



WHEN IS THE POSITIVE SENTINEL NODE NOT ENOUGH FOR SYSTEMIC THERAPY DECISIONS?

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Why send someone with a positive sN back for AXND?

1. Chemo vs no chemo decision
2. Guides which chemo to give
3. Determines the size of RT field
4. It may affect survival
5. Provides prognostic information



1. Chemo versus No Chemo

ANY + node = chemo

how many + nodes determines chemo

- Premenopausal
- Grade 3
- ER negative
- Postmenopausal
- Grade 1, 2
- ER positive



1. Chemo vs no chemo

- Age and ER are prognostic factors for relapse and predictive factor (for benefit from chemo)
- Number of nodes and grade are prognostic factors

2.3cm grade 2 ER+ her2- ductal cancer: (using Adjuvant Online!)

	1 node positive			5 nodes positive		
	No chx	FEC	Chx/HT	No chx	FEC D	Chx/HT
40 yo						
Recurrence	57.6%	34.7%	22.6%	67.5%	36.7%	24.4%
BC death	35%	21.5%	15.3%	44.7%	23.4%	16.9%
60yo						
Recurrence	56%	44.2%	30.3%	65.6%	46.5%	32.1%
BC death	33.7%	26.6%	19.2%	43.3%	29.5%	21.7%



1. Chemo versus No Chemo

Node positive postmenopausal ER+ patients
Multiple trials of chemo + Tam vs Tam:
3 show OS advantage

Trial	Design	%DFS diff	% OS diff	population
INT 100	CAF/tam v tam	9	5	menopausal
PACS 01	6FEC v 3FEC 3D	Hz 0.67	4*	Pre and post up to age 65
BCIRG 001	FAC v TAC	7*	6*	Pre and post up to age 70

*Overall study figures



1. Chemo versus No Chemo

- Would AXND potentially alter your decision to give chemotherapy (vs no chemo) for a ductal cancer, 2.3 cm grade 2, ER 2+, her2neu -, no LVI, one sentinel node + of 2 with a 4mm deposit in a:

	Yes	No
40 year old	3	6
50 year old	4	5
60 year old	8	1
70 year old	5	4

Number of respondents: 9 of 15



2. Which chemo to give

Chemo	%1-3 NP	% MenoP >60	% Upper age limit	5y DFS	OS	Non Heam Gr3, 4 tox	%G3, 4 neut / feb neut	
AC ²	56	21	0	59	62	83	35 n/v	4 / NR
FEC100 ⁶	61	49	53	64	73	87	10 n/v	20 / 1
FEC100 ³	17	NR		64	66	77	35 n/v	25 / NR
AC T ⁴	46	40	13	none	70	80	mucositis	11(17)
AC T ⁸	70	48	19	none	70	85	PNS	3/3
CAF ⁵	58	100	*32	none	76	84	20 n/v	44 / NR
FEC D ⁶	62	50		64	78	91	10 nails	11/5
TAC ⁷	62	50	NR	70	75	87	10 nails asthenia	65/25

* %>65yo

²NSABP B15; ³FASG JCO 01; ⁴CALGB9344; ⁵INT100; ⁶PACS01; ⁷BCIRG001; ⁸B28



2. Which chemo to give

- Would your chemo regimen be altered by AXND following lumpectomy and SNB for a 1.9cm grade 3, ER -, her2neu -, no LVI, one sentinel node + of 1 with a 2mm deposit in a:

	Yes	No	Maybe
40 year old	6	2	1
50 year old	5	1	1
60 year old	4	4	1
70 year old	3	5	1

Number of respondents: 9 of 15



3. Determines the size of RT field

Radiation Field options:

- Breast tangents only (BCT)
- Chest wall only (Mastectomy)
- Breast/chest wall plus low axilla
- Breast/chest wall plus full axilla
- Breast/chest wall plus axilla, supraclav
- Breast/chest wall plus axilla, supraclav, internal mammary chain



3. Determines the size of RT field

Factors which determine who needs RT and how much:

INTENT: LOCAL CONTROL

- Breast surgery
- LVI
- Number and size of nodal deposit
- Extranodal spread
- Age of patient
- Location of the primary

INTENT: LOCAL +/- DISTANT

- Number and size of nodal deposits
- Extranodal spread
- Age of patient
- Location of the primary (internal mammary drainage)



3. Determines the size of RT field

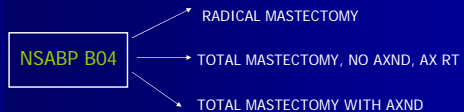
- Do you think that axillary dissection might change the extent of radiation field following lumpectomy and SNB for a 2.0cm grade 3, ER-, her2neu -, LVI +, one sentinel node + (of 1) in a:

Size of sN deposit	2mm deposit			1cm deposit		
	Yes	No	Maybe	Yes	No	Maybe
40 year old	10	0	0	9	0	1
50 year old	9	0	1	8	0	2
60 year old	8	0	1	8	0	2
70 year old	6	2	2	7	3	0

Number of respondents: 10 of 17



4. When it May Affect Survival



No Overall Survival differences with 25 years f/u
Minimal adjuvant therapy given

4. When it May Affect Survival

IBCSG 10-93
 ≥60 yo, cNN
 TAM, No chemo

- AXND
- No AXND

- %NP: 27% (median nodes examined 13) no information about how many NP
- Axillary recurrences: 1% (2) vs 3% (7) (pNS)
- DFS p0.71, OS p0.82 with 6y f/u
- ?Suboptimal therapy for NP and ER- subsets

ASCO 2003

4. When it May Affect Survival

ALMANAC
 cNN operable BC
 N=1031

- AXND 513: NP 23.8%
- SNB + IHC n=120 24.8%
- AXND or AX RT 75 28

RT: more impaired shoulder flexion and abduction at 18m
 AXND: more sensory loss in axilla at 18m
 No data on survival or disease free survival

4. When It May Affect Survival

RCT of Postmastectomy Locoreg RT plus CMF vs CMF; 15 year f/u
 318 Premenopausal women with node positive disease
 T size <2cm in 40%, >5cm in 3.5%

Hz ratio Recurrence 0.67 (0.5-0.9) p0.007; Hz ratio BCS survival 0.71 (0.51-0.99) p0.05; Hz ratio Overall Survival 0.74 (0.53-1.02) p0.07

Figure 3. Breast Cancer-Specific Survival in the Study Groups. Ragaz, NEJM 1997

Figure 4. Overall Survival in the Study Groups. Ragaz, NEJM 1997

4. When It May Affect Survival

Subset Analysis by Number of Involved Nodes

Further analysis suggests RR death w/ RT for 1-3NP with extensive extranodal spread: 0.47 (p0.04) vs w/ no EES 0.73 (p0.3)

Ragaz, NEJM 1997, ASCO 99

4. When It May Affect Survival

RCT of Postmastectomy Locoreg RT plus CMF vs CMF; 10 year f/u
 Premenopausal women with stage II or III disease
 T size <2cm in 39%, >5cm in 14%

	N	%10 DFS		%10 OS		P value
		CMF	CMF/RT	CMF	CMF/RT	
All	1708	34	48	45	54	<0.001
1-3NP	1061	39	54	54	62	<0.001
4+NP	510	14	27	20	32	Not stated

Benefit seen in all subsets
 Criticism: inclusion of stage III disease

Overgaard, NEJM 1997

4. When it may affect survival

Meta-analyses of postmastectomy locoreg RT vs no RT:

- Cuzick n=7941. RCTs 1949-1974. Improved BCSS, no OS advantage due to increased CVS deaths (problems: no adjuvant therapy; older RT tech) (JCO 94)
- EBCTCG: all RCTs prior to 1985. same result, same problems (NEJM 1995)
- Whelan. n=6367 18 RCTs in which pts had adj therapy. Showed reduced locoregional failure Odds 0.25 (0.19-0.34); reduced mortality Odds 0.83 (0.74-0.94) Problems: follow up short for secondary cardiac events; but RT safer (JCO 2000)



Two final points...

1. The number of sentinel nodes removed and the proportion that are positive matters
2. Micrometases vs macrometases (method of detection, processing the sentinel node)



Memorial Sloan Kettering breast nomogram

<http://www.mskcc.org/mskcc/html/15938.cfm>



MSK breast nomogram

Variation	Grade 3	LVI +	4 sN retrieved	Only 1sN retrieved	Detection by IHC
Risk of other NP	36%	41%	20%	41%	9%



Micrometases (<2mm)

- Prognostic significance unclear (missing from MSK nomogram)
- Cytokeratin staining and serial sectioning of sN upstages 10-30% from neg to positive
- Likelihood of further +node is 5-20% (vs up to 50% for sN macromets)
- Predictors of NO further + nodes: T1a, T1b; no LVI; grade 1 (small series up to 160 cases)



Micromets Dilemma

- 80-90% no further + nodes: they need neither AXND nor AX RT. +/- chemo (age, ER, grade)
- 10-20% have further nodal mets: the extent of RT and chemo may be dictated AXND findings
- SO: Dissect in 100 for the 10-20 in whom treatment may change and for whom it *MAY* be therapeutic, OR radiate in 100 for whom 10-20 may benefit (with loss of prognostic info)
- OR forgo AXND AND RT to avoid the toxicity in 80 although it *might* affect outcome in 20?



ONGOING TRIALS to determine the worth of:

- post AXND RT vs nil (pN+):
 - MA20; AMAROS-EORTC
- SNB v AXND (pN0):
 - NSABP B32; KISS; Milan
- SNB v AXND:
 - ACOSOG Z0011 (1-2+nodes, IHC); IBCSG 23-01 (Micromets only)
- AXND vs RT:
 - (ALMANAC)
- Micromets Prognostic import:
 - ACOSOG Z0010



Conclusions

- Since B04, IBCSG10-93... Systemic therapy has improved
- This may reduce or **augment** the therapeutic impact of axillary clearance (+RT) for sN positive disease...
- New chemotherapy choices come with toxicities which are not appropriate for everyone...



Conclusions

What will help us grapple with the evolving need for AXND with a + sN:

- Trials of AXND vs AX RT
- Trials of locoregional RT vs no RT after AXND (for 1-3, 4+ positive nodes)
- Better predictors of no further nodes +
- Whenever possible, >1 sN retrieved
- Better understanding of prognostic import of micrometases



Conclusions

But until we have MORE information:

We will continue to struggle when a pt with a positive sentinel node has not had an AXND....

And we'll probably keep sending them back to you...at least some of them



THANK YOU QUESTIONS?