

REVIEW

From prof. Dr. Krum Sotirov Katsarov, MD, PhD

Head of Gastroenterology department, Military Medical Academy – Sofia.

On the dissertation for acquiring educational and scientific degree "**Doctor**" in the field of higher education 7. Health and Sports, professional field 7.1 Medicine, Doctoral Program "Internal Medicine"

Author: Dr. Krasen Zdravkov Ivanov, PhD student in "Internal Diseases", at "Acibadem City Clinic, University Hospital Tokuda" on the topic "MALIGNANT ASCITES AND PLACE OF PERITONEAL TUNNELED CATHETERS IN THEIR TREATMENT"

Scientific director: Prof. Simeon Stoynov, MD, PhD

1. General presentation of the procedure and the doctoral student

The review has been prepared in accordance with the Academic Staff Development Act (RAS), the Regulations for the Application of the Academic Staff Act (PRZRAS) and the Regulations on the Terms and Conditions for Acquiring Academic Degrees and Occupying Academic Positions (RBRNSZAD) at "Acibadem City Clinic University Hospital Tokuda" EAD. The presented set of materials and documents by Dr. Krasen Ivanov complies with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and the Regulations for its implementation, as well as with the rules of "Acibadem City Clinic University Hospital Tokuda" EAD under the procedure for acquiring NSA "DOCTOR"

The dissertation was discussed and proposed for dissertation defence by an expanded Scientific College of the Clinic of Internal Diseases at Acibadem City Clinic University Hospital Tokuda. At a meeting of the Scientific Council of Tokuda University Hospital EAD (Protocol 19-573/03.10.2023) of the Executive Director and Procurator of the hospital, I was appointed as an external member of the Scientific Jury in connection with the dissertation of Dr. Krasen Ivanov. I'm set to present a review.

No plagiarism is detected from the presented report.

Dr. Krasen Zdravkov Ivanov was born in 1989. In 2014 he graduated in medicine from the Medical University of Varna, and in 2015 he began his professional career as a resident physician in gastroenterology at the Clinic of Gastroenterology at Tokuda Hospital Sofia. In January 2020, after successfully passing a state exam, he acquired a specialty in Gastroenterology at the Medical University of Sofia. then a certificate for "Interventional abdominal ultrasonography – III level" at the Medical University of Plovdiv. In 2023, he was selected as a trainer for Eastern Europe and organized and conducted practical and theoretical courses on tunnel peritoneal catheters.

Annually participates in national and international scientific forums with presentations.

He is a member of the Bulgarian Society of Gastroenterology, Gastrointestinal Endoscopy and Abdominal Ultrasonography and the Bulgarian Association of Ultrasound in Medicine.

2. Topicality of the subject matter

Dr. Krasen Ivanov's dissertation is based on his own practical experience and is dedicated to a current clinical problem in modern gastroenterology-oncology, namely the place of peritoneal tunnel catheters in the treatment of malignant ascites. In recent years, there has been an increase in the number of oncological diseases, respectively, and the number of patients suffering from the problem of malignant ascites. The accumulation of large amounts of fluid leads to very unpleasant symptoms such as difficulty breathing, bloating, nausea, limited mobility, etc. These symptoms can lead to a significant decrease in the quality of life of patients and make it difficult to conduct chemotherapy and specific antitumor treatment of the underlying malignancy. Worldwide, there is a lack of sufficient data and studies on many aspects related to tunnel peritoneal catheters and their application in clinical practice, pre- and post-procedural period, follow-up of patients after the procedure. The role of tunnel peritoneal catheters has not been sufficiently studied, the duration of life and operation of the device has not been traced, complication analysis, analysis of patients' quality of life and ascites associated symptoms before and after catheter insertion. The study of these aspects could contribute to the creation of an algorithm for the selection of patients suitable for this procedure and to the wider application of this type of devices in clinical practice.

The PhD student knows the problem and appreciates the literary material creatively. These data motivate Dr. Ivanov's choice of topic.

3. Characterization and evaluation of dissertation and contributions.

The dissertation work is presented in a fully finished form. It is written in clear scientific Bulgarian on 112 pages. It is structured correctly and in accordance with the generally accepted requirements and includes the following sections: Abbreviations used – 1 page; Introduction – 2 pages; Literature review – 28 pages; Purpose and tasks – 1 page; Materials and methods – 15 pages; Results – 40 pages; Reflection – 9 pages, Main conclusions and contributions – 2 pages and Bibliography – 12 pages. The bibliography contains 1-36 literary sources, of which for the most part have been published in the last 5 years, of which 4 are from Bulgarian authors and 132 from foreign ones.

The introduction is in concentrated form overlaps the literary review in it is a well-formulated problem and the purpose of the dissertation is justified.

The literature review is completely up-to-date and represents (25% of the volume of the dissertation). Extremely well structured and follows logically the course of the diagnostic and therapeutic algorithm. The problem of malignant ascites is very well considered, and all aspects concerning its diagnosis and treatment. The factual prerequisites for the study are derived from the review.

The aim of the dissertation is formulated clearly and precisely in accordance with the topic of the **dissertation** – to study the causes, characteristics and peculiarities of the course of ascites

associated with malignancies in order to determine the role, location and results of the application of tunnel peritoneal catheters.

In order to achieve this objective, the following tasks have been designed and adequately selected:

1. To register the type and stage of oncological disease with a view to assessing the affected organs and systems leading to the occurrence of ascites.
 2. To study the course of ascites syndrome in patients before and after the introduction of tunnel peritoneal catheter - determination of ECOG status, severity of symptoms and type of treatment carried out for the oncological disease.
 3. To determine the macroscopic appearance of ascites and assess its diagnostic severity, to study the results of cytological analysis of ascites fluid with a view to assessing its specificity and sensitivity, to calculate the serum-ascites albumin gradient (SAAG) with a view to determining the type of ascites - transudate and exudate.
 4. To determine the safety and effectiveness of tunnel peritoneal catheters by studying and analyzing the results achieved in our own series of patients who have undergone the procedure (indications for the procedure, preparation of a clinical algorithm for selecting the right patients, registration of complications and adverse events, follow-up)
 5. To assess patients' quality of life and ascites-associated symptoms before and after a tunnel catheter is placed by completing a specialized questionnaire - Edmonton Symptom Assessment System – Modification for Ascites (ESAS:AM).
 6. To record the duration of operation of the catheter and the periodicity of hospitalizations.
 7. On the basis of the conducted research, to propose a clinical algorithm for wider application of tunnel peritoneal catheters in the clinical practice of gastroenterologists in Bulgaria
- The **material** studied is sufficient in volume to meet the set goal and objectives.

The study included 124 patients who underwent the tunnel peritoneal catheter administration procedure between 2016 and 2023. The average age for the entire group of patients was 60.58 ± 11.28 years (from 33 to 87 years). The study is retrospective in nature and includes patients who have passed through the Department of Gastroenterology of Acibadem City Clinic University Hospital Tokuda EAD, where a tunnel peritoneal catheter is placed. The source of the information is the history of disease, medical history, protocol of procedures and data from patient follow-up.

The statistical research methods used are a pledge of credibility and applicability of the cited results. A wide range of specialized statistical interpretative methods was used in the evaluation of the results, which shows high professionalism.

Results and discussion: The dissertation is distinguished by clarity, accuracy and specifics. The results are analyzed in part and correspond to the goals and objectives of the study. The discussion of the results is in-depth, based on the available world scientific information concerning the topic under consideration.

Conclusions and contributions: Dr. Ivanov logically makes 13 conclusions that correspond to the tasks set and the results obtained.

1. The most common oncological disease leading to malignant ascites among the observed group of patients is ovarian cancer, with peritoneal carcinomatosis being the most common pathogenetic mechanism leading to the onset of ascites
2. In the majority of patients tested (73.4%), ascites had exudate characteristics – with SAAG values lower than 1.1 g/dl.
3. The mean value of polymorphonuclear neutrophils in ascites is much higher in hemorrhagic and fibrinous ascites compared to serous macroscopic ascites. ($p=0.007$).
4. Establishes sensitivity of cytological analysis of ascites fluid (45.2%), which is consistent with the data of world authors.
5. Tunnel peritoneal catheters are a highly effective method of treating malignant ascites with low rates of complications.
6. The procedure is mini-invasive, easily assimilated with a short learning curve, does not require expensive equipment and equipment, has high levels of technical success and low procedural risk.
7. Patients with serous and fibrinous macroscopic ascites fluid more often develop complications ($p=0.021$). The risk of developing complications increases with the increase in catheter days ($p = 0.048$)
8. The correct selection of patients, carried out by our proposed algorithm including (anamnestic data, ECOG status, abdominal ultrasound, blood indicators and a negative microbiological sample in front of a procedural one) show that they are key to achieving optimal results
9. A statistically significant relationship ($p = 0.001$) between the ECOG status of patients and the life expectancy and operation of the device is established.
10. The introduction of a tunnel peritoneal catheter eliminates the need for diuretics intake and the risks associated with it. Drainage of small amounts of ascites daily reduces many times the risk of circulatory dysfunction induced by paracentesis (PICD).
11. The procedure improves the quality of life of patients, statistically significant dependence ($p=0.001$) in 8 symptoms - pain, general weakness, nausea, drowsiness, appetite, shortness of breath, bloating and impaired mobility through the Edmonton Symptom Assessment System (ESAS:AM)
12. There is an improvement in the ability of patients to conduct specific chemotherapy treatment .
13. There is a significant reduction in hospitalizations by the 30th and 90th day after the procedure.

The contributions are of a scientifically applied and methodical nature, and the presented algorithm for patient selection and their follow-up is a contribution of a scientifically applied nature.

I accept the above conclusions and contributions of the dissertation. The results of the dissertation Dr. Krasen Ivanov are original and are the work of the dissertant himself. They have a scientifically applied significance and lead to the expansion of our knowledge in the field of treatment of malignant ascites.

4. **The autoreferat** meets the legal requirements. It is written on 57 pages and fully reflects the results set out in the dissertation. In a clear and clear way in summary form it gives an idea of the overall shaping of the work, methods, results and main conclusions.
5. **Judgement of publications and personal contribution of doctrant**

Dr. Krasen Ivanov presents a list of 8 publications and participations in scientific forums related to the topic of the dissertation. Dr. Ivanov has attached 2 publications in national journals, 4 scientific reports in national forums and 2 scientific reports in international forums, and it is noteworthy that Dr. Ivanov is the first author of all. This scientific activity is enough to show that the doctoral student is consistent in his scientific activity and exceeds the national minimum requirements for the educational and scientific degree <<Doctor>>.

I believe that the topics discussed by the doctoral student are among the important issues of modern gastroenterology and express a thorough and consistent assessment of the causes of occurrence, methods of diagnosis and treatment and follow-up of patients with malignant ascites.

CONCLUSION

The dissertation paper contains scientific-theoretical and scientific-applied results that represent an original contribution to science, expanding our knowledge in the field of ascites syndrome. It is written in a strictly scientific style. It meets all the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria (ZRASRB). Dr. Ivanov has completed all tasks and activities set out in the individual curriculum. He has successfully passed an exam for doctoral studies at least in the specialty and methodology of scientific research. The presented materials and dissertation results fully comply with the specific requirements adopted in connection with the Rules of Acibadem City Clinic UMHAT Tokuda EAD for the application of the Law on Active Treatment Tokuda. The PhD student shows qualities and skills for conducting scientific research independently.

Due to the above, I give my *positive assessment* and strongly recommend to the members of the Scientific Jury to positively evaluate the dissertation "MALIGNANT ASCITES AND PLACE OF PERITONEAL TUNNELED CATHETERS IN THEIR TREATMENT" and to award Dr. Krasen Zdravkov Ivanov the scientific and educational degree "DOCTOR" in the field of higher education 7. Health and Sports, professional field 7.1 Medicine, Doctoral Program "Internal Medicine"

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/Prof. Krum Sotirov Katsarov. /

