COLORECTAL CARCINOMA- NUMBER OF EXAMINED LYMPH NODES

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Abstract: *The aim was to estimate the value of sampling limph nodes (LN) located far sidelong colorectal cancer specimens. We analyzed retrospectively surgical specimens from 345 colorectal cancers. The fat from the mezocolon and perirectal space was divided into 2 fractions: close to (less than 5 cm) and distant (more than 5 cm) from the tumor. Tumors were located in the cecum (n=61), ascending colon (n=29), transverse colon (n=31), descending colon (n=27), sigmoid colon (n=108), rectum (n=89). The median number of LN sampled was 17 in the both fractions (range 4-26), 12 (range = 0 - 21), in the close fraction and 3 (range 0 - 28), in the distant fraction. There were 169 pNo, 104 pN1 and 72 pN2 cases. The pN staging was accurate, except 10 based on the close fraction alone: of these, 6 were upstaged from pNo to pN1 and 4 from pN1 to pN2, were the distant fraction was considered. In the colon, we found that LN location is more important then LN number, because metastasis LN were present mostly in the peritumoral area. This suggests that LN should be initially recovered from the pericolic fat, close to the tumor. If there are less than 4 positive LN and less than 12 LN examined in total, additional LN should be retrieved from the distal fraction for potential upstaging. In the rectum, systematic sampling of close and distant LN is very important because rare cases, metastases are detected only in the distant LN, particularly at the patients who have undergone neoadjuvant radiotherapy.*

Cuvinte cheie: *cancer colorectal, noduli limfatici*

Rezumat: *Scopul acestui studiu a fost de a evalua valoarea determinării topografiei nodulilor limfatici, pe piesele de rezecţie colorectale. Am observat retrospectiv piesele de rezecţie obţinute de la 345 de pacienţi cu cancere colorectale. Grăsimea din mezocolon şi spaţiul perirectal a fost împărţită în două fracţiuni: aproape (mai puţin de 5 cm) şi departe (mai mult de 5 cm) faţă de tumoră. Tumorile au fost localizate la nivelul cecului (n=61), al colonului ascendent (n=29), transvers (n=31), descendent (n=27), sigmoidian (n=108) şi rect (n=89). Numărul mediu al ganglionilor limfatici extirpaţi şi cartografiaţi a fost de 17 în ambele fracţiuni (limite între 4 şi 26), 12 (limite între 0 şi 21) în fracţiunea apropiată şi 3 (limite între 0 şi 28) în fracţiunea de la distanţă. Au fost 169 de cazuri pNo, 10 pN1 şi 72 pN2. Stadializarea pN a fost adecvată cu excepţia celor 10 bazate singular pe fracţiunea închisă: din acestea, 6 au fost suprastadializate de la pN0 la pN1 şi 4 de la pN1 la pN2 atunci când s-a luat în considerare fracţiunea de la distanţă. În colon am găsit că topografia ganglionilor limfatici este mai importantă decât numărul lor, întrucât nodulii limfatici metastatici au fost prezenţi de regulă în aria peritumorală. Acest aspect sugerează că nodulii limfatici iniţial pot fi regăsiţi şi culeşi din grăsimea pericolică de lângă tumoră. În cazul în care din nodulii limfatici din grăsimea colică peritumorală, mai puţini de 4 sunt posibili şi mai puţini de 12 sunt în total examinaţi, trebuie aleşi alţi noduli limfatici din fracţiunea distală, pentru a evita riscul suprastadializării. În rect, examinarea sistematică a nodulilor limfatici apropiaţi şi la distanţă faţă de tumoră este mandatată, căci în cazuri rare metastaze au fost decelate doar în noduli limfatici situaţi la distanţă, în particular la pacienţii supuşi radioterapiei neoadjuvante.*

INTRODUCTION

The presence of LN metastases in colorectal cancer is currently the most important factor in determining the indication for adjuvant therapy, and is the most important factor in the estimation of the survival (1,6).The total number of LN examined from colorectal cancer surgical specimens is associated with improved survival, possibly because of increased accuracy in staging(2,6,7).

Cohen showed that the number of positive LN was related inversely to prognosis (pN1, 66% 5 years survival), with the optimal dichotomization between 1 to 3, 4 or more LN (pN2, 37% 5 years) (1,8).

Recovering a larger number of LN reduces the possibility of missing a metastatic LN. The total number of LN required for adequate staging has been a matter of controversy for a long time.

The results from different series suggest that a minimum of 6 to 17 LN should be investigated for reliable node-negative staging (2,4,5,9) and the American Joint Committee on Cancer (AJCC) and IUAC(International Union Against Cancer) recommend a minimal assessment of 12 LN for accurate staging (10,11).

The extend of intestinal resection for colorectal cancer is related to the vascularization of the colon and rectum, this

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leading surgeons to resect broader regions than considered strictly necessary from an oncologic point of view.

The contribution mode by LN located in adjacent tissues relatively distant from the colorectal cancer was not investigated and their relative roles have not been taken into account in nodal staging.

Systematic sampling of LN located in adjacent fat tissue relatively far from the colorectal cancer is both expensive and time consuming and few studies have addressed its potential impact on pN status (9).

To determine the value of systematically sampling distant LN in colorectal cancer surgical specimens in which the mezocolic and perirectal fat was divided into 2 fractions, one close to the tumor(less than 5 cm) and the other distant from the tumor (more than 5 cm from both sides of the tumor).

THE AIM OF THE STUDY

The aim was to estimate the value of sampling limph nodes (LN) located far sidelong colorectal cancer specimens.

MATERIAL AND METHODS

In this retrospectively study, we reviewed reports from the Pathology Department of Sibiu, from the I-st Surgical Clinic for all primary colorectal cancer surgical specimens hospitalized during 1992-2008. A total of 498 cases were reviewed and 153 cases were excluded from the study because: 10 cases of secondary excision for local tumor recurrence, 24 cases of multiple tumors, 119 cases in which proximal and distal fraction of the mezocolic and perirectal fat was not adequately individualized from the colorectal cancer during macroscopy.

In total 345 cases were eligible for this study.

Among the patients who have rectal cancer (n=89), 28% (n=25) had been treated with neoajuvant radiotherapy, the rest of the patients benefited from postoperative radiotherapy as it was recommended in our hospital during the period. The mezocolic fat was divided to harvest LN from the colon cancer surgical specimens, into fractions A and B.

Fraction A was close to the tumor (less than 5 cm from both sides of the tumor).Fraction B was distant from the tumor (more than 5 cm).In colorectal tumor the direct extension of tumor cells in the intestinal wall did not occur more than 5 cm far from the primary tumor (12-14).

To guarantee Ro resection, independently from LN and/or anatomic or vascular consideration, a 5 cm safety surgical border was considered to be adequate. To harvest the LN of the rectal cancer, the perirectal fat (fraction A) and the perisigmoidian fat (fraction B) were separated. The exactly same approach was used for LN dissection in fraction A and B. The 2 fractions were separated in 2 different bottles and LN sampling was made the next day. LN staging was defined according to the TNM classification as pNo (0 positive LN),pN1(1-3 positive LN),and pN2(4 or more positive)(10,11).Cut off values of 12 or 18 LN were chosen according to the minimum number (12) of LN recommended by the IUACC(11)and according to Goldstein (4,5) who recommended a higher number (more than 18)of LN.

RESULTS

The number of LN in colorectal cancer surgical specimens is stored in table 1.

Tumors were located as follows: cecum (n=61), ascending colon (n=29), transverse colon(n=31), descending colon (n=22), sigmoid and rectosigmoidian junction (n=108) and rectum (n=89).The mean number of LN recovered from location was as follows: cecum (n=18),ascending colon(n=20), transverse colon (n=19), descending colon(n=17), sigmoid and rectosigmoidian junction (n=17) and rectum (n=10).

Table no. 1. LN status and location of tumors

Tumor location	Number of cases	Mean total number of LN	Mean number of LN in the close fracture	Mean number of LN in the distal fracture
Cecum	61	18	13	4,6
Ascendent colon	29	20	14	5
Transverse colon	31	19	12	8
Descendent colon	27	17	11	4
Sigma, rectosigmoid junction	108	17	14	3,8
Rectum	89	10	12	3,9
Total	345			

The mean number of the total LN sampled was significantly higher in the ascending and transverse colon and significantly lower in the rectum (p=0.0001).

The mean number of LN sampled in both fractions was 18, the mean number of LN from the close and distant fractions, respectively, were 13 and 4, 9 which is statistically significant. The relationship between tumor infiltration (pT stage) and the LN status (pN stage) is shown in Table 2.

Table no. 2. Relationships between pT stage, pN stage and LN number.

	pN0 (№)	pN1 (№)	pN2 (№)	Total	№ mean LN
pT1 n%	10(91)	0(0)	1(9)	11	14
pT2 n%	26(62)	13(31)	3(7)	42	15
pT3 n%	102(50)	62(30)	41(20)	205	19
pT4 n%	31(36)	29(44)	27(31)	87	19
Total	169	18.2	19.5		
LN mean №	18	18,2	19,5		

There ware 11 pT1, 42 pT2, 20 pT3 and 87 pT4, 169 pNo, 10 pN1, 72 pN2.There was no significant difference in the LN mean number among pNo,pN1 and pN2 whereas the LN mean number was significantly bigger in pT3 and pT4 tumors (both 19) compared with pT1 and pT2 tumor (14 and 15 respectively, p=0,0031).

The percentages of LN found in fractions A and B were respectively 58% and 42 % for pT1, 70% and 30% for pT2, 74% and26% forpT3 and 73% and 27% for pT4 tumors.

The relationship between total LN count and the number of patients with positive LN is shown in table 3.

The number of patients with positive LN was significantly bigger (59%) when they had at least 12 LN sampled compared with patients from whom less than 12 LN were sampled (45 % p=0,127).

There was no significant difference between the group of patients with less than 12 LN sampled (46%) and the group with more than 12 LN but less than 18 LN sampled (44%)p=88,60.

When only LN from fraction A (close to the tumor) were considered the pN (pN0, pN1, pN2) would have been accurate in 97% of the colorectal cancer specimens. After examining LN from fractions A and B, 6 of these 10 cases were upstaged from pN0 to pN1 and 4 were upstaged from pN1 to pN2.

Table no. 3. Relationship between total LN count and LN metastasis

Total LN count	Number of patients	Number of patients with +nodes			Number of patients with + nodes			Number of upstaged cases in fraction B
		Total	pN1	pN2	In A	In B	In A+B	
<12	93	43 (46%)	24 (56%)	19 (44%)	35 80%	2(5%)	6 (15%)	2 to pN1 and 3 to pN2
≥16 <20	104	46 (44%)	33 (72%)	13(28%)	42(92%)	2(4%)	2(4%)	2 to pN1 and 1 to pN2
12-16	148	87(59%)	47 (54%)	40(46%)	72 (84%)	2(1%)	13(15%)	2 to pN1
Total	345	176	104	72	149	6	21	0

In 93 (27%) cases, less than 12 LN were sampled in the proximal and distal fractions of mesorectal and pericolic fat and in 160 (46%) cases, less than 12 LN were sampled in the proximal alone.

DISCUTION

In surgical resection in patients with colorectal cancer it is very important to remove on block the tumor with adequate proximal and distal bowel regions to include any submucosae lymphatic areas to which metastases might spread, including the regional mesenteric draining lymphatic system. (23).

Despite these guidelines, there is an evident amount of variability in the type of the resection performed for colorectal cancer, which could lead to variability in the number of LN removed.

The number of LN found in surgical specimens varies from patient to patient, depending on several factors, including tumor localization, the pathologic examination and the method used to harvest LN (2,3,6,15,16,17,18).

Canessa (15) showed that the mean number of LN found in colorectal cancer surgical specimens varies from 62 to 36 with manual dissection alone. Hence, the minimum recommended number of 12 LN cannot be guaranteed for every colorectal cancer specimen (19).

In many cases the average number LN examined per patient is often lower than 12, suggesting that a large number of patients with colorectal cancer are staged inadequately (3,17,20,21).

In some studies, up to 78% of the patients had less than the minimum required number of LN staged (3).These situation indicated the use of special techniques (acetonal clearing) to try to reach the minimum required LN(19).

An optimal number of LN to be examined in the colorectal cancer specimens probably does not exist (22),and some authors therefore recommended recovering as many LN as possible(22).

In our opinion, the problem is not so much the number of LN to be harvest as how to be detected those LN most susceptible to be metastatic.

In this study, the mean number of total LN sampled was significantly higher in the ascending and transverse colon and significantly lower in the rectum (p=0,0001) with previous studies (3,15). According to other studies (16,23) we found that the mean number of LN retrieved was significantly higher in pT3,pT4 tumors (17,5), compared with pT1 and pT2 tumors(14) (p=0,037) suggesting that there is a close relationship between the tumor stage and detectable LN.

Thorn (16) found a positive correlation between tumor diameter and LN count, a possible explanation for these is that larger tumors are more likely to ulcerate. The tumor necrosis, with ulcerative process, would induce reactive changes in proximal LN, with secondary enlargement of them, this facilitating the identification during the LN dissection. We also found that the median number of LN in the distant fraction was substantially lower than the median number of LN recovered from the close fraction and this result is consistent with other studies (9).We found that the proximal /distal LN ratio increases with tumor pT stage. This is in accordance with the postulate that the total number of LN recovered depends primarily on their distance from the tumor and that if no other causes of lymphadenomegaly (Chron disease, diverticulitis).The LN identifiable by palpation are most often located very close to the tumor and only a small number of such nodes are found at a distance of 3 cm or more from the edges (9).

In our series, the mean number of LN recovered from the distance fraction was 4,9 (range 0-19).

We found a positive correlation between the total LN count and the number of patients with positive LN: patients with 18 or more LN routinely had more potentially metastatic LN than patients with less than 18 LN (p= 0,127).

In contrast, there were no difference in LN metastases in cases with less then 18 LN sampled compared with who had less than 12 LN sampled. This result suggests that for minimum count 12 LN it is not enough and that more LN should be sampled.

In this study we separated LN located in the proximal and distal fractions of the tumor, based on previous findings, that direct the extension of the tumor cells in the intestinal wall and did not detect more than 5 cm apart from the primary tumor.(12,13,14).

In our study we found that 85% of the metastatic LN was located proximal to the tumor and the ratio of distribution (proximal or distal of the tumor) of metastatic LN did not change significantly among patients with more or less than 12 or 18LN sampled.

In a study of 2427 patients with pT3 colorectal cancer resulted in a single institution over 45 years, Goldstein et col.(4,5) showed that no minimum LN accurately or reliably stages all patients (17),and the predictive probability of identifying a single positive LN increased in a linear manner as the number of dissected LN increased.

In our study, in the close fraction alone, 46% of the cases had less than 12 LN sampled and when both proximal and distal fractions were examined that number was decreased to 27%.This finding suggest that by limiting the sampling area to less that 5 cm close to the tumor, we have more cases with a less than optimal number of dissected LN is expected.

The pathologic pN staging (pNo, pN1 and pN2) was accurate in all but 10 (2,9%) of the 345 colorectal cancers when the proximal fraction alone was examined. Of the 10 cases, 6 were upstaged from pNo to pN1 and 4 from pN1 to pN2 when LN from the distant fraction was included.

Our results confirm the results of a similar study from Cserni in which 100 colorectal cancers surgical specimens were analyzed prospectively and LN sampled were separated into 4 fractions, each a certain lateral distance from the tumor. In their study they found that all but one case of colorectal cancer were classified as pNo, pN1, pN2 based on the too closed fraction (at most 3 cm apart from the tumor).(9).Of the 6 cases upstaged to pN 1 it is worth noting that 5 of the cases occurred in the rectum and 3 of those patients pursued neoadjuvant radiotherapy. Neoadjuvant radiochemotherapy is associated with significantly fewer tumor positive LN (24).

Some studies have also shown that radiotheraphy

induces significant shrinking of LN within the radiotherapy field.(2,24),These finding suggest that LN must be retrieved from all of the fat resected with the rectal cancer surgical specimen to sample an adequate number of total LN and to detect LN metastases that may be missed by examining mesorectal fat alone. Arguing that LN size does not correlate with the presence of metastases (up to 78%) of nodes + are smaller than 5 mm (23), and that very small nodes can easily be missed during examination, (some authors 23,25) use several fat clearing methods, but those technique are also expansive and time consuming.

CONCLUSIONS

We conclude that peritumoral LN are the most susceptible to be metastatic in colon cancer. To decrease the cost effect and the time of colonic cancer surgical specimen management, LN should be retrieved only from the pericolic fat close (less than 5 cm) to the tumor. If there are less than 4 positive LN and less than 12 LN examined in total, additional LN should be retrieved from the distal fraction to detect additional metastases, which could result in an upstaged to pN2.

In our study in 66 % of cases with colonic cancer distal fraction dissection was unnecessary, when this recomandation was applied. It is worth noting that the pN2 stage changes the prognosis. In contrast in the rectal cancer cases specimens, systematic sampling of distant LN is mandatory because in rare cases metastases arise in distant LN only, particulary in patients who have had neoadjuvant therapy.

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