

THE IMPORTANCE OF ASSESSING POSITIVE LYMPH NODES FOR A PRECISE PROGNOSTIC OF COLORECTAL CANCER

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Abstract

Introduction. The cancerous invasion of regional lymph nodes is one of the most important prognosis factors in colorectal cancer. For a better prognosis, the lymph node metastasization can be correlated with the degree of tumour differentiation and the presence of vascular invasion.

Method. The study was conducted on 206 patients with colorectal cancer admitted and operated on between 1995-2009 in two surgical units: the 2nd Surgical Clinic of Cluj Napoca and the surgical department of the Blaj Municipal Hospital. The rate of resected and neoplasm invaded lymph nodes was determined by studying the operative protocols and histopathological bulletins.

Results. The patients with node positive CCR totalled 220, from whom 2640 lymph nodes were harvested. No lymph node metastases were detected in 32.17% of the patients; in 31.70% of the patients neoplasm invasion was found in 1-3 lymph nodes (pN1) and in 41.08% of the patients neoplasm invasion was found in more than 4 lymph nodes (pN2). The lymph node invasion rate (LNR), assessed by the ratio of resected to metastatic nodes, was small for the pN1 stage (0.08-0.20) and increased for the pN2 patients (0.30-0.80). The patients with low LNR showed significantly better survival rates than the patients with increased LNR.

Conclusions. The invasion of regional lymph nodes is one of the most important prognosis factors in CCR. LNR is a more valuable prognosis factor than the determination of the number of metastatic lymph nodes in the evaluation of long-term evolution of the operated on colorectal cancer.

Keywords: colorectal cancer, metastatic lymph nodes, lymph node neoplasm invasion rate.

IMPORTANȚA EVALUĂRII NODULILOR LIMFATICI POZITIVI PENTRU PRECIZAREA PROGNOSTICULUI PRECIS AL CANCERULUI COLORECTAL

Rezumat

Introducere. Invazia neoplazică în ganglionii limfatici regionali este unul din cei mai importanți factori de prognostic în cancerul colorectal. Pentru precizarea prognosticului, metastazarea ganglionară poate fi corelată și cu gradul de diferențiere tumorală și cu prezența invaziei vasculare.

Metode. Studiul a fost efectuat pe 296 pacienți cu cancer colorectal, internați și operați în perioada 1995-2009, în două unități chirurgicale: Clinica Chirurgie II din Cluj-Napoca și secția chirurgie a Spitalului Municipal Blaj. Tipul de intervenție chirurgicală practică și invazia ganglionară limfatică au fost determinate prin studierea protocoalelor operatorii și a buletinelor histopatologice.

Rezultate. 220 pacienți au avut metastază ganglionară și 2640 ganglioni limfatici au fost examinați. Metastazele ganglionare au fost detectate la 32.17% din

pacienți; în 31.70% invazia neoplazică a fost găsită în 1-3 limfoganglioni (pN1) și la 41.08% din pacienți invazia neoplazică a fost descoperită în mai mult de 4 limfoganglioni (pN2). Rata de invazie a limfoganglionilor, evaluată prin raportul de rezecabilitate a ganglionului metastazat, a fost mai mică pentru stadiul pN1 (0.08-0.2) și a crescut pentru pacienții aflați în stadiul pN2 (0.30-0.80). Pacienții cu rată de invazie limfoganglionară scăzută au avut o rată de supraviețuire semnificativ mai bună decât pacienții cu rată de invazie limfoganglionară crescută.

Concluzie. *Invazia ganglionilor limfatici regionali este unul dintre factorii de prognostic cei mai importanți în cancerul colorectal. Rata de invazie limfoganglionară este un factor de prognostic mult mai valoros, decât determinarea numărului de ganglioni limfatici afectați în evaluarea evoluției pe termen lung a cancerului colorectal operat.*

Cuvinte cheie: cancer colorectal, metastaze ganglionare, rata de invazie neoplazică a limfoganglionilor.

Introduction

The invasion of regional lymph nodes (LN) is one of the most important factors of the negative prognosis in colorectal cancer. For a better prediction, this factor can be correlated with the degree of tumour differentiation and the presence of lymphatic or vascular invasion. A study of Dukes and Bussey from 1958 conducted on over 2000 cases of rectal cancer finds a 5-year survival rate of only 32% for the patients with positive ganglions, compared to 83% for those with microscopically negative ganglions. The absence of ganglionic invasion at the correctly resected and microscopically examined specimens can predict a 5-year survival rate of 90% [1,2].

The topography of invaded lymph nodes also plays a prognosticating role. The attachment of central lymphatic ganglions (apical ganglions) worsens the prognosis, anticipating the remote dissemination of tumour cells. Thus, the implication of central ganglions leads to the decrease of the survival rate to 13%.

The number of metastasized lymph nodes is very important for the prognosis of the survival rate and tumour recurrence. In the current TNM classification of colorectal cancer according to AJCC, the histopathological presence of tumour metastases in 1-3 regional lymph nodes (N_1) falls into a separate category, compared to the invasion of over 4 lymph nodes (N_2), due to the significant differences in the survival rates between the two situations, independent of the degree of invasion in the intestinal wall. It has been established that for an accurate evaluation of the presence or absence of ganglionic metastases it is necessary to microscopically examine minimum 12 lymph nodes. After analysing over 50,000 cases of patients diagnosed between 1987 and 1993 with stage III colon cancer (with presence of metastases in the lymph nodes), Greene observed that the 5-year survival rate for the patients who had 1-3 invaded lymph nodes and the tumour extended in the wall up to its own musculature ($T_{1-2}N_1$) was 59.8%, whereas it was only

27.3% for those who had lymph nodes, irrespective of the tumour extension in the wall [3,4,5].

Materials and methods

A retrospective non-randomized study was conducted on 296 patients with colorectal cancer admitted and operated on during 1995-2009 in two surgical units: the 2nd Surgical Clinic of Cluj Napoca and the surgical department of the Blaj Municipal Hospital. The objective of the research was the evaluation of the lymph node dissemination of colorectal cancer. We studied the surgical protocols in order to determine the size and location of the tumours and the number and topographical situation of the harvested lymph nodes. We also studied the histopathological bulletins in order to evaluate the number of neoplasm invaded lymph nodes in comparison with the unaffected ones.

The lymph node rate determined by the ratio of metastatic to resected lymph nodes shows an obvious prognosticating significance for the node positive colorectal cancers. The number of resected and metastatic ganglions depends on the patient, surgeon and pathologist.

Results

The total number of resected ganglions was 2640 for an average of 12 ganglions harvested from each patient. The patients with lymph node positive colorectal neoplasm totalled 220, 167 of whom from the 2nd Surgical Clinic of Cluj Napoca and 53 from the Blaj Municipal Hospital.

The examined lymph nodes did not present cancerous metastases in 24.09% of the patients with colorectal cancer (CCR) from the 2nd Surgical Clinic of Cluj Napoca and 30.26% of those from the Blaj lot. In 34.55% of the patients from the Cluj Napoca Clinic and 28.95% of those from Blaj the neoplasm invasion was present in 1-3 regional lymph nodes, a situation which appears in stage C₁, according to Astler and Collier's classification, TNM stage III respectively. 41.37% of the patients who underwent surgical treatment in Cluj and 40.79% of those who underwent surgical treatment in Blaj showed more

Table nr. I. Lymph node metastases (pN), depending on the tumour extension (T) in colorectal cancer at the patients from the 2nd Surgical Clinic of Cluj Napoca.

Tumour size (T)	Degree of lymph node invasion (N)				Total
	pN ₀	pN ₁	pN ₂	pN ₃	
pT ₁	9	-	-	-	4 (1.82%)
pT ₂	31	5	-	-	36 (16.36%)
pT ₃	13	51	26	20	115 (52.27%)
pT ₄	5	20	28	17	65 (29.55%)
TOTAL	53 (24.09%)	76 (34.55%)	54 (24.55%)	37 (16.82%)	220 (100%)

Table nr. II. Lymph node metastases (pN), depending on the tumour extension (T) in colorectal cancer at the patients from the Blaj Municipal Hospital.

Tumour size (T)	Degree of lymph node invasion (N)				Total
	pN ₀	pN ₁	pN ₂	pN ₃	
pT ₁	2	-	-	-	2 (2.63%)
pT ₂	15	3	-	-	18 (23.68%)
pT ₃	6	12	10	7	35 (46.05%)
pT ₄	-	7	9	5	21 (27.63%)
TOTAL	23 (30.26%)	22 (28.95%)	19 (25%)	12 (15.79%)	76 (100%)

than four invaded lymph nodes, falling into the Astler – Collier stage C₂. Within this last category the attachment of regional lymph nodes was accompanied by the invasion of the apical nodes in 27.87% of the cases and by remote (vascular) metastases in 15.57% of the cases (Astler – Collier stage D or TNM IV).

The average number of harvested lymphatic ganglions was max. 10 till the year 2000; afterwards the average number rose to 12 (12.3 ± 7.4). The metastases in the lymph nodes were associated with invasive and poorly histologically differentiated tumours. The tumours located at the level of the proximal colon were sizeable and invasive, having a significantly greater number of harvested lymph nodes. The number of invaded lymph nodes did not grow significantly subsequent to the greater number of harvested ganglions, but it was observed that the patients with less than 12 resected ganglions did not show a significantly smaller number of metastatic ganglions than the patients with 12 or more excised ganglions.

The lymph node rate (LNR), obtained through the division of the number of metastatic lymph nodes by the number of resected lymph nodes, has a great prognosticating significance in CCR. When we refer to the pN₁ patients, the rate value is small and varies between 0.08-0.20; in the case of the pN₂ patients this rate has greater values, between 0.30-0.80.

The patients with low LNR had significantly better survival rates than the patients with increased LNR. The strong prognosticating significance of the LNR holds true irrespective of the number of resected ganglions. The LNR classification showed discrepancies of the survival rate in both pN and TNM staging, correlated with the phenomenon of migration between stages. The possibility

of migration between stages in the pN staging system can be influenced by the 43% of the 5-year survival for the pN₁ group with increased LNR, a result which was significantly less favourable than the 67% for the pN₂ group with low LNR. The patients falling into the same stage (IIIA, IIIB, IIIC) showed significant differences regarding the long-term survival rates when they were grouped according to the LNR classification. The patients from a less favourable stage and low LNR behaved better than the patients from a more favourable stage and increased LNR. The LNR can identify more homogenous groups, thus reducing the phenomenon of migration between stages.

Discussions

The identification of lymph nodes is essential in colorectal cancers, because the patients with metastatic lymphatic ganglions obtain poor long-term results and require adjuvant chemotherapy. Although the current TNM staging system divides the CCR patients into patients with negative and positive lymph nodes irrespective of the number of resected ganglions, it is important to obtain at least 7-14 lymphatic ganglions in radical colorectal resections. There is no general consensus regarding the ideal minimum number of ganglions that must be resected, but the recommendation to remove as many ganglions as possible remains [6,7]. Recent observations show that the number of resected ganglions is an important factor correlated with the evolution of the CCR patients who undergo a potentially curative surgical treatment. The improvement of the survival rates can benefit from the growth of the number of harvested ganglions. Being the ratio of the number of metastatic to harvested ganglions, LNR can be a good indicator of postoperative evolution and

Table nr. III. The value of the lymph node rate in CCR.

Lymph node tumoural stage	No. of resected LN	No. of invaded LNT	Lymph node rate
pN ₁	~ 12	1 – 3	0.08 – 0.20
pN ₂	~ 12	4 – 10 (>3)	0.30 – 0.80

results. In order to identify as many lymphatic ganglions as possible a perfect surgical and histological technique is necessary [8,9].

The probability for a LN to be positive depends on the tumour biology and the tumour – host interaction, not on the number of resected ganglions. The patients with less than 12 ganglions showed a significantly smaller number of positive ganglions, suggesting that an adequate extirpation of lymphatic ganglions is mandatory for a correct staging of the patients. According to recent reports, it is recommended to harvest at least 14 LN and 3 positive ganglions for a proper staging of colon cancers.

LNR is a powerful prognosis factor for long-term evolution. The surviving patients showed significantly lower LNRs than the deceased ones and in comparison with the number of metastatic and harvested ganglions. The tests have selected LNR together with venous invasion as being the best model of prognosticating long-term evolution and sole variable correlated with disease-free survival rate. [10].

Conclusions

1. The invasion of regional lymph nodes is one of the most important prognosis factors in colorectal cancer.
2. Recent observations show that the number of resected lymphatic ganglions is an important factor for the evolution of the patients operated on for CCR.
3. LNR is a better prognosis factor because it does not depend on the number of resected ganglions.
4. LNR helps identify the high risk groups that can be treated with adjuvant chemotherapy and have a more accurate postoperative follow-up.

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