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ORIGINAL PAPERS

Impact of the total number of harvested lymph nodes after colon cancer resections on survival in patients without involved lymph node

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ABSTRACT

Background: the total number of harvested lymph nodes has been demonstrated to be of prognostic significance for colon cancer. Differences can occur in the total number of harvested lymph nodes between different specialists (surgeons and pathologists).

Objective: the aim of this study was to analyse if, in our centre, the number of analysed lymph nodes in patients with colon cancer that are classified as pN0 is also related to survival.

Material and methods: a retrospective study was designed, where 148 patients with colon adenocarcinoma (pN0 of TNM classification) who underwent elective surgery between 1 January 1995 and 31 December 2001, with curative intent were included. Three groups were created according to the number of analysed lymph nodes (< 7, 7-14, > 14 lymph nodes). For survival analysis the Kaplan-Meier and CUSUM curves methods were used.

Results: the total number of analysed lymph nodes was 1,493 (mean 10.1 lymph nodes per patient). The rate of 5-years survival was 63.0% in the group with < 7 lymph nodes; 7-14 lymph nodes: 80.6% and those with > 14 lymph nodes: 91.8% ($p < 0.01$). Prognostic significance was also present for multivariate analysis.

Conclusion: in our centre, harvesting a larger number of lymph nodes is related to improved rates of 5-years survival for patients with colon cancer staged as pN0. It seems reasonable to recommend obtaining as many lymph nodes as possible, and not to establish a minimum number of lymph nodes to be harvested.

Key words: Lymph nodes. Colon cancer. Survival. Prognosis.

RESUMEN

Introducción: el número total de ganglios analizados ha demostrado su influencia pronóstica en el cáncer de colon. Pueden existir grandes diferencias en el número de ganglios obtenidos por diferentes especialistas (cirujanos y anatomopatólogos).

Objetivo: el objetivo del presente estudio fue analizar si, en nuestro medio, el número de ganglios analizados en pacientes con cáncer de colon clasificados como pN0 se relaciona también con la supervivencia.

Material y métodos: estudio retrospectivo, con inclusión de 148 pacientes con adenocarcinoma de colon (pN0 de la clasificación TNM) intervenidos de forma programada con intención curativa entre 1 de enero de 1995 y 31 de diciembre de 2001. Se establecieron 3 grupos según el número de ganglios analizados (< 7, 7-14, > 14 ganglios). Para el análisis de la supervivencia se utilizaron el método de Kaplan Meier y las gráficas CUSUM.

Resultados: el número total de ganglios analizados fue 1.493 (media 10,1 ganglios por paciente). La supervivencia a 5 años fue del 63,0% en el grupo con < 7 ganglios; del 80,6% en el grupo con 7-14; y del 91,8% en el grupo con > 14 ganglios analizados ($p < 0,01$). La influencia pronóstica se mantuvo en el análisis multivariante.

Conclusión: en nuestro medio, la obtención de un mayor número de ganglios analizados se relaciona con una mayor supervivencia a los 5 años en pacientes con cáncer de colon clasificados como pN0. Parece razonable recomendar la obtención de tantos ganglios como sea posible en este tipo de cirugía y no recomendar un número mínimo de ganglios que se deberían analizar.

Palabras clave: Ganglios linfáticos. Cáncer de colon. Supervivencia. Pronóstico.

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INTRODUCTION

Colorectal cancer constitutes the most frequent neoplasia in our environment, with an estimated incidence of nearly 2,359 new cases per 100,000 inhabitants each

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year; it ranks second in deaths caused by neoplasias, after lung cancer in males and breast cancer in females (1). As it happens in the majority of tumours, developmental state at the moment of diagnosis is the main factor in the prognosis of this cancer. Therefore, the degree of tumoral infiltration, the lymph nodal affectation and the presence of metastasis at distance (TNM classification) have proven to be the main factors involved (2).

Several studies have focussed on the influence of the number of analysed lymph nodes in the prognosis of patients. In these studies submitted to resectional surgery in colorectal cancer, the lymph nodal analysis can be either positive or negative for the presence of neoplastic cells (3-9). However, there are several factors that condition the number of analysed lymph nodes and they can show big differences depending on the environment in which they are studied, and for each working group (10). It is therefore of great interest to contemplate whether, in our setting, the total number of harvested lymph nodes in patients submitted to resectional surgery for colon cancer and that are also finally stratified as negatives (pN0 of TNM classification), is related to survival rates and to study these results in accordance with previously published results.

MATERIAL AND METHODS

Retrospective study reviewing medical histories, obtained from the database of our centre, where 148 patients submitted to resectional surgery in colon cancer, which final anatomopathological diagnosis was staged as pN0 of TNM classification. On an elective surgery between 1 January 1995 and 31 December 2001 with curative intent and the diagnosis of colon adenocarcinoma were included. In order to be included in the study, the anatomopathologic report needed to include the tumoral size, the lymph node affectation and the total number of analysed lymph nodes. All the patients should have complied with the protocols set up by our service. This study excluded patients with rectal cancer or tumours located in the vermiform appendix, those with neoadjuvant treatments, either palliative or urgent, or other histopathologic types of cancers, such as lymphomas, sarcomas or carcinoid tumours. Laparoscopic procedures were excluded, because this practice, during the studied period, was not standardized in our centre. Those patients with lymph nodal affectation (pN1 or pN2) or metastasis at distance were also excluded from this study. No patients had received adjuvant treatments. Therefore, 172 patients were excluded from the 320 cases treated in this period, so the total patients analysed were 148.

In order to assess the impact of the number of analysed lymph nodes on the prognosis, three groups of patients were created according to the recommendations of the 6th edition of the TNM classification (< 7, 7-14, > 14 lymph nodes) (11).

For descriptive and univariate survival analysis two methods were used: the Kaplan-Meier method, with the Log-rank test to establish the statistical significance, and CUSUM (cumulative sum) graph method. In the multivariate analysis through Cox regression, the parameters whose influence on the prognosis was significant during the univariate analysis were used. Parameters without statistical significance were not included because they did not provide further information to the regression model.

For the mathematical calculations SPSS 15.0 software for Windows was used. Differences with a value $p < 0.05$ were considered statistically significant. The CUSUM curve was obtained by using STATA 10 software, measuring the state variable (death during the follow up) against the total number of analysed lymph nodes.

RESULTS

Characteristics of the sample

The total number of patients included on the study was 148, 75 males and 73 females. The average age was 68.4 years (range 30-92 years). 64.9% of the patients were older than 65 years and 35.1% were younger than 65 years. Of the 148 patients, 51 (34.5%) did not show any concomitant pathology. Table I shows the comorbidity of the 97 patients left. The average body mass index (BMI) was 27.1 (range 19.4-67.1). 54.1% of individuals belonged to the group with BMI ≥ 25 and 31.8% belonged to the group with BMI < 25. In 60.8% of cases the tumour was located on the left side of the colon, whereas in the other 58 cases it was located on the right side. Only 2 patients (1.4%) were diagnosed as pTis, 6 (4.1%) as pT1, 24 (16.2%) as pT2, 13 (18.8%) as pT4 and, more than half, 103 (69.6%), were classified as pT3. In 116 cases (78.4%), the patients were diagnosed as pT3-4, otherwise the other 32 cases (21.6%) were categorised as not classified as pT3-4. The majority of the patients, 116 (78.4%), were included as stage II of the TNM classification, 30 (20.3%) were classified as stage I, 2 as stage 0 (pTis), and no patients were registered as stage III or IV due to the inclusion and exclusion characteristics of the case study.

Table I. Comorbidity of the sample

Comorbidity	*Cases*	*%*
High blood pressure	26	17.6%
Non- specific cardiopathy	22	14.9%
OCFA	15	10.1%
Diabetes mellitus	13	8.8%
ACV	5	3.4%
Renal failure	3	2.0%
Other pathology	13	8.8%

Lymph node analysis

The total number of analysed lymph nodes was 1,493, with an average of 10.1 per patient. Figure 1 shows the number of patients against the total number of analysed lymph nodes. As can be seen in this graph, less than 14 nodes were obtained in most cases. When the limit was fixed at 12 lymph nodes, 96 patients had less than 12 lymph nodes analysed, whereas in 52 cases more that 12 nodes were obtained. After dividing the patients into 3 subgroups depending on the number of analysed lymph nodes (< 7, 7-14, > 14 nodes), the biggest group was the one with 7-14 nodes, followed by the group with < 7 nodes and, finally, the one with more than 14 lymph nodes (Fig. 2). Lymph node analysis according to the tumoral invasion degree demonstrated interesting differences (Fig. 3). So, when the tumour was classified as pT3-T4, the group with 7-14 harvested lymph nodes was greater than the group who obtained < 7 lymph nodes. However, in the group with different tumoral invasion degree (pTis, pT1 y pT2) the biggest group of patients was the one with < 7 harvested lymph nodes.

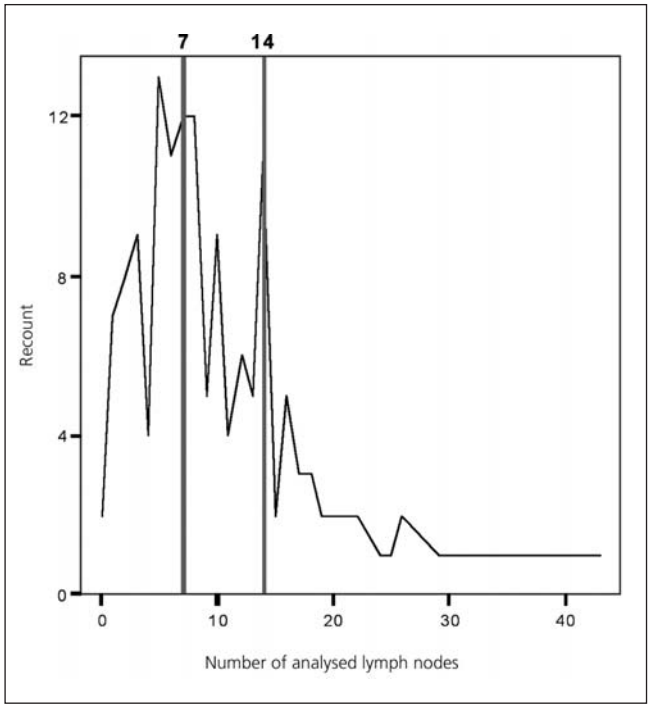

Fig. 1. Number of lymph nodes per patient.

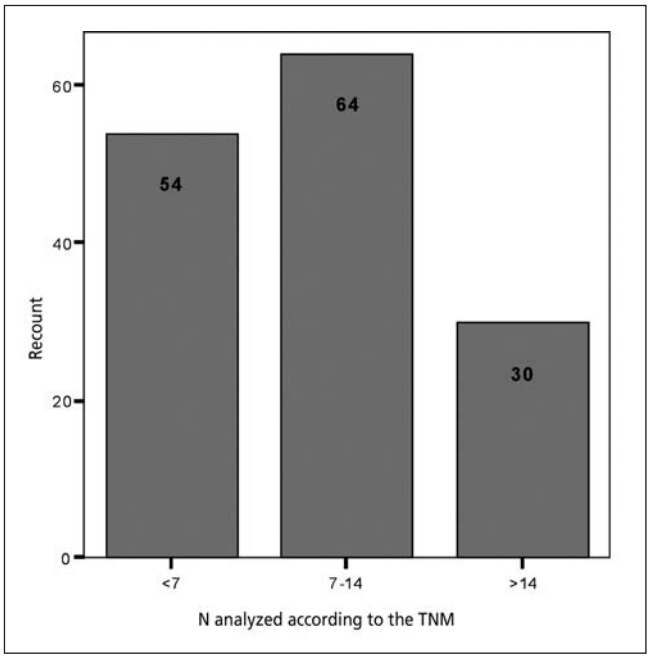

Fig. 2. Number of patients according to the number of analysed lymph nodes.

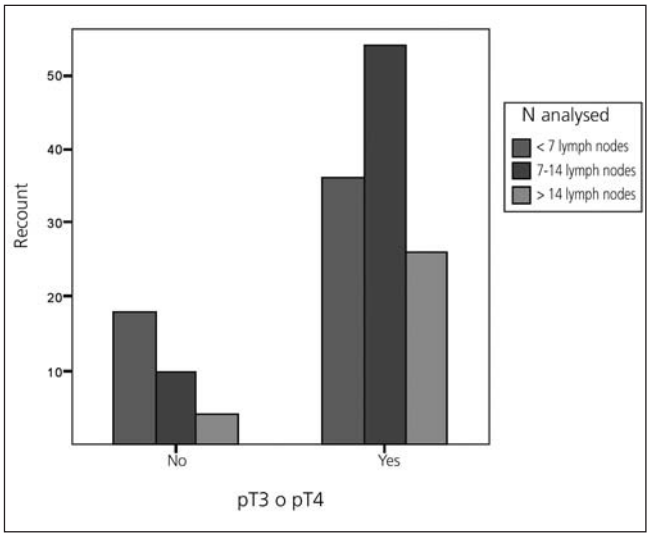

Fig. 3. Distribution of the analysed lymph nodes according to the tumoral invasion degree.

Survival analysis

The rate of 5-years survival for the global series was 81.4%. The majority of deaths occurred during the first 3 years, remaining practically constant from that point. Figure 4 shows the results obtained when the probability of survival according to the number of analysed lymph nodes is compared for each subgroup of patients created. In these terms, the rate of 5-years survival in patients with < 7 analysed lymph nodes was 63.0%, in the group between 7-14 was 80.6% and for the group with >14 this was 91.8%. These differences met the statistical significance ($p < 0.01$).

Figure 5 shows the data obtained when the descriptive curve CUSUM (cumulative sum) was used. In this graph, the U form shows a monotonic general tendency

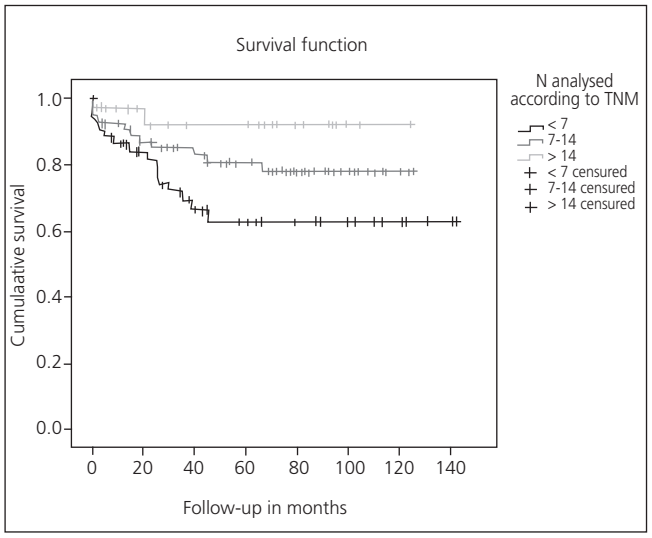

Fig. 4. Overall survival depending on the number of the analysed lymph nodes according to the recommendation of the TNM classification.

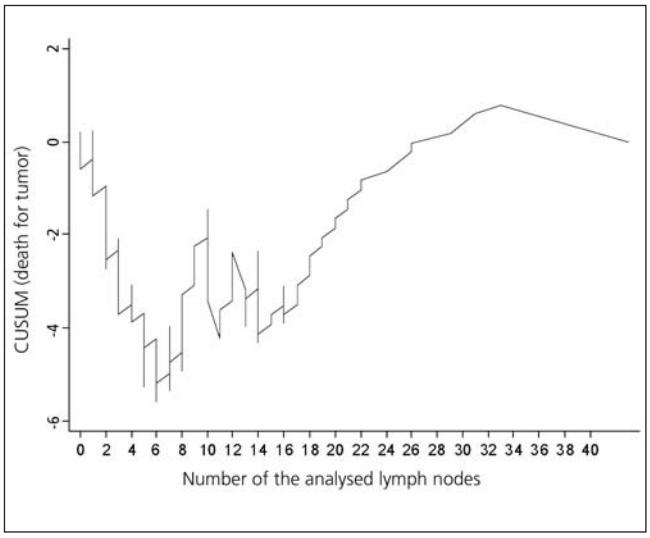

Fig. 5. CUSUM curve for the survival according to the number of the analysed lymph nodes per patient.

favourable to survival, the larger the number of analysed lymph nodes the greater of alive patients. In this figure, a general trend is observed that suggest a maintained increase on the survival for higher numbers of harvested nodes. A more detailed interpretation tracking this general trend can be done as follows: line 0 indicates stabilisation of the probability of dying due to the presence of a tumour. It can be seen that until 6 analysed lymph nodes, the probability of death due to the tumour is cumulative. Figure 4 then demonstrates that from 7 to 14 analysed lymph nodes there is some improvement and at least stabilisation, and further improvement from 16 nodes to around 26 lymph nodes. However, after 26, more analysed lymph nodes do not necessarily show a clear improvement in probability of survival (the graph stabilises or fluctuates around line 0). As stated above, the "U" shape of the graph clearly shows that the probability of survival increases when the number of analysed lymph nodes is increased.

Multivariate analysis

Table II shows the data obtained using a limit of 7-14 harvested lymph nodes. As can be observed in the top half of the table, as the number of analysed lymph nodes as the tumoral infiltration degree (pT) showed prognostic influence. Therefore, the pT3-4 subgroup presented more risk of mortality (positive B value, with a hazard ratio of 5.32) than the rest of patients. On the other hand, the number of analysed lymph nodes maintained its influence over prognosis in the sense that the patients with 7-14 lymph nodes obtained a hazard ratio of 0.44 and the ones > 14 a hazard ratio of 0.16 when compared to patients with less than 7 analysed lymph nodes. In other words, obtaining 7 or more lymph nodes has better prognostic value than obtaining less than 7 nodes. As can be seen in table II, all these differences were statistically sig-

Table II. Multivariate analysis. In the top half the data obtained using the limit 7-14 nodes is shown. In the lower side the data obtained using the limit of 8-25 nodes are shown

	B	*ET*	*Wald*	*gl*	*p value*	*Hazard ratio*
Limit 7-14 nodes						
pT3-4	1.672	0.738	5.134	1	0.023	5.325
N			8.498	2	0.014	
Name of variable N7-14	-0.824	0.386	4.553	1	0.033	0.438
Name of variable N > 14	-1.820	0.752	5.848	1	0.016	0.162
Limit 8-25 nodes						
pT3-4	1.563	0.736	4.518	1	0.034	4.775
N			5.645	2	0.059	
Name of variable N8-25	-0.890	0.386	5.329	1	0.021	0.411
Name of variable N > 25	-0.915	1.028	0.791	1	0.374	0.401

pT3-4 it is compared with pT1-2. As N7-14 as N > 14 are compared with N < 7. As N8-25 as N > 25 are compared with N ≤ 7. N is the variable considered as a whole.

nificant ($p < 0.05$). By using the values obtained with the CUSUM curve (8-25 nodes), similar results were obtained, in that the tumoral invasion degree (pT3-4) and the number of analysed lymph nodes according to the new subgroups met the statistical significance. In this case, the group with more than 25 nodes did not meet the significance because of the small number of cases (only 7 cases with more than 25 analysed lymph nodes).

In summary, in both multivariate analyses, the patients classified according to TNM as pT3-T4 had a worse prognosis than those included in the classification as T1-T2. In the same terms, it can be deduced that the collection of less than 7 or 8 nodes, respectively, also negatively affects the probability of survival of these patients.

DISCUSSION

The number of analysed lymph nodes remains one of the most interesting issues in colorectal surgery; and its impact on prognosis has been demonstrated many times, not only in patients with positive nodes but also in patients with negative nodes.

Several authors have proposed different values for the optimal number of nodes to be analysed in order to correctly staging patients with colon cancer (3,7,12-20). Acknowledging its importance, the majority of scientific associations have adhered to the recommendation of a minimum number of nodes to be analysed, agreeing in 12 as the required minimum (4,21,22). Nevertheless, the use of this recommendation as a quality criterion by centres or, even, surgeons has been recently questioned by Kukreja et al. (23). Possibly, as drastic brake points should be too global, and so globalisation hides shades that could be important.

The present study confirms the prognostic influence of the number of analysed lymph nodes in patients staged as pN0, as previously reported in the literature. The Kaplan Meier analysis showed that the prognosis in patients with > 14 lymph nodes analysed is better than that obtained with 7-14 nodes and this, at the same time, is better than the ones resulting from the analysis of < 7 nodes (91.8, 80.6 and 63%, respectively). Other authors have used this same mathematical method to reach the same conclusions, although the obtained data have been different (4,6,20,24,25). These possible divergences in mathematical methods were exactly the ones that led to the extension of our study about survival using the CUSUM curves. CUSUM curves are used in the control of production processes in many fields (medicine, learning curves, industry, etc.) and are useful in assessing results because their profile is very sensitive to subtle changes in data trends (either positives or negatives) that other methods may not be able to capture. Despite its simplicity and applicability, this kind of analysis has not been previously employed with the specific target of this study, so it is also interesting because of its originality. However, its use in welfare process control is more common each time in medical literature. Nevertheless, the fact that the lower limit in both approaches was similar (7 and 8 lymph nodes, respectively) the differences observed in the higher values (14 and 25 lymph nodes, respectively) corroborate our idea that recommendations can vary in different circumstances.

On the other hand, the number of analysed lymph nodes can vary due to many factors (e.g. depending on the anatomy and biology of the patient, the surgical technique, and on the anatomopathologic study) (4,5,24,26,27) so, any recommendation regarding the number of lymph nodes will unlikely be applicable to all possible situations. Furthermore, another drawback of recommending a minimum number of lymph nodes, lies in the wide group of patients in those the minimum recommended number were not reached (almost 2 out every 3 patients in our study obtained less than 12 nodes). Although these data agree with those in the majority of published studies (6,20,28) their prognostic and therapeutic importance cannot be ignored, as other authors have pointed out (4,5,7). For this reason, we considered that caution must be taken when recommending a minimum number of nodes to be analysed, because different mathematical analysis, the conditions and situations in those in whom the analysis is performed, can present enormous variations, between centres/groups of work and between patients.

Independent of all these discussions about there being a minimum number of lymph nodes to be analysed, what seems clear is that, as it has also been seen in our analysis, the larger the analysed number the better the prognosis, so it seems logical to surmise that as large a number as possible should be obtained (16,29-31).

We emphasize that only patients with colon cancer were included in our study. Thus patients with rectal cancer were excluded and, as a consequence, the results reported here are not necessarily applicable to this kind of patients. One of the limitations of the present study lies in its retrospective nature. Nevertheless, the differences observed are demonstrative enough of the importance of the number of lymph nodes analysed in patients with colon cancer. As has been discussed previously, another important limitation of this kind of analysis lies in the arbitrariness of establishing break points related to the number of lymph nodes to be studied.

Lastly, a limitation, or, better expressed, a particular and pertinent characteristic of the present study, is that it has been carried out in a single institution and the results obtained perhaps will not be comparable to those found in other centres, whose teams, (surgeons and anatomopathologists) will not obtain the same values as those found here. Nevertheless, unicentral studies have the advantage of reducing the number of possible differences in surgical technique and in anatomopathological studies (32).

In summary, based on the literature review and on our own experience, the number of analysed nodes in patients submitted to resectional surgery of colon cancer represents an independent prognostic factor when these are staged as pN0. Taking into account the large number of variables that can modify the lymph nodal analysis, it seems logical to conclude that the surgeon as the anatomopathologist should be motivated to obtain as many nodes as possible from each patient instead of fixing a number of nodes as a target in itself.

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