SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Multicentric examination of prognostic factors in gastric and colorectal adenocarcinomas

by Adrienn Biró MD

Supervisor: Dezső Tóth MD, PhD

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Supervisor: Dezső Tóth PhD

Doctoral School of Clinical Medicine, University of Debrecen

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1. INTRODUCTION

The methodology of evidence-based medicine has become a cornerstone of modern medical practice also in surgery in recent decades. The essence of the method is that doctors make clinical decisions about their patients by taking into account the most reliable scientific knowledge on one hand, and on the other hand, use their own experiences to individualize the treatment for each patient, consulting with them. However, the principles of evidence-based medicine can only be successfully applied if these have been adapted in the health care system of the given country.

In my scientific research, we searched for possibilities in the surgical treatment of malignant tumors that, beyond the evidence-based medicine, took into account the factors of the patient and the disease that were not included in the development of national protocols. We aimed to determine the efficacy of individualized surgical treatments in multicenter studies, mainly with the examination of gastric and colorectal adenocarcinomas.

Gastric cancer is the fifth most common cancer in the world and the fourth leading cause of death due to cancer worldwide. More than one million new cases are estimated to arise each year. Colorectal cancer is the third most common cancer, leading to the second most common cause of mortality globally. We have to take into account of two million new cases per year for this type of cancer. In Eastern Europe, Hungary has the highest incidence of colon cancer in both women and men. In terms of disease incidence, it is important to find new prognostic factors that will assist to improve clinical outcomes with individualized treatment.

2. SPECIFIC AIMS

2.1. To determine the most significant prognostic factor for lymph node stage classification systems in gastric adenocarcinoma

The aim of our multicenter retrospective study was to compare seven different lymph node staging systems in two Hungarian hospitals, examining gastric cancer patients to determine the most significant prognostic factor.

2.2. To determine the most significant prognostic factor for biomarkers in colorectal adenocarcinoma

The aim of our multicenter prospective study was to analyze the prognostic values of inflammatory and coagulation markers and ratios from preoperative blood samples of colorectal cancer (CRC) patients in three county hospitals in Hungary, which can predict clinical outcome and optimize further treatment.

3. PATIENTS AND METHODS

3.1. Multicentric examination of gastric cancer patients

Between 01 March 2005 and 01 March 2010, 460 patients went under surgery for gastric cancer at the Department of General Surgery in the Kenézy Gyula Teaching Hospital, University of Debrecen and at the Department of Surgery in the Moritz Kaposi General Hospital, Kaposvár. The data were analyzed with the approval of the Ethics Committees of the hospitals involved in the study. Eligibility criteria for inclusion were: 1) histologically proved gastric adenocarcinoma; 2) R0 resection; and 3) availability of complete follow-up data. The exclusion criteria were: 1) adenocarcinoma of esophago-gastric junction; 2) gastric stump cancer; 3) distant metastasis; 4) neoadjuvant oncological treatment; or 5) mortality due to postoperative complication. After the elimination, 164 patients were suitable for the analysis.

All patients were followed up trimonthly in the first 2 years, every 6 months during the 3rd to 5th years and annually thereafter. Physical examination, blood test, chest radiography, abdominal ultrasound or abdominal and pelvic computed tomography (CT) scan were performed in every 6 months and an annual gastroscopy was carried out during the follow-up period. Based on our chemotherapy protocols, only patients with T3 and/or node positive gastric cancer had adjuvant treatment. The last follow-up was in December 2016. The median and mean follow-up time was 23.0 and 43.7 (range: 3-136) months, respectively.

The following clinical data were collected: sex (male or female), age at the time of surgery (≤60 or >60 years), size of primary tumor (≤50 or >50 mm), location of the tumor (upper-, middle-, or lower-third) and Borrmann classification (type I-IV) of cancer, and degree of differentiation (well, moderately or poorly differentiated carcinoma).

The extension of lymph node dissection (limited lymph node dissection-D1 or extended lymph node dissection-D2), the 6th Union for International Cancer Control (UICC), the 7th

UICC and the 8th UICC tumor-node-metastasis (TNM) T- and N-staging systems were evaluated in terms of 5-year survival rate. The examined lymph nodes (eLN<16 or ≥16), the number of dissected negative lymph nodes (NLN, 0-9, 10-14, ≥15), the metastatic lymph node ratio (MLR, 0, 0.1%-20.0%, 20.1%-50.0%, ≥50.1%), and the log odds of positive lymph nodes (LODDS< -1.125, -1.125 - -0.251, -0.250 - 0.749, ≥0.750) were determined to measure the 5-year survival data and to compare them to the above mentioned UICC N-staging systems and to each other. The ranges of eLN, NLN and MLR classification were specified by the most common used data from literature. The LODDS's values were defined by statistical analysis, based on the cut-off triplet for the highest rank-sum and product. Finally we investigated the different N-staging systems according to the number of harvested lymph nodes (<16 or ≥16).

3.2. Multicentric examination of colorectal cancer patients

Between 01 September 2017 and 15 December 2020, 430 patients went under surgery for colorectal cancer at the Department of Surgery in the Moritz Kaposi General Hospital, Kaposvár, the Department of General Surgery in the Kenézy Gyula Teaching Hospital, University of Debrecen, and the Department of Surgery in the Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital, Miskolc. Patient involvement and data analysis were performed with the approval of the Ethics Committees of the hospitals involved in the study. The inclusion criteria were as follows: 1) histopathologically confirmed colorectal adenocarcinoma; and 2) laboratory tests, CT, colonoscopy, and in case of rectal cancer magnetic resonance imaging were carried out before surgery. At first, patients were excluded based on the following criteria: 1) patients with distant metastasis; 2) patients who received anti-inflammatory medicine (including antibiotics) or immunosuppressive treatment (including steroids) within three months of surgery, or who had chronic inflammatory disorder including infection and autoimmune diseases; 3) history of thrombosis or embolism; 4) history of

recurrence or other malignant tumors or hematological disorder; 5) patients who received oral anti-thrombotic drugs.

A total of 236 patients were included in the study, of which an additional 35 patients were excluded in the second evaluation when unresectable tumor was revealed during surgery or R1 or R2 resection was performed. After the elimination, 201 patients were suitable for the analysis.

The preoperative routine blood test data achieved within 1 month of surgery included leukocyte count (G/l), neutrophils (G/l), lymphocytes (G/l), monocytes (G/l), platelet count (G/l), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR). D-dimer (ug/l), prothrombin time (PT)- international normalized ratio (INR), fibrinogen (g/l), activated partial thromboplastin time (aPTT, sec), total protein (g/l) and albumin (g/l) were also obtained. In addition, C-reactive protein (CRP, mg/l) and Glasgow prognostic score (GPS) were investigated. The resected tumors were histopathologically classified following the 8th edition of the UICC TNM classification. Besides the laboratory and histological results, we also investigated tumor size, Body Mass Index (kg/m2), smoking habits, type of surgery (laparoscopic or open), type of anastomosis (hand-sewn or instrumental), operating time, the integrity of the mesorectum following total mesorectal excision and the integrity of mesocolon following complete mesocolic excision, postoperative complications, and oncological therapies. Patients were followed-up every six months by physical examination, blood test, and abdominal ultrasound or CT scan. Colonoscopy was performed annually for the first 2 years and then every 2 years.

4. RESULTS

4.1. Results of prognostic examination of gastric cancer

A total of 164 patients with a median age of 66 (range: 35-90) years were evaluated in the two institutions. Sixty percent of patients were male and more than half of the patients (55%) had lower-third tumors. The average number of removed lymph nodes was 10.48 (range: 1-38) per case. The mean number of metastatic lymph nodes was 3.22 (range: 0-23). The overall 5-year survival rate for all patients was 55.5% with a median overall survival (OS) time of 102 months.

The 5-year survival rates and the results of the univariate analysis according to the patient's and tumor's characteristics were calculated and only the T-stage was a significant factor in our multicenter study. The survival difference according to the tumor size was remarkable (65.8% vs. 49.3%); however it was not significant.

All of the evaluated N-staging classifications (6th, 7th, and 8th UICC N-stage, MLR, LODDS), excluding the eLN and NLN were significant ($p<0.001$) prognostic factors for the 5-year OS with univariate analysis. Unfortunately, only 4 patients are representing the N3b group in the 8th UICC staging system and their follow-up period was less than 5 years, so we could not calculate the survival rate.

Our multivariate survival analysis found that 4 of the significant classifications were independent prognostic factors for survival, however during the investigation of hazard ratios (HR), the monotonicity of gradient in the 6th and 8th UICC N-stage did not follow the adequate risk comparing N2 vs. N0 (HR:4.97, 95% confidence interval (CI):2.58-9.56, $p<0.001$) and N3 vs. N0 (HR:3.00, 95%CI:0.68-13.19, $p=0.144$) in the 6th UICC staging system, and comparing N3a vs. N0 (HR:4.98, 95%CI:2.59-9.59, $p<0.001$) and N3b vs. N0 (HR:3.02, 95%CI:0.69-13.27, $p=0.142$) in the 8th UICC staging system. The 6th UICC system was excluded from

further analysis, while the newest 8th UICC system was evaluated keeping in mind that only 4 patients are representing the N3b group with an inadequate follow-up period.

Comparison of performance of the residual N classifications (7th and 8th UICC N-stage, MLR, LODDS) proved that the LODDS system with the highest C-index (0.700) and the lowest Akaike information criterion (AIC) value (618.880) was the first in prognosis prediction. Furthermore, the association between the number of retrieved lymph nodes and survival rates of these N-staging systems was examined. While the LODDS classification (C-index: 0.711, AIC: 471.976) was the best predictor of survival in patients with less than 16 harvested lymph nodes, the MLR (C-index: 0.676, AIC: 90.692) showed the highest results when more than or equal to 16 lymph nodes were examined.

4.2. Results of prognostic examination of colorectal cancer

A total of 201 patients' data were analyzed in the three hospitals. There were 119 (59.20%) males and 82 (40.80%) females, with a median age of 66 years (range: 35-91). The mean and median follow-up period was 23.06 and 24.00 months (range: 7-40). During the follow-up period 8 (3.98%) patients died and 12 (5.97%) patients experienced tumor spreading. Patients with the 8th UICC TNM stages I, II and III accounted for 24.21%, 42.11%, and 33.68%, respectively. Of all the patients, 105 (52.24%) tumors were located in the colon, and 96 (47.76%) tumors were located in the rectum, and 83 (41.29%) and 122 (60.70%) patients underwent neoadjuvant or adjuvant chemotherapy. The mean tumor size was 3.3 (0.5–12) centimeters.

The LMR, NLR and PLR optimal cut-off levels were calculated with receiver operating characteristic curve (ROC) analysis as the maximal Youden Index for both disease-free survival (DFS: 3.21, 3.96, 206.62) and OS (3.61, 3.06 and 176.82 respectively). For other laboratory

parameters the reference value between normal and abnormal data were chosen as cut-off points, for non-laboratory parameters it was the median.

We examined our patients based on their tumor localization: colon cancer group (n=105, 52.24%) and rectal cancer group (n=96, 47.76%). In terms of colon cancer patients, NLR ($p<0.001$), PLR ($p<0.001$), aPTT ($p=0.007$), fibrinogen ($p<0.001$) levels and GPS ($p<0.001$) were all positively correlated with tumor size. LMR ($p=0.003$) and albumin ($p<0.001$) were negatively correlated with tumor size. In the rectal cancer group LMR ($p=0.016$) and fibrinogen ($p=0.007$) were positively correlated with tumor size. There were no statistically significant correlation between PT (INR) or D-dimer and tumor size in either group, however, D-dimer levels were positively correlated with age both in the colon ($p<0.001$) and the rectal cancer group ($p=0.005$).

Examining patients with colon cancer, the Kruskal-Wallis H test showed significant association of NLR ($\chi^2=5.48$, $p=0.019$, degrees of freedom (df)=1), GPS ($\chi^2=6.41$, $p=0.011$, df=1) and aPTT ($\chi^2=13.88$, $p<0.001$, df=1) with perineural invasion. Significant association was revealed between CRP and T stage ($\chi^2=12.41$, $p=0.006$, df=3). Albumin had significant effect on T stage ($\chi^2=17.08$, $p<0.001$, df=3) as well. CRP ($\chi^2=7.16$, $p=0.028$, df=2), aPTT ($\chi^2=6.78$, $p=0.034$, df=2), D-dimer ($\chi^2=8.78$, $p=0.012$, df=2) and albumin ($\chi^2=10.27$, $p=0.006$, df=2) were significantly associated with grade in the colon cancer group.

In terms of patients with rectal cancer, the Kruskal-Wallis H test showed significant association of D-dimer ($\chi^2=4.52$, $p=0.033$, df=1) with vascular invasion. There was significant association between T-stage and the following: platelet count ($\chi^2=11.14$, $p=0.011$, df=3), CRP ($\chi^2=14.05$, $p=0.003$, df=3), albumin ($\chi^2=10.69$, $p=0.014$, df=3), and GPS ($\chi^2=15.95$, $p=0.001$, df=3). APTT ($\chi^2=10.37$, $p=0.006$, df=2) and albumin ($\chi^2=7.37$, $p=0.025$, df=2) were significantly associated with grade in the rectal cancer group. We have not found significant

correlation between D-dimer and N-stage neither in the colon cancer group (p=0.230), nor in the rectal cancer group (p=0.278).

We examined DFS and OS in the two groups separately. In the colon cancer group, we performed univariate and multivariate Cox regression analysis for DFS. In univariate analysis T-stage (p=0.024), neutrophil count (p=0.018), NLR (p=0.011) and albumin (p=0.021) were significantly associated with DFS. Multivariate Cox regression was performed with these individually significant factors, but neutrophil count was excluded due to the correlation with NLR. Albumin (p=0.228) was not significant in the multivariate analysis, but T-stage (p=0.050) and NLR (p=0.048) as a biomarker, were significant variables. Higher NLR (>3.96) was significantly (p<0.001) associated with worse DFS in Kaplan-Meier log-rank analysis.

We performed univariate and multivariate Cox regression analysis also for OS in the colon cancer group. Lymphocyte count (p=0.048), monocyte count (p=0.011) and aPTT (p=0.020) were significantly associated with OS in univariate analysis. In multivariate analysis none of the variables were significantly associated with OS, althought aPTT (p=0.059) had a relevant effect on it.

In the rectal cancer group, only univariate Cox regression analysis was performed for DFS and OS, because none of the variables were significant.

5. DISCUSSION

5.1. Prognostic examination of gastric cancer

During the analysis of our results, we confirmed that the T-stage is a significant predictor for survival in univariate analysis. We found a noticeable variance in survival according to tumor size (66% vs. 49%); however it was not significant statistically. In our multicenter study, we could not prove significant survival differences in tumor location, Borrmann types of lesions and cancer differentiation and we demonstrated that the extension of lymph node dissection (D1 vs. D2) was also a non-significant predictive factor for survival.

Several studies confirmed the superiority of the 7th UICC N-staging system to the 6th UICC N-staging classification in prognosis of OS. The main strength of the Asian studies is the use of data from multiple institutions. Our multicenter study resulted in superiority of the 7th UICC N-staging system to the 6th UICC N-staging classification as well. The evaluation of the 8th UICC N-stage system in terms of prognosis is still an interesting and popular topic for both eastern and western populations.

The UICC N-staging system is criticized for the possibility of stage migration phenomenon and approximately half of the patients are misclassified, so at least 16 harvested lymph nodes are recommended for the accurate prediction. Unfortunately, we did not find any survival benefit according to the total number of harvested lymph nodes, similarly to an Italian study comparing the impact of D1 vs. D2 lymphadenectomy. Although the difference in 5-year survival rates was conspicuous between more and less than 15 negative harvested lymph nodes (73% vs. 52%), it was not significant (p=0.209).

Various study showed the superiority of MLR to the number-based (UICC) N-stage systems, because it is less influenced by the total number of harvested lymph nodes. However, in patients with incomplete lymphadenectomy, this classification had worse performances.

MLR was proved by our study as the best in prognosis prediction of patients with adequate (≥16) lymphadenectomy.

The latest studies demonstrated that the LODDS classification is a better predictor of survival -reducing the phenomenon of stage migration to a minimum- in contrast with UICC N-stage system or MLR, moreover it is not influenced by the number of less than 16 removed lymph nodes. In our multicenter study, the LODDS staging had better discriminatory ability and monotonicity of the gradients with a smaller AIC value and a larger value under the ROC curve, than did the 6th, 7th and 8th edition UICC N-staging, or MLR systems. These results confirmed that the LODDS classification has the best prognostic stratification and the most precise prediction for survival in a region like Hungary with low incidence of gastric cancer and high percentage of advanced, frequently non-resectable disease. The LODDS staging system was the best predictor of survival in gastric cancer during the analysis of all patients as well as, in patients with incomplete (<16) lymphadenectomy.

5.2. Prognostic examination of colorectal cancer

In terms of coagulation factors, our multicenter study showed that fibrinogen levels in both groups and aPTT levels in the colon cancer group were positively correlated with tumor size. Current studies have revealed that elevated plasma fibrinogen plays an important role in malignant behaviors of several tumors through inhibiting the elimination of cancer cells mediated by natural killer cells or cytotoxic cells. As our results show, D-dimer levels were positively correlated with age in CRC patients. In colon cancer patients D-dimer levels were significantly correlated with grade, and in terms of rectal cancer, D-dimer levels were associated with vascular invasion. Much research has been conducted concerning the correlation between D-dimer levels and survival, even prospective ones, and also reported that

higher preoperative D-dimer levels meant significantly shorter postoperative survival even after curative resection, but we could not prove that.

In terms of inflammatory factors, the GPS was positively correlated with tumor size and was associated with perineural invasion in our colon cancer patients. In rectal cancer patients GPS was not correlated with tumor size, but was significantly associated with T-stage. According to a Korean study, GPS was also significantly correlated with tumor size, as we experienced in our colon cancer patients, but they could not prove the significance with TNM stage, as we demonstrated in terms of T-stage in rectal cancer patients.

Studies analyzing the correlation of CRC and LMR reported that LMR with low lymphocyte and high monocyte count indicates insufficient anti-tumor immune response. They also found that low LMR patients did not benefit from 5-fluorouracil-based adjuvant chemotherapy. While our results showed significant association between tumor size and LMR in CRC patients, we excluded LMR from further statistical analysis due to inconsistency between the two groups.

NLR was an independent prognostic factor for DFS in patients with colon cancer and showed significant association with tumor size and perineural invasion. According to previous studies, preoperative high NLR was connected with worse prognosis in patients who underwent surgery for CRC. In our multicenter study, NLR was not significant for OS, presumably due to the short follow-up time. Several studies have suggested the combination of biomarkers to predict survival more accurately.

The inflammatory and coagulation parameters and ratios have their own significance similarly to the prognostic parameters published before. The benefit of these are that it can be easily attained in everyday practice, it is relatively cheap and easy to use in routine work. The present study showed that in colon cancer patients, NLR was the most important prognostic factor among the preoperative biomarkers. Higher NLR (>3.96) meant significantly worse ($p<0.001$) DFS. NLR is an independent prognostic factor, which could be used together with

the well-known factors and tumor markers. This biomarker could be a powerful tool for predicting survival outcome in patients with colon cancer. It might help to recognize the high-risk patients between patients with the same TNM stage and in the future, could help with the decision on adjuvant chemotherapy, as suggested by previous international studies.

This is the first multicenter, prospective study among the Hungarian population examining these preoperative biomarkers in CRC patients in three county hospitals. It is extremely important to find new, relevant, easily attained prognostic factors for our patients to improve clinical outcomes with individualized treatment.

6. NEW OBSERVATIONS, MAJOR RESULTS

1. We were the first to demonstrate in the Eastern European region and Hungary that the log odds of positive lymph nodes (LODDS) classification could determine the prognosis of gastric adenocarcinoma more adequately than the other investigated lymph node staging systems in patients with less than 16 harvested lymph nodes.
2. The metastatic lymph node ratio (MLR) system was proved as the best in prognosis prediction of gastric adenocarcinoma patients with extended lymphadenectomy, thus, 16 or more lymph nodes were harvested.

We suggest the application of the log odds of positive lymph nodes (LODDS) system routinely in Hungarian gastric adenocarcinoma patients, and the usage of the metastatic lymph node ratio (MLR) classification in cases with extended lymphadenectomy.

3. We were the first in Hungary to demonstrate that neutrophil-to-lymphocyte ratio (NLR) is an independent prognostic factor for disease-free survival (DFS) in patients who underwent curative resection for colon adenocarcinoma. A higher neutrophil-to-lymphocyte ratio (NLR> 3.96) means significantly worse ($p<0.001$) disease-free survival (DFS), which is recommended to take into consideration while evaluating adjuvant chemotherapy.
4. We also demonstrated that elevated fibrinogen levels in preoperative blood samples of colorectal adenocarcinoma patients, and elevated activated partial thromboplastin time (aPTT) and Glasgow prognostic score (GPS) in patients with colon adenocarcinoma were shown to indicate larger tumor size. Elevated D-dimer levels were associated with poorer histological differentiation in patients with colon adenocarcinoma and with more frequent vascular invasion in patients with rectal adenocarcinoma. Perineural invasion is more

common in patients with colon adenocarcinoma with a higher Glasgow prognostic score (GPS) and a higher Glasgow prognostic score (GPS) is associated with a more advanced tumor (T) stage in patients with rectal adenocarcinoma. These important results may also progress the application of individualized treatment**.**

This is the first multicenter, prospective study among the Hungarian population examining these preoperative biomarkers in colorectal adenocarcinoma patients in three county hospitals. Based on our results, we recommend the application of the preoperative neutrophil-to-lymphocyte ratio (NLR) in case of the decision on adjuvant chemotherapy.

7. LIST OF PUBLICATIONS

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Registry number: DEENK/130/2022.PL
Subject: PhD Publication List

Candidate: Adrienn Biró
Doctoral School: Doctoral School of Clinical Medicine
MTMT ID: 10064408

List of publications related to the dissertation

1. **Biró, A.**, Kolozsi, P., Nagy, A. C., Varga, Z. J., Káposztás, Z., Tóth, D.: Significance of preoperative blood tests in the prognosis of colorectal cancer: a prospective, multicenter study from Hungary.
   J. Clin. Lab. Anal. 36 (1), 1-8, 2022.
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2. Tóth, D., **Biró, A.**, Varga, Z. J., Török, M., Árkosy, P.: Comparison of different lymph node staging systems in prognosis of gastric cancer: a bi-institutional study from Hungary.
   Chin. J. Cancer. Res. 29 (4), 323-332, 2017.
   DOI: http://dx.doi.org/10.21147/j.issn.1000-9604.2017.04.05
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List of other publications

3. **Biró, A.**, Ternyik, L., Somodi, K., Dawson, A., Csulak, E., Tóth, D., Moizs, M., Káposztás, Z.: Comparison of Resected Malignant Tumors of the Right- and Left-Sided Colon: Is There a Difference?
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4. **Biró, A.**, Ternyik, L., Czoma, V., Hegedűs, G., Bálint, I., Tóth, D., Káposztás, Z.: Epithelioid hemangioma of liver - the first reported case.
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8. Tóth, D., **Biró, A.**, Kincses, Z., Árkosy, P., Török, M.: A számítógépes program szerepe a gyomortumor-sebészetben: túl az evidencián = Role of a computer program in gastric cancer surgery : beyond the evidence.
   Magyar Seb. 70 (1), 48-55, 2017.
   DOI: http://dx.doi.org/10.1556/1046.70.2017.1.7

Total IF of journals (all publications): 11,962
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The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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DEBRECENI EGYETEM * Egyetemi és Nemzeti Könyvtár *

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