

GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 7-8 (364-365) Июль-Август 2025

ТБИЛИСИ - NEW YORK



ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press.
Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებშიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html. В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საყურადღებო!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე, დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემავსებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიის ფოტოსურათები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

| | |
|---|---------|
| Babry I. Oren, Marina I. Devdariani, Gela V. Beselia, Nino N. Sikharulidze, Manana G. Dashniani, Maia A. Burjanadze, Ia R. Kvachakidze, Marina I. Nebieridze, Lena Sh. Davlianidze, Lali M. Gumberidze, Nodar P. Mitagvaria. ROLE OF ANTIOXIDANT FOLIUM EXPOSURE ON OXIDATIVE STRESS IN A VALPROIC ACID-INDUCED ANIMAL MODEL OF AUTISM..... | 6-15 |
| Hajdi Gorica, Pavlo Djamandi, Gentian Vyshka. DELAYED ONSET OF MYASTHENIA GRAVIS FOLLOWING COLECTOMY FOR ULCERATIVE COLITIS: A CASE STUDY..... | 16-17 |
| Zhadyra Yersariyeva, Bagdad Suleyeva, Botagoz Turdaliyeva, Yeldos Tussipbayev. HEMOSTASIS GENE POLYMORPHISM IN RETINAL VASCULAR OCCLUSION: A SYSTEMATIC REVIEW..... | 18-28 |
| Ilia Nakashidze, Nameera Parveen Shaikh, Shota Nakashidze, Aleena Parveen Shaikh, Sarfraz Ahmad, Irina Nakashidze. EVALUATION OF TNF- α LEVELS IN MALE PATIENTS WITH STROKE: PROGNOSTIC IMPLICATIONS..... | 29-32 |
| Yerbolat Iztileuov, Marat Iztileuov, Altynbek Dushmanov, Gulmira Iztileuova. PREVENTION IN THE PARENTAL GENERATION OF EXPOSED RATS: CONSEQUENCES OF TOXIC EXPOSURE TO CHROMIUM AND GAMMA IRRADIATION IN AN EXPERIMENTAL MODEL..... | 33-45 |
| Rashid Nassar, Nadine Khayyat, Michele Halasa, Fahad Hussain. TRAUMATIC ANTERIOR SHOULDER INSTABILITY (TUBS): A NARRATIVE REVIEW OF CURRENT LITERATURE..... | 46-50 |
| Albadawi Abdelbagi Talha, Mawaheip A. Abdo Jeweser, Abubakr Ali Elamin Mohamed Ahmed, Abdelrahman Eldaw Mohammed, Elhadi Abdalla Ahmed, GadAllah Modawe, Sanaa Elfatih Hussein. THE HBV AND HCV SEROPREVALENCE AMONG BLOOD DONORS IN AI-DAMAZIN STATE, SUDAN: A THREE-YEAR RETROSPECTIVE STUDY..... | 51-54 |
| Hiba Salah Hasan, Teeb Ali, Kadhim Adnan Ali, Al Hassan Ali, Hany A. Al-hussaniy. MODELING DRUG-ORGAN INTERACTIONS AND OPTIMIZING IMMUNOTHERAPY: A QUANTITATIVE SYSTEMS PHARMACOLOGY AND ODRONEXTAMAB DYNAMICS..... | 55-60 |
| Zilola Mavlyanova, Davron Ravshanov, Malika Ibragimova, Lola Irbutaeva, Khalimova Fariza, May K. Ismail, Shawgi A. Elsiddig, Marwan Ismail, Salma E R Mohamed, Sara Mohammed Ali. PROGNOSTIC SIGNIFICANCE OF PROLIFERATION (KI-67) AND ANGIOGENESIS (CD34) MARKERS IN MENINGIOMAS FOR THE DEVELOPMENT OF REHABILITATION STRATEGIES..... | 61-65 |
| A.R. Abzaliyeva, K.K. Kurakbayev, A.R. Ryskulova, Z.R. Abzaliyev, E. Tasmagambet, D.Zh. Saussanova. TURNOVER INTENTIONS AMONG PHYSICIANS AND NURSES IN KAZAKHSTAN DURING THE COVID-19 PANDEMIC: A CROSS-SECTIONAL STUDY OF PSYCHOLOGICAL AND PROFESSIONAL CHALLENGES..... | 66-72 |
| A.A. Mammadov, A.N. Mustafayev, A.H. Aliyev. RADIOLOGICAL IMAGING METHODS FOR ACCURATE DIAGNOSIS OF ABDOMINAL POSTOPERATIVE COMPLICATIONS..... | 73-76 |
| I.A. Lebedev, E.V. Zakharchuk, Yu.V. Boldyreva, I.A. Aptekar, E.I. Malinina. OSSIFICATION OF THE POSTERIOR LONGITUDINAL LIGAMENT: A CASE REPORT AND LITERATURE REVIEW..... | 77-79 |
| Zhanar Balmukhamedova, Gulmira Derbissalina, Aliya Dzholdasbekova, Dariga Blyalova, Luiza Murzakhalova. SPECKLE-TRACKING ECHOCARDIOGRAPHY FOR EARLY DETECTION OF SUBCLINICAL SYSTOLIC DYSFUNCTION IN PERIMENOPAUSAL WOMEN WITHOUT APPARENT DIASTOLIC DYSFUNCTION..... | 80-86 |
| Arkam Thabit Al Neama, Musab Mohammed Khalaf, Ahmed A.J. Mahmood. PATTERNS OF ACETYLCHOLINESTERASE AND BUTYRYLCHOLINESTERASE ACTIVITY IN COMMON CARDIOVASCULAR PHENOTYPES..... | 87-94 |
| Argjira Veseli, Shefqet Mrasori, Ivana Čuković-Bagić, Lul Raka, Kaltrina Veseli, Enis Veseli. PARENTAL QUALITY OF LIFE WHEN RAISING CHILDREN WITH AUTISM SPECTRUM DISORDER: A NARRATIVE REVIEW..... | 95-100 |
| Anas Ali Alhur, Daliya T. Sendi, Miad M. AlZahrani, Layla T. Abusharha, Rahaf Y. Abudaak, Rahmah Alsinan, Rama R. Alharbi, Lamia Almadhi, Laila M. Alotaibi, Mona A. Hadadi, Shaima H. Alattas, Fatimah Almisbah, Fathi Almisbah, Abdulrahman Alrashed, Kawkab Alharbi. EVALUATING THE TRUSTWORTHINESS OF CHATGPT-GENERATED HEALTH INFORMATION AMONG FUTURE HEALTH CARE PROFESSIONALS..... | 101-106 |
| Ting-Ting Wang, Yan Wang. HUMANISTIC CARE NURSING FOR PATIENTS IN THE OPERATING ROOM DURING THE PERIOPERATIVE PERIOD: FULL-CYCLE CARE FROM PHYSIOLOGY TO PSYCHOLOGY..... | 107-109 |
| Zauresh Barmanasheva, Mariya Laktionova, Anna Onglas, Ayaulym Kossetova, Ivan Melnikov. PREVALENCE AND RISK FACTORS OF UTERINE FIBROIDS IN WOMEN OF REPRODUCTIVE AGE: A FACILITY-BASED STUDY IN AMEGACITY..... | 110-120 |
| Bolat Ashirov, Assel Kassymova, Jamilya Mansurova, Andrey Orekhov, Meiramgul Tokbulatova, Mirgul Kapakova, Zhanar Toktarova, Aisulu Zhunuspekova. PROGNOSTIC MARKERS OF ISCHEMIC AND HEMORRHAGIC COMPLICATIONS IN PATIENTS WITH ATRIAL FIBRILLATION AFTER PERCUTANEOUS CORONARY INTERVENTION..... | 121-128 |

| | |
|---|---------|
| Khalilov Sh. Dzh. ELECTROCARDIOGRAPHY CHARACTERISTICS OF THE PATIENTS WITH NON-ST-ELEVATION MYOCARDIAL INFARCTION (NS TEMI)..... | 129-132 |
| Salome Kordzaia, Elene Dolmazashvili, Khatuna Tsiklauri, Lasha Khmaladze, Nana Chikhladze. FROM INFUSION REACTION TO IMMUNE CASCADE: A CASE OF SEQUENTIAL TAXANE AND CAPECITABINE TOXICITIES IN TRIPLE-NEGATIVE BREASTCANCER..... | 133-136 |
| Yu Zhu, Fandong Zeng, Weiwei Chang, Liying Wen, Lijun Zhu, Yuelong Jin. AN EMPIRICAL STUDY ON THE ASSOCIATION BETWEEN ASPIRATION INDEX AND ACADEMIC PERFORMANCE AMONG PREVENTIVE MEDICINE STUDENTS..... | 137-142 |
| Alaa O Ahmed, Mubarak S Karsany, Mohamed Elfatih Abdelwadoud, Mutaz Ali, Osama Mohamed, Amged Gaffer Mostafa, Hussam Ali Osman, Elryah I Ali, Elyasa Elfaki, Tagwa Yousif Elsayed Yousif, Ayman H. Alfeel, Mohammed Ibrahim Saeed. MOLECULAR DETECTION OF HIGH RISK HUMAN PAPILLOMA VIRUS SUBTYPES IN CERVICAL SMEARS AMONG SUDANESE WOMEN..... | 143-149 |
| Tchernev G, Tchernev KG Jr, Krastev DS, Krastev NS, Kordeva S. DERMATOLOGIC SURGERY ROUNDS: RECONSTRUCTIVE SURGERY EMPLOYING THE SHARK ISLAND FLAP FOR BASAL CELL CARCINOMA AFFECTING THE NASAL ALA..... | 150-153 |
| Saltanat Imanalieva, Bayan Sagindykova, Rabiga Anarbayeva, Murat Omirali, Gulnara Ospanova, Murat Ashirov. CURRENT STATUS AND PROSPECTS FOR THE DEVELOPMENT OF PEDIATRIC DOSAGE FORMS BY THE EXAMPLE OF COMBINED MELOXICAM AND VITAMIN B12 TABLETS..... | 154-167 |
| Ahmed Miri Saadoun. INCIDENCE OF PRESSURE SORE IN THE INTENSIVE CARE UNIT AT AL-DIWANYIA TEACHING HOSPITAL..... | 168-171 |
| Isoyan A.S, Danielyan M.H, Antonyan I.V, Azizyan N.H, Mkrtchyan A.A, Karapetyan K.V, Nebogova K.A. MORPHOHISTOCHEMICAL ANALYSIS OF CORTICAL STRUCTURES IN AN EXPERIMENTAL MODEL OF PROLONGED COMPRESSION SYNDROME OF THE HIND LIMB IN RATS..... | 172-179 |
| Abdulaziz Alroshodi, Faisal A. Al-Harbi, Rasil Sulaiman Alayed, Fahad M. Alharbi, Khalid A Alkhalifah, Mayadah Assaf Alawajji, Ibrahim S. Alsabhawi. FACTORS IMPACTING HEMODIALYSIS TREATMENT ADHERENCE IN END-STAGE RENAL DISEASE PATIENTS RECEIVING IN- CENTER HEMODIALYSIS IN QASSIM REGION..... | 180-187 |
| Gulshat Alimkhanova, Marat Syzdykbayev, Rinat Ashzhanov, Kulsara Rustemova, Maksut Kazymov, Rustem Kazangapov, Asem Kazangapova, Saule Imangazinova, Yernar Kairkhanov, Bazar Tuleuov, Sanzhar Khalelov, Roman Khripunov, Samatbek Abdrakhmanov, Abay Mijatov. THE TRANSVERSUS ABDOMINIS PLANE BLOCK AS A METHOD OF MULTIMODAL OPIOID-SPARING POSTOPERATIVE ANALGESIA: A NARRATIVE REVIEW..... | 188-194 |
| Zhengmei Fang, Xiaoling Ran, Lijun Zhu, Yingshui Yao, Yuelong Jin. THE IMPACT OF BMAL1 GENE POLYMORPHISM ON SLEEP QUALITY IN HEALTHY CHINESE YOUTH: A GENDER-SPECIFIC ANALYSIS..... | 195-201 |
| Muwafaq H. Zaya, Ahmed A. J. Mahmood, Musab M. Khalaf. CROSS SECTIONAL EVIDENCE FOR OPPOSING EFFECTS OF HYPERGLYCAEMIA AND HYPERLIPIDAEMIA ON CHOLINESTERASEACTIVITIES..... | 202-210 |
| Erleta Muçaj, Erëza Durmishi, Serbeze Kabashi Muçaj, Leart Kuçi, Elza Muçaj, Gerta Durmishi. CHALLENGES IN RADIOLOGICAL DIAGNOSIS: CRANIOPHARYNGIOMA VS ASTROCYTOMA..... | 211-214 |
| Uday Mahajan, Imran Khan, Ria Gupta, Meraj Akhtar, Vibhore Gupta, Edward Spurrier, Mohamed Kabary, Adnan Asif, Salman Shoukat Ali Parpia. NAMING CONVENTIONS FOR UNIDENTIFIED PATIENTS IN EMERGENCY AND TRAUMA SETTINGS: A NARRATIVE REVIEW..... | 215-218 |
| Xuexue Li, Wenjie Wen, Dandan Ren. MOLECULAR MECHANISMS OF DIABETIC PERIODONTITIS: IDENTIFICATION OF KEY OXIDATIVE STRESS-RELATED GENES AND POTENTIAL THERAPEUTIC ROLE OF METFORMIN THROUGH MMP14 AND PXDN..... | 219-231 |
| Davron Ravshanov, Zilola Mavlyanova, Kholmirezayev Bakhtiyor, Malika Tursunovna, Khalimova Fariza. HISTOPATHOLOGICAL PREDICTORS AND FUNCTIONAL RECOVERY IN PATIENTS WITH INTRACRANIAL MENINGIOMAS..... | 232-240 |
| Aymuhambetov Y, Khismetova Z A, Iskakova N, Akhmetova K, Serikova-Esengeldina D, Shalgumbayeva G.M. ASSESSMENT OF QUALITY OF LIFE IN BREAST CANCER PATIENTS BY USING EORTC QLQ-C30 QUESTIONNAIRE IN EAST KAZAKHSTANREGION..... | 241-248 |
| Yujing Tao, Long Hua, Liu Zhang, Ying Feng, Liying Wen, Weiwei Chang. THE CORRELATION BETWEEN STRESS, ACADEMIC PERFORMANCE, AND SLEEP DISTURBANCES AMONG HIGH SCHOOL STUDENTS IN ANHUI PROVINCE: A CROSS-SECTIONAL STUDY..... | 249-257 |
| Fahad AlAmr, Muhannad Essa S. Alghamdi, Ahmed Saeed A. Alghamdi, Osama Khamis A. Alghamdi, Hassan Mahfouz B. Alghamdi, Osama Mesfer S. Alghamdi, Abdullah Ali A. Almimoni, Abdulmalik Ahmed S. Al-Zahrani. PREVALENCE AND ASSOCIATED RISK FACTORS OF NOCTURNAL ENURESIS AMONG CHILDREN AGED 5-18 YEARS IN ALBAHA REGION, SAUDI ARABIA..... | 258-263 |

| | |
|--|---------|
| Aya Saad Aldewachi, Mohammed I Aladul. APPETITIVE TRAITS AND QUALITY OF LIFE IN WOMEN WITH OBESITY USING GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS: INSIGHTS FROM A PCOS-ENRICHED SAMPLE..... | 264-269 |
| George Shaburishvili, Nikoloz Shaburishvili, Georg Becker, Solomon Zeikidze, Bacho Tsiklauri. INCIDENCE OF ADVERSE EVENTS RESULTING FROM BETA-BLOCKER TITRATION IN PATIENTS WITH HEART FAILURE..... | 270-279 |
| Blushinova A.N, Orazalina A.S, Shalgumbayeva G.M. INDUCED ABORTION IN KAZAKHSTAN: WOMEN'S PERCEPTIONS AND EXPERIENCES BASED ON CROSS-SECTIONAL STUDY..... | 280-288 |
| Qunru Hu, Liying Wen, Jingqi Zhang, Weiwei Chang, Yuelong Jin, Anshi Wang, Lijun Zhu. IS CORE SELF-EVALUATION A PROTECTIVE FACTOR FOR COLLEGE STUDENTS' MARITAL ATTITUDES? THE MODERATING ROLE OF PSYCHOLOGICAL STATUS..... | 289-294 |
| Gulfariza Gani, Ubaidilla Datkhayev, Kairat Zhakipbekov, Serzhan Mombekov, Murat Ashirov, Nurgali Rakhymbayev, Zhanerke Seitova. STUDY OF THE CHEMICAL COMPOSITION AND ANTIMICROBIAL ACTIVITY OF SUBCRITICAL CO ₂ EXTRACT FROM <i>EUPHORBIA HUMIFUSA</i> WILLD..... | 295-302 |
| Maysoon Mohammed Hassan, Mohammed Abdulwahab Ati Al-askeri, Naseer Kadhim Jawad. PROGNOSTIC IMPACT OF EGFR2 AND KI-67 OVEREXPRESSION WITH DOWNREGULATION OF <i>miR-17</i> AND <i>miR-1307</i> IN FEMALE BREAST CANCER PATIENTS..... | 303-313 |
| Imzharov Talgat Abatovich, Zhakiev Bazylbek Sagidolievich, Sarkulov Marat Nukinovich, Pavlov Valentin Nikolaevich, Kurmangaliev Oleg Maratovich. THE EFFECTIVENESS OF METAPHYLAXIS OF NEPHROLITHIASIS DURING PERCUTANEOUS NEPHROLITHOTRIPSY: A SYSTEMATIC REVIEW AND META-ANALYSIS..... | 314-322 |
| Yan Wang, Ting-Ting Wang, Chang-Sheng He. PROGRESS IN T-CELL IMMUNE RESEARCH ON HYPERLIPIDEMIC PANCREATITIS..... | 323-326 |
| Marwan I Abdullah. MINING THE CELLMINER DATABASE TO IDENTIFY SHARED BIOMARKERS OF 5-FU AND OXALIPLATIN RESPONSE..... | 327-341 |
| Shyngys Adilgazyuly, Tolky Bulegenov, Akmaral Mussakhanova, Tasbolat Adylkhanov, Kanat Abdilov, Zhannur Altybayeva, Gulmira Bazarova, Malike Kudaibergenova, Makpal Alchimbayeva, Aigul Utegenova, Gulnara Otepova. ASSESSING THE INFLUENCE OF MEDICAL EDUCATION REFORMS ON ONCOLOGIST WORKFORCE AND LUNG CANCER MORTALITY IN KAZAKH-STAN: AN INTERRUPTED TIME SERIES ANALYSIS WITH PREDICTIVE MODELING OF NATIONWIDE DATA FROM 1998 TO 2023..... | 342-351 |
| Wen-Wen Liu, Zhi-Juan Xu, Fang Xu. NEW INSIGHTS INTO THE PATHOGENESIS AND TREATMENT ADVANCES OF AGE - RELATED MACULAR DEGENERATION..... | 352-354 |
| Zhamilya Zholdybay, Zhanar Zhakenova, Madina Gabdullina, Yevgeniya Filippenko, Suria Yessentayeva, Galymzhan Alisherov, Aigerim Mustapaeva, Jandos Amankulov, Ildar Fakhradiyev. ⁶⁸ GA-FAPI PET/CT IN DIAGNOSIS OF THE BREAST CANCER DEPENDING ON THE MOLECULAR SUBTYPES AND EXPRESSION STATUS OF HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2/NEU)..... | 355-363 |
| A.I. Rybin, V.E. Maksymovskiy, O.V. Kuznetsova, V.V. Osyk, A.S. Bohdan. THE RESULTS OF LIFE QUALITY ASSESSMENT IN PATIENTS WITH PRIMARY OVARIAN CANCER DURING TREATMENT: EFFECT OF DIFFERENT TACTICS AND HIPEC..... | 364-368 |
| Miranda Sejdiu Abazi, Arbër Prokshaj, Shpëtim Prokshaj, Fitim Alidema, Nora Leci, Linda Abazi Morina. ASSESSMENT OF PRACTICAL PERFORMANCE IN ORTHODONTIC CLASP FABRICATION AMONG DENTAL TECHNICIAN STUDENTS AT UBT: A REAL-TIME ANALYSIS OF WORKING TIME AND PERCEIVED STRESS..... | 369-377 |
| Abylay Baimakhanov, Ainash Oshibayeva, Temirkhan Kozhakhmetov, Nazarbek Omarov, Dinara Akhmetzhanova, Berikuly Duman. RESULTS OF MEDICAL CARE FOR PERSONS WITH POLYTRAUMA IN ALMATY AND CORRECTION OF THE ORGANIZATIONAL APPROACH..... | 378-382 |
| Khatia Mikeladze, Nino Chikadze, Nino Gachechiladze, Marina Tediashvili, Irina Datikashvili-David, Peter Lydyard, Nina Porakishvili. SERUM IL-6, IL-12, AND IL-10 LEVELS IN EARLY-STAGE, UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS: INSIGHTS FROM GEORGIA..... | 383-387 |
| Musayeva H.H. FREQUENCY OF COMPLICATIONS IN PATIENTS WITH ADENTIA (BASED ON ARCHIVAL DATA)..... | 388-393 |
| Hong-Xia Wang, Xiao-Xia Hou, Jie Xu. NURSING RESEARCH ON EMERGENCY GASTROSCOPIC TREATMENT OF UPPER GASTROINTESTINAL FOREIGN BODIES..... | 394-396 |
| Tolegenova Z.Zh, Tokanova Sh.E, Baibussinova A.Zh, Kalikhanova K, Iskakova A.M, Shalgumbayeva G.M. ASSESSMENT OF INFECTIOUS DISEASE RISK FACTORS, INCLUDING COVID-19, AMONG HEALTHCARE WORKERS IN EAST KAZAKHSTAN REGION..... | 397-405 |

Bassam A. Al- jabery, Majid R. Al-bahrani.

ENVIRONMENTALLY SAFE CsPbBr₃/MXene/MWCNTs HYBRID NANOCOMPOSITES: OPTOELECTRONIC AND STRUCTURAL CHARACTERISTICS FOR POSSIBLE BIOMEDICAL AND HEALTH APPLICATIONS.....406-414

Hasan AlAidarous.

PIGMENTED VILLONODULAR SYNOVITIS IN THE ANKLE OF A PEDIATRIC PATIENT: A CASE REPORT.....415-419

Kuat Zhussupov, Nazarbek Omarov, Sagit Imangazinov, Saule Imangazinova, Yernar Kairkhanov, Olga Tashtemirova, Rustem Kazangapov, Aldiyar Masalov, Darkhan Otkenov.

ENDOSCOPIC INJECTION HEMOSTASIS AND LOCAL TREATMENT OF GASTRODUODENAL BLEEDING. LITERATURE REVIEW AND OWN DEVELOPMENTS.....420-424

⁶⁸Ga-FAPI PET/CT IN DIAGNOSIS OF THE BREAST CANCER DEPENDING ON THE MOLECULAR SUBTYPES AND EXPRESSION STATUS OF HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2/NEU)

Zhamilya Zholdybay¹, Zhanar Zhakenova¹, Madina Gabdullina^{1,2}, Yevgeniya Filippenko¹, Suria Yessentayeva³, Galymzhan Alisherov^{1,4}, Aigerim Mustapaeva¹, Jandos Amankulov^{1,5}, Ildar Fakhradiyev^{1,6*}.

¹*S.D. Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan.*

²*Al-Farabi Kazakh National University (Faculty of Medicine and Healthcare), Almaty, Kazakhstan.*

³*Kazakh-Russian Medical University (Oncology and Radiology Department), Almaty, Kazakhstan.*

⁴*Limited Liability Company "HiLife" (Department of Nuclear Medicine), Almaty, Kazakhstan.*

⁵*Kazakh Oncology Institute (Radiology and Nuclear medicine Centre), Almaty, Kazakhstan.*

⁶*College of medicine, Korea university, Seoul, South Korea.*

Abstract.

This study evaluates the diagnostic potential of ⁶⁸Ga-FAPI PET/CT in women with newly diagnosed breast cancer (BC), with an emphasis on molecular subtypes and HER2/neu expression status. A total of 34 patients (median age: 55.5 years; range: 26–80) with histologically confirmed invasive BC underwent ⁶⁸Ga-FAPI PET/CT prior to initiating treatment. Tumors were classified according to immunohistochemical markers (ER, PR, HER2/neu, Ki-67) into Luminal A, Luminal B (HER2-negative and HER2-positive), and triple-negative subtypes. A total of 46 malignant lesions were identified, including multicentric tumors in 9 patients. The highest FAPI uptake (SUVmax and TBR) was observed in HER2-positive tumors, particularly Luminal B HER2-positive subtypes. Statistically significant differences in FAPI uptake and TBR were found between tumors with HER2 overexpression and those with HER2-zero expression ($p = 0.015$). The study demonstrates that ⁶⁸Ga-FAPI PET/CT may enhance diagnostic accuracy in aggressive BC phenotypes, particularly HER2-overexpressing tumors, and could serve as a valuable complementary imaging modality for staging and treatment planning.

Key words. ⁶⁸Ga-FAPI PET/CT, breast cancer, HER2/neu, tumors.

Introduction.

The breast cancer (BC) remains a significant public health concern due to high rates of morbidity and mortality [1]. According to GLOBOCAN, 2,308,897 women were diagnosed with BC in 2022, of which 665,684 cases were fatal [2]. In the Republic of Kazakhstan, BC occupies a leading position in the structure of cancer morbidity (1st place) and mortality (4th place) among women, the morbidity is 36.9 cases and the mortality is 12.3 cases per 100 thousand population [3].

The increasing morbidity and mortality of BC requires the constant improvement of diagnostic methods and the search for new approaches that allow the timely diagnosis and selection of the optimal treatment strategy.

Positron emission tomography (PET/CT) with ¹⁸F-FDG plays a crucial role in the detection, staging, and evaluation of the effectiveness of treatment [4,5]. Along with advantages, some studies have shown the limitations of ¹⁸F-FDG PET/CT due to the high background activity, low glucose and hexokinase

activity in some malignant neoplasms, as well as insufficient specificity of the method [5,6].

The fibroblast activation protein inhibitor (FAPI) labeled with gallium 68 (⁶⁸Ga) has demonstrated positive outcomes in some malignant neoplasms [5], including BC [5-9]. However, further studies are required to assess its diagnostic value [7-11].

The fibroblast activation protein (FAP) is expressed by cancer-associated fibroblasts (CAFs), which are involved in various aspects of BC, including tumor proliferation, metastatic progression, treatment response, and resistance to cancer therapy [12-14]. The recent studies have shown that changes in features of the breast cancer microenvironment may serve as valuable prognostic indicators and support the development of innovative cancer treatment methods [15].

Prognostic factors for BC include cellular or tissue biomarkers presented in the tumor tissue. Based on the status of estrogen receptors (ER), progesterone (PR), human epidermal growth factor receptor 2 (HER2/neu), as well as the tumor cell proliferation index determined by Ki-67 antigen (Ki-67) expression, distinct subtypes of BC are identified, which differ significantly in prognosis and therapeutic targets. These usually include Luminal A, Luminal B, HER2-enriched subtype, triple negative and normal-like molecular subtypes of BC [16].

The human epidermal growth factor receptor 2 (HER2) serves as a therapeutic target for therapy. In order to standardize and ensure the accurate detection of BC with amplified HER2 gene or overexpressed protein to predict a favorable outcome from HER2-targeted therapy, American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) updated the practical guidelines for testing the human epidermal growth factor receptor 2 in BC, in 2018 [17]. According to the updated guidelines, HER2 expression statuses are divided into three groups: increased HER2 expression, low HER2 expression, and zero HER2 expression [17-19], i.e., the previous HER2-negative status has been reclassified to a status with low HER2 expression and zero HER2 expression.

High expression of HER2/neu receptor serves as a predictor of tumor sensitivity to the targeted therapy, which requires strict patient selection [17]. Molecular imaging techniques may play a meaningful role in improving the detection and treatment outcomes. A number of researchers suggest that FAPI targets the tumor microenvironment, and its role as a diagnostic agent

for BC imaging requires further study [20,21], which revealed that senescent CAFs are present in BC subtypes.

Therefore, the objective of the study is to evaluate the capabilities of ^{68}Ga -FAPI PET/CT in BC imaging depending on its molecular subtypes and expression status of HER2/neu receptor.

Materials and Methods.

Selection of patients:

This study was approved by the local Ethics Committee (No. 1641; individual registration number: AR19679719). Each participant in the study signed an informed consent.

^{68}Ga -FAPI PET/CT was performed in 38 women with newly diagnosed, pathomorphologically verified BC for staging purposes prior to cancer therapy. Four women were excluded from the study, two of whom had DCIS, one had multiple primary malignancies (breast cancer and thyroid cancer), and imaging data (mammography and MR-mammography results) were unavailable for one patient (Figure 1).

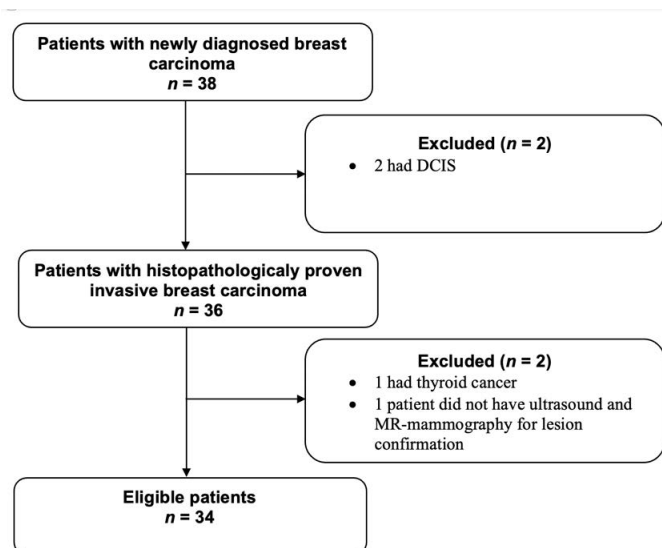


Figure 1. Descriptive flowchart of study.

The final analysis includes 34 patients with newly diagnosed BC (median age: 55.5 years; interquartile range [IQR]: 26-80 years). The criteria for inclusion in the study are: (a) women aged 18 years and older; (b) the presence of pathomorphologically verified invasive BC; (c) completed immunohistochemical evaluation; (d) no prior cancer therapy. The patients were excluded from the study if they were unsuitable for examination due to pregnancy or lactation, or if they received cancer therapy. The final diagnosis of BC was verified by pathomorphological examination. Based on the immunohistochemical examination of HER2 expression status in our study, all breast tumors were divided into three groups: group 1 – tumors with increased HER2 expression, group 2 – tumors with low HER2 expression, and group 3 – tumors with zero HER2 expression. In addition, the malignant neoplasms in our study are divided into subtypes, according to the molecular classification of BC [16].

All patients with BC underwent mammography, breast ultrasound and MR mammography with contrast enhancement.

Patient preparation and PET/CT performance:

Radiopharmaceutical ^{68}Ga -FAPI-04 was synthesized using Ge68/Ga68 generator (50mKi) and an automated module (Modular Lab Easy; Eckert & Ziegler, Berlin, Germany) in accordance with Good Manufacturing Practice (GMP). The radiochemical purity of ^{68}Ga -FAPI-04 solution was > 95%. All quality control parameters corresponded to the recommendations prescribed by the European Pharmacopoeia.

All cases of BC were verified histopathologically. In all cases, the immunohistochemical analysis was performed to evaluate the expression of estrogen receptor, progesterone receptor, proliferative activity index, and HER2 receptor.

The BC subtype that is positive for estrogen and/or progesterone receptors, negative for HER2, with a low Ki-67 proliferative activity index, is defined as Luminal A (ER+, PR±, HER2-, low Ki67); subtype that is positive for estrogen and/or progesterone receptors, or HER2-positive, or HER2-negative, as well as with a high proliferative activity index (Ki-67), is defined as Luminal B (ER+, PR±, HER2±, high Ki67), tumors with negative immunohistochemical expression of hormonal receptors and negative amplification of HER2/neu are defined as a triple negative (TN) subtype (ER-, PR-, HER2-) [16]. HER2 expression was determined by positive staining of tumor cell membranes (+ 1 (score 1): 10 %; + 2 (score 2): ≤30 %; + 3 (score 3): ≥30%). To confirm the positivity of HER2, fluorescent or silver-enhanced in situ hybridization analysis was performed [22].

According to ASCO/CAP guidelines (2018), the expression statuses of HER2/neu receptor are defined as increased HER2 expression (HER2-over = score 3), low HER2 expression (HER2-low = score 1), and zero HER2 expression (HER2-zero = score 0) [17-19]. In addition, the status of HER2+ and HER2- has been determined, according to generally accepted criteria described in ASCO/CAP guidelines (2013) [22]. Tumors with HER2+ status defined according to the previous ASCO/CAP (2013) criteria correspond, under the revised ASCO/CAP (2018) guidelines, to tumors with increased HER2 expression (HER2-over), whereas tumors with HER2- status correspond to those with low (HER2-low = score 1) and zero (HER2-zero = score 0) HER2 expression, respectively [17-19,22].

Interpretation and analysis of images:

After the PET/CT examination, the images were independently reviewed in a blinded manner by two nuclear medicine physicians with over than ten years of experience. Any inconsistencies were resolved through discussion. The classification of additional foci of multicentric breast lesions without histopathological confirmation was based on the results of preliminary ultrasound examinations of the breast and regional lymph nodes, mammography, MR mammography, as well as in the process of follow-up.

The final report included the patient's full name, identifier, weight, height, date of birth, date of examination, as well as the activity of the administered radiopharmaceutical (MBq), effective dose of ionizing radiation (mSv).

The interpretation of images began with images of maximum intensity projection (MIP) of the coronary projection. All images were analyzed in the coronary, axial and sagittal planes using

OsiriX DICOM Viewer, UDI-PI: 14.1.1 (software version).

The radiopharmaceutical uptake was considered positive in cases of increased radiopharmaceutical uptake, when this was not related to physiological biodistribution; the results of other methods were also taken into account in assessment. The absence of radiopharmaceutical uptake was considered to be a negative result. A quantitative assessment of the increased radiopharmaceutical uptake was automatically provided by the lesion's standardized uptake value when selecting a three-dimensional region of interest (3D ROI). SUVmax (standardized uptake value maximum) and TBR (tumor-to-background ratio) for primary breast tumors were determined.

Reference standard:

Histopathological results were the standard for determining malignant breast lesions. In cases of multicentric BC where additional lesions were detected on PET/CT but not histopathologically confirmed, due to the availability of results of histological examination of the main tumor node, these lesions were evaluated based on previously conducted breast and regional lymph node ultrasound, mammography, MR mammography, and through follow-up. In cases of doubtful presence of a malignant neoplasm in an additional breast lesion with multicentric growth after all examinations, as well as with all bilateral BC, a core needle biopsy was performed with further histopathological confirmation. All regional lymph nodes suspected of malignancy according to clinical examination and breast imaging were histopathologically examined.

Statistical analysis:

In the study, continuous variables were used for semi-quantitative data, including SUV (standardized uptake value), TBR (tumor-to-background ratio). The verification of distribution of quantitative data for normality was carried out using the descriptive statistics, statistical Shapiro-Wilk criteria for small samples. The median (Me) and quartiles (Q1 and Q3) were used to describe the asymmetric distributions. Since the distribution of data in our study did not follow the law of normal distribution, the testing of null hypothesis about the absence of differences in two independent samples was carried out using the nonparametric Mann-Whitney U test; the absence of differences in three or more independent samples was carried out using the nonparametric Kruskal-Wallis test, the critical level of statistical significance (p) was assumed to be equal to or less than 0.05. For intra-group post hoc comparisons, Mann-Whitney U test was used with Bonferroni correction (the critical level of statistical significance (p) was assumed to be equal to or less than 0.017). The statistical data analysis was performed using the statistical software package SPSS 17.0 for Windows.

Results.

Characteristics of patients:

This study included 34 patients with newly diagnosed invasive BC (median age: 55.5 years; range: 26-80 years). The bilateral breast cancer was detected in 2 women.

All patients with BC underwent mammography, ultrasound of the breast and MR mammography. The final diagnosis of BC was verified by histopathology. The pathologic and clinical characteristics of the patients are summarized in Table 1.

Table 1. Clinical and Pathologic Features of Patients.

| Number of patients | 34 |
|-----------------------------------|--------------------|
| Median, age (y, range) | 55.5 (range 26-80) |
| Histopathological characteristics | |
| Invasive ductal carcinoma | 31 (91.18%) |
| Invasive lobular carcinoma | 2 (5.88%) |
| Other | 1 (2.94%) |
| Grade | |
| 1 | 4 (11.77%) |
| 2 | 19 (55.88%) |
| 3 | 11 (32.35%) |
| ER | |
| Positive | 29 (85.29%) |
| Negative | 5 (14.71%) |
| PR | |
| Positive | 25 (73.53%) |
| Negative | 9 (26.47%) |
| HER2 | |
| Positive | 8 (23.53%) |
| Negative | 26 (76.47%) |
| Ki-67 | |
| <20% | 12 (35.29%) |
| ≥20% | 22 (64.71%) |
| Molecular subtypes | |
| Luminal A | 12 (35.29%) |
| Luminal B (HER2-) | 9 (26.47%) |
| Luminal B (HER2+) | 8 (23.53%) |
| Triple Negative | 5 (14.71%) |
| Bilateral breast cancer | 2 (5.88%) |
| Multicentric breast cancer | 9 (26.47%) |
| Metastatic breast cancer | 8 (23.53%) |

y – years; ER – estrogen receptor; PR – progesterone receptor; HER2 – human epidermal growth factor receptor 2 (HER2/neu); Ki-67 – tumor cell proliferation index determined by Ki-67 antigen expression

Comparison of ⁶⁸Ga-FAPI PET/CT parameters between different molecular subtypes of lesions:

According to imaging and histopathological data, among 34 patients with BC, 25 patients had a solitary tumor in breasts and 9 had a multicentric process. A total of 46 primary breast lesions were visualized on ⁶⁸Ga-FAPI PET/CT in 34 patients and were subsequently analyzed. Based on the results of ⁶⁸Ga-FAPI PET/CT, the Me size of breast lesions among the patients with BC was Me=18.5 mm (range, 8.0–58.0), and Me SUVmax=9.57 (Q1=6.53; Q3=16.24) and Me TBR=17.0, (Q1=12.76; Q3=21.95) were determined.

Among 46 malignant breast lesions, a Luminal molecular type of BC was identified in 89.13% (41/46). Luminal type A accounted for 39.13% (18/46), Luminal type B accounted for 50.0% (23/46) of cases: 23.91% (11/46) of lesions were B (HER2-positive) and 26.09% (12/46) of lesions were B (HER2-negative) subtypes. Triple negative (TN) breast cancer was the least common molecular subtype, accounting for 10.87% (5/46). Among all the studied tumors of different molecular subtypes, BC with negative amplification of HER2/neu receptor (HER2-negative) was the most common compared with tumors with positive amplification of HER2/neu receptor (HER2-positive) (76.09% vs. 26.83%).

Table 2. Comparison of ^{68}Ga -FAPI-04-PET/CT parameters between different molecular subtypes of breast cancer.

| Characteristics | Molecular subtypes of breast cancer | | | | | p-value* |
|-----------------------------------|-------------------------------------|------------------------|---------------------------|------------------------------|-----------------------|---------------------------------|
| | Luminal A n=18 | Luminal B n=23 | Luminal B (HER2)+ n=11 | Luminal B (HER2)- n=12 | TN n=5 | |
| SUV _{max} Me (Q1; Q3) | 9.19 (6.217; 13.77) | 10.05 (7.83; 17.86) | 16.25 (7.83; 25.25) | 9.515 (5.065; 15.25) | 9.17 (7.52; 12.09) | $H=5.27$ $df=4$ $p=0.261$ |
| TBR Me (Q1; Q3) | 16.0 (12.05; 20.48) | 20.0 (15.0; 24.0) | 21.79 (16.0; 23.0) | 17.50 (8.0; 24.65) | 15.0 (11.0; 16.50) | $H=6.42$ $df=4$ $p=0.170$ |

*Kruskal-Wallis test (H-test), significance p-value <0.05;
Luminal B (HER2)+ – Luminal B HER2-positive subtype; Luminal B (HER2)- – Luminal B HER2-negative subtype; TN – triple negative subtype; SUV_{max} – standardized uptake value maximum; TBR – tumor-to-background ratio; Me – median; Q1 – first quartile; Q3 – third quartile

To identify associative links between FAPI PET parameters (SUVmax, TBR) and molecular subtypes of BC, a statistical analysis was performed between groups of tumors of the main subtypes (Luminal A, Luminal B, Luminal B (HER2-positive), Luminal B (HER2-negative), Triple Negative) (Table 2).

As shown in Table 2, only the molecular subtype Luminal B (HER2+) with Me SUVmax=16.25 (Q1=7.83; Q3=25.25) and Me TBR=21.79 (Q1=16.0; Q3=23.0) slightly differed from other molecular subtypes that had similar PET parameters (Luminal A: Me SUVmax=9.19 [Q1=6.217, Q3=13.77], Me TBR=16.0 [Q1=12.05; Q3=20.48]; Luminal B: Me SUVmax=10.05 [Q1=7.83, Q3=17.86], Me TBR=20.0 [Q1=15.0; Q3=24.0], Luminal B (HER2-): Me SUVmax=9.515 [Q1=5.065, Q3=15.25], Me TBR=17.50 [Q1=8.0; Q3=24.65]; Triple Negative: Me SUV max=9.17 [Q1=7.52, Q3=12.09], Me TBR=15.0 [Q1=11.0; Q3=16.50]). The statistical analysis completed for several independent samples, which included breast lesions of various molecular subtypes of BC (Luminal A, Luminal B, Luminal B (HER2-positive), Luminal B (HER2-negative) and Triple Negative), showed no significant difference between them in terms of ^{68}Ga -FAPI-04 uptake in tumor ($p=0.261$), as well as in terms of the tumor-to-background ratio ($p=0.170$).

To investigate the association between ^{68}Ga -FAPI PET/CT parameters with clinically significant molecular subtypes of BC, an analysis was conducted comparing tumors with a relatively less aggressiveness, grouped into Luminal A+ Luminal B HER2-negative group (corresponding to the group of hormone-positive tumors, negative for HER2 receptor), as well as with subtypes with an aggressive BC, including triple negative BC and tumors, positive for presence of HER2 receptor (HER2-positive); in addition, a separate sample of tumors was included, which included all breast lesions negative for presence of HER2 receptor (HER2-negative) (Figures 2 and 3).

The values of parameters were higher among tumors that are positive for HER2 receptor, which had Me SUVmax=16.25 (Q1=7.83, Q3=25.25) and Me TBR=21.79 (Q1=16.0; Q3=23.0), compared with other samples, the parameters in which were identical to each other, namely, a triple negative subtype with Me SUVmax=9.17 (Q1=7.52, Q3=12.90) and Me TBR=15.0 (Q1=10.0; Q3=17.0), hormone-positive tumors that are negative for HER2 receptor, with Me SUVmax=9.19 [Q1=6.217, Q3=14.56] and Me TBR=17.50 [Q1=12.05; Q3=21.93], tumors

that are negative for HER2 receptor, with Me SUVmax=9.19 (Q1=6.27, Q3=14.5) and Me TBR=17.0 (Q1=12.05; Q3=20.0). The analysis performed for these groups of tumors did not reveal statistical significance between them in terms of ^{68}Ga -FAPI-04 uptake in the tumor ($H=5.07$, $df=3$, $p=0.167$), as well as in terms of TBR ($H=4.69$, $df=3$, $p=0.196$), however it showed that subtypes of HER2-positive tumors had the highest uptake and TBR compared to other subtypes of breast tumors.

To assess the association between the expression status of HER2/neu receptor and the uptake parameters and TBR on ^{68}Ga -FAPI-04 PET/CT, all breast tumors were divided into three groups: tumors with overexpression of HER2 (HER2-over), low expression of HER2 (HER2-low) and zero expression of HER2 (HER2-zero). The group of breast tumors with low HER2 expression accounted for the largest number of cases (47.83%), compared with breast lesions with no expression (28.26%) and overexpression (23.91%) of HER2. The statistical analysis performed for three independent samples (HER2-over, HER2-low, and HER2-zero) is presented in Table 3.

The statistical analysis performed for three independent samples (HER2-over, HER2-low, HER2-zero) identified the significant difference between the degree of ^{68}Ga -FAPI uptake by the tumor node ($p=0.036$) and the TBR ($p=0.042$) (Table 3).

To determine the statistical significance for each studied group of breast lesions depending on the status of HER2neu receptor (HER2-over, HER2-low, HER2-zero), post hoc comparisons were performed between the groups (Figures 4 and 5).

The post hoc comparisons of FAPI-PET parameters among lesions with low expression of HER2/neu receptor and absence of expression of this receptor identified that SUVmax of the tumor and TBR were higher among lesion with low expression of HER2/neu receptor compared with lesion with zero expression of this receptor, however, both parameters had no statistical significance between the compared groups (Me SUVmax=10.68 [Q1=6.61, Q3=15.68] vs. Me SUVmax=9.17 [Q1=4.43, Q3=9.87], $p=0.121$; Me TBR=18.0 [Q1=12.76; Q3=23.25] vs. Me TBR=16.0 [Q1=7.43, Q3=17.25], $p=0.062$). The breast tumors with overexpression of HER2/neu receptor (HER2-over) had higher SUVmax and TBR than tumors with absence of expression of this receptor (HER2-zero): both parameters were statistically significant in the compared groups (Me SUVmax=17.27 [Q1=9.50, Q3=25.25] versus Me SUVmax=9.17 [Q1=4.43, Q3=9.87], $p=0.015$; Me TBR=21.90

Table 3. Comparison of ^{68}Ga -FAPI PET/CT parameters in BC depending on expression status of HER2/neu receptor in the tumor.

| Characteristics | HER2 status | | | p-value* |
|-----------------------------------|-------------------------|-----------------------|----------------------|---------------------------|
| | HER2-over n=11 | HER2-low n=22 | HER2-zero n=13 | |
| SUV _{max} Me (Q1; Q3) | 17.265 (9.495-25.25) | 10.68 (6.61-15.68) | 9.17 (4.43-9.865) | H=6.64 df=2 p=0.036 |
| TBR Me (Q1; Q3) | 21.90 (16.0-23.0) | 18.0 (12.76-23.25) | 16.0 (7.43-17.25) | H=6.32 df=2 p=0.042 |

*Kruskal-Wallis test (H-test), significance p-value <0.05
SUV_{max} – standardized uptake value maximum; TBR – tumor-to-background ratio; Me – median; Q1 – first quartile; Q3 – third quartile; HER2-over – overexpression of HER2/neu; HER2-low – low expression of HER2/neu; HER2-zero – absence of expression of HER2 /neu

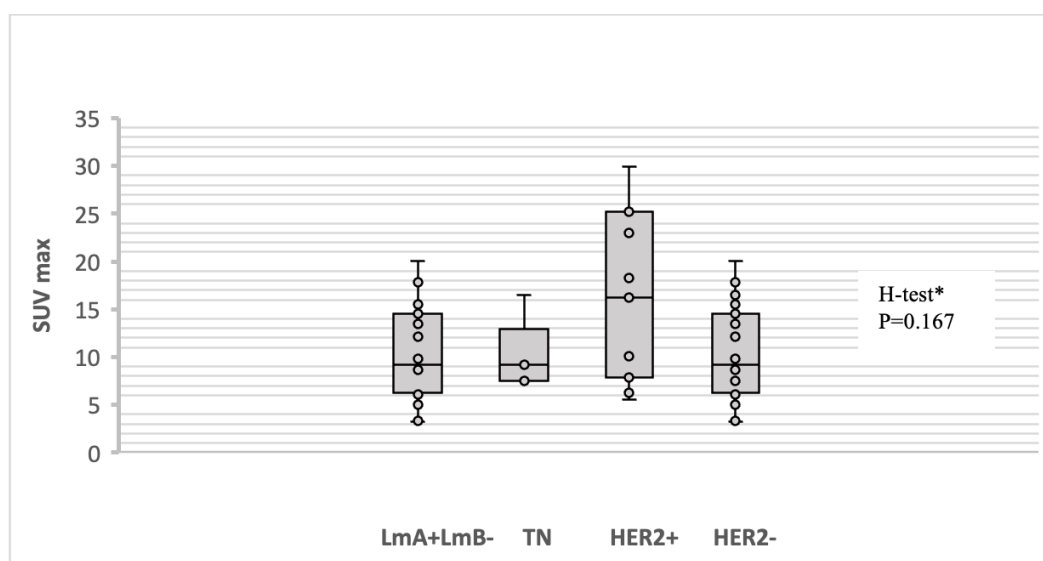


Figure 2. Box plots SUV_{max} of primary tumor according molecular subtypes BC.

*Kruskal-Wallis test (H-test), significance p-value <0.05.

LmA – Luminal A, LmB- – Luminal B HER2-negative, TN – Triple Negative, HER2+ – all subtypes with HER2-positive, HER2- – all subtypes with HER2- negative.

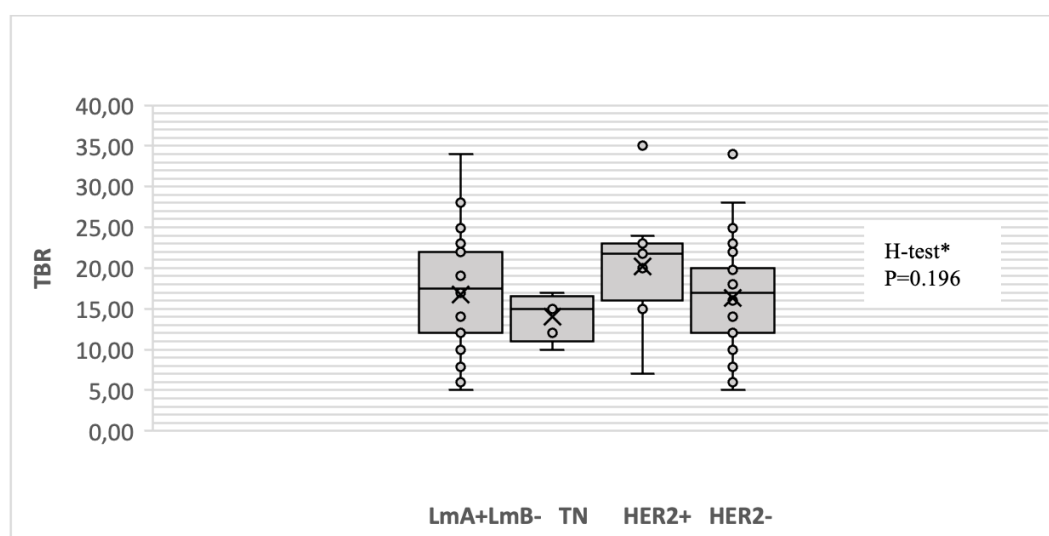


Figure 3. Box plots TBR of primary tumor according molecular subtypes BC.

*Kruskal-Wallis test (H-test), significance p-value <0.05.

LmA – Luminal A, LmB- – Luminal B HER2-negative, TN – Triple Negative, HER2+ – all subtypes with HER2-positive, HER2- – all subtypes with HER2- negative.

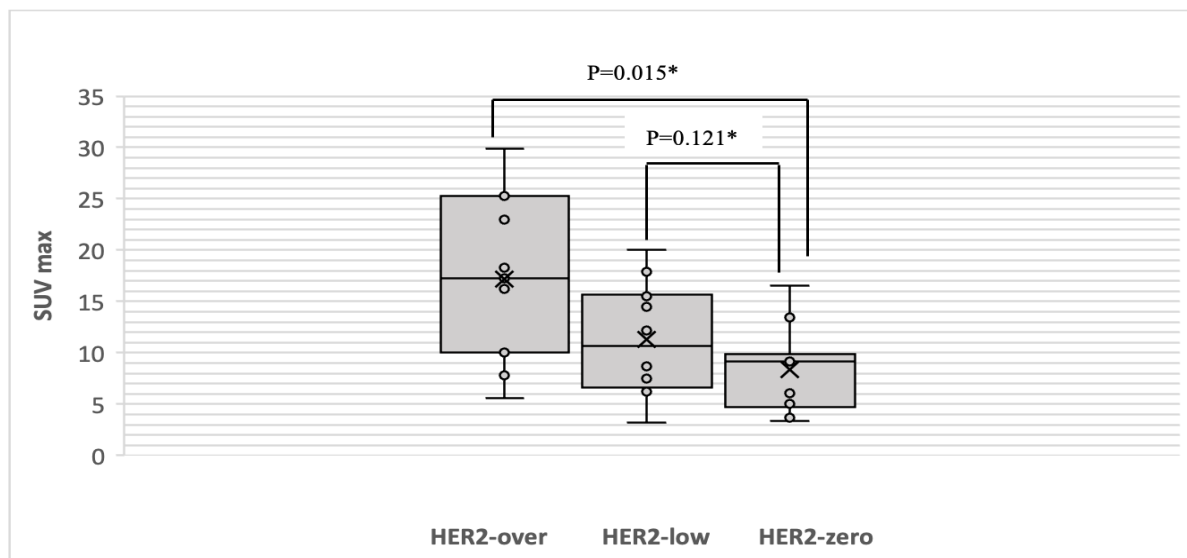


Figure 4. Box plots SUVmax of primary tumor according to HER2-status of BC.

*Mann–Whitney U test, significance p -value <0.017 .

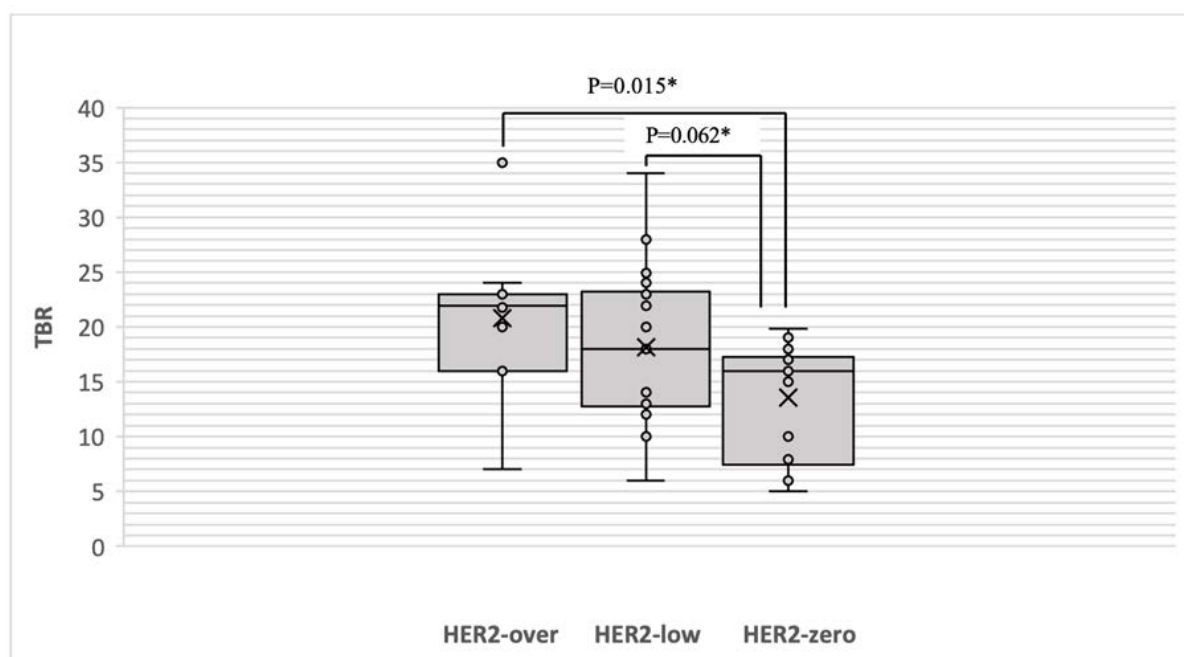


Figure 5. Box plots TBR of primary tumor according to HER2-status of BC.

*Mann–Whitney U test, significance p -value <0.017 .

[Q1=16.0; Q3=23.0] versus Me TBR=16.0 [Q1=7.43, Q3=17.25], $p=0.015$).

Thus, the statistical significance was revealed between SUVmax and TBR values of primary breast tumors with overexpression of the human epidermal growth factor receptor 2 (HER2-over) compared with BC in which there was absence of expression of HER2 receptor (HER2-zero). The degree of ^{68}Ga -FAP uptake by the breast tumor and its TBR were significantly higher in BC with high expression of HER2-over compared with BC with HER2-zero.

Discussion.

The tumor microenvironment (TME) plays a critical role

in carcinogenesis, while gene expression in breast TME is able to predict clinical outcomes [21]. The cancer-associated fibroblasts express certain proteins that can be used as tumor-specific markers. One of them is the membrane protein FAP, which is expressed in the microenvironment and affects various tumors, including BC, and FAPI as a radiotracer achieves optimal results in tissues with high FAP expression, such as BC [23]. Studies on the use of modern targeted therapies show that a simple approach to eliminating only the "seed" of a tumor is usually doomed to failure, therefore, obtaining the expanded knowledge about TME, including the studying of heterogeneous nature and complexity of CAF populations, will

provide the desired clinical benefits [24]. This provides grounds for investigating the possibilities of hybrid imaging methods with ^{68}Ga -FAPI radioactive tracer aimed at TME in malignant neoplasms, including BC.

The median size of the tumor node in this study is 18.5 mm (8.0 – 58.0). The smallest size of breast tumor nodes detected by ^{68}Ga -FAPI PET/CT is 8.0 mm, which demonstrates the potential of the method in the diagnosis of BC. Some authors explain the detection of small foci by the mechanism of action of ^{68}Ga -FAPI-04 impacting on TME, which improves the visualization of small malignant lesions in the range of 3-5 mm on ^{68}Ga -FAPI PET/CT [23], expanding the possibilities of this hybrid imaging method. The study demonstrated high tumor uptake rates (Me SUVmax=9.57) and tumor-to-background ratio (Me TBR=17.0), which coincides with the results of other research groups that demonstrated an overall high uptake of ^{68}Ga -FAPI by primary breast tumors and metastatic foci, in particular compared with FDG [7,8,25-27]. When studying literature sources, Taralli S. et al. noted that most scientific publications report about higher uptake of ^{68}Ga -FAPI indicator and higher TBR of primary breast cancer with this tracer compared to ^{18}F -FDG, agreeing that BC belongs to tumors with a higher frequency of detection on PET/CT with ^{68}Ga -FAPI [27].

The limited available literature data have demonstrated that the values of SUVmax and TBR in BC do not depend on the histopathological phenotype (lobular or ductal), receptor status, and BC grade [6,8,28,29]. However, a tendency has been shown toward increasing the values of SUVmax from Luminal A (lower values) to Luminal B HER2-positive type and HER2-enriched tumors (higher values) [8]. In addition, TME has a complex cellular composition, including various subtypes of CAF. Until now, the contribution of fibroblasts to carcinogenesis remains unclear [21,23]. A group of researchers found that senescent (aging) CAFs contribute to the development of breast tumors and are present in some subtypes of human breast cancer [21]. Given that CAFs are present in human BC samples of ER-positive, HER2-positive, and triple-negative subtypes [21], this study suggests that targeting FAP, specifically using ^{68}Ga -FAPI as a radioactive tracer and determining its association with molecular subtypes, may be beneficial in the diagnosis and treatment of BC.

In this study, the conducted analysis of uptake parameters of ^{68}Ga -FAPI-04 and TBR in breast tumors of main molecular subtypes (triple negative, Luminal A, Luminal B: B HER2-positive, B HER2-negative) did not reveal statistically significant differences between them, which coincides with the limited available literature sources on this topic [8,27-29].

In this study, molecular subtypes of breast cancer were reclassified by their clinical aggressiveness: tumors of the Luminal A + B HER2-negative subtypes were analyzed in contrast to TN and HER2-positive cancers due to differences in prognosis and approaches to systemic therapy. Luminal A and HER2-negative Luminal B tumors are generally associated with responsiveness to hormonal therapy and better outcomes, although luminal B tends to display a broader range of proliferative activity and often shows a less favorable prognosis compared to Luminal A. In contrast, both TN and HER2-positive breast cancers are known for their aggressiveness

and worse clinical prognosis [16,30]. TN BC, in particular, is classified as a high-grade malignancy and remains challenging due to the lack of targeted treatments [16]. Meanwhile, HER2-overexpressing tumors are characterized by early metastatic spread and recurrence but good treatment outcomes [31].

Taking into account the presence of clinically important molecular subtypes of BC and their combinations, a comparative analysis was carried out between tumors with a relatively less aggressive course of BC, combined into Luminal A + Luminal B HER2-negative group, and subtypes characterized by the aggressiveness, including triple negative BC and tumors that are positive for the presence of HER2 receptor (HER2-positive) [16]; as well as all breast lesions that are negative for the presence of HER2 receptor (HER2-negative). Analysis of clinically significant molecular subtypes of BC and their combinations revealed no statistical significance between ^{68}Ga -FAPI-04 uptake ($p=0.167$) and values of TBR ($p=0.196$). The absence of association between ^{68}Ga -FAPI-04 uptake and main molecular subtypes reflects the heterogeneity of breast tumors and the complex structure of the tumor microenvironment. However, this study revealed that HER2-positive tumors, which included only Luminal B HER2-positive subtypes, had the highest uptake and TBR compared to other subtypes of breast cancer. These results coincide with the data of Elboga et al., who determined that HER2 expression appears to provide the highest activity of ^{68}Ga -FAPI among the Luminal group, with significantly higher uptake in Luminal B HER2-positive groups compared with Luminal A or Luminal B HER2-negative groups [8,27].

In 2018, ASCO and CAP updated the practical guidelines for testing the human epidermal growth factor receptor 2 in breast cancer [17-19]. One of the goals of this revision was to predict a favorable outcome from HER2-targeted therapy [17]. According to the updated guidelines, tumors with overexpression of HER2 (HER2-over), low expression of HER2 (HER2-low) and zero expression of HER2 (HER2-zero) have been identified, i.e. HER2-negative status has been reclassified to the status with low expression of HER2 and zero expression of HER2.

The statistical analysis conducted for three groups of tumors with overexpression, low and zero expression of HER2 revealed a significant difference between the degree of ^{68}Ga -FAPI uptake by the tumor node ($p=0.036$) and the tumor-to-background ratio ($p=0.042$). The post hoc (pairwise) comparisons were carried out in these groups. The PET parameters among tumors in HER2-over group, which showed higher SUVmax and TBR values on PET/CT compared to tumors in HER2-zero group, were statistically significant (Me SUVmax: 17.27 vs. 9.17, $P=0.015$; Me TBR: 21.90 vs. 16.0, $P=0.015$). Considering that breast cancer with overexpression of HER2 belongs to tumors with the aggressive type of tumor growth [16], it is logical to assume that ^{68}Ga -FAPI accumulates more actively in such aggressive tumors. In addition, it is known that tumors that are positive for HER2 receptor, the so-called HER2-positive, have a higher percentage of proliferating cells than other molecular types of BC [21]. The literature describes the results indicating that the expression of HER2 in breast tumors appears to provide the highest activity of ^{68}Ga -FAPI [8], which is consistent with the results obtained in our study. Also, the high activity of ^{68}Ga -

FAPI in breast tumors with overexpression of HER2 receptor in this study is explained by the fact that the increased expression of HER2 can enhance the attraction and activation of CAFs, which remodel the extracellular matrix, contributing to tumor invasion. These results may be explained by data showing, on the one hand, a link between the activation of stromal fibroblasts by BC cells and the induction of a phenotype similar to cancer stem cells [13,14], and, on the other hand, estrogen and HER2 receptors are regulated by some of the same signaling pathways as breast tissue stem cells [16]. According to the results of Chen L. et al., the immunohistochemical analysis showed that SUVmax and TBR on ^{68}Ga -FAPI PET/CT positively correlated with high FAP expression in the stroma of BC foci [10].

Statistically significant differences identified between the HER2-over and HER2-zero groups but not between HER2-low and HER2-zero groups suggest that HER2 overexpression may indicate that HER2 overexpression is associated with higher FAPI uptake due to the recruitment and activation of CAFs. In contrast, the absence of significant differences between the HER2-low and HER2-zero groups could be attributed to the greater heterogeneity within the HER2-low group.

This heterogeneity may be attributed to the challenges of immunohistochemical (IHC) assessment. A HER2 IHC score of 1+ is typically assigned when over 10% of tumor cells display weak and incomplete membrane staining that are susceptible to subjective interpretation and may lead to misclassification [30]. Another challenge is heterogeneity of HER2 immunostaining, which complicates accurate subgroup differentiation within HER2-low tumors [30].

This study aims to investigate the association between the metabolic activity of ^{68}Ga -FAPI (targeting the tumor microenvironment) with molecular subtypes of breast cancer and expression of HER2/neu receptor. In general, understanding the complex interaction between HER2, tumor microenvironment, and therapeutic interventions is essential for improving outcomes in HER2-positive breast cancer [32].

In this study, for the first time, as far as we know, the parameters of ^{68}Ga -FAPI PET/CT in BC were compared depending on the status of molecular expression of the human epidermal growth factor receptor 2 (HER2/neu), according to the recommendations of ASCO/CAP (2018) [17].

The study results have shown that PET/CT with ^{68}Ga -FAPI may be used as an additional imaging for BC, emphasizing the importance of this method for breast cancer types with low glucose metabolism [8]. Moreover, considering its theranostic potential and the obtained results, ^{68}Ga -FAPI may be used for selecting breast cancer patients based on molecular and metabolic information.

The association between FAPI uptake and HER2 status observed in this study, particularly related to HER2-targeted therapy or the development of anti-FAP therapies, highlights the clinical and translational relevance of these findings.

Conclusion.

^{68}Ga -FAPI PET/CT is a promising imaging modality for breast cancer, offering distinct advantages in visualizing aggressive subtypes, particularly those with HER2 overexpression. The findings of this study indicate that tumors with high HER2

expression demonstrate significantly elevated tracer uptake and tumor-to-background ratios, suggesting a potential link between FAPI accumulation and tumor biology. This supports the utility of ^{68}Ga -FAPI PET/CT not only for diagnostic purposes but also for treatment planning and potentially for theranostic applications.

Given its ability to detect multicentric lesions and visualize tumors with low glycolytic activity, ^{68}Ga -FAPI PET/CT may serve as a valuable complement to standard imaging techniques, especially in challenging diagnostic scenarios. While current data are encouraging, future studies with larger and more diverse populations, as well as direct comparisons with established PET tracers like 18F-FDG, are essential to fully determine the clinical role and cost-effectiveness of FAPI-based imaging in breast cancer management. Considering the presence of CAFs across ER-positive, HER2-positive, and TN BC subtypes [21], this study proposes that utilizing ^{68}Ga -FAPI as a radiotracer and exploring its correlation with molecular subtypes could be beneficial in breast cancer management.

Strengths and Limitations.

This study presents several notable strengths. First, it addresses a clinically relevant and emerging imaging modality, ^{68}Ga -FAPI PET/CT, which remains under-investigated in breast cancer, particularly in relation to molecular subtypes. Importantly, the study highlights significantly higher tracer uptake in HER2-overexpressing tumors, supporting the hypothesis that FAPI PET/CT may reflect aggressive tumor biology. Finally, the results are corroborated by recent literature, enhancing their validity. However, the study has limitations inherent to its design. The sample size is relatively small and may limit the generalizability of the findings. The representation of triple-negative breast cancer cases is limited (n=5), and the cohort lacks HER2-enriched tumors as a distinct group. Additionally, the absence of a direct comparison with 18F-FDG PET/CT precludes conclusions about diagnostic superiority. Future studies with larger, more diverse cohorts and comparative imaging arms are necessary to confirm and expand upon these findings.

Acknowledgments.

The authors express their gratitude for the administrative and technical support provided by S.D. Asfendiyarov Kazakh National Medical University.

Conflicts of interest statement.

The authors declare no conflict of interest.

Funding.

This research was funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP19679719).

REFERENCES

1. Chhikara B.S, Parang K. Global Cancer Statistics 2022: The Trends Projection Analysis. *Chem Biol Lett.* 2023;10:451.
2. Bray F, Laversanne M, Sung H, et al. Siegel. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74:229-263.

3. Cancer Today. 2024. Available online: <https://gco.iarc.who.int/today/>
4. Paydary K, Seraj SM, Zadeh MZ, et al. The Evolving Role of FDG-PET/CT in the Diagnosis, Staging, and Treatment of Breast Cancer. *Molecular Imaging and Biology*. 2019;21:1-10.
5. Hirnas N, Hamacher R, Sraieb M, et al. Diagnostic Accuracy of ⁶⁸Ga-FAPI Versus ¹⁸F-FDG PET in Patients with Various Malignancies. *J Nucl Med*. 2024;65:372-378.
6. Dendl K, Koerber S.A, Finck R, et al. ⁶⁸Ga-FAPI-PET/CT in patients with various gynecological malignancies. *European Journal of Nuclear Medicine and Molecular Imaging*. 2021;48:4089-4100.
7. Kömek H, Can C, Guzel Y, et al. ⁶⁸Ga-FAPI-04 PET/CT, a new step in breast cancer imaging: a comparative pilot study with ¹⁸F-FDG PET/CT. *Ann Nucl Med*. 2021;35:744-752.
8. Elboga U, Sahin E, Kus T, et al. Superiority of ⁶⁸Ga-FAPI PET/CT scan in detecting additional lesions compared to ¹⁸F-FDG PET/CT scan in breast cancer. *Ann Nucl Med*. 2021;35:1321-1331.
9. Zheng S, Lin J, Zhu Y, et al. ⁶⁸Ga-FAPI Versus ¹⁸F-FDG PET/CT in Evaluating Newly Diagnosed Breast Cancer Patients: A Head-to-Head Comparative Study. *Clin Nucl Med*. 2023;48:E104-E109.
10. Chen L, Zheng S, Chen L, et al. ⁶⁸Ga-Labeled Fibroblast Activation Protein Inhibitor PET/CT for the Early and Late Prediction of Pathologic Response to Neoadjuvant Chemotherapy in Breast Cancer Patients: A Prospective Study. *J Nucl Med*. 2023;64:1899-1905.
11. Evangelista L, Filippi L, Schillaci O. What radiolabeled FAPI pet can add in breast cancer? A systematic review from literature. *Annals of Nuclear Medicine*. 2023;37:442-450.
12. Sharma U, Medina-Saenz K, Miller PC, et al. Heterotypic clustering of circulating tumor cells and circulating cancer-associated fibroblast facilitates breast cancer metastasis. *Breast Cancer Res Treat*. 2021;189:63-80.
13. Desai S.A, Patel V.P, Bhosle K.P, et al. The Tumor Microenvironment: Shaping Cancer Progression and Treatment Response. *J. Chemother*. 2025;37:15-44.
14. Akinsipe T, Mohamedelhassan R, Akinpelu A, et al. Cellular Interactions in Tumor Microenvironment during Breast Cancer Progression: New Frontiers and Implications for Novel Therapeutics. *Front. Immunol*. 2024;15:1302587.
15. Moura T, Laranjeira P, Caramelo O, et al. Breast Cancer and Tumor Microenvironment: The Crucial Role of Immune Cells. *Curr. Oncol*. 2025;32:143.
16. Feng Y, Spezia M, Huang S, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes & Diseases*. 2018;5:77-106.
17. Wolff AC, Somerfield MR, McShane LM, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update. *J Clin Oncol*. 2023;41:3867-3872.
18. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: pathological and clinical landscape. *J Clin Oncol*. 2020;38:1951-1962.
19. Hou X, Chen K, Luo H, et al. Identification of HER2-over-expression, HER2-low-expression, and HER2-zero-expression statuses in breast cancer based on ¹⁸F-FDG PET/CT radiomics. *Cancer Imaging*. 2025;25:62.
20. Gilardi L, Airò Farulla L.S, Ceci F. Imaging for illuminating actionable pathways in breast cancer. *Curr Opin Oncol*. 2022;34:606-613.
21. Ye J, Baer JM, Faget DV, et al. Senescent CAFs Mediate Immunosuppression and Drive Breast Cancer Progression. *Cancer Discov*. 2024;14:1302-1323.
22. Wolff AC, Hammond MEH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31:3997-4013.
23. Loktev A, Lindner T, Mier W, et al. A tumor-imaging method targeting cancer-associated fibroblasts. *J Nucl Med*. 2018;59:1423-1429.
24. Liu T, Zhou L, Li D, et al. Cancer-Associated Fibroblasts Build and Secure the Tumor Microenvironment. *Front Cell Dev Biol*. 2019;24:7:60.
25. Alçin G, Arslan E, Aksoy T, et al. ⁶⁸Ga-FAPI-04 PET/CT in Selected Breast Cancer Patients with Low FDG Affinity: A Head-to-Head Comparative Study. *Clin Nucl Med*. 2023;48:E420-E430.
26. Li T, Zhang J, Yan Y, et al. Applications of FAPI PET/CT in the diagnosis and treatment of breast and the most common gynecologic malignancies: a literature review. *Front. Oncol*. 2024;14:1358070.
27. Taralli S, Lorusso M, Perrone E, et al. PET/CT with Fibroblast Activation Protein Inhibitors in Breast Cancer: Diagnostic and Theranostic Application – A Literature Review. *Cancers*. 2023;15:908.
28. Backhaus P, Burg MC, Roll W, et al. Simultaneous FAPI PET/MRI targeting the fibroblast-activation protein for breast cancer. *Radiology*. 2022;302:39-47.
29. Hope TA, Calais J, Goenka AH, et al. SNMMI Procedure Standard/EANM Practice Guideline for Fibroblast Activation Protein (FAP) PET. *Journal of Nuclear Medicine* January. 2025;66:26-33.
30. Molinelli C, Jacobs F, Marchiò C, et al. HER2-low breast cancer: where are we? *Breast Care*. 2022;17:533-545.
31. Korkaya H, Wicha MS. HER2 and breast cancer stem cells: more than meets the eye. *Cancer Res*. 2013;73:3489-3493.
32. Gupta MK, Gouda G, Vadde R. Role of the Tumor Microenvironment in Mediating Resistance to Anti-HER2 Antibodies. *Crit Rev Oncog*. 2024;29:43-54.