ORIGINAL ARTICLES

CLINICAL IMPLEMENTATION AND SCIENTIFIC DEVELOPMENT OF PHOTODYNAMIC THERAPY IN RUSSIA IN 2010-2020

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Abstract

In recent years, the development of methods of photodynamic therapy (PDT) and fluorescence diagnostic (FD) in Russia is characterized by an intensive rise, steadily growing interest of specialists from various medical specialties in the method of specialists from various medical specialties, an increase in the level of equipment number of hospitals with the necessary equipment for performing FD and PDT, the and the emergence of new photosensitizers on the pharmaceutical market, and an increasing increase in the level of patients' confidence in these methods. This study analyzes the dynamics of the development of the clinical application and scientific developments of FD and PDT over the past decade in Russia in terms of the volume of public procurement of photosensitizers, as well as the activity of research work in the field of FD and PDT, the number of candidate and doctoral dissertations theses on this topic and the number of scientific publications in the RSCI. 688 contracts for the supply of photosensitizers for clinical use were analyzed. The analysis showed a stable annual growth in the volume of public procurement of photosensitizers, an increase in the number of subjects of the Russian Federation and clinical centers that purchase photosensitizers through the portal www.zakupki.gov.ru. From 2014 to 2020, the total volume of public procurement of all photosensitizers increased by 8 times (from 36.42 million rubles (3.58 thousand packages) to 307.37 million rubles (18.99 thousand packages)). The annual increase in the volume of public procurement in numerical terms over the previous 6 years ranged from 9.4% to 63.2% in different years. The main share of state purchases of photosensitizers falls on Moscow and St. Petersburg, h. However, in recent years there has been a noticeable trend towards an increase in sales of photosensitizers in the regions. Thus, in recent years, the share of purchases of photosensitizers in the constituent entities of the Russian Federation with a population of less than 1 million people has significantly increased (from 2.9% of the total number of purchases in 2014 to 25.3% in 2020). Also, in recent years, there has been a significant increase in the activity of research work activity in the field of FD and PDT. The number of defended candidate and doctoral dissertations theses defended in the field of FD and PDT photodynamic therapy and fluorescent diagnostics has been steadily high in recent years and, in some scientific specialties, reaches 2-3% of the total number of defended dissertations theses defended in these specialties. The increase in the total number of publications over 10 years according to the RSCI was 224% (from 218 publications in 2014 to 489 publications in 2019), according to the RSCI. The results obtained confirm the growing demand for photosensitizers for photodynamic therapy and fluorescence diagnostics in clinical practice, the expansion of the geography of the use of methods, as well and the stable interest in this topic in the research environment.

Keywords: photodynamic therapy, fluorescent diagnostics, public procurement, chlorin e6, aluminum phthalocyanine, 5-aminolevulinic acid, 5-aminolevulinic acid methyl ester.

For citations: Filonenko E.V. Clinical implementation and scientific development of photodynamic therapy in Russia in 2010-2020, *Biomedical Photonics*, 2021, vol. 10, no. 4, pp. 4–22. doi: 10.24931/2413–9432–2021–10-4-4-22

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КЛИНИЧЕСКОЕ ВНЕДРЕНИЕ И НАУЧНОЕ РАЗВИТИЕ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ В РОССИИ В 2010-2020 ГГ.

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Резюме

В последние годы развитие методов фотодинамической терапии (ФДТ) и флуоресцентной диагностики (ФД) в России характеризуется интенсивным подъемом, стабильно растущим интересом к методу специалистов различных медицинских специальностей, повышением уровня оснащенности больниц необходимым оборудованием для проведения ФД и ФДТ, появлением на фармацевтическом

рынке новых фотосенсибилизаторов, повышением уровня доверия пациентов к указанным методам. В настоящем исследовании проанализирована динамика развития клинического применения и научных разработок ФД и ФДТ в последнее десятилетие в России по объемам госзакупок фотосенсибилизаторов, а также по активности научно-исследовательской работы в области ФД и ФДТ по числу кандидатских и докторских диссертаций по данной тематике и по числу научных публикаций в РИНЦ. Проанализированы 688 договоров на поставку фотосенсибилизаторов для клинического применения. Анализ показал стабильный ежегодный рост объема госзакупок фотосенсибилизаторов, увеличение числа субъектов РФ и клинических центров, осуществляющих закупку фотосенсибилизаторов через портал www.zakupki.gov.ru. С 2014 по 2020 гг. общий объем госзакупок всех фотосенсибилизаторов увеличился в 8 раз (с 36,42 млн. руб. (3,58 тыс. упаковок) до 307,37 млн. руб. (18,99 тыс. упаковок)). Ежегодный прирост объема госзакупок в численном выражении за предыдущие 6 лет составил от 9,4% до 63,2% в разные годы. Основная доля госзакупок фотосенсибилизаторов приходится на Москву и Санкт-Петербург, однако в последние годы заметна тенденция увеличения объемов продаж фотосенсибилизаторов в регионах. Так, за последние годы значительно выросла доля закупок фотосенсибилизаторов в субъектах РФ с населением менее 1 млн человек (с 2,9% от общего числа закупок в 2014 г. до 25,3% в 2020 г.). Также в последние годы наблюдается значительный рост активности научно-исследовательской работы в области ФД и ФДТ. Число кандидатских и докторских диссертаций, защищенных по тематике фотодинамической терапии и флуоресцентной диагностики, в последние годы стабильно велико и, по некоторым научным специальностям, достигает 2-3% от общего числа диссертаций, защищенных по данным специальностям. Прирост общего числа публикаций за 10 лет по данным РИНЦ составил 224% (с 218 публикаций в 2014 г. до 489 публикаций в 2019 г.). Полученные результаты подтверждают растущий спрос на фотосенсибилизаторы для фотодинамической терапии и флуоресцентной диагностики в клинической практике, расширение географии использования методов, а также стабильный интерес к данной тематике в научно-исследовательской среде.

Ключевые слова: фотодинамическая терапия, флуоресцентная диагностика, государственные закупки, хлорин е6, фталоцианин алюминия, 5-аминолевулиновая кислота, метиловый эфир 5-аминолевулиновой кислоты

Для цитирования: Филоненко Е.В. Клиническое внедрение и научное развитие фотодинамической терапии в России в 2010-2020 гг. // Biomedical Photonics. – 2021. – Т. 10, № 4. – С. 4–22. doi: 10.24931/2413-9432-2021-10-4-4-22

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The history of the use of photodynamic therapy (PDT) and fluorescence diagnostic (FD) in clinical practice has more than 100 years in the world and about 30 years in Russia [1,2,3,4]. The advantages of the PDT method are the focus of the impact on tumor foci and high efficiency in the absence of systemic toxicity. The method is successfully used in clinical oncology. In many oncological diseases, PDT makes it possible to achieve results that are not available with other methods of antitumor therapy. Thus, the method is effective even in a number of metastatic forms of malignant neoplasms, in cases where other methods are no longer applicable. Moreover, PDT makes it possible to avoid the appearance of rough cicatricial tissues in the treatment of precancer and early cancer, which is very important, for example, in gynecology during the treatment of patients of childbearing age; to achieve a good cosmetic effect, to minimally injure healthy tissues surrounding the tumor in the treatment of tumors on the face, etc. Conducting PDT of the surgical area after surgical removal of a tumor (localized, for example, in the bladder, brain, etc.) makes it possible to significantly reduce the risk of recurrence [5,6,7,8,9]. On the other hand, FD is successfully used for the purpose of early diagnosis of the disease, as well as to clarify the boundaries of an already detected neoplasm and identify additional foci during surgical treatment in order to more radically remove the tumor and reduce the likelihood of recurrences. The combination of FD and PDT is a recognized method of oncological theranostics [10,11,12,13,14,15].

As international experience shows, in addition to oncology, FD and PDT are widely used in various fields of medicine: in the treatment of infectious diseases, in dermatology, neurosurgery, ophthalmology, dentistry, etc.

In Russia, the beginning of the clinical application of FD and PDT methods dates back to 1992, when preclinical studies of the first domestically-produced photosensitizer photohem were completed. After obtaining permission from the Ministry of Health of Russia, the PDT method was first used in clinical practice in Russia, as part of the Phase I clinical trials of photohem at the Moscow Scientific and Research Oncological Institute named after P.A. Herzen (V.V. Sokolov, E.V. Filonenko) and at the Center for Laser Medicine (E.F. Stranadko) [1]. From 1992 to 2011, there was a stage of preclinical and clinical study of new domestically-produced photosensitizers, development of optimal FD and PDT methods and effective medical technologies based on them. This work was carried out with the active participation of a group of young scientists from the Moscow Scientific and Research Oncological Institute named after P.A. Herzen, who were able to combine the efforts of specialists from many other institutions – synthetic chemists, physicists, biologists, clinicians, and together go from the formation of an idea, through the development of new molecules of photosensitizers and experimental design samples of laser

equipment for FD and PDT, the development of industrial production of domestic drugs and laser equipment, to the widespread introduction of FD and PDT methods into clinical practice in the regions of Russia. This multistage and multi-directional work was evaluated by the award of the Russian Federation Government Prize in the field of science and technology in 2011. Over time, specialists united in the Russian Photodynamic Association (RPA) to develop and promote the method in Russia and popularize Russian experience abroad.

At present, after years of fruitful work of the RPA, FD and PDT methods are included in the oncological standards and clinical recommendations for a number of nosologies (since 2012), as well as to the program of state financing of treatment using these methods under the OMI system (since 2013). The result of the activities of the field-specific professional community of RPA was the creation of conditions, including economic ones, for the wide development of these methods in clinical practice. The key moment that influenced the beginning of the rapid introduction of the method into wide clinical practice in Russia was the inclusion of the methods in the list of therapeutic measures carried out within the framework of state guarantees in 2013. According to IMS Health, in the first half of 2014 the volume of the Russian market of drugs based on photosensitizers amounted to 33 million rubles, having increased by 90% compared to the same period in 2013, i.e. almost twice [16].

In recent years, the development of FD and PDT methods in Russia has been characterized by an intensive rise, a steadily growing interest in the method of specialists from various medical specialties, an increase in the equipping level of hospitals with the necessary equipment for FD and PDT, the emergence of new photosensitizers on the pharmaceutical market, and an increase in the level of patient confidence in these methods. Furthermore, traditionally, FD and PDT are those scientific areas that are in demand for the latest developments by scientists around the world, including Russia. One of the indicators of this is that in our country the number of dissertations defended in the field of FD and PDT is growing every year. Concurrently, the number of scientific studies in this area is also increasing. The growth of interest in FD and PDT in the regions has been especially evident in the last few years.

The aim of this study was to analyze the dynamics of the development of the clinical application and scientific developments of FD and PDT in the last decade in Russia. These indicators were assessed: by the volume of contracts (according to the website www.zakupki.gov.ru) in the framework of public procurement of photosensitizers in the constituent entities of the Russian Federation, for specific drugs and medical institutions in which this method is introduced into clinical practice; as well as by the activity of research work in the FD and PDT field, estimated by the number of candidate and doctoral dissertations on this topic and by the number of scientific publications in the RSCI.

Materials and methods

The activity of research work in the field of FD and PDT was assessed by the number of defended dissertations for the degree of candidate and doctor of science on the specified topic over the past 9 years (2012-2020). The dynamics of the number of defended dissertations over the years and the share of target dissertations from the total number of defended dissertations in individual specialties were assessed. The source of information about the defense of candidate's and doctoral dissertations was the official website of the State Commission for Academic Degrees and Titles under the Ministry of Science and Higher Education of the Russian Federation www.vak.minobrnauki.gov.ru. The sample of analyzed dissertations was limited to the period for which dissertations are presented in the State Commission for Academic Degrees and Titles archive on the website www.vak.minobrnauki.gov.ru – from 2012, there is no information on the website prior to this period.

The number of scientific publications in the RSCI database (www.elibrary.ru) for 2010-2019 was also analyzed. The dynamics of changes in the number of full-text scientific articles, abstracts of scientific reports and patents on the subject of FD and PDT by years was assessed. The analysis did not include publications of 2020 due to the fact that many periodicals post materials in the RSCI with a significant delay.

The breadth of clinical use of the methods in Russia was assessed by analyzing data on the volume of contracts in the framework of public procurement of photosensitizers intended for FD and PDT in clinical centers, implemented using the www.zakupki.gov.ru portal. Purchase volumes were analyzed in monetary and numerical terms (number of purchased packages of photosensitizers) and by the number of clinical institutions purchasing photosensitizers for PDT. For the analysis, we used data for 2014-2020 (prior to 2014 information on this issue is not available).

Results

Development of scientific research in the field of FD and PDT over the past decade

Analysis of the development of FD/PDT as a separate scientific area was carried out according to the number of defenses of candidate's and doctoral dissertations, data on which are published on the official website of the State Commission for Academic Degrees and Titles (vak.minobrnauki.gov.ru). The number of scientific publications in the RSCI database (www.elibrary.ru) was also analyzed. The dynamics of changes in the number of full-text scientific articles, abstracts of scientific reports

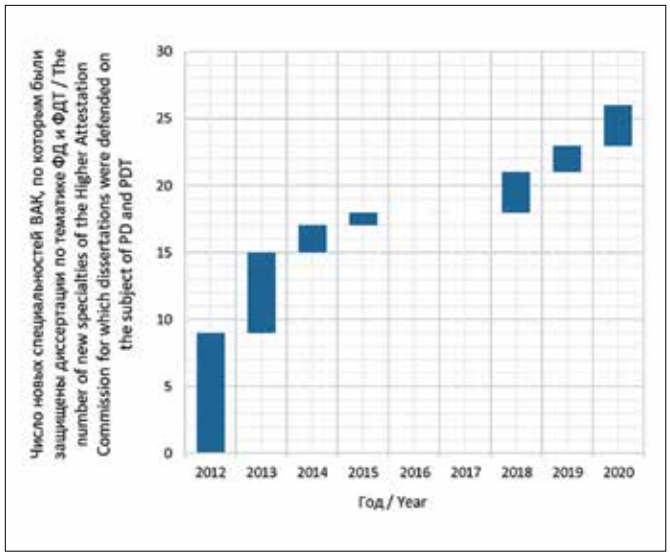
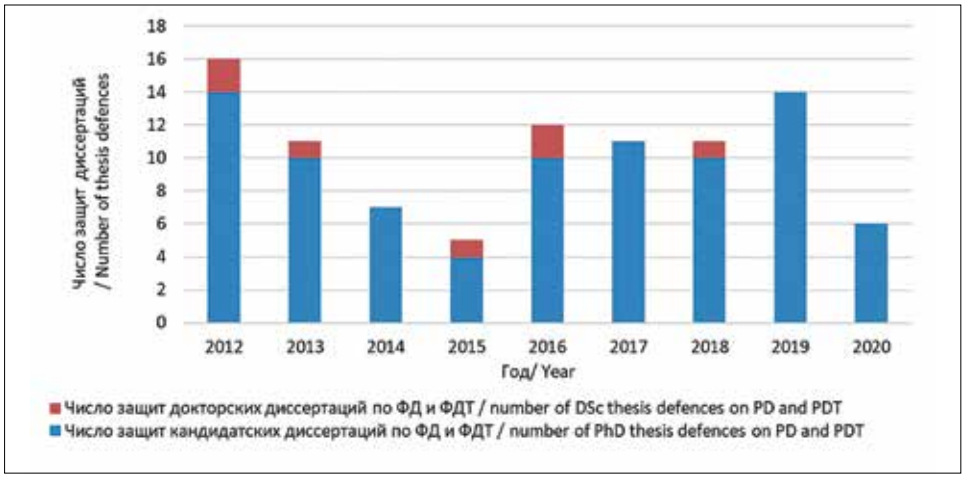
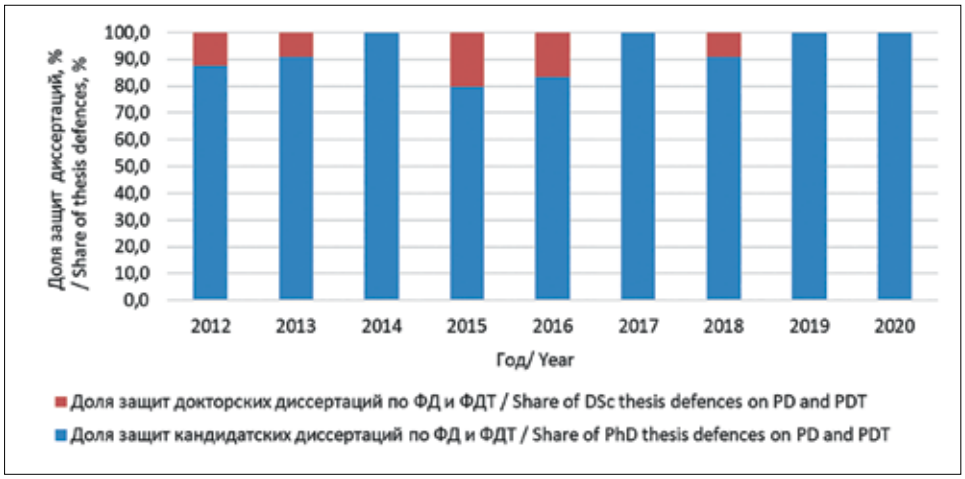


Рис. 1. Ежегодный прирост числа специальностей ВАК, по которым были защищены диссертации по тематике ФД и ФДТ и данные о которых были опубликованы на официальном сайте ВАК (vak.minobrnauki.gov.ru) в 2012-2020 гг.
Fig. 1. The annual increase in the number of specialties of the Higher Attestation Commission, for which theses on FD and PDT were defended and data on which were published on the official website of the Higher Attestation Commission (vak.minobrnauki.gov.ru) in 2012-2020.



a



b

Рис. 2. Распределение защит кандидатских и докторских диссертаций по ФД и ФДТ по годам: a – в абсолютных числах; b – в процентном соотношении.
Fig. 2. Distribution of defenses of candidate and doctoral theses in FD and PDT by years: a – absolute values; b – relative values.

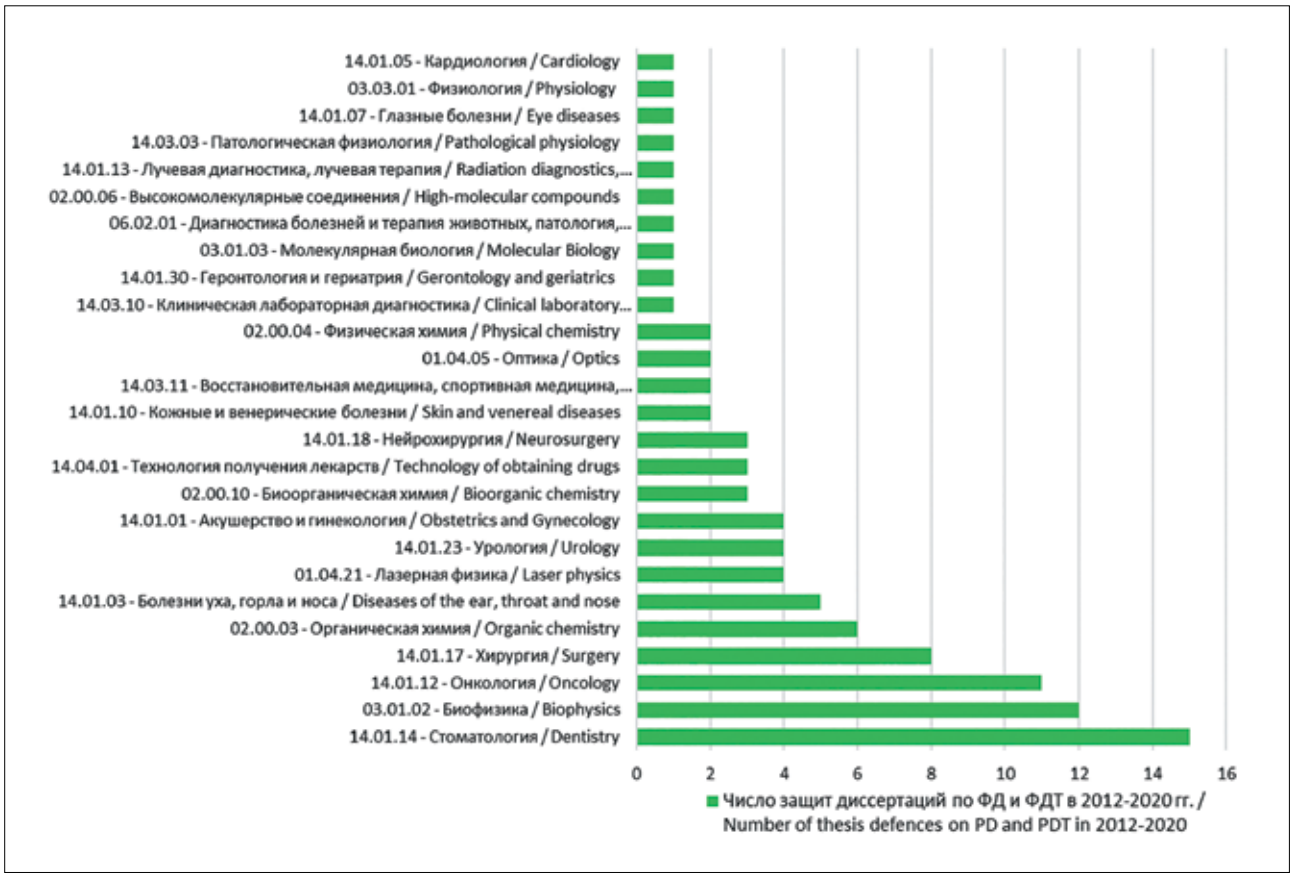


Рис. 3. Распределение диссертаций по ФД и ФДТ, защищенных в 2012-2020 гг., по специальностям.
Fig. 3. Distribution of theses on FD and PDT, defended in 2012-2020, by specialties.

and patents on the subject of FD and PDT by years was assessed.

The total number of candidate's and doctoral dissertations defended in 2012-2020 on the subject of FD and PDT, amounted to 93 dissertations in 26 scientific specialties out of 430 specialties represented in the State Commission for Academic Degrees and Titles. Of these, doctoral dissertations – 7, candidate's – 86. These figures do not exactly correspond to the real number of defenses on these topics, since the analysis only took into account those works in the title of which there was an indication of PD, PDT, as well as chemical and commercial names of photosensitizers. The real number of defenses on these topics is more than the figures given, since not all works have research and/or application of these methods in the title. Examples include the following works: Murshudova S. "Peculiarities of the clinical course and diagnosis of precancer and early vulvar cancer" (2013) – the paper presents a methodology and evaluates the results of fluorescent diagnostics in precancer and vulvar cancer. It is not possible to accurately estimate the number of works that were not included in this analysis for this reason, however, according to experts, they amount to about 25-30%.

The annual growth since 2012 of new scientific specialties in which candidate's and doctoral dissertations on the subject of FD and PDT were defended is shown in Fig. 1.

In 2012, the number of such specialties was 9 (14.01.12 Oncology, 14.01.14 Dentistry, 14.01.03 Diseases of the ear, nose and throat, 06.02.01 Diagnosis of diseases and therapy of animals, pathology, oncology and morphology of animals, 14.01.17 Surgery, 14.01.07 Eye diseases, 14.03.10 – Clinical laboratory diagnostics, 14.01.23 Urology, 14.01.01 Obstetrics and gynecology). By 2020, the number of specialties in which defenses were held on the topics of FD and PDT increased by 17 and the total number of specialties amounted to 26.

The distribution of the number of defenses of dissertations on FD and PDT by years is shown in Fig. 2.

As can be seen from Fig. 2a, in total, from 2012 to 2020 86 dissertations were defended for the degree of the candidate of medical sciences and 7 – the doctor of medical sciences. In those years when both candidate and doctoral dissertations were defended, the proportion of defending doctoral dissertations ranged from 9% to 20% (Fig. 2b). Despite the changes in the number of defenses of candidate's and doctoral dissertations for

Рис. 4. Распределение доли диссертаций по ФД и ФДТ от общего числа диссертаций, защищенных по данным специальностям в 2012-2020 гг.
Fig. 4. Distribution of the share of theses in FD and PDT from the total number of theses defended in the specialties in 2012-2020.

individual years, on average the number of defenses remains approximately at the same level with a tendency to some increase in recent years. So, over the past 3 years (2018-2020), the total number of defenses was 31 (30 candidate's and 1 doctoral), which is slightly more than in the previous similar period (2015-2017): 28 dissertations (25 candidate's and 3 doctoral), and close in terms of values to the previous three-year period (2012-2014): 34 dissertations (31 candidate's and 3 doctoral). The share of candidate's dissertations defended over the past 3 years has grown and in 2018-2020 averaged 96.8% compared to 91.2% and 89.3% in 2012-2014 and 2015-2017.

This fact indicates that research in this area does not stop and is relevant both in fundamental and applied areas. In different years of the analyzed period, the total number of dissertations defenses for the degree of a candidate and a doctor of medical sciences varied from 5 to 16 per year.

Fig. 3 shows the distribution of the number of dissertations on FD and PDT defended in 2012-2020 by individual scientific specialties.

The largest number of dissertations over 9 years was defended in three specialties: 14.01.14 Dentistry (15 dissertations, of which 14 are candidate's and 1 doctoral), 03.01.02 Biophysics (12 theses, of which 11 are candidate's and 1 doctoral) and 14.01.12 Oncology (11 dissertations, including 9 candidate's and 2 doctoral).

Fig. 4 shows the distribution of the share of dissertations in FD and PDT from the total number of dissertations defended in individual specialties for a total of 9 years.

From the data presented in Fig. 4, it can be seen that the largest share in the total number of dissertations defended in a particular specialty over 9 years are dissertations in the specialty 03.01.02 Biophysics – 3.46% of dissertations in this specialty were defended on the topics of FD and PDT. On the second and third places in this indicator are the specialties 02.00.10 Bioorganic Chemistry and 14.04.01 Formulation – 2.14% and 1.82%, respectively.

The number of publications on the subject of FD and PDT in the RSCI was analyzed. The analysis includes data on the number of scientific articles, abstracts of scientific conferences and patents for 2010-2019. The analysis did not include publications of 2020 due to the fact that many periodicals post materials in the RSCI with a significant delay.

Fig. 5 presents data on the annual increase in the number of journals in which articles and abstracts on the subject of FD/PDT were published according to the RSCI data.

As can be seen from the data presented in Fig. 5, in 2010, 94 journals published scientific materials on the subject of FD and PDT, in 2011, scientific materials on

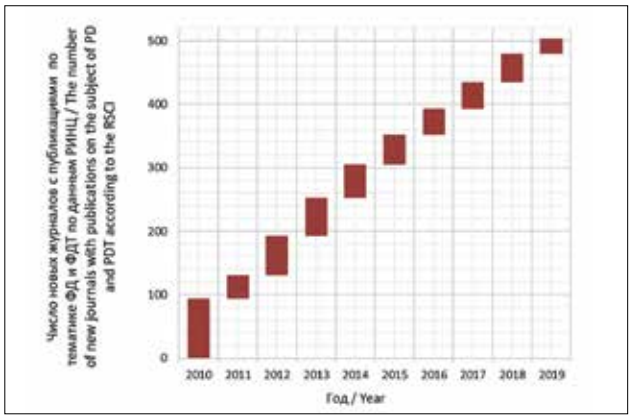


Рис. 5. Ежегодный прирост числа журналов, в которых были опубликованы научные материалы по тематике ФД и ФДТ по данным РИНЦ в 2010-2019 гг.
Fig. 5. An annual increase in the number of journals in which scientific materials on FD and PDT were published according to the RSCI data in 2010-2019.

the subject of FD and PDT were first published in 36 new journals, in 2012 – in 62, in 2013 – in 60, in 2014 – in 53, in 2015 – in 47, in 2016 in – in 41, in 2017 – in 42, in 2018 in 45 and in 2019 in 23 new magazines. The total number of journals in which, according to the RSCI data, scientific materials on the subject of FD and PDT were published during this period was 503.

In the period under review, the number of scientific publications on the subject of FD and PDT is steadily increasing. The total number of publications over 10 years increased by 2.6 times (218 publications in 2014, 565 publications in 2019), including the doubled number of scientific articles (152 articles in 2014, 306 articles in 2019 years), the number of conference abstracts – increased by 8 times (23 abstracts in 2014, 183 abstracts in 2019), the number of patents – by 1.8 times (43 patents in 2014, 76 patents in 2019). The dynamics of

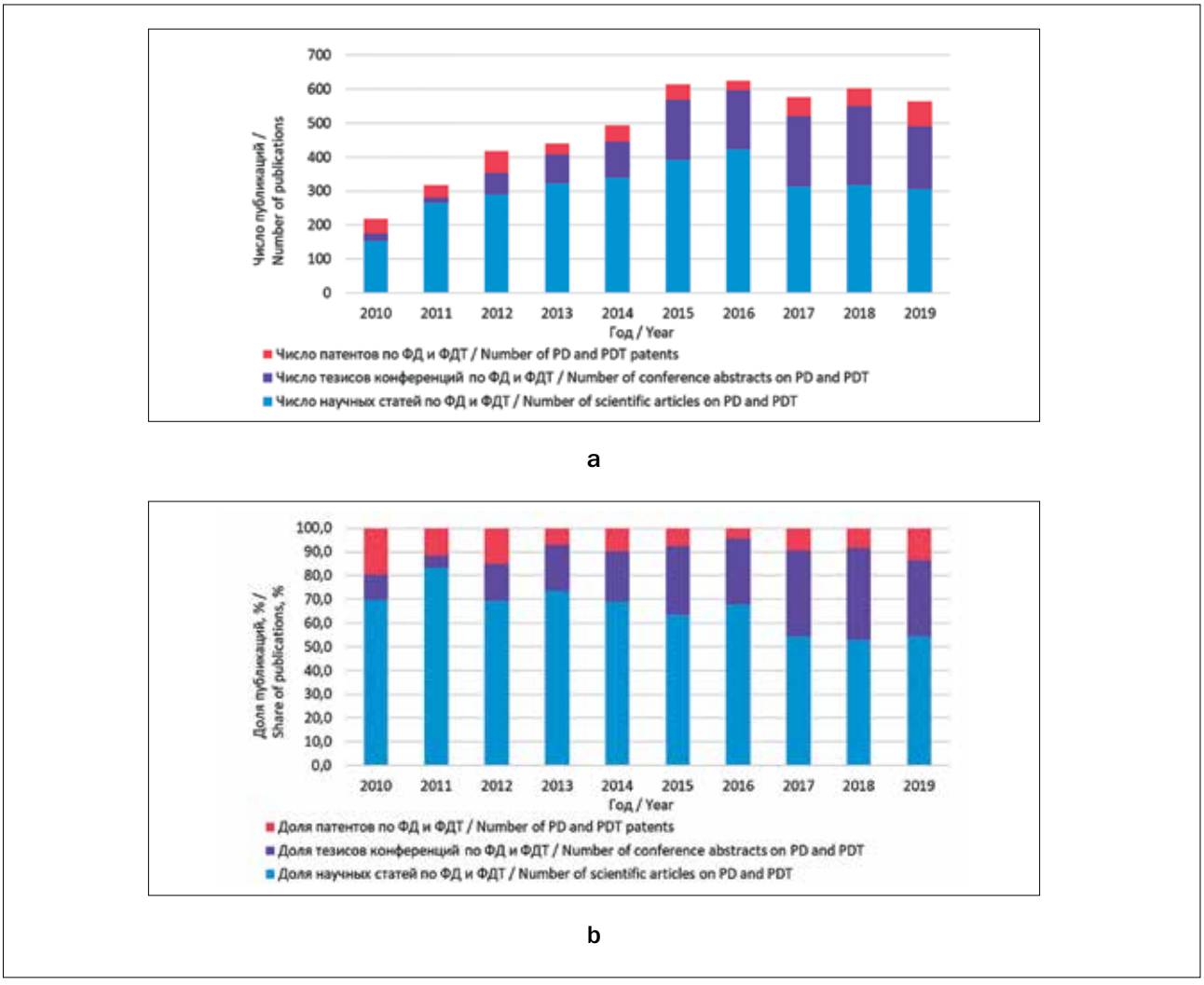


Рис. 6. Динамика числа публикаций в РИНЦ по тематике ФД и ФДТ за период 2010-2019 гг.: a – в абсолютных числах; b – в процентном соотношении.
Fig. 6. Dynamics of the number of publications in the RSCI on the subject of FD and PDT for the period of 2010-2019: a – absolute values; b – relative values.

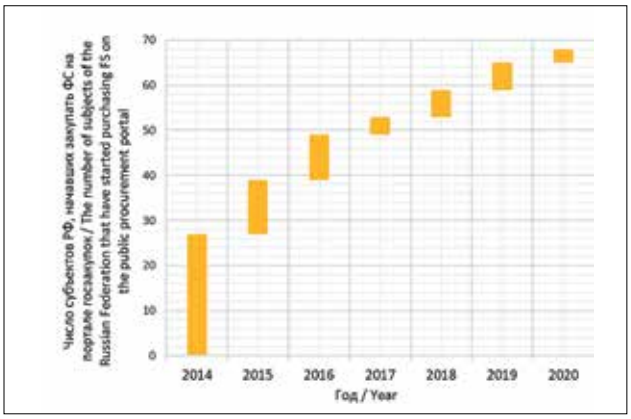


Рис. 7. Ежегодный прирост числа субъектов РФ, заключивших контракты на поставку фотосенсибилизаторов по данным сайта www.zakupki.gov.ru в 2014-2020 гг.
Fig. 7. An annual increase in the number of RF constituent entities that have entered into a contract for the supply of photosensitizers, according to the website www.zakupki.gov.ru in 2014-2020.

the number of publications for the analyzed period is shown in Fig. 6.

As shown by Fig. 6, in addition to an increase in the number of publications on the subject of FD and PDT, there is also a redistribution by the nature of publications. There is a trend towards an increase in the number of conference abstracts, which in 2012 accounted for 10.6% of the total number of publications, and in 2019 – 32.4%. This trend is associated with the active holding of schools, conferences and congresses, in particular, the RPA holds annually: "Winter School on FD and PDT" since 2013 and "International Congress on FD and PDT" since 2012. The Congress in 2012 was attended by 120 specialists from 32 organizations; after 5 years (in 2017), the number of participants increased by 5 times and amounted to more than 600 people from 53 organizations; by 2021, the number of participants exceeded 750 people from 85 organizations.

Introduction of FD and PDT methods into clinical oncological practice in the Russian Federation

An analysis of the dynamics of the introduction of FD and PDT methods into clinical oncological practice in Russia in recent years was carried out on the basis of the data on government purchases of photosensitizers published on the www.zakupki.gov.ru portal. It should be understood that, due to the fact that this resource reflects information only on purchases to federal medical institutions, the number of volumes of purchased photosensitizers, and, therefore, the number of patients treated in commercial clinics, is not taken into account in this analysis, which makes the data presented in the article not absolute. There may also be an error associated with the theoretical possibility of a situation where an already concluded contract has not been implemented.

Analysis of information on the portal www.zakupki.gov.ru revealed 688 contracts concluded for the purchase of photosensitizers for FD and PDT in clinical institutions in the Russian Federation in 2014-2020 (prior to 2014 information on this issue is not available).

During the analyzed period, the number of new constituent entities of the Russian Federation, in which the methods of FD and PDT were first applied, increased by 3-12 per year (Fig. 7).

In 2014, photosensitizers were purchased through the www.zakupki.gov.ru portal, and, accordingly, the FD and PDT methods were used in 27 constituent entities of the Russian Federation. In 2015, for the first time, purchases were made in 12 additional constituent entities of the Russian Federation, in 2016 – in 10, in 2017 – in 4, in 2018 – in 6, in 2019 – in 6 and in 2020 – in 3 constituent entities of the Russian Federation. Thus, by the end of 2020, the method has been implemented in 68 constituent entities of the Russian Federation. At the same time, in a number of the above constituent entities (13 constituent entities), purchases of photosensitizers through the portal www.zakupki.gov.ru are carried out annually, in others (43) – once every 2-3 years, there are also those where there were so far single purchases (12).

We did not find information on public procurement of photosensitizers in 17 constituent entities of the Russian Federation: the Republics of Adygea, Altai, Buryatia, Dagestan, Ingushetia, Kalmykia, Karelia, Tyva, Khakassia, the Udmurt Republic, Magadan, Oryol, Ryazan, Tambov regions, Nenets, Chukotka, Yamalo-Nenets Autonomous okrugs.

Distribution of total volumes of public procurement of photosensitizers by constituent entities of the Russian Federation in 2014-2020 in monetary and numerical terms is presented in Fig. 8 and 9, respectively.

Figs. 8 and 9 show that Moscow dominates in both indicators. In the analyzed period, 113 contracts for the purchase of photosensitizers for clinical practice were concluded in Moscow, while the volume of public procurement amounted to 176.36 million rubles (10.79 thousand packages). St. Petersburg city takes second place. The volume of public procurement of photosensitizers in the analyzed period in this constituent entity of the Russian Federation is comparable to the indicators of Moscow and amounted to 171.45 million rubles (10.61 thousand packages) within the framework of 107 concluded contracts. Chelyabinsk, Murmansk, Rostov and Sverdlovsk regions follow with a significant margin – 87.80 million rubles (5.82 thousand packages), 77.13 million rubles (4.51 thousand packages), 72.31 million rubles (4.09 thousand packages) and 66.54 million rubles (3.48 thousand packages), respectively. Fig. 8 and 9 also show the distribution of the volume of public procurement of photosensitizers in each constituent entity of the Russian Federation by years. In Moscow, the largest volume

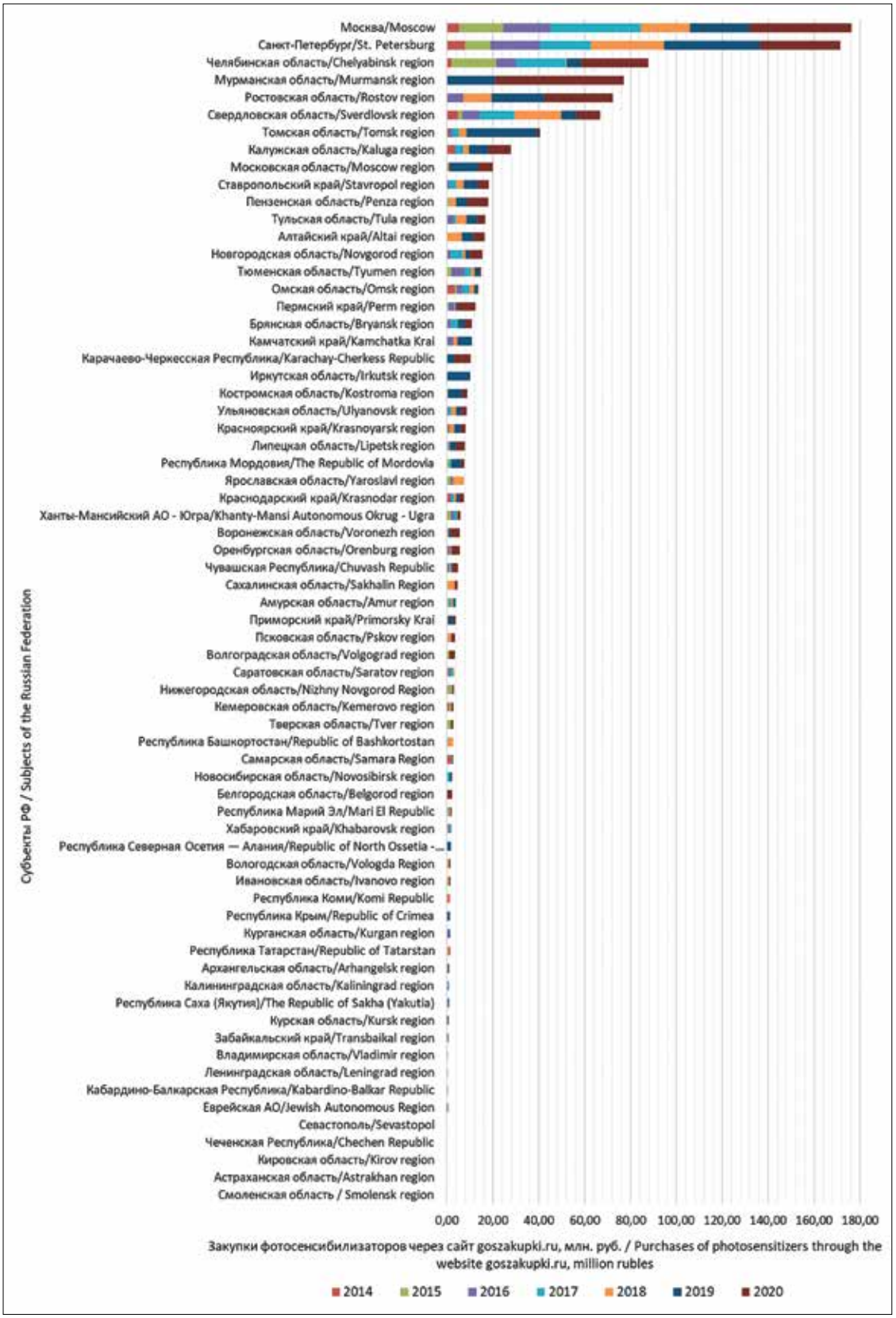


Рис. 8. Распределение ежегодных объемов госзакупок фотосенсибилизаторов по субъектам Российской Федерации в денежном выражении.
Fig. 8. Distribution of annual volumes of state purchases of photosensitizers by constituent entities of the Russian Federation in monetary terms.

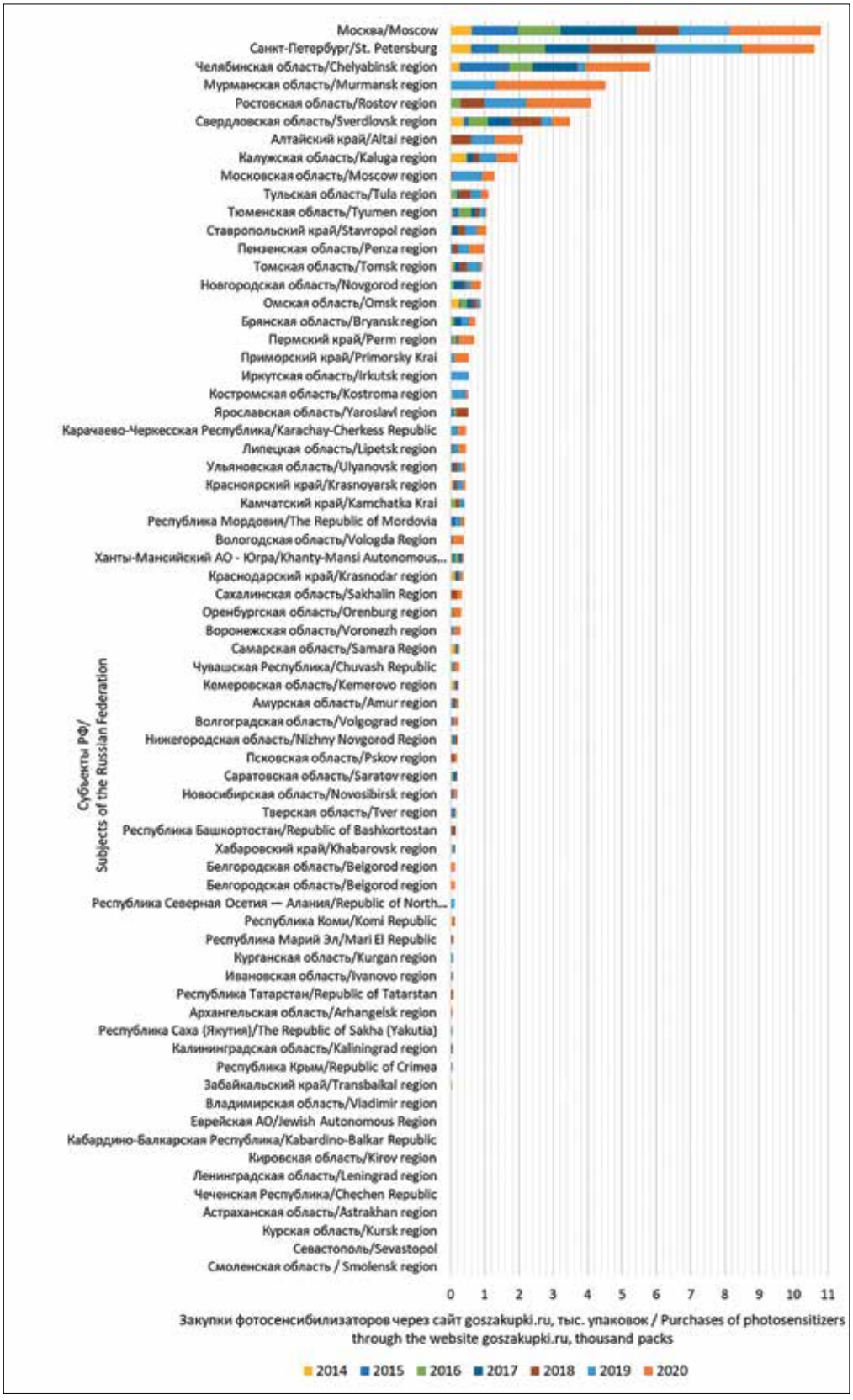


Рис. 9. Распределение ежегодных объемов госзакупок фотосенсибилизаторов по субъектам Российской Федерации в численном выражении.
Fig. 9. Distribution of annual volumes of state purchases of photosensitizers by constituent entities of the Russian Federation in quantitative terms.

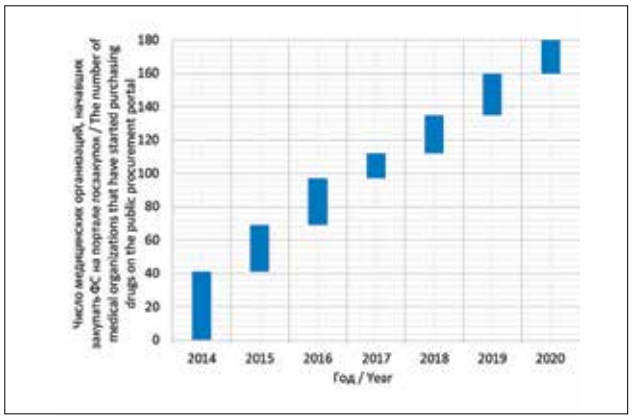


Рис. 10. Ежегодный прирост числа медицинских организаций, заключивших контракты на поставку фотосенсибилизаторов по данным сайта www.zakupki.gov.ru в 2014-2020 гг.
Fig. 10. An annual increase in the number of medical organizations that entered into contracts for the supply of photosensitizers according to the website www.zakupki.gov.ru in 2014-2020.

of procurement was noted in 2020 (44.77 million rubles, 2.63 thousand packages). In St. Petersburg, the largest volume of public procurement of photosensitizers was observed in 2019 (41.93 million rubles, 2.11 thousand packages).

Interestingly, in Murmansk region, information on the availability of public procurement of photosensitizers on the portal www.zakupki.gov.ru appeared only in 2019, while the volume of public procurement in 2019 amounted to 20.93 million rubles, and in 2020 – 56.20 million rubles, which is comparable to the figures for Moscow and St. Petersburg. These data confirm the trends in the development of FD and PDT methods in the regions. Thus, in 2014, the share of public procurement of photosensitizers in Moscow and St. Petersburg was 35.9% of the volume of public procurement of photosensitizers throughout Russia, in 2019 this figure dropped to 26.5%. The share of purchases of photosensitizers in the constituent entities of the Russian Federation with a population of less than 5 million people in 2014 was 60.4% of the total number of purchases of photosensitizers in Russia, and in 2020 it increased by more than 10%, and already amounted to 70.5% of the total number of purchases. Moreover, the share of purchases of photosensitizers in the constituent entities of the Russian Federation with a population of less than 1 million people from 2014 to 2020 increased by 9 times from 2.9% to 25.3% of the total number of purchases.

The number of medical organizations on the basis of which the methods of FD and PDT are introduced is also growing every year. At the same time, during the analyzed period, the number of new medical organizations in which the methods of FD and PDT were first applied, according to the portal www.zakupki.gov.ru, increased annually by 15-28 (Fig. 10).

In 2014, photosensitizers were purchased and, thereof, FD and PDT methods were used in 41 medical organizations; in 2015, for the first time, purchases were made in another 28 new medical organizations, in 2016 – in another 28, in 2017 – in another 15, in 2018 – in another 23, in 2019 – in another 25 and in 2020 – at 21. Thus, in general, during the analyzed period, FD and PDT methods were introduced in 181 oncological medical organizations.

In 2014, out of all constituent entities of the Russian Federation that used FD and PDT methods according to the portal www.zakupki.gov.ru, in 21 (77.8%) the method was used only in one medical organization, in 4 (14.8%) – in two, in 1 (3.7%) – in four and in 1 (3.7%) – in eight.

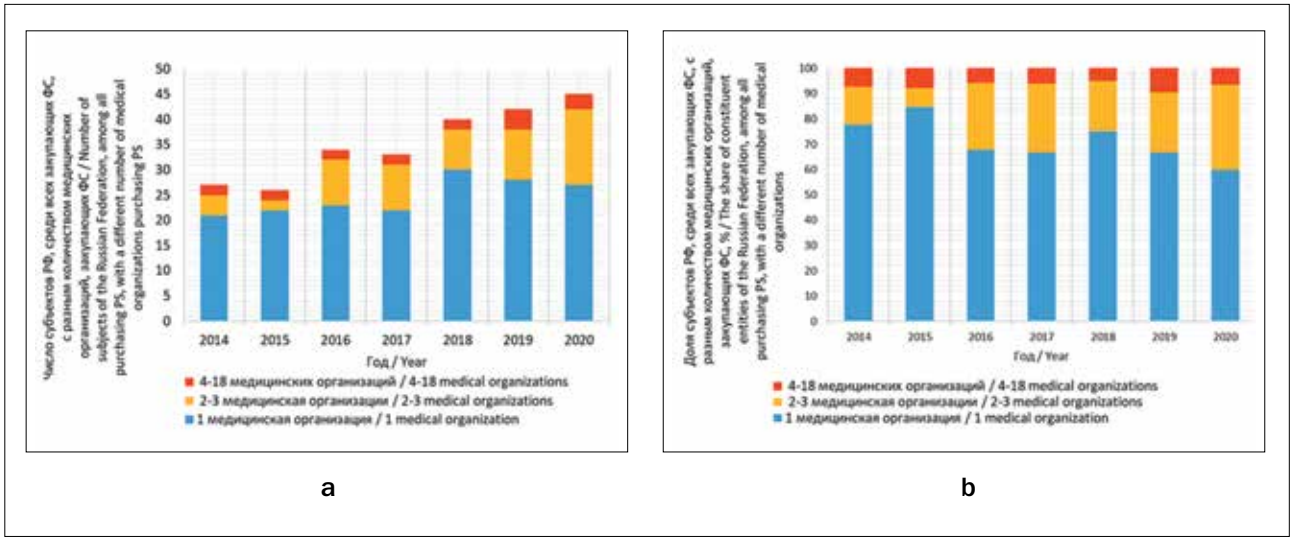


Рис. 11. Динамика числа организаций в отдельных субъектах Российской Федерации, закупавших фотосенсибилизаторы для ФД и ФДТ по данным портала www.zakupki.gov.ru: a – в абсолютных числах; b – в процентном соотношении.
Fig. 11. Dynamics of the number of organizations in individual constituent entities of the Russian Federation that purchased photosensitizers for FD and PDT according to the portal www.zakupki.gov.ru: a – absolute values; b – relative values.

In 2020, out of all constituent entities of the Russian Federation that used FD and PDT methods according to the portal www.zakupki.gov.ru, in 27 (60.0%) the method was used only in one medical organization, in 12 (26.7%) – in two, in 3 (6.7%) – in three, in 1 (2.2%) – in four, in 1 (2.2%) – in seven and in 1 (2.2%) – in thirteen (Fig. 11).

Fig. 11 shows that the number of constituent entities of the Russian Federation, where FD and PDT are used in 4 or more medical organizations, annually remains approximately at the same level (2-4 subjects, 5.0-9.5% of the total number of constituent entities of the Russian Federation using FD and PDT methods in a particular year), while the number of constituent entities in which FD and PDT were used in 4 or more medical organizations over the entire analyzed period was 5: Moscow city, St. Petersburg city, Rostov, Moscow and Tomsk regions.

The number of constituent entities of the Russian Federation, where medicinal products for FD and PDT were purchased from 2-3 medical organizations, is 2-15 (7.7-33.4%) annually, while the number of subjects in which medicinal products for FD and PDT were purchased from 2-3 medical organizations over the entire analyzed period was 23.

The number of constituent entities of the Russian Federation where medicinal products for FD and PDT were purchased from 1 medical organization is 21-30 (60.0-84.6%) annually, while the number of constituent entities in which FD and PDT were used in 1 medical organization for the entire analyzed period was 40.

During the analyzed period, the number of subjects in which FD and PDT are used in 4 or more medical organizations remains approximately the same, and the redistribution occurs due to a decrease in the number of subjects in which PDT is used only in 1 medical organization and an increase in the number of constituent entities in which PDT is used in 2-3 medical organizations. For instance, in 2014 PDT in one medical organization was presented in 21 constituent entities of the Russian Federation (77.8%), in 2-3 organizations – in 4 (14.8%); in 2020 – in 27 (60.0%) and 15 (33.4%), respectively.

The population size in different subjects of the Russian Federation varies greatly, so it was interesting to analyze the results obtained taking into account the population size. Figs. 12 and 13 show the total volume of public procurement of photosensitizers for 7 years in the constituent entities of the Russian Federation, taking into account the population in monetary and numerical terms, respectively.

The largest number of packages of photosensitizers per 100 thousand population was purchased under contracts, information about which is available on the public procurement portal, in Murmansk region – 608.7 packages per 100 thousand population in 2014-2020, which amounted to 10.40 million rubles per 100 thousand population. The second place in terms of the number of packages of photosensitizers per 100 thousand population – St. Petersburg (196.6 packages per 100 thousand population), then Kaluga (194.0 packages per 100 thousand population) and Chelyabinsk regions (167.8 packages per 100 thousand population), in fifth place is Novgorod region (147.5 packages per 100 thousand people).

At the same time, in terms of public procurement of photosensitizers (in monetary terms) per 100 thousand people, the second place after Murmansk region is occupied by Tomsk region (3.75 million rubles per 100 thousand of the population), the third – by Kamchatka Krai (3.44 million rubles per 100 thousand population) and St. Petersburg in fourth place (3.18 million rubles per 100 thousand population). Kaluga, Novgorod and Chelyabinsk regions are in fifth, sixth and seventh places (2.77, 2.57 and 2.30 million rubles per 100 thousand population), respectively.

Moscow ranks eleventh and tenth among the constituent entities of the Russian Federation in terms of public procurement of photosensitizers per 100,000 population in monetary (1.39 million rubles per 100,000 population) and numerical (85.1 packages per 100,000 population) terms, accordingly, yielding, in addition to the listed entities, also Rostov and Sverdlovsk regions and the Karachay-Cherkess Republic.

Figs. 14 and 15 show the distribution of the total volume of public procurement in 2014-2020 for individual photosensitizers in monetary and numerical terms, respectively.

Figs. 16 and 17 present data on the volume of public procurement of individual photosensitizers by years in monetary and numerical terms, respectively.

From the data presented in Figs. 16 and 17, it can be seen that in recent years there has been a steady increase in the volume of public procurement of photosensitizers. In 2014, the total volume of public procurement of all photosensitizers amounted to 36.42 million rubles (3.58 thousand packages), in 2015 – 67.52 million rubles (4.97 thousand packages), in 2016 – 98.18 million rubles (6.12 thousand packages), in 2017 – 134.25 million rubles (7.58 thousand packages), in 2018 – 143.59 million rubles (8.29 thousand packages), in 2019 – 255.46 million rubles (13.65 thousand packages), in 2020 – 307.37 million rubles (18.99 thousand packages).

It can be noted that since 2014, the volume of public procurement of medicinal products photoditazine, radachlorin and alasens has been proportionally increasing. Yearly, throughout the analyzed period, the largest volume of public procurement among photosensitizers falls on radachlorin: 34.1-55.7% in monetary terms and 37.7-49.3% in numerical terms. Thus, it should be noted that since 2014, the share of public procurement of radachlorin has slightly decreased: from 2014 to 2020, by 8.3% in monetary terms (from 55.7% to 47.4%) and by 2.1% in numerical terms (from 49.3% to 47.2%). A sig-

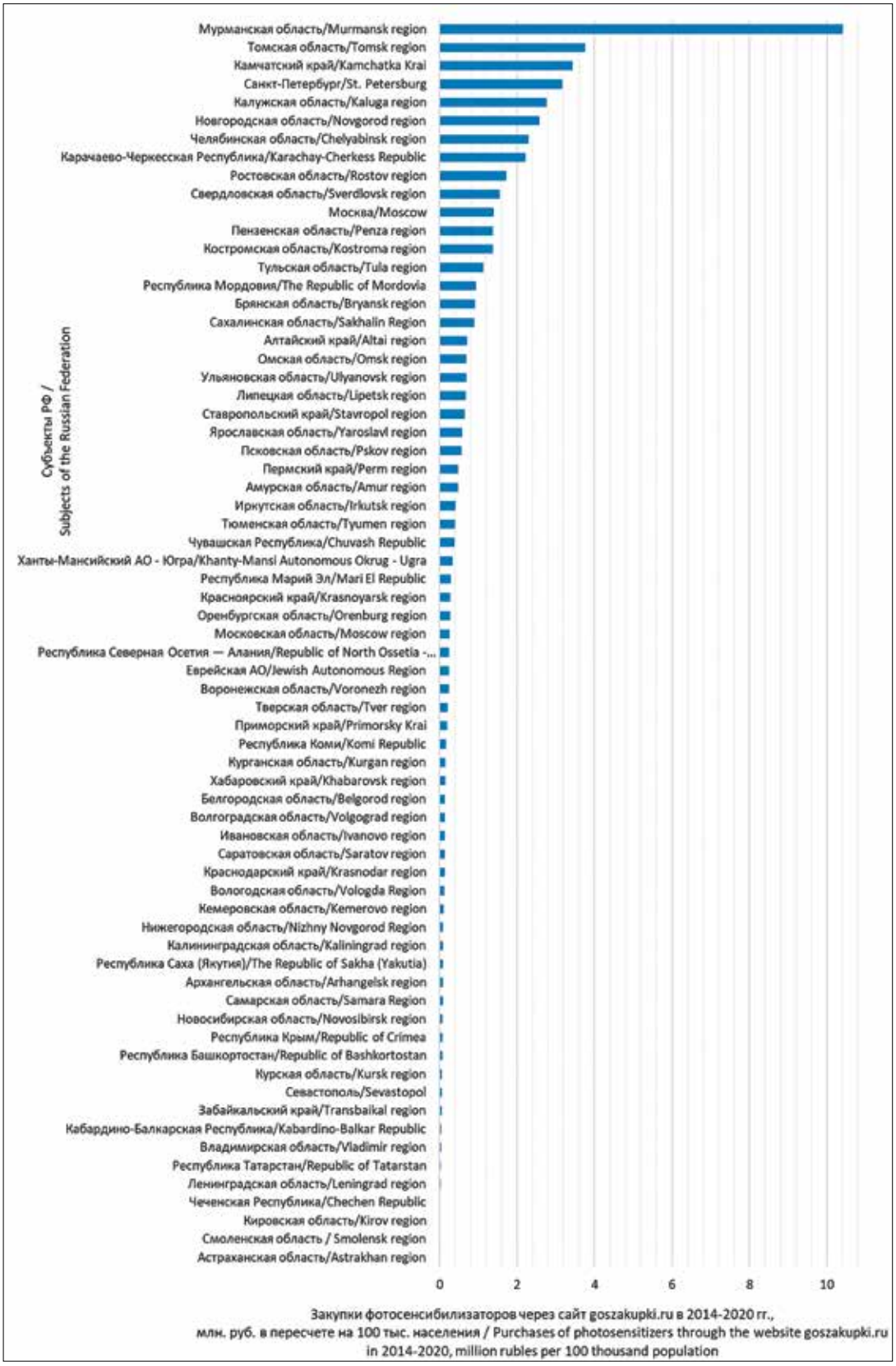


Рис. 12. Распределение объемов госзакупок фотосенсибилизаторов в 2014-2020 гг. в денежном выражении по субъектам Российской Федерации с учетом населения.
Fig. 12. Distribution of volumes of state purchases of photosensitizers in 2014-2020 in monetary terms by the constituent entities of the Russian Federation, taking into account the population.

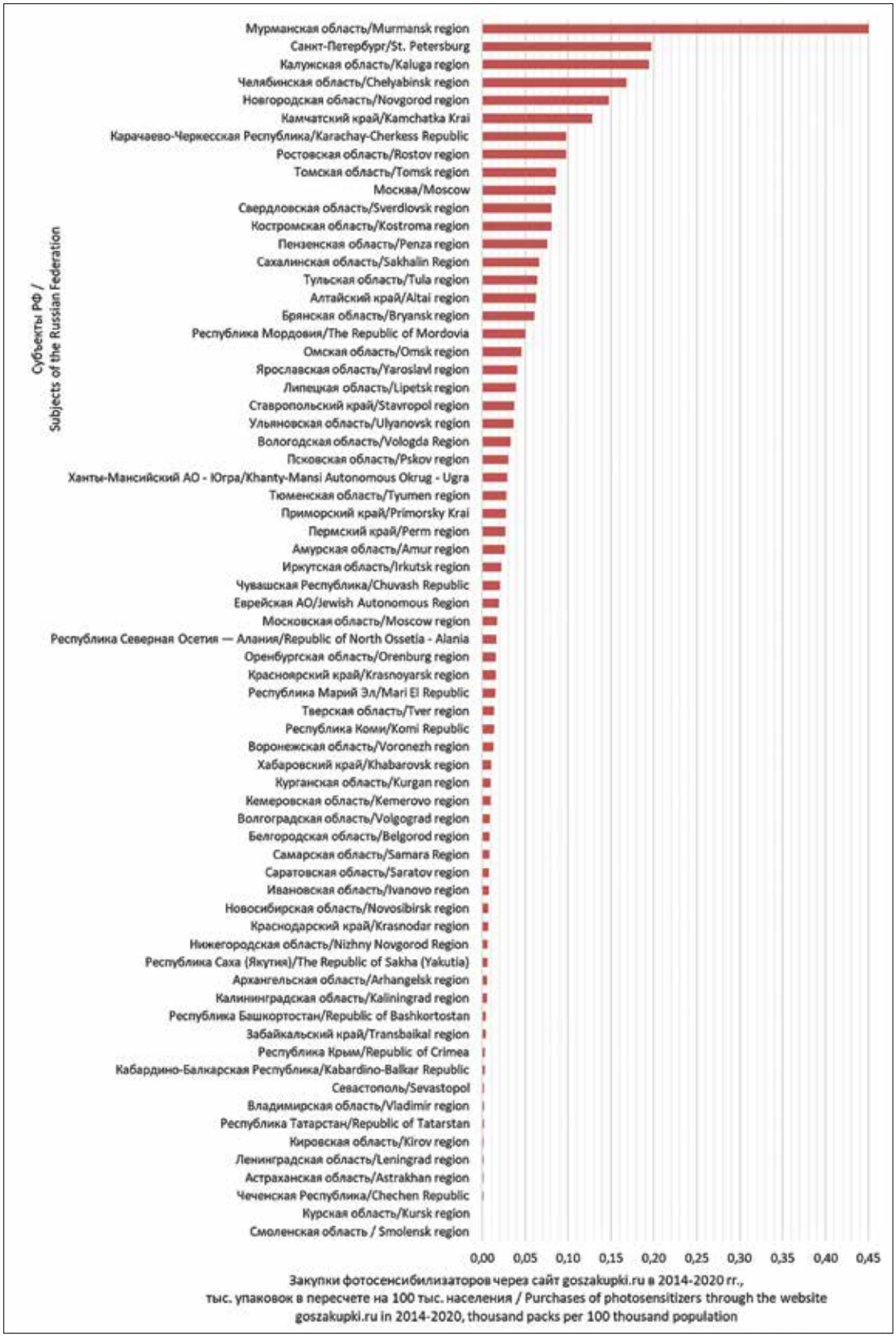


Рис. 13. Распределение объемов госзакупок фотосенсибилизаторов в 2014-2020 гг. в численном выражении по субъектам Российской Федерации с учетом населения.
Fig. 13. Distribution of volumes of state purchases of photosensitizers in 2014-2020 in quantitative terms by the constituent entities of the Russian Federation, taking into account the population.

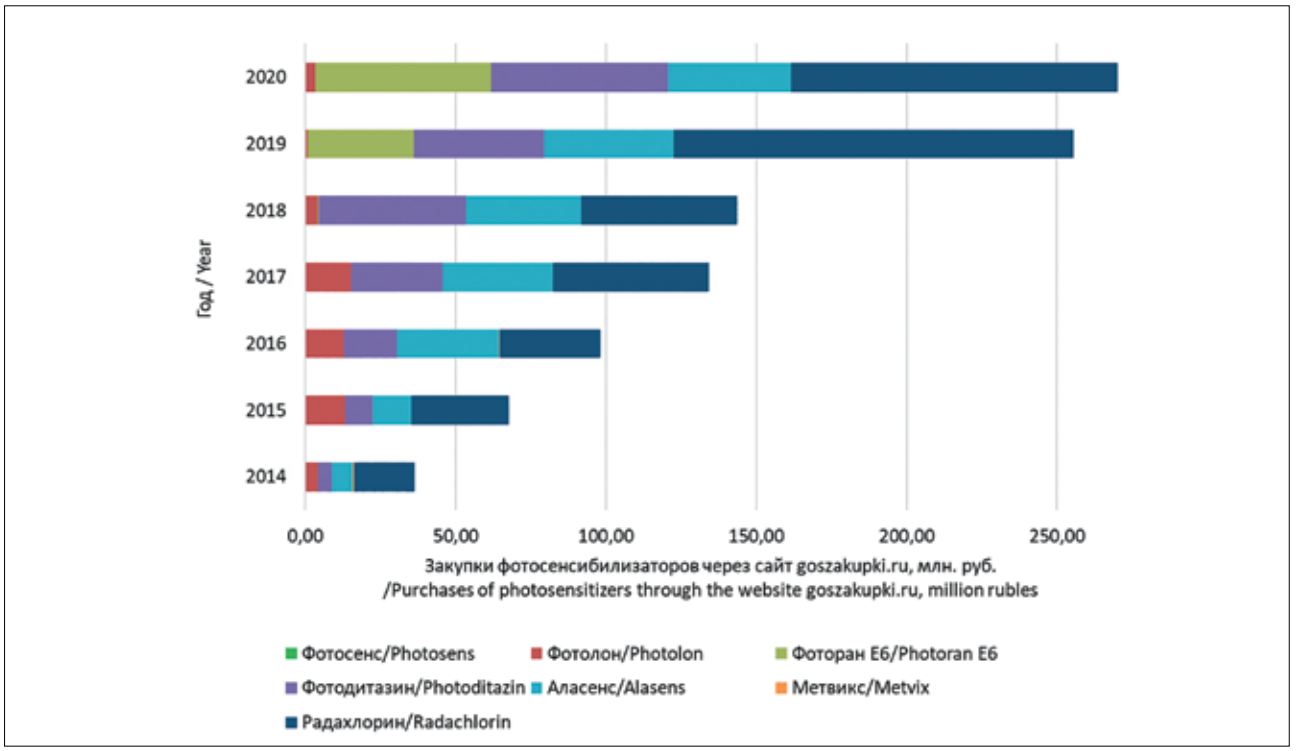


Рис. 14. Распределение ежегодных объемов госзакупок по фотосенсибилизаторам в денежном выражении.
Fig. 14. Distribution of annual volumes of public procurement of photosensitizers in monetary terms.

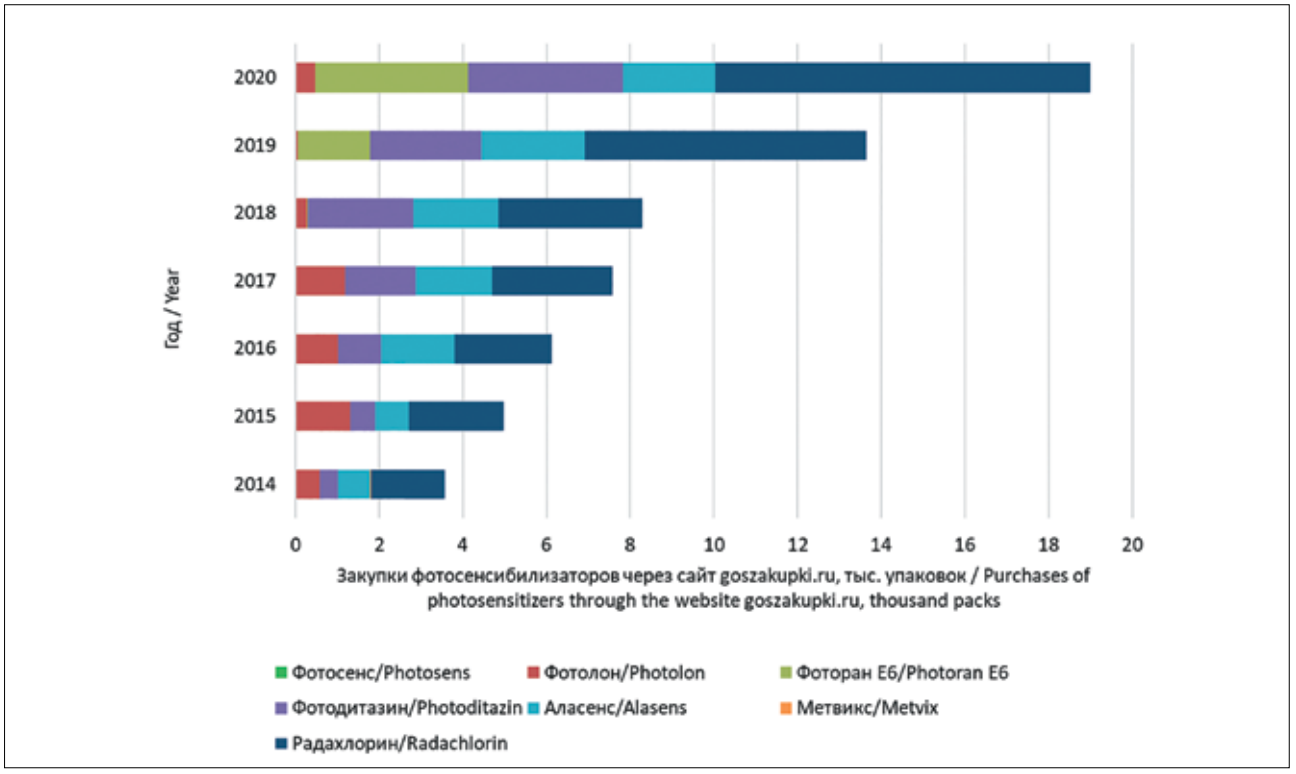


Рис. 15. Распределение ежегодных объемов госзакупок по фотосенсибилизаторам в численном выражении.
Fig. 15. Distribution of annual volumes of public procurement of photosensitizers in quantitative terms.

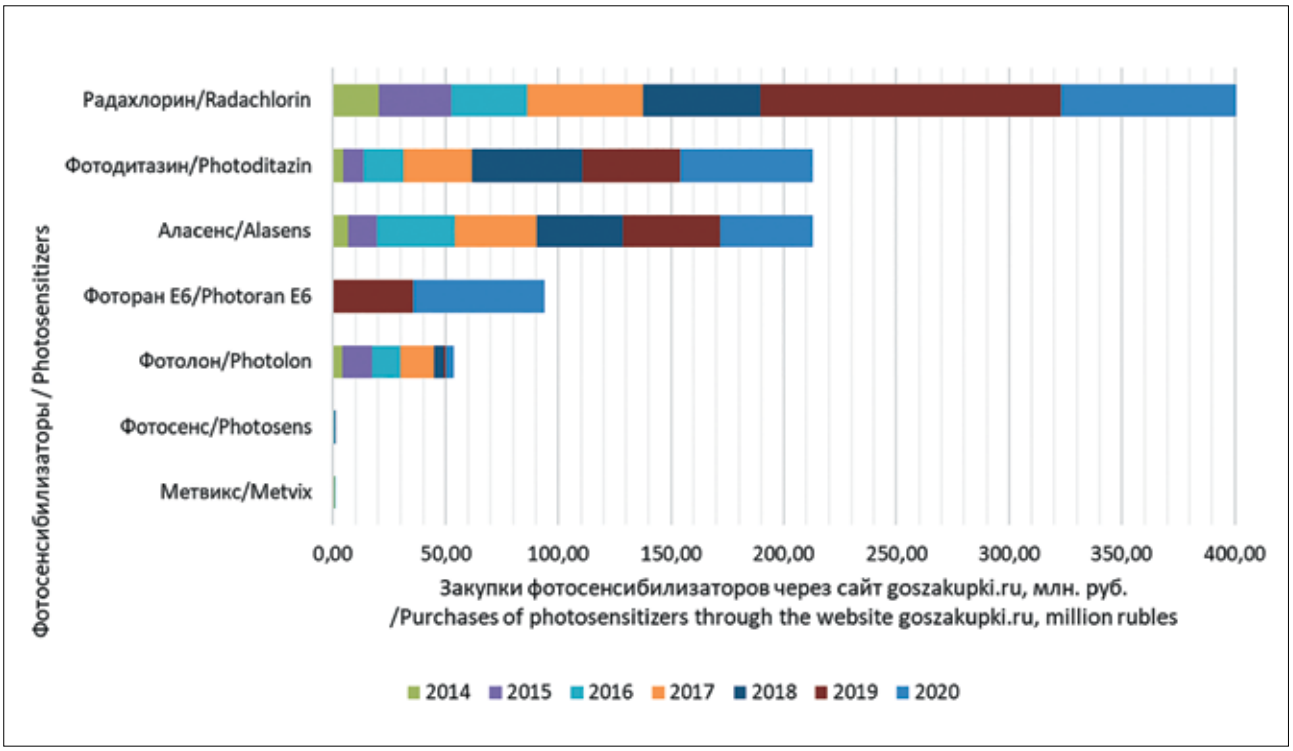


Рис. 16. Распределение госзакупок отдельных фотосенсибилизаторов по годам в денежном выражении.
Fig. 16. Distribution of state purchases of individual photosensitizers by year in monetary terms.

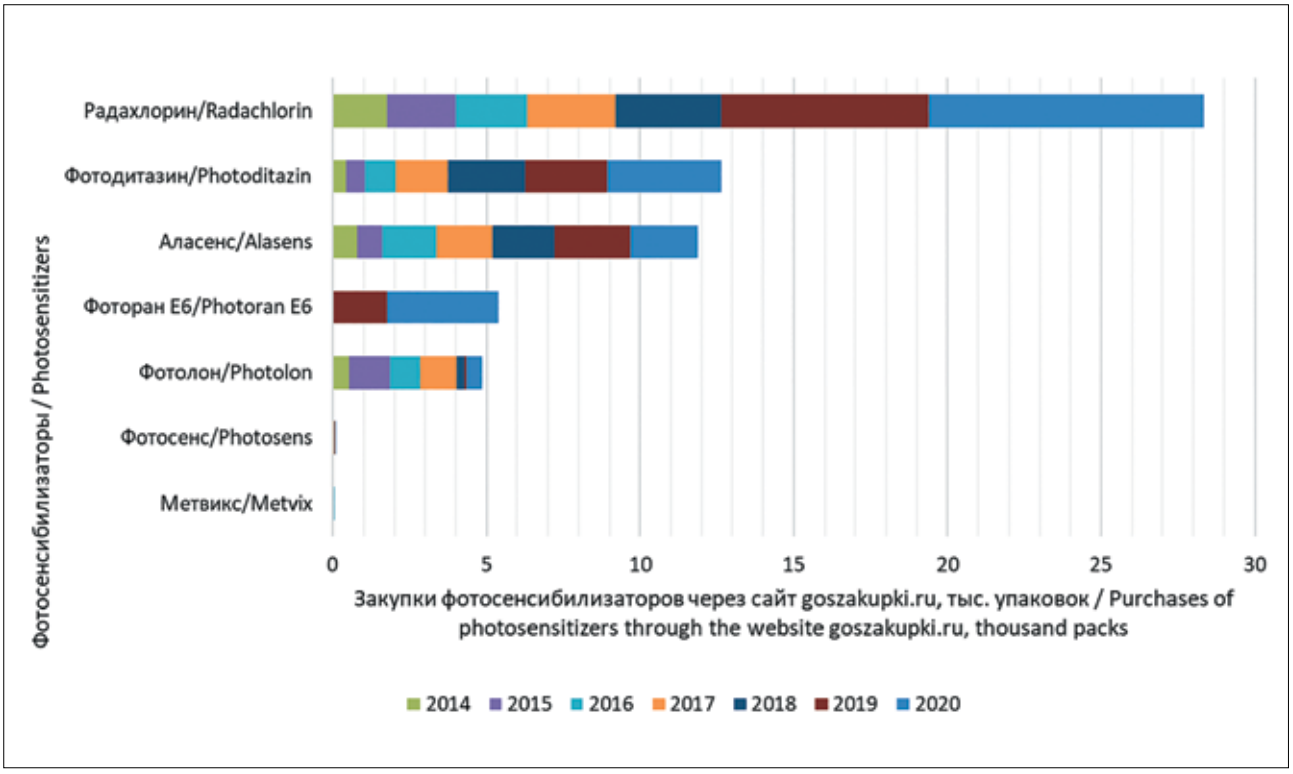


Рис. 17. Распределение госзакупок отдельных фотосенсибилизаторов по годам в численном выражении.
Fig. 17. Distribution of state purchases of individual photosensitizers by year in quantitative terms.

nificant increase in the volume of public procurement over the analyzed years is observed for photoditazine: the volume of public procurement in 2014 amounted to 4.46 million rubles (437 packages), in 2020 – 59.01 million rubles (3719 packages). The same trend is observed for alasens: the volume of public procurement in 2014 amounted to 6.85 million rubles (782 packages), in 2020 – 40.89 million rubles (2196 packages). Over the past three years, the volume of public procurement of photoran E6 has significantly increased: in 2018, the first contracts for the purchase of this medicinal product in the amount of 0.34 million rubles appear on the portal, in 2019, the volume of public procurement doubles and amounts to 35.23 million rubles, and in 2020 – gets to 58.29 million rubles.

From the data presented in Figs. 16 and 17, it can be seen that the total volume of public procurement of radachlorin significantly exceeds the volume of public procurement of other photosensitizers – the share of its procurement over the 7 analyzed years of the total procurement of all photosensitizers is 44.9% in monetary terms and 44.8% in numerical terms. As noted above, there is a trend towards a gradual decrease in the share of radachlorin purchases in the total procurement of photosensitizers: from 55.7% in 2014 to 47.3% in 2020 in monetary terms (from 49.3% in 2014 to 47.2% in 2020 in numerical terms). The shares of the total public procurement of alasens and photoditazine for 7 years are close and amount to 20.39% and 20.42% in monetary terms, and 18.8% and 20.0% in numerical terms, respectively. At the same time, the share of purchases of alasens is gradually falling: from 18.8% in 2014 to 13.3% in 2020 in monetary terms (from 21.9% in 2014 to 11.6% in 2020 in numerical terms). During the same period, the share of purchases of photoditazine almost doubled: from 12.2% in 2014 to 19.2% in 2020 in monetary terms (from 12.2% in 2014 to 19.6% in 2020 in numerical terms). The share of photoran E6 procurement has also grown significantly in recent years: in 2018 (when the first contracts for the supply of this photosensitizer appeared on the website www.zakupki.gov.ru), the share of its procurement was only 0.2% and 0.3% in monetary and numerical terms, respectively. In 2020, this share increased by almost 100 times and already stood at 19.0% and 19.2%, respectively. The total volume of public procurement of photosens and metvix for 2014-2018 (there were no public procurements of these two medical preparations in 2019-2020) is insignificant and amounts to 0.08% and 0.06% in monetary terms and 0.09% and 0.06% in numerical terms, respectively, of the total volume of public procurements of photosensitizers. In recent years, the share of public procurement of photolon has significantly decreased – from 11.2% in 2014 to 1.1% in 2020 in monetary terms (from 15.2% in 2014 to 2.5% in 2020 in numerical terms).

Discussion

Our analysis of information from available information sources in the Russian Federation does not allow us to determine the exact number of medical organizations and scientists who have been dealing with the problems of FD and PDT over the past decade, but it has made it possible to identify trends in the development of both the scientific and clinical components of these methods in Russia.

A systematic increase in both scientific products on this topic and the number of medical institutions and constituent entities of the Russian Federation that have applied the method has been registered.

As a rule, where the method is introduced into clinical practice, it continues to be used, as evidenced by the annual or systematic purchases of photosensitizers in 82.4% of Russian constituent entities that have introduced the method.

The number of patients who underwent FD sessions is growing, as evidenced by the increase in purchases of the drug for diagnostics – alasens. In 2014, 782 packages of alasens were purchased through the public procurement portal www.zakupki.gov.ru. By 2020, this number has increased almost 3 times – up to 2,196 packages.

The number of patients treated by PDT is growing, which is confirmed by the growth in purchases of photosensitizers intended for PDT: photoditazine, radachlorin, photoran E6, photolon. In 2014, the total volume of their purchases through the www.zakupki.gov.ru portal was 2,794 packages, and by 2020 it increased 6 times and amounted to 16,792 packages.

The change in the assortment and ratio of the volumes of purchased photosensitizers registered over the past decade indicates a trend in the introduction of methods into routine clinical practice in the regions of Russia. Thus, the greatest demand is for photosensitizers used mainly for those nosologies that occupy a leading position in the structure of morbidity in our country (drugs based on chlorin e6) and a drug used for diagnosis (alasens). On the contrary, photosensitizers that have a limited number of indications (photosens) or are used in secondary prevention programs (metvix) are becoming less popular or completely leaving the market, which is mainly due to unattractiveness for business.

Conclusion

The results obtained confirmed the growing demand for photosensitizers for photodynamic therapy and fluorescence diagnostics in clinical practice, the expansion of the geography of the photosensitizers use, as well as the stable interest in this topic in the research environment in the Russian Federation over the past decade.

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