BREAST CANCER RADIOTHERAPY MANAGEMENT OF AXILLA

Amir Ghasemi Jangjou

Radiation Oncologist

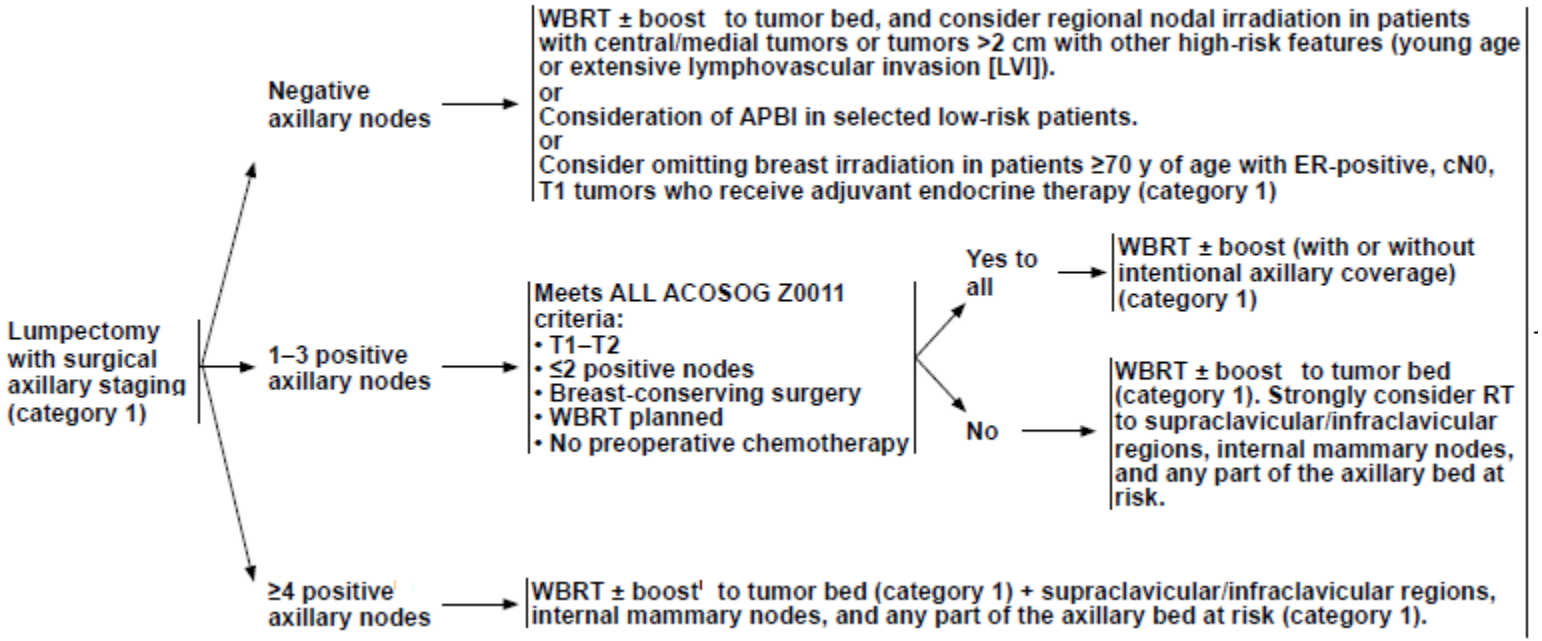
- No cancer patient gains cure without perfect locoregional control .
- Trials showed that whole-breast irradiation significantly reduced the risk of ipsilateral tumor recurrence after resection.

- Whole breast radiotherpy reduces LR recurrence by a factor of 3-4.

- The prevention of 20 isolated loco regional recurrences in 100 women randomized to RT prevents 5 BC deaths. as RT is a LR treatment and BC mortality is caused by DM, these data constitute powerful evidence that DM can prevented by LR therapies.
- Of 4 LR by RT prevents 1 BC death.

- Traditionaly extent of disease in the lymph nodes can help guide decision-making for adjuvant treatments, including radiation indication and fieldes selection of the type of cytotoxic chemotherapy and additional systemic therapy.

LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:
BREAST-CONSERVING THERAPY



2017-Final Report
Z0011 bomb

JAMA | Original Investigation

Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis

The ACOSOG Z0011 (Alliance) Randomized Clinical Trial

Armando E. Giuliano, MD; Karla V. Ballman, PhD; Linda McCall, MS; Peter D. Beitsch, MD; Meghan B. Brennan, RN, ONP, PhD; Pond R. Kelemen, MD; David W. Ollila, MD; Nora M. Hansen, MD; Pat W. Whitworth, MD; Peter W. Blumencranz, MD; A. Marilyn Leitch, MD; Sukamal Saha, MD; Kelly K. Hunt, MD; Monica Morrow, MD

ACOSOG Z0011

- 2005 first report.
- 9.3 Yr-891 women.
- Eligible patients were women with clinical T1 or T2 invasive breast cancer(ductal,lobular) ***no palpable*** axillary adenopathy, and 1 or 2 sentinel lymph nodes containing metastases(micro or ***macro***).
- All patients had planned lumpectomy, planned tangential whole-breast irradiation, and adjuvant systemic therapy. Third-field radiation was prohibited.
- OS-DFS-regional recurrences .

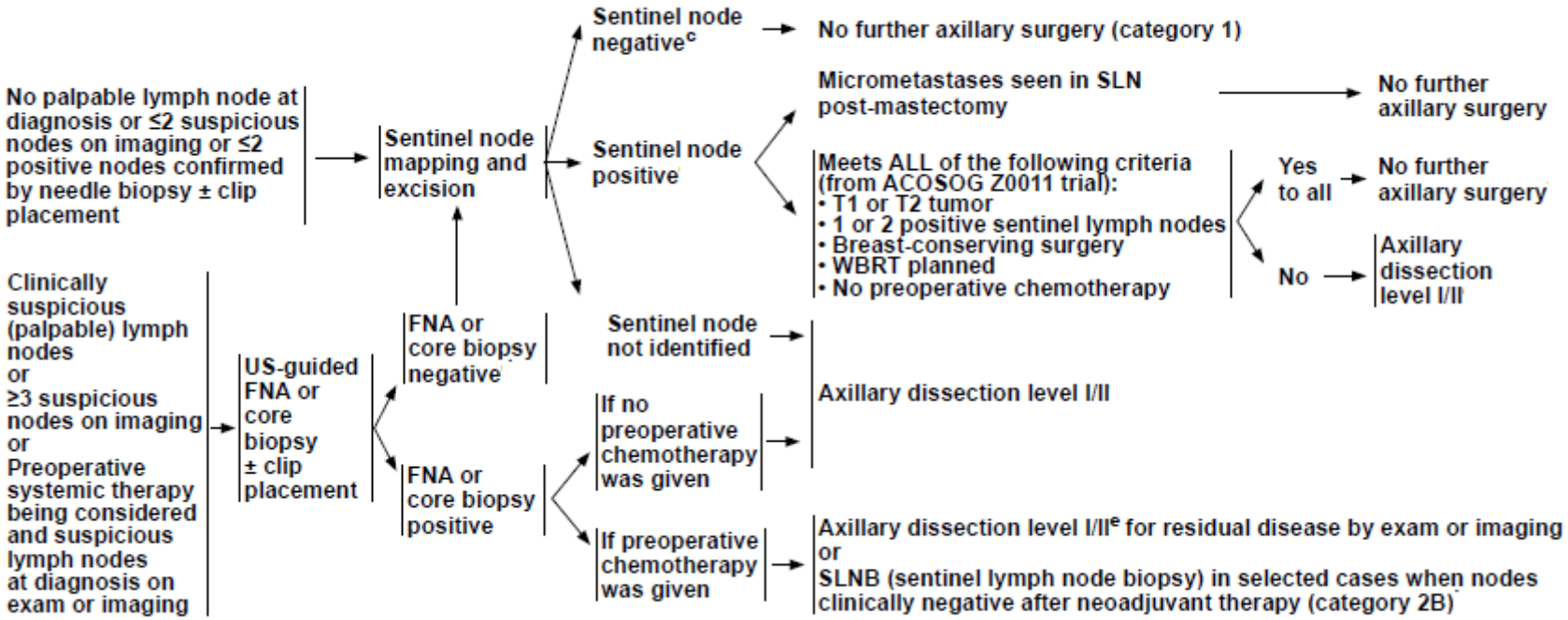
RESULT

- At a median follow-up of 9.3 years, the 10-year overall survival was 86.3% in the SLND alone group and 83.6% in the ALND group
- Noninferiority .
- The 10-year disease-free survival was 80.2% in the SLND alone group and 78.2% in the ALND group.
- Between year 5 and year 10, 1 regional recurrence was seen in the SLND alone group vs none in the ALND group.
- Ten-year regional recurrence did not differ significantly between the 2 groups.

CONCLUSIONS

- Among women with T1 or T2 invasive primary breast cancer, no palpable axillary adenopathy, and 1 or 2 sentinel lymph nodes containing metastases, 10-year overall survival for patients treated with sentinel lymph node dissection alone was noninferior to overall survival for those treated with axillary lymph node dissection.
- These findings do not support routine use of axillary lymph node dissection in this patient population based on 10-year outcomes.

SURGICAL AXILLARY STAGING



- Halstedian concept.
- Since then, it has been recognized that breast cancer biology, rather than the extent of surgery, is a major risk determinant of both systemic and locoregional recurrence, opening the door to new surgical approaches to management.

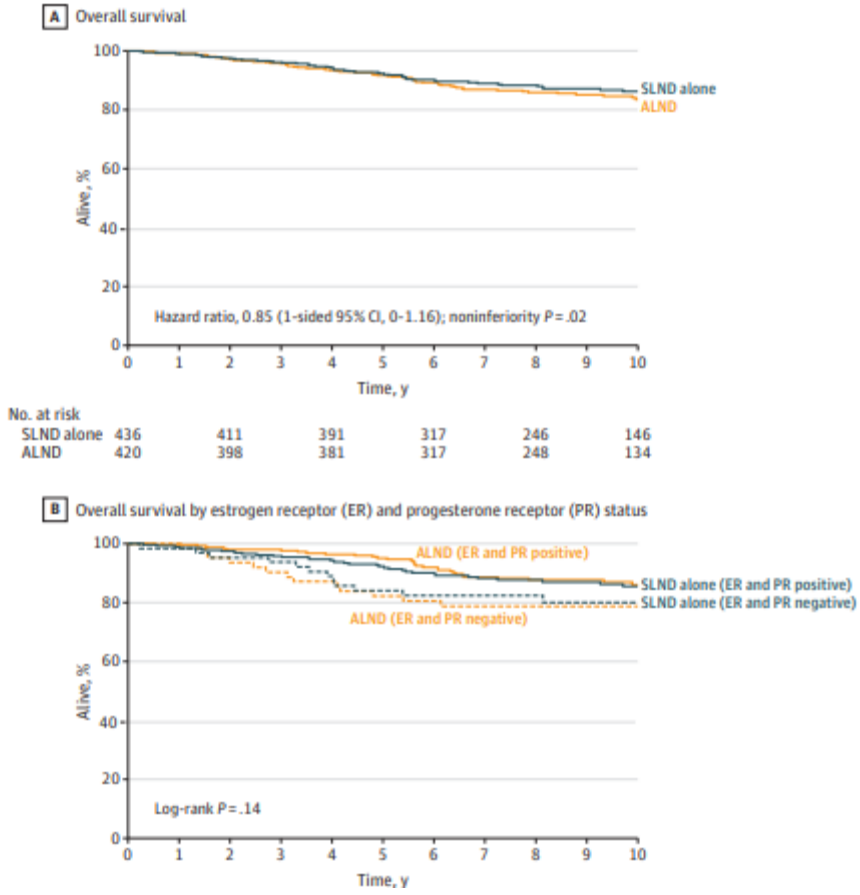
- Between 1998 and 2004, the use of ALND declined from 94% to 36% in women with no axillary nodal metastases
- **Axillary lymph node dissection** is an effective method of maintaining regional control but it is associated with a significant risk of complications such as lymphedema, numbness, axillary web syndrome, and decreased upper-extremity range of motion.

- Breast conservative surgery

- Axillary conservative surgery

- Patients enrolled in ACOSOG Z0011 reflected the demographics of patients with breast cancer in the United States.
- The majority of patients were postmenopausal with hormone receptor–positive breast cancer.

Overall and Disease-Free Survival in the ACOSOG Z0011 (Alliance) Trial



- Management of women in the United States with sentinel node metastases changed substantially as a result of the study.

Limitations

- However, these conclusions apply only to patients meeting ACOSOG Z0011 eligibility criteria and should not be extrapolated to the management of patients with positive palpable nodes, those with metastases in more than 2 sentinel nodes, patients forgoing whole-breast irradiation, those treated with mastectomy without radiation, or patients receiving neoadjuvant therapy because all of these are circumstances in which the elimination of ALND is not known to be safe

Multivariable Analysis of the Association of Treatment and Prognostic Variables With Overall Survival

	No. of Patients	No. of Deaths	Adjusted HR (95% CI)[a]	*P* Value
Lymph node dissection group				
Sentinel alone	426	51	0.93 (0.64-1.36)	.72
Axillary	413	56	1 [Reference]	
Age group, y				
≤50	295	23	1 [Reference]	.002
>50	544	84	2.08 (1.31-3.30)	
Estrogen receptor and progesterone receptor status				
Both negative	101	25	1 [Reference]	.02
≥1 Positive	514	61	0.57 (0.36-0.91)	
Lymphovascular invasion				
Absent	238	31	1 [Reference]	.74
Present	387	48	0.92 (0.59-1.46)	
Sentinel lymph node met size				
Micrometastases (≤2 mm)	296	37	1 [Reference]	.97
Macrometastases (>2 mm)	418	53	1.01 (0.66-1.54)	
Pathological tumor size, cm (continuous)			1.19 (1.07-1.32)	.001
Histological type				
Ductal	687	86	1 [Reference]	.25
Lobular	63	9	1.04 (0.52-2.07)	
Mixed ductal and lobular	32	8	2.06 (0.99-4.27)	
Other	41	4	0.79 (0.29-2.16)	
Grade[b]				
1	150	20	1 [Reference]	.46
2	300	31	0.74 (0.42-1.30)	
3	178	26	1.07 (0.60-1.92)	
Unknown or missing	144	21	1.06 (0.58-1.96)	

- Before publication of the initial ACOSOG Z0011 trial results, there was a general consensus that axillary dissection was necessary for better cancer control when metastases were identified in sentinel lymph nodes.
- This trial demonstrated that morbidity can be avoided without decreasing cancer control.

ER-positive

- 80% of patients had hormone receptor–positive tumors. D.
- This confirms that although distant recurrence among hormone receptor–positive tumors is a later event, nodal recurrence among these patients is primarily an early eventIn
- addition, there was no significant difference in
- disease-free survival between patients treated with SLND
- alone and ALND

TNBC

- Studies examining the application of findings from ACOSOG Z0011 among young women or among those with triple-negative breast cancer have found neither a greater need for ALND in these groups, nor heavier axillary tumor burdens in those undergoing ALND.

Other studies

- Since the initial publication of ACOSOG Z0011, 2 studies (the MA.20 and the European Organization for Research and Treatment of Cancer24 [EORTC] 22922/10925) examined the role of regional nodal irradiation in patients with similar characteristics (T1 or T2 and 1, 2, or 3 axillary nodal metastases) and their findings have caused some to question whether comprehensive nodal irradiation should be routine.
- In the MA.20 study, patients with nodepositive tumors were randomized to axillary dissection or axillary dissection plus extensive postoperative nodal irradiation, including supraclavicular and internal mammary nodal basins.
- The EORTC 22922/10925 study randomized high-risk women postoperatively to whole-breast or chestwall irradiation alone or with regional nodal irradiation.
- These studies, with 10 years of follow-up and 5836 enrolled patients, demonstrate a very modest 1% to 1.5% decrease in regional recurrence with nodal irradiation, and no significant difference in overall survival.

- The 10-year rates of overall survival in the SLND alone and ALND groups of the ACOSOG Z0011 (Alliance) trial were 86.3% and 83.6%, respectively, compared with 82.8% in the nodal irradiation group in MA.20 and 82.3% in EORTC 22922/10925, suggesting that the ACOSOG Z0011 eligibility criteria identified a population that may not benefit from comprehensive nodal irradiation. Thus, although nodal irradiation may be added to the management of some patients with node-positive tumors based on an evaluation of their overall risk profile, the routine use of nodal irradiation for all patients with 1 or 2 sentinel node metastases managed with SLND alone may not be justified.

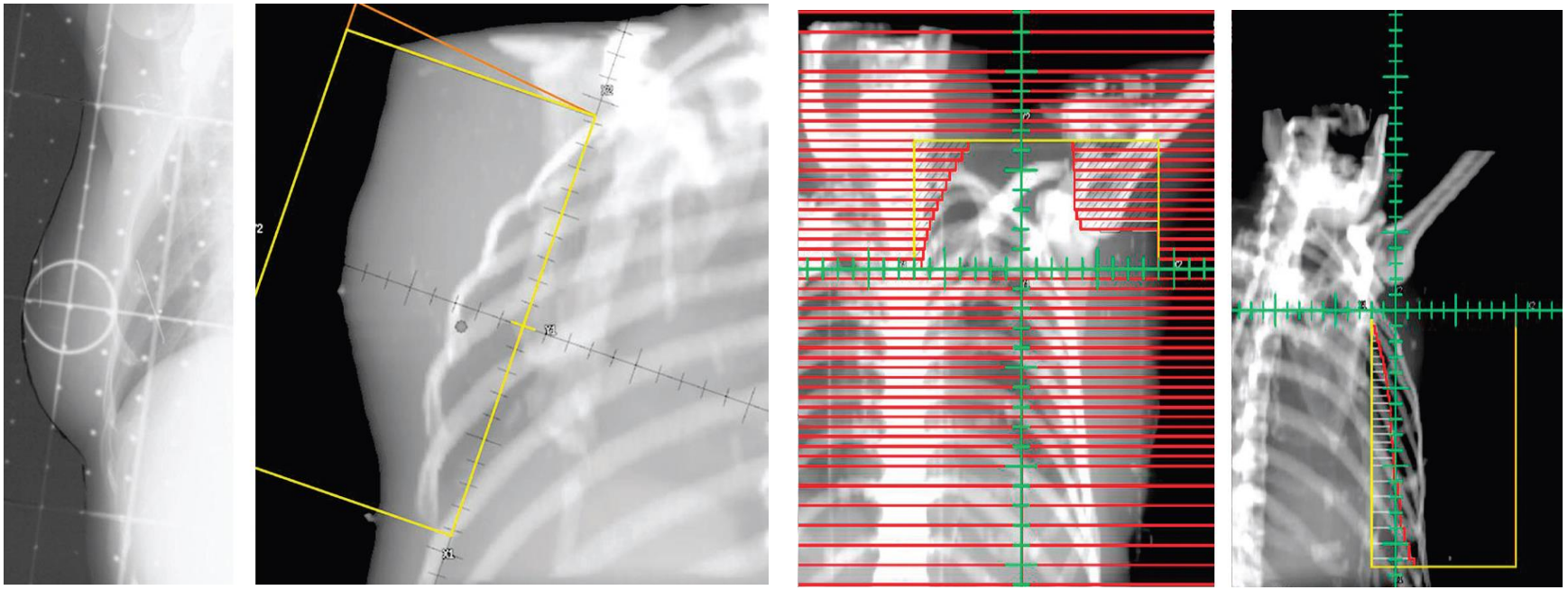
- The 10-year rates of overall survival in the SLND alone
- and ALND groups of the ACOSOG Z0011 (Alliance) trial were
- 86.3% and 83.6%, respectively, compared with 82.8% in the
- nodal irradiation group in MA.20 and 82.3% in EORTC
- 22922/10925, suggesting that the ACOSOG Z0011 eligibility
- criteria identified a population that may not benefit from
- comprehensive nodal irradiation. Thus, although nodal irradiation may be added to the management of some patients
- with node-positive tumors based on an evaluation of their
- overall risk profile, the routine use of nodal irradiation for
- all patients with 1 or 2 sentinel node metastases managed
- with SLND alone may not be justified.

- However, these conclusions apply only to patients meeting ACOSOG Z0011 eligibility criteria and should not be
- extrapolated to the management of patients with positive
- palpable nodes, those with metastases in more than 2 sentinel nodes, patients forgoing whole-breast irradiation, those
- treated with mastectomy without radiation, or patients
- receiving neoadjuvant therapy because all of these are circumstances in which the elimination of ALND is not known
- to be safe

Radiation Field Design in the ACOSOG Z0011 (Alliance) Trial

- 81.1% received tangent-only treatment
- High tangents (cranial tangent border 2 cm from humeral head) were used in 50% of patients.

- high tangents to include a component of axillary level I/II more often than those in the ALNDarm



- Outcomes in Z0011 have been previously reported to be equivalent, and axillary recurrences were rare (0.9%) among the patients who did not receive axillary dissection.
- Indeed,
- the observation of such low regional failure rates despite the 27%
- incidence of additional nodal disease among patients randomly assigned
- to axillary dissection led the investigators and others to speculate
- that incidental irradiation of the low axilla with standard
- tangential fields may have played an important role in ensuring the
- excellent outcomes observed in Z0011.1,14

- Half of patients treated in both arms, the superior border of the tangential field was within 2cm of the humeral head and may have led to substantial incidental axillary irradiation.
- A previous study has suggested that the average dose delivered to the level I axilla increases from 66%of prescribed dose with standard tangents to 86% with high tangents, and average dose to level II increases from 44% to 71%.
- The proportion of level I receiving 95% of prescribed dose increases from 51% with standard tangents to 79% with high tangents, and the proportion of level II receiving 95% of prescribed dose increases from 26% to 51%.
- .

- Therefore, consistent with prior reports from the Z0011 trialists, we believe that the results of Z0011 should not be extrapolated to patients who do not receive adjuvant RT or to those who receive RT using partial-breast or prone techniques, in which substantially less of the axilla is included.

Future

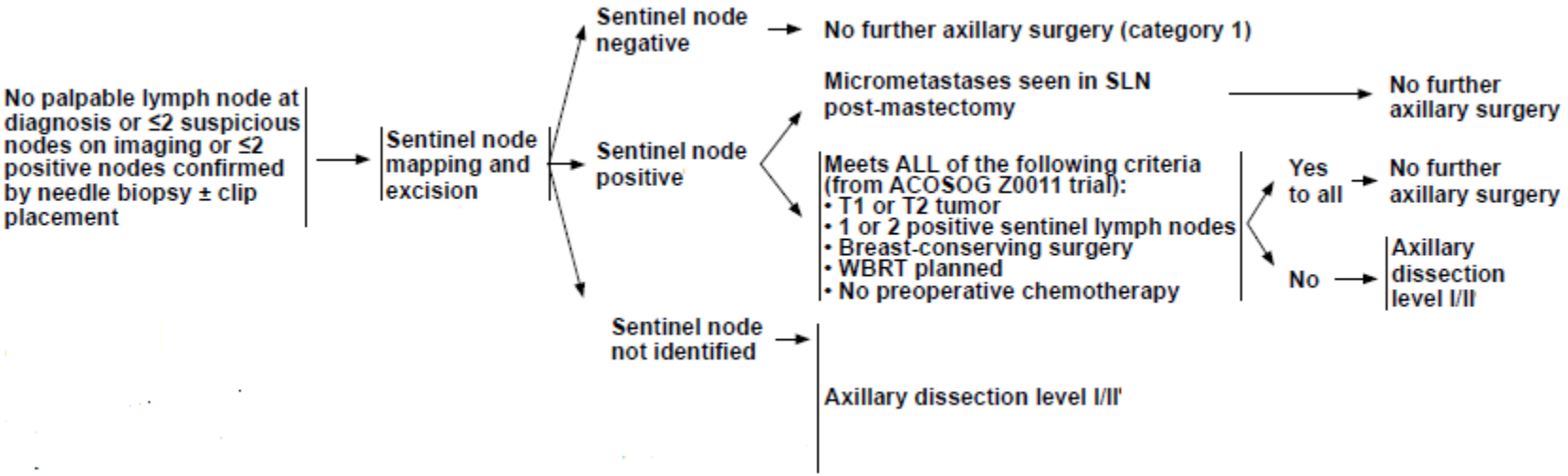
- The preliminary results of the NCIC (National Cancer Institute of Canada) MA2016 and EORTC (European Organisation for Research and Treatment of Cancer) 2292217 studies have suggested that irradiation of the supraclavicular and internal mammary nodal regions may affect the rate of distant metastases developing in node-positive patients who receive axillary lymph node dissection.
- Whether such treatment might benefit patients with minimal axillary disease detected on sentinel node biopsy remains unknown;
- a trial randomly assigning sentinel node–positive patients to breast only or breast plus regional nodal irradiation would be the ideal way to address the impact of such treatment on patient outcomes.
- It is also possible that certain patients with limited axillary disease might not require any RT at all; a trial examining whether select patients might avoid both axillary dissection and RT would therefore also beworthy of consideration.
- These remain important subjects for future investigation, because our findings suggest substantial variability in the extent and even the administration of RT in Z0011.

Europian version

- Survival and axillary recurrence following sentinel node-positive breast cancerwithout completion axillary lymph node dissection:therandomized controlled SENOMAC trial.

- Abandonning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Milan(SOUND:Sentinel node vsObservation after axillary UltraSouND)

SURGICAL AXILLARY STAGING



Management of the Axilla after Neoadjuvant Systemic Therapy

- NAST have led to its increased use in the USA from 2010 to 2015 demonstrated increased use of NAST from 15.7 to 26% .
- This increase in use was most prominent in high pathologic responder subtypes such as ER and PR-/Her2neu- and Her2neu + cohorts.

Clinical staging of the axilla prior to treatment planning

- For patients who are being considered for NAST, the National Comprehensive Cancer Network (NCCN) advises imaging evaluation of the axillary basin by either ultrasound or MRI in addition to clinical exam, followed by biopsy of any radiographically or clinically suspicious lymph nodes .
- The preferred biopsy technique is core needle.
- Fine needle aspiration is also an acceptable technique with similar specificity to core needle biopsy (98% versus 96%). However, the overall sensitivity is lower with FNA compared with core needle biopsy (74% versus 87%), supporting the use of a core needle.

Clinically node negative post systemic therapy

- Patients who are clinically node negative at the time of presentation should undergo a sentinel lymph node (SLN) biopsy as the first step in their axillary staging.
- False negative rate (FNR) of 9.8%. .
- For clinically node-negative patients found to have a positive SLN prior to NAST, an ALND would be recommended as the standard of care.

Clinically node negative after systemic therapy Pre-NAST biopsy

- Controversy exists regarding whether to perform the SLN biopsy prior to versus after NAST.
- Advocates for SLN biopsy prior to NAST argue that this timing provides the most accurate assessment of the axillary nodes at the time of presentation, which has implications on prognosis, selection of chemotherapy agents, and planning of radiation therapy fields .
- The higher accuracy of pre-NAST SLN can be partially explained by alterations of the lymphatic drainage pathways due to treatment-induced fibrosis in the lymphatic channels .
- However, SLN biopsy prior to NAST requires an additional surgical procedure and can delay initiation of systemic therapy.

- Most current clinical practice guidelines recommend performing SLN biopsy after NAST in patients who are clinically node negative Although the accuracy of post-NAST SLN is slightly lower compared with pre-NAST SLN,
- Post-NAST SLN biopsy has an acceptable FNR, especially when dual dye technique is utilized
- Identification rates were high (97% with dual dye, 96% using only blue dye or radiocolloid).

why performing a SLN biopsy after NAST may be preferred

- Post-NAST SLN biopsy spares patients an extra surgery which may delay initiation of NAST.
- For clinically node-negative patients found to have a positive SLN prior to NAST, an ALND would be recommended as the standard of care.
- This recommendation does not change, even if patients go on to have a robust response to the NAST.
- Patients who undergo a SLN biopsy in the postNAST setting and are found to have persistent metastatic disease in the SLN would also be recommended an ALND as standard of care as patients with persistent metastatic disease in the SLN after NAST have a high chance of having disease in additional nodes (as high as 50% in one
- study).

- However, for some patients, NAST may convert a clinically negative but pathologically positive axilla to a pathologically negative one.
- If patients are found to have a negative SLN post-NAST, these patients would not be recommended additional axillary surgery and would be potentially spared the morbidity of an ALND (paresthesias, pain, reduced shoulder range of motion, wound infections, seromas, and lymphedema).
- Performing the SLNbiopsy post-NAST may decrease the extent of axillary surgery required, especially for those patients with a robust response to NAST.

Clinically node positive

- Traditionally, all patients who presented with clinically positive lymph nodes were recommended a full ALND.
- An ALND clears the nodal basin of any lymph node disease, minimizing the risk of local recurrence and providing full pathologic nodal staging. SLN biopsy, intended to be a diagnostic test to identify metastatic disease,

The ACOSOG Z1071 (Alliance) Clinical Trial

Sentinel Lymph Node Surgery After Neoadjuvant Chemotherapy in Patients With Node-Positive Breast Cancer
The ACOSOG Z1071 (Alliance) Clinical Trial

Judy C. Boughey, MD; Vera J. Suman, PhD; Elizabeth A. Mittendorf, MD, PhD; Gretchen M. Ahrendt, MD; Lee G. Wilke, MD; Bret Taback, MD; A. Marilyn Leitch, MD; Henry M. Kuerer, MD, PhD; Monet Bowling, MD; Teresa S. Flippo-Morton, MD; David R. Byrd, MD; David W. Ollila, MD; Thomas B. Julian, MD; Sarah A. McLaughlin, MD; Linda McCall, MS; W. Fraser Symmans, MD; Huong T. Le-Petross, MD; Bruce G. Haffty, MD; Thomas A. Buchholz, MD; Heidi Nelson, MD; Kelly K. Hunt, MD; for the Alliance for Clinical Trials in Oncology

DESIGN, SETTING, AND PATIENTS The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial

- enrolled women from 136 institutions from July 2009 to June 2011 who
- had clinical T0 through T4, N1 through N2, M0 breast cancer and received neoadjuvant
- chemotherapy. Following chemotherapy, patients underwent both SLN surgery and ALND.
- Sentinel lymph node surgery using both blue dye (isosulfan blue or methylene blue) and a
- radiolabeled colloid mapping agent was encouraged.

The ACOSOG Z1071 (Alliance) Clinical Trial Results

- Among women with cN1 breast cancer receiving neoadjuvant chemotherapy who had 2 or more SLNs examined, the FNR was not found to be 10% or less.
- Given this FNR threshold, changes in approach and patient selection that result in greater sensitivity would be necessary to support the use of SLN surgery as an alternative to ALND.

Response rate to neoadjuvant chemotherapy

- With modern-era systemic therapy, a substantial proportion of patients will have a pCR to NAST. According to data from the ACOSOG Z1071 trial, approximately 65% of patients with Her2neu + disease, 50% of patients with ER and PR-/Her2neu- disease, and 21% of patients with ER and/or PR+/Her2neu- disease had a pCR in the axilla .

Response after neo

- However, for patients who receive NAST, there is an increasing body of evidence supporting more conservative axillary surgery for patients who have a good clinical response to treatment
- Patients who have had a pCR in the nodal basin derive no oncologic benefit from ALND.
- Performing SLN following NAST is one proposed way of tailoring the extent of axillary surgery and attempting to differentiate those patients with residual axillary disease who would benefit from a full ALND from those patients with a nodal pCR.

Sentina
Europian version of ACOSOC Z1071

- Arm C (N = 592) of this trial was comparable with the ACOSOG Z1071 study design, consisting of patients who were clinically node positive and converted to clinically node negative following neoadjuvant chemotherapy. This arm underwent a SLN biopsy followed by an immediate ALND.
- In Arm C of SENTINA false negative rate of 14.2%

SNFNC

- Finally, the SN FNAC trial analyzed the use of SLN biopsy followed by immediate ALND after neoadjuvant chemotherapy for patients with biopsy-proven lymph node-positive breast cancer.
- This study enrolled 153 patients. The study design was unique in that it mandated the use of IHC after H&E staining to confirm SLN negativity. Further, the study classified isolated tumor cells (ypN0[i + 1], ≤ 0.2 mm) in the SLN as node positive.
- With these criteria, the SLN identification rate in SN FNAC trial was 87.6% with a false negative rate of ***8.4%.***

- All three of these clinical trials assessing the role of SLN biopsy after NAST for patients with clinical N1 disease reported lower identification rates and higher false negative rates than has historically been observed for the SLN biopsy in the setting of clinically negative lymph nodes

FNR

- dual dye technique
- Dual dye also improved the false negative rate in all three trials, dropping to 10.8% for ACOSOG Z1071, 8.6% in SENTINA, and 5.2% in SN FNAC.

- One additional factor observed to improve the false negative rate was sampling of a greater number of lymph nodes .
- As the collection of more SLNs (at least 2 or 3) and a dual dye technique improved the false negative rates to below the clinically acceptable threshold of 10% set in ACOSOG Z1071 and SN FNAC

- Many oncologists argue that SLN biopsy can be considered a safe alternative for women with cN1 who undergo NAST. However, other surgeons argue that a FNR near 10% is still too high for a cohort of women known to have metastatic disease in their axillary nodes and would present too great of a risk of leaving residual disease in the axilla

Clinical staging of the axilla prior to treatment planning

- For patients who are being considered for NAST, the National Comprehensive Cancer Network (NCCN) advises imaging evaluation of the axillary basin by either ultrasound or MRI in addition to clinical exam, followed by biopsy of any radiographically or clinically suspicious lymph nodes .
- The preferred biopsy technique is core needle.
- Fine needle aspiration is also an acceptable technique with similar specificity to core needle biopsy (98% versus 96%). However, the overall sensitivity is lower with FNA compared with core needle biopsy (74% versus 87%), supporting the use of a core needle.

Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection

Abigail S. Caudle, Wei T. Yang, Savitri Krishnamurthy, Elizabeth A. Mittendorf, Dalliah M. Black, Michael Z. Gilcrease, Isabelle Bedrosian, Brian P. Hobbs, Sarah M. DeSnyder, Rosa F. Hwang, Beatriz E. Adrada, Simona F. Shaitelman, Mariana Chavez-MacGregor, Benjamin D. Smith, Rosalind P. Candelaria, Gildy V. Babiera, Basak E. Dogan, Lumarie Santiago, Kelly K. Hunt, and Henry M. Kuerer

- A prospective study of patients with biopsy-confirmed nodal metastases with a clip placed in the sampled node was performed. After neoadjuvant therapy, patients underwent axillary surgery and the pathology of the clipped node was compared with other nodes. Patients undergoing TAD had SLND and selective removal of the clipped node using iodine-125 seed localization. The FNR was determined in patients undergoing complete axillary lymphadenectomy (ALND).
- The clipped node revealed metastases in 115 patients, resulting in an FNR of 4.2% for the clipped node.

Response to Radiotherapy After Breast-Conserving Surgery in Different Breast Cancer Subtypes in the Swedish Breast Cancer Group 91 Radiotherapy Randomized Clinical Trial

Martin Sjöström, Dan Lundstedt, Linda Hartman, Erik Holmberg, Fredrika Killander, Anikó Kovács, Per Malmström, Emma Niméus, Elisabeth Werner Rönnerman, Mårten Fernö, and Per Karlsson

- RT reduced the cumulative incidence of ipsilateral breast tumor recurrence (IBTR) as a first event within 10 years for luminal A–like tumors (19% v 9%),
- luminal B–like tumors (24% v 8%;)
- triple-negative tumors (21% v 6%;), but not for human epidermal growth factor receptor 2–positive (luminal and nonluminal) tumors (15% v 19%;); however, evidence of an overall difference in RT effect between subtypes was weak (P = .21). RT reduced the rate of death from breast cancer (BCD) for triple-negative tumors (hazard ratio, 0.35; P = .06), but not for other subtypes. Death from any cause was not improved by RT in any subtype. A hypothesized clinical low-risk group did not have a low risk of IBTR without RT, and RT reduced the rate of IBTR as a first event after 10 years (20% v 6%; P = .008), but had no effect on BCD or death from any cause. Conclusion Subtype was not predictive of response to RT, although, in our study, human epidermal growth factor receptor 2–positive tumors seemed to be most radioresistant, whereas triple-negative tumors had the largest effect on BCD. The effect of RT in the presumed low-risk luminal A–like tumors was excellent. J