Back to the Basics: Axillary Staging in Breast Cancer

8:30 – 9:15 Friday, November 24, 2006

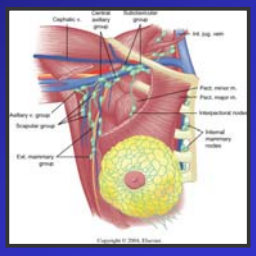
Dr. N. Davis
Surgical Oncology Network
BCCA Annual Conference

Objectives

- To review Axillary Staging in Breast Cancer
- To review issues related to axillary sentinel lymph node biopsy
- To review indications and outcomes related to standard Axillary Node Dissection for Breast Cancer
- To propose quality indicators for lymph node dissection

Background

- Axillary node receives 97% of the lymphatic drainage from the breast
- Axillary lymph node dissection (ALND)
  - Provides important prognostic information
  - Improves regional control
  - Improves survival
- Trend towards less axillary surgery

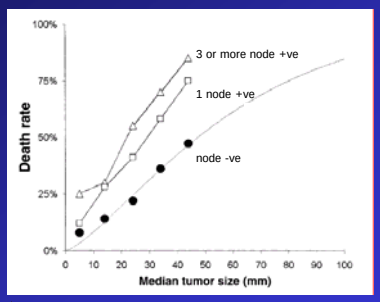


From Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice – 17th ed. Townsend CM, Beauchamp, RD, Evers MB, Mattox KL. 2004.

Why assess nodes?

- Prognosis
- Guide adjuvant therapy
- Regional control
- Survival

Prognosis



Fifteen-year Kaplan–Meier death rates by lymph node status for women.

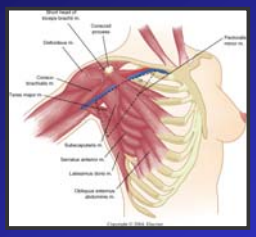
Michaelson et al, Cancer 2003;98:2133–43

Guide adjuvant therapy

- 50% of adjuvant systemic therapy decisions are based nodal status
- 30% of breast cancer patients[+] might be considered for adjuvant post-mastectomy radiotherapy.

* Olivotto, Cancer 1998;83:948–55.
+ Manitoba Breast Cancer Outcomes Initiative

Regional control



- Axillary lymph node recurrence
  - Relatively rare (1-3%)
  - 19 – 27 months after initial treatment
  - 5-year overall survival 27 – 49%

From Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice – 17th ed. Townsend CM, Beauchamp, RD, Evers MB, Mattox KL. 2004.

Risk of axillary recurrence

- NSABP trial B-04 - clinically negative
  - 0 nodes removed - 28 % recurrence
  - 6 nodes removed - 0
- 0.3% in node negative patients

  Int J Rad Oncol Biol Phys 1993;26:593-9
- 2.1% in node positive (< 4) patients

  J Clin Oncol 1991;9:988-96

Regional control

Study	N	Follow-up (Years)	Treatment	Axillary Recurrence	Uncontrolled Disease in Axilla
NSABP B-04 Fisher, NEJM 1985;312:674-81.	365	10	SM	17.8%	1.1%
CRC Houghton, WJ Surg 1994;18: 117-22.	1424	20	SM	19.5%	6.3%

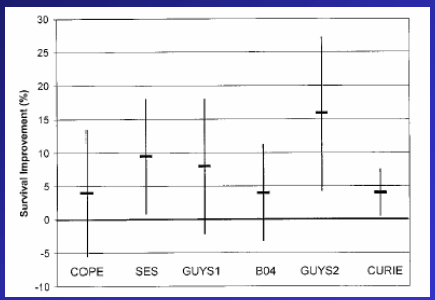
Rate of axillary failure with no surgery (median f/u = 62 months) n = 401

Table 2. AXILLARY NODAL RELAPSES AND DISTANT METASTASIS IN PATIENTS GROUPED ACCORDING TO TUMOR SIZE

Patient Subgroup	Events	No. of Events/Total Cases	%
T1a	Nodal relapses	2/102	2.0
	Distant metastases	6/102	5.9
T1b	Nodal relapses	2/114	1.7
	Distant metastases	3/111	2.7
T1c	Nodal relapses	15/143	10.5
	Distant metastases	22/143	15.4
T2	Nodal relapses	7/38	18.4
	Distant metastases	13/38	34.2

Greco et al:Ann Surg v.232(1): Jul 2000

Survival



Survival benefit from axillary dissection from six randomized trials.

Orr, Ann Surg Onc, 1999;6:109–16

Conclusion

Axillary sampling remains the standard of care for women with breast cancer

Question

- Should patients undergo formal Axillary Node Dissection or is Sentinel Node biopsy the standard of care for axillary sampling?

What is accepted

- SNB accurately stages the axilla
- It has less morbidity than axillary node dissection
- Modern techniques have made it technically easier

SLNBx

- High False negative rate (10%)
- Similar complications to ALNDx
- Impact on Survival and Local-Regional recurrence unknown
- Tends to detect micrometastatic disease for which the surgical management remains controversial

Contra-indications for SLNB

- ✓ Absence of experienced surgeon + team
- ✓ DCIS (BCS)
- ✓ Prophylactic mastectomy
- Multifocal tumours
- Locally advanced cancer
  - T3
  - Inflammatory
- Clinically palpable nodes
- Previous breast/axillary surgery/radiation
- Pre-op chemotherapy
- Pregnancy
- ✓ Breast feeding
- ✓ Allergies

✓ True contra-indications
▪ Relative contra-indications

What is debatable

- Is SLNBx accurate enough?
- Does it compromise regional control?
- Does it lower DFS and OS?

What is Confusing

- Using National Guidelines, ALNDx is still considered the “gold standard” of care in Canada
  - No evidence that SLNBx is equivalent with respect to survival and local recurrence
- Associated with lower quality of life scores than Sentinel Node Biopsy

Canadian Guidelines: AND

Removal and pathological examination of axillary lymph nodes should be standard procedure for patients with early, invasive breast cancer.

Omission of axillary dissection may be considered when the risk of axillary metastasis is very low or when knowledge of node status will have no influence on therapy.

The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. CMAJ. 1998 Feb 10;158 Suppl 3:S22-6.

Clinical practice guidelines for the care and treatment of breast cancer: 13. Sentinel lymph node biopsy

Jacques Cantin, Hugh Scarth, Mark Levine, Maria Hugi, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer

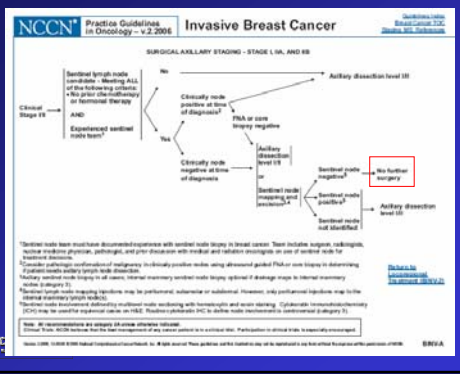
Canadian Guidelines: SLNB

Axillary dissection is the standard of care for the surgical staging of operable breast cancer.

If a patient requests or is offered SLN biopsy, the benefits and risks as well as what is and is not known about the procedure should be outlined.

The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. CMAJ 2001;165(2):166-73

NCCN Guidelines 2006



Cancer Care Ontario Guidelines

Removal and pathological examination of levels I and II axillary lymph nodes should be the standard practice in most cases of stages I and II breast carcinoma.

Can J Surg, Vol. 48, No. 3, June 2005 185

ASCO Guidelines

Conclusion

SNB is an appropriate initial alternative to routine staging ALND for patients with early-stage breast cancer with clinically negative axillary nodes. Completion ALND remains standard treatment for patients with axillary metastases identified on SNB. Appropriately identified patients with negative results of SNB, when done under the direction of an experienced surgeon, need not have completion ALND. Isolated cancer cells detected by pathologic examination of the SLN with use of specialized techniques are currently of unknown clinical significance. Although such specialized techniques are often used, they are not a required part of SLN evaluation for breast cancer at this time. Data suggest that SNB is associated with less morbidity than ALND, but the comparative effects of these two approaches on tumor recurrence or patient survival are unknown.

J Clin Oncol 23:7703-7720. © 2005 by American Society of Clinical Oncology

Question

- Should patients undergo formal Axillary Node Dissection or is Sentinel Node biopsy the standard of care for axillary sampling?

To Clarify:

- Do we be concerned about the False Negative rate?
- Does stand alone SLNBx compromise local recurrence rates?
- Does stand alone SLNBx compromise survival?
- Can we monitor quality of surgery?

FNR 0f SLNBx

Author	Year	Patients #	Agent	SLN Id %	FN Rate %	Accuracy %
Krag	1998	443	IPC	91	11	97
Tafra	2001	535	IPC, IPD	87	13	96
Shivers	2002	426	Varied	86	4	99
McMaster	2003	3975	Varied	94	8	96
Chua (BC)	2003	547	Varied	88	22	92
Krag	2004	2461	IPC, IPD	97	10	97
Goyal	2006	836	IPC, IPD	96	7	98

* modified from Kelley et al., Am J Surg 2004;188:49–61

Misunderstanding??

		AND +	AND -	Total	
SLNB	+	650	0	650	PPV=100%
	-	70	1741	1811	NPV=96%
	Total	720	1741	2461	

FNR=10.7%

Sensitivity=90% Specificity=100%

Krag et al, San Antonio, 2004.

Negative Predictive Value

- 96% NPV = 4/100 women incorrectly diagnosed or @1/25
- 10% FNR implies 1/10 women misdiagnosed which is not the case if the entire cohort is considered

FN rate of Axillary Node Dissection

Author	Year	N (node negative)	# with occult mets	%
Reed	2004	385	45	12% (@32% FN rate)
Ludwig group	1990	921	83	9%
Millis	2001	477	60	13 % FN rate 33%
Cote	1999	736	148	20%
Nasser	1993	159	50	11%

False negative rate of ALND is similar to the FNR of SLNBx.

Should ALND be considered the "Gold Standard" for axillary sampling?

Loco-regional recurrences following SLNBx

- N = 149
- f/u = 65 months (mean)
- 4 patients had an axillary recurrence at 10, 12, 14, and 56 months (2.7%)
- 3 patients free of disease
- One died from systemic disease but no regional recurrence

De Kanter et al: EJSO 32, 2006

Prospective Study SNB vs. Routine AND

- N = 516
- <= 2 cm tumors
- Patients randomized to SNB or routine AND
- Intra-operative frozen sections
- Median follow-up 46 mos

Veronesi et al NEJM – 349: 546, 2003

Outcome AND vs. SNB

	AND	SNB
Recurrence		
Axilla	0	0
Supraclavicular	2	0
Breast	1	1
Contralateral breast	2	3
Distant	10	6
Death		
Breast Cancer	2	1
Other	4	1

* Median follow-up = 46 months

Veronesi et al NEJM – 349: 546, 2003

AND compared to SNB: Side Effects (24 mos)

Mobility	AND (n=100)	SN (n=100)
80 – 100 %	79	100
Swelling (circumference)		
No difference	25	93
< 1 cm	38	6
1 – 2 cm	25	1
> 2 cm	12	0

Veronesi et al NEJM – 349: 546, 2003

OS of SNB patients compared to AND (n = 2458)

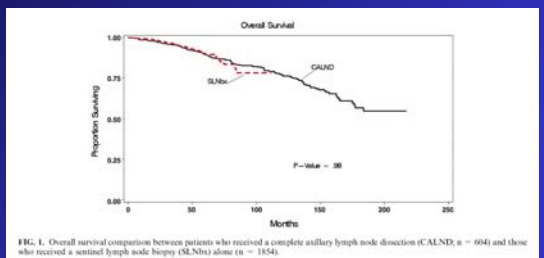


FIG. 1. Overall survival comparison between patients who received a complete axillary lymph node dissection (CALND; n = 604) and those who received a sentinel lymph node biopsy (SLNbx) alone (n = 1854).

Cox et al: Annals of Surgical Oncology 13(5) 2006

Complications of Axillary Surgery

Dr. Rona Cheifetz

CAGS/CSSO & BC SON
National Advisory Panel on Management of the Axilla
Kelowna September 29, 2006

ALMANAC Trial: SNB vs. AND

Mansell et al: JNCI, 2006

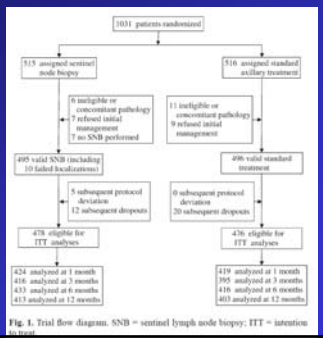


Fig. 1. Trial flow diagram. SNB = sentinel lymph node biopsy; ITT = intention to treat

Best Evidence

- ALMANAC Trial 2006 JNCI 98(9)
  - Randomized, intention to treat analysis
  - 495 SLNB vs 496 'standard' treatment
  - Terminated early after ethical review (initial was for 610 per group)
  - All validated SLNB with 40 cases first
  - + SLNB offered either XRT or CLND
  - 12 month follow-up data reported

Limitations in the Evidence

- Few prospective randomized trials
- Measurement tools differ btw studies
- Short follow-up
- Apples and Oranges
  - Axillary node sampling = ALND
  - Level I-III = ALND
  - SLNB + radiation = SLNB
  - SLNB + completion ALND = SLNB

ALMANAC Lymphedema at 12 months

	SLNB	ALND
Self none	95%	87%
Self mild	4%	11%
Self mod/severe	1%	2% p<.001
Change in arm volume (mean)	1.028	1.028 ns

ALMANAC Sensory Deficit at 12 months

	SLNB	ALND
Self reported	11%	31% p<.001
Median area of loss	59 cm^2	35 cm^2 ns
Clinical opinion none	91%	69% p<.001
mild	8%	30% p<.001
severe	1%	1% p<.001 for trend

ALMANAC Shoulder Function at 12 Months (Mean Change)

	SLNB	ALND
Flexion *	2.7 degrees	0.1 ns
Abduction *	2.5	1.9 ns
Ext Rotation	0.6	0.7 ns
Int Rotation	1.7	0.4 ns

ALMANAC QOL

- Significantly different favouring sentinel node biopsy at all time points (1, 3, 6 and 12 months)
- Gradually improved over time for both groups
- More 'clinically meaningful' declines in ALND group
- SLNB group did not have more anxiety

Conclusions:

- Loco-regional recurrence: SLND may have slightly higher recurrence rate 2- 3% vs 1 % for ALND
- Survival appears to be similar in prospective and meta analysis studies
- Complications are fewer but more significant than anticipated in patients undergoing SLNBs

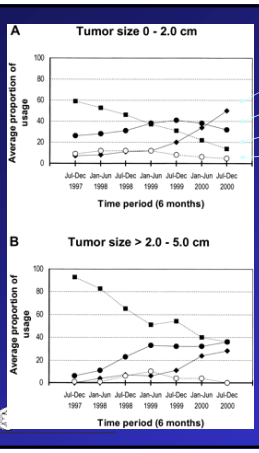
Surgeons "Vote With Their Feet" for Sentinel Node Biopsy for Breast Cancer Staging Tracy Hampton, PhD

JAMA. 2003;290:3053-3054.

SNBx in U.S.

- N = 410 surgeons
- 77% performed SNB for breast cancer
- 28% performed SNB for high grade DCIS

Lucci et al: J Am Coll Surg 2001 192:466



Trends in Axillary Surgery For Breast Cancer U.S.A

Edge et al:
J Natl Cancer Inst 2003; 95: 1514-1521

Conclusions thus far:

- SLNBx is associated with a similar false negative rate as ALND
- SLNBx is probably not associated with statistically increased regional recurrence
- SLNBx is not associated with decreased overall survival
- SLNBx is associate with reduced QOL scores but still has morbidity

Kelowna Breast Consensus Panel

- SLNB will be offered as an alternative to AND to all patients with clinically node negative T I or II breast cancer.
- Before the patient decides between AND and SLNB, the physician must make a full and balanced presentation to the patient concerning the pros and cons of the two procedures.

Canadian Issues:

- Large geographic area that is not fully resourced
- Volumes of breast cancer cases and equipment availability will limit access
- SLNBx will not be available in every community in the Province
- Not every patient will want to travel from their community

Axillary Dissection Revisited

- Indications
- What is a quality axillary dissection?

Indications

- Staging
- Clinical axillary disease
- Unable to do a sentinel node bx
- Unable to find the sentinel node
- ? Positive sentinel node bx

Axillary Lymph Node Dissection: Quality Indicators

An inadequate axillary node dissection may result from a technical failure or pathologic understaging.

A small number of patients may develop an axillary recurrence due to disease biology/ resistance to therapies.

Axillary Dissection: adequate surgical resection

- Adequate anatomic dissection of level 1 & 2 lymph nodes
- Axillary lymph nodes: 3 levels defined by the pectoralis minor muscle
- Level 1 : lateral or below the muscle
- Level 2 : deep to the muscle
- Level 3 : medial to the muscle in the infraclavicular fossa

Axillary Dissection

- Level 1& 2 dissection – 10 or more lymph nodes:
  - sufficient for staging in 97% of patients
  - Dissection is defined by specific anatomic planes

Danworth et al J Clin Oncol 1986;4:655-2

Axillary Lymph Node Dissection: Level III?

- Tominaga et al Br J Surg 2004
  - 1209 pts with Stage II breast cancer randomized to Level I/II vs Level I/II/III axillary dissection
  - 10 year OA survival 86.6% vs 85.7% (HR= 1.02, p=0.931)
  - 10 year DFS 73.3% vs 77.8% (HR=0.94, p=0.666)

Axillary Lymph Node Dissection: Quality Indicators

Axellsson, CK, et al. 1992

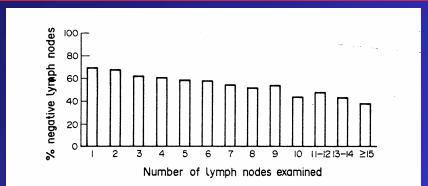


Fig. 1. The frequency of negative lymph nodes (%) in each group of patients classified according to the number of lymph nodes examined in the resected specimens (n = 13851)

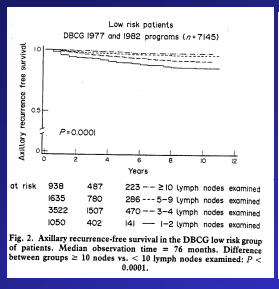


Fig. 2. Axillary recurrence-free survival in the DBCG low risk group of patients. Median observation time = 76 months. Difference between groups ≥ 10 nodes vs. < 10 lymph nodes examined: $P < 0.0001$.

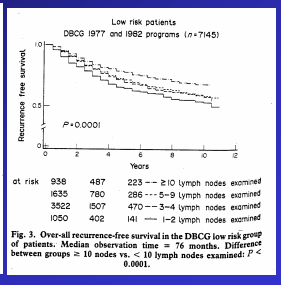
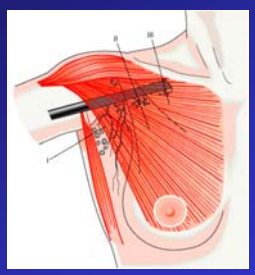


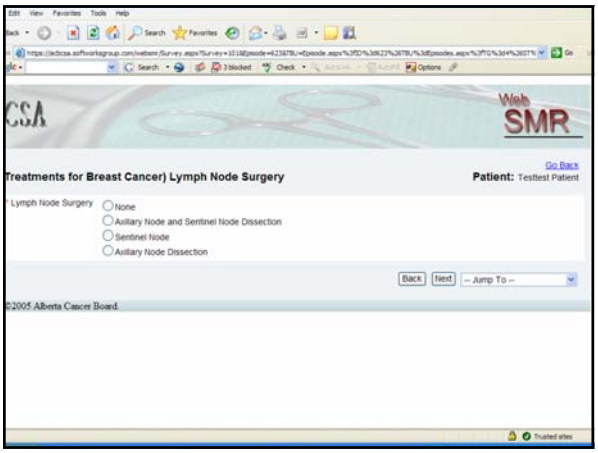
Fig. 3. Over-all recurrence-free survival in the DBCG low risk group of patients. Median observation time = 76 months. Difference between groups ≥ 10 nodes vs. < 10 lymph nodes examined: $P < 0.0001$.

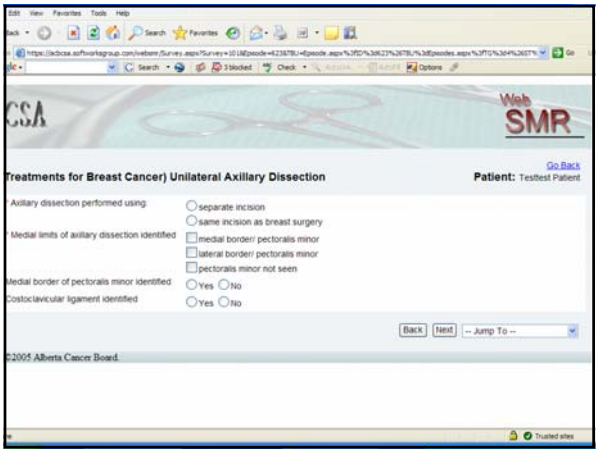


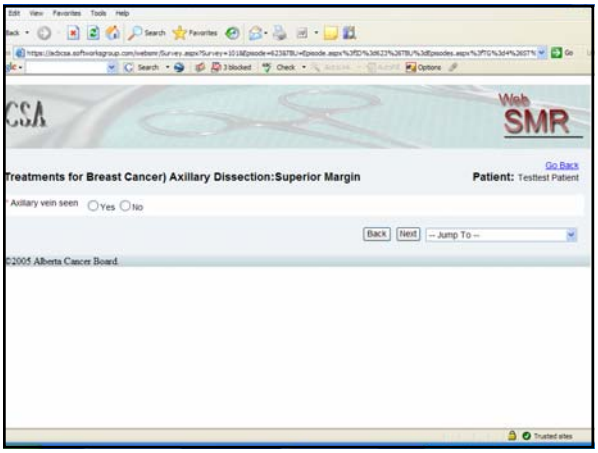
Avoiding complications:

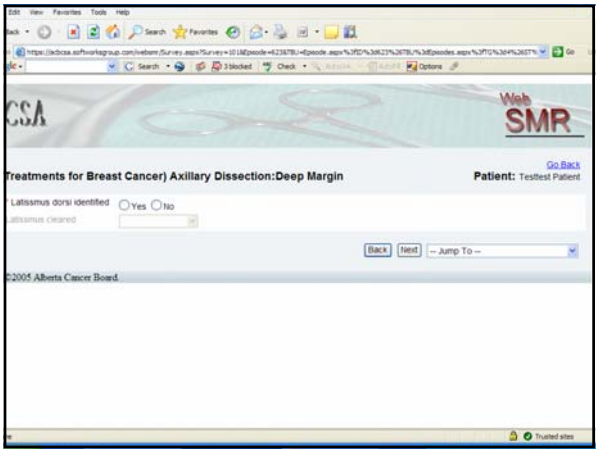
- Lymphedema: Do not raise thin flaps
  Do not strip the axillary vein
- Neuralgia: Sparing or dividing Intercoastal-brachial nerves does not seem to be associated with reduced neuralgia
- Infection: Use iv antibiotics preoperatively
- Hemorrhage: Titanium clips
- Use Synoptic Reports

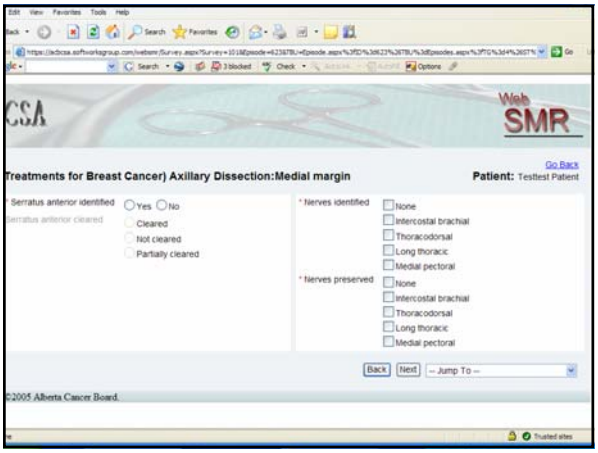
BC Cancer Agency

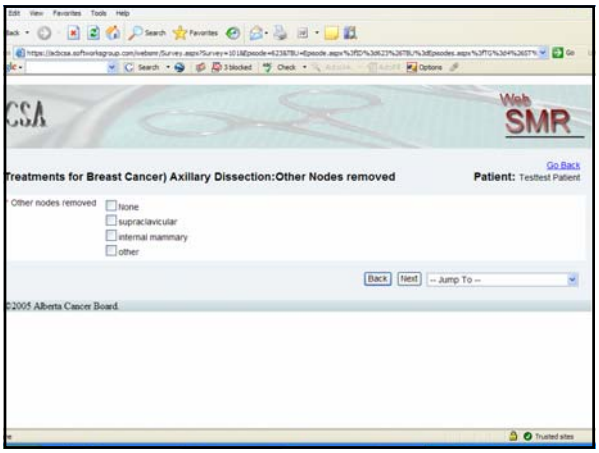








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Treatments for Breast Cancer) Axillary Dissection:Other Nodes removed
Patient: Testtest Patient
Other nodes removed
None
supraclavicular
internal mammary
other
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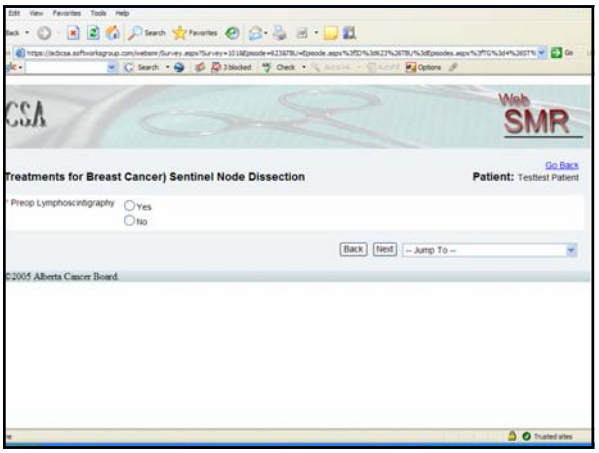
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Treatments for Breast Cancer) Sentinel Node Dissection
Patient: Testtest Patient
Preop Lymphoscintigraphy
Yes
No
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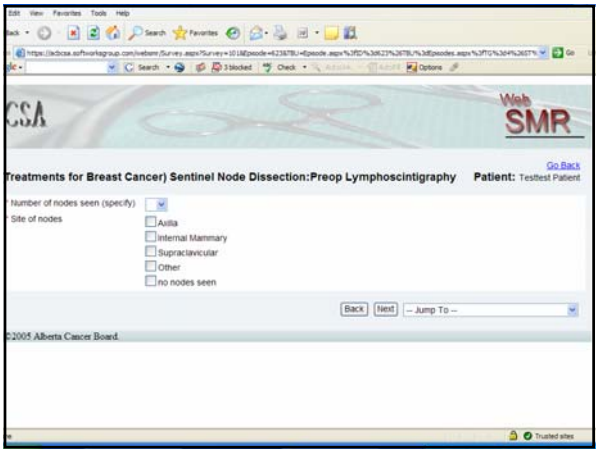
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Treatments for Breast Cancer) Sentinel Node Dissection:Preop Lymphoscintigraphy
Patient: Testtest Patient
Number of nodes seen (specify)
Site of nodes
Axilla
Internal Mammary
Supraclavicular
Other
no nodes seen
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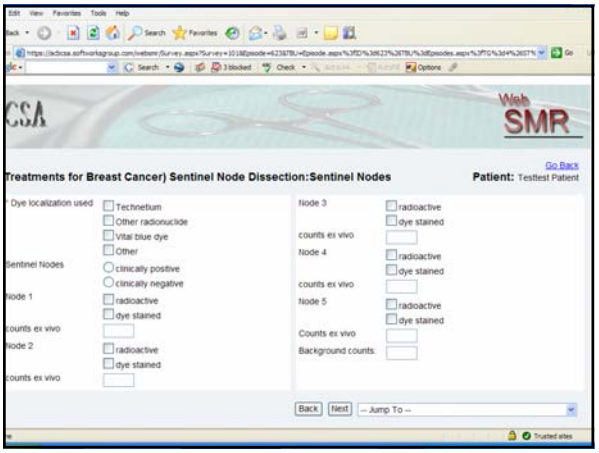
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Treatments for Breast Cancer) Sentinel Node Dissection:Sentinel Nodes
Patient: Testtest Patient
Dye localization used
Technetium
Other radionuclide
Vital blue dye
Other
Sentinel Nodes
clinically positive
clinically negative
Node 1
radioactive
dye stained
counts ex vivo
Node 2
radioactive
dye stained
counts ex vivo
Node 3
radioactive
dye stained
counts ex vivo
Node 4
radioactive
dye stained
counts ex vivo
Node 5
radioactive
dye stained
Counts ex vivo
Background counts.
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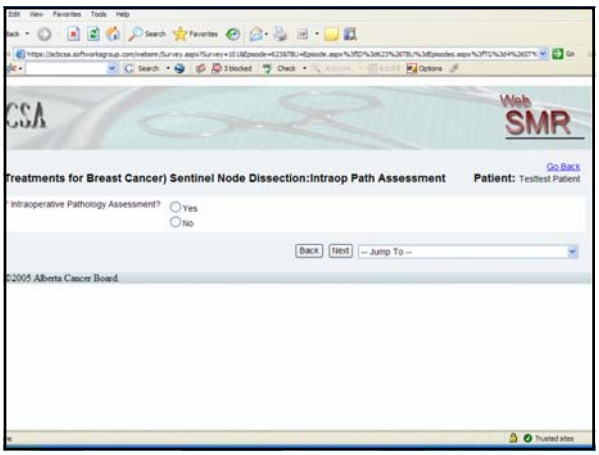
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Treatments for Breast Cancer) Sentinel Node Dissection:Intraop Path Assessment
Patient: Testtest Patient
Intraoperative Pathology Assessment?
Yes
No
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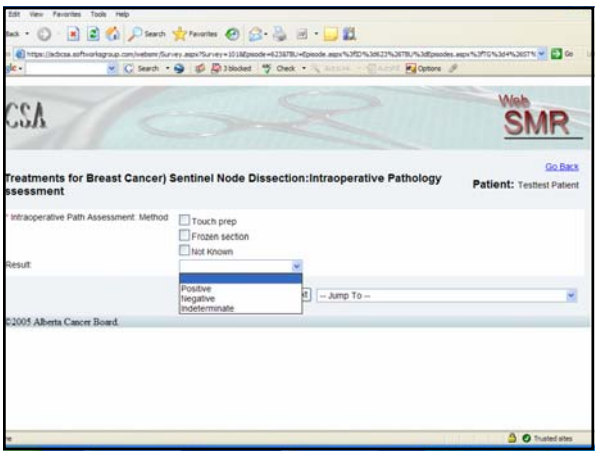
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Treatments for Breast Cancer) Sentinel Node Dissection:Intraoperative Pathology ssessment
Patient: Testtest Patient
Intraoperative Path Assessment: Method
Touch prep
Frozen section
Not Known
Result
Positive
Negative
Indeterminate
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Consensus Statement

Nodal staging is indicated in invasive breast cancer to determine prognosis, need for adjuvant therapy and to reduce risk of local/regional recurrence.

Consensus Statement

Sentinel lymph node biopsy causes less morbidity than a Level I and II axillary lymph node dissection.

Consensus Statement

Sentinel lymph node biopsy is an accurate staging alternative to axillary lymph node dissection for breast cancer.

Consensus Statement

Routine Level I and II axillary lymph node dissection can be eliminated for patients with histologic negative sentinel lymph nodes.

Conclusions

- ALND is indicated as a staging procedure when SLNBx is not available
- Surgeons managing breast cancer patients should use synoptic operative reports where available and should enrol their patients in quality outcome monitoring programs using national standards for reporting.

Conclusions

- SLNB should be offered as an alternative to AND to all patients with clinically node negative stage I or II breast cancer.
- Before the patient decides between AND and SLNB, the physician must make a full and balanced presentation to the patient concerning the pros and cons of the two procedures.