REVIEW

By Prof. Alexander Petrov Chervenyakov, M.D., Ph.D., D.Sc.,
UMHATEM "N.I.Pirogov", Sofia

Concerning: dissertation work for the award of the educational and scientific degree "**Philosophy doctor**", professional direction *MEDICINE*, scientific specialty *THORACIC SURGERY*

Author: Todor Yuriev Dzhendov M.D.

On topic: **"Multimodal approach in the treatment of esophageal carcinoma. Prognostic and predictive markers."**

Scientific supervisor: Associate professor Stoyan Sopotenski, M.D., Ph.D.

Subject: Participation in a scientific jury under Art. 10 of the Regulations for the development of the academic staff at UMHATEM "N.I.Pirogov", according to order № RD-26-1322/30.05.2022 from a meeting of the Scientific Council

1. Information about the doctoral student

The doctoral student studied in a free doctoral program at the Department and Clinic of Surgery at UMHATEM "N.I.Pirogov", Sofia in the scientific specialty THORACIC SURGERY. The training was carried out in a free form.

The presented set of materials is in accordance with the requirements of the Scientific Council of the UMHATEM " N.I.Pirogov", Sofia for the disclosure of the procedure for defense of the dissertation work.

2. Brief biographical data for the doctoral student

Todor Dzhendov M.D. completed his medical education in 2007 from Medical University, Sofia and obtained a master's degree in Health Management in 2010. He specializes in Thoracic Surgery at Tokuda Hospital Sofia and UMHATEM "N.I.Pirogov", Sofia. He specializes in General Surgery at UMHATEM "N.I.Pirogov", Sofia and at University Hospital, Linköping, Sweden. He acquired a specialty in Thoracic surgery in June 2014, and in General surgery in January 2018. Since 2014, he has been working as an assistant professor and is a doctoral student at the First Surgical Clinic of UMHATEM "N.I.Pirogov", Sofia. Since May 2016, he has been working as a specialist at the University Hospital of Linköping, Sweden, where he still works.

He has completed over 15 courses and specializations in laparoscopic and minimally invasive surgery with the main topic "Surgery of the esophagus and stomach", "Lung surgery" and "Trauma and surgical complications", etc., successively in Bulgaria, Slovenia, Poland, Sweden, Belgium and USA. He undergoes individual training on the subject. He speaks three languages.

3. Relevance of the topic

Carcinoma of the esophagus and gastro-oesophageal junction remains a serious challenge to modern medicine. Accurate diagnosis, staging and histological verification improve the prognosis of the disease, but still the results of its treatment remain unsatisfactory. In 50 years, the TNM classification of esophageal cancer has been changed eight times due to unsatisfactory criteria, including the last UICC/AJCC one. Despite the introduction of a multimodal approach with neoadjuvant, surgical, chemo and radiation therapy, the five-year survival rate remains below 50%.

Staging criteria and therapeutic algorithms for esophageal cancer have undergone rapid development in the past decade, but treatment outcomes have not progressed significantly. In addition to the accepted staging, objective criteria determining the prognosis and the method of treatment are sought. A number of authors are looking to define diagnostic markers for a precise therapeutic approach and better outcomes. This shows the relevance and timely development of the topic.

4. General characteristics of the presented dissertation work

Structure, volume, purpose, tasks, object, subject matter, main thesis, used scientific literature.

The dissertation paper is written on 146 standard typewritten pages, distributed in the following order:

I. Table of contents, abbreviations and introduction – up to 8 pages
II. Literature review – 38 pages
III. Goals and objectives – 1 page
IV. Materials and methods – 13 pages
V. Results – 22 pages
VI. Discussion – 18 pages
VII. Conclusion – 2 pages
VIII. Consequences – 1 page
IX. Publications – 1 page

Appendices – 14 pages

Bibliography – 23 pages

The dissertation paper is illustrated with 33 figures and 14 tables.

The literature review is divided into seven main paragraphs and reflects the problem in a multifaceted and comprehensive manner. It covers the epidemiology, etiology and pathogenesis, the clinical presentation, histological and TNM staging of esophageal cancer. Current trends in the multidisciplinary approach to the treatment of

esophageal carcinoma are comprehensively reviewed in 7 subsections with the accepted diagnostic-treatment algorithms. Current data on prognostic factors in post-surgical disease are presented with the most up-to-date scientific data, from demographics to viral infections and genetics. 301 contemporary publications are cited.

Research methodology

The goal is set clearly and specifically. The tasks are precisely formulated and sufficient to achieve the set goal and the doctoral student achieves an adequate response to these tasks.

The dissertation work covers a period of 8 years: from 2010 to 2018 in the First Surgical Clinic of UMHATEM "N.I.Pirogov", 117 patients and University Hospital, Linköping, Sweden, 115 patients. They were operated radically and an ambispective analysis was performed on these patients.

The operations applied in the two hospitals as well as the methodology of the genetic analysis and HPV testing are indicated. Patients were followed up until the month of April 2022. In the analysis, overall survival was determined from the date of surgery to the date of death.

The obtained data were processed with IBM SPSS Statistics 28.0.0.0 statistical package, with a significance level of $p<0.05$ by means of descriptive analysis and demographic characteristics were analyzed. Overall survival was analyzed using the Kaplan-Meier method, and the log-rank test was used to assess differences between groups.

Multivariate analysis was performed with Cox regression method, calculating Hazard ratio with 95% confidence interval (95% CI).

In the Results chapter, a comparative study of the two cohorts (Sweden and Bulgaria) was performed. Statistically processed data and obtained dependencies are presented. Table 6 shows the data obtained in both cohorts of the Hazard ratio for survival at the 95% CI from the Cox regression analysis. Kaplan-Meier survival curves by sex, age, comorbodity, T stage, N stage and resection volume (R) are presented.

The results of the genetic testing of 20 patients and the HPV analysis are peresented in separate sections.

The discussion is presented in 19 pages and follows the sequence of the analysis of the literature data and the data of the obtained results.

Major factors influencing survival and treatment outcomes of patients with adenocarcinoma and squamous cell carcinoma of the esopphagus in both cohorts are reported. Demographic parameters, histological results and comorbidity were found to be statistically significant. Dr Todor Dzhendov detects a dependence on T stage, tumor size and length, and N stage for predicting outcomes. He establishes the prognostic significance of tumor length and recommends that it be taken into account in staging.

The radicality of the resection, lymph node dissection and the volume of the surgical intervention are of essential importance. It again verifies statistically the prognostic significance of the lymph node ratio. The advantage of neoadjuvant therapy (mainly performed in the Swedish cohort) is clearly statistically significant for better patient survival and has been investigated in several large-scale international studies. The author also discusses other factors with presumed prognostic significance, but without establishing statistically significant relationships.

At the end of the discussion, an extremely valuable therapeutic algorithm is proposed, separately for adenocarcinoma and squamous cell carcinoma.

The conclusion summarizes tha data from the study.

The consequences are 7, correctly formulated and meet the set tasks, fully outlining the fullfillment of the purpose of the dissertation work.

I accept as contributions:

1. An ambispective clinico-epidemiological study was carried out in two esophageal surgery centres in two European countries of patients operated for esophageal carcinoma and data on frequency, clinico-histological characteristics were presented.

2. Analysis of the current methods of treatment of esophageal carcinoma by stages is performed.
3. Methods of treatment in the early stages of the tumour and in patients who are not candidates for surgical resection are presented.
4. The role of the perioperative oncological therapy in the complex treatment of this type of carcinoma has been confirmed.
5. Additional prognostic indicators regarding survival were derived.
6. A therapeutic algorithm was developed according to the histological type and the stage of the tumor.
7. A DNA bank for esophageal tumors has been established and is stored in the Centre for Molecular Medicine and can be used for future studies.

The autoreferat meets the requirements for doctoral work and reflects the main results achieved in the dissertation.

CONCLUSION:

The presented dissertation work is unique with the conducted comparative study of the results in two large European clinics in Linköping, Sweden and UMHATEM "N.I.Pirogov", Sofia, Bulgaria. It definitely proves the prognostic significance of a number of factors in esophageal cancer. It offers an algorithm for successful treatment of patients.

The dissertation"Multimodal approach in the treatment of esophageal carcinoma. Prognostic and predictive markers" by Todor Dzhendov M.D. fully covers the criteria for awarding the scientific and educational degree "Philosophy doctor" and meets all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the Implementation of LDASRB and the relevant Regulations of the UMHATEM "N.I.Pirogov". The presented mate-

rials and dissertation results fully correspond to the specific requirements of UM-HATEM “N.I.Pirogov”.

This gives me the reason to give a positive vote and recommend to the honorable members of the scientific jury to award Todor Dzhendov M.D. the educational and scientific degree “Philosophy doctor”.

27.07.2022 Reviewer:.…….....

Prof. Alexander Chervenyakov, M.D., Ph.D., D.Sc.