

COMBINED ENDOSCOPIC TREATMENT OF A PATIENT WITH CANCER OF THE HYPOPHARYNX TO THE UPPER THIRD OF THE ESOPHAGUS WITH COMPLETE CLINICAL AND ENDOSCOPIC EFFECT

Legostaev V.M., Babenkov O.Y., Balitskiy G.V.

Rostov Research Institute of Oncology, Rostov-on-Don, Russia

Abstract

We present a clinical case with a complete endoscopic and clinical effect after endoscopic treatment of a patient with laryngeal cancer involving the upper third of the esophagus. The patient was treated as follows: conformal radiation therapy TFD = 40 gr, targeted chemotherapy using Cetuximab (total dose of 1800 mg). 1.5 months after the end of the treatment, a residual laryngopharyngeal tumor with a spread into the upper third of the esophagus was found during videolaryngoscopy examination. The result of the following histological examination was G2 squamous cell carcinoma. From August 2015 to February 2017, the patient underwent 8 photodynamic therapy sessions in combination with argon plasma coagulation. A control videolaryngoscopy, carried out 1 month after the final session, showed complete tumor regression without cicatricial deformity and narrowing of the esophageal lumen.

Keywords: photodynamic therapy, laryngopharyngeal tumor, fotoditazin.

For citations: Legostaev V.M., Babenkov O.Y., Balitskiy G.V. Combined endoscopic treatment of a patient with cancer of the hypopharynx to the upper third of the esophagus, *Biomedical Photonics*, 2018, vol. 7, no. 4, pp. 35–40. (in Russ.) doi: 10.24931/2413–9432–2018–7–4–35–40.

Contacts: Legostaev V.M., e-mail: oncoendo@aaanet.ru

КОМБИНИРОВАННОЕ ЭНДОСКОПИЧЕСКОЕ ЛЕЧЕНИЕ БОЛЬНОГО РАКОМ ГОРТАНОГЛОТКИ С РАСПРОСТРАНЕНИЕМ НА ВЕРХНЮЮ ТРЕТЬ ПИЩЕВОДА

В.М. Легостаев, О.Ю. Бабенков, Г.В. Балицкий

Ростовский научно-исследовательский онкологический институт, Ростов-на-Дону, Россия

Резюме

Авторы описывают клиническое наблюдение с полным клиническим эффектом после эндоскопического лечения больного раком гортаноглотки, вовлекающим верхнюю треть пищевода. Пациент получал лечение в объеме: конформная лучевая терапия СОД = 40 Гр, таргетная химиотерапия препаратом цетуксимаб, суммарной дозой 1800 мг. Через 1,5 мес после окончания лечения на видео-ларингоскопии была выявлена остаточная опухоль гортаноглотки с распространением на верхнюю треть пищевода. Результат гистологического исследования – плоскоклеточный рак, G2. С августа 2015 по февраль 2017 г. пациенту было проведено 8 курсов фотодинамической терапии в сочетании с аргоноплазменной коагуляцией. На контрольной видеоларингоскопии, выполненной через 1 мес после последнего курса, зарегистрирована полная регрессия опухоли без рубцовой деформации или сужения просвета пищевода.

Ключевые слова: фотодинамическая терапия, опухоль гортаноглотки, фотодитазин.

Для цитирования: Легостаев В.М., Бабенков О.Ю., Балицкий Г.В. Комбинированное эндоскопическое лечение больного раком гортаноглотки с распространением на верхнюю треть пищевода // *Biomedical Photonics*. – 2018. – Т. 7, № 4. – С. 35–40. doi: 10.24931/2413–9432–2018–7–4–35–40.

Контакты: Легостаев В.М., e-mail: oncoendo@aaanet.ru

Introduction

The laryngopharynx is an anatomically complex area that plays an important role in the body's processes of respiration and digestion, which led to the creation of the term still used in the literature, «decussation of respira-

tory and digestive tracts» [1]. The prevalence of laryngopharyngeal cancer in the Russian Federation amounted to 11.7 people per 100,000 population in 2016, while the prevalence of esophageal cancer was 9.2 people per

100,000 population. In 2016, laryngopharyngeal cancer at the 1st and 2nd stages was only diagnosed in 3.2% and 13.5% of cases, respectively. Similar indicators for esophageal cancer are significantly higher and amount to 6.2% at the 1st stage and 24.2% at the 2nd stage. This difference can be explained by the fact that dysphagia is manifested much earlier in the case of esophageal cancer compared to laryngopharyngeal cancer due to narrowing of the organ lumen diameter.

The average rate of late-stage diagnosis of laryngopharyngeal cancer in Russia is 43.1%, which is second only to pancreatic cancer (60.5%). These figures are directly correlated to the high mortality rates in the first year after the diagnosis, which are 41.0% and 58.5% for laryngopharyngeal cancer and esophageal cancer, respectively. The search for ways to improve early diagnosis and treatment of laryngopharyngeal cancer and esophageal cancer is a critical task of the modern medicine [2].

In Russia, there is the following trend in the application of different methods of treating malignant tumours: the proportion of surgeries as an independent type of treatment continues to grow. In 2016, it amounted to 54.3% (53.7% in 2015), while the proportion of combination or comprehensive treatment continued to decrease and reached 31.2% (31.3% in 2015), and the proportion of the radiological method alone was 9.8% (10.1% in 2015). The frequency of use of the radiation therapy as an independent type of treatment for laryngopharyngeal cancer amounted to 17.1% in 2016. The combination or comprehensive method was used to treat laryngopharyngeal cancer in 50.8% of cases and esophageal cancer in 49.1% of cases. The rate of using the chemoradiation as an independent type of treatment for laryngopharyngeal cancer was an order of magnitude higher than the one for esophageal cancer and amounted to 15.7% and 1.4%, respectively [3].

In recent years, photodynamic therapy (PDT) has been increasingly used in oncology along with generally accepted methods of treating malignant tumours (surgeries, radiation therapy, medical therapy and their combinations). This treatment method is based on the interaction between a photosensitizer (PS) and light radiation having a wavelength corresponding to the absorption maximum of the applied PS. As a result, photochemical processes are initiated in cells of a malignant tumour and then lead to its death [4].

The development of methods of a direct destructive effect on malignant tumours, such as electroresection, argon plasma coagulation, laser destruction, cryodestruction, radio frequency ablation, significantly expanded the capabilities of surgeons, allowing them to perform cytoreductive surgeries more safely and efficiently. However, none of these methods has a systemic exposure on cancer patients due to significant limitations and contraindications. In contrast to the above mentioned methods

of tumour exposure, PDT has a number of advantages, including the following:

1. The direct selective cytotoxic (apoptosis, necrosis) effect on cancer cells that have accumulated a photosensitizer [5–7].
2. The selective damage to the endothelium of blood vessels of a malignant tumour [10, 11].
3. The activation of antitumour immunity due to the selective damage to cell membranes and blood vessels of a malignant tumour [8, 9].
4. PDT is exceedingly rare complicated by perforation, bleeding, fistula and cicatricial strictures formation [10].
5. The latest generation photosensitizers are non-toxic, so the number of PDT courses is unlimited.

Indication for endoscopic PDT:

1. The main organ-preserving method of minimally invasive treatment of malignant tumours at the Tis-T1N0M0 stage for the complete eradication of the tumour.
2. Reopening of respiratory and gastrointestinal tracts.
3. Cytoreduction and stabilisation of the tumour growth.
4. The treatment method chosen for malignant tumours, when the possibilities of other treatment methods are exhausted [10].

According to the Rostov Cancer Research Institute (RCRI), in cases where other methods of antitumour treatment have been exhausted, endoscopic PDT allowed to achieve the full or partial (a decrease in the tumour lesion size by more than 50%) effect in 81.8 % of cases [10].

There are no absolute contraindications to PDT. Relative contraindications to endoscopic PDT are a patient's severe general somatic condition and unstable hemodynamics.

In the department of intraluminal diagnostics of the RCRI, endoscopic photodynamic therapy (PDT) is successfully used in combination with argon plasma coagulation (APC) of malignant tumours of the laryngopharynx and esophagus when surgical or combined treatment is not possible.

The patient K., 59 years old, was referred to the RCRI with a diagnosis of T2N0M0 laryngopharyngeal cancer, the 2nd stage, clinical group 2. The conclusion of the histological examination was moderately differentiated squamous cell cancer without keratinisation, G2. Coexisting diseases: coronary heart disease, stable angina, postinfarction cardiosclerosis (2005), chronic heart failure, myocardiodystrophy, arterial hypertension at the 3rd stage, gastric ulcer in remission.

According to the results of the computed tomography of the chest and abdominal cavity, ultrasound investigation of the neck and abdominal cavity, no data on the presence of regional and distant metastases of the

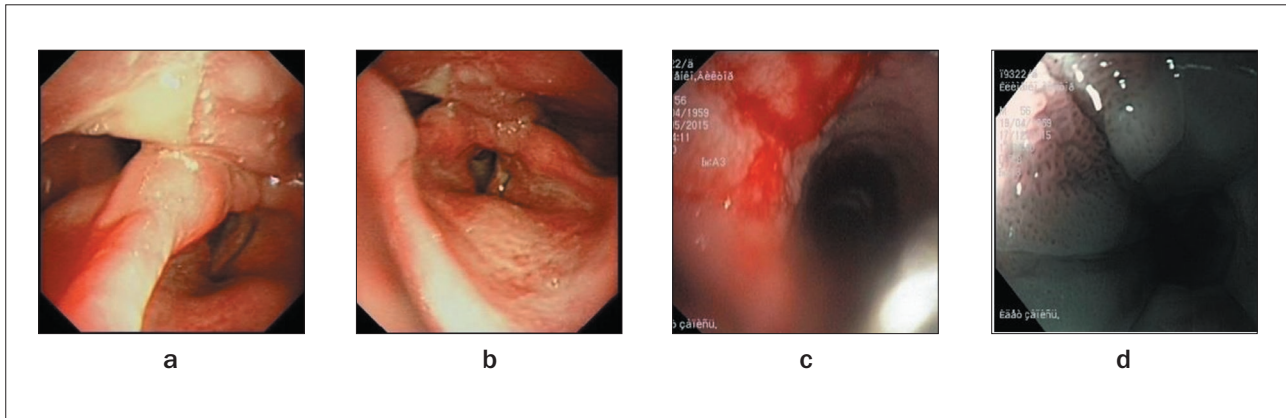


Рис. 1. Результаты видеоларингоскопии и видеоэзофагоскопии:

a, b – резидуальная опухоль задней стенки гортаноглотки;

c – рак устья пищевода с вовлечением его верхней трети (d – осмотр в режиме узкоспектральной эндоскопии)

Fig. 1. Results of videolaryngoscopy and videoesophagoscopy:

a, b – residual tumor of the hypopharynx posterior wall;

c – cancer of the mouth of the esophagus with the involvement of its upper third (d – narrow-band imaging endoscopy examination)

tumour were found. In April 2015, the patient underwent combined chemoradiation therapy (conformal radiation therapy, a single boost dose = 2.4 Gy x 5 fractions per week, a total boost dose = 40 Gy) and targeted chemotherapy with cetuximab at a total dose of 1800 mg.

1.5 months after the treatment, the patient underwent the follow-up videolaryngoscopy (VLS): the mucosa of arytenoid cartilages was swollen and hyperaemic; the tumor infiltrate of 2x2.5 cm in size with a 0.8 cm triangular carcinelcosis was visible on the posterior wall of the laryngopharynx above the arytenoid cartilages. The infiltrate spread over the posterior wall of the pharynx dorsally to the arytenoid cartilages of the larynx, its lower edge was visible in the region of the lower third of the left pyriform sinus (Fig. 1a, b).

The patient had no complaints of dysphagia, however, given the outcomes of our previous study confirming the frequent involvement of the esophagus in laryngopharyngeal cancer [11], we decided to perform videoesophagoscopy (VES). When imaged in the narrow band mode, the esophageal mucosa had a pathologically changed relief and an atypical vascular pattern with distinctive signs of neoplasia over the 4 cm circular area in the mouth of the esophagus and right after it (Fig. 1c, d). Pathological changes were more severe on the lateral walls of the esophagus. The biopsy was performed. Histological findings: squamous cell cancer, G2.

From April to June 2015, the patient underwent the second stage of the chemoradiation therapy: a single boost dose = 2.4 Gy and 1 Gy x 5 fractions per week (a total boost dose = 60 Gy for the primary site and 50 Gy for the regional lymph nodes), cetuximab at a total dose of 3400 mg. During the follow-up VLS after 1.5 months, a tumour in the laryngopharynx was not detected, but when imaged in the narrow band mode, a residual

tumour was found in the mouth of the esophagus and its upper third, which was morphologically confirmed (Fig. 2a, b).

Due to the exhausted possibilities of chemoradiation therapy, PDT of the affected area was assigned to the patient at the case conference.

All PDT sessions were conducted 2 hours after IV infusion of the Fotoditazine (VETA-GRAND LLC, Russia, registration licence No. LS 001246 of 18.05.2012) at a dose of 1 mg/kg-BM using the GIF H-180 EXERA II video gastroscope (Olympus, Japan) under general endotracheal anesthesia with artificial lung ventilation. An endoscope with a transparent cap mounted on its distal end was inserted in the laryngopharynx; a quartz light guide with a 2 cm long cylindrical diffuser was inserted through its instrument channel. The light guide was positioned at a

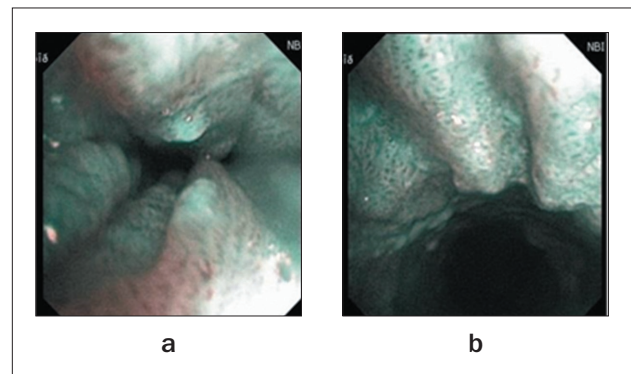


Рис. 2. Остаточная опухоль пищевода (осмотр в узкоспектральном режиме эндоскопии):

a – устье пищевода;

b – верхняя треть пищевода

Fig. 2. Residual esophageal tumor (narrow-band imaging endoscopy examination):

a – the mouth of the esophagus;

b – upper third of the esophagus

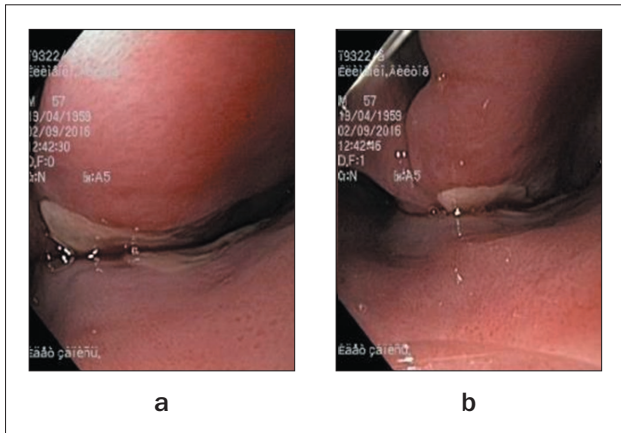


Рис. 3. Результаты видеоларингоскопии, выполненной после 1-го курса ФДТ:

a, b – фаза некроза опухоли гортаноглотки

Fig. 3. Results of videolaryngoscopy performed after the 1st PDT session:

a, b – necrosis phase of the hypopharynx tumor

distance of 1 mm from the tumour. Then the surface of the tumour was irradiated with light using a laser light source ($\lambda=662$ nm) (Lakhta-Milon, Russia). The laser irradiation power was 1000 mW, and the energy density was 200 J/cm². The irradiation was performed from 4 positions in the laryngopharynx and 6 fields in the esophagus. The time of the irradiation at each point was 4 minutes.

During the first week after PDT, the patient experienced moderate pain in the laryngopharynx, which was

managed by taking non-steroidal anti-inflammatory drugs (nimesulide).

10 days after the PDT a follow-up VLS was performed: tumour necrosis with fibrinous deposition, hyperemia and oedema of the surrounding mucosa were detected (Fig. 3a, b).

In total, the patient underwent 7 PDT courses under general anesthesia at an interval of 1.5–2 months during the year, while the PDT was conducted three times in combination with argon plasma coagulation of the exophytic area of the tumour (0.8 cm) using the ERBE VIO 300 D electro-surgery unit. 3 weeks after each PDT course, follow-up endoscopic examinations of the laryngopharynx and esophagus were conducted. During each examination, the improvement was observed in the form of a gradual decrease in the size of the residual tumour.

After the 7th course, the full endoscopic effect was achieved in the form of the disappearance of infiltration of the laryngopharyngeal mucosa and the mouth and the upper third of the esophagus (Fig. 4a, b).

After 2 months, a rough mucosa site of about 1 cm in diameter with signs of neoplasia was detected in the mouth of the esophagus in a 7 o'clock position with the patient's left lateral position. After the biopsy, histological findings were obtained: squamous cell cancer, G2 (Fig. 5).

The 8th PDT course with APC was conducted. During the follow-up VLS after 1 month, a complete regression

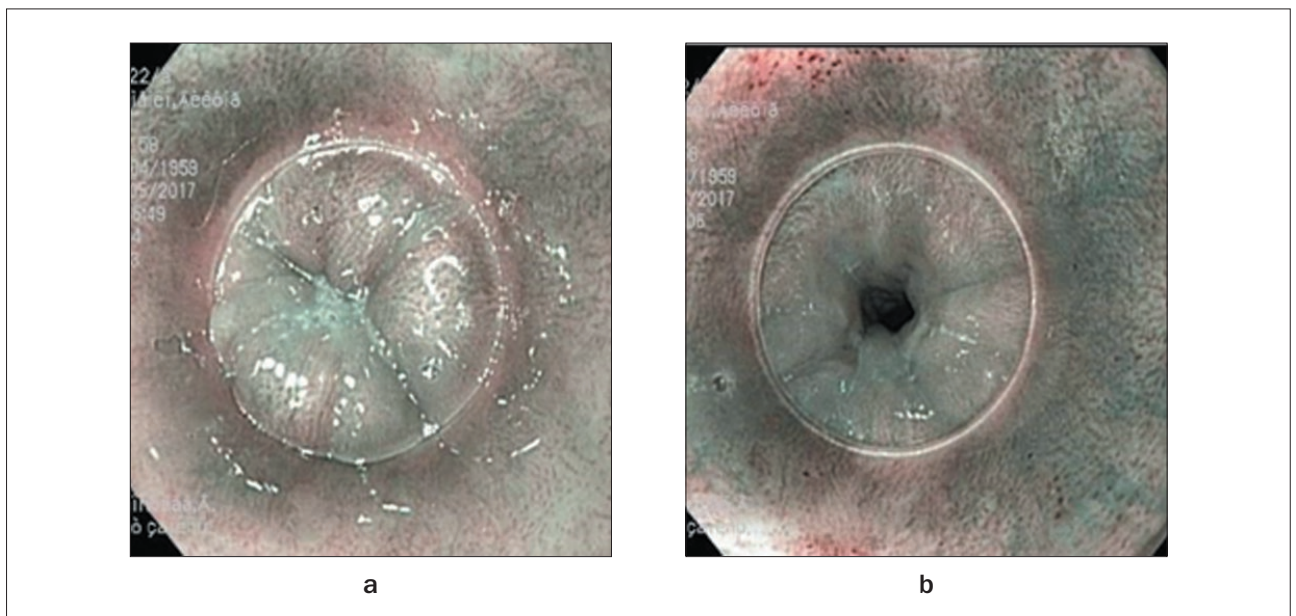


Рис. 4. Результаты узкоспектральной эндоскопии, выполненной после 7 курсов ФДТ:

a – полная регрессия опухолевой инфильтрации устья пищевода;

b – полная регрессия опухолевой инфильтрации верхней трети пищевода

Fig. 4. Results of narrow-band imaging endoscopy performed after 7 PDT sessions:

a – complete regression of tumor infiltration of the mouth of the esophagus;

b – complete regression of tumor infiltration of the upper third of the esophagus



Рис. 5. Рецидив рака пищевода в области его устья (осмотр в режиме NBI)

Fig. 5. Recurrence of cancer in the mouth of the esophagus (NBI examination)

of the tumour without cicatricial deformity and narrowing of the esophageal lumen was detected (Fig. 6). At the moment, the duration of the recurrence-free period is 3 months. The patient has no complaints. Dynamic monitoring is carried out.

Conclusion

The described clinical follow-up indicates that photodynamic therapy of residual laryngopharyngeal and esophageal tumours in combination with argon plasma coagulation shows high efficiency and can be a treatment method chosen for patients with malignant tumours of this localization.

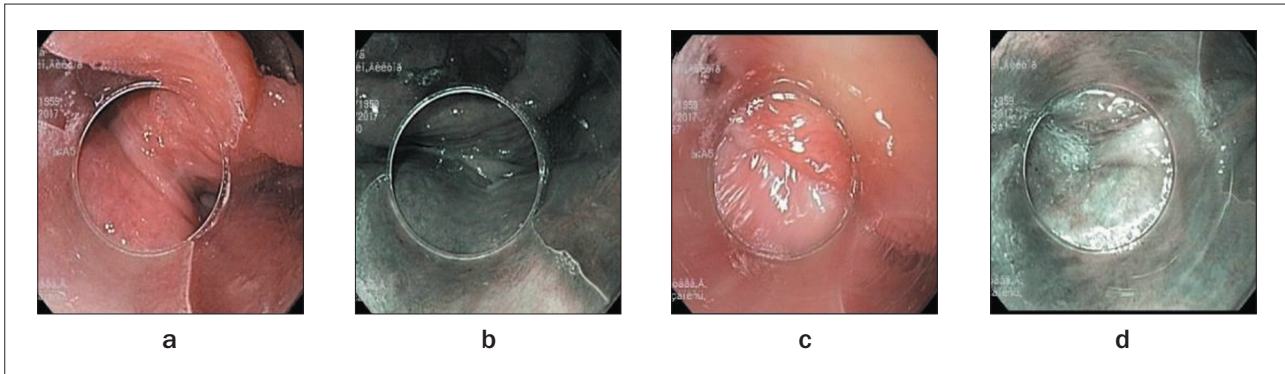


Рис. 6. Результаты контрольной видеоларингоскопии, выполненной после 8 курсов ФДТ (б, г – осмотр в режиме NBI):
а, б – полная регрессия опухолевой инфильтрации гортаноглотки;
с, д – полная регрессия опухоли устья пищевода

Fig. 6. Results of control videolaryngoscopy performed after 8 PDT sessions esophagus (б, г – NBI examination):
а, б – complete regression of the hypopharynx tumor infiltration;
с, д – complete regression of the tumor in the mouth of the esophagus

REFERENCES

1. Paches A.I., Ol'shanskij V.O., Lyubaev V.L., Tuok T.H. *Zlokachestvennye opuholi polosti rta, glotki i gortani* [Malignant tumors of oral cavity, pharynx and larynx]. Moscow, Meditsina Publ., 1988. 304 p.
2. *Rukovodstvo po onkologii* [Guide to Oncology] by eds V.I. Chissova, S.L. Dar'yalova. Moscow, OOO "Meditsinskoe informacionnoe agentstvo" Publ., 2008. 904 p.
3. *Sostoyanie onkologicheskoy pomoshchi naseleniyu Rossii v 2016 godu* [Evaluation of the oncological help to the population of Russia in 2016] by eds Kaprina A.D., Starinskiy V.V. Moscow, MNIОI im. P.A. Gertsena – filial FGBU «NMIRC» Minzdrava Rossii Publ., 2017. 236 p.
4. Akopov A.L., Kazakov N.V., Rusanov A.A., Karlson A. The mechanisms of photodynamic action for treating of cancer patients, *Photodynamic therapy and photodyagnosis*, 2015, vol. 4, no. 2., pp. 9–16. (in Russian) <https://doi.org/10.24931/2413-9432-2015-4-2-9-16>
5. Agarwal R., Korman N.J., Mohan R.R., Feyes D.K., Jawed S., Zaim M.T., Mukhtar H. Apoptosis is an early event during phthalocyanine photodynamic therapy-induced ablation of chemically induced squamous papillomas in mouse skin, *J. Photochem Photobiol*, 1996, vol. 63, no. 4, pp. 547–552.
6. Kerr J.F., Wyllie A.H., Currie A.R. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics, *Brit. J. Cancer*, 1972, vol. 26, pp. 239–257.

ЛИТЕРАТУРА

1. Пачес А.И., Ольшанский В.О., Любаев В.Л., Туок Т.Х. Злокачественные опухоли полости рта, глотки и гортани. – М.: Медицина, 1988. – 304 с.
2. Руководство по онкологии / под ред. В.И. Чиссова, С.Л. Дарьяловой. – М.: ООО «Медицинское информационное агентство», 2008. – 904 с.
3. Состояние онкологической помощи населению России в 2016 году / под ред. А.Д. Каприна, В.В. Старинского. – М.: МНИОИ им. П.А. Герцена – филиал ФГБУ «НМИРЦ» Минздрава России, 2017. – 236 с.
4. Акопов А.Л., Казаков Н.В., Русанов А.А., Карлсон А. Механизмы фотодинамического воздействия при лечении онкологических больных // Фотодинамическая терапия и фотодиагностика. – 2015. – Т. 4, № 2. – С. 9–16. <https://doi.org/10.24931/2413-9432-2015-4-2-9-16>
5. Agarwal R., Korman N.J., Mohan R.R., et al. Apoptosis is an early event during phthalocyanine photodynamic therapy-induced ablation of chemically induced squamous papillomas in mouse skin // *J. Photochem Photobiol*. – 1996. – Vol. 63, No. 4. – P. 547–552.
6. Kerr J.F., Wyllie A.H., Currie A.R. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics // *Brit. J. Cancer*. – 1972. – Vol. 26. – P. 239–257.

7. Oleinick N. L., Morris L., Varnes M. E. The peripheral benzodiazepine photosensitizer Pc4, *J. Photochem. and Photobiol.*, 2002, vol. 75(6), pp. 652–661.
8. Krosi G., Korbek M. Potentiation of photodynamic therapy by immunotherapy: the effect of schizophyllan (SPG), *Cancer Lett.*, 1994, vol. 84, pp. 43–49.
9. Coutier S., Bezdetnaya L., Marchal S., Melnikova V., Belitchenko I., Merlin J.L., Guillemin F. Foscan (mTHPC) photosensitized macrophage activation: enhancement of phagocytosis, nitric oxide release and tumour necrosis factor-alpha-mediated cytolytic activity, *Br. J. Cancer*, 1999, Vol. 81, pp. 37–42.
10. Legostaev V.M., Babenkov O. Yu., Maldonado G. M., Islamova E.F., Balitskiy G.V. Endoscopic photodynamic therapy of malignant tumors as a method of choice with exhausted possibilities of other methods of treatment in *Materials XLIX International Scientific and Practical Conference "Application of Lasers in Medicine and Biology" and "2nd Gamaleia's Readings"*. Kharkiv, 2018. 42–47 p.
11. Kravchenko A.B., Legostaev V.M., Babenkov O.Yu., Nosov V.A. Skriningovaya ehzofagoskopiya u patsientov, napravlennykh na endoskopicheskoe issledovanie dyhatel'nyh putej [Screening esophagoscopy in patients aimed at endoscopic examination of the respiratory tract] in *Vserossiyskaya molodezhnaya konferenciya «Aktualnye voprosy eksperimentalnoi i klinicheskoy onkologii. Sbornik tezisov*. Rostov-na-Donu, 2016. p. 60
7. Oleinick N.L., Morris L., Varnes M.E. The peripheral benzodiazepine photosensitizer Pc4 // *J. Photochem. and Photobiol.* – 2002. – Vol.75(6). – P. 652–661.
8. Krosi G., Korbek M. Potentiation of photodynamic therapy by immunotherapy: the effect of schizophyllan (SPG) // *Cancer Lett.* – 1994. – Vol. 84. – P. 43–49.
9. Coutier S., Bezdetnaya L., Marchal S., et al. Foscan (mTHPC) photosensitized macrophage activation: enhancement of phagocytosis, nitric oxide release and tumour necrosis factor-alpha-mediated cytolytic activity // *Br. J. Cancer.* – 1999. – Vol. 81. – P. 37–42.
10. Legostaev V.M., Babenkov O.Yu., Maldonado G.M., et al. Endoscopic photodynamic therapy of malignant tumors as a method of choice with exhausted possibilities of other methods of treatment / *Materials XLIX International Scientific and Practical Conference "Application of Lasers in Medicine and Biology" and "2nd Gamaleia's Readings"*. – Kharkiv, 2018. – 42–47 p.
11. Кравченко А.Б., Легостаев В.М., Бабенков О.Ю., Носов В.А. Скрининговая эзофагоскопия у пациентов, направленных на эндоскопическое исследование дыхательных путей / *Всероссийская молодежная конференция «Актуальные вопросы экспериментальной и клинической онкологии». Сборник тезисов.* – Ростов-на-Дону, 2016. – С. 60.