STATEMENT

by

Associate professor Teodor Dimitrov Atanasov, M.D., Ph.D.

University Hospital "Sofiamed"

of a dissertation work for awarding of the educational and scientific degree "Philosophy doctor" (Ph.D)

professional direction *MEDICINE*

Author: Todor Yuriev Dzhendov M.D.

Title: "Multimodal approach in the treatment of esophageal carcinoma. Prognostic and predictive markers."

Scientific supervisor: Associate professor Stoyan Sopotenski, M.D., Ph.D., UMHATEM "N.I.Pirogov", Sofia

1. General presentation of the procedure and the doctoral student

The presented set of materials on paper/ electronic media is in accordance with Art. 4 , para. 2 of the Law on the Development of the Academic Staff in the Republic of Bulgaria and on Article 10 of the Regulations for the Development of the Academic Staff at UMHATEM " N.I.Pirogov", according to protocol № NS-01/02.04.2015г. from a meeting of the Scientific Council.

The doctoral student has attached 3 publications in Bulgarian magazines and collection of reports.

2. Brief biographical data for the doctoral student

Todor Yuriev Dzhendov M.D. was born on 18.10.1982. He graduated from Medical University, Sofia in 2007. He worked at the Department of Thoracic Surgery, Tokuda Hospital, Sofia from 2008 to 2010 and at UMHATEM "N.I.Pirogov" from 2010 to 2016. In 2014, he acquired a specialty in "Thoracic Surgery". During the period of 2014 began specialization in general surgery, which was successfully completed in 2017. Master in Health Management since 2010. From 2016 to the present, he works at the Department of Surgery, Linköping University Hospital, Sweden.

He speaks three languages. He has participated in over 30 congresses and conferences in the country and abroad. He has completed courses in minimally invasive surgery in our country, in Sweden and Slovenia, as well as in emergency medicine in Sweden and the USA. He is a member of Bulgarian medical council, Swedish Surgical Society, The European Association for Cardiothoracic surgery, The European Society of Thoracic Surgeons and The European Asssociation of Endoscopic Surgery.

3. Topic's actuality and expediency of the set goals and tasks

Esophageal carcinoma is one of the most aggressive visceral tumors. Symptoms appear late, usually in the advanced stages of the disease, requiring aggressive approach, and treatment is not always successful. In the Western world, adenocarcinoma is dominant histological type with incidence which has quadrupled in recent decades. In the east, the squamous cell carcinoma predominates.

Surgical resection of the tumor with an adequate lymph node dissection is still the mainstay of treatment for these tumors. The multimodal approach improves survival and is recommended for all patients, but even in these cases 5 –year survival rate does not exceed 46%.

Diverse treatment algorithms, mainly in the fields of oncology, in different parts of the world lead to different outcomes in terms of survival. Differences in survival rates between patients with the same histological variant and tumor location and at the same clinical stage necessitate the search for additional prognostic markers to help identify patients at high risk of developing recurrence or metastases. These patients would be candidates for more aggressive therapeutic protocols aimed at achieving remission and prolonging survival.

All the listed factors determine the actuality of the topic – a multimodal approach to treatment and analysis of prognostic predictive markers.

4. Understanding the problem

The presented literature review is on 37 pages and covers the problems of epidemiological features, etiology, classifications, developmental features, diagnostics and multimodal treatment of esophageal carcinoma. It is analytical and presents the current approach in this disease. The problems in the complex treatment of patients are considered. The prognostic factors described in the literature in patients who underwent curative resection for esophageal carcinoma, were analyzed in detail.

5. Research methodology

A set goal is clear, specific and is a logical consequence of the title of the topic. There are six tasks and they are formulated in accordance with the set goal.

6. Characterization and evaluation of the dissertation work

The dissertation submitted for review is written in 146 typewritten pages and is structured as follows:

1. Introduction – 2 pages
2. Literature review – 37 pages
3. Aim and tasks – 1 page
4. Clinical material - 2 pages
5. Materials and methods – 14 pages
6. Results – 23 pages
7. Discussion – 19 pages
8. Conclusion – 2 pages

9. Consequences – 1 page
10. Scientific works related to the dissertation - 1 page
11. Appendices – statistical tables – 15 pages
12. References – 22 pages

The dissertation work is illustrated with 13 tables and 33 figures.

The presented dissertation covers two groups of patients and two time periods.

The first group includes 117 patients operated for carcinoma of the esophagus and gastro-esophageal junction at the First Surgical Clinic of UMHATEM "N.I.Pirogov", Sofia, Bulgaria in the period 2013 – 2015. A prospective analysis was performed on these patients. The operative techniques used are Sweet- Garlock (left transthoracic transdiaphragmatic esophagectomy), Orringer (conventional transhiatal esophagectomy), transhiatal esophagectomy, Ivor-Lewis and McKeown.

A group of 20 patients also underwent genetic analysis and HPV testing, and tumor and blood samples were collected from all patients.

The second group consisted of 115 patients operated between 2010 and 2017 at the Department of Surgery of Linköping University Hospital, Sweden. An ambispective analysis was performed. The operative techniques used are Ivor-Lewis and McKeown. Preoperatively, some patients underwent PET-CT in case of suspicion of distant metastases. Most of the patients underwent preoperative chemo-radiotherapy.

Statistical processing of the study was performed with IBM SPSS Statistics 28.0.0.0. The significance level was $p<0.05$.

Results

Men predominate, with the ratio being 4:1 in the Bulgarian cohort and 3:1 in the Swedish one. Almost half of the patients in the Bulgarian group are of working age, while in the group from Sweden, young patients are three times less than retirees.

A large proportion of patients in Sweden (90%) received neo-adjuvant therapy. More than half of the patients (60%) have a negative nodal status (N0).

No significant differences were observed between the two groups regarding M and R status.

The predominant histological variant in both cohorts was adenocarcinoma.

For the Bulgarian group, the three-year survival rate was 12.8% and the five-year survival rate was 11.1%. For the Swedish group, the values were 53.04% three-year survival and 43.5% five-year survival.

Factors affecting survival are male gender (in the Swedish cohort), age (in the Bulgarian cohort), radicality of resection (in both cohorts), histological type (squamous cell carcinoma for the Swedish cohort).

Survival by sex and age

In Bulgarian patients up to 60 years, the average survival for women is 17.5 months and for men is 23.0 months. Over the age of 60, the values are 36.6 months for women and 11.8 months for men.

In the Swedish cohort, women up to 60 lived 110.7 months and men – 65.4 months. Over 60 years, women - 84.0 months , men-61.6 months.

Survival by T stage

In the Bulgarian group, the average survival in months for patients with T2 tumors was 32.5 months, with T3 – 14.5 months, with T4 – 15.3 months. In the Swedish cohort with T1 tumors it was 89.8 months, with T2 tumors – 57.1 months, with T3 tumors – 66.7 months.

Survival by tumor length

For the Bulgarian patients, it was 42.9 months in the group up to 3 cm and 22.1 months for those with tumors longer than 3 cm. For the Swedish cohort, survival was 91.5 months in patients with tumors up to 3 cm and 61.6 months in the group with tumors greater than 3 cm.
Survival according to N status and according to the ratio of metastatic to total number of lymph nodes was also analyzed.
Survival after non-radical resection – for the Bulgarian R1 group – 4.8 months, for the Swedish group – 43.6 months.
In none of the examined 20 patients with esophageal carcinoma was the presence of HPV-DNA proven, i.e. probably this mechanism of esophageal cancer's occurrence does not occur in Bulgarian patients or occurs less often, which necessitates the study of a larger group of patients.
6 consequences have been drawn that correspond to the set goal and tasks.

7. Contributions and significance of the dissertation work for science and practice

An analysis of current methods of treatment of esophageal carcinoma by stage was performed. New treatment methods are presented in the early stages of the tumor and in patients who are not candidates for surgical resection.

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

The role of perioperative oncological therapy in the complex treatment of this type of carcinoma has been confirmed.

Additional prognostic indicators regarding survival were derived.

A therapeutic algorithm was developed according to the histological type and stage of the tumor.

A DNA bank for esophageal tumors has been created which is stored in the Centre for Molecular Medicine and can be used for future studies.

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8. Evaluation of publications on the dissertations work

Two publications and one scientific communication are presented. One in "Emergency medicine" and one in "Medical review". The scientific communication is at a national forum and is published in a collection of reports.

9. Personal participation of the doctoral student

The doctoral student personally conducted the dissertation research, participating in every step of the process.

10. Abstract (autoreferat)

The abstract is made according to the requirement of the relevant regulations and reflects the main results achieved in the dissertation.

Conclusion

The presented dissertation work contains scientific and applied results, which represent an original contribution to science and meet 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 UMHATEM "N.I.Pirogov". The presented materials and dissertation results fully correspond to the specific requirements of UMHATEM "N.I.Pirogov".

The dissertation paper shows that the doctoral student Todor Yuriev Dzhendov M.D. possesses in depth theoretical knowledge and professional skills in the scientific specialty of Thoracic surgery, demonstrating qualities and skills for independent conduct of scientific research.

Due to the above, I confidently give my positive assessment of the conducted research, presented by the above reviewed dissertation work, abstract, achieved results and contributions, and I propose to the honorable scientific jury to award the educational and scientific degree "Doctor" to Todor Yuriev Dzhendov M.D. in a doctoral program in " Thoracic surgery".

21.07.2022

Reviewer:……..

Assoc. Prof. Teodor Atanasov, M.D., Ph.D., FACS