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Lymph Node Recovery from Colorectal Tumor Specimens: Recommendation for a Minimum Number of Lymph Nodes to Be Examined

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Abstract. Lymph node involvement is the most important prognostic factor for patients who have undergone radical surgery for colorectal carcinoma. An accurate examination of the surgical specimens is mandatory for the correct assessment of the lymph node status of the tumor. The risk of understaging is particularly high for patients with tumors classified as Dukes B (TNM stage II). The aim of this study was to determine if a specified minimum number of lymph nodes examined per surgical specimen could have any effect on the prognosis of patients who had undergone radical surgery for Dukes B colorectal cancer. Between 1988 and 1995 a total of 140 patients underwent radical resection of Dukes B colorectal cancer by the same surgeon (C.C.). The relation between clinicopathologic variables and survival was estimated using the Kaplan-Meier method. The Cox proportional hazard regression model was used to identify the variables that can independently influence survival. A median of 12 lymph nodes (range 3–38) was examined per tumor specimen. The 5-year survival rate of Dukes B patients who had had eight or fewer lymph nodes examined after surgery was 54.9%, whereas the survival rate for those who had had nine or more lymph nodes examined was 79.9% ($p < 0.001$). Cox regression analysis identified the number of lymph nodes as the only independent prognostic factor ($p = 0.01$). Seventy patients with one to four metastatic lymph nodes (Dukes C patients) who had been operated on during the same period were included in the survival analysis for comparison. The 5-year survival rate of the Dukes B patients with eight or fewer lymph nodes examined was similar to that of the 70 Dukes C patients (54.9% and 51.8%, respectively). Examination of eight or fewer lymph nodes in Dukes B colorectal patients may be considered a high risk factor for missing positive lymph nodes in the surgical specimens. Our results suggest that harvesting and examining a minimum of nine lymph nodes per surgical specimen may be sufficient for reliable staging of lymph node-negative tumors.

The presence or absence of lymph node metastasis is pivotal for predicting the clinical outcome of patients who have undergone radical surgery for colorectal carcinoma and for deciding whether postoperative adjuvant therapy should be recommended. The involvement of one or more lymph nodes dramatically decreases the 5-year survival when it is compared to the absence of any metastases in patients with tumors with the same depth of local invasion. An accurate assessment of the pathologic status of the tumor lymph nodes in the resected specimen is essential for reducing the risk of understaging.

The fat-clearance technique has been shown to increase the accuracy of lymph node harvest in surgical specimens when compared with manual dissection [1–4]. More recently, immunohistochemistry to cytokeratin [5–7] and genetic techniques, such as the polymerase chain reaction (PCR) for carcinoembryonic antigen (CEA) [8–10], have been proposed to identify small clusters of cancer cells ("micrometastases") within lymph nodes. What constitutes an adequate, reliable conventional examination must be defined to establish the real prognostic value of these time-consuming, labor-intensive methods and to permit meaningful comparisons between conventional histopathologic examinations and any of these other techniques. An important question that remains to be answered is the minimum number of lymph nodes that must be harvested with the surgical specimen and examined so that a tumor can be considered lymph node-negative. Many factors that can lead to difficulty in establishing the minimum number have been identified. Among them are the lack of a constant number of lymph nodes in the various parts of the large bowel, the extent of surgical lymphadenectomy, and the skill and energy of the pathologist.

The risk of understaging is particularly high in patients with tumors classified as Dukes B (i.e., tumors that extend beyond the bowel wall with negative lymph nodes). The cancer-related mortality rate of these patients may be explained in part by examining an insufficient number of lymph nodes, which could lead to overlooking one or more positive lymph nodes. The probability of failing to detect the presence of positive lymph nodes may also be increased as a consequence of the fact that most (61–77%) metastatic lymph nodes are less than 5 mm in diameter [6, 11]. The aims of this study were to evaluate the clinical outcome of patients who had undergone radical surgery for Dukes B colorectal cancer and to determine if a specified minimum number of examined

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lymph nodes per surgical specimen could have any effect on prognosis.

Materials and Methods

Between 1988 and 1995 a total of 301 consecutive patients underwent radical resection of colorectal cancer by the same surgeon (C.C.), at our operative unit. Altogether, 140 patients, 82 men (58.6%) and 58 women (41.4%) with a median age of 67 years (range 38–88 years) had tumors classified as Dukes B (TNM stage II), that is, tumors that extend beyond the large bowel wall and have no lymph node metastases. The clinical outcome of these patients was studied retrospectively. Cases with known distant metastases or incomplete clearance of the tumor were excluded to avoid any factors that could interfere with the survival analysis. In all cases, radical resection had included lymphadenectomy. For proximal colon tumors, lymphadenectomy was extended to the origin of the ilecolic, right colic, and middle colic arteries. For distal colon lesions and rectal tumors, it was extended to the origin of the inferior mesenteric artery and to the common iliac vessels along the preaortocaval space. Total mesorectal excision was performed in all patients with tumors of the middle and lower rectum; a distal clearance of at least 2 cm of healthy mucosa from the lower edge of the tumors was provided in all cases. Altogether, 39 tumors (27.8%) were located in the proximal colon (up to the splenic flexure), 47 (33.6%) in the distal colon (up to the end of the sigmoid colon), and 54 (38.6%) in the rectum.

Histopathology

All the surgical specimens were fixed in 10% formalin solution and routinely processed for paraffin embedding. The number of examined lymph nodes was ascertained by reference to the histopathology report of each patient. Lymph nodes were identified in the surgical specimens by sight and palpation. Routine histologic examination was performed using hematoxylin and eosin staining. Histologic processing of the specimens was the same for all patients. No special fat clearance or staining techniques were employed. Histopathologic examination was performed by one pathologist (A.P.) and reviewed by another (L.M.). The following histopathologic features were assessed for each tumor specimen: tumor type (classified as adenocarcinoma or mucinous carcinoma if more than 50% of the tumor volume was composed of mucin); tumor differentiation (classified as good, moderate, or poor, according to the World Health Organization criteria) [12]; and the character of the invasive margin (pushing or infiltrating, according to criteria defined by Jass et al. [13]).

Other Factors

The average duration of follow-up was 66.7 months (range 29–110 months). Patients were routinely followed up every 6 months for the first 2 years and then once a year. Clinical assessment, serum CEA measurement, abdominal ultrasonography, and chest radiography were always carried out. The last follow-up took place in December 1999. The survival rate of the 70 patients (41 men, 29 women; 13 tumors in the proximal colon, 21 in the distal colon, 36 in the rectum) who had been operated on during the same period for colorectal tumors and classified as having one to four metastatic lymph nodes (Dukes C tumors) was determined for comparison.

Table 1. Clinicopathologic features of 140 Dukes B patients.

Feature	No.
Age	
≤ 67 Years	72 (51.4%)
> 67 Years	68 (48.6%)
Gender	
Male	82 (58.6%)
Female	58 (41.4%)
Tumor site	
Proximal colon	39 (27.8%)
Distal colon	47 (33.6%)
Rectum	54 (38.6%)
Tumor type	
Adenocarcinoma	114 (81.4%)
Mucinous	26 (18.6%)
Tumor differentiation	
Well differentiated	17 (14.9%)
Moderately differentiated	93 (81.6%)
Poorly differentiated	4 (3.5%)
Character of invasive margin	
Pushing	36 (25.7%)
Infiltrating	104 (74.3%)
No. of lymph nodes examined	
≤ 8	55 (39.3%)
≥ 9	85 (60.7%)

Statistical Analysis

Associations between the number of examined lymph nodes and tumor location were evaluated using the Kruskall-Wallis test. Clinicopathologic features of the Dukes B and Dukes C patients were compared using the chi-square test. The relation between clinicopathologic variables and survival was estimated using the Kaplan-Meier method [14]. Differences among the survival curves were tested for statistical significance with the help of the log-rank test. The numbers of lymph nodes examined per specimen were recorded to determine if a specific cutoff could affect clinical outcome. The survival curves of the patients with the number of lymph nodes above and below each cutoff value were compared. The cutoff we considered to be the best indicator for separating the patients with regard to survival was that which showed the clearest rise in statistical significance (the highest chi-square). The Cox proportional hazard regression model [15] was used to identify the clinicopathologic factors that could independently influence survival. STATA Statistical Software release 6.0 (College Station, TX, USA) was used for all the analyses. A p value of < 0.05 was considered significant.

Results

A median number of 12 lymph nodes (range 3–38) was examined per tumor specimen. There were no significant differences regarding the number of lymph nodes identified and examined in tumors of the proximal colon, distal colon, and rectum (median values 13, 12, and 11.5, respectively). Clinical and pathologic data regarding the 140 Dukes B patients are summarized in Table 1. When all 140 patients were considered, the 5-year survival rate was 71.8% (Fig. 1). Tumor location and tumor type did not have any prognostic effect. The 5-year survival rate for the 72 patients (51.4%)

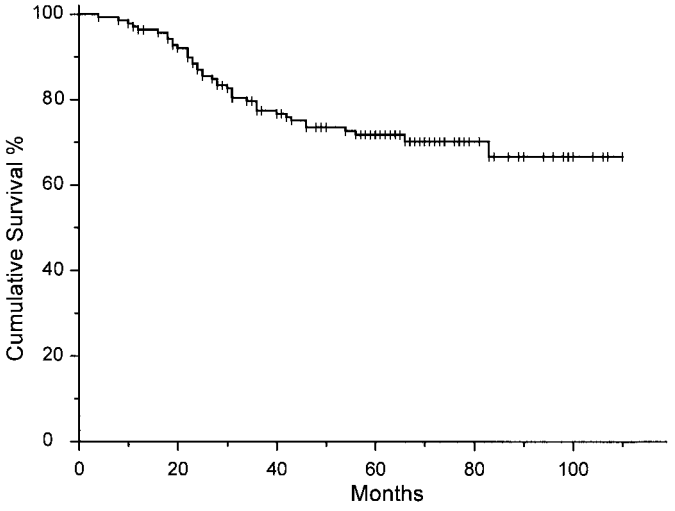

Fig. 1. Overall survival of 140 Dukes B patients.

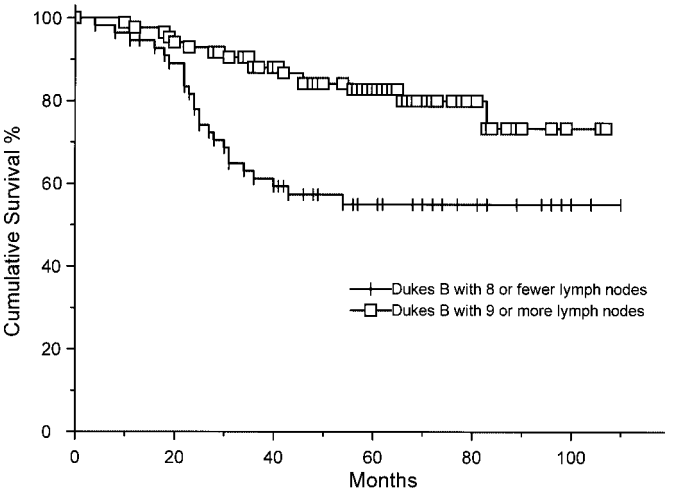

Fig. 2. Survival of Dukes B patients according to the number of lymph nodes examined.

who were ≤ 67 years was 81.6%, whereas the 5-year survival rate for the 68 patients (48.6%) who were > 67 years was 60.8% ($p = 0.01$). The 58 women (41.4%) had an 81.7% 5-year survival rate, whereas the 82 men (58.6%) had a 64.5% 5-year survival rate ($p = 0.01$). The 5-year survival rate of the 93 patients (81.6%) with moderately differentiated adenocarcinomas was 74.9%; it was 64.7% for the 17 patients (14.9%) with well differentiated adenocarcinomas and 0% for the 4 patients (3.5%) with poorly differentiated adenocarcinomas ($p = 0.02$). The character of the invasive margin of the tumor was also considered: the 5-year survival rate of the 36 patients (25.7%) with pushing tumors was 84.8%, whereas that of the 104 patients (74.3%) with infiltrating tumors was 68.8% ($p = 0.04$). The number of lymph nodes thought best to separate the Dukes B patients into subgroups with different survival rates was eight. The 5-year survival rate of the 55 patients (39.3%) with eight or fewer lymph nodes examined was 54.9%, whereas the survival rate of the 85 patients (60.7%) with nine or more lymph nodes examined was 79.9% ($p < 0.001$) (Fig. 2). Cox regression analysis identified the number of examined lymph nodes as the only significant and independent prognostic factor (Table 2).

Seventy patients with one to four metastatic lymph nodes (Dukes C patients) who had been operated on during the same period and by the same surgeon (C.C.) were included in the survival analysis for comparison. A median of 10 lymph nodes (range 2–38) was examined per tumor specimen in this group of patients. As shown in Table 3, the age groups of the patients, the male/female ratio, the tumor location, the tumor type, and the character of the invasive margin were comparable in the Dukes C patients and in the Dukes B patients with eight or fewer lymph nodes examined. However, well and moderately differentiated tumors were more frequent in the Dukes B patients than in the Dukes C patients. The 5-year survival rate of the Dukes B patients with eight or fewer examined lymph nodes was similar to that of the Dukes C patients with one to four metastatic lymph nodes (54.9% and 51.8%, respectively) (Fig. 3).

Table 2. Multivariate analysis (Cox regression model) of prognostic factors

Prognostic factor	Hazard ratio	95% Confidence interval	*p*
Age (> 67 vs. ≤ 67)	2.286	0.998–5.238	0.051
Gender (male vs. female)	2.244	0.971–5.185	0.058
Differentiation (poor vs. moderate and good)	2.228	0.703–7.057	0.173
Invasive margin (infiltrating vs. pushing)	2.858	0.943–8.660	0.063
No. of lymph nodes examined (≤ 8 vs. ≥ 9)	2.669	1.256–5.669	0.011

Discussion

Lymph node involvement is the most important prognostic factor after radical surgery for colorectal carcinoma [16–18]. It is currently the basis for including high risk patients in adjuvant therapeutic protocols.

An accurate examination of the surgical specimen is mandatory to assess the lymph node status of the tumor correctly. All the lymph nodes should be harvested from the surgical specimens and examined to establish that a tumor is lymph node-negative. At present, this goal is not practical. The aim of some recently reported studies has been the identification of the largest quantity of lymph nodes per specimen using various special techniques such as fat clearance [1–4]. This method seems to increase the number of harvested lymph nodes in the specimens significantly and thus the accuracy of tumor staging. However, because fat clearance is generally time-consuming and labor-intensive, it is often not even taken into consideration during normal histopathologic procedures. The fact that processing the specimens can take up to 9 or 10 days for dehydration and defatting is its principal drawback [11, 19].

The target of every pathologist should not be finding the maximum number of nodes in the specimen but, instead, examining a definite minimum number of lymph nodes. This number should significantly reduce the risk of overlooking one or more positive

Table 3. Comparison of clinicopathologic features of 70 Dukes C patients and 55 Dukes B patients with ≤ 8 examined lymph nodes.

Feature	Dukes B patients with ≤ 8 lymph nodes examined (no.)	Dukes C patients (no.)	*p*
Age			
≤ 67 Years	28 (51.0%)	36 (51.4%)	NS
> 67 Years	27 (49.0%)	34 (48.6%)	
Gender			
Male	34 (61.8%)	41 (58.6%)	NS
Female	21 (38.2%)	29 (41.4%)	
Tumor site			
Proximal colon	9 (16.4%)	13 (18.6%)	NS
Distal colon	19 (34.5%)	21 (30.0%)	
Rectum	27 (49.1%)	36 (51.4%)	
Tumor type			
Adenocarcinoma	47 (85.4%)	65 (92.8%)	NS
Mucinous	8 (14.6%)	5 (7.2%)	
Tumor differentiation			
Well differentiated	7 (14.9%)	0	0.005
Moderately differentiated	38 (80.9%)	62 (95.4%)	
Poorly differentiated	2 (4.2%)	3 (4.6%)	
Character of invasive margin			
Pushing	13 (23.6%)	11 (15.7%)	NS
Infiltrating	42 (76.4%)	59 (84.3%)	

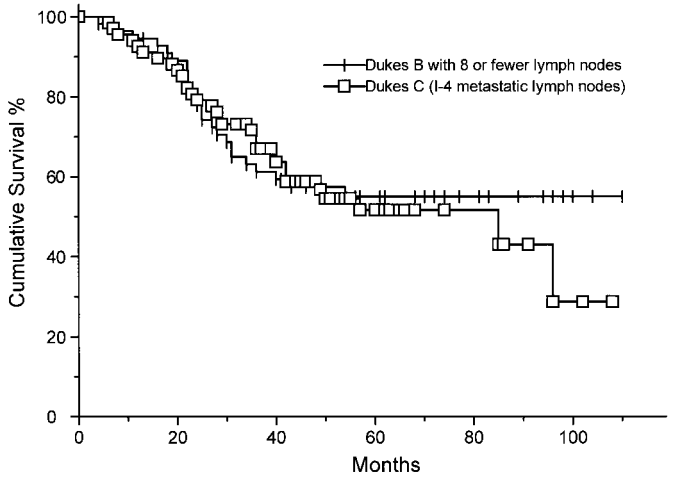

Fig. 3. Comparison of survival curves between Dukes B patients with ≤ 8 lymph nodes examined and Dukes C patients with 1–4 metastatic lymph nodes.

lymph nodes. Unfortunately, this number has not yet been definitively determined. There are objective difficulties that impede its assessment. The variability in the number of lymph nodes in the various regions of the large bowel, the extent of surgical lymphadenectomy, and the different statistical methods employed in different studies are among the problems. These variables most probably explain the lack of agreement in determining a universally valid minimum number of lymph nodes, above which there is no risk of understaging. Scott and Grace [20] showed that 13 lymph nodes had to be examined to identify 94% of their Dukes C tumors correctly. However, that number of lymph nodes cannot be considered the minimum necessary to establish that a tumor is lymph node-negative. In 1990 the Working Party Report to the World Congress of Gastroenterology in Sydney [21] recommended that a minimum of 12 lymph nodes should be recovered. Although the paper did not state how this number was determined, it was adopted by the American Joint Committee on Cancer and TNM Committee of the International Union against Cancer. Hernanz et al. [22], using binomial distribution, estimated that a minimum of six lymph nodes examined per specimen was necessary for correct Dukes B staging. Goldstein et al. [23] and more recently Maurel et al. [24] showed that the probability of correctly classifying a colorectal tumor as node-positive increased with the number of harvested lymph nodes. They also reported that this increase had a plateau. In their two series of patients, this plateau was reached when 17 lymph nodes in one and 18 in the other had been examined.

Even if all these studies were carried out correctly from a methodologic point of view, the absence of any statistical method that could determine the probability of metastases in the remaining unexamined lymph nodes in a surgical specimen remains the major problem. We can only indirectly evaluate this probability by analyzing the prognostic value of the number of lymph nodes examined in a subgroup of tumors with the highest risk of missed lymph nodes (i.e., tumors that extend beyond the bowel wall). If a poor prognosis can be demonstrated for Dukes B patients with an examined number of lymph nodes that is below a specified value and this prognostic factor is independent of others, substaging is most likely to be involved.

Caplin et al. [25] demonstrated that examination of six or fewer lymph nodes in Dukes B patients correlated with poorer survival when compared with examining seven or more. The mean number of lymph nodes examined in their Dukes B patients was 9.8. Moreover, they found a significant correlation between tumor site and the number of lymph nodes examined. There was a higher percentage of tumors with seven or more lymph nodes examined for right-sided tumors than for left-sided tumors. They explained this difference by considering the fact that right-sided resection specimens often contain larger amounts of mesentery. Nevertheless, this finding could even be explained by some surgeon- or pathologist-related factors. The low number of recovered lymph nodes in their left-sided and rectal tumor specimens could have been due to either inadequate extension of the mesorectal excision or to inadequate skill and energy on the part of the pathologist in locating lymph nodes by palpation. Perirectal lymph nodes are known to be smaller than those in other regions of the large bowel.

In our study, we harvested a median number of 12 lymph nodes. This number corresponds to the number that previous studies had reported when using manual dissection [1, 23, 26]. We did not find any significant differences in the number of lymph nodes examined in the proximal, distal, and rectal tumor specimens (median values: 13, 12, and 11.5, respectively). Moreover, all patients were operated on by the same, experienced surgeon (C.C.). This probably eliminates the variable of surgeon-related prognostic factors noted in previously published multicenter studies. Our results showed that examination of eight or fewer lymph nodes was related to a poorer prognosis when compared to examining nine or more lymph nodes. Cox regression analysis demonstrated that only the number of lymph nodes examined had a prognostic significance that was independent from that of the other clinicopathologic factors. The negative prognostic effect of examining eight or fewer lymph nodes in our Dukes B patients is most likely

explained by the presence of at least one unexamined metastatic lymph node in some of the surgical specimens. Therefore, some tumors with eight or fewer lymph nodes examined and reported as Dukes B should have actually been considered Dukes C tumors. This hypothesis seems to be supported by the fact that the survival rate of the Dukes B patients with eight or fewer lymph nodes examined is similar to that of the Dukes C patients who had been operated on during the same period and by the same surgeon (C.C.). However, we cannot exclude the presence of other factors that can negatively influence the survival of this subgroup of Dukes B patients, such as a diminished immune response, which can lead to smaller lymph nodes and thus to a lower number of lymph nodes identified.

Other questions must still be addressed. One of the most important ones regards the best way to identify the positive lymph nodes among those recovered. Triple sectioning of lymph nodes, immunohistochemistry, and genetic techniques, such as PCR, have all been suggested. These means can identify small clusters of cancer cells that may not be evidenced in lymph nodes when using hematoxylin and eosin staining [6, 7, 9, 10, 27]. Although many authors have reported some improvement in positive lymph node harvest and thus the upstaging of tumors their results have not always been confirmed [1, 28, 29]. The prognostic significance of lymph nodes that bear "micrometastases" is still controversial [5, 10, 30, 31], and the most accurate information provided by conventional histopathologic examination should always be evaluated before immunohistochemical and genetic techniques are used as the basis for clinical decisions. Recent studies have evaluated the feasibility and reliability of sentinel lymph node biopsy in colorectal cancer [32–34]. These preliminary results indicate that this procedure should not be utilized to predict lymph node status and the extent of lymphadenectomy as it is now used for melanoma and breast cancer surgery. However, sentinel lymph node mapping in colorectal cancer may provide more accurate tumor staging: the attention of the pathologist could be focused on specific blue-stained lymph nodes in the resected specimens, which are most likely to contain micrometastases [32].

Conclusions

Our results showed that the examination of eight or fewer lymph nodes in Dukes B colorectal patients is related to a poorer prognosis when compared to the examination of nine or more lymph nodes. Caution must be exercised when trying to define a "golden number" above which there is no risk of understaging. Our results suggest that the recovery and examination of at least nine lymph nodes per surgical specimen is sufficient to reach an acceptable level of accuracy when staging a tumor as being lymph node-negative. Only in those cases in which this number cannot be reached by manual dissection should special techniques such as fat clearance be used to improve the lymph node harvest. However, the total number of the lymph nodes examined should always be reported and used as an adjustment variable in survival studies and adjuvant therapy clinical trials.

Résumé. L'anvahissement ganglionnaire est le facteur pronostique le plus important chez les patients ayant eu une chirurgie radicale pour cancer colorectal. L'examen précis de la pièce d'exérèse est essentiel pour évaluer l'état ganglionnaire de la tumeur. Le risque de sous-classification est particulièrement élevé pour les patients ayant des tumeurs Dukes B (TNM stade II). Le but de cette étude a été de déterminer si un nombre minimal spécifique de ganglions lymphatiques examinés par pièce chirurgicale pourrait avoir une influence sur le pronostic des patients ayant eu une colectomie radicale pour un cancer colorectal Dukes B. Entre 1988 et 1995, 140 patients ont eu une résection radicale pour cancer colorectal Dukes B par le même chirurgien (C.C.). Le rapport entre les paramètres clinico-pathologiques et la survie a été évalué par la méthode de Kaplan-Meier. Un modèle de Cox (proportional hazard regression model) a été utilisé pour identifier les facteurs indépendants de survie. Une médiane de 12 ganglions lymphatiques (extrêmes 3–38) a été examinée par pièce de résection. La survie à 5 ans des patients Dukes B qui avaient huit ou moins ganglions lymphatiques a été de 54.9% alors que la survie des patients qui avaient neuf ganglions ou plus a été de 79.9% (p) < 0.001). L'analyse multivarié par la méthode de Cox a identifié comme seul facteur pronostique indépendant ($p = 0.01$) le nombre de ganglions. Soixante-dix patients ayant 1–4 ganglions lymphatiques métastatiques (patients Dukes C), qui ont aussi été opérés pendant la même période, ont été inclus dans l'analyse de survie à titre de comparaison. La survie à 5 ans des patients Dukes B avec huit ganglions ou moins était similaire à celle des 70 patients Dukes C (54.9% et 51.8%, respectivement). L'examen de huit ganglions lymphatiques ou moins peut être considérée comme un facteur de risque élevé pour ne pas détecter les ganglions lymphatiques positifs dans la pièce chirurgicale. Nos résultats suggèrent que de recueillir et d'examiner au moins neuf ganglions pari pièce chirurgicale pourrait suffire pour faire un staging fiable des tumeurs colorectales considérées à prior N-.

Resumen. La afectació de los ganglios linfáticos constituye uno de los factores pronósticos más importantes en el devenir de os pacientes sometidos a una resección colorrectal por cáncer. Por ello, el examen minucioso de la pieza operatoria es obligatorio, con objeto de valorar correctamente la afectación metastásica de los ganglios linfáticos. El riesgo de una estadificación deficitaria (mas baja) es grande, sobre todo en pacientes contumores clasificados como Dukes B (TNM estadio II). El objetivo del este trabajo es determinar si se precisa examinar un número mínimo específico de ganglios en cada espécimen operatorio, por si ello podria modificar el pronóstico de los pacientes sometidos a cirugía radical por un cáncer colorrectal tipo B de Dukes. Entre 1988 y 1995, 140 pacientes sufrieron una reseccion radical por un cáncer colorrectal (CC). La relación existente entre las variables anatomoclinicas y la superiviencia se valoró utilizando el método de Kaplain-Meier; la regresión de Cox para identificar las variables que puedan tener alguna ascendencia independiente sobre la supervivencia. Se examinaron un promedio de 12 ganglios linfáticos (rango 3–38) por cada pieza tumoral extirpada. La supervivencia a 5 años en pacientes con un Dukes B, en los que tras cirugía pudieron examinase 8 o menos ganglios linfáticos, fue del 54.9%, mientras que la supervivencia de aquellos pacientes en los que se pudieron examinar más de 9 ganglios linfáticos, fue del 79.9% ($p < 0.001$). El análisis de regresión de Cox demostró que el número de ganglios linfáticos es el único factor pronóstico independiente ($p = 0.01$). 70 pacientes con 1–4 metástasis ganglionares (Dukes C) que fueron intervenidos durante el mismo periodo de tiempo, se utilizaron con fines comparativos en el análisis de la supervivencia. La tasa de supervivencia en pacientes Dukes B, en los que 8 o menos ganglios linfáticos pudieron ser analizados, fue similar a la de los 70 pacientes con un Dukes C (54.9% y 51.8% respectivamente). El análisis histopatológico de 8 o menos ganglios linfáticos en el cáncer colorrectal Dukes B constituye yn gran factor de riesgo, pues propicia la no detección de ganglios linfáticos positivos (metastásicos) en la pieza quirúrgica. Nuestros resultados sugieren, que han de aislarse y analizarse un mínimo de 9 ganglios linfáticos en cada espécimen quirúrgico para poder establecer una estadificación fiable por lo que a la ausencia de adenopatías metastásicas se refiere.

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