Commentary

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

One of the concerns of using sentinel node biopsy (SNB) is the risks of a false-negative result (FNR). We have created a mathematical model to estimate the effects of FNR on mortality because of excess local recurrence and adjuvant therapy inappropriately withheld. With a FNR of 9.7%, the absolute effect on 10-year mortality is estimated to be less than 0.6% for all patients with tumours < 2 cm in size. Since the impact of FNR on mortality is small and FNR rates do not improve with training, we suggest that detection rate alone is an adequate criterion for judging competence in SNB.

Introduction

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 because of axillary relapse or a missed opportunity to institute systemic adjuvant therapy. There appears to be a general consensus that it is extremely important to achieve a low FNR by adequate training. We modelled the local and systemic effect of not treating a falsely negative axilla (Table 1).

Method

We used the false negative rate (FNR; specifically the proportion of true positives missed by SNB) of 9.7% obtained in the NSABP B-32 trial [1] and estimated the node positivity from Surveillance, Epidemiology, and End Results (SEER) data [2]. We used Adjuvant! software [3] to estimate the benefit of adjuvant systemic chemotherapy for oestrogen receptor (ER)-negative patients. This would be similar to the additional benefit of chemotherapy for ER-positive patients on top of hormone therapy. The absolute number of patients with a falsely negative axilla is the product of the estimated node positivity and the FNR (AFN = estimate node positivity × FNR). To calculate the effect of the lost opportunity to institute adjuvant systemic therapy, we multiplied the estimated number of patients with a falsely negative axilla (AFN) by the difference between the benefit from treating node-positive and node-negative patients (AFN × [NP – NN]). To calculate the effect of leaving axillary disease untreated, we estimated (NSABP B-04 [4]) that 50% of involved nodes cause local recurrence at 10 years and that about a fifth of this translates into mortality [5]. This would be equal to AFN × 0.1. Unsuspected harm from a falsely negative axilla is calculated by adding the increased mortality from axillary recurrence to the effect of a lost opportunity to institute adjuvant systemic chemotherapy for those women with false-negative axilla, and the resulting values are shown in Table 1.

In this model, it is assumed that patients with tumours larger than 2 cm will receive adjuvant systemic therapy anyway and hence are not shown. The bottom rows of Table 1 show the effect of a 100% FNR, which simulates the effect of not doing any axillary staging. These values could be used during discussions with patients to illustrate the benefit, or lack thereof, of treating the axilla in these patients with good prognosis.

Results

Let us assume that SNB is negative. To use the model, first look up the figures in row 3 and decide whether the benefit in node-negative women is sufficient to recommend chemotherapy. If the patient will be receiving chemotherapy anyway, then look at row 8, 12, or 16 to see the estimated harm from a false-positive SNB for FNRs of 9.7%, 20% and 100%, respectively. If your decision is not to recommend chemotherapy because the potential benefit from chemotherapy in node-negative women (in row 3) is too small, then look at rows 10, 14 and 18 to see the unsuspected harm that would come to the patient because of a falsely negative SNB. Now add the values in row 3 to those in row 10, 14, or 18 to estimate the total harm that may come to a patient who is SNB negative and is not given chemotherapy, and see whether this is enough to tip the balance in favour of recommending chemotherapy.

AFN = estimated number of patients with a falsely negative axilla; ER = oestrogen receptor; FNR = false-negative rate; SNB = sentinel node biopsy.

Table 1

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
14			**Total**		**0.61**	**1.16**	**0.49**	**1.00**	**0.30**	**0.67**	**0.52**	**1.16**	**0.39**	**0.82**	**0.25**	**0.59**

Continued opposite

Table 1

Continued

				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%)
15	Unsuspected harm in a SNB-negative woman = (overall risk for missing	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	positive axilla [AFN = FNR × ENP] × difference between benefit for NP and NN women		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	[NP – NN]) + (harm from axillary relapse [AFN × 0.1])		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.

In each of these examples, these decisions could even be made before surgery. If the harm from a 100% FNR (row 18) is acceptable, then the axilla need not even be touched.

Conclusion

This mathematical model could be used in day-to-day decision making in joint consultation with the patient. The values generated are absolute values and relate to the very patients who would be considered the best candidates for SNB, and therefore are easier to discuss with patients than hazard ratios or relative risks. Table 1 can be used to vary the FNRs and even the benefit from chemotherapy when results of newer drug trials become available. The expanded Excel version is available from the authors.

The fact that the FNR does not reduce with increasing experience raises a fundamental biological doubt over the mechanistic model of lymphatic spread on which SNB is based. It is likely that in 10% of patients tumour cells truly skip the sentinel node, just as blood-borne metastases that travel via the veins frequently skip the lungs. If we wish to identify accurately and treat axillary spread, then we must find methods based on newer biological markers, perhaps in combination with functional imaging, to identify these patients better. Until then, each patient must participate in informed decision making about whether and when SNB is to be used as a definitive treatment, with discussion about its absolute risks.

On an allied issue, nationwide studies [1,6] have found that training improves the detection rate but does not reduce the FNR. This model suggests that in absolute terms a FNR has a small impact on mortality. Thus, it seems prudent to use only the 'detection rate' in judging competence in SNB, avoiding the validation phase with concurrent axillary dissection.

Competing interests

The author(s) declare that they have no competing interests.

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