

IMPACT OF TUMOR MOLECULAR PHENOTYPE ON SURVIVAL OF PATIENTS WITH GASTRIC CANCER AFTER RADICAL SURGERY

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The strategy for the treatment of gastric cancer (GC), in particular the use of the extended surgical interventions in different countries varies. The different proportion of specific molecular GC subtypes in various populations frequently is not taken into account for comparing treatment outcomes. This pilot study analyzes the association of survival of GC patients after the extended combined surgical interventions depending on the molecular subtype of the tumors. An improved survival for patients with diffuse cancer types (p53⁻, VEGFR⁺, HER2/neu⁺, Ki-67⁺ phenotype) was demonstrated. The authors propose their point of view on the importance of recognizing GC molecular heterogeneity.

Key Words: gastric cancer, molecular classification, tumor biology.

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Gastric cancer (GC) is the third leading cause of worldwide cancer mortality. In Ukraine, the majority of GC patients (68.8%, 7,669 cases) present the late stages of malignant disease at initial diagnosis. At the same time, only 45.5% of patients received special treatment, and 58.1% did not survive one year from the moment of diagnosis [1]. GC is often detected at a stage that narrows the options for the effective surgical treatment. Despite the extended surgical interventions (combined and extended operations, lymph node dissection in the volume of D2, D3), the use of modern schemes of chemotherapy, the indices characterizing the effectiveness of such treatment (average life expectancy, cancer-specific survival rate) leave much to be desired.

The treatment of the advanced GC envisages the combined and multi-organ surgical interventions — multivisceral resection (MVR) [2, 3]. Taking into account the massive tumor invasion and lymph node involvement, surgical intervention is always combined with dissection of various groups of lymph node defined as lymph dissection in the extent of D2 or D3. Standard D2 dissection with radical surgery reduces mortality and increases

five-year survival. Nevertheless, D3 dissection with removal of para-aortal lymph nodes is the subject of the discussion among the oncologists.

The fact of the discrepancy in the outcomes of the surgical treatment of GC encompassing the extended lymphatic dissections between conventional East and Western practices is well known [4]. While since the 90s of the last century, lymphatic dissections for GC became the standard of the surgical treatment in Japan, in Europe and North America for the past 20 years there has been still a debate about the necessity of this technique. For example, in Germany D2 lymph dissections were included into the national guidelines as late as in 2010. The famous British MAGIC study, which has become a classic and even encyclopedic one, is still criticized for the fact that D2 lymph dissection was provided only to 60% of the enrolled GC patients. As the involuntary observers and to some extent participants in this discussion, our team posed a simple question: *whether the dissimilar data on GC treatment obtained by different groups of authors [5, 6] could be explained by the different contribution of the genetic and biological parameters to the tumor biology in different human populations?* Therefore, the search for new ways of the GC assessment and prognosis in each specific cancer case is extremely relevant [7]. The importance of the analysis of molecular markers and molecular classifications of GC for answering the question of the disparity of GC outcomes

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Abbreviations used: ACRG – Asian Cancer Research Group; GC – gastric cancer; MVR – multivisceral resection; TCGA – The Cancer Genome Atlas Consortium.

in different human populations cannot be overemphasized [8].

Currently, there are at least two molecular classifications of GC: classification of the Asian Cancer Research Group (ACRG) and The Cancer Genome Atlas Consortium (TCGA) [9]. ACRG [10] classifies GC into microsatellite-unstable and microsatellite-stable; in turn, microsatellite-stable cancer is divided into p53 positive, p53 negative and microsatellite-stable cancer with the presence of epithelial-mesenchymal transition. TCGA distinguishes similar categories with the presence of microsatellite-stable, genetically stable, chromosomally unstable, and Epstein — Barr virus-associated. Nevertheless, the association between outcome of the surgical treatment and molecular GC subtypes has not been extensively analyzed [11].

Our team of oncologists from the National Cancer Institute of the Ministry of Health of Ukraine in Kyiv and Odesa Regional Clinical Cancer Center attempted to analyze whether the survival of GC patients who underwent radical surgical interventions varies according to molecular subtypes of GC. The data on 221 GC patients treated in 2007–2013 (143 gastrectomies and 78 distal subtotal resections) were evaluated. All patients gave the informed consent for using their data for scientific purposes. The data on a group subjected to gastrectomies, distal subtotal resections + D2, in combination with MVR (26 patients) that demonstrated better survival in comparison with other modes of surgical treatment were further analyzed in detail.

Focusing on the combination of biomarkers [12], we delineated four biological types of GC characterized as follows: 1) p53⁻, VEGFR⁺, HER2/neu⁺, Ki-67⁺ — diffuse cancer; 2) p53⁺, VEGFR⁻, HER2/

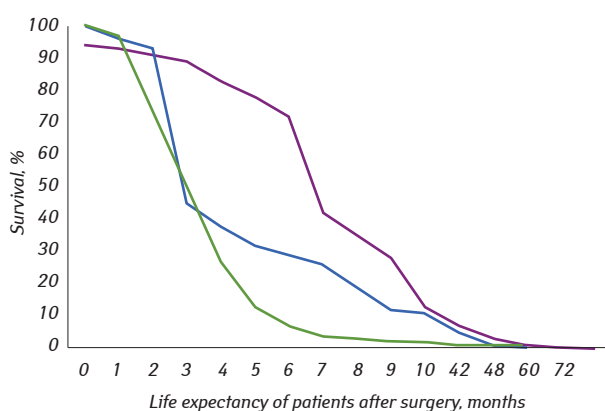


Figure. Survival of GC patients with different biological tumor types after extended combined surgical interventions (D2 + MVR). Kaplan — Meier curves for groups 1 (violet), 2 (blue) and 4 (green) demonstrate significant difference verified by log-rank test ($p < 0.05$). The group 3 is omitted since only 2 cases with this phenotype were present

neu⁺ — intestinal form; 3) p53⁺, VEGFR⁻, HER2/neu⁻ — mucinous form, “non-cardia cancer I”; 4) p53⁻, VEGFR⁻, HER2/neu⁺ — “non-cardia cancer II”. These groups were in many aspects similar to TCGA classification [9] and shared some features with ACRG classification [10] focusing on p53 status and microsatellite instability.

As shown in the Figure, the survival of GC patients after the extended combined surgical interventions (D2 + MVR) depended on the biological type of the tumor. Kaplan — Meier curves for groups 1, 2 and 4 diverge significantly. An improved survival of patients with diffuse cancers (group 1) was demonstrated.

Therefore, the survival of patients with GC of different biological types after the identical extended surgical treatment differs significantly. The survival difference associated with the biological type of GC was demonstrated also in GC patients subjected to other modes of surgery, even though the format of the article does not allow us to describe all the biological features between which the corresponding comparisons were made. Such features as differentiation grade, the number of detected metastases in distant intraoperative lymph nodes, the presence of perineural and perivascular growth and other criteria should be taken into account. Therefore, the number of the subgroups with different biological features of GC increases substantially. Unfortunately, at present the number of patients in each subgroup is too small for valid statistical comparisons. Nevertheless, our data point to the fact that the recognition of GC molecular heterogeneity could be prognostically important allowing for improvement of treatment outcomes.

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ВПЛИВ МОЛЕКУЛЯРНОГО ФЕНОТИПУ ПУХЛИНИ НА ВИЖИВАНІСТЬ ХВОРИХ НА РАК ШЛУНКА ПІСЛЯ РАДИКАЛЬНОГО ХІРУРГІЧНОГО ВТРУЧАННЯ

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Стратегія лікування пацієнтів з раком шлунка, зокрема, застосування радикальних хірургічних втручань, у різних країнах є неоднаковою. Разом з тим різне співвідношення тих чи інших молекулярних субтипів раку шлунка в різних популяціях нерідко не береться до уваги під час порівняння результатів лікування. У нашому пілотному дослідженні проаналізовано зв'язок між молекулярним субтипом пухлин та виживаністю хворих на рак шлунка після розширених комбінованих хірургічних втручань. Продемонстровано кращі показники виживаності в разі дифузного раку шлунка з фенотипом пухлини p53⁻, VEGFR⁺, HER2/neu⁺, Ki-67⁺. Автори пропонують свій погляд на клінічне значення молекулярної гетерогенності раку шлунка.

Ключові слова: рак шлунка, молекулярна класифікація, біологія пухлини.