

O P I N I O N

by: Prof. Dr. Geno Kirov Kirov, MD

on a dissertation submitted by Dr. Stoyan Nikolaev Nikolov

for an educational and academic doctor's degree on topic:

MODERN CLINICAL APPROACHES AND SURGICAL TREATMENT OF PATIENTS WITH BREAST CANCER

General information on the candidate:

Dr. Stoyan Nikolaev Nikolov was born on February 5, 1969. He graduated in medicine in 1996 at the Faculty of Medicine at the Thracian University in Stara Zagora town (Bulgaria). He was acknowledged a specialty in Surgery in 2001 and in 2004 specialized in Oncology.

Breast cancer is a diagnosis of extremely important issue in terms of treatment and as a social problem. In the last 30 years, new and radically different diagnostic, surgical and therapeutic approaches have been introduced into the clinical practice within the overall integrated treatment of this serious pathology. Nevertheless, the approach to each patient remains strictly individual and is directly correlated with the type and stage of the disease. The doctoral thesis of Dr. Stoyan Nikolov is developed and devoted to this problem. It covers 206 pages and is properly structured into chapters: introduction, literature review, purpose and objectives, material and methods, results, discussion, conclusions, contributions, bibliography, and supplement. Cites of 485 authors are used, 3 of them in Cyrillic and 482 in Latin.

The literature review is a voluminous one, including the candidate's analytical and critical view. The morbidity and mortality, surgical anatomy, and staging of breast cancer are all generally considered in relation to the locations and sizes of tumors and spreading in the lymphatic basins. Etiologically, a complex of factors is listed, and

attention is paid to genetic mutations in the mammary gland with high penetration of cancer genes. In the section on the biology of tumors, attention is drawn to the genetic nature of tumor suppressions of different gene complexes, while focusing in particular on TP53, HER2 /new, etc. Further, invasion and metastasis are included, and cell motility is of particular importance for this and it leads to the various types of cellular migration of the tumor process. An integrated model for breast cancer spreads is presented.

Operative approaches focus on the gold standard, i.e. organ-preserving surgery with adjuvant therapy for early cancer. The term "conservative mastectomy" is a complex of techniques combining oncological safety and a positive aesthetic result with the preservation of the areola mamillary complex and the skin.

Molecular phenotypes are an important component, and efforts aim at classifying breast cancer based on gene expression profiles. Attention is drawn to the prognostic and predictive factors associated with the tumor progression, invasion, and metastases and the evaluation of a specific type of adjuvant therapy. In this respect, particular consideration is paid to the histopathological factors and the prognostic evaluation from excellent to very poor prognosis. Tumor biomarkers and biological factors ER, PR and HER-2 are used as a predictive response. Also Ki-67 (a nonhistone DNA-binding nuclear protein), CK 5/6 (intermediate filaments detected by monoclonal antibody CK 5/6) are further provided. Subsequently, all classical and modern methods for accurate breast cancer diagnosis are reviewed. As for medical treatment, emphasis is placed on all surgical methods with their indications, and depending on the age, general and local status of patients, while stressing on reconstruction and axillary staging as well.

Purpose and tasks

The purpose of the academic thesis is formulated in accordance with the title, the Tasks are 5 and all are structured according to the topic and the objective of the research.

Materials and methods

The candidate Dr. Stoyan Nikolov offers in his work 142 patients with breast cancer, operated and treated over a period of 15 years, mainly at the main hospital (UMBAL) in the town of Stara Zagora. All modern diagnostic methods are presented. Furthermore, all operative techniques applied by the author are described in detail: modified radical mastectomy after Patey or Pirogov, subcutaneous mastectomy, quadrantectomy with axillary lymphatic dissection. Two particularly important cases are described – a standard histological examination and immunohistochemical technique performed for all 142 patients. Of particular importance is radiotherapy treatment of patients with organ storage operations and of those with radical mastectomy, with the approach being strictly individual in both groups. Drug treatment is a very important component in the complex treatment of breast cancer, which includes chemotherapy, hormone therapy, targeted therapy, each of them individually presented in a worthy manner in accordance with the modern achievements of medical science. Particular emphasis is placed on Herceptin treatment against HER2 receptor. At the end of this section, statistical methods used in this work are presented.

Results

This chapter of Dr. Nikolov's dissertation makes most contributions. First, all prognostic factors are taken into account and accordingly, appropriate therapies have been assigned and followed up in the overall integrated treatment for breast cancer. The main clinical and pathologic features are reported, with focus on histopathological and immunohistochemical features, molecular subtypes and prognostic variables for stages of the disease. Survival analysis covered 15 years when 46 patients have passed away (32.4%) throughout the reported period. In 27 patients (58.7%) deaths were related to breast cancer while the remaining 19 (41.3%) were caused by another pathology. Survival was reported in relation to tumor size, age, disease stage, histopathology and degree of differentiation, nodal status, HER-2 status, Ki-67 factor, molecular subtype, type and volume of surgical treatment, type of

chemotherapy. It is all about different types of statistical analyses and degree of certainty.

Discussion

This chapter is rather voluminous with some tautology, but it is extremely contributive. It shows the personal experience and analysis of the dissertation compared to international standards. The principles of modern diagnostics and an adequate surgical approach are examined in sequence, with main focus on prognostic and predictive factors. Tumor sizes, degrees of lymphatic aggression, and molecular diagnoses are evaluated, especially with organ-preserving treatment combined with adequate adjuvant therapy, an increase in the number of targeted agents. Anti-HER-2 therapy is reported to improve overall survival and reduce the risk of local recurrence. Of particular importance for the dissertation is the gold standard of conservative surgery, combining oncological safety with a positive aesthetic result. Expression of estrogen and progesterone receptors for hormonal and chemotherapy are especially important for reducing the risk of recidivism and reducing mortality with significantly higher survival rates. The author's personal observation and conclusion is that Luminal B/HER2-positive cancers show unfavorable pathological features, lower survival rates, whereas tumors of the Luminal A subtype have a better prognosis. This is important for determining a strictly individual therapeutic approach and a step towards personalized medicine.

Conclusions

The conclusions are 8 and are reference leads from the tasks set in this highly academic dissertation.

In connection with the dissertation, 3 publications are presented, and in 2 of them the candidate is a leading doctor.

In our opinion, the contributions of this academic work include:

1. For the first time in Bulgaria, a productive and comprehensive breast cancer research is presented.

2. The corresponding sequence in the different moments of diagnostics, preoperative preparation, anesthesia, surgical approach and postoperative therapy is presented.
3. An important contribution is the combination of organ-preserving surgery and a positive aesthetic result.
4. Molecular subtypes and breast cancer predictivity (survival rate) estimates are made for the first time.
5. On the basis of molecular subtypes, the therapeutic strategy is determined and attention is drawn to Luminal B/HER2 for further optimization of therapy.
6. The choice of adjuvant therapy is related to the proliferative activity established by the Ki-67 proliferative factor.
7. Targeted therapy for HER2-positive tumors significantly improves prognosis.
8. Metastases in the axillary lymph nodes are also a main predictive factor.
9. Molecular classification by immunohistochemistry allows for a better predictability and is fundamental at this stage.

Conclusion

Dr. Stoyan Nikolov is a highly skilled and experienced surgeon. His dissertation is of high academic and practical value, which gives me reason to suggest to the highly respected academic jury to award Dr. Stoyan Nikolov an educational and academic degree "Doctor".

Stara Zagora

October 21, 2019

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(Prof. Dr. G. Kirov, MD)