A MATHEMATICAL MODEL FOR THE EFFECT OF A FALSE-NEGATIVE SENTINEL NODE BIOPSY ON BREAST CANCER MORTALITY: A TOOL FOR EVERYDAY USE

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Abstract

A falsely negative sentinel node biopsy for breast cancer may be harmful in two ways:
a) axillary relapse
b) a missed opportunity of appropriate systemic adjuvant therapy.

We created a mathematical model that estimates the risks of false negative sentinel node biopsy (SNB) based on published data and Adjuvant! software (adjuvantonline.com).

For example, if a 0.8cm ER negative grade 2 tumour in a 40 year old is not offered chemotherapy because her SNB is negative then she will risk an increased mortality of 0.24% (1 in 400) if the FNR was 9.7%. The model could facilitate an informed consent.

We suggest that since the effect of FNR on mortality and of training on FNR are both small, only the 'detection rate' (and not FNR) could judge competence in SNB technique thus avoiding the "validation" phase with concurrent axillary dissection.

Background

Sentinel node biopsy (SNB) is being adopted as a standard of care for breast cancer amidst concerns about the effect of a false negative result.

A high false negative rate (FNR) could be harmful in two ways:
a) axillary relapse and b) missed opportunity of appropriate systemic adjuvant therapy.

There appears to be a general consensus that it is extremely important to achieve a low FNR rate with adequate training.

We modelled the local and systemic effect of not treating a falsely negative axilla (see table).

The Mathematical Model

The known facts

(NSABP B-32) trial[1]	False Negative Rate (FNR)
SEER dataset[2]	Estimated node positivity (ENP
www.adjuvantonline.com	Benefit from chemotherapy in ER negative women. This would be similar to additional benefit of chemotherapy in ER positive women on top of hormone therapy
NSABP B-04[3] (Fisher, 2002)	50% of untreated involved nodes cause local recurrence
Overview[4] (Peto R, 2004)	20% of local recurrence translates into mortality (for example, if LR increases by 10% the mortality increases by 2%)

Thus, if 10% of patients have untreated axillary disease then:

5% will have local recurrence
1% more will die as a consequence

The Mathematical Model

Estimates of increase in 10-year mortality for different prognostic groups and for false-negative rates of 9.7%, 20% and 100% (all values are in percentages)

				ER-negative patients[a]											
				Age 40 years						Age 60 years					
				Grade 3		Grade 2		Grade 1		Grade 3		Grade 2		Grade 1	
Row	Risk/risk reduction	FNR	Explanation of calculations	ENP[b] → <1 cm (15%)	1–2 cm (35%)	<1 cm (12%)	1–2 cm (30%)	<1 cm (10%)	1–2 cm (25%)	<1 cm (15%)	1–2 cm (35%)	<1 cm (12%)	1–2 cm (30%)	<1 cm (10%)	1–2 cm (25%)
1	10-year mortality risk in NN women			8	17	5	14	3	6	3	6	5	14	3	6
2	10-year mortality real risk in those with 1–3 positive nodes			33	33	30	30	13	13	33	33	30	30	13	13
3	Reduction in 10-year mortality with adjuvant therapy in NN women			3.8	7.6	2.4	6.3	1.3	2.8	0.8	1.6	1.4	3.8	0.8	1.6
4	Reduction in 10-year mortality with adjuvant therapy in NP women (as would apply to the false-negative patients)			14.2	14.2	13	13	6.1	6.1	8.1	8.1	7.5	7.5	3.4	3.4
5	Difference in absolute benefit between NN and NP women from chemotherapy (NP – NN)			10.4	6.6	10.6	6.7	4.8	3.3	7.3	6.5	6.1	3.7	2.6	1.8
6															
7	Unsuspected harm in a SNB-negative woman = (overall risk for missing positive axilla [AFN = FNR × ENP] × difference between benefit for NP and NN women [NP – NN]) + (harm from axillary relapse [AFN × 0.1])	9.7%	Actual % of patients with missed positive axilla (AFN = ENP × FNR)	1.5	3.4	1.2	2.9	1.0	2.4	1.5	3.4	1.2	2.9	1.0	2.4
8			Mortality due to axillary recurrence (AFN × 0.1)	0.15	0.34	0.12	0.29	0.10	0.24	0.15	0.34	0.12	0.29	0.10	0.24
9			Mortality due to no chemotherapy (AFN × [NP – NN])	0.15	0.22	0.12	0.19	0.05	0.08	0.11	0.22	0.07	0.11	0.03	0.04
10			**Total**	**0.30**	**0.56**	**0.24**	**0.49**	**0.14**	**0.32**	**0.25**	**0.56**	**0.19**	**0.40**	**0.12**	**0.29**
11	Unsuspected harm in a SNB-negative woman = (overall risk for missing positive axilla [AFN = FNR × ENP] × difference between benefit for NP and NN women [NP – NN]) + (harm from axillary relapse [AFN × 0.1])	20.0%	Actual % of patients with missed positive axilla (AFN = ENP × FNR)	3.0	7.0	2.4	6.0	2.0	5.0	3.0	7.0	2.4	6.0	2.0	5.0
12			Mortality due to axillary recurrence (AFN × 0.1)	0.30	0.70	0.24	0.60	0.20	0.50	0.30	0.70	0.24	0.60	0.20	0.50
13			Mortality due to no chemotherapy (AFN × [NP – NN])	0.31	0.46	0.25	0.40	0.10	0.17	0.22	0.46	0.15	0.22	0.05	0.09
15	Unsuspected harm in a SNB-negative woman = (overall risk for missing positive axilla [AFN = FNR × ENP] × difference between benefit for NP and NN women [NP – NN]) + (harm from axillary relapse [AFN × 0.1])	100.0%	Actual % of patients with missed positive axilla (AFN = ENP × FNR)	15	35	12	30	10	25	15	35	12	30	10	25
16			Mortality due to axillary recurrence (AFN × 0.1)	1.50	3.50	1.20	3.00	1.00	2.50	1.50	3.50	1.20	3.00	1.00	2.50
17			Mortality due to no chemotherapy (AFN × [NP – NN])	1.56	2.31	1.27	2.01	0.48	0.83	1.10	2.28	0.73	1.11	0.26	0.45
18			**Total**	**3.06**	**5.81**	**2.47**	**5.01**	**1.48**	**3.33**	**2.60**	**5.78**	**1.93**	**4.11**	**1.26**	**2.95**

The values for patients aged 40 years with a grade 2 or 3 tumour between 1 and 2 cm may be ignored because the benefit from chemotherapy is high (>5%) even if they are node negative. A 100% false-negative rate would be achieved if no axillary surgery was performed. [a]The values given are for oestrogen receptor (ER)-negative patients and approximate those for additional benefit from chemotherapy in ER-positive patients on top of hormone therapy. [b]Estimated node positivity (ENP) is given in parentheses. AFN, estimated number of patients with a falsely negative axilla; FNR, false-negative rate; NN, node negative; NP, node positive.

Example 1

Age 60 years, Grade 1, Size 0.5cm, ER negative

Estimated Node Positivity (ENP) = 10%

The 10-Year mortality risk
Node negative women = 3%
1 to 3 - Node positive women= 13%

The Benefit from adjuvant chemotherapy (reduction in 10 year mortality)
If Node negative = 0.8%
If (1 to 3) Node positive = 3.4%

Difference in benefit "if NN" vs. "if NP" is 3.4% minus 0.8% = 2.6%

Actual (chance of)False Negative (AFN) axilla in this patient undergoing SNB is = FNR x ENP

thus if FNR =9.7% and ENP is 10%

AFN= 10% of 9.7% = 1%

thus, Increased mortality due to axillary recurrence 1/10th of 1% = 0.1%

and, Increased mortality due to "no chemotherapy" = 2.4% times D (diff. in benefit in NN and NP)
= 1% x 2.6%= 0.02%

Unsuspected harm from omitting chemotherapy on assumption that she is node negative is

Increased Mortality due to axillary recurrence + "no chemotherapy"
0.1% + 0.02% = 0.12%

Example 2

Same scenario as example 1 but False Negative Rate is 20%

***Unsuspected harm* = 0.2% + 0.05% = 0.25%**

Example 3

Same scenario as example 1 but False Negative Rate is 100% (no axillary staging)

***Unsuspected harm* = 1% + 0.26% = 1.26%**

Example 4

Age 60 years, Grade 2, Size 2cm, ER negative
FNR=9.7%
Unsuspected harm from omitting chemotherapy on assumption that she is node negative is

Increased Mortality due to axillary recurrence + "no chemotherapy"
0.29% + 0.11% = 0.40%

Example 5

Age 60 years, Grade 2, Size 2cm, ER negative
FNR = 20%
Unsuspected harm from omitting chemotherapy on assumption that she is node negative is

Increased Mortality due to axillary recurrence + "no chemotherapy"
0.6 + 0.22% = 0.82%

Example 6

Age 40 years, Grade 3, Size 2cm, ER negative
FNR=9.7%
Unsuspected harm from omitting chemotherapy on assumption that she is node negative is

Increased Mortality due to axillary recurrence + "no chemotherapy"
0.34% + 0.22% = 0.56%
(only 0.34% is of concern because these patient will get chemotherapy anyway)

Example 7

Age 40 years, Grade 3, Size 2cm, ER negative
FNR=20%
Unsuspected harm from omitting chemotherapy on assumption that she is node negative is

Increased Mortality due to axillary recurrence + "no chemotherapy"
0.7 + 0.46% = 1.16%
(only 0.70% is of concern because these patient will get chemotherapy anyway)

False negative rate calculations are unreliable
Consider 30 cases of which 10 are node positive
and 1 positive case is missed by SNB
the FNR is 10%
but this could be just chance
because the probability that
this is equal to 0% or 20% is 78% (that is p=0.78)

FALSE NEGATIVE RATE is
- **Not measurable reliably**
- **Does not improve with experience[1,6]**
- **Has minimal impact on mortality**
- **FNR of 10% -15% is perhaps not a correctable technical error–**
- **It is probably an indicator of the biology of breast cancer that does not always obey the "sentinel" rule!**

CONCLUSION

We need to inform our patients of these small risks of relying on a Sentinel node biopsy.

This mathematical model could be used in day-to-day decision making in joint consultation with the patient.

Sampling up to 4 lymph nodes could significantly reduce this false negative rate.[6,7]

We need to give patients a choice of axillary sampling techniques and make a shared decision.

Finally,
since FNR is an unsuitable measurement, only the 'detection rate' should be used in judging competence in sentinel node biopsy, avoiding the validation phase with concurrent axillary dissection.

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THIS STUDY HAS BEEN PUBLISHED in Breast Cancer Research 2005, 7:225-227 (DOI 10.1186/bcr1311) and is available online at http://breast-cancer-research.com/contents/7/5/225