

Functional form of the effect of the numbers of axillary nodes on survival in early breast cancer

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Abstract. The change in survival in function of the numbers of involved and uninvolved axillary nodes in early breast cancer - i.e. the functional form - was investigated to search for prognostic cutoffs and to assess if ratio-based characterization of node involvement is a significant prognostic factor or not. Women aged 40-69, diagnosed in 1988-1997 with T1-T2 invasive breast carcinoma, who underwent axillary dissection, are selected from the SEER public database. The method determines the functional form by applying smoothed plots to the martingale residuals obtained from a proportional hazards model. The results on 55,267 selected patients find that the ratio of involved nodes on examined nodes, in a multivariate model that takes into account known prognostic factors (age, race, tumor size, topography, histology, grade, hormone receptors), is associated with a relative mortality hazard of 1.012 (95% confidence interval 1.010-1.014; relative increase of mortality of 1.2% for each 1% increase in the percentage of involved nodes). The functional form for the number of uninvolved nodes shows that the relative mortality hazard initially steeply decreases and then tends to level off beyond 5-10 uninvolved nodes. For the number of involved nodes, the relative mortality hazard continues to

increase with each involved node without any obvious cutpoint. Even when the number of involved nodes is already large, each additional involved node increases the relative mortality hazard by at least 1.3%.

Introduction

What is the clinical utility of counting nodes? In operable primary breast cancer, lymph node status as assessed by axillary lymph node dissection (ALND) is regarded as one of the most important prognostic factors (1-4). But complications of ALND such as pain, numbness, shoulder mobility impairment or arm edema might severely burden patients' quality of life. The risk and the degree of these complications may increase with the extent of ALND and with the number of nodes removed (5-8). Limited ALND aims at reducing the risk of complication. More extensive ALND aims at improving the pathological assessment, and aims at improving tumor control by removing possibly involved nodes. The extent of ALND is measured by the anatomical definition of the type of dissection (level I, II or III) or by the amount of tissue removed, or by the number of nodes examined. The number of nodes examined is dependent on the amount of tissue removed by surgery, on the patient anatomical variability, on the pathology examination (9). The extent and the minimum number of nodes required for an adequate assessment of the axilla has been debated, ranging from a limited sampling with a cutpoint of 4 nodes (10), through 6 nodes (11), 10 nodes (12), 15 nodes (in T1N0 breast cancer) (13), level I-II dissection with median 16 nodes (14), to full clearance yielding a variable number of nodes (15-17).

Meanwhile, during the last few years the technique of sentinel node biopsy has gained wide acceptance and might be expected to replace ALND, thus the debate on the number of axillary nodes might seem obsolete (9). However, there are situations that require ALND, i.e. the validation by backup ALND during the sentinel node biopsy learning curve and the management of the axilla if the sentinel node is involved or if there are clinically suspicious non-sentinel nodes at the time of surgery (18). Therefore, what constitutes a quantitatively adequate ALND - whether or not there is a prognostic cutpoint - remains a critical question (and

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Abbreviations: ALND, axillary lymph node dissection; N0, node-negative, negative nodal status; N⁺, node-positive, positive nodal status; nneg, number of uninvolved (negative) nodes; npos, number of involved (positive) nodes; nex, number of examined nodes; npnex, ratio npos/nex; invnneg0, ratio 1/nneg for N0 patients; SEER, Surveillance, Epidemiology, and End Results

Key words: breast neoplasms, axilla, lymph nodes, dissection, SEER program, survival analysis, diagnostic techniques, surgical, prognosis, neoplasm staging, models, biological, ratio-based staging

perhaps the question is even more important if ALND is not performed).

What are the conditions for a quantitatively adequate axillary node dissection? In an independent study (19), we investigated the impact of numbers of nodes on survival in T1-T2 breast cancer by a descriptive analysis of the SEER data.

The descriptive analysis suggested that: i) A high number of negative nodes (n_{neg}) was not a sign of poor prognosis. ii) Survival was not markedly influenced by n_{neg} in node-negative patients. iii) Survival in function of n_{neg} improved towards a plateau in node-positive patients. iv) Survival deteriorated gradually when the number of involved nodes (n_{pos}) increased. v) Irrespectively of the absolute numbers of nodes, similar ratios of n_{pos}/n_{neg} were associated with similar survivals.

Altogether, these findings implied that the problem of what is a quantitatively adequate ALND cannot be stated solely in terms of number of nodes examined (n_{ex}). Since n_{ex} is the sum of n_{neg} and n_{pos}, results of investigations that are based on n_{ex} will fluctuate in function of the relative distributions of n_{neg} and n_{pos}. That is, if a group of patients was at higher risk of node involvement, inferences based on n_{ex} from that group of patients (more nodes involved) cannot apply to another group of patients who are at lower risk (less nodes involved), and vice versa. In light of the previous results, what is a quantitatively adequate ALND would necessarily require specifying two of the three n_{neg}, n_{pos}, and n_{ex} numbers.

Objectives. The method used in our previous investigation (19) was descriptive. There was no formal test of significance for the observed patterns. Major known prognostic factors such as tumor size or histological grade were not taken into account. Consequently, the findings might potentially have been confounded by selection bias or by an imbalance in the distribution of prognostic factors. To investigate this issue, in the present study, the respective roles of the numbers of negative nodes and of the numbers of involved nodes were examined to verify: i) whether a high number of negative nodes is a sign of good prognosis; ii) whether there is a survival cutpoint in function of n_{neg}; iii) whether there is a survival cutpoint in function of n_{pos}; iv) what is the impact of n_{pos}/n_{neg} or n_{pos}/n_{ex} (n_{pnex}) ratio on survival; when other known prognostic factors are taken into account.

In essence, all these questions amounted to addressing the issue of what is the functional form of the node numbers as covariates - i.e. how does survival or mortality change when the number of nodes changes. To investigate the functional form while adjusting for other prognostic factors required an analysis that used extended survival modeling tools (20). Results of that analysis are presented here.

Patients and methods

Patient records were selected from the SEER database April 2001 release (21): women aged 40-69 with non-inflammatory invasive carcinoma, year of diagnosis 1988-1997, primary tumors with maximal diameter ≤ 50 mm and confined to

breast, no previous diagnosis of cancer, no known internal mammary node involvement, no distant metastases, treated by partial or by total mastectomy, with or without post-surgery radiation, and in whom axillary dissection was performed with at least one node examined. Follow-up cutoff date was December 31, 1998. The selection criteria are the same as in the descriptive study (19), except the range of nodes examined is larger (n_{ex} > 0, no upper bound), and follow-up is one year longer.

An event was defined as death from any cause. Survival time was defined as length of time from date of diagnosis to date of death, to date last known to be alive, or to follow-up cutoff date. The multivariate survival analysis used the Cox proportional hazards model (22) and was performed in three stages.

At the first stage a core model was selected. The covariates to be included had been examined during previous work done with the SEER data (23). Examination of Schoenfeld residuals in function of time (20) showed substantial departure from the assumption of constant hazard for the variable 'multiple primaries'. Based on these results and the previous examinations (23), the core model selected for the present study was stratified on the 'multiple primaries' variable and included an interaction term between type of surgery and radiotherapy.

At the second stage the functional form of the dependence of the risk of death on the numbers of nodes was investigated using the method of martingale residuals (20). We briefly describe that method here. The martingale residual for an individual is the difference between the observed event status and the expected value calculated from a Cox model. Under certain assumptions the smoothed plot of the martingale residuals resulting from a Cox model can display the functional form of that covariate (24). The plot can be used to verify whether there exists, e.g., a cutpoint (threshold) in the effect of the covariate. If there is a cutpoint, the smoothed martingale residual plot should display an S-shape curve.

The method of martingale residuals was applied here to the variables: n_{neg} (number of uninvolved nodes), n_{pos} (number of involved nodes), n_{ex} (number of nodes examined) and the ratio n_{pos}/n_{ex} (n_{pnex}) in node-positive patients or the ratio 1/n_{ex} in node-negative patients. Smoothing of the residuals plots was performed by Poisson regression on cubic spline of the covariate of interest, the procedure providing also a formal test for non-linearity (20). Approximate pointwise 95% confidence intervals were computed by multiplying by 2 the standard errors of the smoothed residuals. The procedure was performed separately for node-negative (N₀) and on node-positive (N⁺) patients datasets.

At the third stage the core proportional hazards model was updated by including the transformed variables, based on the results obtained from the martingale residual plots. The predicted form of the dependence of the logarithm of the hazard ratio on the number of negative nodes, on the number of positive nodes and on the ratio of positive nodes to all nodes examined was computed from the updated model and plotted to facilitate the interpretation.

Data management and computation of proportional hazard models were performed with SAS v.8 (SAS Institute Inc., Cary, NC, USA) and with Stata (Stata Corporation,

Table I. Summary of patient characteristics.

SEER release 2001 Characteristic	N0			N ⁺		
	Total (n)	nex ≥20 (n)	nex <20 (n)	Total (n)	nex ≥20 (n)	nex <20 (n)
	37965	8853	29112	17302	4836	12466
Age ≥50 years	27662	6266	21396	11331	3079	8252
Multiple primaries	3707	875	2832	1543	413	1130
Tumor T2-stage	8769	2180	6589	8475	2472	6003
Histologic grade 3	9206	2255	6951	6029	1734	4295
ER negative (1990+)	6303	1509	4794	3186	915	2271
PR negative (1990+)	8016	1849	6167	3971	1125	2846
Radiation	17372	3763	13609	6657	1855	4802
Dead of breast cancer	1612	406	1206	2884	838	2046
Dead of other cause	1683	382	1301	894	261	633

N0, node-negative; N⁺, node-positive; nex, number of nodes examined.

College Station, TX, USA). Plots of smoothed residuals was done with S-PLUS (Insightful Corporation, Seattle, Washington, DC, USA).

Results

Table I summarizes the patient characteristics. The larger number of patients compared to a previous descriptive study (19) is due to enlarging the selection and to the SEER additional registration. The larger number of deaths is due to the longer follow-up period.

Table II presents the core proportional hazards model including the nneg and npos variables. It shows for nneg a significantly reduced mortality hazard ratio of 0.978 [95% confidence interval: 0.974-0.982] (this corresponds to an estimated average 2.2% mortality reduction per negative node) and for npos a significantly increased mortality hazard ratio of 1.067 [1.063-1.072] (this corresponds to an estimated average 6.7% mortality increase per positive node).

Fig. 1 presents smoothed residual plots for N0 (upper-left) and N⁺ (upper-right and bottom row) patients. The top row is smoothed over the number of negative nodes (nneg). The bottom row is smoothed over the number of positive nodes (npos, lower-left graph) and over the percentage of the number of positive nodes among all examined nodes (npnex, lower-right graph). A set of tick marks has been produced on the x-axis of each graph, one at the location of each of the x-values for the data. Smaller tick marks indicate data based on 10 or less patients at the corresponding x-value. In all plots (except that for npnex), the rightmost part of the smooth curve should be treated with caution, as it is based on a small number and scarcely spaced residuals.

For the number of negative nodes it is apparent that both in N0 and N⁺ there is an initial rapid decrease in the risk of death up to 10-15 nodes, which slows down (or even stabilizes) afterwards. Especially in N⁺, the shape looks

hyperbolic, suggesting a function proportional to the inverse of the number of negative nodes.

For the number of positive nodes in N⁺ the shape suggests an initial increase in the risk, which levels off afterwards. For the percentage of the number of positive nodes among all examined nodes, the shape is approximately linear.

Based on the above findings, an updated stratified proportional hazards model was fitted (Table III). Note that, for N0 patients, number of positive nodes npos=0 and, since npnex = npos/(npos+nneg), 'npnex' is also identically zero. Hence, the covariate 'invnneg0' can be thought of as an effect 'corresponding' to 'npnex' for N0 patients: in both covariates, the number of negative nodes appears in the denominator.

Fig. 2 presents the predicted form of the dependence of the logarithm of the hazard ratio on the number of negative nodes for different numbers of positive nodes. The shapes of the curves qualitatively agree with the smoothed curves presented for nneg in the first row of Fig. 1. The shapes indicate a rapid initial drop, which slows down. For a large number of positive nodes, however, the decrease happens later than for a small number of positive nodes. In N0 patients, the curve predicts a rapid decrease of the risk up to around 10 negative nodes, say. After that, a linear decrease takes place. The unfavorable effect of the number of positive nodes is seen in the upward shifts of the curves. The important unfavorable effect of N⁺ is reflected by the upward shift from the curve corresponding to N0 patients to the curve for N⁺ with 1 positive node; the magnitude of the shift is much bigger than the magnitude of the shift due to one additional positive node.

Fig. 3 presents the predicted form of the dependence of the logarithm of the hazard ratio on the number of positive nodes for different numbers of negative nodes. The triangles indicate the point estimates for N0 (npos=0). Apart from the case when all examined nodes were positive (nneg=0), the

Table II. Basic proportional hazards model.

Variable	Hazard ratio	95% confidence interval	p-value
SEER central registries (/East)	0.925	0.868-0.985	0.015
SEER Western registries (/East)	0.873	0.826-0.923	<0.0001
Year of diagnosis (year)	0.966	0.954-0.978	<0.0001
Age at diagnosis (year)	1.024	1.021-1.027	<0.0001
Race black (/else)	1.476	1.368-1.594	<0.0001
Marital status married (/else)	0.830	0.790-0.871	<0.0001
Inner quadrants (/else)	1.190	1.116-1.269	<0.0001
Histology ductal (/else)	1.273	1.199-1.351	<0.0001
Estrogen negative receptor status (1990+) (/else)	1.428	1.315-1.550	<0.0001
Progesterone negative receptor status (1990+) (/else)	1.262	1.168-1.363	<0.0001
Histological grade 2 (/grade 1)	1.415	1.240-1.614	<0.0001
Histological grade 3 (/grade 1)	1.987	1.744-2.264	<0.0001
Histological grade 4 (/grade 1)	2.152	1.816-2.549	<0.0001
Histological grade unspecified (/grade 1)	1.542	1.354-1.755	<0.0001
Tumor size (mm)	1.029	1.026-1.031	<0.0001
Breast conserving surgery (BCS) (/total mastectomy)	1.057	0.942-1.186	0.343
Radiation given (RT) (/not given)	1.009	0.926-1.100	0.836
Interaction BCS x RT (/else)	0.710	0.612-0.825	<0.0001
Number of uninvolved nodes (nneg) (n)	0.978	0.974-0.982	<0.0001
Number of involved nodes (npos) (n)	1.067	1.063-1.072	<0.0001

Model based on the full population of 55,267 patients, stratified on the multiple primaries variable. Reference level for categorical variables or unit scale for continuous variables are indicated in brackets respectively with or without a leading slash. Hazard ratio >1 (<1) indicates increased (decreased) risk of death from any cause, relative to the reference level for categorical variables or per unit scale for continuous variables. The martingale residuals method is applied by removing the npos and/or nneg variable, estimating the reduced model, then plotting a smoothed plot of the residuals in function of the variable that was removed.

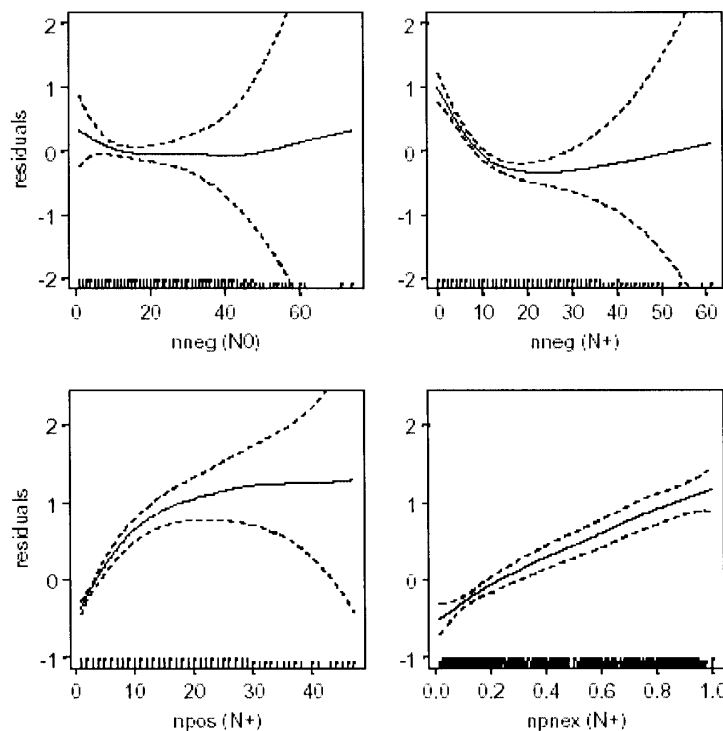


Figure 1. Smoothed residual plots for node-negative (N0) and node-positive (N+) patients, in function of the number of negative nodes (nneg, top graphs), in function of the number of positive nodes (npos, lower-left graph), and in function of the ratio of positive nodes on the number of nodes examined (npnex, lower-right graph).

Table III. Updated proportional hazards model.

Variable	Hazard ratio	95% confidence interval	p-value
SEER central registries (/East)	0.921	0.864-0.981	0.010
SEER Western registries (/East)	0.881	0.834-0.932	<0.0001
Year of diagnosis (year)	0.966	0.955-0.978	<0.0001
Age at diagnosis (year)	1.026	1.023-1.028	<0.0001
Race black (/else)	1.468	1.360-1.584	<0.0001
Marital status married (/else)	0.837	0.797-0.879	<0.0001
Inner quadrants (/else)	1.250	1.171-1.333	<0.0001
Histology ductal (/else)	1.221	1.150-1.297	<0.0001
Estrogen negative (/else)	1.448	1.334-1.571	<0.0001
Progesterone negative (/else)	1.258	1.165-1.358	<0.0001
Histological grade 2 (/grade 1)	1.363	1.194-1.555	<0.0001
Histological grade 3 (/grade 1)	1.893	1.662-2.157	<0.0001
Histological grade 4 (/grade 1)	2.045	1.726-2.423	<0.0001
Unspecified grade (/grade 1)	1.489	1.308-1.695	<0.0001
Tumor size (mm)	1.025	1.022-1.027	<0.0001
Breast conserving surgery (BCS) (/total mastectomy)	1.042	0.929-1.169	0.480
Radiation given (RT) (/not given)	0.925	0.848-1.008	0.075
Interaction BCS x RT (/else)	0.818	0.704-0.950	0.008
Node-negative status (N0) (/N ⁺)	0.627	0.581-0.677	<0.0001
Number of uninvolved nodes (nneg) (n)	0.998	0.993-1.002	0.335
Number of involved nodes (npos) (n)	1.013	1.005-1.022	0.003
Inverse of nneg in N0 (invnneg0) (%)	1.010	1.004-1.016	0.002
Ratio npos on examined nodes (npnex) (%)	1.012	1.010-1.014	<0.0001

Model including a node-negative indicator (N0), the inverse of the number of uninvolved nodes in N0 patients (invnneg0, expressed in %) and the ratio of positive nodes among all examined nodes (npnex, expressed in %), stratified on a multiple primaries indicator. This model was used for computing the dependence of the logarithm of the hazard ratio on the number of negative nodes and the number of positive nodes.

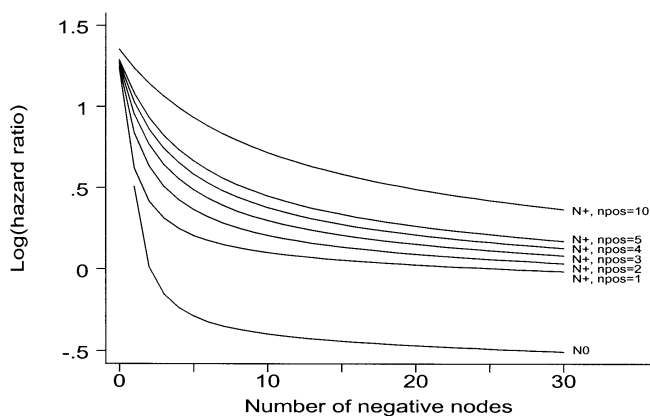


Figure 2. Logarithm of the mortality hazard ratio in function of the number of negative nodes, for different numbers of positive nodes (npos).

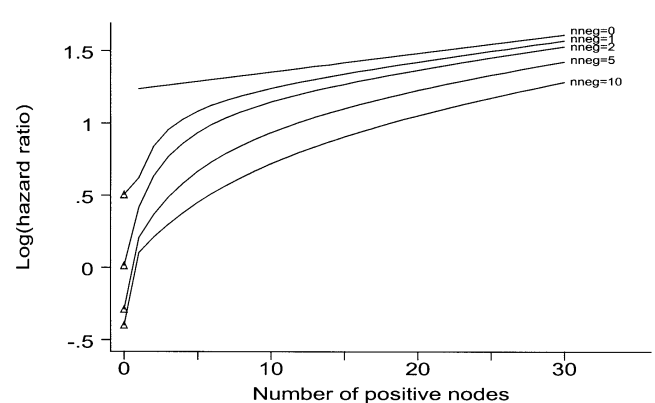


Figure 3. Logarithm of the mortality hazard ratio in function of the number of positive nodes, for different numbers of negative nodes (nneg).

curves indicate a quick initial increase of the risk, which linearizes afterwards. When all examined nodes were positive, the increase was linear from the beginning (for this case,

there is no estimate at 0 -or N0- as there can be no patients with 0 negative and 0 positive nodes). The favorable effect of a smaller number of positive nodes is seen in the downward

shifts of the curves. The ‘jumps’ between the estimates obtained for $n_{pos}=0$ (N0, triangles) and $n_{pos}=1$ (N⁺) indicate the difference in the risk of death for two patients with the same number of negative nodes, but without (N0) or with at least one (N⁺) positive node. The increasing magnitude of the ‘jumps’ suggests that the more negative nodes are found, the more dramatic increase in the risk associated with finding a positive node. The following explanation comes to mind: the risk of a patient with, e.g., only one negative node as the only examined node is high anyway; thus, for a patient for whom, apart from the one negative node, a positive node is also found, the risk increases, but not that dramatically. On the other hand, the risk of a patient for whom, e.g., all of ten examined nodes are negative, is relatively low. ‘Adding’ a positive node in this situation does make a big difference.

Discussion

Survival effect of the number of negative and positive nodes

Negative nodes. The presence of negative nodes is a favorable prognostic factor but the effect is non-linear. Though the U shape of the smoothed martingale residuals suggests an adverse prognosis with very large number of negative nodes (Fig. 1, top row), estimates at these points are based on scarce data as already mentioned. It is therefore more prudent to take into consideration the range up to 30-40 nodes, where the estimates are based on a larger number of data and are thus more reliable. In that range, for N⁺ patients we have earlier observed that the survival probability in function of the number of negative nodes showed an initial rapid increase which then tended to level off (19). The pattern is in qualitative agreement with the initial decrease in the relative mortality hazard predicted using the Cox model from Table III and shown in Fig. 2. The multivariate analysis allows to infer a qualitatively similar trend for node-negative cases (Fig. 2). The leveling-off occurs somewhere between 5 and 10 negative nodes in N0 patients. For N⁺ patients, the threshold moves towards larger values and depends on the number of positive nodes.

Positive nodes. The pattern of survival in function of the number of positive nodes is also non-linear except when all nodes are involved (Fig. 3). The increase in the risk of death per positive node declines with larger number of positive nodes, e.g. the risk of death increases more from 1 to 2 positive nodes than from 20 to 21 positive nodes. But unlike the pattern in function of negative nodes, the predicted curves do not suggest any leveling-off of the relative mortality hazard (Fig. 3). Even at 20 or 30 positive nodes, each additional positive node increases the mortality hazard ratio by at least 1.3% (Fig. 3 and Table III).

Proportion of positive nodes. The proportion of the number of positive nodes among the number of nodes examined shows a remarkable linearity (Fig. 1, bottom right). The estimated effect is a 1.2% increase in the relative risk of death per 1% increase in the proportion (Table III).

Summary on negative and positive nodes. In summary, after adjusting for other prognostic variables, the number of

negative nodes remains a globally favorable factor. Its effect tends to level off beyond about 5-10 nodes. The number of positive nodes is an unfavorable factor. Its effect does not level off. Even in the case of extensive nodal involvement each additional positive node contributes a substantial increase in the risk of death. Lastly, the proportion of involved nodes appears to be an important prognostic factor as well.

Number of nodes examined: the wrong question? In different proportional hazards models for breast cancer that we have explored until now, the number of nodes examined has always emerged as a significant prognostic factor with an approximate average reduction of risk of death of 2% per node examined. However in the present extended analysis we found that the information content of that number, without any reference to the split between the number of positive and negative nodes, is poor. To illustrate, consider a patient with 10 nodes examined. For such a patient the split between negative and positive nodes can range from anywhere between all 10 negative nodes, to all 10 positive nodes. The hazard ratio between the two extremes equals 5.63 (logarithm=1.73) (see Fig. 3). If N⁺ were specified, the 10 nodes examined still could contain only one or all positive nodes. The hazard ratio between the two extremes equals 3.40 (logarithm=1.22) (Fig. 3).

Clearly, the question of what is a quantitatively adequate axillary node dissection without any other specification, is insufficiently stated. As already noted in the introduction and commented above, the number of examined nodes as a separate variable contributes limited information. But, when the number of examined nodes is considered through a well specified context, either as a denominator in the proportion of involved nodes or implicitly as the sum of the numbers of involved and uninvolved nodes, there is a remarkable gain of information.

The utility of counting nodes. Several researchers have noted in animal models in which tumor cells are inoculated, using various routes and various tumor cell lines, that the success in developing metastases is influenced by the number of cells injected (25-27). When tumor cells are inoculated subcutaneously, there is a threshold number of cells - above, a tumor will develop; below, no tumor will appear. When tumor cells are inoculated in the circulation, a minimum number of cells depending on conditioning and on cell line is needed to develop tumor metastatic colonies. When less than 1×10^6 cells are inoculated into the left ventricle, they fix in every organ of the body, but they are not present in the target organs in numbers sufficient to reach the threshold required for growth. However, metastases are rapidly growing when the inoculation succeeds. Single cell suspensions of spontaneous C3H mouse mammary tumors did not produce colonies in the lungs of syngeneic mice after intravenous injection whereas cell aggregates obtained from similar tumors did (the number of macroscopic colonies that developed was linearly related with the number of aggregates injected into the recipients) (28).

The present study finds an abrupt change of prognosis from node-negative status to node-positive status, between zero and a single involved node. In keeping with the experimental

models, the analysis suggests that node-negative represents some state of equilibrium between host and tumor despite tumor growth and despite possible circulating tumor cells. The finding of a positive node would then express a rupture of the host-tumor balance in which some set of biological conditions favoring tumor metastasis has been reached (29), with the subsequent dramatic increase in mortality risk (Fig. 2). How fast or how late that threshold is reached is perhaps related to the intensity of the underlying disease process as expressed by the proportion of positive nodes, or related to tumor size and other tumor characteristics. Within that background, each additional involved node contributes to a further increase in mortality risk (Fig. 3).

Martingale residuals method. When facing a sophisticated statistical tool like the method of martingale residuals, the question that the clinician might ask is, how useful is it? We have applied the method to the SEER data to investigate the role of node examination in T3N0M0 colo-rectal carcinoma (30). In 2001, the conventional view considered that there was a cutoff point in the assessment of nodal status (31). We found that the relation between the number of nodes examined and survival in T3N0M0 colo-rectal carcinoma was linear, no cutpoint could be defined (30). This was an unexpected result that has been very recently confirmed in a large single institution study (32). While to the statistician there is no doubt on the utility of the method, the clinicians among us gained experience and learned in that concrete example that the method was able to detect important clinical information from apparently very heterogeneous data.

The method is somewhat more advanced than the routinely used statistical techniques, but the core proportional hazards model that we used in this study is relatively conventional. Without going into every detail of Table II, we note that the major prognostic factors found are tumor size, histological grade and nodal involvement, showing a concordance with findings that are the basis of the Nottingham prognostic index (33,34). The concordance between results from an apparently heterogeneous collection of data from the SEER and an apparently homogeneous study from Nottingham suggests that a careful and systematic analysis is able to extract fundamental disease characteristics that are similar across different populations of patients.

One should of course treat with due caution the inferences drawn in this study. They are based on Figs. 2 and 3 which were obtained as predictions from the model presented in Table III. Obviously, the validity of the conclusions depends very much on whether the chosen form of the model is indeed correct. The functional form of the covariates of interest (the number of positive and negative nodes, the percentage of positive nodes out of those examined) was suggested by the data at hand (Fig. 1). It is of course possible that the form is entirely specific for this particular dataset. Unless verified in an independent study, this conjecture cannot be completely ruled out.

Conclusion. This study finds that the number of negative nodes is a favorable prognostic factor in T1-T2 breast cancer. The influence of the number of negative nodes levels off at about 5-10 nodes.

There is an abrupt increase of risk of death associated with the change from the node-negative to node-positive status. The presence of positive nodes is an unfavorable prognostic factor, effect of which does not appear to level off. Within node-positive patients, there is no clear prognostic cutoff associated with the number of positive nodes.

The different patterns for involved and uninvolved nodes suggest that the adequacy of axillary dissection cannot be quantified solely by a number of nodes examined. Assessment of quantitative adequacy of axillary dissection requires that relative nodal involvement should be specified.

Among the variables included in the analyses, ratio-based characterization of node involvement appears as an important prognostic factor.

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