

## SIGNIFICANCE OF HISTOPATHOLOGIC CRITERIA IN SURVIVAL RATES OF PATIENTS WITH COLORECTAL CANCER: MULTIVARIATE ANALYSIS

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### Summary

**Background:** Risk factors predicting the presence of lymph node metastasis have not been fully investigated. To determine the criteria for local excision of colorectal cancer, histopathologic factors independently predicting the lymph node metastasis were investigated. **Methods:** We performed a retrospective histological study on 301 patients who underwent resection of colorectal cancer and dissection of regional lymph nodes between January 1, 2000 to December 31, 2007. **Results:** In multivariate analysis when we compared patients who have been less than 3 node metastases (n=165) with patients who have been 4 and more than node metastases (n=136) were characterized by tumor larger than 60 mm (28% vs. 0%), serosal invasion (46% vs. 19%), venous invasion (33% vs. 21%), histologic grade II -III (62% vs. 28%). Multivariate analysis showed that factors independently associated with lymph node metastasis were serosal invasion, venous invasion and histologic grade. When these three risk factors were negative, lymph node metastasis was rare (5%). When one, two or three factors were negative, lymph node metastasis was 38%, 66% i 85% respectively. **Conclusions:** Factors independently associated with lymph node metastasis are serosal invasion, venous invasion and histologic grade. When these three factors are favorable, local treatment of colorectal cancer does not require additional lymph node dissection.

KEYWORDS: *multivariate analysis, histopathologic criteria*

### ZNAČAJ HISTOPATOLOŠKIH KRITERIJA U PREŽIVLJAVANJU PACIJENATA S KOLOREKTALNIM KARCINOMOM: MULTIVARIJANTNA ANALIZA

#### Sažetak

**Uvod:** Faktori predviđanja prisutnosti metastaza u limfnim čvorovima do danas nisu u potpunosti ispitani. Histopatološki faktori nezavisno predviđaju prisutnost metastaza u limfne čvorove i na taj način određuju kirurgiju kolorektalnog karcinoma. **Pacijenti i metode:** U retrospektivnoj studiji analizirali smo tri stotine jednog (301) pacijenta kojima je urađena resekcija kolorektalnog karcinoma i disekcija regionalnih limfnih čvorova u razdoblju između 1. siječnja 2000. do 31. prosinca 2007. **Rezultati:** U multivarijantnoj analizi usporedili smo pacijente koji su imali metastaze u manje od 3 limfna čvora (n=165) u odnosu na pacijente koji su imali metastaze u 4 i više od 4 limfna čvora (n=136), tumore veće od 60 mm (28% vs. 0%), zahvaćenost seroze (46% vs. 19%), vensku invaziju (33% vs. 21%), histološki gradus II -III (62% vs. 28%). Multivarijantnom analizom utvrdili smo da su nezavisni faktori udruženi s metastazama u limfnim čvorovima: invazija seroze, venska invazija i histološki gradus tumora. Kad su ovi faktori bili negativni, metastaze u limfne čvorove bile su prisutne u 5% bolesnika. Kada su jedan, dva ili tri faktora bili pozitivni, učestalost metastaza u limfne čvorove bila je 38%, 66% i 85%. **Zaključci:** Nezavisni faktori udruženi s metastatskim limfnim čvorovima su zahvaćenost seroze, venska invazija, histološki gradus. Kad su ovi faktori udruženi u kirurgiji kolorektalnog karcinoma, nije potrebno poduzeti disekciju limfnih čvorova.

KLJUČNE RIJEČI: *multivarijantna analiza, histopatološki kriterij*

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## INTRODUCTION

In order to achieve the most precise prediction of a lifetime and/or treatment of a patient in oncology, physicians use prognostic and prediction factors. Prognostic factors are used to determine basic prognosis at a time of neoplasm diagnosis, which predict biological potential of the malignant disease. There are several prognostic tools to determine evolution of colorectal carcinomas. They can be classified into: clinico-surgical, histopathologic and laboratory immunologic (1) carcinomas.

The most common type of colorectal carcinomas is adenocarcinoma. This is an immature, malignant tumor of the glandular epithelium.

In case of almost all human tumors, tumor size is important for its further lymphogenic and/or hematogenic dissemination. Mc Sherry et al. have demonstrated that of 908 patients with colorectal carcinoma, patients that lived for 5 years had tumor diameter up to 49mm whereas patients that died had tumors larger than 50mm (2).

Tumor grading is based on certain histologic criteria, in an attempt to assess an aggressive potential of tumor itself. Classical grading system comprises determination of tumor type, level of differentiation, cytologic atypia, mitotic activity and host response. Broders in 1928, was the first who made an attempt to rank carcinomas of the rectum. He divided the tumors based on the number of differentiated cells, in agreement with his hypothesis that the level of differentiation is correlated with tumor invasion (3).

The most important prognostic factor for colorectal carcinomas is the presence or absence of metastases in the lymph nodes. The number of lymph nodes with metastases decreases the chance for 5-year survival. Spreading of metastases through lymph in case of colorectal carcinomas is evaluated by: estimation of the position of metastases in lymph nodes during the surgical resection, detection of the position of recurrence after surgery, investigation of autopsy reports of patients that died of inoperable carcinomas and histopathologic verification of colon and/or rectum specimens (4, 5).

Brown and Warren investigated autopsy material of 170 cases of colorectal carcinomas and found that the frequency of venous invasion and

visceral metastases increased in parallel with the rise of the histologic grade (6, 7).

## PATIENTS AND METHODS

Patients included in this study were treated at the General Hospital "Sveti Vračevi" in Bijeljina, Bosnia and Herzegovina, in the period between January 1, 2000 and December 31, 2007. In total, data from 301 patients with carcinomas in the left colon and rectum were analyzed. General, surgical, histologic and immunologic parameters were followed, both prospectively and retrospectively.

### Histologic parameters

Monitored macropathologic features were: tumor size, tumor type as determined by macroscopic evaluation, circumferential margin involvement, depth of mural spread, concomitant tumors, number of collected regional and distant lymph nodes.

Monitored histologic features were: histologic tumor grade, nuclear grade, percent of mucinous cells, invasion depth (Dukes, Astler-Coller), necrosis, fibrosis and inflammation, extramural vascular invasion, peritumor changes (dysplasia, adenomas), metastases in the lymph nodes and stimulation type (number, grade, regional and distant lymph nodes), metastases in parenchymal organs (most often in the liver).

Statistical analyses were performed with respect to the nature and value of the results. SPSS software package was used for analyses.

## RESULTS

Patients who had less than 3 node metastases (n=165) were compared with those who had 4 and more node metastases (n=136).

The patients with colorectal carcinoma who had metastases in 4 and more lymph nodes had much lower survival rate than those who had metastases in up to 3 lymph nodes, and this was highly statistically significant (Test: Log Rank,  $p < 0.01$ ; Figure 1).

There were 270 patients (90%) who had tumors with the transversal diameter smaller than 60 mm whereas 31 patients (10%) had tumors with

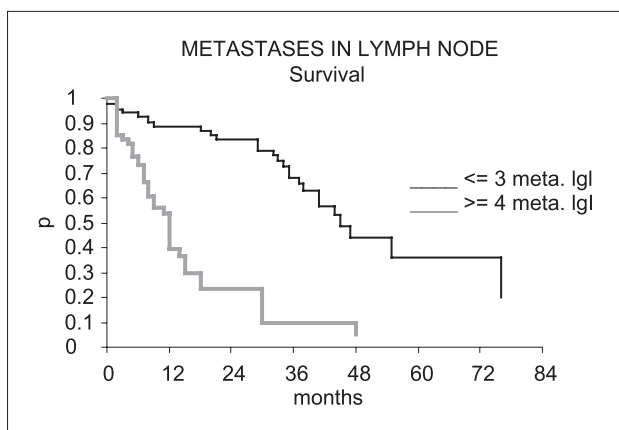


Figure 1. Survival rate of patients with  $\leq 3$  metastases in lymph nodes in relation to the patients with  $\geq 4$  metastases in lymph nodes.

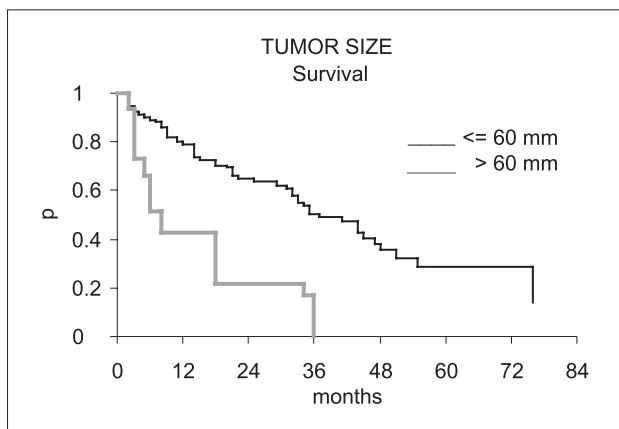


Figure 2. Survival rate of the patients with tumors  $\leq 60$  mm in relation to the patients with tumors  $> 60$  mm.

transversal diameter bigger than 60 mm. The patients with transversal diameter bigger than 60 mm had lower survival rate as compared to the patients whose transversal tumor diameter was smaller than 60 mm, and this difference was highly statistically significant (Test: Log Rank,  $p < 0.01$ ; Figure 2 and Photographs 1 and 2).

There were 39 patients (13%) who had a histologic tumor grade I, 241 patients (80%) had a histologic tumor grade II and 21 patients (7%) had a histologic tumor grade III. The patients with the histologic tumor grade III had considerably lower survival rate when compared to the patients with the histologic grade II, and this difference was statistically significant (Test: Log Rank,  $p < 0.01$ ; Figure 3).

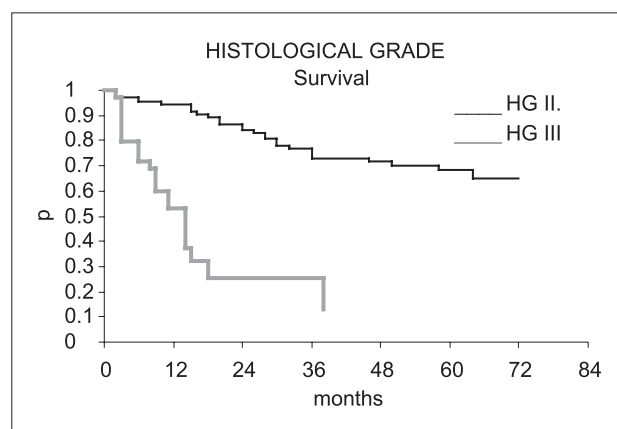
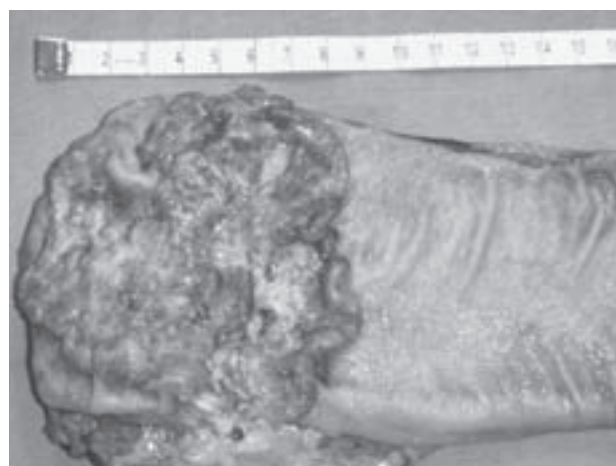


Figure 3. Survival rate of patients with histologic tumor grade II in relation to the patients with histologic tumor grade III



Photograph 1. Tumor smaller than 60 mm



Photograph 2. Tumor larger than 60 mm

Multivariate analysis was applied to compare the patients who had metastases in more than 4 lymph nodes with the patients who had metastases in less than 3 lymph nodes and who had tumors bigger than 60 mm (28% vs. 0%), serosal involvement (46% vs. 19%), venous status (33% vs. 21%), histologic grade II-III (62% vs. 28%). Using multivariate analysis, we found that independent factors associated with lymph nodes metastases were serosal involvement, venous invasion, and histologic grade. When these three factors were negative, lymph node metastases were present in 5% of patients. When one, two or three factors were positive the occurrence of lymph node metastases was 38%, 66% and 85%, respectively.

## DISCUSSION

Nowadays, there is enough to support that the quality of surgical intervention has direct implications on the time of survival of patients with colorectal carcinoma. In rectal carcinoma, a significant improvement was achieved by introducing a total excision of the mesorectum. It resulted in lower percentage of local recurrent tumors and better 5-year survival. However, it has been found that the skills of a surgeon in performing this surgery may influence the number of local recurrent tumors (20-30%), after potentially curative resections. If this surgery is performed by experienced surgeons, the percentage of local recurrences can be reduced to less than 3%. By further perfecting the total mesorectum excision procedure, an improvement in the five-year survival rate was achieved in over 60%.

When the size of a tumor was analyzed in all patients, 90% of tumors were smaller than 60 mm while about 10% of patients had tumors bigger than 60 mm. It must not be forgotten that often after the pathoanatomical and histologic examination of the surgical specimen, it becomes evident that the tumor is smaller than it appeared to be during the operation, because of the inflammatory area between the tumor and the surrounding organs. In our clinical study, the patients with the transversal diameter bigger than 60 mm had a highly statistically significant low survival rate in relation to the patients with transversal tumor diameter under 60 mm ( $p < 0.01$ ). MC Sherry et al, showed 908 patients with carcinoma of colon and

rectum: the tumor diameter in patients who lived 5 years was 5.9 cm, those who died had tumors over 6.1 cm (8).

The number of positive lymph nodes is still the most reliable determinant of survival rate, which is a ground to differentiate pN1 status (up to three positive lymph nodes) from pN2 status (4 and more positive lymph nodes). The probability of five-year survival in patients is inversely proportional to the number of lymph node metastases. In this clinical study, the patients with the carcinoma of colon and rectum, who had 4 and more lymph node metastases had statistically significant lower rate of survival than those patients who had up to 3 lymph node metastases ( $p < 0.01$ ). The five-year survival in patients with malignant obstruction of the colon and rectum who had metastases in less than 3 lymph nodes was 42.74%. The patients who had 4 and more lymph node metastases had 3.99 % five-year survival rate. In the studies by Kim et al, it is reported that the five-year survival rate of the patients who had 4 lymph nodes infiltrated with malignant cells was 60%, while in patients with 5 and more infiltrated lymph nodes the five-year survival rate was 25%. The five-year survival rate was only 10% in patients with 6 and more lymph node metastases, and 0% if there were more than 16 lymph node metastases (9).

Disease stage, weather determined by Dukes, by TNM or some other classification, represents a combination of two or more separate factors, firstly tumor infiltration depth (pT) and a number of potentially invaded lymph nodes (pN), which is supplemented by investigation of distant metastases (pM). The invasion depth is regarded as prognostic feature independent of metastases in lymph nodes. Analysis of the five-year survival rate showed that there is a highly statistically significant difference in survival of patients with serosal tumor involvement when compared to the patients who had no serosal involvement. Indeed, the degree of mural penetration has been accepted as a significant prognostic factor for two reasons. Firstly, lymphogenic metastases are rarely found prior to the primary tumor penetration of the bowel wall. Secondly, deep penetration through bowel wall, serosal involvement and metastases in lymph nodes are an adverse prognostic sign (10).

The degree of histologic malignity or the degree of tumor differentiation is a very important and independent prognostic factor. The patients who had histologic tumor grade III had a significantly lower survival rate in relation to the patients with the histologic tumor grade II ( $p < 0.01$ ). Patients with the histologic grade III had a five-year survival rate of 23.7% versus 32.8% of the patients with histologic grade II. Among patients with well-differentiated carcinomas who had been operated at the Surgical Clinic in Erlangen, Germany, 24.3% had metastases. The patients with metastases in lymph nodes and poorly differentiated carcinoma had significantly less favorable prognosis in relation to the patients who had no metastases in lymph nodes and well-differentiated carcinoma (11). The patients with histologic grade III had a significantly earlier tumor recurrence than the patients with histologic grade II.

## CONCLUSION

There are numerous parameters with known and probable prognostic importance in tumor analysis and clinical value of each new factor is evaluated by comparison with known factors. Simultaneous assessment of more prognostic factors is known as multivariate analysis in contrast to univariate analysis where only one factor is sufficient for prognosis.

In this clinical study, both univariate and multivariate analyses were applied. The prognostic factors in multivariate analysis were divided into three groups, namely three models: clinico-surgical, histologic and laboratory immunological.

In multivariate analysis, independent factors like serosal involvement, venous invasion, and histologic grade were combined with metastases in lymph nodes. When these independent factors are joined in surgery of colorectal carcinoma, there

is no need of undertaking the lymph node dissection since extensive surgeries like these do not improve the survival rate of patients.

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