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A method for individualising the risk of a negative lymph node classification error in cancer of the colon

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A B S T R A C T

Introduction: In cancer of the colon, the number of lymph nodes that should be analysed before a patient is classified as free of lymph node involvement has been widely discussed. A mathematical model is proposed which is based on the Bayes Theorem for calculating the probability of error (PE) similar to that normally used to evaluate a diagnostic test, but adapted to a quantitative variable, the lymph node count.
Methods: The clinical histories of 480 patients routinely operated on in attempt to cure cancer of the colon were reviewed. Cases with any kind of metastasis were excluded. The proposed formula based on the Bayes Theorem was applied with the aim of calculating the PEs for the complete series and for different patient sub-groups (T2, T3, and T4 tumours).
Results: For the probabilities of error of classifying a patient as N negative, which varied between 5% and 1‰ (near or practically 0), the minimum number of negative lymph nodes required for analysis fluctuated between 7 and 17, respectively, for the complete series. This minimum figure was also variable for the different sub-groups (T2, T3, and T4 tumours) studied. These numbers mainly depended on the case characteristics of a specific study group as regards the prevalence of the N+ cases that they dealt with, and of its historically demonstrated ability to collect and identify positive lymph nodes in those patients that had them.
Conclusion: From a mathematical point of view, the minimum number of lymph nodes that have to be analysed in cancer of the colon in order to classify a patient as N negative is not a constant. This depends on the error that is prepared to be assumed for that diagnosis, possibly depending on certain tumour traits, and also may be adapted to the cases of each study group.

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Un método para individualizar el riesgo de una errónea clasificación ganglionar negativa en el cáncer de colon

Palabras clave:
Carcinoma colorrectal
Ganglios negativos
Metástasis ganglionar
Teorema de Bayes

RESUMEN

Introducción y objetivos: En el cáncer de colon, el número de ganglios linfáticos que se deberían analizar antes de clasificar a un paciente como libre de afectación ganglionar ha sido ampliamente discutido. Se propone un modelo matemático basado en el teorema de Bayes para calcular la probabilidad de error (PE) similar al utilizado habitualmente para la evaluación de una prueba diagnóstica pero adaptado a una variable cuantitativa como es un recuento ganglionar.

Métodos: Se revisaron las historias clínicas de 480 pacientes intervenidos de forma programada de cáncer de colon con intención curativa, excluyendo los casos que presentaban metástasis de cualquier tipo. Con el fin de calcular las PE, para la serie completa y para diversos subgrupos de pacientes (tumores T2, T3, y T4) se aplicó la fórmula que proponemos basada en dicho teorema de Bayes.

Resultados: Para las probabilidades de error al clasificar un paciente como N negativo que oscilaran entre un 5% hasta un 1‰ (próximo o prácticamente 0), la mínima cifra de ganglios negativos necesarios para analizar fluctuó entre 7 y 17 respectivamente para la serie completa. Esta cifra mínima también fue cambiante para los diversos subgrupos (tumores T2, T3, y T4) considerados. Fundamentalmente, tales cifras dependen de las características de la casuística de un grupo de trabajo concreto en cuanto a prevalencia de casos N+ que man ejen, y de su capacidad históricamente demostrada para recolectar e identificar ganglios positivos en los pacientes que los presentaran.

Conclusión: Desde el punto de vista matemático, el número mínimo de ganglios que se deberían analizar en el cáncer de colon para clasificar a un paciente como N negativo no es una constante. Este depende del error que se esté dispuesto a asumir para tal diagnóstico, puede estar en función de ciertos rasgos del tumor, y además, se debería adaptar a la casuística de cada grupo de trabajo.

Introduction

The N-negative (pN_0) classification of patients operated on for colon cancer has significant implications on the prognosis of survival and the indications for postoperative adjuvant treatment. As such, any error made in classifying these patients could have important consequences.

To date, most work groups have followed certain general recommendations for evaluating the safety of negative lymph node staging, such as analysing at least 12 negative nodes. This recommendation come from the TNM staging system and several expert groups,[1-5] but holds the drawback of not measuring the probability of error in individually considered patients, especially if it has been impossible to measure the requisite number of nodes. In any case study, and for several reasons, the possibility always exists that in a certain patient, this number might not be reached.

In 1992, Kiricuta and Tausch[6] published a mathematical model based on Bayes' theorem, which approximates the negative predictive value (NPV) of each patient given a certain number of axillary nodes analysed in breast cancer. We used a similar model in this study, in order to approximate the risk of error in the classification of patients as pN_0 based on the universal law of conditional probabilities that constitutes Bayes' theorem. We have used colon cancer as an example and historical patient characteristics from a case study as the reference data, as is customary in the evaluation of any diagnostic test (empirical Bayesian method).

Methods

We performed a retrospective study based on 480 consecutive patients that underwent programmed operations for tumour resections due to non-metastatic malignant neoplasm of the colon in the University of Castellon General Hospital during an 8-year period, from January 1, 1994 to December 31, 2001. Patients also had completed a follow-up period of at least 5 years following the procedure, in accordance with the hospital protocol. After the surgical procedure, patients were classified according to the 6th edition of the TNM staging system. A total of 328 patients were classified as pN_0. We also

recorded the number of lymph nodes that were analysed and the number of positive nodes in each patient when present. Finally, we recorded the stage of the disease from the last available record. In all cases, the histological examination of the lymph nodes was performed by manual identification of adenopathies, sections through the midline, and staining with haematoxylin and eosin. We did not use any other detection techniques, such as fat clearance, sectioning by zones, or immunohistochemical or molecular techniques. In no cases did any practitioners, pathologists, or surgeons with particular specialisation or dedication to colorectal pathologies intervene, since our hospital did not have a specialised unit in this field at the time. A total of 16 general surgeons and 12 pathologists participated in procuring our data. The criteria for oncological radicality in resections were not completely in line with the generally accepted today standards. Only 6 surgeons consistently performed ligations of the pedicles at their roots, constituting 58% of all operations. However, the total number of nodes collected by these surgeons did not differ significantly from the rest of the group.

The application of the mathematical model was derived from the formula for Bayes' theorem for the calculation of [1-Negative Predictive Value], which represents the final probability of erring when classifying a node as negative:

$$(1 - \mathrm{NPV}) = \frac{(\text{Prevalence pN+}) \times (\text{False negatives})}{(\text{Prevalence of pN+}) \times (\text{False negatives}) + (\text{Prevalence of pN0}) \times (\text{True Negatives})}$$

The prevalence of positive nodes [Prevalence pN+] is a simple quotient between the number of patients with at least one positive node and the total number of cases in the study. The prevalence of negative nodes [Prevalence pN_0] is the complementary value [1-Prevalence pN+]. The probability of True Negatives, or Diagnostic Specificity, is always equal to 1, as if the pathologist finds positive nodes, the existence of false positives is impossible.

According to Kiricuta and Tausch,[6] the probability of False Negatives [1-Diagnostic sensitivity] for a quantitative variable, such as lymph node count, can be calculated by applying a hypergeometric distribution with 4 parameters, in which the following variables are used: (A) the total sum of nodes isolated from all patients pN_1 and pN_2 (pN+) in the study, or from a given subgroup; (B) the total sum of positive nodes found in these patients; (C) the total number of nodes isolated in patients initially labelled as pN_0; and (D), the parameter 0, or in other words, 0 positive nodes, which defines these patients as pN_0. In mathematical terms, the hypergeometric distribution is expressed in the following manner:

As a result, the calculation of p(n–/N+) from the hypergeometric distribution is composed of 4 parameters, which are: 1) the total number of nodes obtained throughout the entire study (or in a given subgroup of patients) that were finally diagnosed as N+ (*M* from the formula); 2) the total number of positive nodes from among this total number of nodes analysed (*N* from the formula); 3) each concrete case that is analysed in a patient, or in other words, the number of nodes analysed in this patient (*n* from the formula), and 4) a final parameter equal to zero that indicates that no positive nodes were found (*m* from the formula).[7]

In reality, this probability and the formula for Bayes' theorem are easily computed using normal statistical functions in any commercial spreadsheet (Appendix 1). In this manner, the final value of [1-NPV] refers to a single patient in which a given number of negative nodes have been analysed. Thus the *minimum number* of negative nodes to be analysed, in said patient, so as to be considered as truly pN_0, would be that number that produces a sufficiently low value of [1-NPV], which must be established arbitrarily according to the confidence limits that we impose.

We used SPSS statistical software, version 15, for all descriptive calculations in this study, and an Excel® spreadsheet for probability calculations.

Results

The demographical and tumour characteristics from the 480 cases analysed are summarised in Table 1. Figure 1 displays the frequency of each number of nodes analysed. Table 2 demonstrates the factors from the study that were necessary for developing the calculations. Table 3 displays the results produced by applying the model. Here it becomes evident that if we decide upon a probability of error in the labelling of a patient as N negative at less than 5% for the entire case series, at least 7 negative nodes per patient would be required. However, the minimum necessary number of nodes analysed would be 12 if the error limit was placed at 1%, and should really be 20 or more if we seek values less than 1‰, which in practice could be considered as a limit close to or similar to 0. These calculations are repeated for certain subgroups that we have selected as an example. Therefore, for a patient with a T2 tumour, this limit of 1‰ would be obtained in our study by analysing 8 negative nodes, whereas a patient with a T3 tumour would require at least 26 negative nodes. Naturally, if the values from Table 2 that define the capacity to find positive nodes were different for another study group, their results would not coincide with ours. In any case, large numbers of negative nodes analysed will logically always lead to very low values for the probability of making a diagnostic error. As a result, the proposed model is able to quantify this probability of diagnostic error in a model adapted to the qualities of each case study or subgroup of patients within the study. The error limits that this model assumes, which

Table 1 – General characteristics of the study (480 patients)

Age	67.5 (12)
Sex:	
Men	268 (56%)
Women	212 (44%)
Location:	
Caecum	60 (12.4%)
Ascending colon	32 (6.7%)
Hepatic angle	52 (10.8%)
Transverse colon	32 (6.7%)
Splenic angle	24 (5%)
Descending colon	32 (6.7%)
Sigmoid	164 (34.2%)
Rectosigmoid	84 (17.5%)
Parietal invasion:	
pT_1	16 (3.5%)
pT_2	88 (18%)
pT_3	316 (66%)
pT_4	60 (12.5%)
Lymph node status:	
pN_0	328 (68%)
pN_1	104 (22%)
pN_2	48 (10%)
Nodes analysed (study)	9.6 (2)
Positive nodes (study)	0.87 (0.4)
Nodes analysed (N+ cases)	9.3 (3)
Positive nodes (N+ cases)	2.7 (0.8)
Nodes analysed (pN_0 cases)	9.8 (2)
TNM stage:	
I	84 (17%)
IIA	212 (44%)
IIB	36 (8%)
IIIA	8 (2%)
IIIB	92 (19%)
IIIC	48 (10%)
Survival, months	
Tumour specifics (study)	103 (97-108)
pN_0 cases	104 (98-111)*
N+ cases	94 (83-104)*
T3N0 cases with ≤2 nodes analysed	87 (60-116)[a]
T3N0 cases with >25 nodes analysed	95 (86-104)[a]
pN_0 with less than 7 nodes analysed	90 (78-103)**
pN_0 with between 7 and 12 nodes analysed	96 (88-105)**
pN_0 with more than 12 nodes analysed	100 (90-111)**
Disease free (study)	95 (89-101)
pN_0 cases	99 (91-106)***
N+ cases	83 (73-94)***

Mean (standard deviation); frequencies (%); survival: actuarial mean (with 95% confidence interval). Medians cannot be calculated since a probability ≤50% was not reached in any group.
*P-value (Log-Rank)=.802.
**P-value (Log-Rank)=.02.
***P-value (Log-Rank)=.177.
[a]P-value (Log-Rank)=.236.

determine the minimum number of nodes to be analysed based on these limits, will depend on the accuracy imposed by each group. We insist that the objective of this study is not to fix any of these limits, but rather to offer an approach to their calculation, whatever they may be.

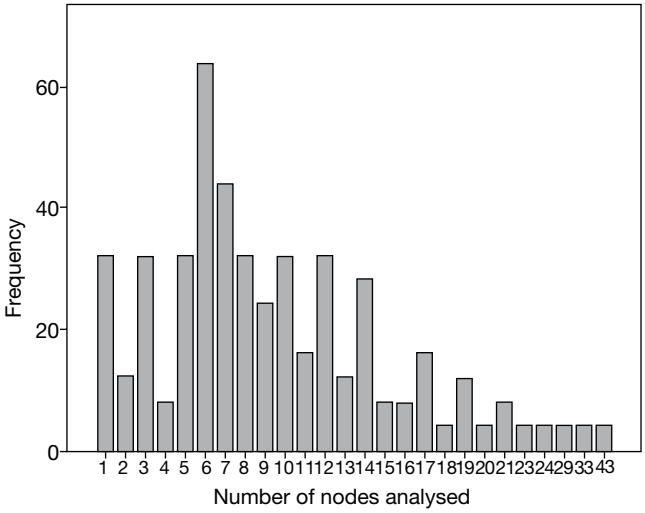


Figure 1 – Algorithm for the prophylaxis and treatment of PONV. *After 6 h, the antiemetics used in prophylaxis can be repeated, except for dexamethasone.

Discussion

Above all, the Bayesian model offers additional information of great value in patients that do not comply with the recommendation of having at least 12 nodes analysed. The factors that modify the number of lymph nodes analysed can be broadly grouped into three categories: 1) factors dependent on the anatomy of the patient; 2) factors depending on the surgical procedure, and 3) factors dependent on the histopathological study.[8,9] The main advantage of this mathematical model is that it adapts the results of each group to these three variables.

Furthermore, a negative predictive value, or its complementary value, which here we denominate as PE, cannot be extrapolated to other studies since, by definition, it lacks external validity. As a result, each work group must calculate the cut-off point for the minimum number of nodes analysed according to the proposed model and a predetermined level of error. As has been published in several different studies,[10-13] major differences can exist in terms of surgical technique and histopathological examinations of the surgical specimen between different health institutions. Therefore, the differences between different centres in terms of the number of nodes analysed could be considerable, which also provokes differences in the probability of error when staging a node as negative. Thus, for example, the probability of error will not be the same in a group that performs broad intestinal resections and in one whose histopathological studies include more sensitive detection techniques such as fat clearance and immunohistochemical and molecular techniques. As a result, we believe that recommendations on the number of nodes that must be analysed in order to achieve a low probability of error cannot be universal, but should be adapted to the conditions in which the procedure is performed, such as the surgical techniques used and

Table 2 – Information needed to construct the proposed model

	Study	T2	T3	T4
Prevalence of N+[P(N+)] patients	0.317	0.227	0.329	0.467
N=total sum of nodes analysed in N+ patients	1.408	132	988	288
N+=total sum of positive nodes in N+ patients	416	68	212	136
	480 cases	88 cases	316 cases	60 cases

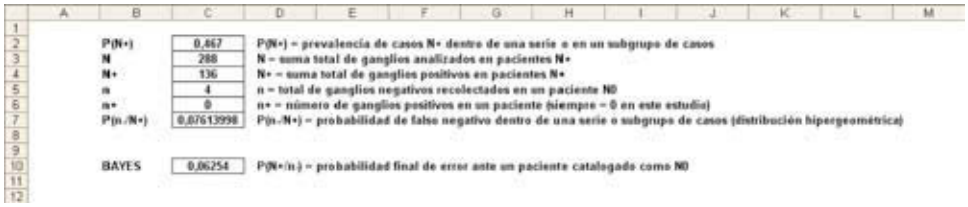
Table 3 – Probabilities of error according to the number of nodes analysed

	Final probability of error when patient is pN0 (1 - negative predictive value)			
n	Study	T2	T3	T4
1	0.246	0.125	0.278	0.316
2	0.187	0.064	0.232	0.196
3	0.140	0.032	0.192	0.113
4	0.102	0.015	0.157	0.063
5	0.074	0.007	0.128	0.034
6	0.053	0.003	0.103	0.018
7	0.038	0.002	0.082	0.009
8	0.027	0.001	0.066	0.005
9	0.019	0.0003	0.052	0.002
10	0.014	0.0001	0.041	0.001
11	0.010	0.0001	0.033	0.0007
12	0.007	0.00003	0.026	0.0003
13	0.005	0.00001	0.020	0.0002
14	0.003	0.00001	0.016	0.0001
15	0.002	0	0.013	0.00004
16	0.002	0	0.010	0.00002
17	0.001	0	0.008	0.00001
18	0.001	0	0.006	0.00001
19	0.001	0	0.005	0
20	0.0004	0	0.004*	0

n=total number of negative nodes collected in a pN_0 patient.
*in T3, for <0.001 26 or more negative nodes must be analysed.

histopathological studies. Therefore, there is no constant minimum number of negative nodes to be analysed, but rather this value will depend on the capacity of the surgeon and pathologist to collect and assess nodes and the diagnostic error that we are willing to assume.

Here we must point out that the proposed model allows for calculating individualised probabilities for each patient of the possible risk of a false classification as pN_0, in contrast with general recommendations, and especially when these recommendations have not been complied with. Therein lies its primary practical use. Indeed, the main novelty of this mathematical model with respect to other models based on Bayes' theorem of probability is that the use of only those data from patients with affected lymph nodes [which we referred to in the prevalence of patients with positive nodes P(N+) and the insensitivity or rate of possible false negatives P(n–/N+)] in performing our calculations allows for individualisation of the results and their adaptation through time if the operational circumstances for the study were to change. The model is automatically updated as we add the data from new patients. As a result, a study group that normally detects more lymph nodes will have better results, in terms of diagnostic confidence, than those groups with less capacity for detection. This characteristic is derived from the nature of the probability calculations made by Bayes' theorem. The general recommendations circulating in our field come from classical statistical models, such as multivariate statistics, which do not allow for an individualised interpretation of the probabilities obtained, but rather only within a group of cases that are globally assessed. The classification of a patient as pN_0 is the result of performing a diagnosis like any other, and thus is subject to the same probability laws that condition any diagnostic process, as defined by Bayes' theorem, or the theorem of conditional probabilities, with regard to the final probability of being true or false. On this subject, our model has an indisputable validity, since the same steps are followed and the same formula used in any evaluation process of a diagnostic test. However, when dealing with quantitative



P(N+)	0,667	P(N+) = prevalencia de casos N+ dentro de una serie o en un subgrupo de casos	
N	288	N = suma total de ganglios analizados en pacientes N+	
N+	136	N+ = suma total de ganglios positivos en pacientes N+	
n	4	n = total de ganglios negativos recolectados en un paciente N0	
n+	0	n+ = número de ganglios positivos en un paciente (siempre = 0 en este estudio)	
P(n-/N+)	0,07613998	P(n-/N+) = probabilidad de falso negativo dentro de una serie o subgrupo de casos (distribución hipergeométrica)	
BAYES	0,06254	P(N+/n-) = probabilidad final de error ante un paciente catalogado como N0	

Figure 2 – Flowchart of the patients included in the study.

variables, such as lymph node counts, the calculations are somewhat more complex, although still perfectly accessible using a spreadsheet (Appendix 1).

Several different authors have researched the minimum number of negative nodes to be analysed in order to validate classifying a patient as pN_0, or a correct node classification in colon cancer,[14-24] using non-Bayesian statistical methods, generally multivariate tests such as the Cox regression test. Curiously, these are much more complex methods because they require powerful statistical software instead of simple calculation spreadsheets. The results are inconsistent among them, as they would be with the model we have proposed here. This is due to the different characteristics of the cases that make up each study analysed, since neither the prevalence of N-positive cases or negative cases, nor the diagnostic sensitivity can be identical in all work groups.

The recommendation of 12 nodes that many have proposed and accepted[3-5] is made with the intention of being a universal guideline, and therefore must be a very safe and well-supported recommendation, as are roadside traffic speed signs. In fact, in all cases from our study, analysing 12 negative nodes in each patient would have implied a probability of diagnostic error lower than 1%, which can be considered as quite low. Bearing in mind that this is a recommendation, and not an absolute law, our Bayesian model allows us to consider the necessary aspects and precise patient information to be included for patients where less than 12 nodes have been analysed, allowing us to assume that we are dealing with true pN_0, without too much of an error risk. This will therefore imply a better prognosis than true pN_1 y pN_2 nodes. It is well known by all medical professionals in this field that it is not always possible to analyse 12 nodes in colon cancer,[25-28] and in these cases, additional information regarding the risk of improperly classifying the patient can be very valuable.

To conclude, we believe that it is possible to individualise the risk of erroneously classifying a patient as negative through node analysis in resected colon cancer by calculating this probability according to Bayes' theorem. Furthermore, this could act as a useful complement for the recommendation of obtaining a minimum of 12 nodes for the correct classification of node status in these patients, most importantly, a negative status when this recommendation has not been fulfilled. Currently, the implications are important in terms of offering useful additional information, and possibly, this model could even have treatment implications on an individual basis, such by giving complementary information for a given patient being discussed by a tumour committee.

Conflict of interest

The authors affirm that they have no conflicts of interest.

Appendix 1

The following is a description of how to formulate the data in an Excel® spreadsheet in order to obtain probabilities of error. Assuming that we will situate the data in the same cells as is shown in Figure 2, we would proceed as follows:

- In C2, we place the prevalence of N+ cases in the study or subgroup of cases.
- In C3, we place the value corresponding to the total sum of nodes analysed (whether positive or negative) obtained in those patients classified as N+ in the study or subgroup.
- In C4, we place the value of the total sum of positive nodes obtained in those patients classified as N+.
- In C6, we type 0, which should not be modified, as this is the cell that indicates that we are analysing those patients that had 0 positive nodes.
- In C7, we introduce the hypergeometric function referring to the previous cells. For this, the following function text must be written: =DISTR.HIPERGEOM (C6;C5;C4;C3)
- In C10 we type the formula for Bayes' theorem for the final calculation of the probability of a diagnostic error in an N-negative patient with the number of nodes obtained. For this, the following formula text must be entered: =(C2*C7)/((C2*C7)+((1–C2)*(1)))
- Lastly, C5 is where we type the number of negative nodes that have been analysed in each patient, after which cell C10 will automatically display the final resulting risk of diagnostic error. As a simulation or test of the model, we can also type in cell C5 any number other than 0, and cell C10 will provide the corresponding probability of diagnostic error. If we have demarcated a permissible limit of error, the minimum number of negative nodes to be analysed will be the number that, when placed in C5, yields a result in C10 that is less than this value of error.

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