

STATEMENT

by Prof. Hristo Ivanov Shivachev, M.D., Ph.D.,

member of the Scientific Jury, assigned by

Order Nr RD-1323/30.05.2022

UMHATEM “N.I.Pirogov”, Sofia

Concerning:

procedure for awarding the educational and scientific degree (Philosophy doctor, Ph.D.) to
Todor Yuriev Dzhendov M.D., for a dissertation paper on

**“Multimodal approach in the treatment of esophageal carcinoma. Prognostic and
predictive markers.”**

in scientific specialty **“Thoracic surgery”**

in professional direction 7.1 **Medicine**

in the field of higher education 7. **Healthcare and sports**

Biography

Todor Yuriev Dzhendov M.D. graduated in Medicine from the Medical University, Sofia in 2007 and got his second master’s degree in Health Management in 2010. He has two medical specialties – “Thoracic surgery” and “ Surgery”, acquired in 2014 and 2018, respectively. His professional experience began in 2008 as a resident doctor at Tokuda Hospital, Sofia. From 2010 to 2016, he worked as a resident doctor at the UMHATEM “N.I.Pirogov”, Sofia. From May 2016 to the present, he works as a specialist at the University Hospital in Linköping, Sweden. He has completed a number of specialized courses in the field of minimally invasive and endoscopic surgery. He speaks Swedish, English and French. He is a member of the Bulgarian and Swedish surgical societies, The European Association for Cardiothoracic Surgery, The European Society of Thoracic Surgeons and The European Association of Endoscopic Surgery.

Dissertation data

Dr Dzhendov's dissertation is titled "Multimodal approach in the treatment of esophageal carcinoma. Prognostic and predictive markers". It is in a volume of 146 pages, of which 22 papers are a bibliographical reference with 301 literary sources. The paper is illustrated with 33 figures and 14 tables. It is formatted as required.

In the literature review, modern literary data on esophageal carcinoma are presented in detail, and esophageal carcinoma is thematically presented with statistical information. The disease's etiology and pathogenesis are presented. Postoperative mortality was predicted to be lower in centres with a higher volume of esophageal resections. Survival data are provided by global geographical region and stage of the disease. An analysis of the clinical picture and the method of diagnosis was made. The following operative procedures are described: Sweet, Ivor-Lewis, Orringer, McKeown and transabdominal resection of the esophagus.

The aim of the dissertation work is clearly defined: to evaluate the current methods for the treatment of esophageal cancer and to define the prognostic markers for the optimization of the therapeutic protocol. To achieve it, six tasks have been identified:

1. To carry out an ambispective analysis of the results of the treatment of patients with carcinoma of the esophagus operated in the Surgical departments of two university hospitals in two European countries.
2. Comparison of the results in the analyzed samples and correlation with the literature data.
3. Finding a correlation between choice of therapeutic protocol and survival.
4. Analysis of prognostic markers for survival.
5. Genetic analysis of tumor samples in part of the patients.
6. Preparation of a recommended therapeutic protocol according to the histological type and stage of the tumor.

Research material

The study analyzes the results of the treatment of patients operated for carcinoma of the esophagus and cardia at the First Surgical Clinic of the UMHATEM “N.I.Pirogov”, Sofia, Bulgaria and at the Clinic of Surgery of the University Hospital, Linköping, Sweden. There are two groups. The first included 129 patients admitted for treatment and operated for carcinoma of esophagus and gastro-esophageal junction at the First Surgical Clinic of the UMHATEM “N.I.Pirogov”, Sofia, Bulgaria in the period 2013 – 2015. 12 patients who intraoperatively were diagnosed with advanced (unresectable) or metastatic tumour were excluded.

The remaining 117 patients underwent curative esophageal resection and were prospectively analyzed. The decision which of the operative methods previously described in the literature review was made according to the localization of the tumour, the data on previous operations and the general condition of the patient. Part of the operative interventions were performed using a minimally invasive approach, and all procedures were performed according to standardized protocols.

The second group of patients consisted of 115 patients operated between 2010 and 2017 at the Clinic of Surgery of Linköping’s University Hospital, Sweden. An ambispective analysis was performed. There were no patients excluded from the analysis in this group. All the patients were examined preoperatively according to the algorithm existing in Sweden (Nationellt vårdprogram för matstrups- och magsäckscancer).

Most of them underwent preoperative chemoradiotherapy according to the CROSS protocol with Carboplatin/ Paclitaxel in 5 cycles on day 1, 8, 15, 22 and 29 in combination with concomitant radiotherapy with a total dose of 41,1 Gy, divided into 23 cycles of 1,8 Gy starting on the first day of the chemotherapy, a total of 5 fractions per week (excluding Saturdays and Sundays). The surgical intervention was performed at least 4 weeks after the last cycle of chemotherapy. The two types of operative procedures performed were Ivor-Lewis and McKeown operations.

Conclusions

The conclusions of the dissertation work are drawn logically and on basis of the obtained results. There are 6 of them.

1. In the treatment of patients with carcinoma of esophagus and gastro-esophageal junction, the multimodal therapy provides significantly better survival compared to surgery as the only therapeutic method.
2. When choosing oncological therapy, two alternatives are available that achieve the same results – neoadjuvant chemoradiotherapy (CROSS protocol) or perioperative chemotherapy (FLOT protocol). However, in esophageal squamous cell carcinoma, the inclusion of radiotherapy is desirable due to the higher radiosensitivity of this histological type.
3. Tumor staging is performed according to the latest 8th revision of the TNM classification, which is consistent with the histological type and the neoadjuvant therapy performed.
4. Along with TNM stage, additional statistically significant predictive markers such as tumor length over 3 cm, ratio of metastatic to total number of harvested lymph nodes over 10 %, microscopically non-radical resection, presence of comorbidities are available to determine patients prognosis. Secondary prognostic indicators are young age, male gender and squamous cell carcinoma.
5. In the presence of negative predictive markers, an aggressive therapeutic protocol is recommended with addition of adjuvant oncological therapy.
6. HPV infection is not a factor in the etio-pathogenesis of esophageal carcinoma in the Bulgarian population.

Contributions

Seven main contributions of the dissertation work can be identified.

1. An analysis of the contemporary methods of treatment of esophageal carcinoma by stages is performed.
2. New methods of treatment in the early stages of the tumor and in patients who are not candidates for surgical resection are presented.

3. An ambispective clinico –epidemiological study was conducted in two esophageal surgery centres in two European countries and data on the incidence, clinico-histological characteristics and survival of patients with esophageal carcinoma were 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.

Scientific publications related to the dissertation work.

The doctoral student submitted as full text publications related to the dissertation work two articles, one independent and one co-authored, and one report published in a collection.

In conclusion

The dissertation work of Todor Yuriev Dzhendov M.D. “Multimodal approach in the treatment of esophageal carcinoma. Prognostic and predictive markers” is thorough and multifaceted study and presents a serious multimodal therapeutic protocol for the individual stages of adenocarcinoma and squamous cell carcinoma of the esophagus. The topic is focused on one of the most aggressive visceral tumors in modern oncological morbidity, and therefore the presented research is of high value.

The dissertation work fully meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for the Development of the Academic Staff at UMHATEM “, Sofia and for the stated reasons I strongly recommend to the members of the esteemed Scientific Jury to award the educational and scientific degree “

Philosophy doctor” in the scientific specialty “ Thoracic Surgery” to Todor Yuriev Dzhendov
M.D.

With respect,

Prof Hristo Shivachev M.D., Ph.D.