La radioterapia dopo terapia sistemica neoadiuvante: irradiazione delle catene linfonodali? Cons

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BACKGROUND

Neoadjuvant chemotherapy is widely used in locally advanced breast cancer treatment.

It is increasingly used in women with early stage disease.

Equivalent survival outcomes to chemotherapy after upfront surgery.

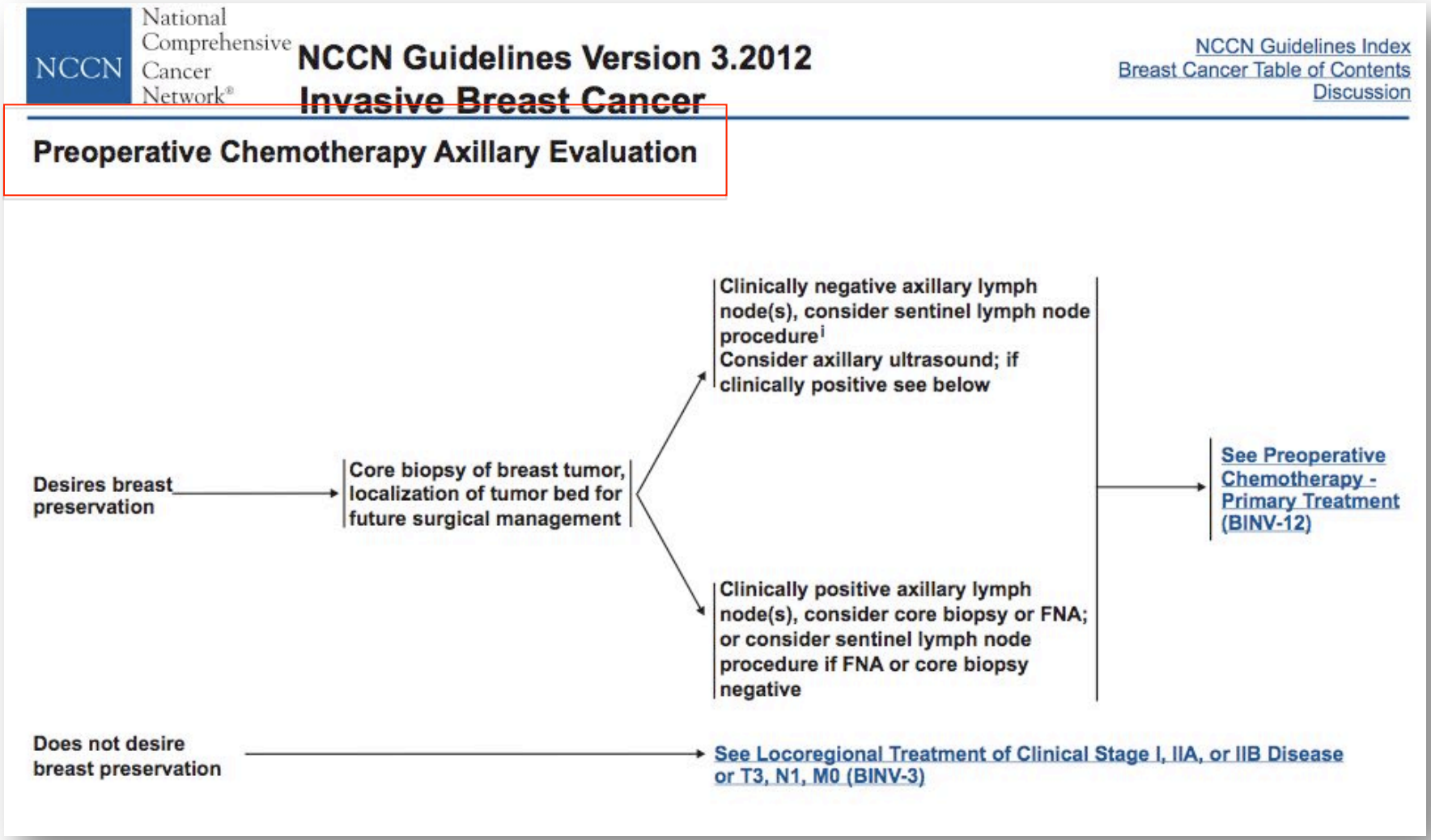
Mieog JS, et al. Br J Surg, 2007

To observe tumor response and modify chemotherapy plan.

To decrease the tumor size and increase the number of patients who can undergo breast-conserving surgery rather than mastectomy.

Hoffman KE, et al. Lancet Oncol, 2012

NCCN Guidelines 2012



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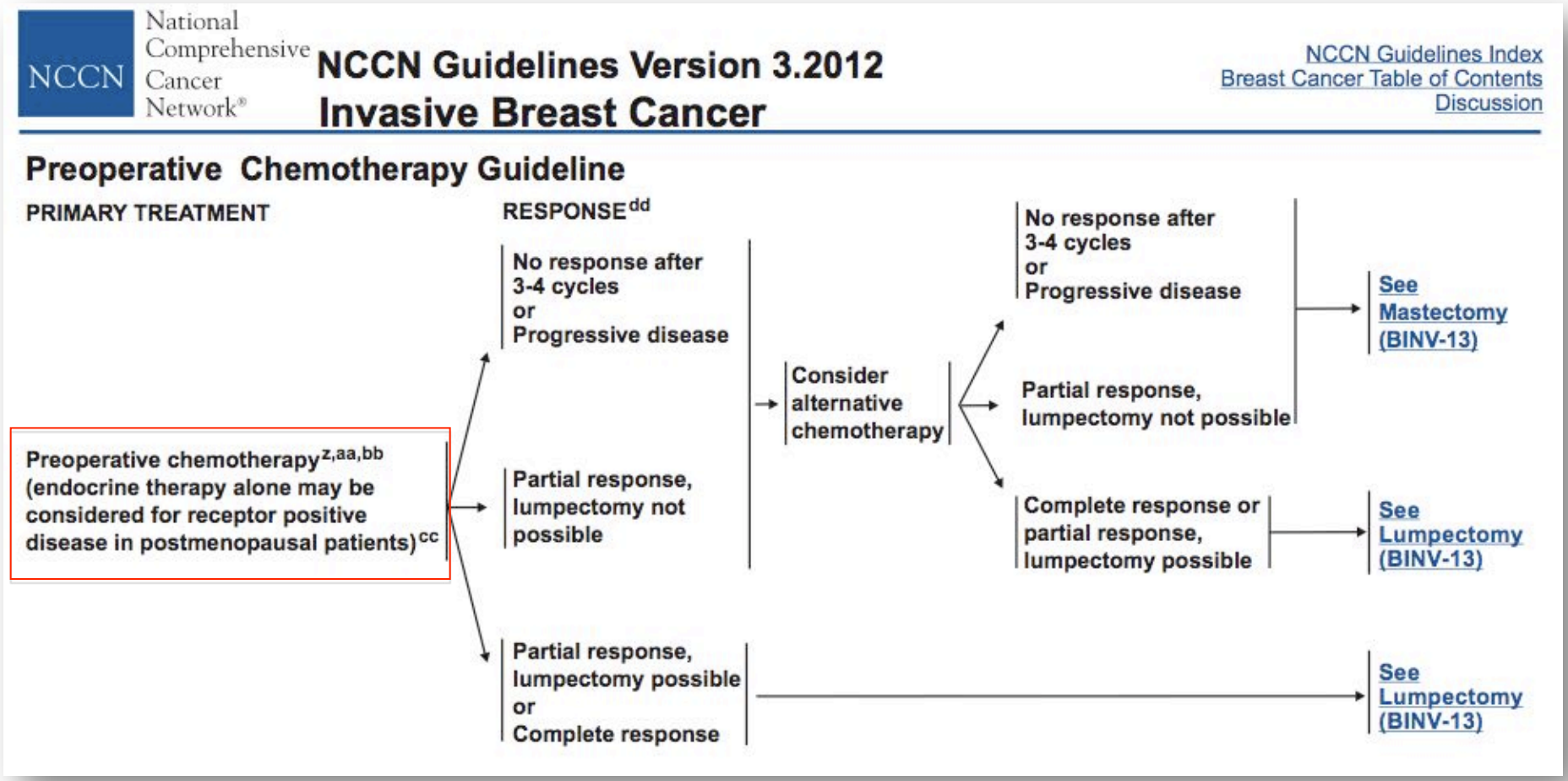

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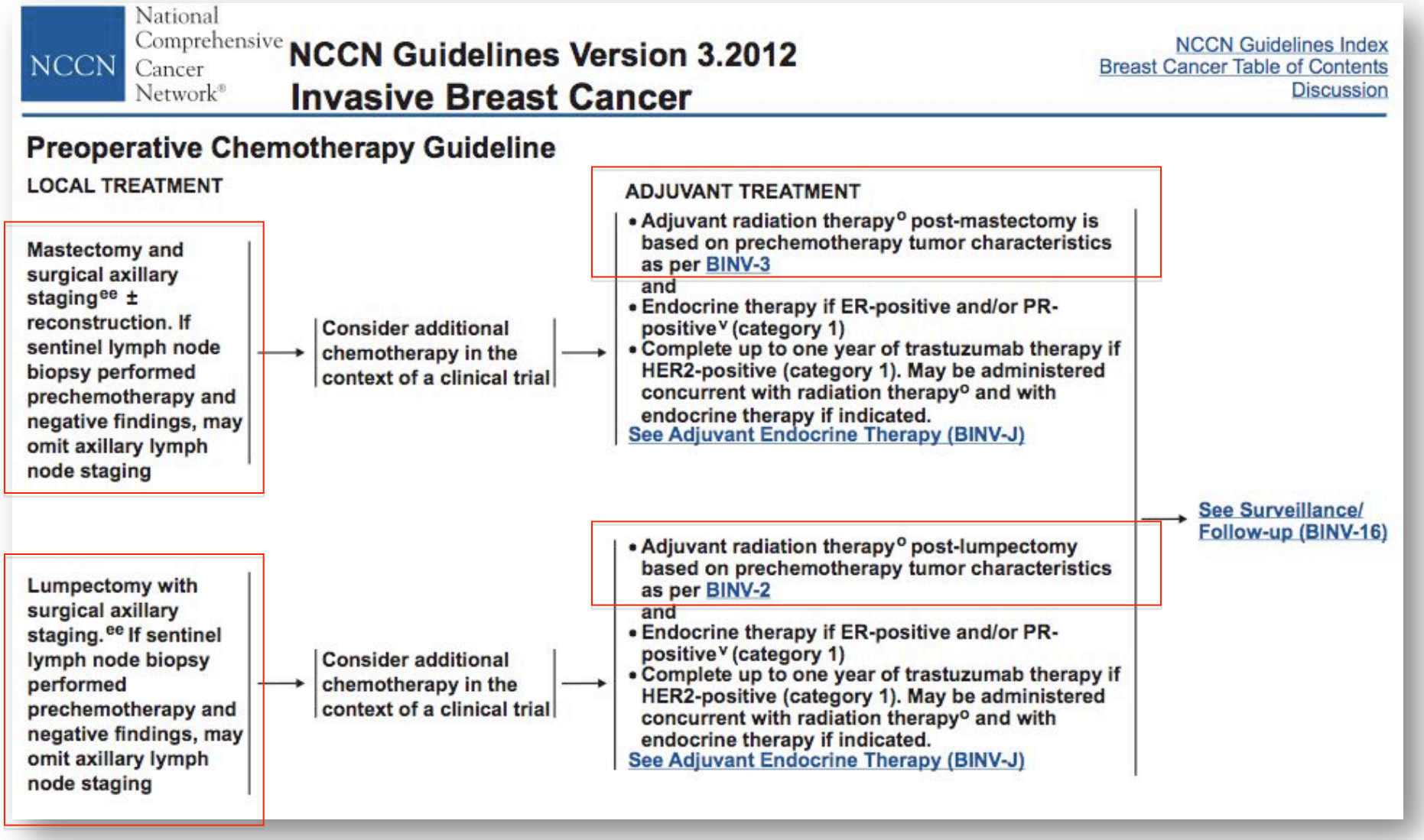

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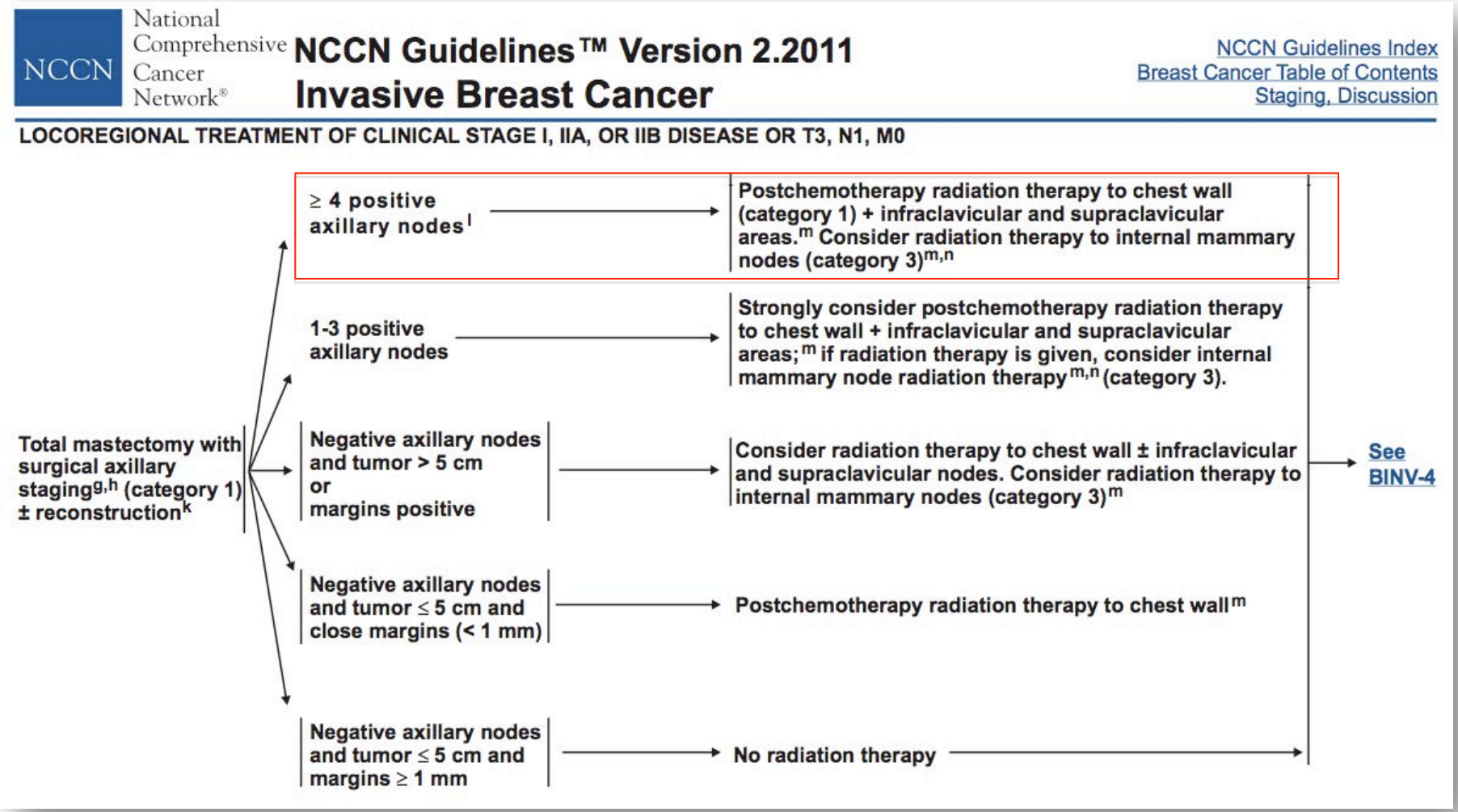

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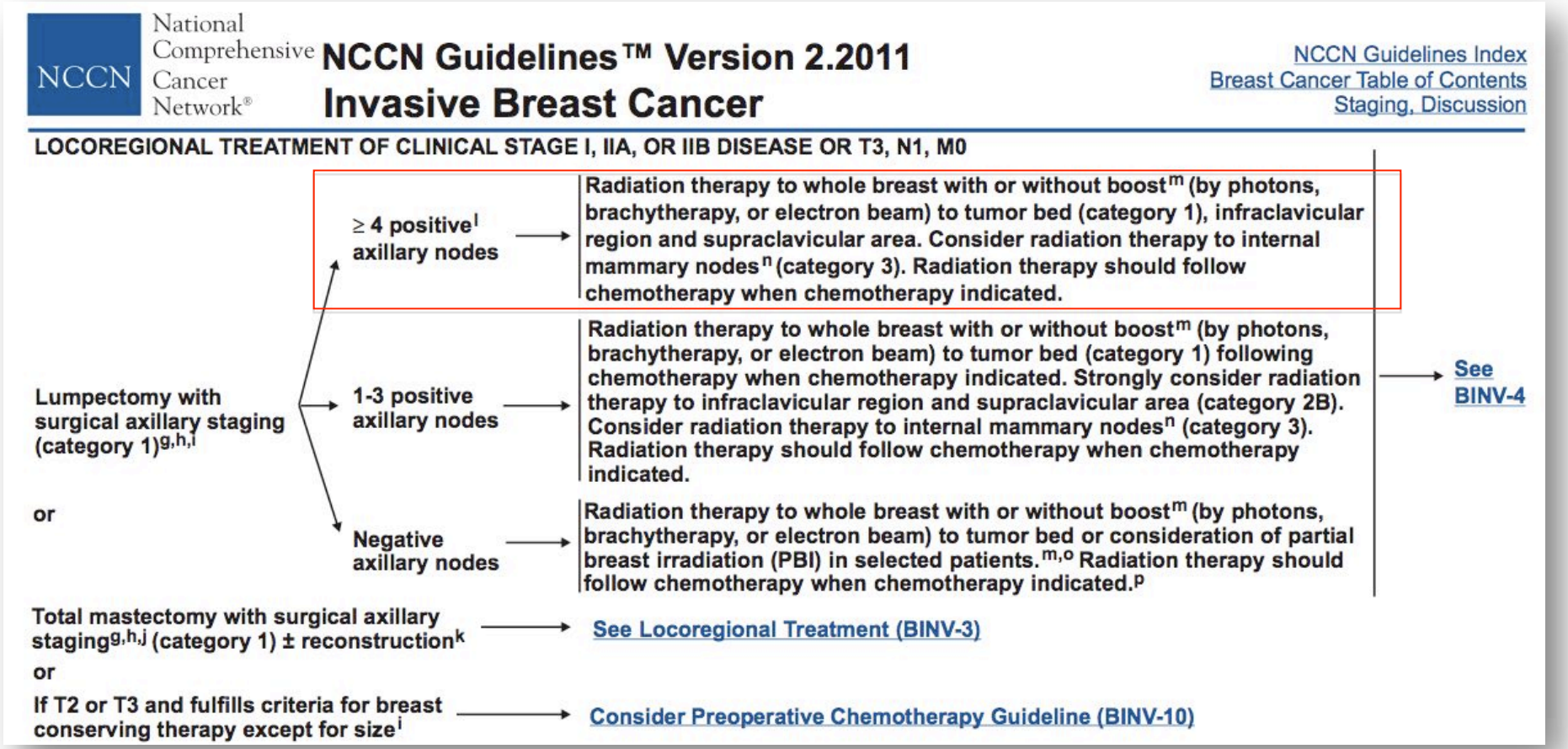


BACKGROUND
Postmastectomy Radiotherapy

The Danish and the British Columbia trials have established the **survival advantage** following radiotherapy in post mastectomy patients

Overgaard M, et al. N Engl J Med, 1997
Ragaz J, et al. N Engl J Med, 1997

The EBCTCG **meta-analysis** has demonstrated that radiotherapy, besides improving **local control** rates, confers a **survival** benefit in breast conservation treatment as well as in post mastectomy patients

Poortmans PM, et al. IJROBP, 2001

Postmastectomy Radiotherapy

The Danish and British Columbia trials and the EBCTCG meta-analysis were **unable** to discern the **direct contribution** from **internal mammary and medial supraclavicular** (IM-MS) nodes treatment.

Survival gains associated with improvements in loco-regional control may be **diminished** by **RT-associated cardiac mortality** and its implication in the radiotherapy plan.

Prosnitz RG, et al. Cancer 2007
Roychoudhuri R, et al. BMC Cancer 2007
Taylor CW, et al. Int J Radiat Oncol Biol Phys 2008
Harris EE. Cancer Control 2008

The **EORTC 22922/10925 trial** investigates therefore if elective irradiation of the IM-MS chain improves overall survival at 10 years.

Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925)

Toxicity reported until **year 3** after treatment.

Toxicity rates and performance status (PS) changes at three years were compared by $\chi 2$ tests and logistic regression models in **3 866 patients**.

IM-MS irradiation seems well tolerated and **does not significantly impair WHO PS** at three years.

Matzinger O et al, Acta Oncologica, 2010

Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925)

Patients characteristics: IM/MS treated versus No treated

Adjuvant hormonal therapy		
None reported	775 (39.9)	786 (40.9)
yes	1169 (60.1)	1136 (59.1)
Adjvuant chemotherapy		
No chemotherapy	886 (45.6)	871 (45.3)
Adiuvant	243 (12.5)	242 (12.6)
Neo-adjuvant	815 (41.9)	809 (42.1)
Adjuvant treatment		
None	294 (15.1)	316 (16.4)
Chemotherapy	481 (24.7)	470 (24.5)
Hormonal therapy	592 (30.5)	555 (28.9)
Both	577 (29.7)	581 (30.2)

Matzinger O et al, Acta Oncologica, 2010

Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925)

Toxicity up to year three according to treatment arm

	No IM-MS (N=1944) N (%)	IM-MS (N=1922) N (%)	P-value
Lung Fibrosis (to year 3)*	17 (0.9)	54 (2.8)	<0.0001
Cough	5 (0.3)	10 (0.5)	0.19
Dyspnoea	1 (0.1)	14 (0.7)	0.0007
Pneumonitis	1 (0.1)	13 (0.7)	0.0012
Pleuritis	5 (0.3)	2 (0.1)	0.26
Other lung toxicity	2 (0.1)	4 (0.2)	0.41
Any lung toxicity	**26 (1.3)**	**83 (4.3)**	**<0.0001**

Significant more LUNG FIBROSIS – DYSPNOEA – PNEUMONITIS with irradiation of the internal mammary and medial supraclavicular nodes

Matzinger O et al, Acta Oncologica, 2010

Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925)

Toxicity up to year three according to treatment arm

Cardiac fibrosis (to year 3)*	5 (0.3)	7 (0.4)	**0.55**
Evidence of cardiac disease (to year 3)*	28 (1.4)	31 (1.6)	**0.64**
Mastitis	7 (0.4)	6 (0.3)	
Breast Infection	4 (0.2)	3 (0.2)	
Radionecrosis	2 (0.1)	1 (0.1)	
Osteonecrosis	22 (1.1)	27 (1.4)	
Oedema			
Yes, unspecified	81 (4.2)	81 (4.2)	
Presternal	0 (0.0)	1 (0.1)	
Arm/hand	70 (3.6)	73 (3.8)	
Breast/chestwall pain	45 (2.3)	35 (1.8)	
Retrosternal pain	1 (0.1)	2 (0.1)	
Other pain	15 (0.8)	26 (1.4)	
Dysphagia	0 (0.0)	4 (0.2)	
Fatigue	20 (1.0)	22 (1.1)	
Arm or shoulder function impairment	8 (0.4)	1 (0.1)	
Other — unspecified	[illegible]	[illegible]	
Any toxicity (to year 3)	**424 (21.8)**	**491 (25.5)**	**0.006**

Matzinger O et al, Acta Oncologica, 2010

Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925)

Influence of various parameters on WHO performance status deterioration

Deterioration by year 3	No Change/ improvement (N=3056) N (%)	Deterioration (N=285) N (%)	OR	95% CI	P-value
Any lung toxicity					
No	2972 (91.5)	276 (8.5)			
Yes	84 (90.3)	9 (9.7)	1.19	0.59-2.41	0.62
Lung Fibrosis (to year 3)					
No	2996 (91.5)	280 (8.5)			
Yes	56 (91.8)	5 (8.2)	1.02	0.40-2.59	0.96
Missing	4 (100.0)	0 (0.0)			
Cardiac Fibrosis (to year 3)					
No	3038 (91.4)	285 (8.6)			Too small
Yes	11 (100.0)	0 (0.0)			sample for
Missing	7 (100.0)	0 (0.0)			testing
Evidence of cardiac disease (to year 3)					
No	2989 (91.9)	265 (8.1)			
Yes	38 (76.0)	12 (24.0)	3.71	1.90-7.24	<0.0001
Missing	29 (78.4)	8 (21.6)			

Matzinger O et al, Acta Oncologica, 2010

Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925)

Further follow-up is required to confirm the absence of any deleterious impact of IM-MS treatment on cardiac function because late cardiac toxicity often appears 10 or even 15 years after treatment.

Prosnitz RG, et al. Cancer 2007 - Roychoudhuri R, et al. BMC Cancer 2007
Taylor CW, et al. Int J Radiat Oncol Biol Phys 2008 - Harris EE. Cancer Control 2008

Authors observed already a significant detrimental impact of the presence of cardiac disease on the PS of the patients.

Are sufficient 3 years of median follow-up in order to show that pulmonary fibrosis is not getting worse performance status?

Effect		OR	95% CI		P-value
Neo-Adjuvant chemotherapy	Yes vs. No	**0.30**	**0.18**	**0.52**	**<0.0001**

Matzinger O et al, Acta Oncologica, 2010

ANTHRACYCLINES AND CARDIAC TOXICITY

Standard AC chemotherapy is associated with frequent decreases in LVEF

(North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial)

1 458 patients

51.1% had ≤ 15% decrease in LVEF

2.5% had an LVEF decrease > 15%

6.6% Grade 2 LVEF toxicity

Perez EA, et al. JCO, 2004

Trastuzumab with paclitaxel after AC increases congestive heart failure (CHF)

(National Surgical Adjuvant Breast and Bowel Project trial B-31)

5 of 814 control patients subsequently had confirmed cardiac events (4 CHFs and 1 cardiac death) compared with 31 of 850 trastuzumab-treated patients (31 CHFs and no cardiac deaths)

The difference in cumulative incidence at 3 years was 3.3%

CHFs were more frequent in older patients and with marginal post-AC LVEF

Tan-Chiu E, et al. JCO 2005

TRASTUZUMAB AND CARDIAC TOXICITY

High incidence of **congestive heart failure** (CHF) among patients who had received trastuzumab and anthracycline-based therapy simultaneously

4% rates of symptomatic or **severe CHF**

30% asymptomatic declines in LVEF (>10%)

Ewer MS, et al. Clin Breast Cancer, 2007

4% of patients enrolled onto the adjuvant trastuzumab trials experienced severe CHF during treatment

14% of patients in the NSABP B-31 trial **discontinued trastuzumab** because of asymptomatic decreases in LVEF

Continued cardiac follow-up of these women is of critical importance

Telli ML, et al. JCO, 2007

TAXANES AND LUNG TOXICITY

Docetaxel → **pleural effusion** secondary to capillary leak syndrome

Piccart MJ, et al. J Clin Oncol, 1997

Paclitaxel is associated with pulmonary toxicity

Khan A, et al. Ann Pharmacother, 1997

Ramanathan RK, et al. Chest, 1996

Pulmonary infiltrates have been reported **48 hours** after initiation of treatment

Docetaxel-induced **pneumonitis** → long duration of symptoms; in some cases pulmonary toxicity has been fatal

Read WL, et al. Cancer, 2002

Mileshkin L, et al. Bone Marrow Transplantation, 2001

Docetaxel could increase **reactive oxygen metabolites** production with direct lung injury

Immunomodulatory effects of taxanes, with the resulting pulmonary insult lasting the lifespan of the leukocytes

Merad M, et al. Ann Oncol, 1997

PREDICTORS OF LOCOREGIONAL RECURRENCE IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER

To identify the clinical and pathologic factors predictive of locoregional recurrence (LRR) after **neoadjuvant chemotherapy, mastectomy, and radiotherapy**.

542 patients treated on six consecutive institutional prospective trials.

Stage II in 17%, Stage IIIA in 30%, Stage IIIB in 43%, and Stage IV (ipsilateral supraclavicular disease) in 10%.

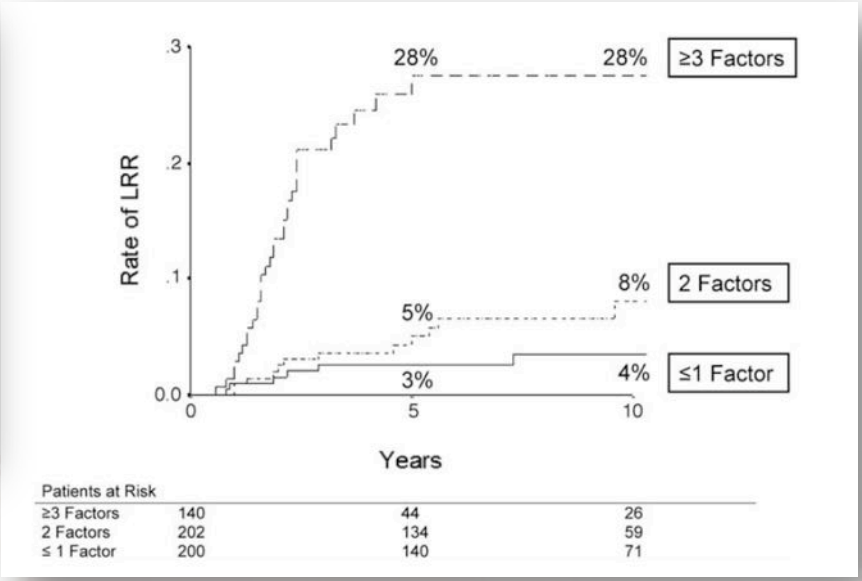
Median **follow-up** was **70** months.

5-year and 10-year actuarial LRR rate was **9%** and **11%**, respectively.

Huang EH, et al. IJROBP, 2005

PREDICTORS OF LOCOREGIONAL RECURRENCE IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER

Factor	Hazard ratio	95% Confidence interval	*p*
Skin or nipple involvement	2.8	1.5–5.2	0.001
Supraclavicular nodal involvement	2.7	1.3–5.6	0.009
No tamoxifen use	2.7	1.2–6.0	0.019
Extracapsular extension	2.1	1.1–4.0	0.020
Estrogen receptor negative disease	2.1	1.2–3.7	0.013



Multivariate analysis of locoregional recurrence

Locoregional recurrence (LRR) rates according to number of independent risk factors

28% *vs* 3% at 5 years *(III vs I factors)*

28% *vs* 4% at 10 years *(III vs I factors)*

Huang EH, et al. IJROBP, 2005

PREDICTORS OF LOCOREGIONAL RECURRENCE IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER

150 cases treated on prospective institutional trials with **neoadjuvant chemotherapy and mastectomy without postmastectomy radiation**.

Median **follow-up 4.1 years**.

The **5- and 10-year** actuarial rates of **LRR** were both **27%**.

The relatively small number of LRR events in this series **does not allow us to make conclusive statements** regarding the **appropriate treatment volume** that should be included in postmastectomy radiation fields. It has been our **philosophy** to treat with comprehensive fields that include the chest wall and draining lymphatics.

Bucholz TA, et al. IJROBP, 2002
Bucholz TA, et al. JCO 2002

PREDICTORS OF LOCOREGIONAL RECURRENCE IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER

Factor	5-Year Rate (%)	P	Crude Rate No.	Crude Rate %	Sites of Failure
Clinical stage					
I	0*	< .0001	0/1	0	
IIA	5		1/21	5	CW-1, SCF-0, AX-0, ICF-0, IMC-0
IIB	16		5/44	11	CW-5, SCF-2, AX-1, ICF-[illegible], IMC-0
IIIA	17		5/35	14	CW-3, SCF-2, AX-1, ICF-[illegible], IMC-1
IIIB	50		16/38	42	CW-14, SCF-5, AX-3, IC[illegible]0, IMC-0
IV	79		7/11	64	CW-4, SCF-3, AX-1, ICF-[illegible], IMC-0
Clinical T stage, pathologic LN status					
T1-2, negative LN	5	.004	1/19	5	CW-1, SCF-0, AX-0, ICF-0, IMC-0
T3-4, negative LN	34		6/23	26	CW-4, SCF-4, AX-1, ICF-0, IMC-0
T1-2, positive LN	13		4/42	10	CW-2, SCF-2, AX-1, ICF-[illegible], IMC-0
T3-4, positive LN	36		21/64	33	CW-18, SCF-5, AX-4, IC[illegible]1, IMC-1
Pathologic T size, pathologic LN status					
≤ 2.0 cm, negative LN	10	.002	2/21	10	CW-2, SCF-1, AX-0, ICF-0, IMC-0
2.1-5.0 cm, negative LN	49		3/14	21	CW-1, SCF-2, AX-1, ICF-0, IMC-0
> 5.0 cm, negative LN	20		1/5	20	CW-1, SCF-1, AX-0, ICF-0, IMC-0
≤ 2.0 cm, positive LN	20		9/52	17	CW-8, SCF-2, AX-1, ICF-0, IMC-0
2.1-5.0 cm, positive LN	30		11/41	27	CW-8, SCF-5, AX-3, ICF-[illegible], IMC-1
> 5.0 cm, positive LN	63		5/9	55	CW-4, SCF-1, AX-1, ICF-0, IMC-0

3/97 internal mammary recurrences at 10 years

3.1 %

Bucholz TA, et al. IJROBP, 2002; Bucholz TA, et al. JCO 2002

Predictors of Locoregional Recurrence After Neoadjuvant Chemotherapy: Results From Combined Analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27

Patterns and predictors of LRR as first event in **combined analysis** of two National Surgical Adjuvant Breast and Bowel Project (NSABP) neoadjuvant trials.

NC was either doxorubicin/ cyclophosphamide (AC) alone or AC followed by neoadjuvant/adjuvant docetaxel. Lumpectomy patients received breast radiotherapy alone; mastectomy patients received no radiotherapy.

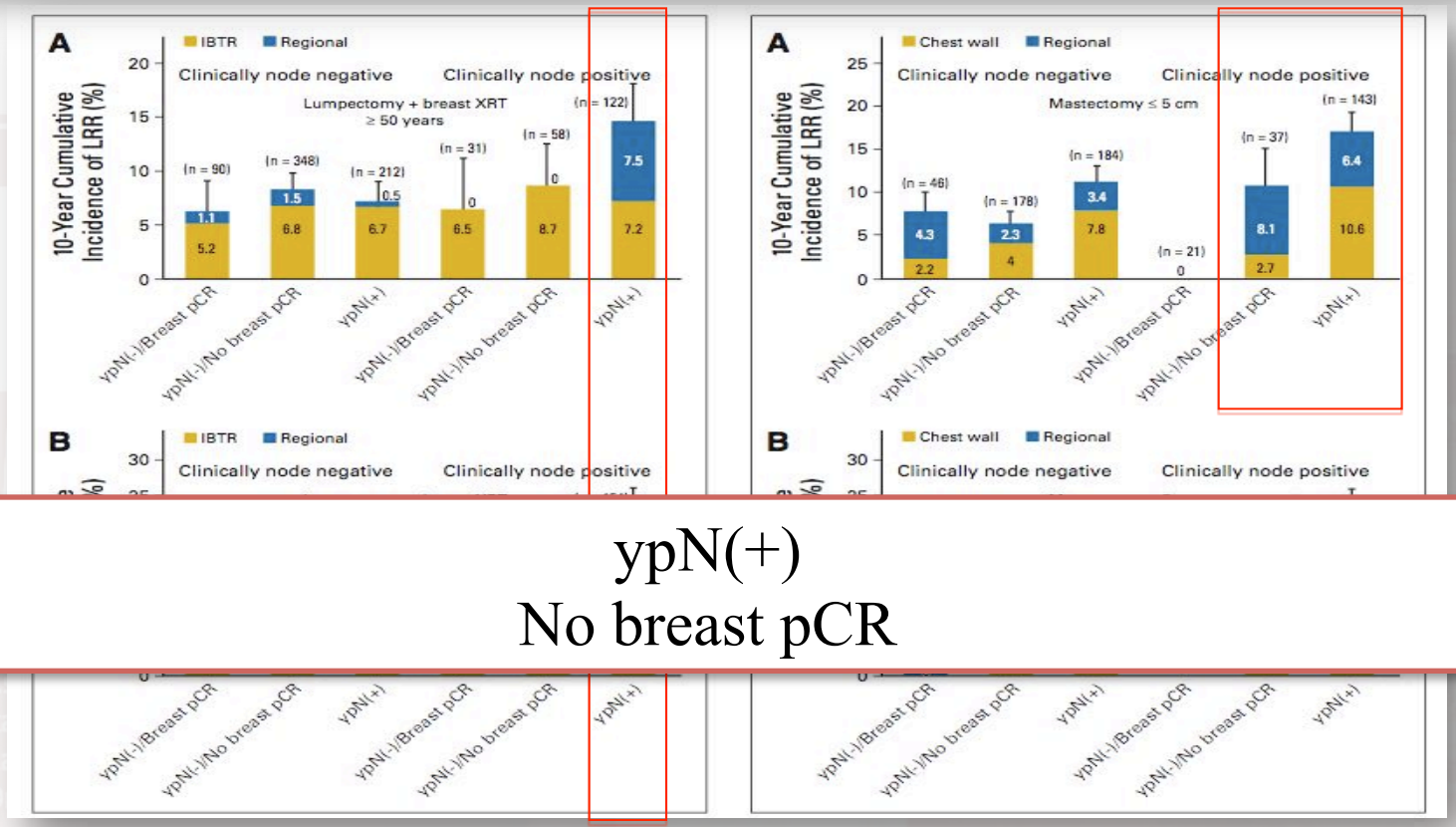
In 3,088 patients, 335 LRR events had occurred after 10 years of follow-up.

The 10-year cumulative incidence of LRR was 12.3% for mastectomy patients (8.9% local; **3.4% regional**) and 10.3% for lumpectomy plus breast radiotherapy patients (8.1% local; **2.2% regional**).

Mamounas EP, et al. JCO, 2012

Predictors of Locoregional Recurrence After Neoadjuvant Chemotherapy

Variable	No. of Patients	LRR Events	HR	95% CI	P
Patients treated with mastectomy*	1,071	131			
Clinical tumor size > 5 *v* ≤ 5 cm†			1.58	1.12 to 2.23	.0095
Clinical nodal status cN(+) *v* cN(−)†			1.53	1.08 to 2.18	.017
Nodal/breast pathologic status					< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†			2.21	0.77 to 6.30	
ypN(+) *v* ypN(−)/breast pCR†			4.48	1.64 to 12.21	
Patients treated with lumpectomy plus breast XRT*	1,890	189			
Age ≥ 50 *v* < 50 years†			0.71	0.53 to 0.96	.025
Clinical nodal status cN(+) *v* cN(−)†			1.70	1.26 to 2.31	< .001
Nodal/breast pathologic status					< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†			1.44	0.90 to 2.33	
ypN(+) *v* ypN(−)/breast pCR†			2.25	1.41 to 3.59	



ypN(+)
No breast pCR

Mamounas EP, et al. JCO, 2012

Predictors of Locoregional Recurrence After Neoadjuvant Chemotherapy

In patients treated with NC, age, clinical tumor characteristics before NC, and pathologic nodal status/breast tumor response after NC can be used to predict risk for LRR and to optimize the use of adjuvant radiotherapy.

Lack of information on ER, PgR and HER2/neu status.

Pathologic response in the breast and pathologic axillary nodal status have a major impact on the rates and patterns of LRR.

The impact of age, clinical tumor size, and clinical nodal status on the absolute LRR rates are **low** if a patient achieves a pCR in the breast with pathologically negative axillary nodes.

Mamounas EP, et al. JCO, 2012

Role of Postmastectomy Radiation After Neoadjuvant Chemotherapy in Stage II-III Breast Cancer

Critical review was an initiative of the Athena Breast Health Network.

To identify a cohort of women treated with neoadjuvant chemotherapy and mastectomy for whom post-mastectomy radiation may be omitted based on the risk of local- regional failure.

Initial clinical stage	Pathologic stage	Patient age (y)	Adverse risk factors LVI, ECE, TN	LRF ± DM (%)
Low risk (≤10% LRF risk)				
I T1N0	ypN0 or 1-3+	Any	None	Insufficient data
I-II	pCR	Any	Any or none	6
IIA T2N0	pCR	Any	Any or none	0
T1N1	ypN0	Any	None or TN	0-7
	ypN1-3+	≥35-40	None	4-5
IIB T2N1	pCR	Any	None or any	0
	ypN0	≥35-40	None or TN	0-7
	ypN1-3+	≥35-40	None	4-5
T3N0	pCR	Any	None or any	0
IIIA T3N1	ypN0		Any	9
				Limited data

Fowble BL, et al. IJROBP, 2012

CONCLUSIONS

Randomized trials have established which patients might benefit from post-mastectomy radiotherapy after upfront surgery.

No randomized trials exist to define which women benefit from post-mastectomy radiotherapy after neoadjuvant chemotherapy.

From non-randomized data we can obtain who can be spared from the morbidity of radiation treatment.

Disease at presentation and response (**T3-T4 clinical disease** at presentation, clinical **N2-N3 at presentation**) to neoadjuvant chemotherapy (lymph-node-positive disease at resection) can be used to tailor post-mastectomy radiotherapy recommendations.

Also **selected patients with clinical stage II** disease (young age, triple negative, poor response to chemotherapy).

Hoffman KE, et al. Lancet Oncol, 2012

CONCLUSIONS

Loco-regional nodal irradiation **increased** treatment-related toxicity (mostly lung fibrosis).

Not all the patients that underwent neoadjuvant chemotherapy seems to benefit from postsurgical radiotherapy.

No prospective data are available concerning direct comparison between nodal irradiation versus exclusive thoracic wall irradiation.

T1-T2 and node-negative at resection patients should omit post-surgical radiotherapy.

Randomized trials are needed to asses whether post-mastectomy radiotherapy could be safely omitted in women with good response to chemotherapy.

CONCLUSIONS – OPEN QUESTIONS

CARDIOTOXICITY

- TAXANES
- TRASTUZUMAB
- ANTHRACYCLINES

MATURE RESULTS FROM EORTC TRIAL 22992

- TOXICITY IN SUPRACLAVICULAR AND INTERNAL MAMMARY IRRADIATION

IMPACT OF **HER2 STATUS**

IMPACT OF **TRIPLE NEGATIVE STATUS**

APPROPRIATENESS→MULTIFACTORS EVALUATION

NOT SINGLE-FACTOR DECISION MAKING

Thanks for your attention…