excision margins (4), younger age at diagnosis, high-nuclear-grade tumors, and the presence of comedo necrosis (3, 5–7). Less is known about the molecular biological markers that could aid prediction of prognosis.

The type 1 tyrosine kinase receptors (RTK) are a group of four growth factor receptors HER1(*c-erb*B1/epidermal growth factor receptor), HER2(*c-erb*B2/*neu*), HER3(*c-erb*B3), and HER4(*c-erb*B4) characterized by their homology to the avian erythroblastosis virus transforming protein (8), which have a significant influence on the prognosis of invasive breast cancer. HER2 expression is associated with a poor prognosis, early recurrence, resistance to endocrine therapy and low estrogen receptor (ER) expression (9–13), whereas HER4 expression has been associated with increased ER expression (14) and low cell proliferation rates (15). HER2 expression has been claimed to be a univariate predictor of DCIS recurrence risk ($P = 0.012$, log-rank) being present in ~56% of all tumors (16), but the association of HER4 to DCIS recurrence has not previously been characterized. The type 1 RTKs share a common molecular structure—an extracellular ligand binding domain that contains two cystine-rich regions, a short transmembranous domain, and an intracellular tyrosine kinase domain (8)—enabling signaling across the cell membrane. The receptors can homo- or heterodimerize for activation after either ligand binding of the extracellular domain or gene overexpression (except for HER3, which has no intrinsic kinase activity and requires heterodimerization for signaling; ref. 14). With many possible receptor combinations, there is potential activation of multiple signaling pathways, the clinical effects of which are incompletely understood. In cell line experiments, when HER2-positive cancer cells were transfected to overexpress HER4, a reduction in proliferation and an increase in apoptosis was seen (17), suggesting that HER4 produces a "braking effect" on HER2 signaling activity. The effect of RTK expression on DCIS recurrence is unclear. To determine the relationship of type 1 RTKs to ER, cell proliferation, and recurrence risk of DCIS after surgical excision we looked at primary cases of pure DCIS that had either recurred or not recurred by 5 years of follow-up.

MATERIALS AND METHODS

Patient Selection. Cases were selected from a database at the University Hospital of South Manchester, composed of ~850 women diagnosed with DCIS from 1979 onward. Fifty women with subsequent recurrence were identified upon case-note review. From this, 39 formalin-fixed, paraffin-embedded

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ublication of this article were defrayed in part by the ge charges. This article must therefore be hereby marked in accordance with 18 U.S.C. Section 1734 solely to ct.
eprints: Nigel J. Bundred, Department of Academic rch and Education Building, 2nd Floor, South Manchester pital, Southmoor Road, Wythenshawe, Manchester, M23 ngdom. Phone: 44-161-291-5859; Fax: 44-161-291-5860; dnj@man.ac.uk.

REVIEW ARTICLE

Tibor Tot

DCIS, cytokeratins, and the theory of the sick lobe

Received: 24 February 2005 / Accepted: 12 April 2005 / Published online: 31 May 2005

Abstract We postulate that ductal carcinoma in situ (DCIS), and consequently breast carcinoma in general, is a lobar disease, as the simultaneously or asynchronously appearing, often multiple, in situ tumor foci are localized within a single lobe. Although the whole lobe is sick, carrying some form of genetic instability, the malignant transformation of the epithelial cells may appear localized to a part or different parts of the sick lobe at the same time or with varying time difference. It may be confined to terminal ductal lobular units (TDLUs), to ducts or both. The malignant transformation is often associated with aberrant branching and/or aberrant lobularization within the sick lobe. Involvement of a single individual TDLU or of a group of adjacent TDLUs generates a unifocal lesion. Multifocal lesions appear if distant TDLUs are involved. Diffuse growth pattern in DCIS indicates involvement of the larger ducts. The extent of the involved area in multifocal or diffuse cases varies considerably. Diffuse growth pattern with or without evidence of aberrant arborisation within the sick lobe seems to characterize a subgroup of DCIS with unfavourable prognosis. In this paper, we discuss the anatomical, embryological and pathological background of the theory of the sick lobe and present supporting evidence from modern radiological breast imaging, long-term follow-up studies and from our own series of 108 DCIS cases.

Keywords Breast · Ductal carcinoma in situ · Cytokeratins · Neoplasia · Hypothesis

Introduction

Breast carcinoma is a heterogeneous and progressive disease with many variations in morphological appearance, which has always made attempts of classification of b tumors very difficult. Mammography screening durin last decades has changed the panorama of breast car ma, detecting small invasive tumors in asymptomatic w and also detecting malignant lesions in their non-inv state [3, 16]. Under the circumstances of adequate su removal of the lesions, proper histopathologic wo and systematic mammographic-pathologic correlation evolution offers the opportunity of studying breast cinoma at the earliest stages in its natural history, w in turn may offer a key to better understanding the variations of breast cancer morphology.

Classical whole organ studies had long ago demon ed that the vast majority of in situ and invasive b carcinomas are multifocal/multicentric/diffuse [10, However, the traditional technique used routinely in breast pathology laboratories today does not allow tition of the results of whole organ studies in most c The "modern" approach of focusing on histological, ir nohistological and molecular analysis of the dom invasive lesion may lead to underestimation of the portance of the alterations in the tissue adjacent t dominant mass. In our laboratory, the diagnostic rout specially adapted to the work-up of quadrantectomy imens (the method of choice in breast conserving surge Scandinavia). This method of two- and three-dimens large (up to 10×8 cm) histological sections gives the tiguous piece of tissue necessary for proper analysis extent and distribution of the lesions belonging to a b carcinoma and represents an ideal background for det and systematic radiopathologic correlation [13, 31, Based on our 20 years experience and more than consecutive breast cases documented and analysed way, we have become more and more convinced tha multiple malignant lesions exhibit a lobar distribution in the breast. Thus, we postulate that ductal carcinor situ, and consequently breast carcinoma in general

T. Tot (✉)

Identificazione potenziale evolutivo lesioni basso grado/precursori

Morphologic and Molecular Evolutionary Pathways of Low Nuclear Grade Invasive Breast Cancers and Their Putative Precursor Lesions: Further Evidence to Support the Concept of Low Nuclear Grade Breast Neoplasia Family

Tarek M. A. Abdel-Fatah, MD, Desmond G. Powe, PhD,* Zsolt Hodi, MRCPath,* Jorge S. Reis-Filho, MD, PhD,† Andrew H. S. Lee, FRCPath,* and Ian O. Ellis, FRCPath**

Abstract: We have previously provided evidence showing an association between some precursor lesions with low nuclear grade breast carcinomas (LNGBCs). In this study, further immunophenotypic support to our proposed route of pathogenesis of LNGBC and their precursor lesions was provided. Precursor lesions including columnar cell lesions, atypical ductal hyperplasia, ductal carcinoma in situ, usual epithelial hyperplasia, and lobular neoplasia were compared with matching "morphologically normal" terminal lobular duct units and matching invasive carcinoma. The epithelial cells in the putative precursor flat epithelial atypia, atypical ductal hyperplasia, lobular neoplasia, ductal carcinoma in situ lesions, and their coexisting LNGBC were negative for basal and myoepithelial markers, but positive for CK19/18/8, estrogen receptor (ER)-α, Bcl-2, and cyclin D1. The ER-α/ER-β expression ratio increased during carcinogenesis, as did expression of cyclin D1 and Bcl-2. p53 immunopositivity was found 3% in LNGBC versus 43% in high nuclear grade breast carcinoma (HNGBC), whereas ataxia telangiectasia mutated expression was absent or reduced in 22% of LNGBC versus 53% of HNGBC cases. In summary, our findings support the concept that flat epithelial atypia is the earliest morphologically identifiable nonobligate precursor lesion of LNGBC. These may represent a family of precursor, in situ and invasive neoplastic lesions belonging to the luminal "A" subclass of breast cancer. The balance between ER-α and ER-β expression may be important in driving cyclin D-1 and Bcl-2 expression. Ataxia telangiectasia mutated may be one of the alternative regulatory mechanisms to TP53 mutation or dysfunction in low-grade and high-grade breast carcinoma. Our findings support the concept that progression of LNGBC to HNGBC (basal-like or HER2+) phenotype is an unlikely biologic phenomenon.

Key Words: TDLUs, columnar cell lesions, flat epithelial atypia, ADH, DCIS, luminal "A" subclass of breast carcinoma, tissue microarray, immunoprofile of precursors lesions and their coexisting breast carcinoma

(*Am J Surg Pathol* 2008;32:513–523)

Breast cancers (BCs) are heterogeneous in their morphology, response to therapy, and clinical course.[22] Molecular profiling studies have shown the existence of at least 5 different BC subtypes, each with different clinical outcomes. The luminal subtype "A" have higher levels of estrogen receptor (ER)-α and a better survival outcome compared with luminal subtypes "B."[26,46] Moreover, there is convincing genetic evidence to suggest that low-grade (LGBC) and high-grade BCs evolve through distinct evolutionary pathways.[11,45] LGBCs are usually diploid/near-diploid and harbor recurrent loss of chromosome 16q and gains of chromosome 1q. In contrast, high-grade BCs are usually aneuploid with complex genetic profiles and infrequent deletion of 16q.[13,23] In high-grade BCs, even when loss of 16q is present, the underlying genetic mechanism appears to be distinct from that seen in LGBCs.[14] Taken together, these findings suggest that progression from LGBC to high-grade BCs is an unlikely biologic phenomenon.[14,36,45]

We have recently[2] proposed the concept of a family of low nuclear grade breast neoplasia based on the significant coexistence of columnar cell lesions (CCLs), lobular neoplasia (LN), and atypical ductal hyperplasia/low grade ductal carcinoma in situ (ADH/low-grade DCIS) with invasive tubular carcinoma (TC), tubulolobular carcinoma (TLC), and classic invasive lobular carcinoma (ILC). In this paper, we expand our investigation to explore the phenotype of the putative precursor lesions and related cancers. We include invasive cribriform, mixed invasive tubular/classic lobular carcinoma, and invasive low nuclear grade ductal carcinoma and compare with high nuclear grade carcinoma. Phenotype was assessed using immunohistochemistry (IHC) on tissue microarrays (TMA) and full-face sections

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Reprints: Ian O. Ellis, FRCPath, Department of Histopathology, Nottingham City Hospital, Hucknall Road, Nottingham, NG5 1PB, UK (e-mail: ian.ellis@nottingham.ac.uk).

Molecular Evidence for Progression of Microglandular Adenosis (MGA) to Invasive Carcinoma

Sandra J. Shin, MD, Peter T. Simpson, PhD,†‡ Leonard Da Silva, MD,†‡ Janani Jayanthan, BSc,†‡§ Lynne Reid, BSc,†‡ Sunil R. Lakhani, FRCPA,†‡‖ and Paul Peter Rosen, MD**

Abstract: Microglandular adenosis (MGA) is an uncommon, benign breast lesion that is characterized by a proliferation of small uniform, round glands lined by a single layer of epithelial cells around open lumina with haphazard infiltrative growth in fibrous and fatty breast tissue. Although MGA usually has an indolent course, there is morphologic evidence that MGA can be a precursor for the development of intraductal and invasive ductal carcinoma. To investigate the possibility of such a transition, we studied 17 cases of MGA or atypical MGA some of which had given rise to carcinoma in situ (CIS) and/or invasive ductal carcinoma using the reticulin stain, immunohistochemistry (S-100, p63, Ki-67, and p53), and a molecular approach involving microdissection and high-resolution comparative genomic hybridization and *MYC* chromogenic in situ hybridization. MGA and carcinomas arising from MGA were typically negative for p63 and positive for S-100 and Ki-67 and occasionally positive for p53. High-resolution comparative genomic hybridization identified recurrent gains and losses in MGA (2q+, 5q−, 8q+, and 14q−) and atypical MGA (1q+, 5q−, 8q+, 14q−, and 15q−). Some examples of MGA and carcinomas arising from MGA harbored few gross chromosomal abnormalities whereas others had considerable genetic instability with widespread aberrations affecting numerous chromosomal arms. Such widespread genetic changes, together with recurrent loss of 5q and gain of 8q were reminiscent of those reported specifically for basal-like, estrogen receptor-negative, and BRCA1-associated breast tumors. Concordant genetic alterations were identified between MGA, atypical MGA, and higher risk lesions (CIS and invasive ductal carcinoma) and in some cases there was an accumulation of genetic alterations as cases "progressed" from MGA to atypical MGA, CIS, and invasive ductal carcinoma. The molecular data suggests that MGA, atypical MGA, and carcinoma arising in MGA in a single case were clonally related. This result implicates MGA as a nonobligate precursor for the development of intraductal and invasive ductal carcinoma.

Key Words: microglandular adenosis, breast carcinoma, comparative genomic hybridization

(*Am J Surg Pathol* 2009;33:496–504)

Microglandular adenosis (MGA) is an uncommon, benign entity arising in the breast, which may present as an inconspicuous microscopic lesion or as a palpable mass.[21] The term "microglandular adenosis" is believed to have been coined by McDivitt et al[17] and the lesion is best known for its histologic and gross resemblance to tubular carcinoma.[3,17,21,25]

MGA is a proliferation of small, uniform round glands formed by a single layer of epithelial cells around lumina containing secretion and/or calcifications. The glands haphazardly infiltrate the adipose or fibrous breast tissue.[3,17,21,25] The epithelial cells are cuboidal with clear to eosinophilic cytoplasm. Nuclei are bland, mitotic figures uncommon, and gland lumina usually have an eosinophilic secretion that can stain positively for periodic acid-Schiff or mucicarmine.[25] The epithelium is positive for S-100 and cytokeratins (CK) and negative for estrogen (ER) and progesterone receptors (PgR) and HER2/CerbB2.[4,8,10,14,24] The glands are surrounded by a multilayered basement membrane that stains for collagen type IV and laminin.[24,25] There is an absence of a myoepithelial cell layer around the glands of the lesion.[5,24,25]

Although MGA usually has a benign clinical course, some examples of MGA have been described as giving rise to ductal carcinoma.[8,12,14,21,22,25] MGA is rarely associated with separate, coincidental carcinoma, but in most instances carcinoma arises in and apparently

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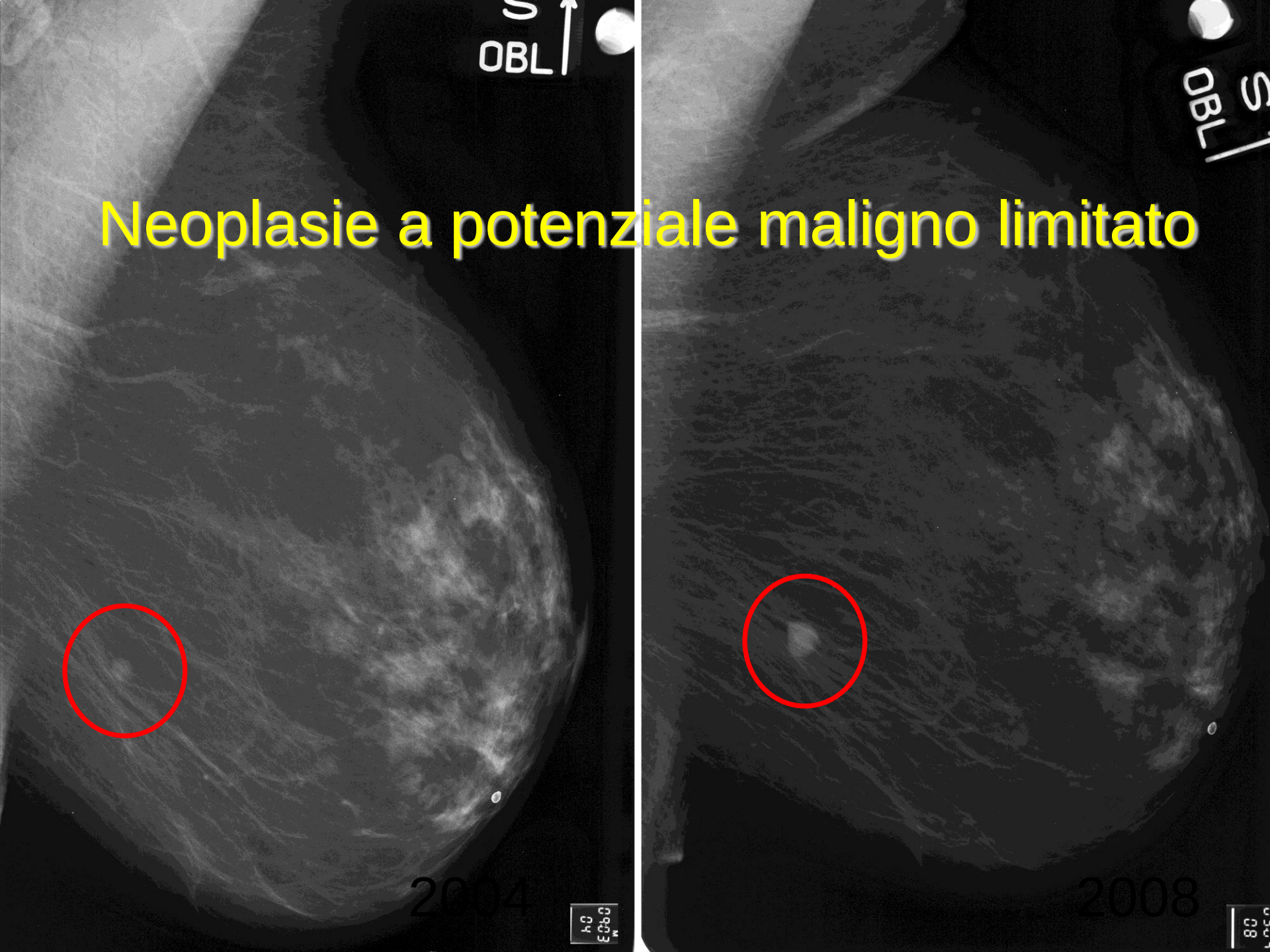
Sandra J. Shin and Peter T. Simpson contributed equally to this study.
Leonard Da Silva is the recipient of a PhD Fellowship from the Ludwig



Neoplasie a potenziale maligno limitato

evolutivo lesioni basso grado/precursori

The challenge remains to accurately identify the small number of low-grade lesions likely to progress in order to provide the most appropriate treatment without over-treating the vast majority of patients with lesions that will be cured by breast conserving surgery alone.

Rischio di sovratrattamento quantitativo????

SI !!!, ma…

Quando si è di fronte ad una diagnosi iniziale, non ci si può astenere da un trattamento chirurgico !!!!!

Le conseguenze negative di un NON trattamento potrebbero essere di gran lunga SUPERIORI ai “danni” di questo

Sovratrattamento

Screen-detected *vs* symptomatic breast cancer: is improved survival due to stage migration alone?

GC Wishart*[,1], DC Greenberg[2], PD Britton[1], P Chou[3], CH Brown[2], AD Purushotham[4] and SW Duffy[3]

[1]Cambridge Breast Unit, Box 97, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK; [2]Eastern Cancer Registration and Information Centre (ECRIC) Unit C, Magog Court, Shelford Bottom, Hinton Way, Cambridge CB22 3AD, UK; [3]Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ, UK; [4]King's College London, Department of Academic Oncology, Guy's Hospital, Guy's and St Thomas' NHS Foundation Trust, 3rd Floor, Thomas Guy House, St Thomas Street, London SE1 9RT, UK

Clinical Studies

This paper examines whether screen-detected breast cancer confers additional prognostic benefit to the patient, over and above that expected by any shift in stage at presentation. In all, 5604 women (aged 50–70 years) diagnosed with invasive breast cancer between 1998 and 2003 were identified by the Eastern Cancer Registration and Information Centre (ECRIC) and mammographic screening status was determined. Using proportional hazards regression, we estimated the effect of screen detection compared with symptomatic diagnosis on 5-year survival unadjusted, then adjusted for age and Nottingham Prognostic Index (NPI). A total of 72% of the survival benefit associated with screen-detected breast cancer can be
continuous NPI showed a small but systematic survival benefit for screen-
although most of the screen-detected survival advantage is due to a shift
patients with equivalent NPI scores. This residual survival benefit is small b
biology. Current prognostication tools may, therefore, overestimate the
and lead to overtreatment of these patients.
British Journal of Cancer (2008) **98,** 1741–1744. doi:10.1038/sj.bjc.6604

British Journal of Cancer (2008) 98, 1741 – 1744

symptomatic) of detection. Two recent papers, however, have suggested that screen detection confers an additional survival benefit beyond stage shift (Shen *et al*, 2005) and reduces the risk of systemic recurrence when compared with symptomatic cancers of a similar stage (Joensuu *et al*, 2004). This current paper, therefore,

2002). The rational for this survival benefit is that screening enables breast cancers to be diagnosed at an earlier stage of disease. It is now well documented that screen-detected cancers are generally smaller, of lower grade and less likely to have axillary lymph node involvement (Weaver *et al*, 2006).

Sovratrattamento

These data confirm the known survival advantage for patients with screen-detected cancers. They show that although most of this advantage is due to a shift in NPI, the mode of detection does impact on survival in patients with equivalent NPI scores. This residual survival benefit is small but significant, and is likely to be due to differences in tumour biology between screen-detected and symptomatic cancers.

Wishart GC et al, BJC 2008

Sovratrattamento

Current prognostication tools that do not include known biological markers may overestimate the benefit of systemic treatments in screen-detected cancers and lead to overtreatment of these patients. A prognostic tool combining clinical, pathological and biological factors might allow more accurate prognostication, and more appropriate systemic therapy, for all patients with breast cancer regardless of their mode of detection.

Wishart GC et al, BJC 2008

SOVRATRATTAMENTO QUALITATIVO

Importanti conseguenze psicofisiche

- Mastectomie, Dissezioni ascellari inopportune
- Radioterapia, Ormonoterapia, Chemioterapia,
- (Ansia, depressione, alterazioni emotive)

SOVRATRATTAMENTO QUALITATIVO

- Mastectomie, Dissezioni ascellari inopportune
- Radioterapia, Ormonoterapia, Chemioterapia,
- (Ansia, depressione, alterazioni emotive)

Trattamento inadeguato

=

CATTIVO TRATTAMENTO !!!!

Sovratrattamento qualitativo

Parametri utilizzati per indicatori qualità trattamento SQTM

Modalità di exeresi lesioni benigne
% chirurgia conservativa nei T1
% mastectomia con ricostruzione immediata
% chirurgia conservativa nei DCIS
% non attuazione dissezione ascellare nei DCIS

Sovratrattamento qualitativo : lesioni benigne

Studio GISMa Benigni

Seguendo indicazioni Foncam e GiSMa, per valutare quante lesioni benigne sono state escisse in modo corretto abbiamo richiesto alle Regioni Piemonte, Emilia Romagna e Toscana gli istologici di 175 lesioni benigne di screening trattate nel 2007 (abbiamo escluso i benigni associati a un cancro).

I centri hanno contribuito con **152 istologici**, che abbiamo analizzato in modo più approfondito per quanto riguarda:

Rischio evolutivo

Escissione della cute

Volume del pezzo operatorio e del tumore (STVR)

Sovratrattamento qualitativo :lesioni benigne

Conclusioni studio gisma

Almeno la metà delle lesioni benigne sono escisse senza indicazione oncologica.

Solo in 1/3 la quantità di tessuto è asportata in modo corretto.

In 1/3 dei casi è inspiegabilmente escissa la cute.

Conclusioni studio gisma

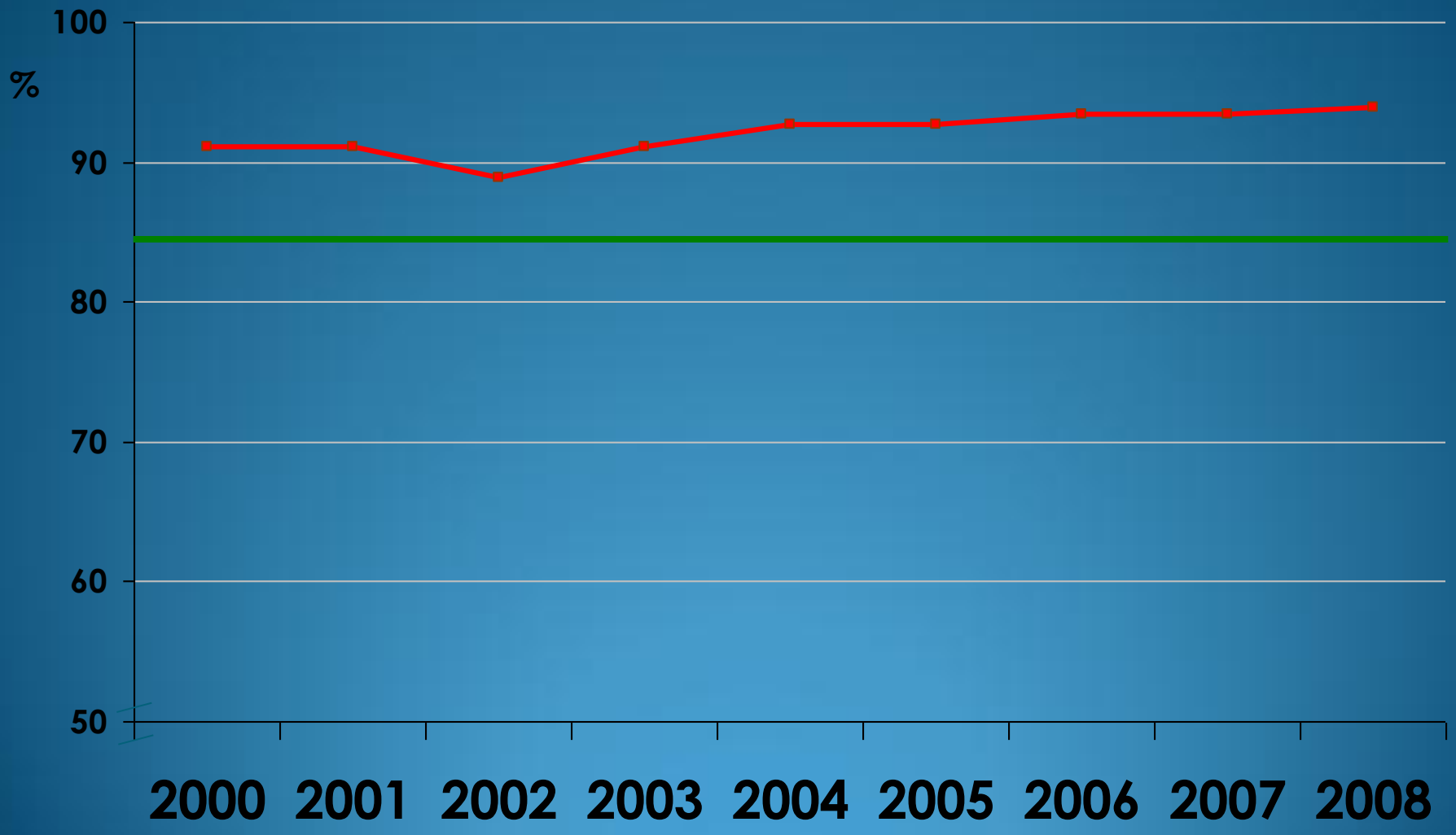
Soltanto 12 casi su 114* (10,5%) sono benigni:

- ad alto rischio
- senza escissione di cute
- con STVR accettabile (≤ 30)

* Dei 150 casi raccolti, 36 non avevano le dimensioni per calcolare l'STVR.

Intervento conservativo in casi pT1

Dati: SQTM Screening Italia 2000-2008



GISMa/ONS 2009

Mastectomy rates are decreasing in the era of service screening: a population-based study in Italy (1997–2001)

M Zorzi[1], D Puliti[2], M Vettorazzi[1], V De Lisi[3], F Falcini[4], M Federico[5], S Ferretti[6], IF Moffa[7], L Mangone[8], MP Mano[9], C Naldoni[10], A Ponti[11], A Traina[12], R Tumino[13] and E Paci*[,2] for the IMPACT Working Group[14]

[1]Istituto Oncologico Veneto, Padova, Italy; [2]Clinical and Descriptive Epidemiology Unit-CSPO-Research Institute of the Tuscany Region, Firenze, Italy; [3]Parma Cancer Registry, Parma, Italy; [4]Romagna Cancer Registry, Forlì, Italy; [5]Modena Cancer Registry, Modena, Italy; [6]Ferrara Cancer Registry, Ferrara, Italy; [7]Epidemiology Unit-ASL 2, Perugia, Italy; [8]Reggio-Emilia Cancer Registry, Reggio-Emilia, Italy; [9]University of Turin-Department of Biological Sciences and Human Oncology, Turin, Italy; [10]Screening program-Emilia-Romagna Region Health Department, Bologna, Italy; [11]Epidemiology Unit-CPO Piemonte, Turin, Italy; [12]Department of Oncology-ARNAS Ascoli, Palermo, Italy; [13]Cancer Registry and Human Pathology Department-Arezzo Hospital, Ragusa, Italy

We enrolled all 2162 *in situ* and 21 148 invasive cases of breast cancer in 17 areas of Italy, diagnosed in 1997–2001. Rates of early cancer increased by 13.7% in the screening age group (50–69 years), and breast conserving surgery by 24.6%. Advanced cancer rates decreased by 19.4%, and mastectomy rates by 24.2%. Service screening did not increase mastectomy rates in the study population.
British Journal of Cancer advance online publication, 17 October 2006; doi:10.1038/sj.bjc.6603405 www.bjcancer.com

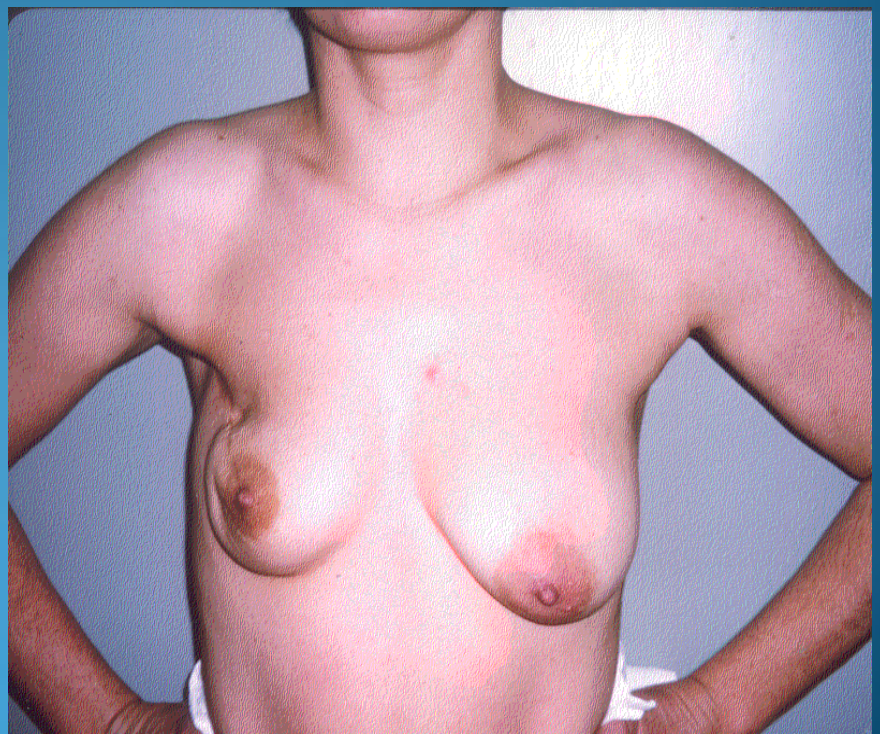
Keywords: breast cancer screening; breast conserving surgery; screening mammography

SOVRATRATTAMENTO QUALITATIVO

MODALITÀ DI ATTUAZIONE DELL'INTERVENTO

IERI

QUADRANTECTOMIA CLASSICA



SOVRATRATTAMENTO QUALITATIVO

Evoluzione chirurgia conservativa

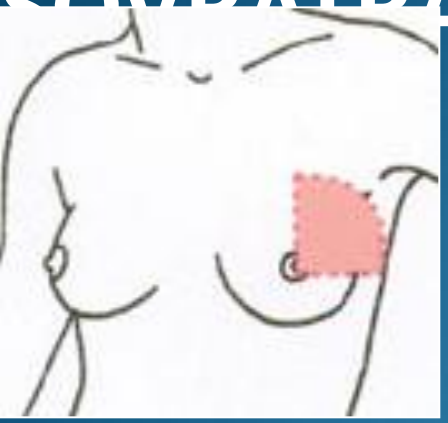
superamento del concetto di

“conservazione del seno indipendentemente dall’aspetto “

a favore di quello relativo alla

“conservazione dell’ aspetto del seno “

SOVRATRATTAMENTO



Sempre **meno** quadrantectomie classiche

Sempre **più** ampie biopsie escissionali

AMPIA BIOPSIA ESCISSIONALE

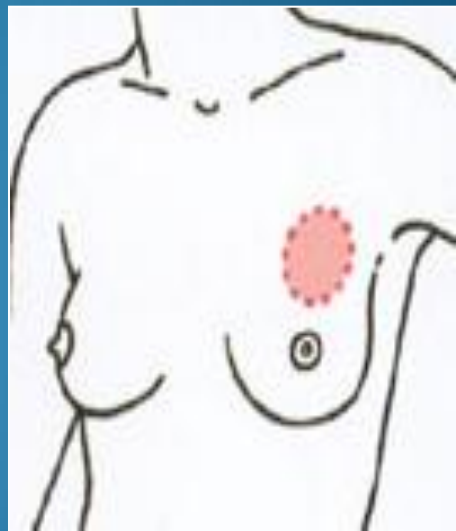
=

Intervento di riferimento in termini di chirurgia conservativa

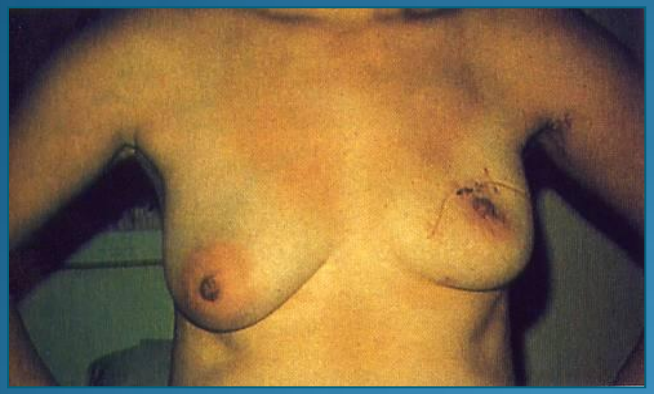
~~Exeresi del quadrante intero~~?

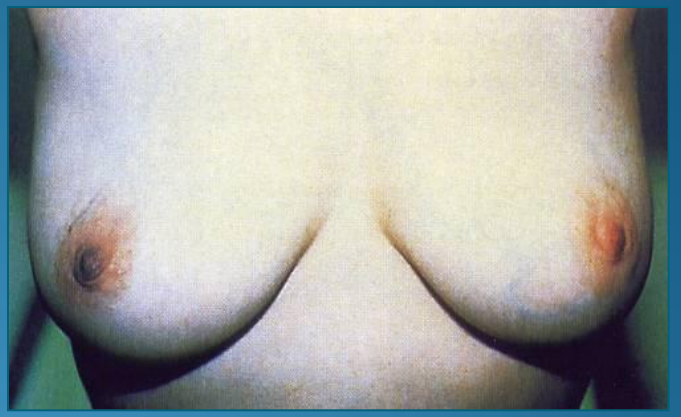
~~Exeresi della cute?~~

~~Margini di exeresi sempre ≥ di 1-2 cm~~?



EVOLUZIONE CHIRUGIA CONSERVATIVA





ESITO FREQUENTE

ESITO OTTIMALE

SOVRATRATTAMENTO:

MODALITÀ DI ATTUAZIONE DELL'INTERVENTO

IERI

CHIRURGIA CONSERVATIVA
A TUTTI I COSTI

OGGI

CHIRURGIA CONSERVATIVA
"MODULATA"

- *Sedi sfavorevoli*
- *Quadri difficili*
- *Necessità ampia exeresi*
- *Seni ptosici*

CHIRURGIA ONCOPLASTICA

Sovratrattamento sulla mammella

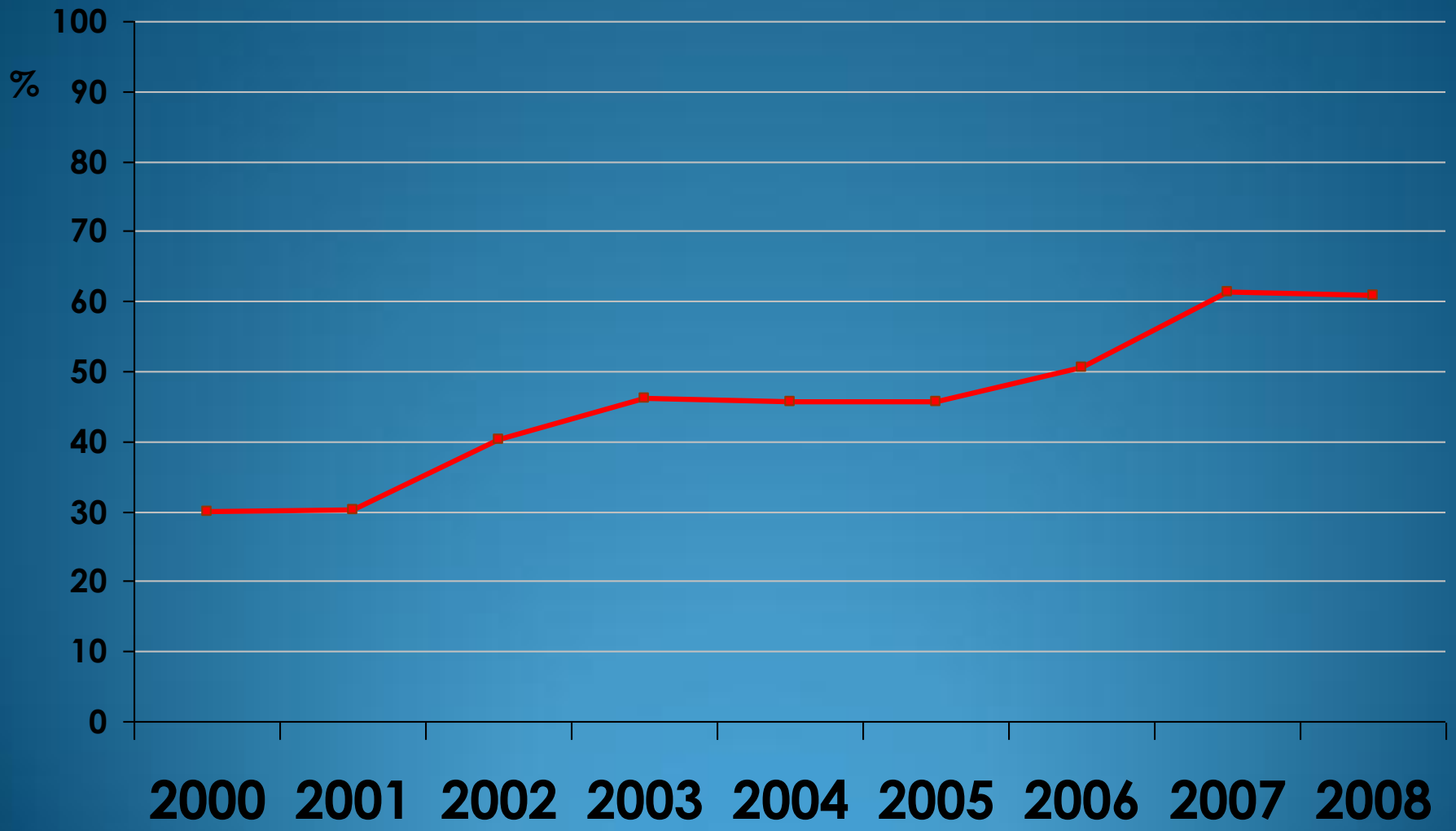
...in

MODO ECCESSIVAMENTE MUTILANTE

MASTECTOMIE TOTALI
SENZA RICOSTRUZIONE

Ricostruzione immediata

Dati: SQTM Screening Italia 2000-2008



GISMa/ONS 2009

Sovratrattamento sulla mammella

...in

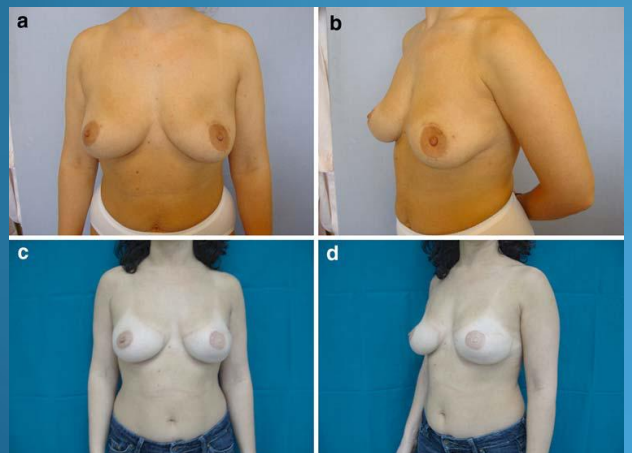
MODO ECCESSIVAMENTE MUTILANTE

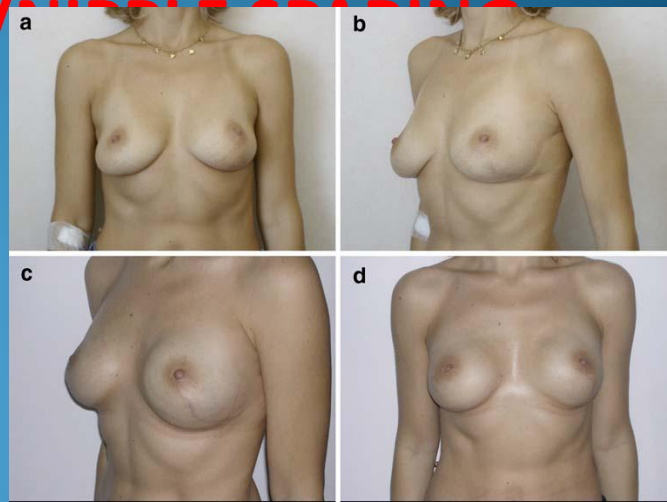
MASTECTOMIE TOTALI

CON RICOSTRUZIONE

V

MASTECTOMIE SKIN SPARING /





Documento di consenso: Novembre 2009

QUADRANTECTOMIA vs MASTECTOMIA:

MASTECTOMIA + RICOSTRUZIONE

IERI

DIFFICOLTA' LOGISTICHE

tempi/ spazi /operatori

IMPIEGO LIMITATO ANCH
DA TECNICHE LIMITATE

BREAST UNIT

OGGI

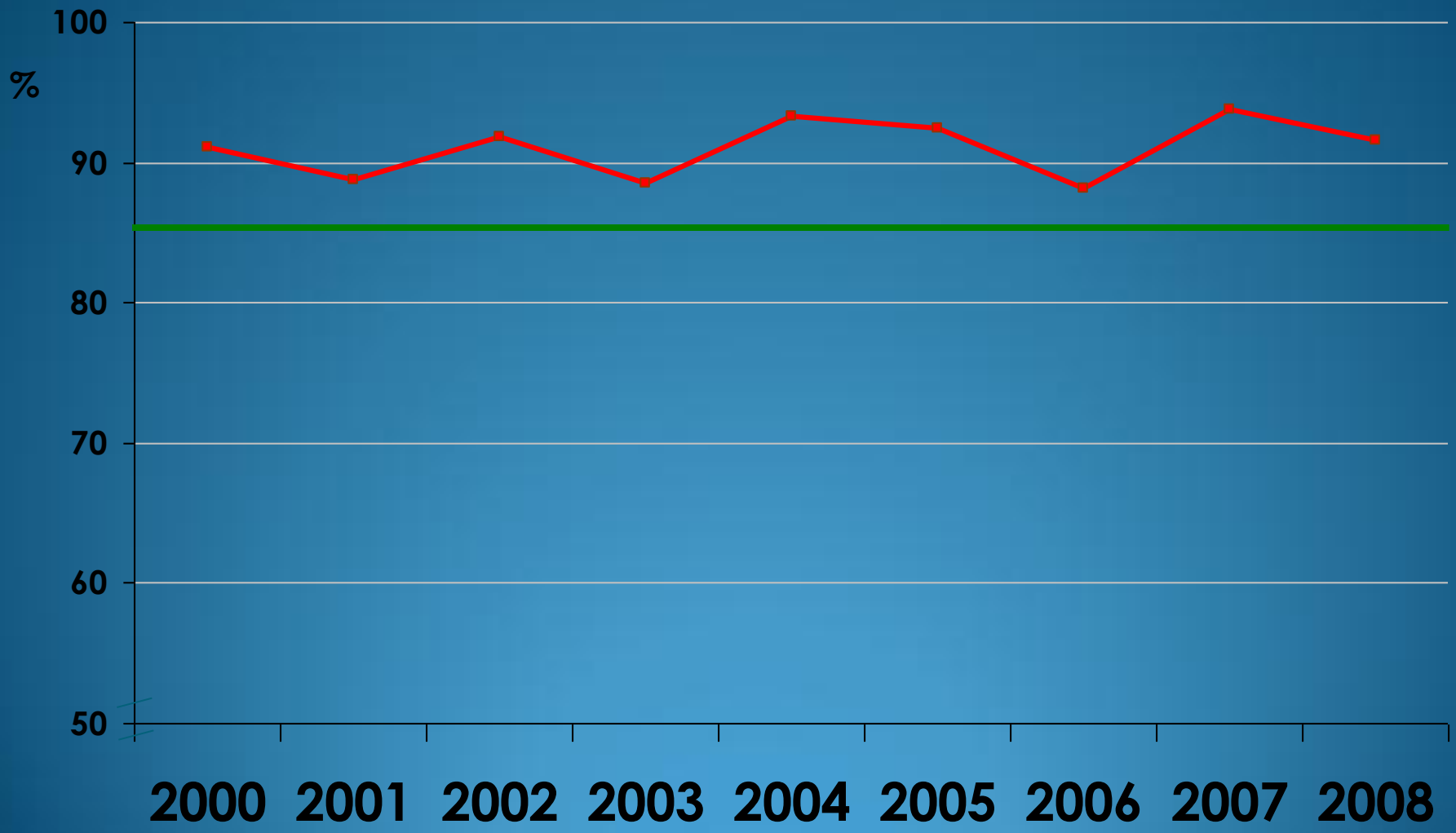
OTTIMIZZAZIONE
INDICAZIONI
E TECNICHE

MODULAZIONE TECNICHE

- ✓ *Ricostruzione protesica*
- ✓ *Ricostruzione con lembi*

Chirurgia conservativa nei CDIS < 20mm

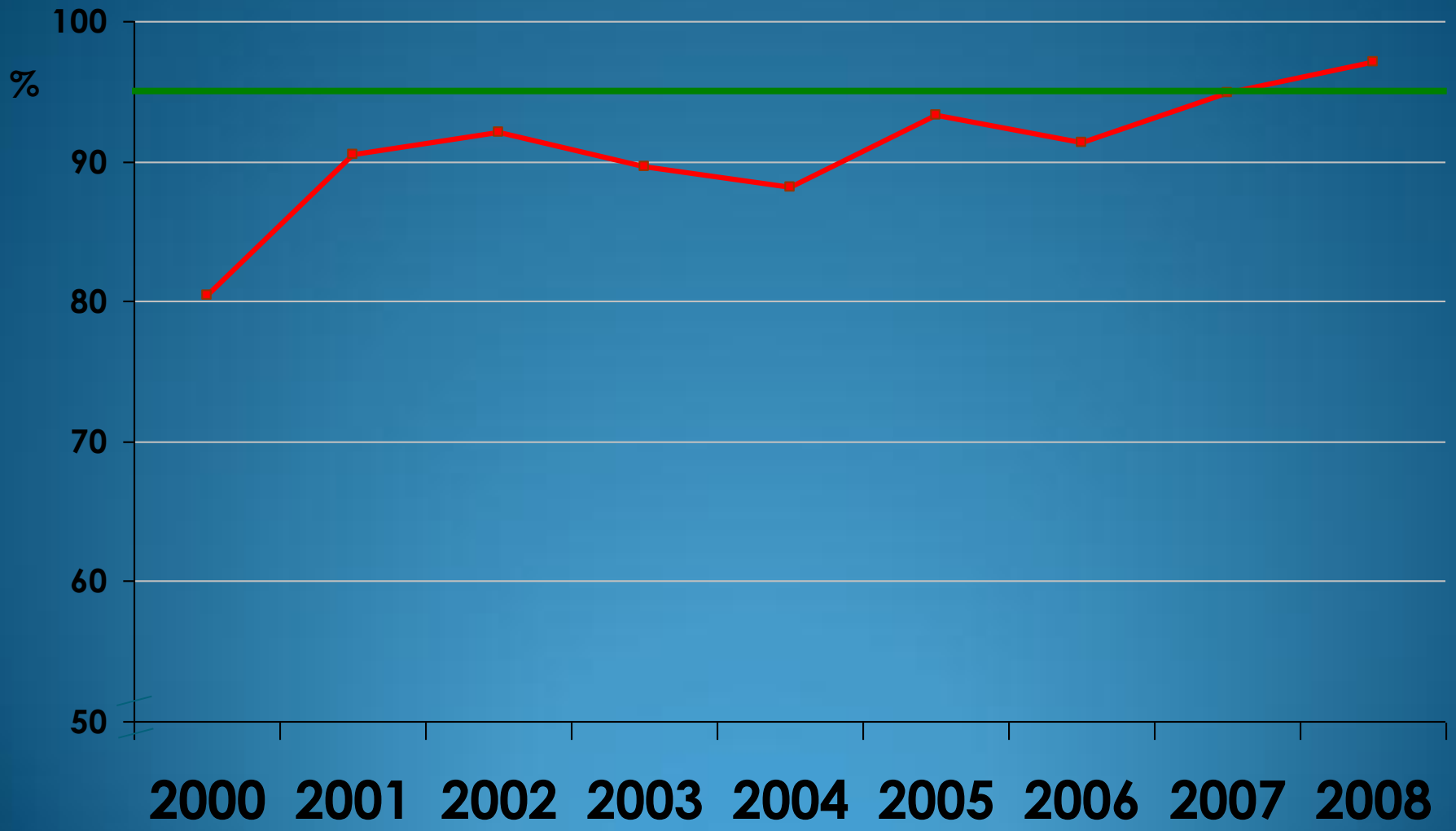
Dati: SQTM Screening Italia 2000-2008



GISMa/ONS 2009

CDIS senza dissezione ascellare

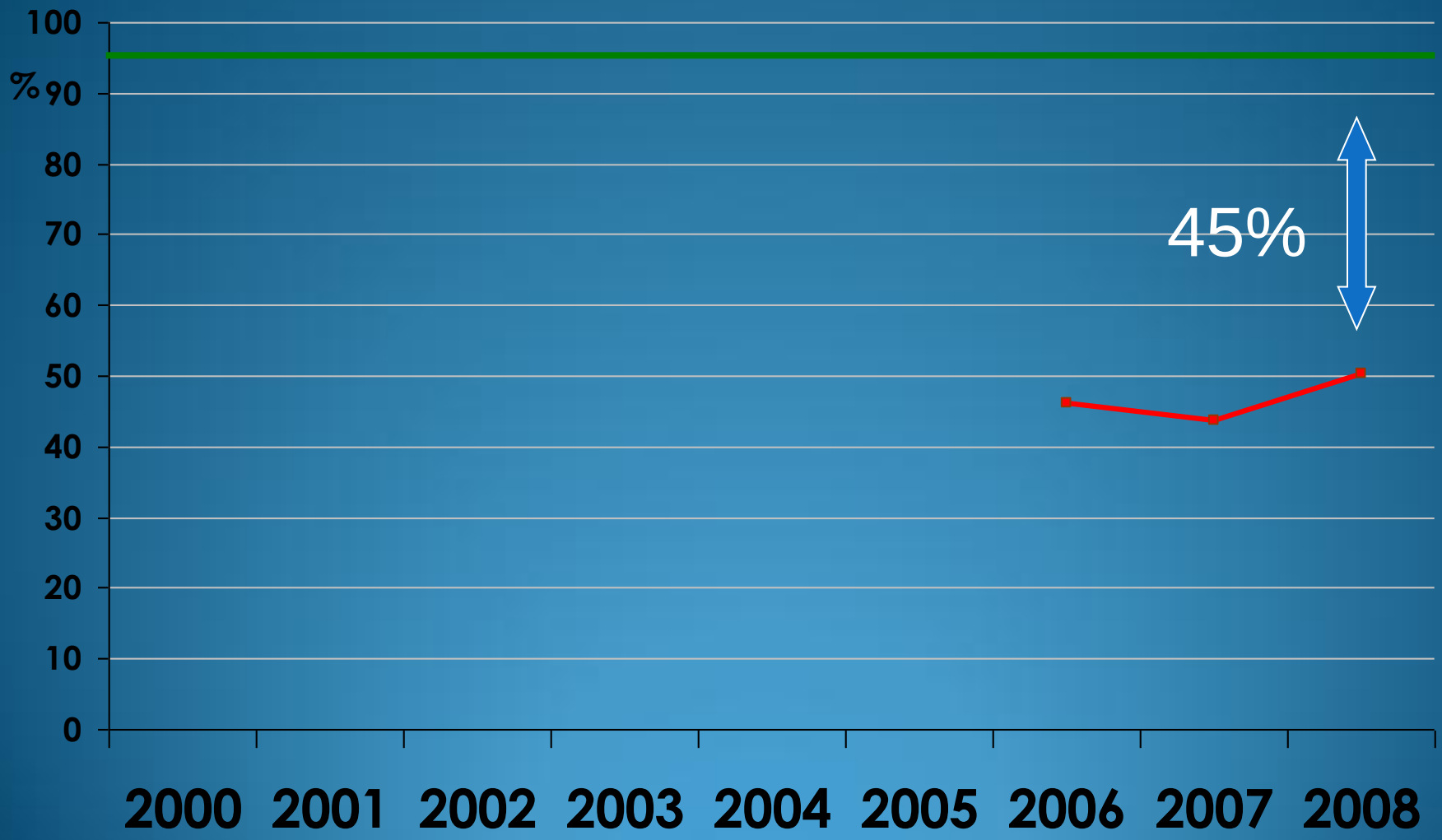
Dati: SQTM Screening Italia 2000-2008



GISMa-ONS 2009

DCIS GI-II senza DA o SN

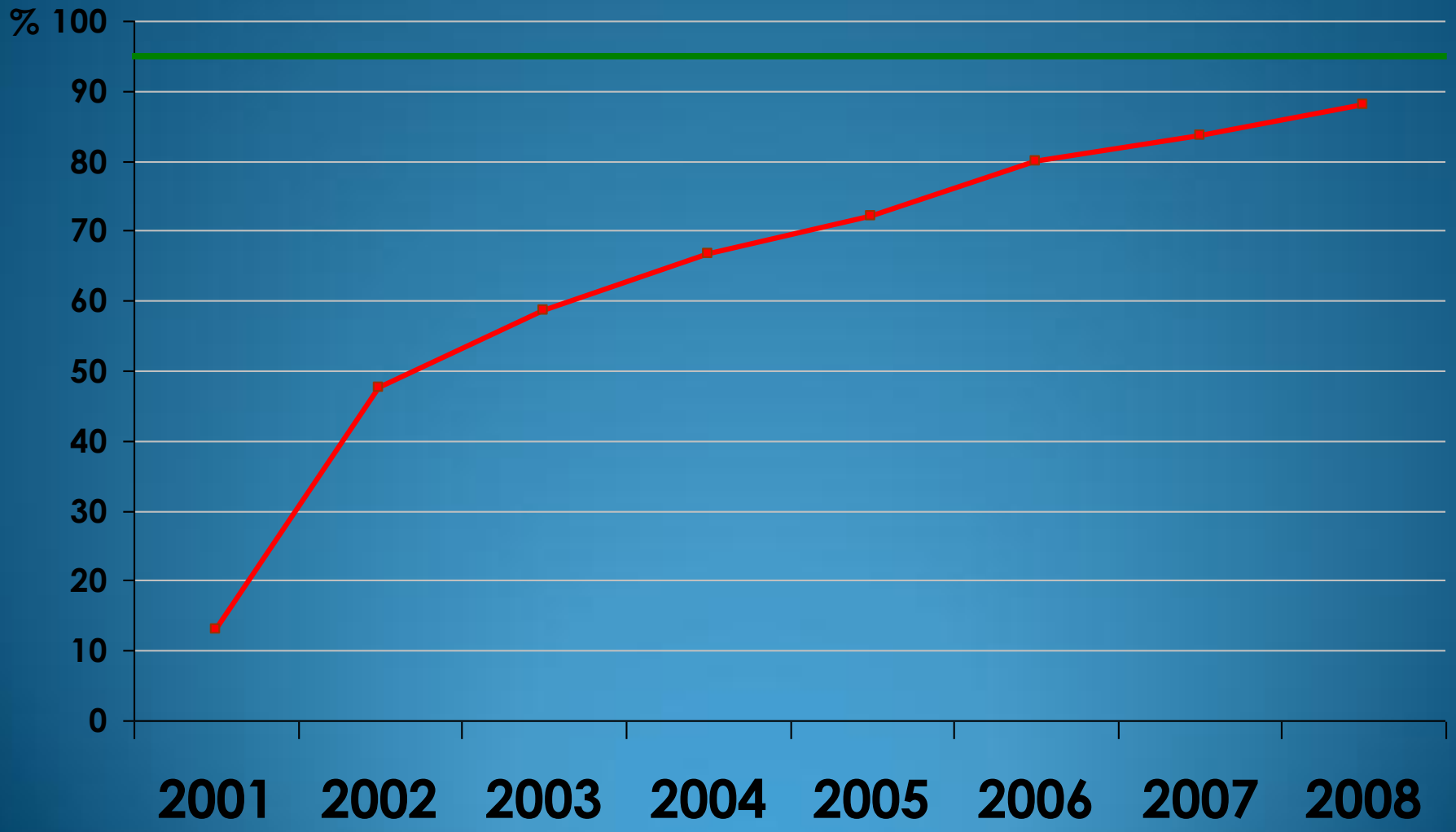
Dati: SQTM Screening Italia 2006-2008



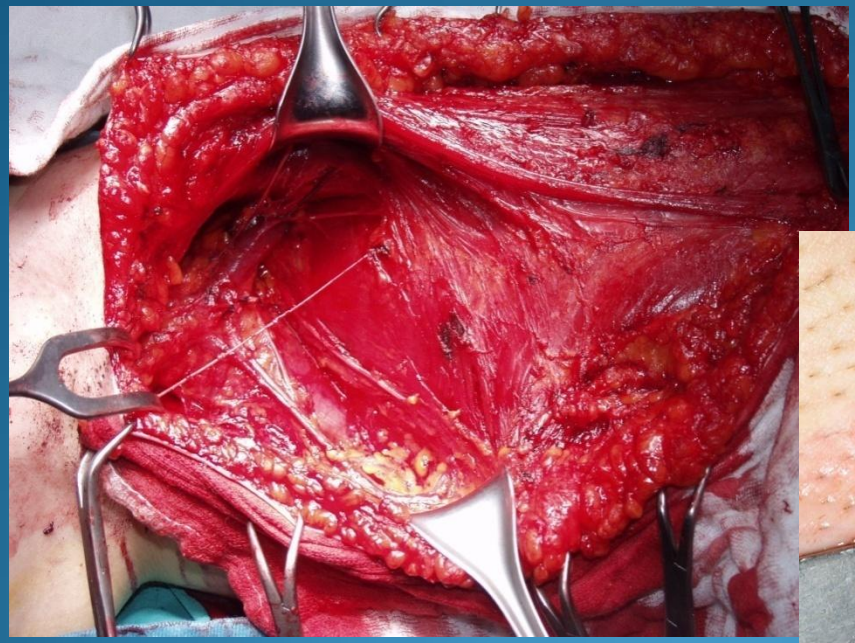
GISMa/ONS 2009

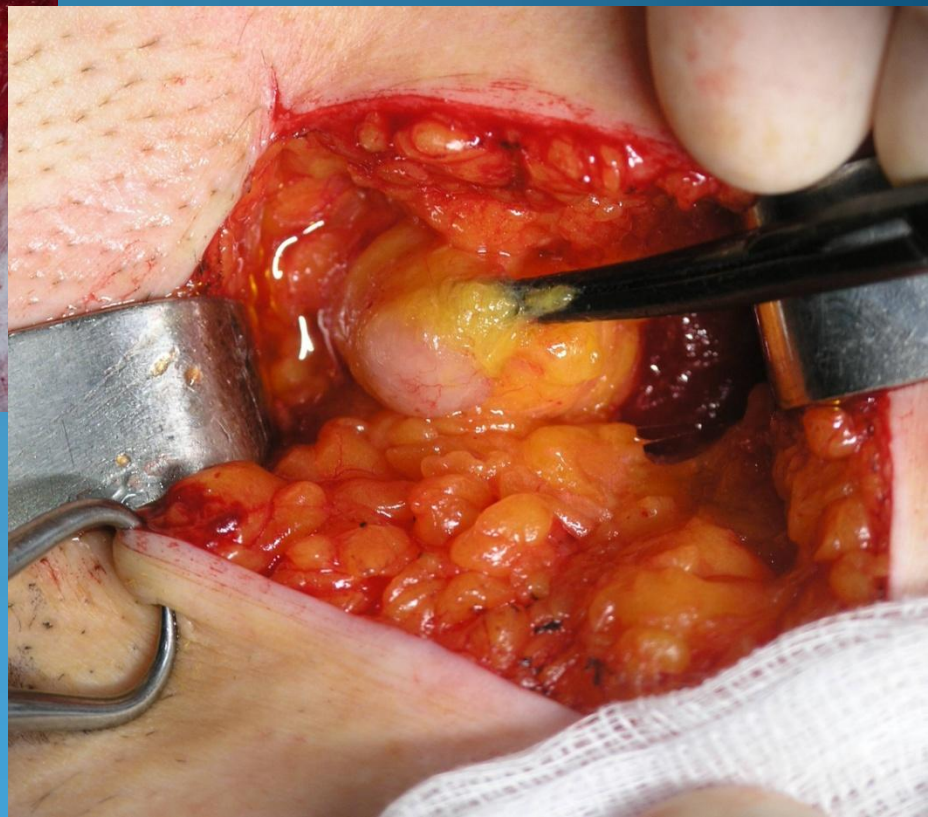
Stadiaz. ascellare con solo linf. sentinella negli N0

Dati: SQTM Screening Italia 2001-2008



Dissezione acellare e biopsia lfn sentinella





Sovratrattamento qualitativo

Non è vero che la biopsia del linfonodo sentinella non determini alcuna morbilità!!!!

La morbilità è notevolmente ridotta rispetto all'ALND ma….è comunque presente ...se la si cerca

A 30 gg

Infezione ferita	**1%**
Sieroma ascell.	**7%**
Ematoma	**1.4%**

Correlato con n. di LN asportati (sono tutti LS ????)

A 6 mesi

Parestesie	**8.6%**
Ridotta motilità arto	**3.8%**
Linfedema > 2 cm	**6.9%**

Z0010 Trial - Am College Surgeons Oncology Group
5539 pz (Wilke,Ann Surg Oncol; 2006)

La morbilità è notevolmente ridotta ma….

ALMANAC Trial (U.K.) 1031pz. (Mansell,JNCI 2006)

A 12 mesi:

Deficit sensoriale **11%** (soggettivo) 31% ALND

8% (obiettivo) 30% ALND

Linfedema moderato **4%** 11% ALND

Sovratrattamento qualitativo

APPROCCIO ALLA PAZIENTE

Health Affairs

From Policy To Patients And Back: Surgical Treatment Decision Making For Patients With Breast Cancer

Steven J. Katz and Sarah T. Hawley

Persistent use of mastectomy for breast cancer has motivated concerns about overtreatment by surgeons and lack of patient involvement in decisions. However, recent studies suggest that patients perceive substantial involvement and that some patients prefer more invasive surgery, while other research suggests that surgical treatment choices might be poorly informed. Decision-making quality can be improved by increasing patients' knowledge about treatments' risks and benefits and by optimizing their involvement. The mastectomy story underscores the limitations of utilization measures as quality indicators. Strategies to improve patient outcomes should focus on tools to improve the quality of decision making and innovations in multispecialty practice.

S J Katz et al, Health Aff 2007

Sovratrattamento qualitativo

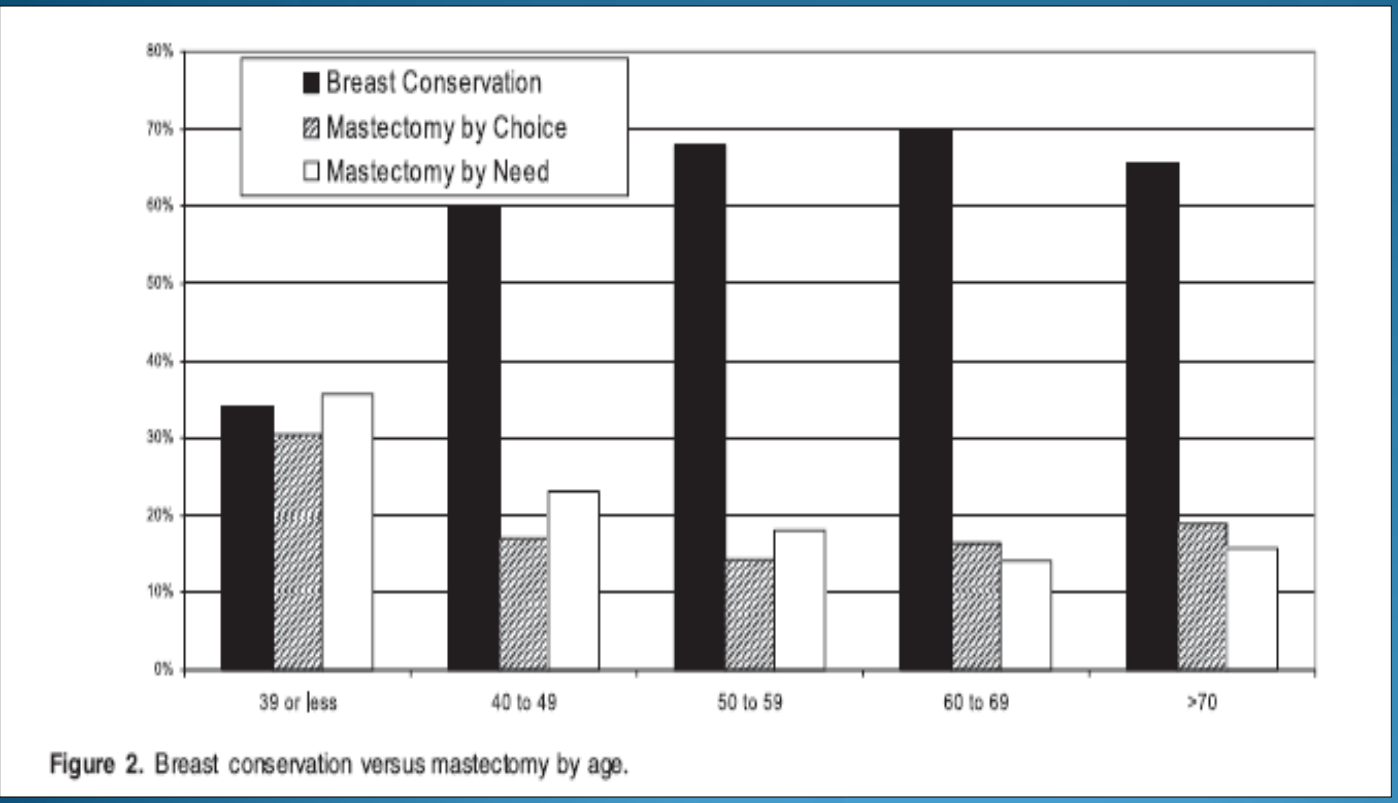


Figure 2. Breast conservation versus mastectomy by age.

M C Lee et al, The Breast Journal 2009

QUADRANTECTOMIA vs MASTECTOMIA:

Sovratrattamento qualitativo

Rischio reale ???

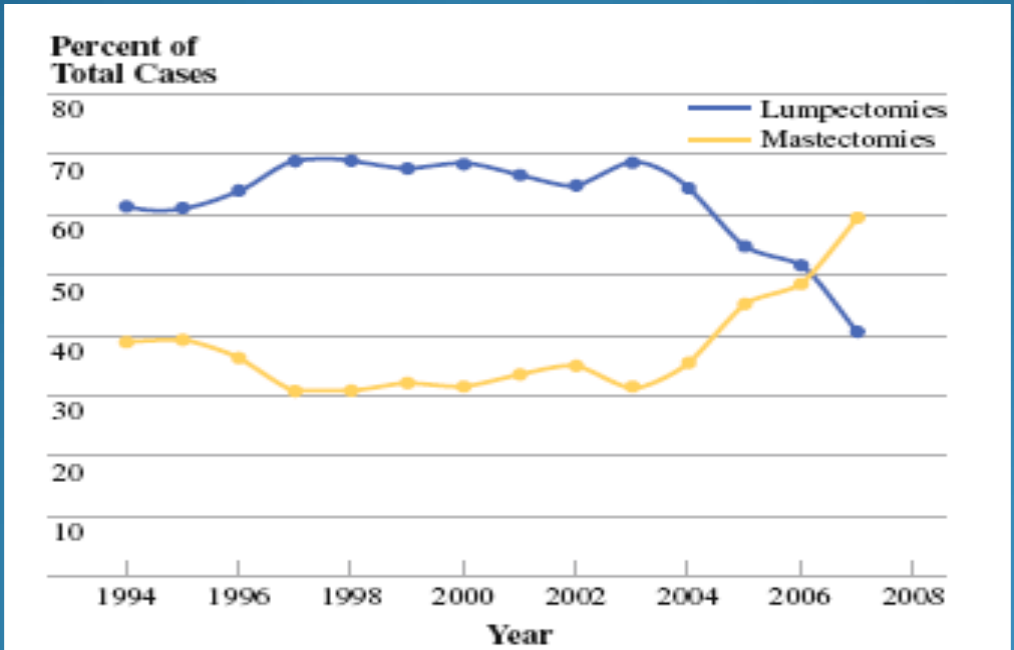
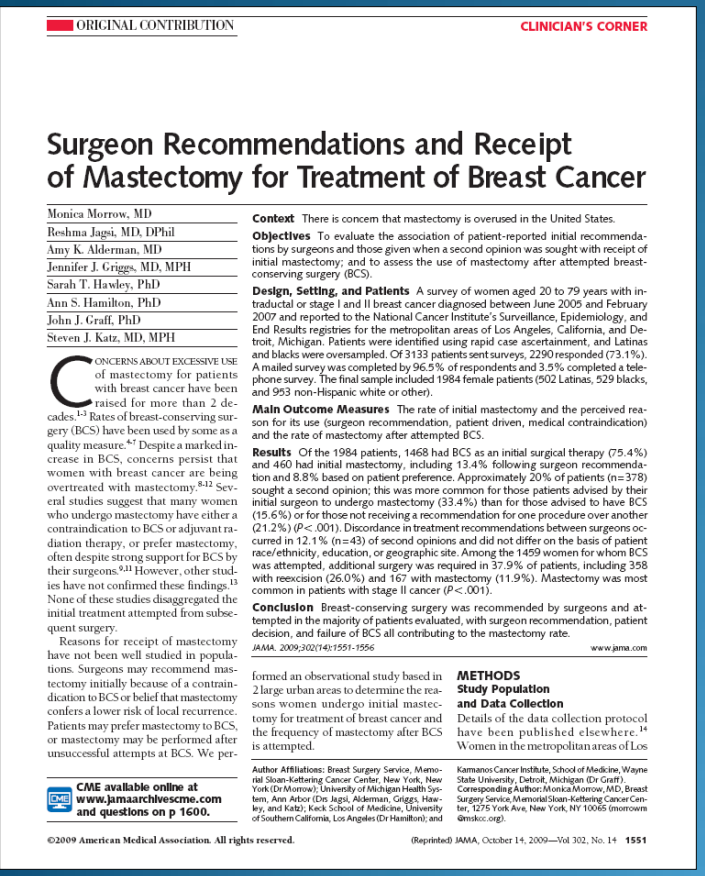


FIG. 4 Rate of mastectomy versus lumpectomy compared with overall surgical volume, 1994–2007

K P McGuire et al, Ann Surg Oncol 2009

Sovratrattamento qualitativo



ORIGINAL CONTRIBUTION

CLINICIAN'S CORNER

Surgeon Recommendations and Receipt of Mastectomy for Treatment of Breast Cancer

Monica Morrow, MD
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Amy K. Alderman, MD
Jennifer J. Griggs, MD, MPH
Sarah T. Hawley, PhD
Ann S. Hamilton, PhD
John J. Graff, PhD
Steven J. Katz, MD, MPH

Context There is concern that mastectomy is overused in the United States.

Objectives To evaluate the association of patient-reported initial recommendations by surgeons and those given when a second opinion was sought with receipt of initial mastectomy; and to assess the use of mastectomy after attempted breast-conserving surgery (BCS).

Design, Setting, and Patients A survey of women aged 20 to 79 years with intraductal or stage I and II breast cancer diagnosed between June 2005 and February 2007 and reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results registries for the metropolitan areas of Los Angeles, California, and Detroit, Michigan. Patients were identified using rapid case ascertainment, and Latinas and blacks were oversampled. Of 3133 patients sent surveys, 2290 responded (73.1%). A mailed survey was completed by 96.5% of respondents and 3.5% completed a telephone survey. The final sample included 1984 female patients (502 Latinas, 529 blacks, and 993 non-Hispanic white or other).

Main Outcome Measures The rate of initial mastectomy and the perceived reason for its use (surgeon recommendation, patient driven, medical contraindication) and the rate of mastectomy after attempted BCS.

Results Of the 1984 patients, 1468 had BCS as an initial surgical therapy (75.4%) and 460 had initial mastectomy, including 13.4% following surgeon recommendation and 8.8% based on patient preference. Approximately 20% of patients (n=378) sought a second opinion; this was more common for those patients advised by their initial surgeon to undergo mastectomy (33.4%) than for those advised to have BCS (15.6%) or for those not receiving a recommendation for one procedure over another (21.2%) ($P<.001$). Discordance in treatment recommendations between surgeons occurred in 12.1% (n=43) of second opinions and did not differ on the basis of patient race/ethnicity, education, or geographic site. Among the 1459 women for whom BCS was attempted, additional surgery was required in 37.9% of patients, including 358 with reexcision (26.0%) and 167 with mastectomy (11.9%). Mastectomy was most common in patients with stage II cancer ($P<.001$).

Conclusion Breast-conserving surgery was recommended by surgeons and attempted in the majority of patients evaluated, with surgeon recommendation, patient decision, and failure of BCS all contributing to the mastectomy rate.

JAMA. 2009;302(14):1551-1556 www.jama.com

of mastectomy for patients with breast cancer have been raised for more than 2 decades.[1-3] Rates of breast-conserving surgery (BCS) have been used by some as a quality measure.[4-7] Despite a marked increase in BCS, concerns persist that women with breast cancer are being overtreated with mastectomy.[8-12] Several studies suggest that many women who undergo mastectomy have either a contraindication to BCS or adjuvant radiation therapy, or prefer mastectomy, often despite strong support for BCS by their surgeons.[9,11] However, other studies have not confirmed these findings.[13] None of these studies disaggregated the initial treatment attempted from subsequent surgery.

Reasons for receipt of mastectomy have not been well studied in populations. Surgeons may recommend mastectomy initially because of a contraindication to BCS or belief that mastectomy confers a lower risk of local recurrence. Patients may prefer mastectomy to BCS, or mastectomy may be performed after unsuccessful attempts at BCS. We performed an observational study based in 2 large urban areas to determine the reasons women undergo initial mastectomy for treatment of breast cancer and the frequency of mastectomy after BCS is attempted.

CME available online at www.jamaarchivescme.com and questions on p 1600.

METHODS

Study Population and Data Collection

Details of the data collection protocol have been published elsewhere.[14] Women in the metropolitan areas of Los

Author Affiliations: Breast Surgery Service, Memorial Sloan-Kettering Cancer Center, New York, New York (Dr Morrow); University of Michigan Health System, Ann Arbor (Drs Jagsi, Alderman, Griggs, Hawley, and Katz); Keck School of Medicine, University of Southern California, Los Angeles (Dr Hamilton); and Karmanos Cancer Institute, School of Medicine, Wayne State University, Detroit, Michigan (Dr Graff). Corresponding Author: Monica Morrow, MD, Breast Surgery Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065 (morrowm@mskcc.org).

not likely to have a major effect. Our findings suggest that a combined approach of education for patients and health care professionals targeting specific areas may improve decision making.

M Morrow et al, JAMA 2009

SOVRATRATTAMENTO
nei trattamenti adiuvanti

1. Impiego dei taxani in combinazione con antracicline nelle pazienti N neg
2. Inpiego del trastuzumab in aggiunta alla chemioterapia in pazienti con N neg e T<1cm (in particolare < 0,5 cm)
3. Impiego di LhRh analoghi associati a TAM in aggiunta alla chemioterapia adiuvante nelle donne in premenopausa
4. Impiego prolungato (oltre 2 anni) di LhRh analoghi in associazione a TAM nelle donne in premenopausa
5. Impiego di IA in donne RO pos in postmenopausa a basso profilo di rischio
6. Impiego di IA in perimenopausa
7. Impiego della chemioterapia precauzionale nelle donne > 70 aa

Impiego di IA in donne RO pos in postmenopausa a basso profilo di rischio

65 aa, T1a-b N0M0 G1-2 RO pos.
Nessun vantaggio di sopravvivenza

Beneficio assoluto in DFS con AI = 2% NNT=50

Probabilità incrementale di frattura con AI= 4% NNH= 25

Probabilità incrementale di carcinoma dell'endometrio in paziente esposta a TAM= 0,5% NNH= 200

Rapporto di costo AI/TAM ~ 12

Distorsione nella percezione e valutazione del rischio/beneficio incrementale

- **Assenza di valutazione quantitativa del bilancio rischio/beneficio**
- **Attitudine a sovrastimare i benefici e a sottostimare i rischi**
- **Non diffusa considerazione relativa all'impiego delle risorse nel "decision making"**
- **Attitudine consapevole o inconsapevole verso una medicina difensiva**
- **Logica "facciamo il massimo"**

In poche circostanze il rischio viene misurato quantitativamente e più spesso viene stimato in modo approssimativo con tendenza alla sovrastima

Come contenere il sovratrattamento ?

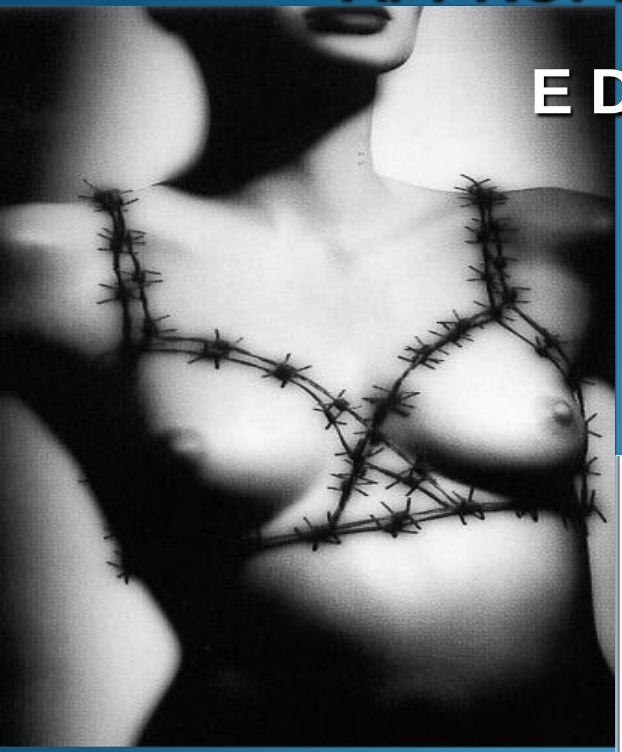
- Programmi di screening di qualità
- Monitoraggio continuo dei dati e audit multidisciplinari
- Professionisti dedicati alla diagnosi ed al trattamento del carcinoma della mammella
- **Trattamento della paziente all'interno di percorsi multidisciplinari certificati**
- Ricerca!!! per comprendere meglio la biologia e il potenziale di progressione di "queste "neoplasie... e non solo queste!

SOVRATRATTAMENTO E SCREENING

GOLD STANDARDS :

APPROPRIATEZZA DEL TRATTAMENTO

E DELLA COMUNICAZIONE



Health Expect. 2008 Dec;11(4):366-75.

Informed decision making before initiating screening mammography: does it occur and does it make a difference?

Nekhlyudov L, Li R, Fletcher SW.

Department of Ambulatory Care and Prevention, Harvard Medical School/Harvard Pilgrim Health Care, Boston, MA 02215, USA. larissa_nekhlyudov@harvardpilgrim.org

Abstract

OBJECTIVE: Informed decision making regarding screening mammography is recommended for women under age 50. To what extent it occurs in clinical settings is unclear. METHODS: Using a mailed instrument, we surveyed women aged 40-44 prior to their first screening mammogram. All women were members of a large health maintenance organization and received care at a large medical practice in the Greater Boston area. The survey measured informed decision making, decisional conflict, satisfaction, and screening mammography knowledge and intentions to undergo screening. RESULTS: Ninety-six women responded to the survey (response rate 47%). Overall, women reported limited informed decision making regarding screening mammography, both with respect to information exchange and involvement in the decision process. Less than half (47%) reported discussing the benefits of screening; 23% the uncertainties; and only 7% the harms. About 30% reported discussing the nature of the decision or clinical issue; and 29% reported their provider elicited their preferred role in the decision; 38% their preferences; and 24% their understanding of the information. Women who were uninformed had higher decisional conflict (2.37 vs. 1.83, P=0.005) about screening mammography and were more likely to be dissatisfied with the information and involvement. Women's screening mammography knowledge was limited in most areas; however being presented with information did not diminish their intentions to undergo screening. CONCLUSION: Informed decision making before initiating screening mammography is limited in this setting. There appears to be little indication that information about the benefits and harms decreases women's intentions to undergo screening. Methods to communicate information to women before initiating screening mammography are needed.

PMID: 19076664 [PubMed - indexed for MEDLINE]

GRAZIE PER L ‘ATTENZIONE !!!