S.S. FORMAZIONE PERMANENTE E AGGIORNAMENTO

UN KEY ARTICLE PER UN CHIRURGO

MASSIMILIANO BORTOLINI

UNITA DI SENOLOGIA

ASL CITTA DI TORINO

THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center

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ORIGINAL ARTICLE – BREAST ONCOLOGY

Nonoperative Management for Invasive Breast Cancer After Neoadjuvant Systemic Therapy: Conceptual Basis and Fundamental International Feasibility Clinical Trials

Henry M. Kuerer, MD, PhD[1], Marie-Jeanne T. F. D. Vrancken Peeters, MD, PhD[2], Daniel W. Rea, MBBS, PhD[3], Mark Basik, MD[4,5], Jennifer De Los Santos, MD[6], and Joerg Heil, MD[7]

Problemi

- L’imaging non è sufficientemente sensibile
- Selezione dei pazienti
- Affidabilità delle biopsie

Vantaggi

- Evita la chirurgia e le sue complicanze
- Migliora la qualità di vita
- Diminuisce i costi

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Annals of Oncology **10**: 47[illegible]52, 1999.
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Original article

Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: A unicentre randomized trial with a 124-month median follow-up

L. Mauriac, G. MacGrogan, A. Avril, M. Durand, A. Floquet, M. Debled, J. M. Dilhuydy & F. Bonichon on behalf of Institut Bergonié Bordeaux Groupe Sein (IBBGS)

Institut Bergonié, Regional Cancer Center, Bordeaux, France

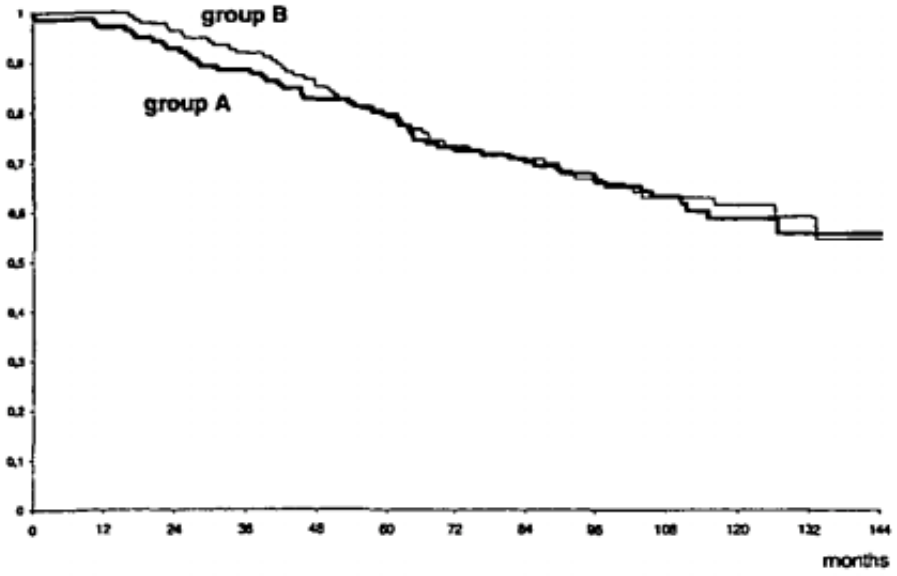


Figure 1. Overall survival.

Table 2. Relapses according to local treatment in group B.

	Exclusive irradiation on breast and nodal areas	Tumorectomy + axillary dissection + breast irradiation	Mastectomy + axillary dissection without irradiation
Patients (*n*)	44	40	49
Relapses (*n*)	21	17	28
Local	15	9	11
Breast	6	6	–
Breast + axilla	7	–	–
Breast + axilla + metastasis	7	–	–
Breast + metastasis	–	3	–
Nodal	10	–	1
Metastatic	7	11	20

2003

Journal of Clinical Oncology®

An American Society of Clinical Oncology Journal

Remission ... Breast Cancer?

By A. Ring, A. Webb, S. Ashley, W.H. Allum, S. Ebbs, G. Gui, N.P. Sacks, G. Walsh, and I.E. Smith

Purpose: **This retrospective analysis aimed to identify whether breast cancer patients receiving radiotherapy alone following a complete clinical remission (cCR) to neo-**

For surgery and no surgery, respectively, there were no significant differences in disease-free survival or overall survival (5-year, 74% v 76%; 10-year, 60% v 70%, *P* = .9)

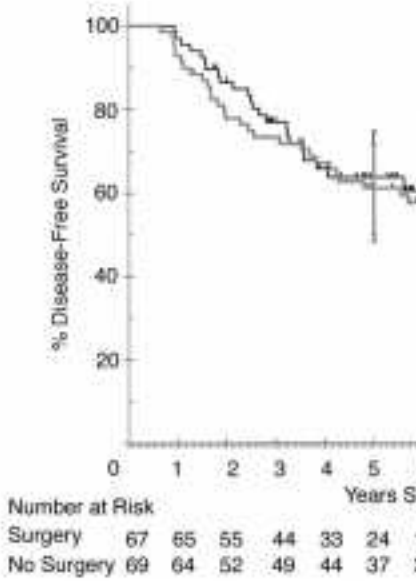


Fig 1. Disease-free survival in pa... radiotherapy) compared with those no...

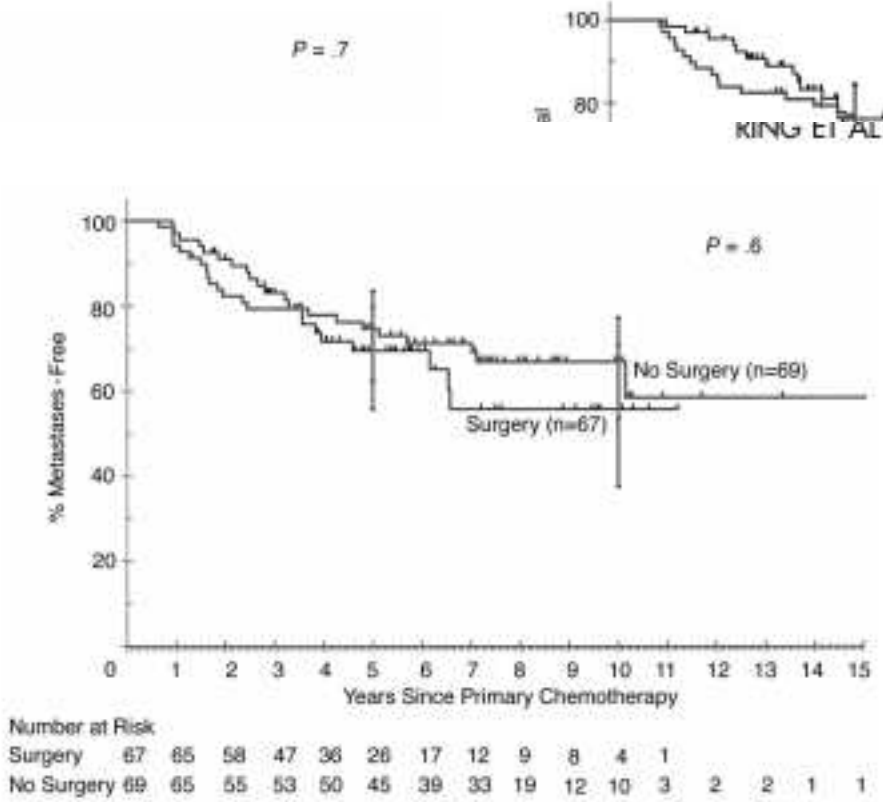
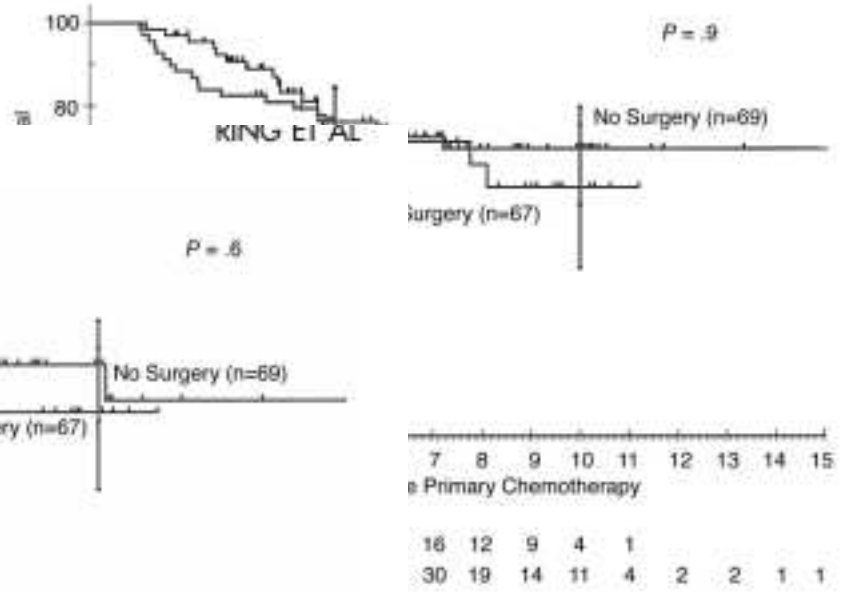


Fig 2. Metastasis-free survival in patients undergoing surgery (with or without radiotherapy) compared with those not undergoing surgery (radiotherapy alone).



g surgery (with or without radiotherapy) gery (radiotherapy alone).

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2011

Cancer/Radiothérapie 15 (2011) 106–114

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Article original

Cancers du sein de stade II-IIIA : la radiothérapie exclusive est-elle une option en cas de réponse clinique complète à la chimiothérapie néoadjuvante ?☆

Early stage breast cancer: Is exclusive radiotherapy an option for early breast cancers with complete clinical response after neoadjuvant chemotherapy?

C. Daveau[a], A. Savignoni[b], S. Abrous-Anane[a], J.-Y. Pierga[c], F. Reyal[d], C. Gautier[b], Y.-M. Kirova[a], R. Dendale[a], F. Campana[a], A. Fourquet[a], M.-A. Bollet[a,*]

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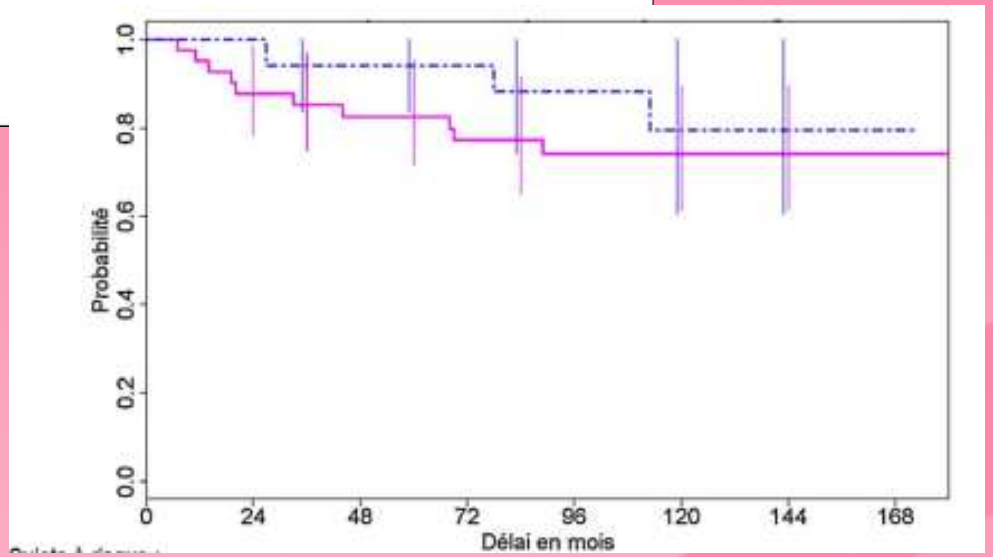

Intervalle sans récidive locorégionale chez les patientes avec une réponse complète à l'imagerie: **(––): radiothérapie (RT) exclusive; (– - –): chirurgie ± radiothérapie,** p = 0,45.

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Trials Clinici completati

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TABLE 1 Completed, ongoing, and planned clinical feasibility trials utilizing percutaneous biopsy after neoadjuvant therapy to select patients for omission of breast cancer surgery

Status	Group/author-PI	Eligibility criteria/lesion size criteria	Type of biopsy	No. of patients	Study unique characteristics	Performance results
Completed trials	MD Anderson Cancer Center/ Kuerer et al.[16]	All lesions <5 cm on imaging after NST; included only TN and HER2-amplified cases	VACB and FNA; median number sampled 12 using 9G under radiologist defined image guidance (63% by stereotactic and 37% by ultrasound)	40	Meticulous image guided sampling in radiology suite Subtype specific with highest probability of pCR (no invasive and in situ)	Accuracy = 98%; FNR = 5%; NPV = 95%
	German Breast group/Heil et al.[4,6]	Invasive breast cancer patients; nonmetastatic; with clinical imaging after neoadjuvant chemotherapy/No lesion size criteria	Core cut (CC) and vacuum-assisted biopsy (VACB)	164 (111 with CC and 46 with VACB)	Explorative comparison of different techniques: CC and VACB, ultrasound and mammographic guidance	Entire cohort (n = 164): NPV 71.3%; FNR 49.3%; Mammographic guided VACB (n = 16): NPV 100%; FNR 0%
	University of Heidelberg/ Heil et al.[5]	Histologically confirmed, unilateral breast cancer; clinical partial or complete response to NST; target lesion visible by ultrasound/No lesion size criteria	Ultrasound-guided VACB	50	Explorative comparison of three evaluation methods of biopsy specimen pathologic representativeness	Entire cohort (n = 50): NPV 76.7%; FNR 25.9%; Histopathological evaluation of representativeness (n = 38): NPV 94.4%; FNR 4.8%
	University of Birmingham/ Rea-Francis et al./NOSTRA PRELIM[15]	Invasive breast cancer with any receptor subtype receiving NST/No lesion size criteria	Ultrasound guided core biopsy; 4 to 6; mammography and stereotactic biopsy not utilized for malignant calcifications	22	Designed to inform biopsy protocol for larger study	Number of patients with a false-negative result (4/18 total patients)

Trials clinici in corso

TABLE 1 continued

Status	Group/author-PI	Eligibility criteria/lesion size criteria	Type of biopsy	No. of patients	Study unique characteristics	Performance results
Ongoing trials	MD Anderson Cancer Center/ Kuerer et al.[18]	TN or HER2-positive initial imaging size < 5 cm and final size < 2 cm and or >90% of lesion sampled after NST; N0 or biopsy confirmed N1 with < 4 abnormal nodes on initial ultrasound	Minimum of 12 9G VACB; image guidance method dependent on radiologist decision	50	No breast surgery treatment trial	Primary endpoint is local recurrence with continuous monitoring and early stopping rules; secondary endpoints listed in Fig. 1
	Netherlands Cancer Institute MICRA Trial/ MACRA Trial Vrancken-Peeters et al.[11]	Invasive breast cancer patients; non-metastatic; with radiologic partial or complete response on CE-MRI after NST/No lesion size criteria	Ultrasound-guided 14G biopsies targeted around pre-NST placed marker (4 central; 4 peripheral)	525 (150 with partial radiologic response on CE-MRI and 375 with complete radiologic response on CE-MRI)	All breast cancer subtypes; Response monitoring with CE-MRI	Primary endpoint is a specificity of >92% (proportion of patients with residual disease in the surgical specimen that is also confirmed by biopsy) In addition, FNR, will be calculated
	University of Heidelberg/ RESPONDER Trial Heil et al.[10]	Invasive breast cancer after NST; clinical partial or complete response; target lesion visible on ultrasound or mammography/No lesion size criteria	Ultrasound- or mammographic-guided VABC	600	Confirmative analysis to identify a pCR using VACB	Primary endpoint <10% FNR. Standardization of histopathological evaluation of post-NST samples
Planned trials	University of Birmingham/ Rea/NOSTRA feasibility	ER-negative or HER2-positive invasive breast cancer receiving NST/lesion size must be > 1 cm on ultrasound or node-positive	Ultrasound-directed biopsy, minimum of 6	150	Microcalcifications will not be targeted; no upper limit of size criteria	FNR < 10%
	NRG/BR005 Basik and De Los Santos	Operable focal or multifocal (T1-T3, stage II and IIIA invasive ductal carcinoma/with no size criteria (all receptor phenotypes)), completed NST with a clinical complete response (by clinical examination) Patients must have achieved a complete or near complete radiologic tumor response on breast imaging with mammogram, ultrasound, and MRI Patients must be undergoing breast conserving therapy Patients must have a biopsy marker placed within the tumor bed with imaging confirmation (preferably mammogram but ultrasound or MRI is acceptable) of marker placement prior NST	6 8-11G VACB, stereotactic	175	Multicenter cooperative group study with trimodality imaging required	NPV = 90% and FNR = 10%

GERMAN BREAST GROUP

Scopo dello studio:

Miglior tecnica bioptica per evitare errori

- 164 PZ CON RISPOSTA COMPLETA DOPO NACT
- 111 CB e 46 VACB
- ENDPOINT quale sistema ha miglior FNR
- MIGLIOR RISULTATO MX +VACB

Mammographic guided VACB (n = 16): NPV 100%; FNR 0%

Entire cohort (n = 164): NPV 71.3%; FNR 49.3%;

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RESPONDERS

- Partito nel 2017: multicentric, confirmative, intra individue controlled, one armed diagnostic trial
- 600 pz raccolti in 21 centri
- SCOPO DELLO STUDIO :Vacb dopo nact con fnr - 10%
- Posare le basi per un successivo trial

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NETHERLANDS CANCER INSTITUTE AMSTERDAM

- MICRA (Minimally Invasive Complete Response Assessment of the breast after neoadjuvant systemic treatment) is a prospective, multicenter, observational cohort study
- 525 pz: 375 risposta completa radiologica a MRI e 150 risposta parziale
- Confronto tra istologici delle biopsie del pezzo operatorio.
- L'endpoint primario è una specificità > 92% oltre la valutazione del FNR
- Associato al MACRA trials

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UNIVERSITY OF BIRMINGHAM, UK

NOSTRA prelim e NOSTRA

•23 pazienti inseriti in un trial preliminare

•Conclusioni: almeno 6 biopsie per evitare missing della malattia residua.

NOSTRA FEASIBILITY TRIAL

•150 pazienti triple neg o her2 +

•6 biopsie per FNR <10%

•progettato per esplorare la sicurezza dell'omissione della chirurgia dopo un efficace trattamento neoadiuvante

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NRG ONCOLGY GROUP BR005

- 175 pazienti con risposta completa all'imaging (RMN,US e MX) ER neg o HER2 pos
- 6-8 biopsie VABB (11 g)
- Obiettivo: VPN >90% e FNR < 10%
- Fase tre: No Surgery randomized study

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MD ANDERSON CANCER CENTER
Feasibility Trial for Identification of Patients for Eliminating Breast Cancer Surgery Following Neoadjuvant Systemic Therapy

- Risultati preliminari su 40 pz:
- Risposte complete 20%
- Risposte complete e parziali 80%
- Accuratezza 98%
- FNR 5%
- NPV 95%
- Complicanze 20% (grado lieve)

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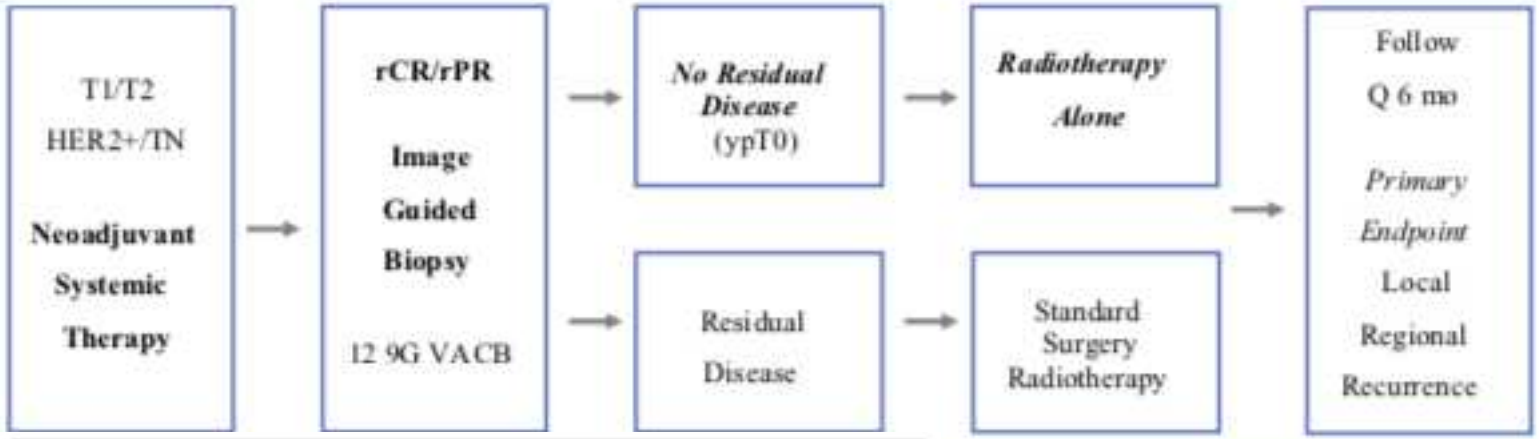
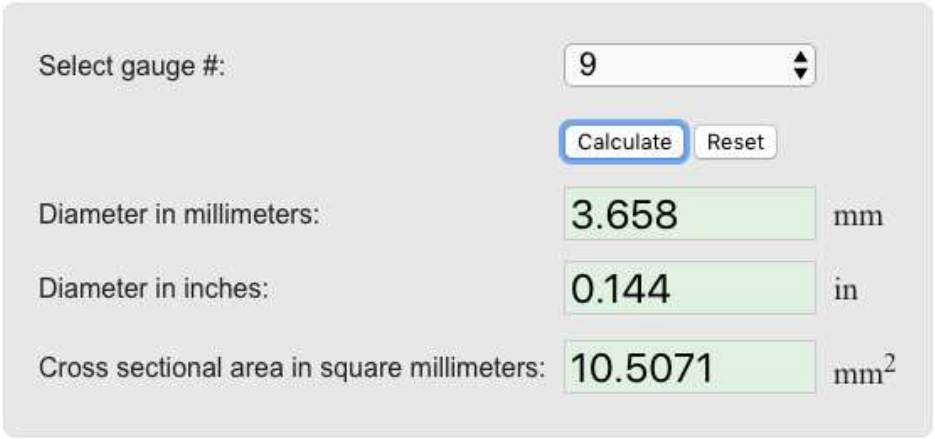
MD ANDERSON CANCER CENTER
Feasibility Trial for Identification of Patients for Eliminating Breast Cancer Surgery Following Neoadjuvant Systemic Therapy





Secondary Endpoints

Need for biopsy on F/u

Cosmetic Outcome

Quality of Life

Correlate CTC and cDNA

Cost

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PROBLEMI APERTI

GENERALI

General matters

Which patients are most likely to achieve a pathologic complete response for both invasive and in situ disease?

What specific systemic therapy agents are associated with maximal chances of a pCR (no residual invasive or in situ disease) in the breast and nodes?

What is the best imaging modality or combination of imaging per breast cancer subtype to select patients for potential biopsy and elimination of surgery?

What are the potential costs and cost savings of eliminating the need for surgery?

What proportion of patients will be interested in clinical trial participation in which surgery will be avoided and what will be their willingness to participate in a single-arm versus randomization between surgery and no-surgery?

What is the optimal oncologic endpoint and study design of a single arm "no surgery" or a randomized clinical trial of surgery vs. no-surgery trials in patients with biopsy confirmed pCR?

Which are the optimal patients for consideration of eliminating surgery with respect to size and characteristics of the breast cancer, considering potential for under sampling and long term need for imaging follow-up?

Can circulating tumor cells and/or circulating DNA or other serum markers be utilized in combination with imaging to better select patients with a pCR?

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PROBLEMI APERTI

BIOPSIA

Biopsy-related

What is the acceptable FNR of a minimal invasive biopsy to demonstrate a pCR without influencing oncologic outcome if no surgery will be performed?

What is the optimal method of minimal invasive biopsy: core cut vs. VACB in the post-NST setting (and is this influenced by sub-type)?

What is the optimal number of core biopsies necessary to ensure the highest accuracy/lowest false-negative results (and is this influenced by sub-type)?

What is the best method with respect to sectioning for evaluating core biopsies after NST to ensure the lowest chance of missing residual carcinoma?

How much of the residual lesion(s) needs to be biopsied?

Can residual microcalcifications that are no longer associated with malignancy on biopsy be left in situ and followed?

What are objective and reliable diagnostic pathological signs of pCR of the breast in VAB specimen?

How often will there be no histopathologic evidence of biopsy related changes when pCR occurs?

Are there specific locations in the breast where optimal biopsy may not be feasible due to technical factors and how can this be overcome?

PROBLEMI APERTI

GESTIONE ASCELLA

Management of the axilla

What is the best imaging tool; or combination of imaging tools for staging nodal disease prior to and following NST depending on subtype?

Can patients with initial documented nodal metastases participate safely in clinical trials of eliminating breast surgery?

What is the correlation among exceptional responders with a pCR in the breast compared with final axillary nodal status?

Does the axilla need to be treated with radiotherapy in cases with a pCR who do not undergo surgery?

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PROBLEMI APERTI

RADIOTERAPIA

What is the optimal delivery method and fractionation for breast radiation when surgery is omitted (whole breast, hypofractionation, partial breast radiation)?

Which nodal fields should be treated, if any?

Should all patients receive a boost to the prior region of carcinoma?

Is radiotherapy needed when there is complete pathologic response in the breast after NST?

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PROBLEMI APERTI

FOLLOW UP

What is the best imaging modality for following patients who do not undergo surgery for breast cancer and how often should it occur?

What will the imaging characteristics of the breast and nodal regions among patients who do not have surgery and how often will biopsy be recommended based on imaging to rule out recurrence?

What impact will eliminating surgery have on the quality of life, decisional comfort, and cosmetic outcome for patients?

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«Drastic rethinking of all diagnostic and therapeutic management strategies that are ordinarily utilized for patients who receive standard breast cancer surgery is required».

H.M.Kuerer

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