V ZOOM Journal Club 2016
Bologna, 17 Febbraio 2017

Impatto della RT nei diversi profili biomolecolari

Caso clinico

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UNIVERSITA' CAMPUS BIO-MEDICO DI ROMA

Familiare

52 anni

Nega familiarità

Fisiologica

Menarca a 12 anni

Una gravidanza a termine

Allattamento al seno

Patologica prossima

Febbraio 2016 all'autopalpazione: indurimento della mammella destra.

EO: area di consistenza duro-lignea a livello di tutta la mammella destra.

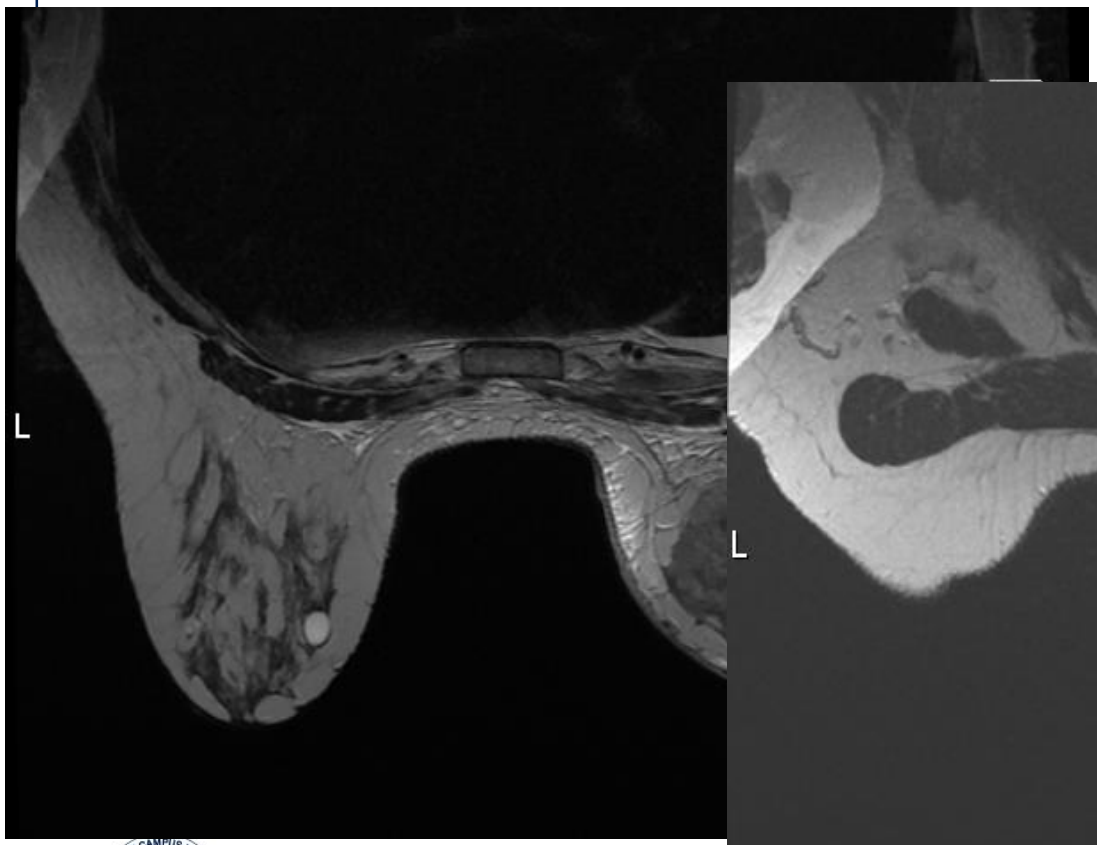
Spremitura del capezzolo negativa.

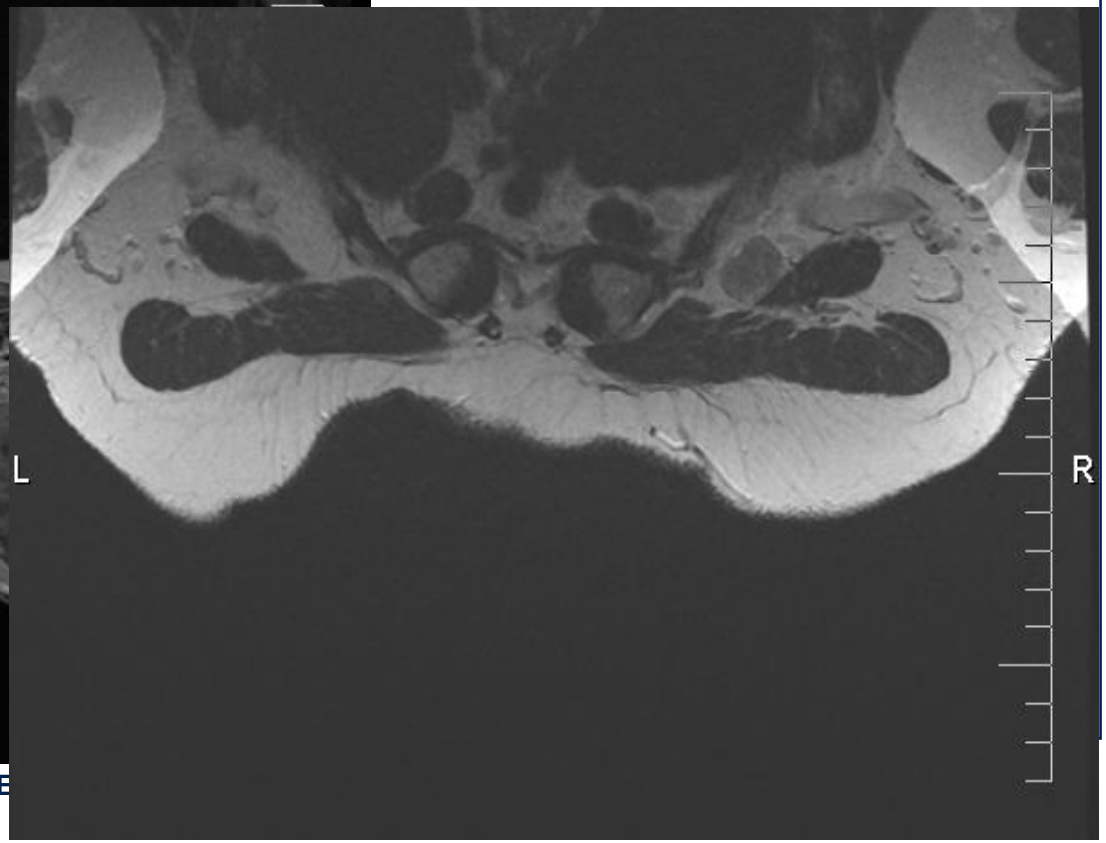
Pacchetto linfonodale ascellare destro, fisso sui piani profondi.

Non adenopatie palpabili a livello sovraclaveare

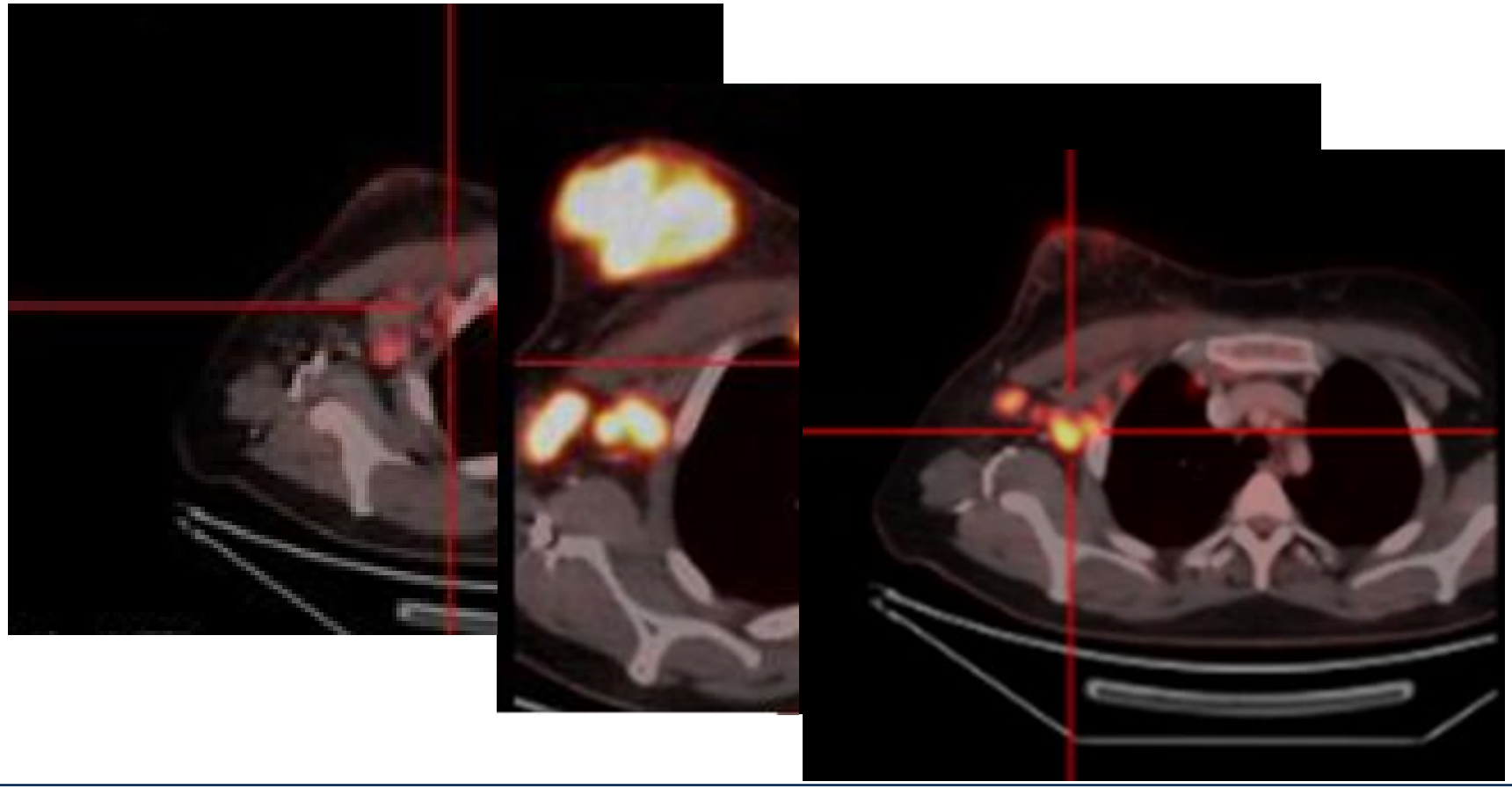
Cute e capezzolo nella norma.

RM mammella bilaterale: formazione espansiva nodulare a margini polilobati e irregolari che occupa gran parte della mammella destra (80*86mm). Concomitante edema diffuso della mammella. Presenza di alcune linfoadenopatie di aspetto nerotico-colliquativo, globoso in sede ascellare omolaterale (24mm e 11mm).



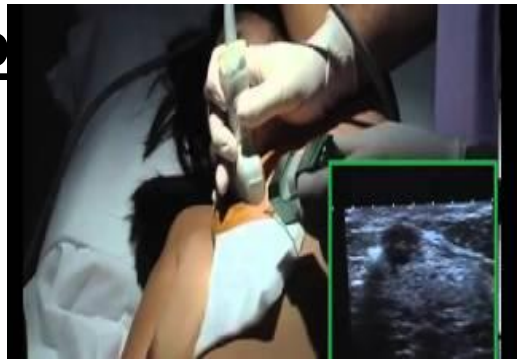


FDG PET-TC: iperaccumulo a livello della mammella destra (SUV 28.9), della regione retropettorale (SUV 8.8) e della regione ascellare omolaterale (SUV 28.9).
Escluse lesioni secondarie.



Core biopsy eco-guidata su nodulo mammario:

EI: Carcinoma scarsamente differenziato estesamente necrotico



ER neg PR neg, ki67 59%

Determina rpo policlonale incomplet neoplastic

Indagine m **non significativa**

STADIO CLINICO IIIA
cT3 cN2a cM0
SOTTOTIPO MOLECOLARE
Triplo negativo

Agoaspirato su linfonodo ascellare destro: C5

Sottoposta a ***CT neoadiuvante:***

FEC per 6 cicli

FDG PET-TC post-chemioterapia: iperaccumulo a livello della mammella destra e a livello linfonodale in sede ascellare destra (1.7) di intensità ridotta rispetto il precedente.

Mastectomia radicale dx + svuotamento ascellare omolaterale di I e II livello.

EI: ampio focolaio di necrosi con marcata reazione infiammatoria costituita da elementi istiocitari, rare cellule giganti. Non si osservano strutture duttali o lobulari atipiche.

Si rivelano nel tessuto adiposo del cavo ascellare sette strutture verosimilmente linfonodali interamente costituite da elementi istiocitari e sette stru[illegible]i da cellule atipiche

pCR

ypT0 ypN0 pMx

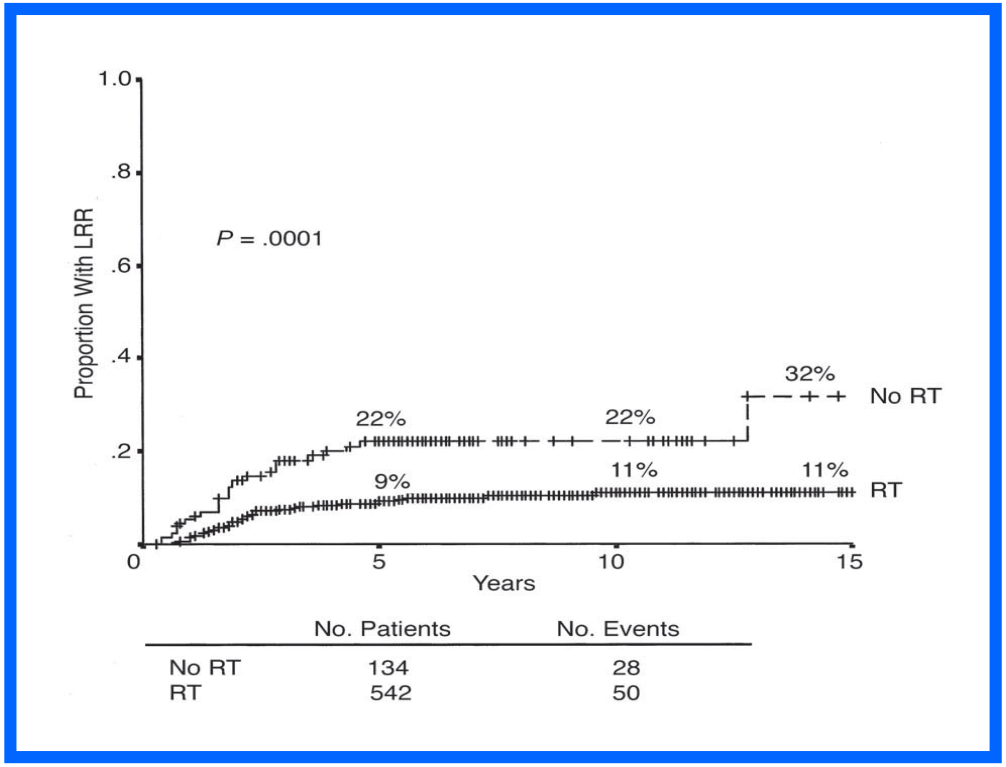
<u>ER neg, PR neg, Ki67 45%, HER-2 negativo</u>

Ristadiazione post-intervento: negativa sia locale che a distanza

Quale indicazione nel trattamento adiuvante?

Fattori clinico-patologici

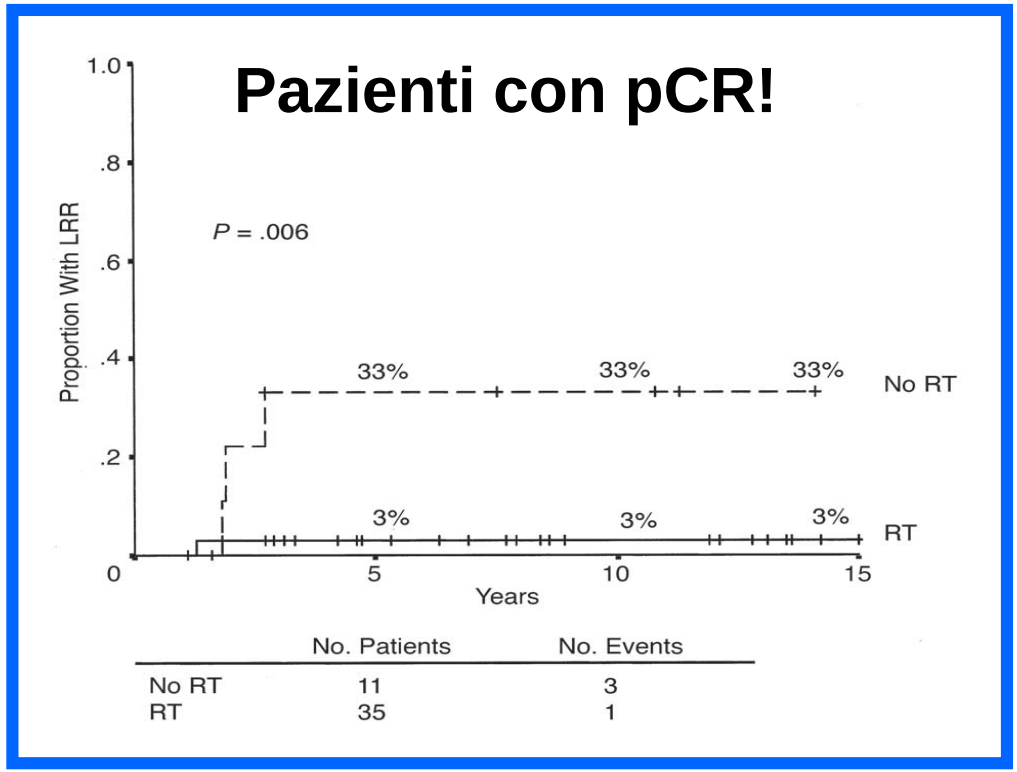
RT dopo chemioterapia NAD



cT3-4, cN2-3, pT >2cm e pN+ >4 linf

Huang EH, JCO 2004

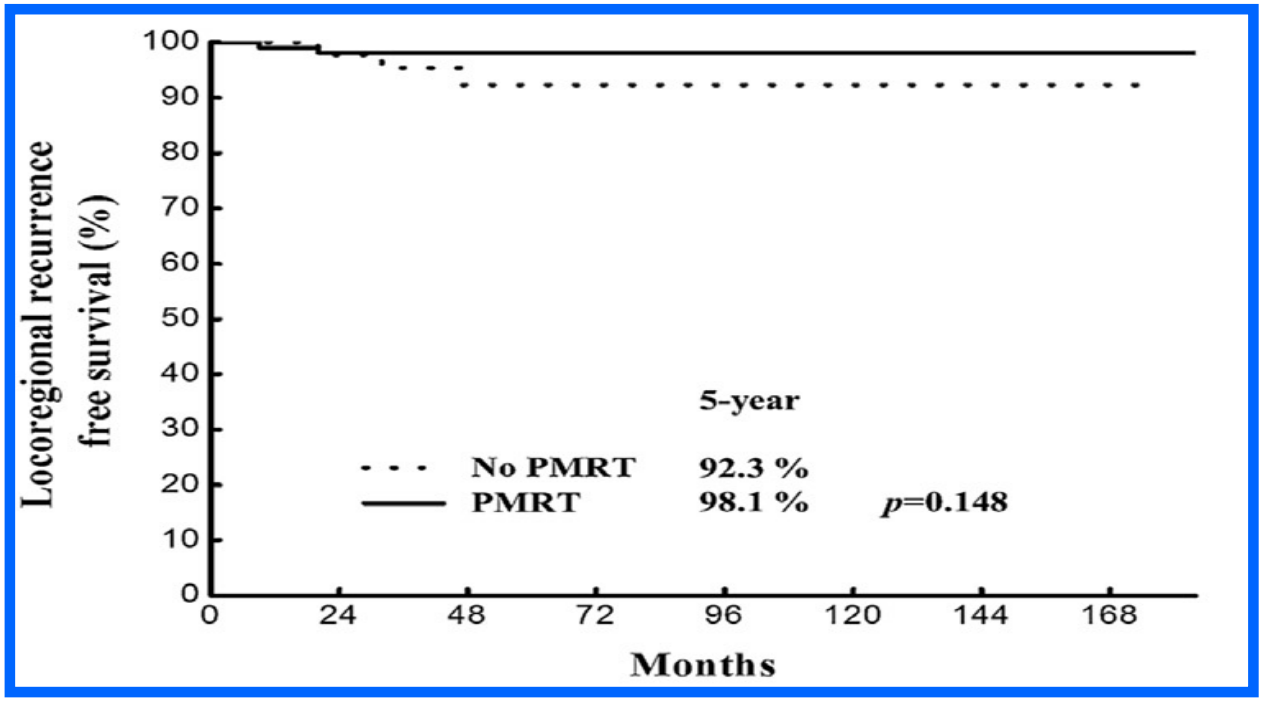
RT dopo chemioterapia NAD



>30%
NO RT

Huang EH, JCO 2004

RT dopo chemioterapia NAD



NB:
stadio III
45%

Shim SJ, IJBROP 2014

Fattori molecolari

Review

Surgery and radiation therapy of triple-negative breast cancers: From biology to clinics

Jacques Bernier [a, *], Philip M.P. Poortmans [b]

2016

It is generally associated with **high tumour grade**, **basal cytokeratins 5/6**, **p53 overexpression and BRCA1 mutations, younger age**, **cell necrosis**, **large tumor size** and **high mitotic indices**.

The type of surgery was not found to affect significantly the treatment outcome in this patient population

Compared to other molecular sub-types:

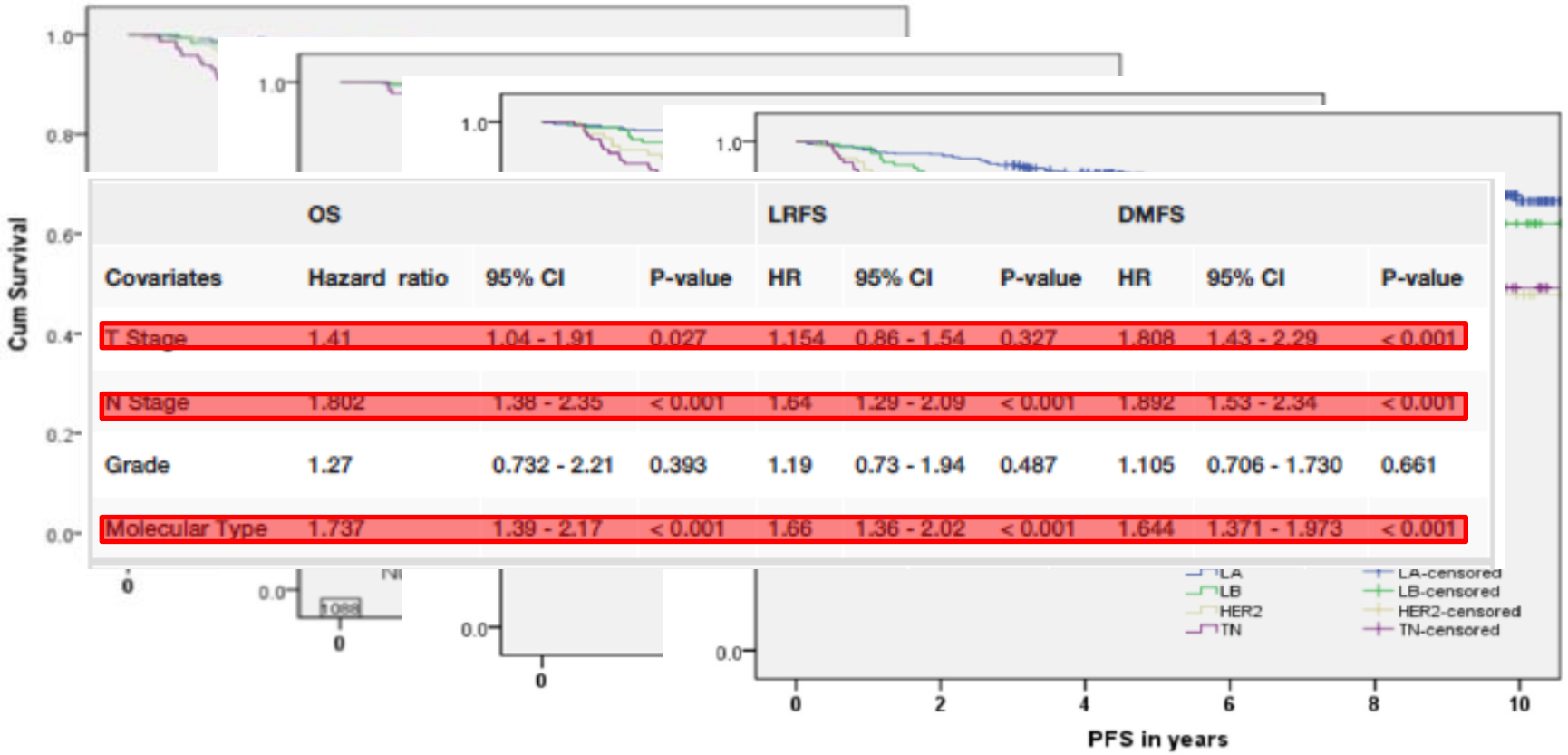
- affect **negatively local-regional recurrence (LRR) rates** during the first 3 years following the treatment,
- often associated with **distant metastases**.
- **elevated 5-year death rate**.

Pattern of Local Recurrence and Distant Metastasis in Breast Cancer By Molecular Subtype

Cureus

2016

Xingrao Wu [1], Ayesha Baig [2], Goulnar Kasymjanova [3], Kamran Kafi [2], Christina Holcroft [4], Hind Mekouar [2], Annie Carbonneau [2], Boris Bahoric [5], Khalil Sultanem [2], Thierry Muanza [6]



	OS			LRFS			DMFS		
Covariates	Hazard ratio	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
T Stage	1.41	1.04 - 1.91	0.027	1.154	0.86 - 1.54	0.327	1.808	1.43 - 2.29	< 0.001
N Stage	1.802	1.38 - 2.35	< 0.001	1.64	1.29 - 2.09	< 0.001	1.892	1.53 - 2.34	< 0.001
Grade	1.27	0.732 - 2.21	0.393	1.19	0.73 - 1.94	0.487	1.105	0.706 - 1.730	0.661
Molecular Type	1.737	1.39 - 2.17	< 0.001	1.66	1.36 - 2.02	< 0.001	1.644	1.371 - 1.973	< 0.001

Breast Molecular Profiling and Radiotherapy Considerations

Omar Mahmoud and Bruce G. Haffty

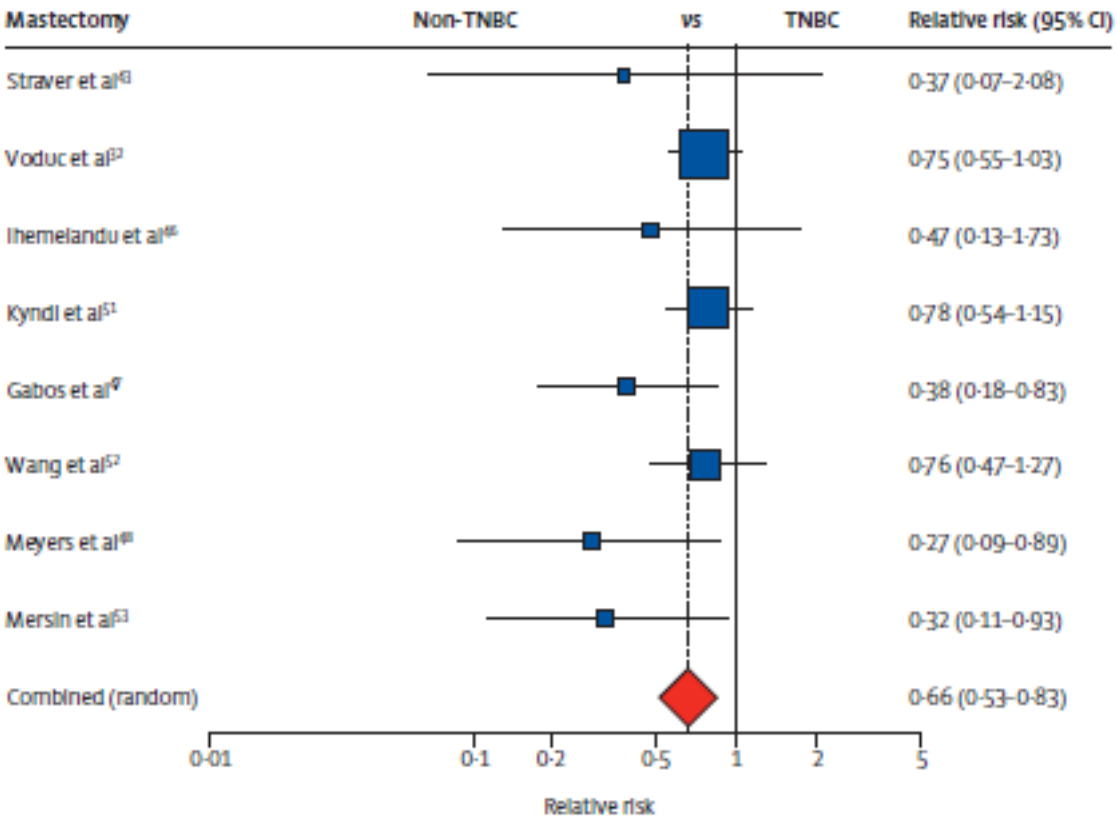
Adv Exp Med Biol 2016

Author	N	MFU	Systemic therapy (%)	RT	5 Y-LRF by subtype (%)			
					LumA	LumB	HER	TN
Voduc [14]	2985	12	57(20% C; 31% HT)	Comp[d]	8[b,c]	10[b,c]	21[b,c]	14[b,c]
					8[b,h]	14[b,h]	17[b,h]	19[b,h]
Kyndi [16]	1000	17	100 (CMF 82b, Tamoxifen 83b)	Comp	2[a]	2[a]	10[a]	9[a]
				None	23[a]	28[a]	21[a]	25[a]
Gabos [37]	618	4.8	57 CT; 63 HT	Comp[d]	3.4	8.5	14.7[+]	11[+]
Meyers [39]	149	4.5	100[f,e]	Comp[d]	4	4	5	14
Kreubil [54]	1742	6.1	18 CT[n]; 33HT; 45 both	Non-comp	2.5	9.8	3.8	10.9
Dominici [46]	819	4.8	47 CT; 67 HT[n]	Comp[d]	1[i]	6.5[i]	2[i]	10.9[i]
Park [30]	1006	5.8	82 CT;56 HT	Comp[d]	2.4[i]	9.6[i]	12.1[i]	7.4[i]
Dent [29]	1601	8.1	27CT; 51HT	NR	12			13

Radiation therapy in the locoregional treatment of triple-negative breast cancer

2015

Meena S Moran



Systematic or Meta-analysis Studies

The value of adjuvant radiotherapy on survival and recurrence in triple-negative breast cancer: A systematic review and meta-analysis of 5507 patients

M.A. O'Rorke [a,*], L.J. Murray [a], J.S. Brand [b], N. Bhoo-Pathy [c]

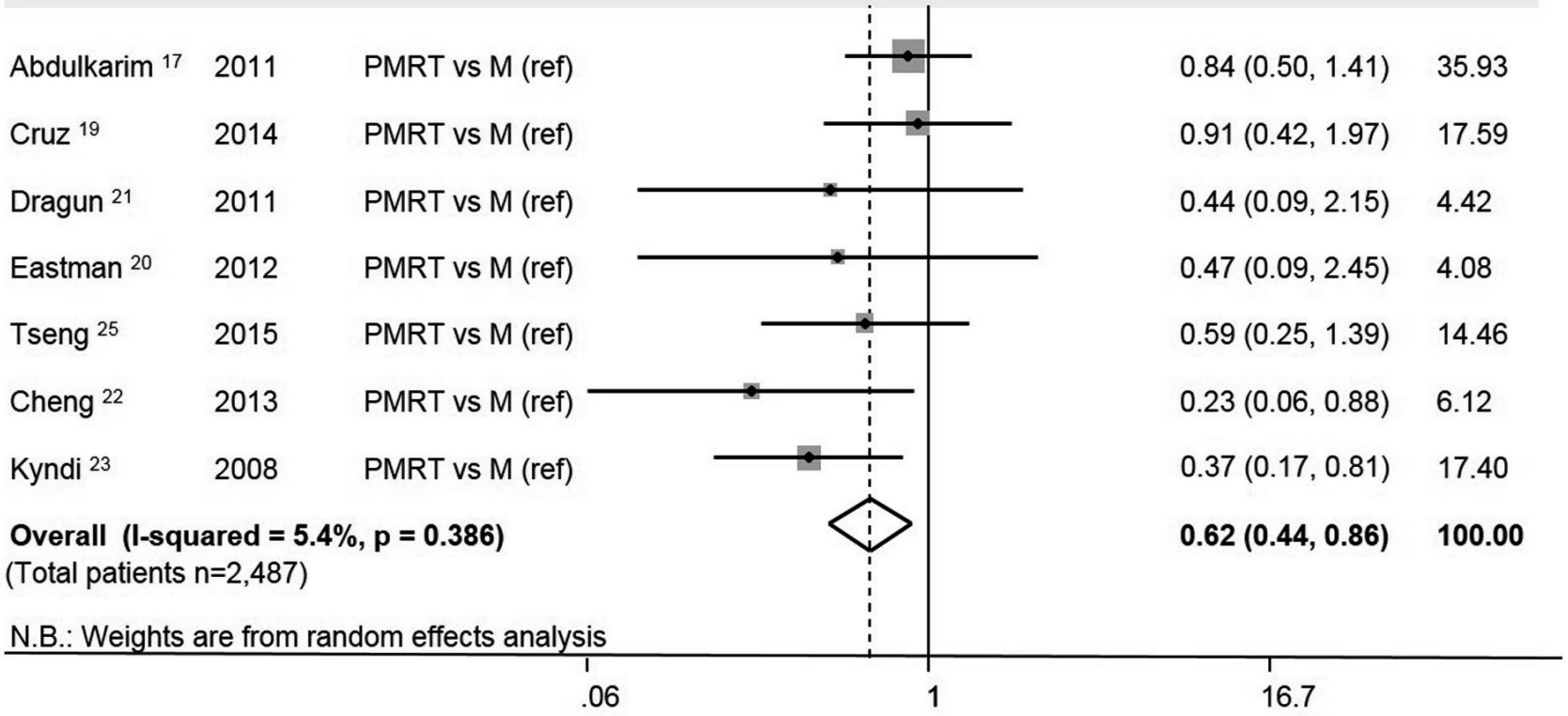
2016

Loco-regional recurrence: PMRT vs. MT

Abdulkarim [17]	2011	PMRT vs M (ref)	0.84 (0.50, 1.41)	35.93
Cruz [19]	2014	PMRT vs M (ref)	0.91 (0.42, 1.97)	17.59
Dragun [21]	2011	PMRT vs M (ref)	0.44 (0.09, 2.15)	4.42
Eastman [20]	2012	PMRT vs M (ref)	0.47 (0.09, 2.45)	4.08
Tseng [25]	2015	PMRT vs M (ref)	0.59 (0.25, 1.39)	14.46
Cheng [22]	2013	PMRT vs M (ref)	0.23 (0.06, 0.88)	6.12
Kyndi [23]	2008	PMRT vs M (ref)	0.37 (0.17, 0.81)	17.40
Overall (I-squared = 5.4%, p = 0.386)			**0.62 (0.44, 0.86)**	**100.00**

(Total patients n=2,487)

N.B.: Weights are from random effects analysis



Neoadjuvant chemotherapy has been widely used:

- to treat **locally advanced and inflammatory** breast cancer
- in operable BC with the initial aim to **downstage** the tumor for better loco-regional control and **increased conservative surgery rate**
- early identification of **un-responsive tumors**; that gives an opportunity to terminate the ineffective therapy and/or to switch to an alternative regimen.

Von Minckwitz G, JCO 2008

Intrinsic breast cancer **subtypes** varies in their response to neoadjuvant chemotherapy with a **pCR rate** reaching as **high as 30 % in hormone receptor-negative tumors** compared to **< 10 % in hormone receptor-positive tumors.**

de Azumbuja E et al, Lancet Oncol 2014

Achieving **pCR** following neoadjuvant chemotherapy has been **constantly associated with an improved disease outcome.**

Cortazar P et al, Lancet 2014

Can pathologic complete response (pCR) be used as a surrogate marker of survival after neoadjuvant therapy for breast cancer?

Qian Wang-Lopez [a,b], Nassera Chalabi [a,c,d], Catherine Abrial [a,c,d], Nina Radosevic-Robin [a,c],

CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

2016

References	Subpopulation definition	Regimen	N	Median FU (months)	DFS		p-value pCR vr non-pCR	OS		p-value pCR vr non-pCR
					HR	95% CI		HR	95% CI	
Triple negative subgroup										
Hurley et al. [70]	HR−/HER2−	- Platinum salts/anthracyclines or, - Platinum salts	144	48	0.22	[0.10–0.52]	<0.001[b]	0.32	[0.14–0.76]	0.009[b]
Asaga et al. [86]	HR−/HER2−	- Anthracyclines or, - Taxanes or, Anthracyclines/taxanes	135	34.8						
Von Minckwitz et al. [33]	HR−/HER2−	- Anthracyclines/taxanes or, - Taxanes/antimetabolites or, - Anthracyclines/taxanes/alkylating agents	911	46.3	6.020	[3.92–9.25]	<0.001[b]	12.41	[5.82–26.49]	<0.001[b]
Cortazar et al. [30]	HR−/HER2−	- Anthracyclines/taxanes or, - Taxanes/antimetabolites or, - Anthracyclines/taxanes/vinca-alkaloids/antimetabolites agents	1157	64.8(DFS) 64.4 (OS)	0.24	[0.18–0.33]	NR	0.16	[0.11–0.25]	NR

Achieving a pCR was clearly **predictive of improved outcome** either in terms of DFS or OS

In TNBC patients who achieved a pCR, the **risk of recurrence and mortality decreased significantly**.

Cortazar P et al, Lancet 2014

Patients who did **not achieve a pCR had a 6-fold higher risk of relapse and a 12-fold higher risk of death** compared to patients with pCR.

Von Minckwitz G et al, Breast Cancer Res Treat 2013

In case of **relapse disease**, TNBC group had a **significantly worse OS** compared with non-TNBC .

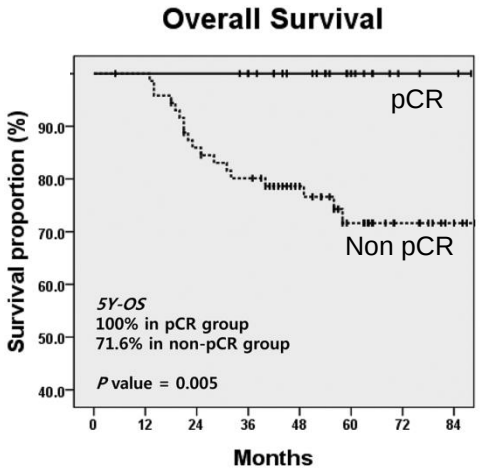
Liedtke C et al, JCO 2007

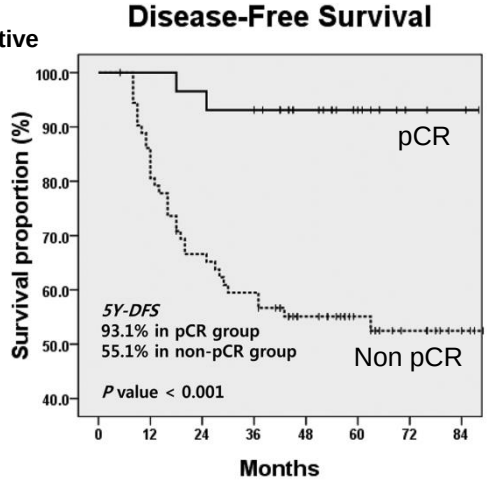
Clinical outcomes according to molecular subtypes in stage II–III breast cancer patients treated with neoadjuvant chemotherapy followed by surgery and radiotherapy

2016

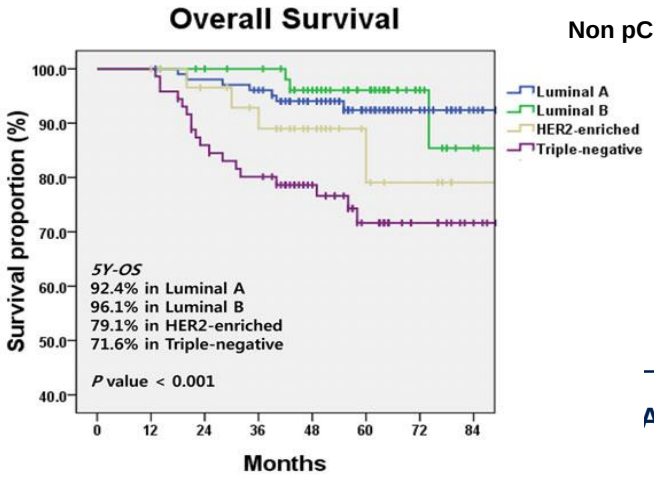
Hakyoung Kim, Won Park ✉, Seung Jae Huh, Doo Ho Choi, Jae Myoung Noh,

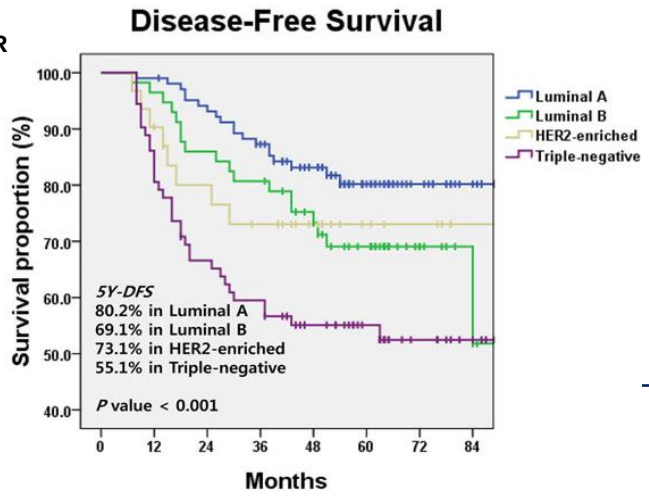
Triple-negative





Non pCR





ASCO Special Articles

Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update

Practical Radiation Oncology (2016)

Clinical Question 3

Is PMRT indicated in patients presenting with clinical stage I or II cancers who have received NAST?

Recommendation

Patients with axillary nodal involvement that persists after NAST (eg, less than a complete pathologic response) should receive PMRT. Observational data suggest a low risk of locoregional recurrence for patients who have clinically negative nodes and receive NAST or who have a complete pathologic response in the lymph nodes with NAST. However, there is currently insufficient evidence to recommend whether PMRT should be administered or can be routinely omitted in these groups. The panel recommends entering eligible patients in clinical trials that examine this question (type: informal consensus; evidence quality: low; strength of recommendation: weak).

Gruppo di Lavoro AIRO per la Patologia Mammaria

1.2.2.2 Quesito Clinico: In pazienti in stadio clinico III (ogni cTcN2; cT3cN1; cT4) è sempre indicata l'irradiazione delle stazioni linfonodali regionali dopo NACT e ALND?

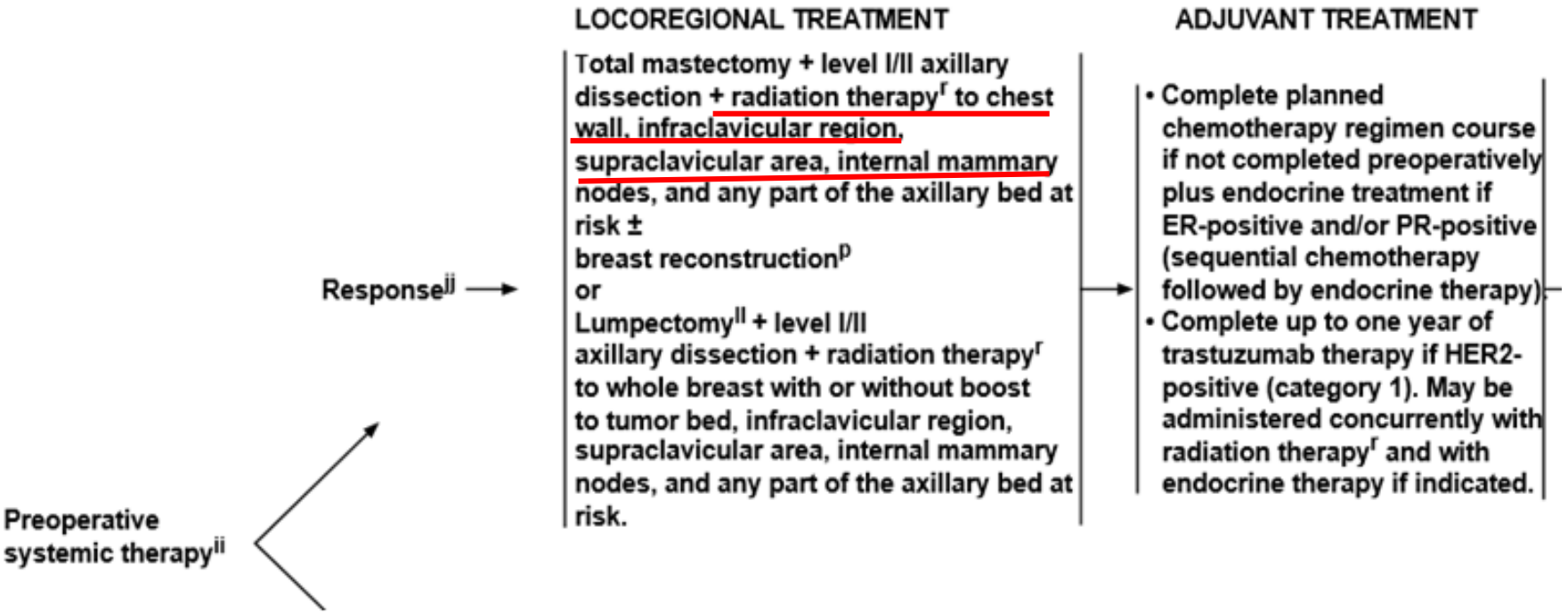
Attualmente, pertanto, non vi è parere unanime sulla necessità di una radioterapia delle stazioni linfonodali nelle pazienti con confermata risposta patologica completa dopo ALND. Non si può pertanto prescindere da una valutazione individualizzata del singolo caso in ambito multidisciplinare per la formulazione della strategia terapeutica da condividere con la paziente adeguatamente informata (11).

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Invasive Breast Cancer

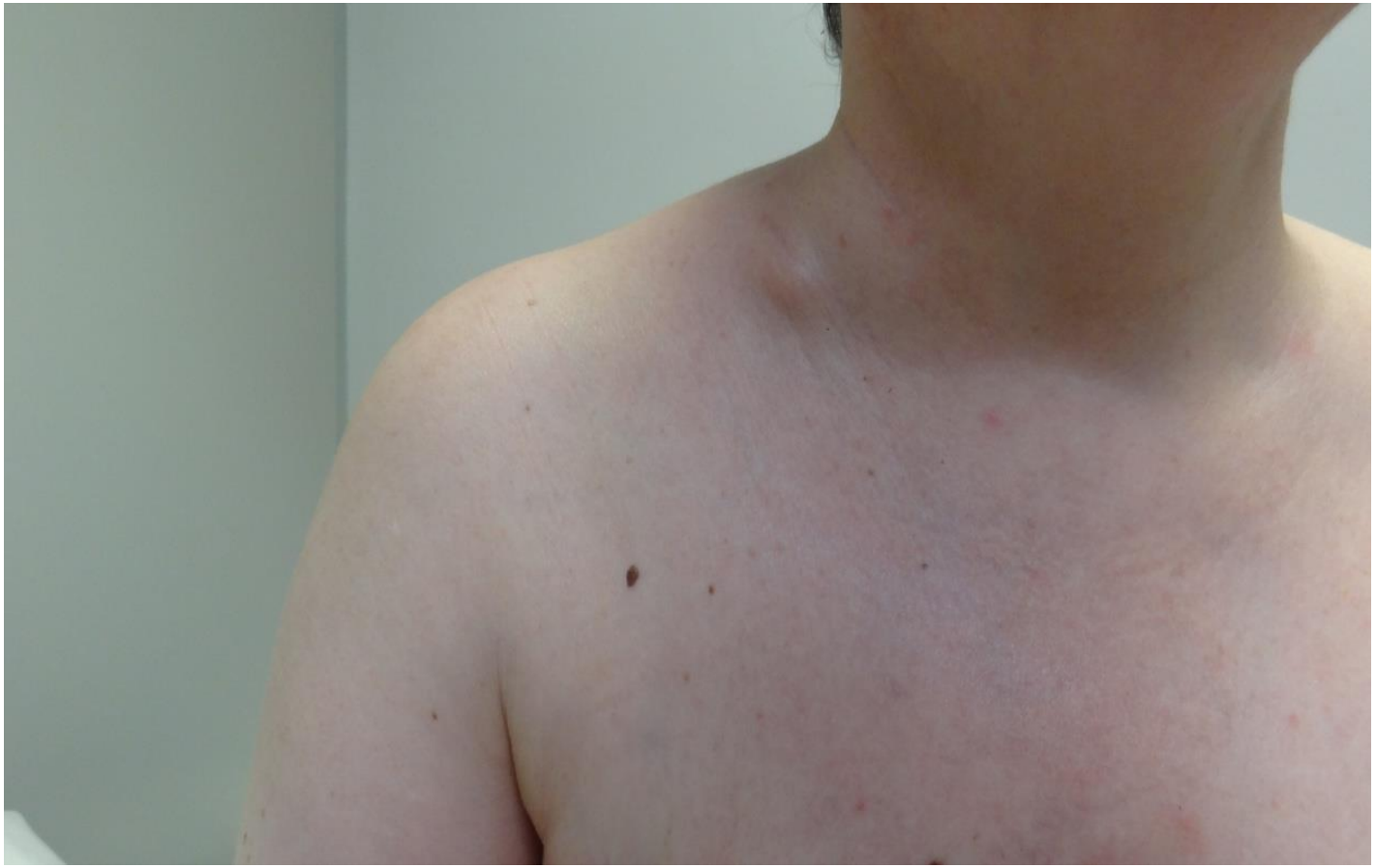
NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

PREOPERATIVE SYSTEMIC THERAPY FOR INOPERABLE OR LOCALLY ADVANCED BREAST CANCER (NON-INFLAMMATORY)

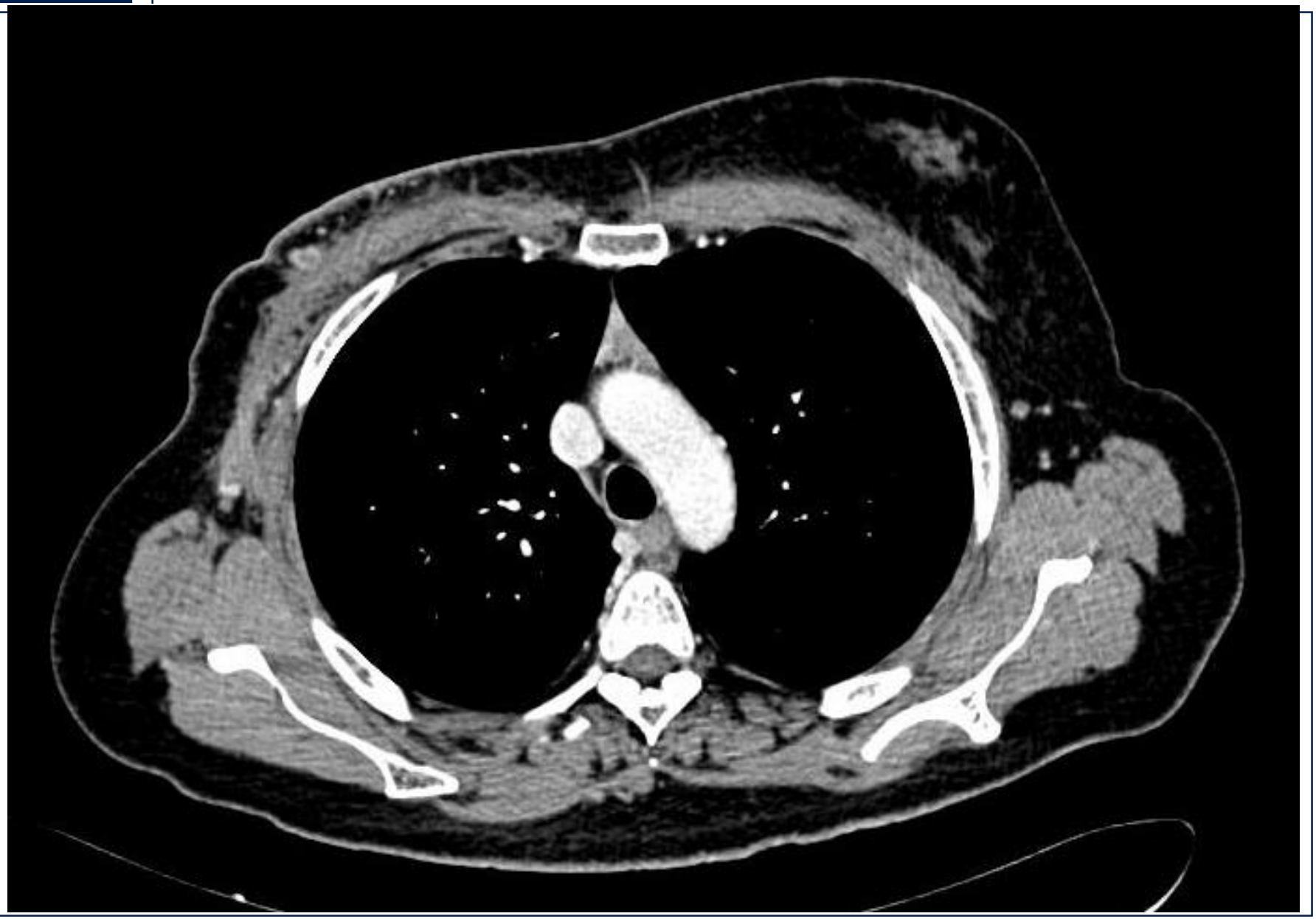


Quale indicazione nel trattamento adiuvante?

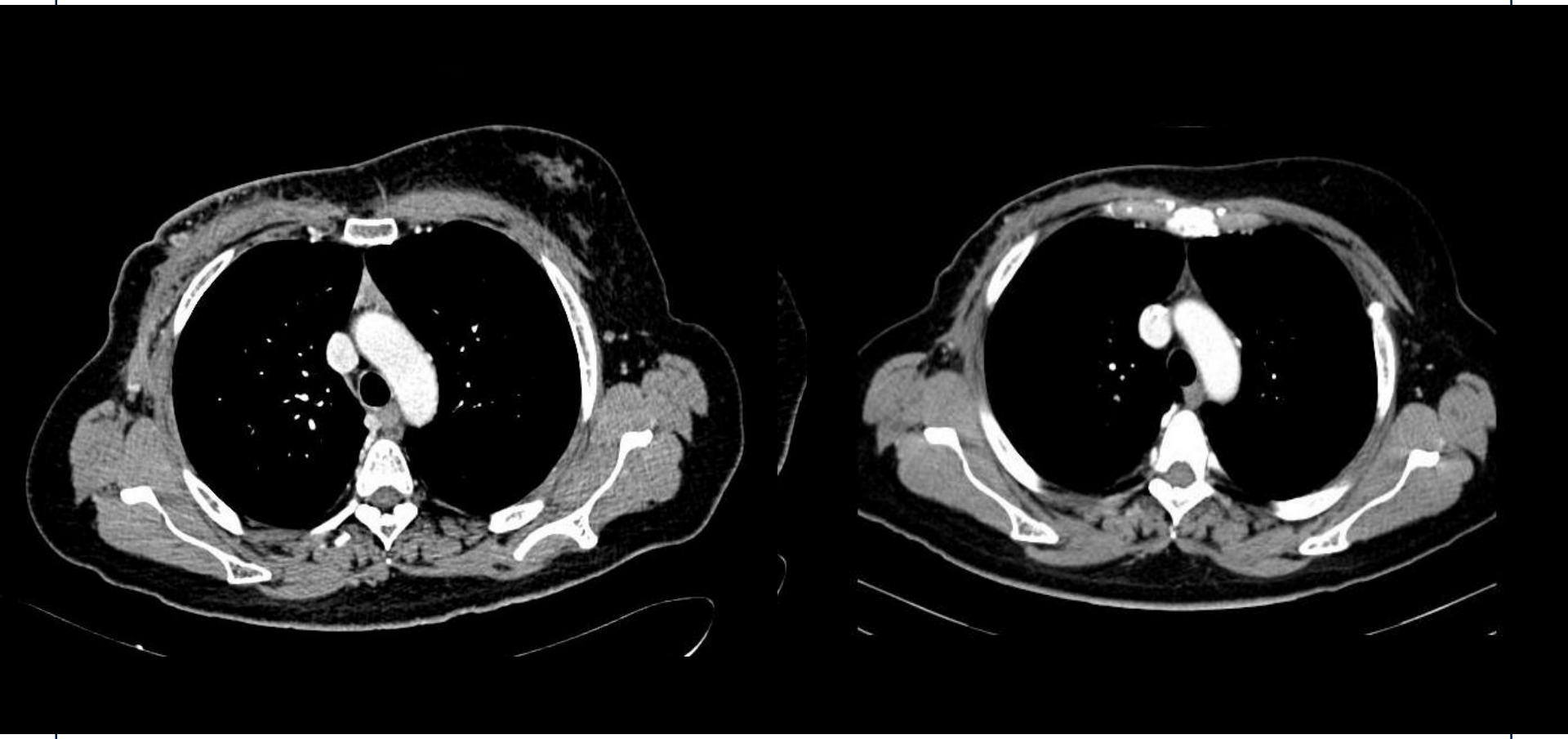
A 5 mesi dalla chirurgia….

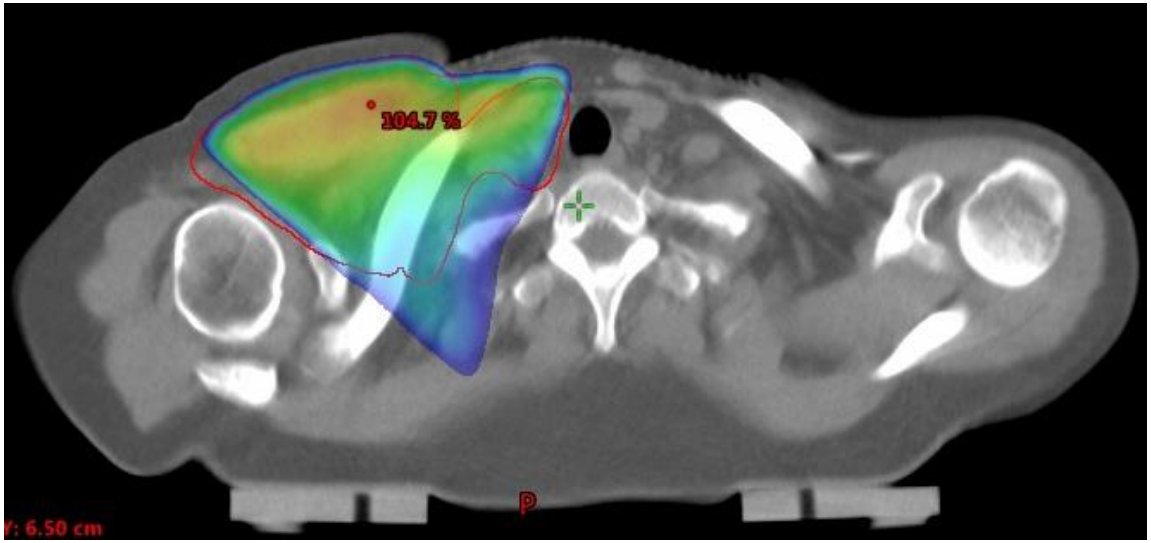


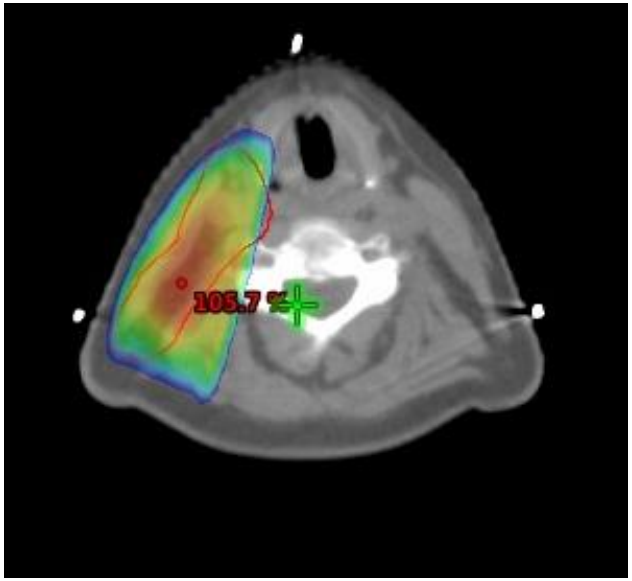
Agoaspirato a livello della tumefazione sovraclaveare destra.
EI: emazie, linfociti e gruppi di cellule epiteliali con atipie deponenti per carcinoma

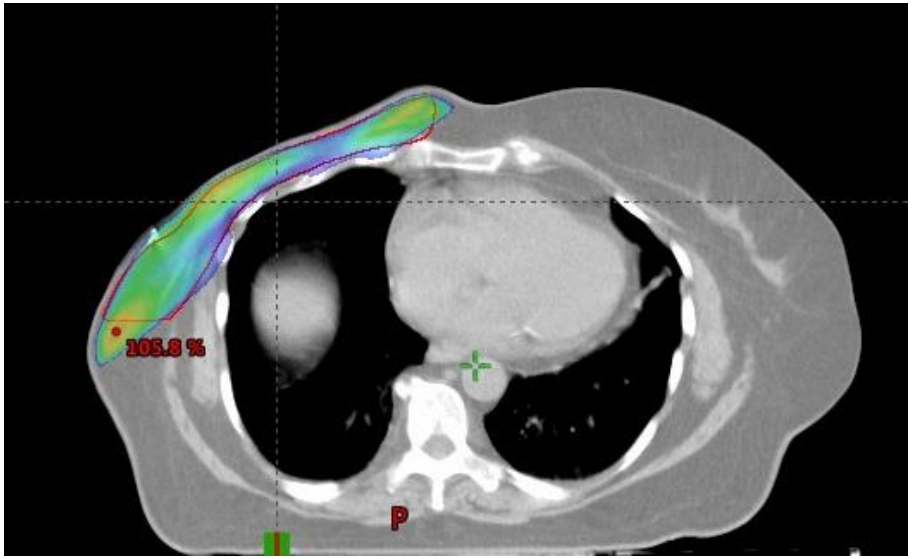


CT Docetaxel+Carboplatino




104.7 %
P


105.7 %


105.8 %
P

TNBC ***impatta negativamente sull'outcome***

Il ***trattamento radiante*** adiuvante si associa ad un ***beneficio in controllo locale***

La conoscenza della biologia tumorale offre l'opportunità di meglio ***individualizzare la terapia***, intensificando i trattamenti nelle pazienti ad alto rischio.

Dato il basso livello di evidenza, le attuali linee guida, non considerano il sottotipo molecolare come ***unico criterio per l'indicazione al trattamento radiante***.

Studi prospettici saranno utili per ottimizzare i trattamenti adiuvanti, basandosi sia sul ***sottotipo molecolare che sulle caratteristiche clinico-patologiche piu convenzionali***.


Grazie