Allina Health
VIRGINIA PIPER CANCER INSTITUTE

Oncology Clinical Service Line
System-wide Consensus Guidelines: **Pathological Evaluation of the Axillary Sentinel Lymph Nodes in Patients Undergoing Lumpectomy and Radiation Therapy**

These guidelines apply to clinical interventions that have well-documented outcomes, but whose outcomes are not clearly desirable for all patients

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Approved Date:
Approval By:

System-wide Ownership Group: Allina Health Breast Program Committee

System-wide Information Resource: Manager of Clinical Programs

Hospital Division Quality Council: August 2018

Stakeholder Groups
Virginia Piper Cancer Institute

SCOPE:

Sites, Facilities, Business Units	**Departments, Divisions, Operational Areas**	**People applicable to**
Abbott Northwestern Hospital, Buffalo Hospital, Cambridge Medical Center, District One Hospital, Mercy Hospital, Mercy Hospital – Unity Campus, New Ulm Medical Center, River Falls Area	Breast Surgeons, Pathology, Radiation Oncology, Medical Oncology	Physicians, Advanced practice providers

Hospital, Regina Hospital, St. Francis Medical Center, United Hospital		

PICO (TS) Framework

Population: Breast cancer patients undergoing lumpectomy and sentinel lymph node (SLN) biopsy, followed by radiation therapy.

Intervention: Evaluation of the axillary sentinel nodes at the time of lumpectomy, and on subsequent permanent section evaluation by immunohistochemistry (IHC)

Comparison: N/A

Outcomes:

1. Routine frozen section evaluation of the SLNs in patients undergoing lumpectomy for invasive breast cancer (who have not had neoadjuvant chemotherapy) is not routinely performed unless there is clinical evidence of gross disease within the lymph nodes, matted nodes, or 3 or more involved nodes.
2. Frozen section of SLNs is generally performed in patients undergoing lumpectomy following neoadjuvant chemotherapy.
3. The evaluation of SLNs by immunohistochemistry (IHC) is not routinely performed. However, IHC stains may be performed at the discretion of the pathologist (such as to evaluate atypical cells identified on H&E stains which require further clarification).

Timing: During initial breast surgery

Setting: Inpatient/hospital

CLINICAL PRACTICE GUIDELINES:

1. Routine frozen section is not recommended for the evaluation of the sentinel lymph nodes (SLNs) in most patients with invasive breast cancer undergoing breast conservation therapy (BCT) followed by whole breast radiation therapy.

2. Routine frozen section of SLNs is generally recommended for patients undergoing BCT who have undergone neoadjuvant chemotherapy.

3. Routine frozen section is currently recommended for the evaluation of the SLN in patients with invasive breast cancer undergoing mastectomy.

4. Patients with clinical T1 or T2 N0M0 undergoing BCT with < 3 positive SLN's generally do not require axillary lymph node dissection (ALND)., assuming they undergo radiation therapy. Patients undergoing BCT with ≥3 positive SLNs, "gross" clinical disease, or matted nodes should be advised to undergo ALND.

5. The evaluation of the axillary sentinel nodes by immunohistochemistry (IHC) will not be routinely performed on SLNs. However, IHC stains may be performed at the discretion of the pathologist (in attempts to clarify atypical cells seen on routine H&E levels).

6. Controversial cases should be discussed in a multi-disciplinary breast conference.

SUPPORTING EVIDENCE:

The use of the SLN biopsy procedure was begun in the 1990s, and has become the standard for staging the axilla in breast cancer patients. Several large national studies have established the use of the SLN biopsy procedure, with a false negative rate of 3-5%. Immunohistochemical cytokeratin staining of the SLN was also begun in the 1990s, as an adjunct to the H&E evaluation of the SLN. The detection of even a single cancer cell by IHC in a SLN established its sensitivity and specificity in identifying possible metastatic disease.

More recent studies have questioned the significance of detecting isolated tumor cells (ITC) in the SLN in the staging and treatment of breast cancer patients. Several national studies have shown no difference in survival or recurrence in patients with negative SLN (without IHC staining) from those patients with positive SLN containing ITC's who underwent ALND. In addition, some studies found no significant survival difference in patients with ITC from those with metastatic tumor deposits < 0.02 cm (micrometastases).

These studies questioned the use of IHC in the staging of the axilla for breast cancer patients. ALND causes considerable morbidity for patients with breast cancer including risk of lymphedema, musculoskeletal disability, infection and pain.

The ACOSOG Z0011 trial, published in 2010, was designed to determine whether ALND was necessary after detection of metastases in the SLN in patients undergoing breast conservation therapy (BCT) with whole breast radiation. Patients with a positive SLN were randomized to axillary dissection or no further axillary surgery. The patients enrolled in this trial were a select group of patients. Only patients with clinical T1 or T2N0M0 staged tumors were included. Most patients had a tumor size that was smaller than 2 cm. If patients had suspicious lymph nodes by exam, they were not included in this study. Additionally, if patients had 3 or more positive sentinel lymph nodes, extra-nodal disease or had neoadjuvant therapy, they were excluded from the study. IHC staining was not used in this study thus eliminating ITC's as a factor in the staging of the axilla. SLN's were evaluated by standard H&E staining techniques.
At a median follow-up of 6.3 years, there was no significant difference in loco-regional recurrence, 4% for axillary dissection vs. 2.8% for SLN alone. Overall survival was the same between both groups as well at 92%.

There are several important features to this study that need to be emphasized. First, this study did not include patients undergoing mastectomies. At present the standard of care for patients treated with mastectomy is to perform a sentinel lymph node biopsy; if the sentinel lymph node is positive then an axillary dissection should be recommended. Second, over 95% of patients had either chemotherapy and/or endocrine therapy. It is important for patients to understand the best outcomes for treating breast cancer occur when a multidisciplinary approach is used. If patients are unwilling to receive whole breast radiation, or chemotherapy/endocrine therapy then those patients may still benefit from an axillary dissection. Third, the patients in this study had very early staged cancers, small tumors with no evidence of lymph node involvement by exam.

There have been recent reviews that have yielded similar results, supporting eliminating axillary dissection for early staged breast cancer.(18).

Table 1 shows the results of 3 studies that show similar axillary recurrence rates for observation vs. axillary dissection, observation vs. axillary radiation, and axillary dissection vs. axillary radiation. After a median of 5 year follow-up, recurrence rates are less than 3%.

Table 1	ALND vs obs	AxRT vs obs	ALND vs AxRT
Author	**Martelli 2005**	**Veronesi 2005**	**Louis 2004**
Study population	**T1, >70 y.o.**	**T1, >45 y.o.**	**T<3cm, <70 y.o.**
N	**219**	**435**	**658**
Median F/U	**5**	**5.3**	**15**
Axillary Recurrence	**0 vs 1.8%**	**0.5% vs 1.5%**	**1% vs 3%**

Bilomoria et al reviewed the NCDB database and retrospectively compared recurrence rates and survival for patients with positive SLN and no further axillary dissection vs. positive SLN followed by axillary dissection. Results are displayed in Table 2. There again was no difference between the two groups.

Table 2	Axillary LR	5yr survival
SLN Micrometastases		

SLN (N=802)	**0.6%**	**98%**
SLN&ALND (n=2,357)	**0.2%**	**98%**
SLN Macrometastases		
SLN (n=5,596)	**1.2%**	**91%**
SLN&ALND (n=22,591)	**1.1%**	**88%**

The recommendations of the Allina Health Breast Program Committee are based on these studies and the recommendations made by the authors of the "Z-11" study. Patients with <3 positive SLN's who are undergoing BCT followed by whole breast radiation therapy will not routinely require ALND. These recommendations do not currently apply to patients undergoing mastectomy.

The detection of ITC's in the SLN by IHC staining does not affect survival or locoregional recurrence. Therefore IHC will not be routinely used for the evaluation of the SLN. This applies to both patients undergoing BCT and mastectomy. Rare exceptions may occur, such as the evaluation of atypical cells within the sentinel node.

Since frozen section of the axillary SLN is used primarily for the detection of minimal disease in the SLN, and the Z-11 trial has shown that ALND for minimal disease in the axilla does not improve survival or recurrence in patients undergoing BCT followed by whole breast RT and adjuvant therapy, routine frozen section of the SLN is not recommended for patients undergoing BCT (exceptions listed above). However, frozen section evaluation of SLN will be used for patients having mastectomy.

These recommendations do not apply to patients who have had neoadjuvant therapy.

ADDENDUM:

Metric: % patients undergoing BCT for invasive breast cancer who have a frozen section of the SLN (with the understanding that frozen section is indicated for certain subgroups of patients, including those undergoing neoadjuvant therapy).

Who will be measured for guideline adherence?

- All sites performing breast surgeries

What will be measured?

- % patients who underwent BCT for invasive breast cancer at an Allina facility with the SLN(s) evaluated by frozen section at the time of surgery (patients who have had neoadjuvant chemotherapy prior to surgery will be excluded).

Where is the data located?

- EDW/ERS

How will adherence be monitored?

- Monitored by Breast Program Committee

When will adherence data be collected?

Minimally every year

REFERENCES:

1. Giuliano AE, McCall L, Beitsch P et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010;252:426-433.

2. Giuliano AE, Hunt KK, Ballman KV et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011, 305:569-575.

3. Weaver DL et al. Effect of occult metastases on survival in node-negative breast cancer. N Engl J Med 2011, 364;412-21.

4. Van der Ploeg, et al. Axillary recurrence after a tumour-negative sentinel node biopsy in breast cancer patients: A systematic review and meta-analysis of the literature. Eur J Surg Oncol 2008 Dec;34(12):1277-84. Epub 2008 Apr 10. Review

5. Park et al. A declining rate of completion axillary dissection in sentinel lymph node-positive breast cancer patients is associated with the use of a multivariate nomogram. Ann Surg 2007 Mar; 245(3):462-8.

6. Bilimoria KY, Bentrem DJ, Hansen NM, Bethke KP, Rademaker AW, Ko CY, Winchester DP, Winchester DJ. Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer.. J Clin Oncol 2009 Jun;27(18):2946-53. Epub 2009 Apr 13.

7. Cote R, Giuliano AE, Hawes D et al. ACOSOG Z0010: A multicenter prognostic study of sentinel node (SN) and bone marrow (BM) micrometastases in women with clinical T1/T2 N0 M0 breast cancer. J Clin Oncol (Meeting Abstracts) 2010;28:CRA504.

8. Weaver DL, Ashikaga T, Krag DN et al. Effect of Occult Metastases on Survival in Node-Negative Breast Cancer. N Engl J Med 2011, epub Jan 19, 2011.

9. Erb KM, Jullian TB. Completion axillary dissection for a positive sentinel node: necessary or not? Curr Oncol Rep 2009 Jan;11(1):15-20.

10. Fischer B et al. Twentyfive-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy and total mastectomy followed by irradiation. N Engl J Med 2002;347:567-75.

11. Pernas S et al. Avoiding axillary treatment in sentinel lymph node micrometastases in breast cancer: a prospective analysis of axillary or distant recurrence. Ann Surg Oncol 2010;17:772-777.

12. Hwang RF et al. Low locoregional failure rates in selected breast cancer patients with tumor-positive sentinel lymph nodes who do not undergo completion axillary dissection. Cancer 2007;110:723-30.

13. Fant JS et al. Preliminary outcome analysis in patients with breast cancer and a positive sentinel lymph node who declined axillary dissection. Ann Surg Oncol 2003;10(2):126-130.

14. Guenther JM et al. Axillary dissection is not required for all patients with breast cancer and positive sentinel nodes. Arch Surg 2003;1(38):52-56.

15. Marteli G et al. A randomized trial comparing axillary dissection to no axillary dissection in older patients with T1N0 breast cancer. Ann of Surg 2005;242:1-6.

16. Veronesi U et al. Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy. Ann of Oncology 2005;16:383-388.

17. Louis-Sylvestre C et al. Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. JCO 2004;22:97-101.

18. Rao R; Euhus D; Mayo H, Balch C: Axillary node interventions in breast cancer; a systematic review. JAMA. 2013;310(13):1385-1394. doi:10.1001/jama.2013.277804.

Alternate Search Terms:

Related Guidelines/Documents

Name	Content ID	Business Unit where Originated