ISSN: 2687-0533 Print
ISSN: 2686-9039 Online

PEER-REVIEWED SCIENTIFIC AND PRACTICAL

SOUTH RUSSIAN JOURNAL OF CANCER

РЕЦЕНЗИРУЕМЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ

ЮЖНО-РОССИЙСКИЙ ОНКОЛОГИЧЕСКИЙ ЖУРНАЛ

Vol. 1, № 4, 2020
Том 1, № 4, 2020

www.cancersp.com

ISSN: 2687-0533 (Печ.)
ISSN: 2686-9039 (Сет.)

PEER-REVIEWED SCIENTIFIC AND PRACTICAL

SOUTH RUSSIAN JOURNAL OF CANCER

РЕЦЕНЗИРУЕМЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ

ЮЖНО-РОССИЙСКИЙ ОНКОЛОГИЧЕСКИЙ ЖУРНАЛ

Designer: **Sergei I. Khodosov**
Corrector: **Lyubov V. Elivanova**

Дизайнер: **Ходосов С.И.**
Корректор: **Эливанова Л.В.**

Founder and Publisher:
Autonomous Non-profit Organization "Perspectives of Oncology " (ANO "Perspectives of Oncology")

Editorial and publisher address:
63, G, room 1, 14 line, Rostov-on-Don 344037,
Russian Federation
E-mail: info@cancersp.com
Pfone: +7 903-547-04-62, +7 863-295-53-62
www.cancersp.com

Registration number:
PI No. FS 77-77100, 28 Oct. 2019.

Printed by "P-Center"
13 Akademika Koroljova, 129515 Moscow, Russia
Circulation of 50 copies, quarterly. Free price.

Submitted for publication 01.12.2020

Издатель и учредитель:
Автономная некоммерческая организация «Перспективы онкологии» (АНО «Перспективы онкологии»)

Адрес редакции и издателя:
344037, Российская Федерация, Ростовская область,
г. Ростов-на-Дону, 14-я линия, 63, литер Г, комната 1
E-mail: info@cancersp.com
Телефон: +7 903-547-04-62, +7 863-295-53-62
www.cancersp.com

Регистрационный номер:
ПИ № ФС 77 - 77100 от 28 октября 2019 г.

Отпечатано в типографии «П-Центр»
129515, Россия, Москва ул. Академика Королева, 13
Тираж 50 экз., ежеквартально. Цена свободная.

Подписано в печать 01.12.2020

СОДЕРЖАНИЕ

ОРИГИНАЛЬНЫЕ СТАТЬИ

КЛИНИЧЕСКИЕ НАБЛЮДЕНИЯ

CONTENTS

South Russian Journal of Cancer 2020, v.1, №4, p. 6-14
https://doi.org/10.37748/2687-0533-2020-1-4-1

ORIGINAL ARTICLE

THE FIRST RESULTS OF COMBINED TREATMENT OF GIANT CELL TUMOR OF BONE

A.A.Barashev, V.V.Mozulyaka, T.V.Ausheva*, Yu.R.Vinnik, L.N.Vashchenko, E.M.Nepomnyashchaya, P.V.Chernogorov

National Medical Research Centre for Oncology of the Ministry of Health of Russia,
63 14 line str., Rostov-on-Don 344037, Russian Federation

ABSTRACT

Purpose of the study. To evaluate the effectiveness and possibility of wide clinical use of denosumab in neoadjuvant mode in patients with giant-cell bone tumors to simplify the operation by reducing the size of the tumor, consolidating pathological fractures, improving the quality of life, restoring the function of adjacent joints, by conducting 2 courses of denosumab as neoadjuvant targeted therapy for patients with giant-cell bone tumors, as well as evaluating morphological changes in tumor.

Materials and methods. Considering the data on the efficacy of denosumab, all 10 patients underwent 2 courses of Denosumab 120 mg subcutaneously 1 time per month, as a neoadjuvant targeted therapy for a giant cell bone before performing a surgical treatment. The morphological picture was analyzed before and after the start of treatment, and the clinical and radiological results were evaluated.

Results. A similar clinical picture was observed in all 10 cases involving pain relief and restoration of support ability of the bone. X-ray changes demonstrated the development of sclerotic processes in the foci of lytic destruction. Consolidation of pathological fractures was observed.

The main changes determining the clinical and radiological characteristics were associated with the morphological processes occurring in the tumor under the influence of denosumab.

The morphological picture in the surgically removed bone samples was associated with the development of fibrosclerotic processes leading to the consolidation of pathological fractures.

The histological changes were assessed at the light-optical level. Tumor cells (osteoblasts and osteoclasts) were replaced with fibrous tissue of varying maturity. That is, a response to the therapy (pathomorphosis in the tumor) was observed under the action of denosumab.

Conclusions. Denosumab in neoadjuvant targeted therapy for patients with giant cell bone tumors prior to surgical treatment allows reduction in tumor sizes and consolidation of pathological fractures. The functions of adjacent joints were restored during Denosumab treatment. Improvements in the quality of life of patients were registered. The clinical and radiological effect of the therapy corresponded to the morphological changes occurring in the tumor. All of the above made it easier to perform surgery.

Keywords:
giant cell tumor of bone, denosumab, targeted therapy, therapeutic pathomorphosis, tumor sclerosis, a monoclonal human antibody.

For correspondence:
Tatyana V. Ausheva – Cand. Sci. (Med.), oncologist at the Department of bone, skin, soft tissue and breast tumors № 1, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: tatanaauseva@gmail.com
ORCID: https://orcid.org/0000-0002-7073-9463
SPIN: 5069-4010, AuthorID: 264138
Researcher ID: AAQ-9943-2020

Information about funding: no funding of this work has been held.
Conflict of interest: authors report no conflict of interest.

For citation:
Barashev A.A., Mozulyaka V.V., Ausheva T.V., Vinnik Yu.R., Vashchenko L.N., Nepomnyashchaya E.M., Chernogorov P.V. The first results of combined treatment of giant cell tumor of bone. South Russian Journal of Cancer. 2020; 1(4): 6-14. https://doi.org/10.37748/2687-0533-2020-1-4-1

Received 21.01.2020, Review (1) 02.07.2020, Review (2) 07.07.2020, Accepted 01.12.2020

Южно-российский онкологический журнал 2020, т.3, №4, с. 6-14
https://doi.org/10.37748/2687-0533-2020-1-4-1
ОРИГИНАЛЬНАЯ СТАТЬЯ

ПЕРВЫЕ РЕЗУЛЬТАТЫ КОМБИНИРОВАННОГО ЛЕЧЕНИЯ ГИГАНТОКЛЕТОЧНОЙ ОПУХОЛИ КОСТИ

А.А.Барашев, В.В.Мозуляка, Т.В.Аушева*, Ю.Р.Винник, Л.Н.Ващенко, Е.М.Непомнящая, П.В.Черногоров

ФГБУ «НМИЦ онкологии» Минздрава России,
344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63

РЕЗЮМЕ

Цель исследования. Оценить эффективность и возможность широкого клинического использования препарата деносумаб в неоадъювантном режиме у больных с гигантоклеточной опухолью костей для упрощения выполнения операции за счёт уменьшения размеров опухоли, консолидации патологических переломов, улучшения качества жизни, восстановления функции смежных суставов, путём проведения 2-х курсов деносумаба в качестве неоадъювантной таргетной терапии больным с гигантоклеточными опухолями костей, а также оценки морфологических изменений в опухоли.

Материалы и методы. Учитывая данные об эффективности деносумаба, всем 10 пациентам было проведено 2 курса деносумаба 120 мг подкожно 1 раз в месяц в качестве неоадъювантной таргетной терапии по поводу гигантоклеточной опухоли кости перед проведением хирургического лечения. Осуществлено изучение морфологической картины до и после лечения, а также оценены клинико-рентгенологические результаты.

Результаты. Во всех 10 наблюдениях была отмечена однотипная клиническая картина, выражавшаяся в уменьшении болевого синдрома, восстановлении функции конечности.

Рентгенологические изменения позволили констатировать развитие склеротических процессов в очагах литической деструкции. В местах патологических переломов наблюдали их консолидацию. Основные изменения, обусловливающие клинико-рентгенологические характеристики были связаны с морфологическими процессами, происходящими в опухоли под действием деносумаба. Морфологическая картина в удаленных операционных препаратах костей была связана с развитием фиброзносклеротических процессов, приводящих к консолидации патологических переломов. Гистологические изменения были оценены на светооптическом уровне. При этом происходило замещение опухолевых клеток (остеобластов и остеокластов) фиброзной тканью разной степени зрелости. То есть под действием деносумаба наблюдался ответ от проводимой терапии (патоморфоз в опухоли).

Заключение. Данный способ применения деносумаба в качестве неоадъювантной таргетной терапии больных с гигантоклеточными опухолями костей перед проведением хирургического лечения позволяет добиться уменьшения размеров опухоли, консолидации патологических переломов. Под действием препарата в ходе лечения происходило восстановление функции смежных суставов. Было отмечено улучшение качества жизни пациентов. Доказательством клинико-рентгенологического эффекта проводимой терапии являлись морфологические изменения, происходящие в опухоли.

Всё вышеизложенное давало возможность выполнения оперативного вмешательства.

Ключевые слова:
гигантоклеточная опухоль кости, деносумаб, таргетная терапия, терапевтический патоморфоз, склероз опухоли, моноклональное человеческое антитело.

Для корреспонденции:
Аушева Татьяна Валерьевна – к.м.н., врач-онколог отделения опухолей костей, кожи, мягких тканей и молочной железы № 1, ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: tatanaauseva@gmail.com
ORCID: https://orcid.org/0000-0002-7073-9463
SPIN: 5069-4010, AuthorID: 264138
Researcher ID: AAQ-9943-2020

Информация о финансировании: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Барашев А.А., Мозуляка В.В., Аушева Т.В., Винник Ю.Р., Ващенко Л.Н., Непомнящая Е.М., Черногоров П.В. Первые результаты комбинированного лечения гигантоклеточной опухоли кости. Южно-российский онкологический журнал. 2020; 1(4): 6-14.
https://doi.org/10.37748/2687-0533-2020-1-4-1

Получено 21.01.2020, Рецензия (1) 02.07.2020, Рецензия (2) 07.07.2020, Принята к печати 01.12.2020

INTRODUCTION

Bone tumors are one of the most difficult sections in the diagnostic aspect, so they occupy a special place in human pathology.

Giant cell tumor of bone (GCT) — a tumor of the skeleton that are related to tumors with uncertain potential of malignancy. In the mid-20th century, J.C. Bloodgood considered this tumor to be absolutely benign, but now this view is revised, since according to a number of authors, primary malignant variants (up to 5% of cases) and the ability of this tumor to malignancy (in 1.5–13% of cases) are described [1]. The peak incidence of GCT is detected in the age group from 18 to 40 years, in children under 12 years of age practically does not occur. Currently, due to the use of immunohistochemical (IHC) research methods, it is possible to isolate malignant fibrous histiocytes from the group of malignant giant cell tumors, which have a similar microscopic picture, and formed a group of malignant giant cell tumors. The most frequent localization of a giant cell tumor is the epimetaphysis of long tubular bones, somewhat less often-the pelvic bones, spine, scapula, and ribs [2].

Clinical manifestations in giant cell tumors are non-specific. The disease manifests itself in discomfort and moderate pain at rest. Patients go to the clinic, in the absence of sufficient examination, they are prescribed non-steroidal anti-inflammatory drugs, physiotherapy, blockades, at the initial stages with a positive clinical effect. In the absence of adequate treatment, the clinical symptoms progress, the pain syndrome becomes persistent. It is also possible to establish a diagnosis of a giant cell bone tumor when contacting a doctor after a previous injury, where an x-ray examination diagnoses a pathological fracture against the background of a giant cell tumor [1].

The x-ray picture of a giant cell tumor is characterized by an eccentrically located focus of destruction of a rounded shape, bone swelling is characteristic, the cortical layer is thinned, and in some places it may not be traced at all. In half of the patients, the lesion is clearly separated from the healthy bone, which takes the form of a sclerotic rim. When the tumor is located in the pelvic bones, ribs, spine, sternum, and scapula, the contours are usually indistinct [1, 3–6].

To date, the method of choice in the treatment of giant cell tumors has been surgical, but with the deepening of knowledge about the pathogenesis of development and molecular genetic features of giant cell tumors, it has been proposed to use in its treatment a targeted effect on RANKL of an inhibitory monoclonal antibody — denosumab. Most of the cases described in the available literature indicate the use of denosumab in the treatment of giant cell cancerous bone tumors as the only treatment method that does not involve surgical removal of the tumor at one stage due to its unresectability [1, 7].

Molecular pathophysiological aspects of a giant cell tumor are characterized by proliferation of mesenchymal stromal cells-bone progenitors that serve as a trigger and support osteoclastogenesis instead of differentiation into osteoblasts and osteocytes. It follows that the main component of the tumor is stromal cells. Resorbing giant cells are the product of interaction between stromal cells and attracted monocytes, which are transformed into tumor cells. Cell markers give a positive reaction with CD45 in multicore giant cells, which indicates that they belong to monocytes. In addition, overexpression of receptors to the ligand of nuclear factor-b activators (RANKL) and stromal factor SDF-1 is detected. Stromal cells produce chemoattractants that can attract monocytes and transform them into resorbing giant cells. Stromal cells also secrete various chemokines, monocyte chemoattractant proteins, and SDF-1 factor, which attract monocytes from the bloodstream and promote their migration to the tumor tissue. These monocytes eventually turn into osteoclast-like multinucleated giant cells. Monocytes Express RANK, which is necessary for differentiation of Mature osteoclasts and their activation in the presence of co-factor, macrophage colony-stimulating factor M–CSF. These osteoclast-like giant multinucleated cells resorb bone tissue leading to osteolysis [8].

Denosumab is a fully human monoclonal antibody (IgG2) that has a high affinity and speci-

ficity for the ligand of the nuclear factor activator receptor APPA B (RANKL) and prevents the activation of the only RANKL receptor — the nuclear factor activator kB (RANK) located on the surface of osteoclasts and their precursors. The RANK ligand is a protein present in the body as a membrane-bound and soluble form. RANKL is the main mediator of the metabolic pathway necessary for the formation, functioning, and survival of osteoclasts, the only cell type responsible for bone resorption. Increased osteoclast activity induced by RANKL is the main cause of bone destruction in metastases of solid tumors to bone tissue and in multiple myeloma. Preventing the RANKL/RANK interaction inhibits the formation, activation, and survival of osteoclasts. As a result, denosumab reduces bone resorption and destruction of bone tissue caused by malignant neoplasms [9–11].

The purpose of the study: to evaluate the effectiveness and possibility of wide clinical use of the drug denosumab in neoadjtuvant mode in patients with giant cell bone tumors to perform surgery by reducing the size of the tumor, consolidating pathological fractures, restoring the function of adjacent joints, and morphological changes occurring in the tumor tissue by conducting 2 courses of denosumab as a neoadjuvant targeted therapy for patients with giant cell bone tumors.

MATERIALS AND METHODS

The authors ' research has shown that 2 courses of denosumab as a neoadjuvant targeted therapy for patients with a giant cell bone tumor before surgical treatment reduces the size of the tumor (Fig. 1A, B), promotes the fusion of pathological fractures, helps restore the function of adjacent joints, and causes sclerotic processes in the tumor tissue (Fig. 2 A-D) [12].

All patients underwent a comprehensive examination, including anamnesis, physical examination, General clinical analysis of blood and urine, biochemical blood analysis, coagulogram, EKG, radiation diagnostic methods (radiography, spiral computed tomography).

In the biopsy material, the tumors had the usual histological structure characteristic of a giant cell tumor with destruction of bone beams, focal hemorrhages, and the presence of osteoblasts and osteoclasts (Fig. 2A). After treatment, all observations showed marked signs of therapeutic pathomorphosis. Between the preserved bone beams, the tumor tissue underwent pronounced dystrophic changes with edema, the disappearance of giant multinucleated cells, and the formation of connective tissue. There were areas of hemorrhage, but a much larger area was occupied by foci of fibrosis, sometimes with the presence of hemosiderin

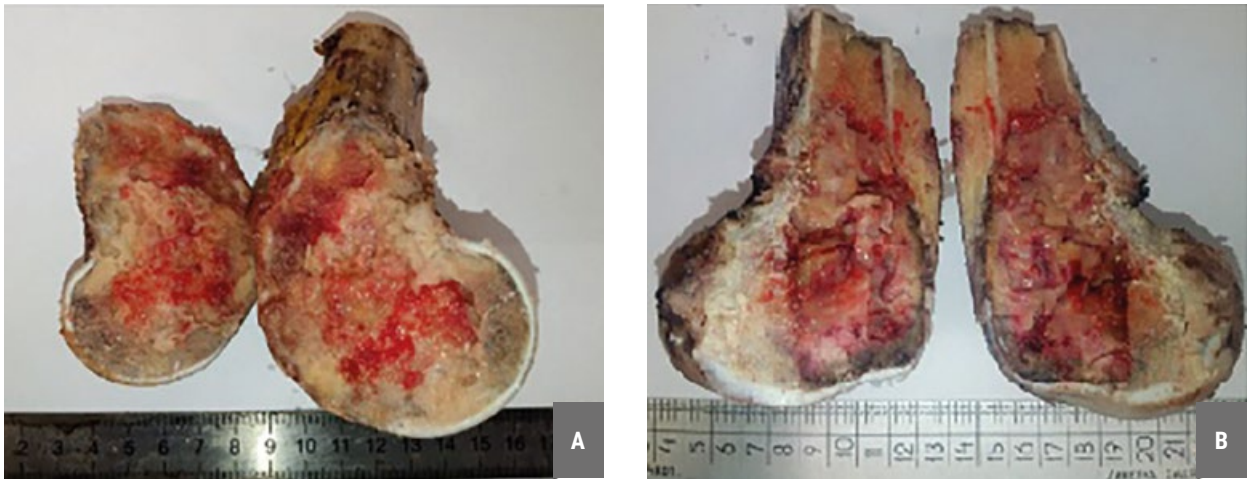


Fig. 1. Type of macroslides on the cut after neoadjuvant targeted therapy with denosumab and in the absence of treatment. A – the lower third of the femur after 2 courses of neoadjuvant targeted therapy with denosumab, a significant reduction in the size of the tumor, and sclerosis of the tumor tissue. B – the lower third of the femur with a tumor before neoadjuvant targeted therapy with denosumab, a large tumor, liquid.

(Fig. 2B, C). In some cases, the tumor tissue was completely absent and was represented by loose and dense fibrous connective tissue with a small number of osteoblasts (Fig. 2G).

Using this method, we treated 10 patients with giant cell bone tumors of various localization.

Clinical, radiological and morphological dynamics were evaluated after 2 courses of denosumab treatment.

In the course of our study, all patients showed a clinical effect of the treatment.

By gender, the patients are distributed equally: 5 men and 5 women.

The median age was 36±3.14 years. The localization of tumors was as follows: the upper third of the tibia-3, the lower third of the tibia-3, the Ilium, the heel bone, the lower third of the femur and the lower third of the humerus according to one observation. Operations performed after neoadjuvant therapy were as follows: bone defect reconstruction using bone grafting for marginal resections and endoprosthetics for segmental resections.

Before starting treatment and including patients for treatment, all patients signed an informed consent.

Here are clinical examples of the use of this method of treatment.

1. Patient A. 51 years old. In June 2017, he was injured at home and received conservative treatment with a temporary positive effect. At the place of residence, he was examined by radiation diagnostic methods: R-gr from 11.12.2017-signs of osteolytic formation of the proximal part of the right femur, pathological fracture (Fig. 3A). Independently asked NMRCO surveyed. A trepan biopsy was performed. The trepan biopsy contains

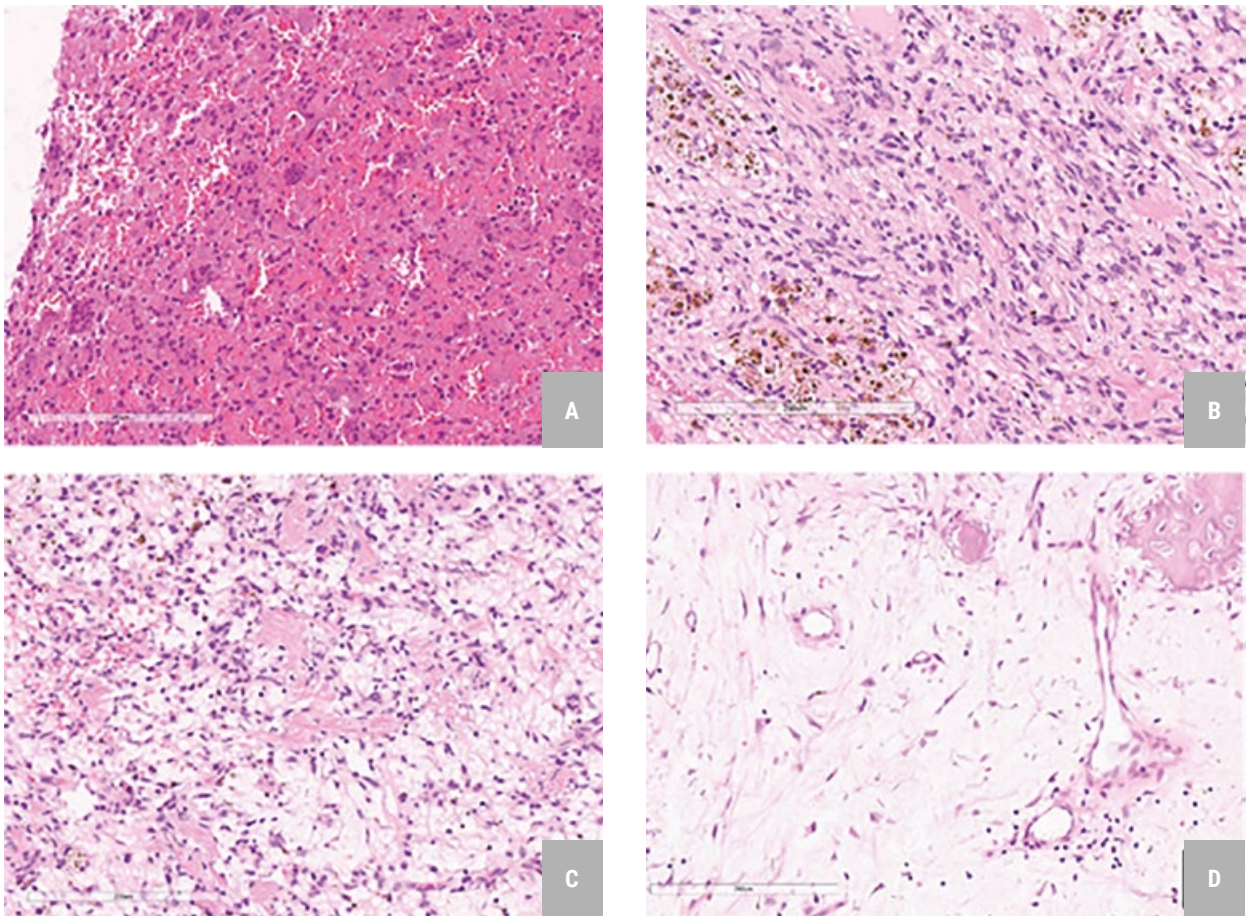


Fig. 2. Morphological changes in giant cell tumors before and after treatment. A – giant cell tumor with hemorrhages-biopsy. B, C – fibrotic tumor tissue with focal hemorrhages, hemosiderin deposition. D – pronounced fibrosis of the tumor between the preserved bone beams. Color: G-E. Magnification: X200

extensive layers of giant cell tumor with hemosiderin deposition and destruction of bone beams. Diagnosis: giant Cell tumor of the upper third of the right femur. Three courses of neoadjuvant therapy with denosumab (120 mg once a month) were performed. After that, the patient had a decrease in pain, he completely refused painkillers, and partially restored his ability to support himself. Radiologically, we observed sclerosis of the focus of lytic destruction, signs of consolidation of the pathological fracture (Fig. 3B). Then the operation was performed in the following volume: segmental resection of the upper third of the right femur with a tumor, replacement of the defect with a hip replacement (Fig. 3B). When examining the surgical material, macroscopically complete consolidation of the pathological fracture of the upper third of the femur. On the cut, the pathological focus is filled with a dense whitish tissue. Histological examination of the surgical material between the bone beams shows fibrous tissue with hemorrhages and foci of myxomatosis.Significant response to the therapy is admitted.

2. Female patient G., aged 45 years. Since October 2016, I have been concerned about pain in my left elbow joint. The pain syndrome gradually increased, there was a restriction of extension. She was observed by an orthopedist at the place of residence, received conservative therapy without effect. In may 2017, she applied to the NMRCO and was examined. SCT of the chest, abdominal cavity, and pelvic organs was performed, but no pathology was detected. On the radiograph of the left elbow joint, there is a focus of lytic destruction in the distal metaepiphysis of the humerus (Fig. 4A). A trepan biopsy was performed. In the biopsy among the blood bundles, single bone beams layers of giant cell tumor. Diagnosis: giant Cell tumor of the lower third of the left humerus. Two courses of neoadjuvant targeted therapy with denosumab (120 mg once a month) were performed. Repeated radiography of the left elbow joint was performed, where sclerosis of the focus of lytic destruction was observed (Fig. 4B). The patient experienced relief of pain, restoration of full range of motion in the left elbow joint. After that, the operation was performed in the following volume: segmental resection of the lower third of the left humerus with a tumor, replacement of the defect with an endoprosthesis of the elbow

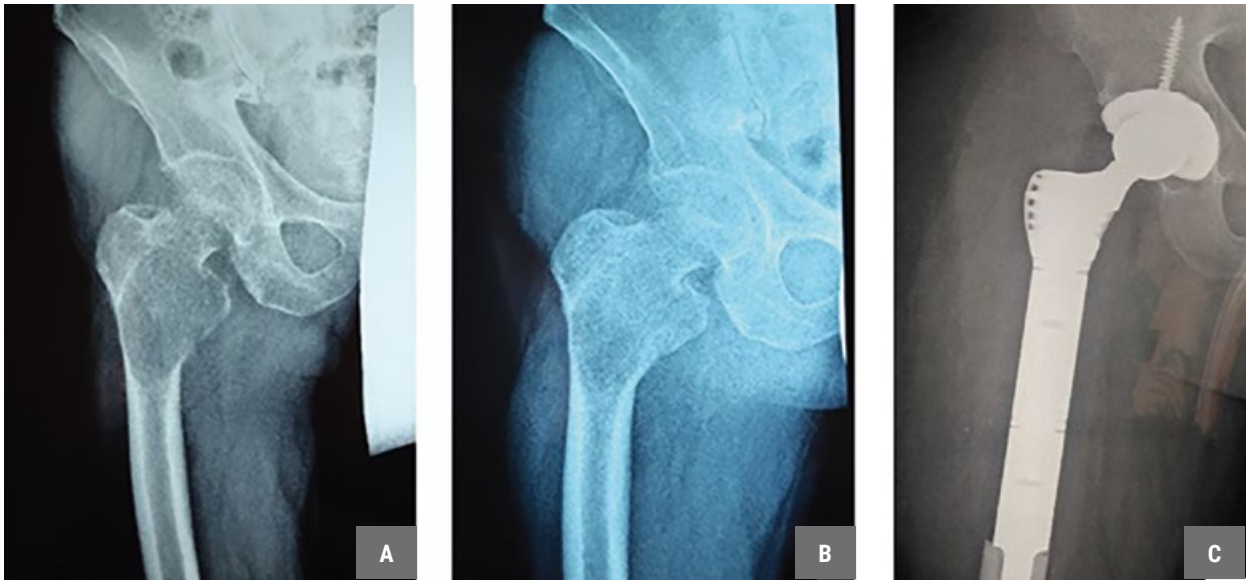


Fig. 3. x-Ray images of the patient. A – before the start of neoadjuvant therapy with denosumab, signs of osteolytic formation of the proximal part of the right femur, pathological fracture. B – after completion of neoadjuvant therapy with denosumab, sclerosis of the focus of lytic destruction, signs of consolidation of the pathological fracture. C – condition after segmental resection of the upper third of the right femur with a tumor, replacement of the defect with a hip replacement.

joint (Fig. 4 C, D). In macroscopic assessment of the surgical material, the lower third of the left humerus with a lumpy bone density tumor in the condyle region, the pathological focus is filled with dense whitish tissue on the cut. When histological examination of the surgical material in the preparations after treatment, there are extensive fields of fibrous tissue with few cellular elements, which can be regarded as a response to the therapy (therapeutic pathomorphosis).

3. Patient K., 68 years old. Pain in the right wrist joint is noted for 6 months. He received conservative treatment with a temporary effect. Radiography was performed at the place of residence, and the volume formation of the distal third of the radius on the right was revealed (Fig. 5A). Asked for a consultation in NMRCO. A trepan biopsy ofthe lower third of the right radius was performed. In the trepan biopsy, there are extensive fields of giant cell tumor among the blood clots. SCT of the forearm and hand bones most likely show signs of the cellular-trabecular phase of a giant cell tumor. SCT of the chest cavity, abdominal cavity and small pelvis from 20.10.2018 year-without a pathology. Diagnosis: giant Cell tumor of the distal third of the right radius. Three courses of neoadjuvant targeted therapy with denosumab (120 mg once a month) were performed. After that, the patient had a decrease in pain, which allowed more than twice to reduce the dose of analgesics taken. X-ray sclerosis of the destruction site (Fig. 5B). Then the operation was performed in volume: segmental resection

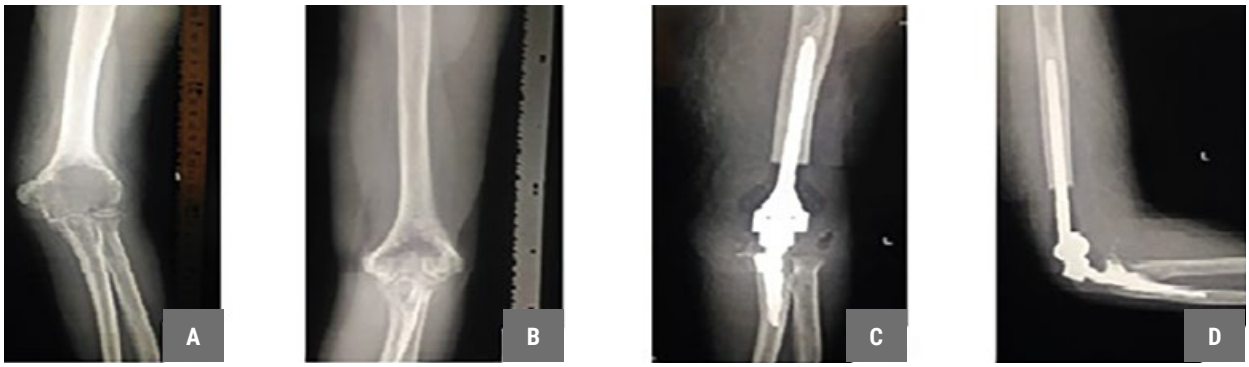


Fig. 4. x-Ray images of the patient. A – before starting neoadjuvant targeted therapy with denosumab, the image shows the presence of a focus of lytic destruction. B – after completing the course of neoadjuvant targeted therapy with denosumab, reducing the size and sclerosing the focus of lytic destruction. C, D – show condition after segmental resection of the lower third of the left humerus with a tumor, replacement of the defect with an elbow joint endoprosthesis in direct and lateral projections.

Fig. 5. X-Ray images of the patient. A – before the start of neoadjuvant targeted therapy with denosumab, volume formation of the distal third of the radius on the right. B – after completion of neoadjuvant targeted therapy with denosumab, sclerosis of the focus of lytic destruction is determined. C – condition after segmental resection of the lower third of the right radius with a tumor, replacement of the defect with a wrist joint endoprosthesis.

of the lower third of the right radius with a tumor, replacement of the defect with an endoprosthesis of the wrist joint (Fig. 5B). In macroscopic assessment of the surgical material, the lower third of the right radius is uneven, bumpy, and the pathological focus is filled with dense whitish tissue on the cut. Histological examination of the surgical material in the tumor has extensive fields represented by fibrous tissue. There are tumor fields consisting of loose fibrous connective tissue with multiple myxomatosis, a small number of cellular elements. Histological picture of a giant cell tumor with pronounced therapeutic pathomorphosis.

CONCLUSION

This method of using denosumab as a neoadjuvant targeted therapy for patients with giant cell bone tumors before surgical treatment allows to reduce the size of the tumor and consolidate pathological fractures. Under the influence of the drug during treatment, the function of adjacent joints was restored. There was an improvement in the quality of life of patients. The clinical and morphological effect of the therapy corresponded to the morphological changes occurring in the tumor.

The duration and number of courses are discussed in the literature. However, there is no clear opinion on this issue. In this regard, the observed clinical and radiological data that occur during 2 courses allowed us to implement this technique. At the same time, the result was similar for 2-course therapy. Our results are consistent with the literature data on morphological changes that occur when using denosumab.

Authors contribution:
Barashev A.A. – collection, analysis and interpretation of data, perform operations, the preparation of this article.
Mozulyaka V.V. – concept and design of study,the text writing , processing of the material..
Ausheva T.V. – technical editing, design of the bibliography, preparation of figures.
Vinnik Yu.R. – assistance on surgeries, preparation of an article.
Vashchenko L.N. – scientific editing.
Nepomnyashchaya E.M. – morphological research, scientific editing.
Chernogorov P.V. – scientific editing.

References

1. Zatsepin ST. Bone pathology of adults: a guide for doctors. Moscow: Medicine, 2001, 640 p. (In Russian).
2. Snetkov AI, Frantov AR, Morozov AK, Berchenko GN, Bratkov SYu, Anisimov MA. Diagnosis and treatment of benign tumors and tumor-like diseases in children. Ed. by S.P. Mironov. Moscow: GEOTAR-Media, 2017. (In Russian).
3. Ward WG, Li G. Customized treatment algorithm for giant cell tumor of bone: report of a series. Clin Orthop Relat Res. 2002 Apr;(397):259–270.
https://doi.org/10.1097/00003086-200204000-00030
4. Soloviev YuN. Bone tumor pathology: Practical guidance. Moscow: Practical medicine, 2019, 272 p. (In Russian).
5. Neyshtadt EL, Markochev AB. Tumors and tumor-like bone lesions]. St. Petersburg: Foliant, 2007, 344 p. (In Russian).
6. Berchenko GN, Morozov AK, Semenova LA, Frantov AR. Diagnosis of giant cell reparative granuloma of bones of hands and feet. Bulletin of traumatology and orthopedics named After N.N.Priorov. 2001;2:87–92. (In Russian).
7. Mahson AN, Schupak MU, Bondarev AV. Denosumab. Experience of conservative treatment giant cell bone tumor. Sarcomas of bones, soft tissues, and skin tumors. 2014;(2):24–28. (In Russian).
8. Vladimirova LYu, Abramova NA, Lyanova AA, Storozhakova AE, Popova IL, Tikhanovskaya NM, et al. Denosumab in treatment of bone metastases from solid tumors. Farmateka. 2018;7(360):76-81. (In Russian).
9. VIDAL reference book. Pharmaceuticals in Russia, 2017. (In Russian).
10. Barkowska A, Goryń T, Pieńkowski A, Wągrodzki M, Jagiełło-Wieczorek E, Rogala P, et al. Denosumab treatment

of inoperable or locally advanced giant cell tumor of bone. Oncol Lett. 2016 Dec;12(6):4312–4318.
https://doi.org/10.3892/ol.2016.5246

11. Traub F, Singh J, Dickson BC, Leung S, Mohankumar R, Blackstein ME, et al. Efficacy of denosumab in joint preservation for patients with giant cell tumour of the bone. Eur J Cancer. 2016;59:1–12.
https://doi.org/10.1016/j.ejca.2016.01.006

12. Kit OI, Barashev AA, Mozulyaka VV, Nepomnyashchaya EM, Vashchenko LN, Ausheva TV, et al. Method of combined treatment of giant-cell bone tumor. Patent RU 2696097 C1, IPC A61K; A61R; patent Holders: Federal state budgetary institution "Rostov research oncological Institute" of the Ministry of health of the Russian Federation (RU). Application: no. 2018127819 dated 27.07.2018, published 31.07.2019. Byul. No. 22. (In Russian).

Information about author:

Artem A. Barashev – Cand. Sci. (Med.), traumatologist-orthopedist, Department of bone, skin, soft tissue and breast tumors № 1, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-7242-6938, SPIN: 4590-5745, AuthorID: 697517

Viktoriya V. Mozulyaka – resident pediatric oncologist, Department of bone, skin, soft tissue and breast tumors №1, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.

Tatyana V. Ausheva* – Cand. Sci. (Med.), oncologist, Department of bone, skin, soft tissue and breast tumors №1, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-7073-9463, SPIN: 5069-4010, AuthorID: 264138, Researcher ID: AAQ-9943-2020

Yuliya R. Vinnik – resident pediatric oncologist, Department of bone, skin, soft tissue and breast tumors №1, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.

Larisa N. Vashchenko – Dr. Sci. (Med.), professor, head of the Department of bone, skin, soft tissue and breast tumors №1, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-7302-7031, SPIN: 5573-4396, AuthorID: 286598

Evgeniya M. Nepomnyashchaya – Dr. Sci. (Med.), professor, pathologist at the pathology Department, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-0521-8837, SPIN: 8930-9580, AuthorID: 519969

Pavel V. Chernogorov – traumatologist-orthopedist, Department of bone, skin, soft tissue and breast tumors №1, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 4643-4485, AuthorID: 922419

South Russian Journal of Cancer 2020, v.1, №4, p. 15-21
https://doi.org/10.37748/2687-0533-2020-1-4-2

ORIGINAL ARTICLE

AN INTEGRATED APPROACH TO THE DIAGNOSIS OF BACTERIAL AND FUNGAL BLOODSTREAM INFECTIONS IN CANCER PATIENTS

O.Yu.Kutsevalova*, Yu.Yu.Kozel, V.V.Dmitrieva, O.V.Kozuk, I.B.Lysenko

National Medical Research Centre for Oncology of the Ministry of Health of Russia,
63 14 line str., Rostov-on-Don 344037, Russian Federation

ABSTRACT

Purpose of the study. To evaluate the diagnostic significance of accelerated and affordable verification of a bloodstream infection pathogen using biomarkers: procalcitonin and the Platelia™ Candida Ag Plus mannan antigen.
Patients and methods. 349 cancer patients with febrile fever were examined from 6 medical and diagnostic oncological hospitals in the Southern Federal District of the Russian Federation during 2019. Patients aged from 1 to 85 years were hospitalized in intensive care, pediatric oncology and hematology oncology departments. Patient informed consent for the study was obtained. The diagnostic algorithm included: a blood test using an automatic BacT /ALERT 3D analyzer and a parallel study of the level of biomarkers with enzyme immunoassay. Identification of strains and determination of sensitivity to antimicrobial agents was determined on a Vitek 2 automatic analyzer (BioMerieux, France). Procalcitonin levels greater than 10 ng/ml were registered to determine the development of bacterial inflammation. Procalcitonin was determined with Procalcitonin — ELISA-BEST kits (Russia). Mannan antigen was determined using Platelia Candida Ag kits (France). The result was considered positive at the antigen concentration of ≥125 pg/ml. Candida mannan antigen allowed us to decide on the involvement of *Candida spp*. in the infectious process.
Results. An integrated approach to the diagnosis of bloodstream infections increased the percentage of detection of pathogens up to 58.7%. Bacterial infection testing both with the blood culture method and the procalcitonin determination in blood serum revealed similar diagnostic values. Candida mannan antigen testing significantly improved the early diagnosis of Candidal infection, despite negative blood culture, which was probably associated with prolonged cultivation of *Candida spp*. in the blood (from 2 to 5 days). The inclusion of biomarker testing in the diagnostic algorithm in cases of suspected bloodstream infection allowed early pathogen identification and starting an adequate antibacterial or antifungal therapy.
Conclusion. An integrated approach to the diagnosis of bloodstream infections improved and, just as importantly, significantly accelerated the pathogen verification. Bacterial infection cases showed comparable results of hemoculturing and biomarker testing; however, in case of candidal infection, determination of Candida mannan antigen appears critical, as it was significantly more sensitive than the result of blood culture and allowed to identify the etiology of fever of unknown origin in many patients.

Keywords:
procalcitonin, mannan, bloodstream infection, *Candida spp*., diagnosis of sepsis, biomarkers.

For correspondence:
Olga Yu. Kutsevalova – Cand. Sci. (Biol.), head of the laboratory of clinical Microbiology, bacteriologist National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: Olga_kutsevalova@mail.ru
ORCID: https://orcid.org/0000-0001-7452-6994
SPIN: 6271-1942, AuthorID: 363005
ResearcherID: AAM-9837-2020

Information about funding: no funding of this work has been held.
Conflict of interest: authors report no conflict of interest.

For citation:
Kutsevalova O.Yu., Kozel Yu.Yu., Dmitrieva V.V., Kozuk O.V., Lysenko I.B. An integrated approach to the diagnosis of bacterial and fungal bloodstream infections in cancer patients. South Russian Journal of Cancer. 2020; 1(4): 15-21. https://doi.org/10.37748/2687-0533-2020-1-4-2

Received 06.04.2020, Review (1) 08.07.2020, Review (2) 19.10.2020, Accepted 01.12.2020

Южно-российский онкологический журнал 2020, т.4, №2, с. 15-21
https://doi.org/10.37748/2687-0533-2020-1-4-2
ОРИГИНАЛЬНАЯ СТАТЬЯ

КОМПЛЕКСНЫЙ ПОДХОД К ДИАГНОСТИКЕ БАКТЕРИАЛЬНЫХ И ГРИБКОВЫХ ИНФЕКЦИЙ КРОВОТОКА У ПАЦИЕНТОВ ОНКОЛОГИЧЕСКОГО ПРОФИЛЯ

О.Ю.Куцевалова*, Ю.Ю.Козель, В.В.Дмитриева, О.В.Козюк, И.Б.Лысенко

ФГБУ «НМИЦ онкологии» Минздрава России,
344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63

РЕЗЮМЕ

Цель исследования. Оценить диагностическую значимость ускоренной и доступной верификации возбудителя инфекции кровотока с помощью биомаркеров: прокальцитонина и маннанового антигена Platelia™ Candida Ag Plus.

Пациенты и методы. Обследовано 349 онкологических больных в течение 2019 года с фебрильной лихорадкой из 6 лечебно-диагностических стационаров онкологического профиля Южного Федерального округа Российской Федерации. Пациенты в возрасте от 1 года до 85 лет находились в отделениях реанимации, детской онкологии и онкогематологии. Информированные согласия пациентов на исследования получены. Диагностический алгоритм включал исследование крови с помощью автоматического анализатора BacT/ALERT 3D и параллельное исследование уровня биомаркеров имунноферментным методом. Идентификацию штаммов и их чувствительность к антимикробным препаратам проводили на автоматическом анализаторе Vitek 2 (BioMerieux, Франция). Одновременно определяли уровень прокальцитонина с помощью наборов Прокальцитонин — ИФА-БЕСТ (Россия) и маннанового антигена *Candida spp*. —Platelia Candida Ag (Франция) соответственно. Учитывали значения прокальцитонина более 10 нг/мл для определения развития бактериального воспаления. Результат определения маннанового антигена расценивался как положительный при концентрации ≥125 пг/мл. Маннановый антиген *Candida spp*. позволил судить о причастности к инфекционному процессу грибов *Candida spp*..

Результаты. Комплексный подход к диагностике инфекций кровотока увеличил процент выявления патогенов до 58,7%. Следует принять во внимание, что тестирование бактериальной инфекции как методом гемокультивирования, так и методом определения прокальцитонина в сыворотке крови выявило их почти одинаковое диагностическое значение. Тестирование маннанового антигена *Candida spp*. значительно улучшило раннюю диагностику кандидозной инфекции несмотря на отрицательную гемокультуру, что, вероятно, связано с длительным культивированием *Candida spp*. в крови (от 2 до 5 суток). Включение тестирования биомаркеров в алгоритм диагностики при подозрении на инфекцию кровотока позволило выявить возбудителя как можно раньше и начать адекватную антибактериальную или противогрибковую терапию.

Заключение. Комплексный подход к диагностике инфекций кровотока позволил улучшить и, что не менее важно, существенно ускорить верификацию возбудителя. Если в случае бактериальной инфекции результаты гемокультивирования и тестирования биомаркеров были сопоставимы, то в случае кандидозной инфекции ключевым в диагностическом плане представляется исследование маннанового антигена *Candida spp*., т.к. именно оно оказалось значительно чувствительнее, чем результат посева крови, и позволило идентифицировать этиологию лихорадки неясного генеза у существенной части пациентов.

Ключевые слова:
прокальцитонин, маннан, инфекции кровотока, *Candida spp*., диагностика сепсиса, биомаркеры.

Для корреспонденции:
Куцевалова Ольга Юрьевна – к.б.н., заведующая лабораторией клинической микробиологии, врач-бактериолог ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: Olga_kutsevalova@mail.ru
ORCID: https://orcid.org/0000-0001-7452-6994
SPIN: 6271-1942, AuthorID: 363005
ResearcherID: AAM-9837-2020

Информация о финансировании: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Куцевалова О.Ю., Козель Ю.Ю., Дмитриева В.В., Коюзк О.В., Лысенко И.Б. Комплексный подход к диагностике бактериальных и грибковых инфекций кровотока у пациентов онкологического профиля. Южно-российский онкологический журнал. 2020; 1(4): 15-21.
https://doi.org/10.37748/2687-0533-2020-1-4-2

Получено 06.04.2020, Рецензия (1) 08.07.2020, Рецензия (2) 19.10.2020, Принята к печати 01.12.2020

INTRODUCTION

Worldwide, cancer is the second leading cause of death and it kills about 8.8 million people every year, according to statistics from the World Health Organization (www.who. Int / mediacentre / factheets / fs297). Severe bloodstream infections and sepsis complicate treatment and the outcome of recovery, antitumor treatment, and have a significant negative impact on the life expectancy and cost of treatment of cancer patients. Rapid diagnosis of sepsis and initiation of treatment are key factors in reducing mortality in cancer patients [1–5]. Infection-mediated mortality during chemo-induced immunosuppression is an urgent issue that requires studying risk factors and developing strategies to reduce mortality by optimizing diagnostic methods and accompanying therapy [6]. In the etiology of bloodstream infection, both gram-positive and gram-negative bacteria are most common. Yeast-like fungi of the genus Candida play a significant role. Using modern equipment to get the pathogen from the blood is still problematic. In addition, it takes from a day to several days. In this situation, biomarkers are an objective and reliable way for a clinician to quickly respond to the possible development of an infectious complication [7–8].

It was discovered by chance that bacterial infection increases the concentration of procalcitonin in the blood. This contributed to the procalcitonin usage as a marker of bacterial infections. In contrast to all known markers of inflammation, the method for determining procalcitonin is more sensitive and highly specific for severe bacterial infection [9–14]. Yeast fungi of the genus *Candida spp* are one of the most common pathogens of invasive mycoses. Diagnosis of invasive candidiasis is difficult due to the non-specific clinical symptoms and insufficient sensitivity of the hemocultivation method. One of the available biomarkers of invasive candidiasis that allow us to judge the presence of invasive candidiasis is mannan, one of the *Candida spp*. antigens, which is a soluble polysaccharide bound to the walls of yeast cells [15].

So, the development and application of new and improvement of existing methods for determining the pathogen, which allow to accelerate and clarify the etiological factor of bloodstream infection for the earliest possible start of specific treatment, is an urgent task of modern medicine.

The purpose of the study: to evaluate the diagnostic significance of accelerated and accessible verification of the bloodstream pathogen using biomarkers: procalcitonin and mannan antigen.

PATIENTS AND METHODS

349 cancer patients with febrile fever from 6 medical and diagnostic hospitals of the southern Federal district of the Russian Federation were examined during 2019. Patients (men and women) aged from 1 to 85 years were in intensive care units, pediatric oncology and oncohematology departments. There are informed patient consents for research.

The diagnostic algorithm included a blood test using an automatic bact/ALERT 3D analyzer. Two sets of vials were used for one septic episode. Each set included: for patients with a body weight of more than 36 kg: a bottle for aerobic and anaerobic cultivation and a volume of 10 ml of blood in each bottle. For children with a body weight of up to 36 kg (inclusive), two pediatric vials and a volume of blood from 0.5 to 5.0 ml per vial, also depending on body weight. Each blood culture was accompanied by a parallel study of the level of biomarkers by the immune-enzyme method. Identification of strains and their sensitivity to antimicrobial agents was performed using an automatic Vitek 2 analyzer (BioMerieux, France). Simultaneously with the seeding, a sample was taken into a vacuum tube for an enzyme-linked immunoassay (determination of the level of procalcitonin and the mannan antigen *Candida spp*). Procalcitonin values of more than 10 ng/ml were taken into account to determine the development of bacterial inflammation. The *Candida spp*. manann antigen, as one of the available biomarkers of invasive candidiasis, allowed us to judge the involvement of *Candida spp* fungi in the infectious process. The result was considered positive at an

antigen concentration of ≥125 PG/ml. Given the low specificity of the study of the *Candida spp*. manann antigen, the results were compared with risk factors for the development of invasive candidiasis (perforation or surgery of the gastrointestinal tract, infected pancreonecrosis, Central venous catheter, broad-spectrum antibiotics, diabetes mellitus, complete parenteral nutrition, severe patient condition, steroids, immunosuppressors, acute renal failure, colonization of *Candida spp*. more than 2 loci) [16]. The level of procalcitonin was studied using Procalcitonin-ELISA-BEST (Russia). Determination of manann antigen — using kits Platelia Candida Ag (France). Statistical data processing was performed using the statistical package STATISTICA 13.3 (StatSoft Inc., USA). Pearson's Chi-square test was used to compare the data.

The results of the study and their discussion

As a result of the microbiological study, positive blood cultures were obtained in 84 patients, which was 24.1%. Pathogens were distributed as follows: bacteria made up 73.8% (65 strains), yeast-like fungi of the genus *Candida spp*. they made up 22.6% (19 isolates). Bacterial-Candida associations were detected in 3 (3.6%) cases in particularly severe patients, which significantly worsened the condition of patients.

In a parallel study of biomarkers (procalcitonin and manann antigen *Candida spp*.), an increased level of one of them was found in 205 (58.7%) patients (Fig.1). Procalcitonin values of 10 ng/ml or more were observed in 68 (33.2%) patients, which indicated in favor of severe bacterial inflammation. A positive result of the *Candida spp*. manann antigen was found in 118 (57.6%) patients. The results allowed us to suggest Candida infection of the bloodstream in the presence of appropriate clinical signs and risk factors for the development of invasive candidiasis. In 19 (9.2%) patients, two biomarkers were elevated, indicating a possible mixed infection. The results obtained when comparing the informative characteristics of the two methods for diagnosing blood flow infection showed statistically significant indicators (p<0.0001).

The results obtained made it possible to optimize treatment tactics and start adequate etiotropic therapy in a timely manner.

In a comparative analysis of the study using biomarkers and hemocultivation for bacteria, almost comparable values were obtained: positive hemoculture in 65 (73.8%) patients and 68 (33.2%) patients with procalcitonin levels of 10 ng/ml or

Table 1. Characteristics of patients

Characteristics		Abs. numbers	Percentage
Sex	Male	140	40.1
	Female	209	59.9
Age, years	1-7 years	5	1.4
	8-12 years	12	3.4
	13-17 years	42	12.0
	18-40 years	40	11.4
	41 and more	250	71.6
Leading disease	oncohematological	212	60.7
	tumors of the gastrointestinal tract	89	25.5
	Lung Tumors	48	13.8
The management	Surgical	122	35.0
	polychemotherapy	227	65.0

more. According to Pearson's Chi2 criterion, the difference was significant, p=0.0001. Slightly different results were obtained for the yeast-like fungi Candida. Candida from the blood was isolated in only 19 (9.2%) patients, at the time, as the level mannopova antigen R. Candida was elevated in 118 (57.6%) patients (according to Pearson's Chi2 criterion, the difference was significant, p=0.0006). Taking into account the clinical manifestations and risk factors, despite the negative result of blood seeding, which was probably due to long-term cultivation of *Candida spp*. antifungal therapy was prescribed to all patients, with the positive dynamics. Positive results with the use of biomarkers suggested the presence of bacterial-Candida associations in 19 (9.2%) patients, while associations were obtained only in three (according to Pearson's Chi2 criterion, the difference in this case was not significant, p=0.12). All these patients were in the departments of anesthesiology and intensive care after surgery. Their condition was assessed as extremely serious. In this case, the measurement of the mannan antigen *Candida spp*. compared with the risk factors for the development of invasive candidiasis, allowed suggesting an invasive candidiasis infection and prescribing an adequate timely therapy. The data obtained are shown in figure 2.

When diagnosing a bacterial pathogen of blood flow, the culture method showed an advantage and amounted to 73.8%. The use of the biomarker in this study was 33.2%. The advantage of the culture method was the identification of the pathogen and the determination of antibiotic sensitivity. However, the culture method for diagnosing the bacterial pathogen was significantly comparable with the results of the study of the level of procalcitonin (p=0.0001).

When diagnosing Candida infection, the best result was obtained when using the *Candida spp* mannan antigen and was 57.6%, and in hemoculture – 22.6%, which was a statistically reliable indicator (p=0.0006). The result can be explained by the complexity of fungal cultivation in hemoculture.

In bacterial-Candida Association, diagnosis using biomarkers was 9.2%, and in blood culture

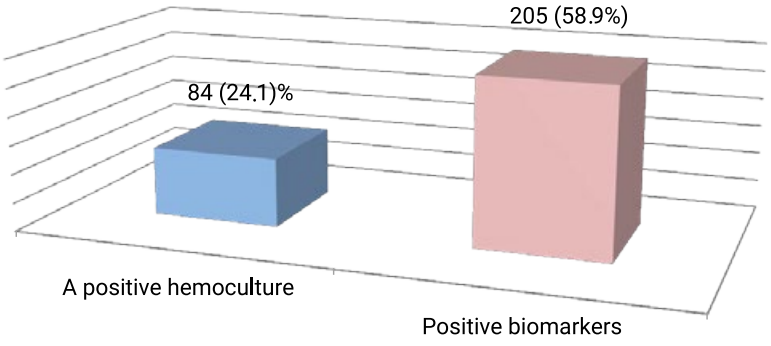


Fig. 1. Comparative characteristics of the information content of two methods for diagnosing bloodstream infection.

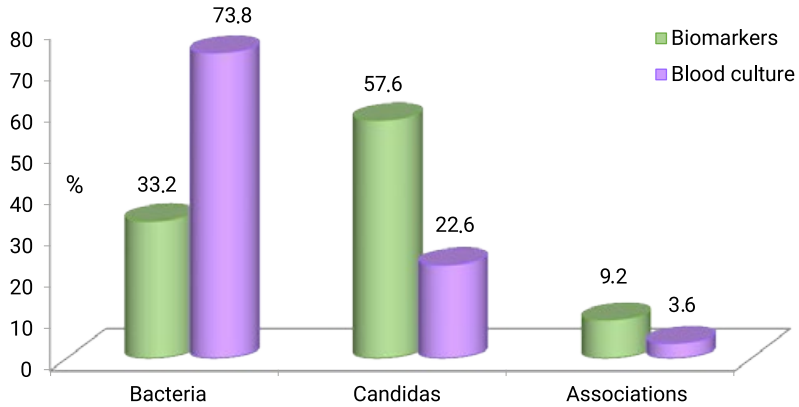


Fig. 2. Comparative values of diagnostics of bacteria and Candida by two diagnostic methods in percent.

— 3,6%. During statistical processing, the difference was not significantly significant (p=0.12). The result can be explained by a small number of cases of bacterial-Candida Association.

Additional and/or repeated clinical and laboratory tests were performed for 60 (17.2%) patients with negative hemoculture and biomarker levels within the normal range.

As a result of these studies, much later, but the pathogen was verified in 10 more patients. All 10 patients had a positive level of biomarkers, of which 4 had an increased level of procalcitonin, and 6 had positive values of the *Candida spp* mannan antigen. When repeated blood cultures were sown in 6 patients, the growth of hemoculture was also obtained (bacteria were isolated from 4 samples, and Candida from 2 samples).

In 26 patients with persistent febrile fever, the condition was regarded as a manifestation of cancer.

24 patients were diagnosed with fever of unknown origin (no infectious agent was detected in additional studies, and no data were found for the progression and recurrence of the cancer process).

Thus, the culture method of hemoculture research allowed us to verify the causative agent of blood flow infection in 24.1% of cancer patients during the initial study and with additional repeated blood cultures in 6 more patients. Multiple (dynamic) studies of the level of biomarkers in this diagnosis improved the result to 61.6% with a significant difference of p<0.0001.

CONCLUSION

In case of bacterial infection of the bloodstream, the culture method showed an advantage in identifying the pathogen and allowed to determine antibiotic sensitivity in comparison with the use of a biomarker, but the determination of procalcitonin allowed to reduce the time for obtaining the result, which is extremely important for determining the direction of the pathogen of bloodstream infection in cancer patients.

The use of the mannan antigen *Candida spp*. in diagnostics demonstrated a significantly higher sensitivity than the result of hemocultivation, which is probably due to the extended period of cultivation of Candida in the blood.

An integrated approach with the study of the level of biomarkers in the diagnosis of bloodstream infections in cancer patients allowed to improve and significantly accelerate the verification of the pathogen, which in turn contributed to timely adequate antibacterial or antifungal therapy.

Authors contribution:
Kutsevalova O.Yu. – research concept and design, text writing, material processing.
Kozel Yu.Yu. – scientific editing.
Dmitrieva V.V. – collection, analysis and interpretation of data.
Kozyuk O.V. – collection, analysis and interpretation of data.
Lysenko I.B. – research concept and design, material processing.

References

1. Sepsis: classification, clinical and diagnostic concept and treatment. Ed. Acad. RAS B. R. Gelfand. 4th ed., add. and pererab. Moscow: Medical information Agency, 2017, 408 p. (In Russian).
2. Chirsky VS, Andreeva EA, Yuzvinkevich AK, Gayvoronsky IV. Pathological characteristics of gram-negative and gram-positive types of sepsis. Vyatka Medical Bulletin. 2020;1(65):56–62. (In Russian).
3. Kurmukov IA, Kashiya ShR, Obukhova OA, Pronina AM, Yunaev GS. Primary diagnosis of sepsis in patients receiving drug treatment for cancer: comparison of SIRS and SOFA criteria. Translational medicine. 2017;4(2):46–51. (In Russian).
4. Anisimova NYu, Gromova EG, Kuznetsova LS, Kiselevsky MV. The content of bacterial endotoxin and cytokines in the blood of cancer patients with postoperative complications. Allergology and Immunology. 2010;11(4):310–313. (In Russian).
5. Obukhova OA, Kurmukov IA, Borovkova NB, Golovnya EG, Petukhova IN, Pronina AM, et al. Diagnostic sensitivity of sepsis biomarkers in severe infection in cancer patients who received antitumor treatment. Oncogynecology. 2018;2(26):54–61. (In Russian).

6. Toshina YuK, Dinikina YuV, Smirnova AYu, Egorov AS, Chervonyuk YuE, Zasulskaya AA, et al. Analysis of infectious complications in children with hematological malignancies: data from one. Russian Journal of Pediatric Hematology and Oncology. 2019;6(S1):118. (In Russian).

7. Noskova OA, Agapova ED, Baturina EA, Gvak GV. Microbiological Monitoring in the System of Epidemiological Surveillance of Purulent-Septic Infections in a Multidisciplinary Hospital. Acta Biomedica Scientifica. 2019;4(5):122–126. (In Russian). https://doi.org/10.29413/ABS.2019-4.5.19

8. Gusarov VG, Lashenkova NN, Petrova NV, Dementienko MV, Shilkin DN, Nesterova EE, et al. Protocols of empirical antimicrobial therapy as a tool for improving the quality of emergency medical care for patients with infection in a multidisciplinary surgical hospital. Medical Alphabet. 2016;4(33):24–28. (In Russian).

9. Bagirova NS, Petukhova IN, Grigorievskaya ZV, Tereshchenko IV, Dmitrieva NV. Advantages and disadvantages of using procalcitonin in the clinic. Malignant tumors. 2019;9(3-S1):32–42. (In Russian).

10. Dinikina YuV, Belogurova MB. Invasive candidiasis in children with cancer: epidemiology, diagnosis (review). Problems of medical mycology. 2018;20(4):3–9. (In Russian).

11. Chebotkevich VN, Bessmel'tsev SS, Kiseleva EE, Stizhak NP, Kaytandzhan EI, Burylev VV. Clinical and microbiological characteristics of bloodstream infections in hematological cancer patients. Oncohematology. 2016;11(3):58-67. (In Russian). https://doi.org/10.17650/1818-8346-2016-11-3-851-863

12. Kit OI, Shikhlyarova AI, Maryanovskaya GY, Barsukova LP, Kuzmenko TS, Zhukova GV, et al. Theory of health: successfui translation into the real life. General biological prerequisites. Cardiometry. 2015;(7):11-17. https://doi.org/10.12710/cardiometry.2015.7.1117

13. Bilyakova KI, Arinova AZh, Temirbaeva ZhS. Bloodstream infections in hematological patients. Problems of medical mycology. 2015;17(3):19–21.

14. Kit OI, Shikhlyarova AI, Zhukova GV, Maryanovskaya GY, Barsukova LP. Activation therapy: theoretical and applied aspects. Cardiometry. 2015;(7):22–29. https://doi.org/10.12710/cardiometry.2015.7.2229

15. Kit OI, Kutsevalova OYu, Lysenko IB, Dmitrieva VV. A method for determining the etiology of fever of unknown origin in cancer patients. Patent for invention RUS 2647456 10.04.2017.

16. Diagnosis and treatment of mycoses in intensive care units: Russian recommendations. Resp. ed. N.N.Klimko. 2nd ed. add. andreslave. Moscow: Pharmtek. 2015, 96 p.

Information about author:

Olga Yu. Kutsevalova* – Cand. Sci. (Biol.), head of the laboratory of clinical Microbiology, bacteriologist National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-7452-6994, SPIN: 6271-1942, AuthorID: 363005, ResearcherID: AAM-9837-2020

Yuliya Yu. Kozel – Dr. Sci. (Med.), professor, head of the Department of pediatric Oncology National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-6681-3253, SPIN: 6923-7360, AuthorID: 732882

Viktoriya V. Dmitrieva – Cand. Sci. (Med.), pediatric oncologist at the Department of pediatric Oncology National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-2124-3218, SPIN: 4416-7947, AuthorID: 312405

Olga V. Kozyuk – pediatric oncologist at the Department of pediatric Oncology National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-0676-7398, SPIN: 1962-1920, AuthorID: 734366

Irina B. Lysenko – Dr. Sci. (Med.), professor, head of the Department of Oncohematology National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-4457-3815, SPIN: 9510-3504, AuthorID: 794669

South Russian Journal of Cancer 2020, v.1, №4, p. 22-31
https://doi.org/10.37748/2687-0533-2020-1-4-3
ORIGINAL ARTICLE

MINIMALLY INVASIVE SURGERY FOR OBSTRUCTIVE JAUNDICE CAUSED BY MALIGNANT TUMORS

E.N.Kolesnikov, S.S.Mezentsev*, A.V.Snezhko, M.N.Chernyak, F.N.Grechkin, T.M.Kecheryukova, O.Yu.Kaimakchi

National Medical Research Centre for Oncology of the Ministry of Health of Russia,
63 14 line str., Rostov-on-Don 344037, Russian Federation

ABSTRACT

Purpose of the study. On the basis of the accumulated experience to optimize approaches to the preoperative preparation, technical aspects of X-ray surgical antegrade minimally invasive endobiliary interventions, rational postoperative management of patients in order to reduce postoperative complications, improving treatment outcomes and quality of life of patients.

Materials and methods. We analyzed 1610 percutaneous transhepatic endobiliary surgeries with separate examination of 1186 X-ray surgical procedures of percutaneous external biliary drainage (PEBD) and 424 cases of antegrade endobiliary stenting (AEBS)

Results. Complications after PEBD were developed in 9 (0.76%) patients: the procedure-related bleeding was noted in 3 (0.25%) cases, and bleeding caused by the progression of hepatic failure, hypocoagulation in 6 (0.5%) cases. 3 patients (0.25%) of this group died. Complications after AEBS were registered in 35 (8.3%) patients: acute postoperative pancreatitis in 24 (5.7%) cases, progression of liver failure, hypocoagulation in 9 (2.1%), tumor-induced duodenal stenosis in 2 (0.47%) cases. One patient (0.24%) of this group died. Reduction in complications after PEBD and AEBS is directly associated with surgery techniques, the use of special tools, and tactics of patient management.

Conclusion. The prevention of complications, treatment outcomes, and the quality of life of patients receiving interventional antegrade endobiliary surgery are inextricably associated with the technical aspects of interventions, the tools and tool materials, necessary correction of endogenous toxicosis, pancreatitis, hepatic failure, and hemostatic system disorders. Constant monitoring of the results of new technologies is necessary to analyze gathered experience for possible correction and optimization of tactical approaches and schemes for more effective treatment of patients with this severe pathology.

Keywords:
oncological interventions, obstructive jaundice, biliary stenting, biliary drainage, hepatoduodenal tumors, pancreatic cancer.

For correspondence:
Stanislav S. Mezentsev – Cand. Sci. (Med.), specialist in X-Ray endovascular diagnostics and treatment National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: stas@mezentsev.me
ORCID: https://orcid.org/0000-0002-4041-7535
SPIN: 2580-5712, AuthorID: 794786
ResearcherID: AAO-5612-2020

Information about funding: no funding of this work has been held.
Conflict of interest: authors report no conflict of interest.

For citation:
Kolesnikov E.N., Mezentsev S.S., Snezhko A.V., Chernyak M.N., Grechkin F.N., Kecheryukova T.M., Kaimakchi O.Yu. Minimally invasive surgery for obstructive jaundice caused by malignant tumors. South Russian Journal of Cancer. 2020; 1(4): 22-31. https://doi.org/10.37748/2687-0533-2020-1-4-3

Received 28.05.2020, Review (1) 25.06.2020, Review (2) 30.10.2020, Accepted 01.12.2020

Южно-российский онкологический журнал 2020, т.3, №4, с. 22-31
https://doi.org/10.37748/2687-0533-2020-1-4-3
ОРИГИНАЛЬНАЯ СТАТЬЯ

МИНИИНВАЗИВНЫЕ ХИРУРГИЧЕСКИЕ ОПЕРАЦИИ ПРИ ОБТУРАЦИОННОЙ ЖЕЛТУХЕ, ВЫЗВАННОЙ ЗЛОКАЧЕСТВЕННЫМИ ОПУХОЛЯМИ

Е.Н.Колесников, С.С.Мезенцев*, А.В.Снежко, М.Н.Черняк, Ф.Н.Гречкин, Т.М.Кечерюкова, О.Ю.Каймакчи

ФГБУ «НМИЦ онкологии» Минздрава России,
344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63

РЕЗЮМЕ

Цель исследования. На основе накопленного опыта оптимизировать подходы к предоперационной подготовке, техническим аспектам выполнения рентгенохирургических антеградных миниинвазивных эндобилиарных вмешательств, схемам рационального послеоперационного ведения пациентов для снижения послеоперационных осложнений, улучшения результатов лечения и качества жизни пациентов.
Материалы и методы. В статье проведен анализ 1610 чрескожных чреспечёночных эндобилиарных хирургических операций с раздельным исследованием рентгенохирургических наружных чрескожных дренирований желчных протоков печени (РЧДЖП) — 1186 случая и антеградных эндобилиарных стентирований жёлчных путей (АСЖП) — 424 случая.
Результаты. Осложнения при РЧДЖП развились у 9 (0,76%) пациентов: кровотечение, связанное непосредственно с манипуляцией, отмечено в 3 (0,25%) наблюдениях, вызванное прогрессированием печеночной дисфункции, гипокоагуляцией — в 6-и (0,5%) случаях. В этой группе умерло 3 пациента (0,25%). Осложнения при АСЖП отмечены у 35 (8,3%) больных: острый послеоперационный панкреатит — в 24 (5,7%) случаях, прогрессирование печёночной недостаточности, гипокоагуляции в 9 (2,1%), дуоденальный опухолевый стеноз — в 2-х (0,47%) случаях. В этой группе умер 1 больной (0,24%). Снижение количества осложнений при выполнении РЧДЖП и АСПЖ напрямую связано с техникой выполнения операций, применением специального инструментария, тактикой ведения пациентов.
Заключение. Профилактика осложнений, исход лечения и качество жизни пациентов при выполнении интервенционных антеградных эндобилиарных операций неразрывно связаны с техническими аспектами выполнения вмешательств, используемого инструментария и материалов для их изготовления, необходимостью коррекции эндогенного токсикоза, панкреатита, печёночной дисфункции и нарушений системы гемостаза. Необходимым представляется постоянный мониторинг результатов использования новых технологий с целью анализа накопленного опыта для возможной коррекции и оптимизации тактических подходов и схем для более эффективного лечения пациентов с этой тяжёлой патологией.

Ключевые слова:
интервенционные вмешательства в онкологии, обтурационная желтуха, стентирование желчных протоков, дренирование желчных протоков, опухоли гепатодуоденальной зоны, рак поджелудочной железы

Для корреспонденции:
Мезенцев Станислав Станиславович – к.м.н., врач специалист по рентгенэндоваскулярным диагностике и лечению ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: stas@mezentsev.me
ORCID: https://orcid.org/0000-0002-4041-7535
SPIN: 2580-5712, AuthorID: 794786
ResearcherID: AAO-5612-2020

Информация о финансировании: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Колесников Е.Н., Мезенцев С.С., Снежко А.В., Черняк М.Н., Гречкин Ф.Н., Кечерюкова Т.М., Каймакчи О.Ю. Миниинвазивные хирургические операции при обтурационной желтухе, вызванной злокачественными опухолями. Южно-российский онкологический журнал. 2020; 1(4): 22-31. https://doi.org/10.37748/2687-0533-2020-1-4-3

Получено 28.05.2020, Рецензия (1) 25.06.2020, Рецензия (2) 30.10.2020, Принята к печати 01.12.2020

RELEVANCE

Today, percutaneous transhepatic endobiliary surgery (PTES) is an important branch of interventional radiology, especially when applied to the treatment of patients with obstructive jaundice (OJ) caused by malignant neoplasms (MN). The combination of minimally invasive surgical interventions makes it possible to solve a large number of emerging medical and diagnostic problems in this severe pathology. Such operations are usually characterized by a low degree of trauma and a small number of complications compared to traditional "open" surgery. In the practice of treatment of malignant tumors complicated by OJ, the commonly used methods of PTES are operations of antegrade cholangiostomy. The variety of clinical situations determines the features of using various technical options for the purpose of solving A wide range of tasks facing the Clinician. Large multi-specialty medical institutions in our country have a rich experience in using minimally invasive percutaneous operations. at present, their implementation in surgical practice is quite well developed, and the methods of PTES have become every day and routine [1–3].

After performing PTES, complications associated with the manipulation itself develop in patients in the range from 2.4 to 32.7%, and their mortality is from 0.4 to 13.8% of patients [4–6]. such significant fluctuations determine the relevance of the search for unified approaches and techniques for performing these interventions. There is no doubt that there is a need for a clearer definition of the indications for performing PTES in various types of cholestasis and localization of the level of bile tree obstruction [7, 8].

Over the past 10 years, the operation of choice for the syndrome of tumor origin is minimally invasive surgical operations of internal and external bile drainage in the FSBI "NMRC of Oncology" of the Ministry of health of the Russian Federation. The most commonly used methods are x-ray surgery for percutaneous external biliary drainage (PEBD) and antegrade endobiliary stenting (AEBS). Sufficient experience has been accumulated in these operations, which requires analysis to optimize and standardize approaches to all aspects of treatment of these patients.

The purpose of the study: based on the accumulated experience, to optimize approaches to preoperative preparation, technical aspects of performing x-ray surgical antegrade minimally invasive endobiliary interventions, and rational postoperative management of patients with obstructive jaundice, caused by malignant tumors to reduce postoperative complications, improve treatment results and quality of life of patients.

MATERIALS AND METHODS

In 2010–2019, 1610 percutaneous transhepatic endobiliary surgeries were performed at the FSBI "NMRC of Oncology" of the Ministry of health of the Russian Federation, of which 1186 patients underwent PEBD and 424 patients underwent AEBS. In the majority of patients (408 cases — 96.3%), AEBS surgery was performed as the second stage of palliative minimally invasive treatment of subhepatic jaundice of tumor etiology after reducing the level of bilirubin in the blood to 40–60 mmol/l, and only in 16 (3.7%) patients such intervention was performed simultaneously.

The number of patients with OJ events of tumor etiology who underwent PEBD surgery was 1,145. In 841 patients (73.5%) of them, according to the survey, a tumor of the periampular region was detected, in 157 (13.7%) cases, MN of the liver and/or proximal bile ducts was detected, in 147 (12.8%) patients, OJ was the result of local or metastatic progression of malignant neoplasms of other localities, in most cases of cancer of the stomach, breast, colon and rectum.

In 919 patients, PEBD surgery was the first stage of surgical treatment, which accounted for 77.5% of all cases. At the second stage, 270 (29.4%) patients underwent gastropancreatoduodenal resections, and 354 (38.6%) patients underwent biliodigestive and/or gastroenteroanastomoses. In patients with advanced tumors, only external drainage was performed in 295 (32%) cases.

Antegrade endobiliary stenting of the biliary tract was performed in patients with malignant neoplasms that were morphologically verified in all cases (from the primary or metastatic focus). In 247 (58.4%) cases, these were mn of the periampular region, in 132 (31.2%) cases — of the liver and proximal bile ducts. Other complicated MN was an indication for AEBS in 45 (10.4%) patients. In 19 cases, AEBS was performed for metastatic bowel cancer, in 11 cases for stomach cancer, in 9 cases for breast cancer, in 2 and 1 cases for kidney and lung cancer, respectively. In 3 patients, mechanical jaundice was a manifestation of metastatic lesions of the lymph nodes of the retroperitoneal space and the hepatoduodenal ligament MN without a primary focus.

RESULTS OF THE STUDY

In all patients who underwent an X-ray external percutaneous drainage of the bile ducts of liver under ultrasound guidance (1186 cases), bile was obtained intraoperatively during puncture of the segmental or lobar bile duct and the drainage system was reliably installed in the bile tree. Complications during the implementation of PEBD developed in 9 (0.76%) patients are introduced in the Table 1. All of them were associated with the bleeding.

The development of bleeding directly related to manipulation was observed in 3 (0.25%) cases: the first patient was found to have a wound to the hepatoduodenal ligament with a portal vein injury and massive intra-abdominal bleeding. The second had an intraparenchymatous hematoma with a rupture of the liver along the puncture channel and blood entering the free abdominal cavity. In these two cases, urgent surgical intervention was required to suture the bleeding site, and after the end of treatment, patients were discharged to prepare for the next stage of treatment at their place of residence. The third patient suffered damage to intercostal vessels with massive intrapleural bleeding. The cause of death of this patient was post-hemorrhagic shock, despite urgent thoracotomy and stopping bleeding on the 2nd day after urgent intervention. The development of bleeding associated with severe coagulopathy (hypocoagulation), due to the progression of hepatic dysfunction, was noted in 6 (0.5%) cases after successful

Table 1. Complications in PEBD

Causes of complications	The nature of the complications	Outcome of hospitalization
bleeding directly related to manipulation: 3 cases (0.25%)	damage to the hepatoduodenal ligament with intra-abdominal bleeding: 1 case	Releases
	development of intraparenchymatous hematoma with its rupture: 1 case	Released
	damaged intercostal vessels with intrapleural bleeding: 1 case	Passed away
bleeding associated with hepatic dysfunction, hypocoagulation: 6 cases (0.5%)	angiodysplasia of the small bowel: 1 case	Passed away
	development of acute erosive and ulcerative bleeding: 3 cases	1 passed away
	the development of hemophilia: 2 cases	Released

Table 2. Complications after AEBS

Complications' character	Hospitalization outcome
Development of acute postoperative reactive pancreatitis: 24 cases (5,7%)	Released
Progression of liver failure, hypocoagulation: 9 cases (2.1%)	1 passed away
Development of duodenal stenosis 3-4 degrees: 2 cases (0.47%)	Released

drainage surgery. The first patient died of profuse small bowel hemorrhage due to congenital vascular angiodysplasia of the small intestine. Three other patients from them developed acute erosive gastrointestinal bleeding, which led to a fatal outcome in one patient against the background of DIC progression. Two more patients were complicated by the development of hemobilia within 2 days after the operation. In these cases, the bleeding was conservatively stopped against the background of hemostatic and hepatotropic therapy.

Complications after performing antegrade endobiliary stenting of the biliary tract were noted in 35 (8.3%) patients, which is comparable to the data of other authors of 8–18% [9–12], presented in table 2.

The most frequent of them was acute postoperative pancreatitis, the development of which was noted in 24 (5.7%) patients. 9 (2.1%) patients were diagnosed with progressive liver failure, accompanied by severe coagulopathy, manifested by significant hypocoagulation. 2 patients (0.47%) were diagnosed with duodenal stenosis of the 3rd degree during hospitalization, which required performing bypass gastroenteroanastomosis. After performing AEBS, 1 patient (0.24%) with generalized pancreatic head cancer, multiple metastatic lesions of retroperitoneal lymph nodes, liver, and bones died. The cause of death was massive gastrointestinal bleeding, the source of which was numerous erosions of the stomach and upper small intestine against the background of pronounced hypocoagulation. In other patients, the phenomena of hypocoagulation were managed to be stopped conservatively. Overall postoperative mortality after PTES was 0.19%.

DISCUSSION

According to the literature, it is mini-invasive PTES in OJ of tumor Genesis that have become one of the most widespread mini-invasive interventions in General clinical practice. Tactical approaches to the use of biliary drainage techniques to eliminate OJ of tumor and non-tumor Genesis are different [13]. To date, antegrade (external or external-internal) and retrograde (internal) drainage of the bile tree in OJ caused by malignant neoplasms have taken the character of routine minimally invasive intervention. Depending on a particular surgical school, specialists performing these operations prefer the first or second method, as well as combined "rendez-vous" methods. The Russian and world literature describes the positive and negative aspects of each of them, and a huge experience has been accumulated for each of them. According to summary statistics, it is not possible to perform endoscopic papillosphincterotomy in 5–12% of patients, complicated cases occur in 6–10%, and the mortality rate is 1–4% [14].

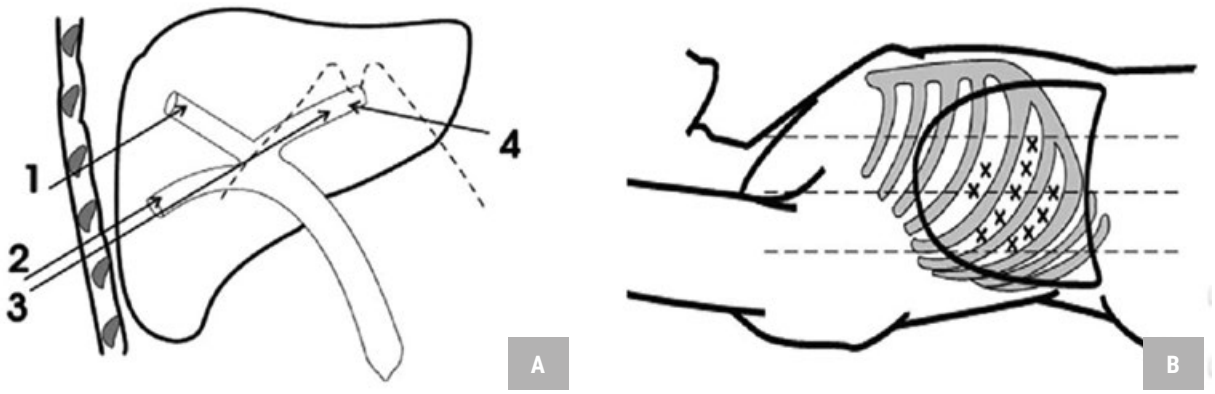


Fig. 1. Variants of surgical access for PEBD used in NMRC Oncology: A – vectors of directions for access to the right 1, 2 and left 3, 4 lobe bile ducts of the liver; B – variants of skin puncture sites depending on the intraoperative ultrasound picture and the height of the costal-diaphragmatic pleural sinus.

The production of antegrade intervention has an undeniably higher percentage of successful results, allows you to leave the tumor block intact, minimize the development of the perioperative inflammatory process (pancreatitis, papillitis), and create prerequisites for a more unhindered and rapid fusion of the anastomosed tissues in the upcoming radical intervention. Today, based on our experience, we can confidently state that the most safe for patients and convenient for surgeons in prognostic terms (before performing radical surgical interventions) method of decompression of the bile tree in OJ of tumor Genesis is precisely antegrade x-ray external percutaneous drainage of the bile ducts of the liver under ultrasound guidance and x-ray control.

Technical aspects of performing PEBD are the most important factor in reducing the number of complications [4, 7, 15]. We associate the fundamental aspect of successful execution of the PEBD with the use of seldinger puncture access along the anterior or mid-axillary line on the right side in the 6, 7 or 8 intercostal spaces. In this case, the vector of the puncture needle runs almost parallel to the course of the right lobar bile duct (Fig. 1)

Often, with such access, the puncture trajectory affects elements of the right costal-diaphragmatic pleural sinus, and various complications may occur, but we have not noted cases of lung injury or bile entering the pleural cavity. Only in one case, hemothorax developed due to damage to the intercostal artery against the background of severe hypocoagulation, which required urgent surgical intervention. In some cases, x-ray examination showed a slightly pronounced pneumothorax, which had no clinical manifestations and was resolved independently within 3–5 days after manipulation.

The second important aspect of the successful completion of PTES is the evolution of the creation of special tools and materials used for their manufacture. In particular, one of the factors that we achieved relatively few complications when performing PEBD is the use of catheters for draining ducts made of structural polyurethane resins (ultratan) instead of plastic materials. In our experience, ultratane drainage systems do not injure the wall of the choledochus, minimize the risk of intraoperative bleeding, dislocation of drainage, bile leaks into the abdominal cavity, have a good hydrophilic coating and x-ray contrast marks for atraumatic and easy installation, are installed in the choledochus or lobar bile duct with virtually no radial ruptures of the liver capsule and the walls of the segmental or lobar bile ducts, are resistant to kinks, well maintain patency, consist of a very smooth and soft material, providing high comfort for the patient, they provide a reliable fixation inside the bile duct and have a large internal lumen. Drainage perforations (side holes) are located on the inner diameter of the fixing ring "pig-tail" of the drainage, which prevents blocking of the holes.

The use of modern consumables has led to the correction of management tactics for patients with biliary tract tumor obstruction. It is considered that if the patient is not shown to perform radical surgery due to the local spread and/or generalization of the cancer process and the predicted life expectancy is less than 3–4 months, biliary stenting should be performed after performing the PEBD. With a longer predicted life expectancy, it is preferable to perform an open (or endoscopic) pallative surgical aid — the formation of a bypass biliodigestive anastomosis (most often a hepaticoenteroanastomosis on a small bowel loop that is turned off by Rue) and the imposition of a gastroenteroanastomosis according to indications [16, 17]. In our opinion, this is justified in cases where plastic tubular stents with side holes are used. During the period of use of such stents, the ratio of patients who underwent AEBS and patients with the formation of these bypass anastomoses was 1 to 1.5 (180 stents, 269 anastomoses).

When using self-extracting Nickel-titanium stents in the subsequent period, we noted a decrease in the number of complications (reduction of cholangitis by 73% ($p \leq 0.01$), pancreatitis by 52% ($p \leq 0.05$), pain syndrome by 68% ($p \leq 0.01$) and, as a result, an improvement in the quality of life of patients, no need for frequent periodic maintenance/replacement of stents (the average stent maintenance interval increased from 1–3 months to 1–1.5 years), as well as due to the lack of access

to the skin (under the skin) of the end face plastic stent tube. The internal diameter of the lumen of such stents reaches 8–10 mm, which makes it possible to adequately and reliably perform bile drainage into the 12-and duodenum (Fig. 2).

Nowadays we do not perform balloon dilation of the stent lumen during its installation and leave a closed safety cholangiostomy after stenting for 3 months. This reduced the incidence of early postoperative pancreatitis and cholangitis by 84% ($p \leq 0.01$). During this time, patients receive special antitumor treatment. If after 3 months during the control study (cholangiography and MRI) there is no deformation of the lumen and funnels of the stent, the safety cholangiostoma is removed on an outpatient basis. At the moment, we perform balloon plastic surgery (dilation) of the tumor block only for extremely dense and extended strictures, in case of severe difficulties in removing the delivery device of the stent-endoprosthesis.

We have experience in monitoring a fairly large number of patients with installed Nickel-titanium stents-endoprostheses for 18–24 months or more without any complications from the stent and manipulations for its maintenance. If stents fail due to tumor growth or lumen obstruction, we perform stent-to-stent restenting. The number of such observations during 2 years was 6 cases. In this regard, we consider the presence of signs of duodenal tumor stenosis or a high risk of its development to be

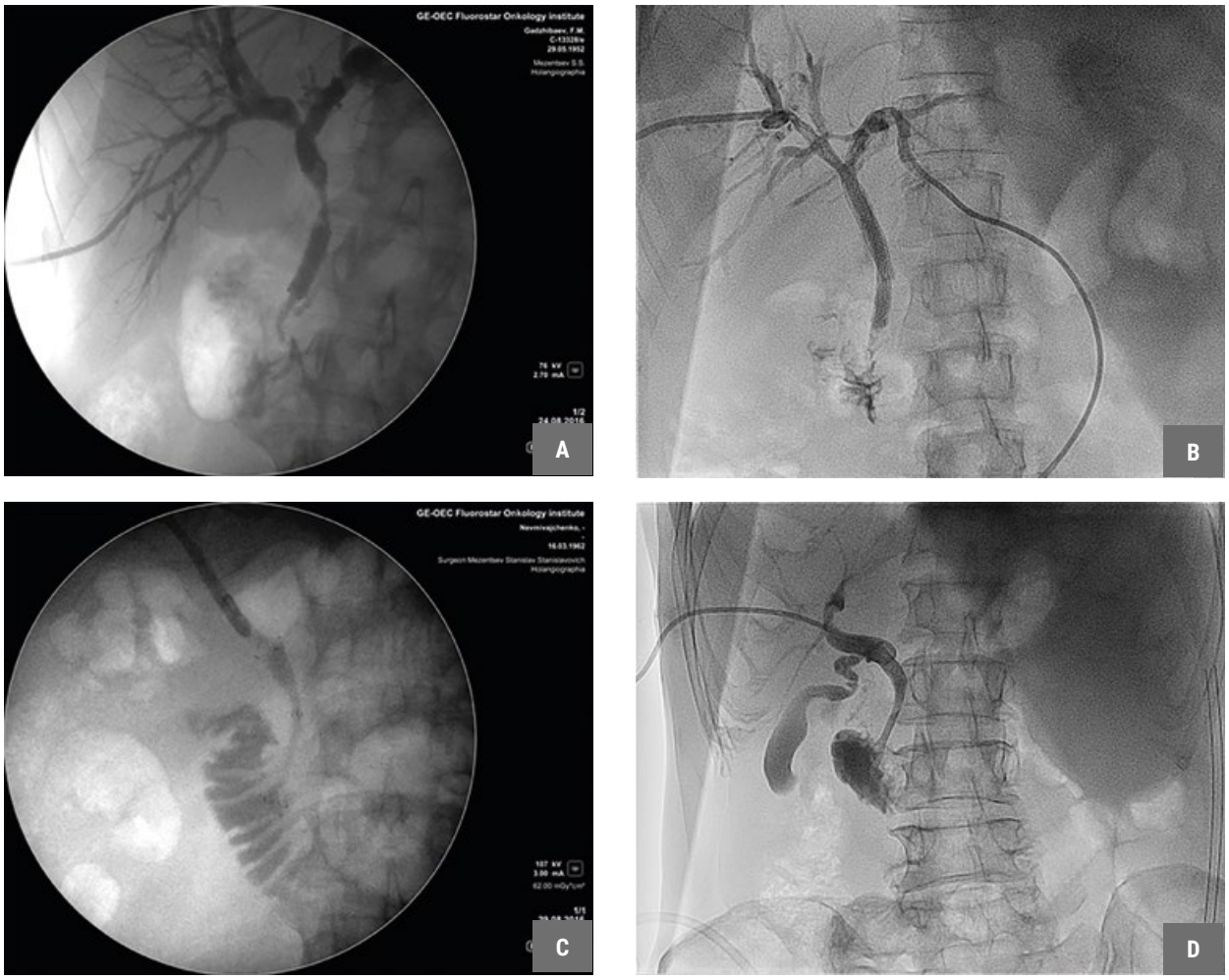


Fig. 2. Cholangiograms of patients after installing self-extracting stents with a proximal block of choledoch (a), a proximal block at the level of confluence of the lobe ducts in a Klatskin tumor – Y-shaped stenting (b) and distal blocks (c, d) of the biliary tract.

an absolute indication for the formation of bypass anastomoses. After the start of using self-extracting stents, the ratio of the number of patients who underwent stenting or bypass anastomosis formation was 3.5 : 1.0 (244 and 69, respectively).

It seems appropriate to differentiate the management tactics of patients with the prospect of performing radical surgery in the future and patients with unresectable forms of MN. Thus, when the lobular ducts of the liver were separated (15 cases of Klatskin's tumor and metastatic lesion of lymph nodes or liver gate parenchyma), we used separate drainage of the lobular bile ducts of the liver. In these cases, the operation was performed simultaneously or at intervals of 3 to 7 days during one hospitalization. We consider it impractical to drain more than two bile ducts when liver segments are separated. According to our experience, in these cases, the probability of complications of drainage operations increases dramatically (three patients had 3 segmental ducts drained; in all cases, we observed bleeding from puncture wounds of the liver capsule, which could be stopped by active conservative therapy), while the clinical effect (elimination of mechanical jaundice) due to the progression of the tumor process is very short-term and does not affect life expectancy and its quality. Radical surgery was performed only in 3 patients of this observation group.

During the analyzed period of time, we performed percutaneous transhepatic drainage of the gallbladder through its bed only in 3 cases (due to insufficient diameter of the ductal system of the liver for conducting the conductor and catheter). This manipulation is technically simpler, but has a number of disadvantages. The main ones are edema of the gallbladder duct in the postoperative period, a high probability of inadequate drainage of the bile tree due to the spread of the tumor to the hepatoduodenal ligament with the “shutdown” of the gallbladder, the inability to perform AEBS if radical surgery is not possible. When performing percutaneous drainage of the gallbladder (including according to our earlier experience), more pronounced pain syndrome is often observed compared to drainage of the ductal system of the liver. This is probably due to the good innervation of the gallbladder bed from the hepatic plexus. In one case, we were able to perform AEBS after cholecystostomy in a clinic from the place of residence. The need to perform an attempt to perform this manipulation was dictated by the severity of the patient's condition, due to large losses of bile, and the inability to perform General anesthesia due to water-electrolyte disorders. It is impossible to perform such interventions in everyday practice due to the narrowness and tortuosity of the specified duct.

Prevention of complications during interventional PTES in patients with OJ, especially caused by MN, is inextricably linked with the need to correct endogenous toxicosis, hepatic dysfunction, and hemostatic disorders [5, 7, 18]. According to our experience, patients with an international normalized ratio in the coagulogram greater than 1.8 and a prothrombin index less than 45% need to undergo preoperative preparation for 5–7 days to correct the phenomena of hypocoagulation. All patients with an initial level of total blood bilirubin over 300 mmol/l during the first day after performing the operation were treated with gravitational plasmapheresis. Some patients needed 2–3 sessions of plasmapheresis to correct hepatic dysfunction at 1–2-day intervals. The plasmapheresis procedure was also performed as planned in all patients who were predicted to perform radical surgery after the elimination of OJ in order to prevent liver failure [19]. This allowed us to normalize homeostasis indicators 2–3 weeks faster than when performing only traditional infusion detoxification therapy, reducing the likelihood of tumor progression by reducing the time before radical intervention. In most cases, patients after performing AEBS experienced reactive pancreatitis, accompanied by hyperamylasemia, which is more pronounced when using self-extracting Nickel-titanium stents. This is due to the pressure of the opening device in the process of “shrinking” (increasing the diameter of the lumen of the installed stent by reducing its length) on the pancreas. The perioperative therapy regimen for all patients with AEBS necessarily included octreotide, as well as proteinase inhibitors (when the level of pancreatic amylase is higher

than 200 u/l). Octreotide was used in a dosage of 0.1–0.3 mg (depending on the severity of pancreatitis) subcutaneously 1–3 times a day. This therapy was performed in the acute period for 3–7 days before the elimination or clinically pronounced reduction of pancreatitis. After performing AEBS, patients received ursodeoxycholic acid 250 mg 1–3 times a day to improve the rheological properties of bile, reduce the phenomena of biliary sludge and reflux of intestinal contents through a stent.

CONCLUSIONS

The use of minimally invasive drainage operations on the biliary tract is currently the most effective and frequent method of treating patients with obstructive jaundice of tumor Genesis. According to our data, when using minimally invasive antegrade percutaneous biliary interventions, there is a relatively low level of complications (0.76% for drainage operations and 8.3% for stenting, which is comparable to the data of other authors) and mortality (the total postoperative mortality for these two methods was 0.19%). This depends both on the experience of specialists (over the past 10 years, FSBI " NMRC of Oncology" has performed more than 1,610 of these techniques), and on the improvement of tools and supplies used in interventional Oncology (the use of catheters for drainage of ducts made of structural polyurethane resins, the use of stents made of Nickel-titanium threads with thermal memory, covered with a silicone membrane). It is necessary to constantly monitor the results of using new technologies in order to analyze the accumulated experience for possible correction and optimization of tactical approaches and schemes for more effective treatment of patients with this severe pathology.

Authors contribution:

Kolesnikov E.N. – research concept and design, scientific editing

Mezentsev S.S. – writing text, processing material, preparing illustrations and tables, collecting, analyzing and interpreting data, making bibliographies, performing surgery, surgery assisting.

Snezhko A.V. – research concept and design, text writing, scientific editing, material processing, technical editing, data analysis and interpretation, article preparation.

Chernyak M.N. – text writing, technical editing, article preparation, operations execution, surgery assistance.

Grechkin F.N. – writing text, processing material, performing surgeries, assisting surgeries.

Kecheryukova T.M. – writing text, processing material, performing surgeries, assisting surgeries.

Kaimakchi O.Yu. – concept and design of the study, scientific editing, preparation of the article.

References

1. Kit OI, Kolesnikov EN, Mezentsev SS, Snezhko AV. Antegrade biliary drainage surgery for obstructive jaundice. Annals of HPB Surgery. 2017;22(2):89–93. (In Russian).
https://doi.org/10.16931/1995-5464.2017289-93

2. Vetshev PS, Musaev GKh, Bruslik SV. Percutaneous minivasive technologies: history, traditions, negative trends and perspectives. Annals of HPB Surgery. 2014;19(1):12–16. (In Russian).

3. Kulezneva YuV, Bruslik SV, Musaev GKh, Izrailov RE, Kirillova MS. Percutaneous modalities of biliary decompression: development and disputable items. Annals of HPB Surgery. 2011;16:(3):35–43. (In Russian).

4. Ivshin VG, Lukichev OD, Makarov YuI, Starchenko GA, Yakunin AYu, Malafeev IV. Comparative characteristics of various methods of percutaneous bile-removing interventions in patients with mechanical jaundice. Annals of HPB Surgery. 2003;8(2):14–18. (In Russian).

5. Karimov SI, Khakimov MS, Adylkhodzhaev AA, Rakhmanov SU, Khasanov VR. Correction of Complications of the Transhepatic Endobiliary Interventions for Obstructive Jaundice Caused by Periampullar Tumors. Annals of HPB Surgery. 2015;20(3):68–74. (In Russian).
https://doi.org/10.16931/1995-5464.2015368-74

6. Tarabukin AV, Mizgirev DV, Epshtein AM, Pozdeev VN, Pozdeev SS, Duberman BL. Biliary Decompression in Malignant Obstructive Jaundice. Annals of HPB Surgery. 2015;20(3):54–58. (In Russian).
https://doi.org/10.16931/1995-5464.2015354-58

7. Dolgushin BI, Nechipai AM, Kukushkin AV, Khachaturov AA. Percutaneous transhepatic puncture cholangiostomy: systematization of representations. Diagnostic and Interventional Radiology. 2012;6(3):31–60.

8. Kasatkin VF, Kit OI, Trifanov DS. Experience in transcutaneous biliary drainage for patients with mechanical jaundice of tumor genesis. Siberian Journal of Oncology. 2008;4:51–54.

9. Gusev AV, Balagurov BA, Borovkov IN, Konkov OI, Martinsh ChT, Pokrovskii EZh, et al. Drainage and endoprosthesis of the bile ducts in case of mechanical jaundice. Bulletin of New Medical Technologies. 2008;15(4):97. (In Russian).

10. Kulezneva YuV, Izrailov RE, Urakova NA. Percutaneous transhepatic stenting of the bile ducts (indications, methods, results). Diagnostic and Interventional Radiology. 2008;2(4):87–93. (In Russian).

11. Lee TH. Technical tips and issues of biliary stenting, focusing on malignant hilar obstruction. Clin Endosc. 2013 May;46(3):260–266.
https://doi.org/10.5946/ce.2013.46.3.260

12. Kalakhanova BKh, Mumladze RB, Chechenin GM, Lebedev SS, Barinov YuV, Gogolashvili DG. Antegrade biliary stenting: the problem of choosing a stent. Annals of Surgery. 2014;5:16–20. (In Russian).

13. Kozlov AV, Tarazov PG, Granov DA, Polikarpov AA, Polysalov VN, Rozengauz EV, et al. Effectiveness of x-ray endobiliary methods of treatment in patients with unresectable liver and bile duct cancer complicated by mechanical jaundice. Annals of HPB Surgery. 2013;4:45–52. (In Russian).

14. Gusev AV, Solov'ev AYu, Lebedev AK, Vakheeva YuM, Efremov AV, Yushinov AA, et al. Immediate and distant results of endoscopic papillosphincterotomy. Modern Problems of Science and Education. 2015;5:323. (In Russian).

15. Aidemirov AN, Shakhnazaryan NG, Vafin AZ, Shakhnazaryan AM. Current approach to mechanical jaundice management. Annals of HPB Surgery. 2015;20(4):62–67. (In Russian). https://doi.org/10.16931/1995-5464.2015462-67

16. Patyutko YuI, Kotelnikov AG. Surgery for cancer of the biliopancreatoduodenal zone. Moscow: Meditsina. 2007, 448 p. (In Russian).

17. Mann CD, Thomasset SC, Johnson NA, Garcea G, Neal CP, Dennison AR, et al. Combined biliary and gastric bypass procedures as effective palliation for unresectable malignant disease. ANZ J Surg. 2009 Jun;79(6):471–475.
https://doi.org/10.1111/j.1445-2197.2008.04798.x

18. Kabanov MYu, Yakovleva DM, Sementsov KV, Gorshenin TL, Rybakov SM, Aksenova TE, et al. Role and Place of Minimally Invasive Interventions in Treatment of Hepatopancreatoduodenal Diseases in Elderly Patients. Annals of HPB Surgery. 2015;20(3):37–46. (In Russian).
https://doi.org/10.16931/1995-5464.2015337-46

19. Gridasov IM, Ushakova ND, Goroshinskaya IA, Nemashkalova LA, Maksimov AYu. The severity and ways of correction of endogenous intoxic index syndrome in patients with obstructive jaundice with cancer of biliopancreatoduodenal area. Journal of Fundamental Research. 2013;9-4:627–631. (In Russian).

Information about author:

Evgenii N. Kolesnikov – Cand. Sci. (Med.), head of the Department of Abdominal Oncology №1 with a group of x-ray endovascular methods of diagnosis and treatment National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 8434-6494, AuthorID: 347457

Stanislav S. Mezentsev* – Cand. Sci. (Med.), specialist in x ray endovascular diagnostics and treatment National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-4041-7535, SPIN: 2580-5712, AuthorID: 794786, ResearcherID: AAO-5612-2020

Aleksandr V. Snezhko – Dr. Sci. (Med.), Associate Professor, surgeon National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 2913-3744, AuthorID: 439135

Maksim N. Chernyak – specialist in x ray endovascular diagnostics and treatment National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 7418-7320, AuthorID: 917426

Fedor N. Grechkin – Cand. Sci. (Med.), surgeon National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 4144-5304, AuthorID: 734515

Takhmina M. Kecheryukova – specialist in x ray endovascular diagnostics and treatment National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.

Oleg Yu. Kaimakchi – Dr. Sci. (Med.), Associate Professor of Oncology National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. AuthorID: 335064

South Russian Journal of Cancer 2020, v.1, №4, p. 32-37
https://doi.org/10.37748/2687-0533-2020-1-4-4
ORIGINAL ARTICLE

NOVALIS TX RADIOSURGICAL PLATFORM EXPERIENCE IN NATIONAL MEDICAL RESEARCH CENTRE FOR ONCOLOGY OF THE MINISTRY OF HEALTH OF RUSSIAN

O.I.Kit, V.I.Voshedskii, P.G.Sakun*, M.A.Gusareva, S.G.Vlasov, K.N.Museiko, M.A.Komandirov, Yu.A.Kultysheva

National Medical Research Centre for Oncology of the Ministry of Health of Russia,
63 14 line str., Rostov-on-Don 344037, Russian Federation

ABSTRACT

Purpose of the study. The primary study presents an analysis of the results of stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (SRBT) of extra — and intracranial tumors obtained during four years of observation at «National Medical Research Centre for Oncology».

Material and methods. The study enrolled 277 patients. 184 patients (66.4%) received SRS, 54 patients (19.5%) received intracranial SRT, 39 patients (14.1%) received extracranial SRBT. Radiation treatment plans were developed with iPlan and Elements planning software, BrainLab. Radiation therapy was performed with Novalis Tx, Varian linear accelerator. Outcome assessment was performed with iPlan and Elements software, BrainLab, by comparing tumor volumes based on brain MRI series for brain tumors (or CT imaging for extracranial pathology) before the treatment and during four-year follow-up. Stereotactic radiosurgical and hypofractive radiotherapy techniques were used. In radiosurgical surgery, radiation therapy was performed with a single high-precision approach of the therapeutic dose to the target for the purpose to reach biological effect in the irradiated volume with minimal impact on the surrounding tissues. Single focal doses (SFD) were selected due to histology, and the dose was prescribed according to the accepted criteria of The International Commission on Radiation Units and Measurements (ICRU) (2010) Report 83. Hypofractionated stereotactic radiotherapy was performed using 2–5 Fractions (FR) with an average range of 3–10 Gy.

Results. During the entire period of observation tumor volume and clinical symptoms in patients who received SRS were reported to reduce in 69.8%, to be stable in 19.6%, increased in 9.8%, respectively. For patients, who received intracranial SRT, tumor volume and clinical symptoms were reported to reduce in 59.3%, increased in 21.4%, to be stable in 9.3%. For patients with extracranial tumors, who went SRBT, tumor volume and clinical symptoms were reported to be stable in 58.9%, reduced in 38.5%, increased in 6.7%.

Conclusion. The analysis of the obtained data shows the high efficiency of SRS and SRBT methods, which allow to achieve local control over both malignant and benign tumours.

Keywords:
radiation therapy, radiosurgery, SRS, SBRT, SRT, tumor.

For correspondence:
Pavel G. Sakun – Cand. Sci. (Med.), radiation oncologist, National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: pavelsg78@gmail.com
ORCID: https://orcid.org/0000-0003-1405-8329
SPIN: 3790-9852, AuthorID: 734600
Scopus Author ID: 56531945400

Information about funding: no funding of this work has been held.
Conflict of interest: authors report no conflict of interest.

For citation:
Kit O.I., Voshedskii V.I., Sakun P.G., Gusareva M.A., Vlasov S.G., Museiko K.N., Komandirov M.A., Kultysheva Yu.A. Novalis Tx radiosurgical platform experience in National Medical Research Centre for Oncology of the Ministry of Health of Russian. South Russian Journal of Cancer. 2020; 1(4): 32-37. https://doi.org/10.37748/2687-0533-2020-1-4-4

Received 09.06.2020, Review (1) 11.09.2020, Review (2) 29.09.2020, Accepted 01.12.2020

Южно-российский онкологический журнал 2020, т.3, №4, с. 32-37
https://doi.org/10.37748/2687-0533-2020-1-4-4
ОРИГИНАЛЬНАЯ СТАТЬЯ

ОПЫТ ПРИМЕНЕНИЯ РАДИОХИРУРГИЧЕСКОГО КОМПЛЕКСА NOVALIS TX В ПРАКТИКЕ ФГБУ «НМИЦ ОНКОЛОГИИ» МИНЗДРАВА РОССИИ

О.И.Кит, В.И.Вошедский, П.Г.Сакун*, М.А.Гусарева, С.Г.Власов, К.Н.Мусейко, М.А.Командиров, Ю.А.Култышева

ФГБУ «НМИЦ онкологии» Минздрава России,
344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63

РЕЗЮМЕ

Цель исследования. Анализ полученных в течение четырех лет наблюдений результатов проведенной стереотаксической радиохирургии (SRS) и стереотаксической радиотерапии в режиме гипофракционирования (SRBT) экстра- и интракраниальных опухолей в ФГБУ «НМИЦ онкологии» МЗ РФ.

Пациенты и методы. В исследование включено 277 пациентов, разделенные на 3 группы. В первой группе 184 пациента (66,4%) с примененной SRS, во второй группе 54 пациента (19,5%) с примененной SRT, в третьей группе 39 больных (14,1%) с проведенной SRBT экстракраниальных опухолей. Разработка планов лучевой терапии проводилась на системах планирования iPlan и Elements, BrainLab. Лучевая терапия проводилась на линейном ускорителе Novalis Tx, Varian. Оценка проводилась с использованием программного обеспечения iPlan и Elements, BrainLab, путем сравнения объемов опухолей по данным МРТ исследования головного мозга и СРКТ для экстракраниальной патологии в момент лечения и в течение четырех лет наблюдения. Использовались стереотаксические радиохирургические и гипофракционные методики лучевой терапии. При радиохирургическом лечении лучевая терапия проводилась с однократным высокоточным подведением терапевтической дозы к мишени с целью биологического эффекта в облучаемом объеме при минимальном воздействии на окружающие ткани. Разовые очаговые дозы (РОД) подбирались в зависимости от гистологии, а предписание дозы проводилось согласно принятым критериям The International Commission on Radiation Units and Measurements (ICRU) (2010) Report 83. Гипофракционированная стереотаксическая лучевая терапия проводилась с использованием 2–5 Фракций (Фр) со средним диапазоном РОД 3–10 Гр.

Результаты. В течение всего периода наблюдений в группе пациентов после SRS в 69,8% случаев отмечена положительная динамика, в 19,6% отмечена стабилизация процесса, в 9,8% — отрицательная динамика. В группе SRT у 59,3% больных наблюдается положительная динамика, в 21,4% — отрицательная динамика и в 9,3% — стабилизация процесса. В группе SRBT экстракраниальных опухолей в 38,5% — положительная динамика, в 58,9% отмечена стабилизация процесса, в 6,7% — отрицательная динамика.

Заключение. Анализ полученных данных говорит о высокой эффективности методик SRS и SRBT, которые позволяют добиться локального контроля как над злокачественными, так и доброкачественными новообразованиями.

Ключевые слова:
лучевая терапия, радиохирургия, SRS, SBRT, SRT, новообразования.

Для корреспонденции:
Сакун Павел Георгиевич – к.м.н., врач-радиотерапевт, ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: pavelsg78@gmail.com
ORCID: https://orcid.org/0000-0003-1405-8329
SPIN: 3790-9852, AuthorID: 734600
Scopus Author ID: 56531945400

Информация о финансировании: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Кит О.И., Вошедский В.И., Сакун П.Г., Гусарева М.А., Власов С.Г., Мусейко К.Н., Командиров М.А., Култышева Ю.А. Опыт применения радиохирургического комплекса Novalis Tx в практике ФГБУ «НМИЦ онкологии» Минздрава России. Южно-российский онкологический журнал. 2020; 1(4): 32-37. https://doi.org/10.37748/2687-0533-2020-1-4-4

Получено 09.06.2020, Рецензия (1) 11.09.2020, Рецензия (2) 29.09.2020, Принята к печати 01.12.2020

INTRODUCTION

Recently, stereotactic methods of radiation therapy for various pathological formations have come to the forefront of combined treatment of neoplasms [1]. In the classical version, radiation therapy was based on the quantitative doctrines of classical radiobiology and was performed with single focal doses up to 2 Gy. the goal of standard fractionation was to reduce the risk of damage to surrounding tissues. However, the appearance of stereotactic techniques that provide high accuracy and conformality of irradiation of the pathological focus, and the development of target visualization techniques, significantly increased the single dose of radiation and reduced the number of radiation fractions without increasing the risk of damage to normal tissues, increasing the effectiveness of radiation exposure [2]. For example, in the treatment of vestibular sutures, recent articles confirm that the control of tumor growth after radiosurgery is achieved in 93–100%. Lunsford L. D. with co-authors, he studied the results of treatment after 5 and 10 years in 829 patients with vestibular schwannomas who underwent radiosurgery at the University of Pittsburgh. This article reported 98% control of tumor growth during long-term follow-up. In 62% of cases had positive dynamics in the form of a reduction of lesions in 33% of the stabilization process, 6% negative trend in higher education [3]. Today, stereotactic radiosurgery has been considered as the first line of treatment for patients with metastatic brain damage [4]. The management of patients with brain metastases has become a serious problem due to the increasing frequency and complexity of diagnostic and therapeutic approaches [5, 6]. in 2014, the European Association of neuro-oncologists (EANO) created an interdisciplinary working group to develop evidence-based recommendations for patients with brain metastases from solid tumors [7]. Stereotactic radiation therapy and radiosurgery today play a crucial role in the treatment of not only cancer lesions, but also vascular and functional pathologies of the brain and spinal cord. For a number of diseases, this is an important part of combined treatment, and if it is impossible or there is an increased risk of surgical intervention, it is an alternative to direct surgery, often the only possible method of influencing the pathological process [8]. Available clinical data confirm the important role of stereotactic radiosurgery in achieving high local control of brain metastases.

The purpose of the study: analysis of four — year results of stereotactic radiosurgery (SRS) and stereotactic radiotherapy in hypofractionation mode (SRBT) of extra-and intracranial tumors in the Federal state budgetary institution NMRC of Oncology of the Russian Ministry of Health.

PATIENTS AND METHODS

The study included 277 patients divided into 3 groups. In the first group, there were 184 patients

Table 1. Dynamics in groups of stereotactic radiation therapy for 4 years

	Patients' number	Positive dynamics		Process stabilization		Negative dynamics	
		Benign formation	Malignant formation	Benign formation	Malignant formation	Benign formation	Malignant formation
Group I (SRS)	184	68	60	19	17	-	8
The percentage		69.8 %		19.6 %		9.8 %	
Group II (SBRT)	57	9	5	14	8	-	1
The percentage		38.5 %		58.9 %		6.7 %	
Group III (SRT)		23	8	9	-	-	11
The percentage		59.3 %		9.3 %		21.4 %	

(66.4%) with SRS: 77 (41.8%) with metastatic brain damage; 57 (31.0%) with meningiomas; 31 (16.8%) with cranial nerve neurinomas; 9 (4.9%) patients with recurrent glial tumors, 8 (4.3%) with vascular malformations, 2 (1.0%) with hemangiopericytoma and pineoblastoma.

In the second group, 54 patients (19.5%) with SRT: 23 (42.6%) with meningiomas; 14 (25.9%) with cranial nerve neurinomas; 11 (20.4%) with metastatic brain damage; 3 (5.6%) with recurrent glial tumors; 1 (1.9%) with vascular malformations; 1 (1.9%) patient with hemangiopericytoma, 1 (1.9%) patient with craniopharyngioma.

In the third group, 39 patients were (14.1%) with SRBT extracranial tumors: 21 (53.8%) with vertebral body hemangiomas; 12 (30.8%) with primary and metastatic lung lesions, 3 (7.7%) with vertebral neurinomas, 3 (7.7%) with metastatic vertebral lesions.

All patients with intracranial pathology were immobilized using a three-layer thermoplastic mask. In patients with extracranial pathology, immobilization was performed using a thermoplastic head-neck-shoulders mask and a vacuum mattress for lesions of the cervical and upper thoracic spine, and using the Stradivarius™ SBRT system using an abdominal press to exclude mobility of the area of interest during breathing of the patient with lesions of the lower thoracic, lumbar and sacral spine. Topometric computed tomography was performed on a Siemens SOMATOM tomograph. Contouring and planning was carried out using iPlan/ELEMENTS software, BrainLab. The prescription dose coverage, D95%=100%. Verification of the radiation therapy plan was performed by independent recalculation of the dose by another algorithm, verification of the treatment plan on the matrix of the ArcCheck detector, Sun Nuclear. The assessment was performed using the iPlan RT Image, Elements (BrainLab) software and by comparing tumor volumes based on MRI data of the brain and IPT for extracranial pathology from the beginning of treatment and after four years of follow-up. Stereotactic radiosurgical and hypofractive radiotherapy techniques were used. In radiosurgical radiation, radiation therapy was performed with a single high-precision approach of the therapeutic dose to the target for the purpose of biological effect in the irradiated volume with minimal impact on the surrounding tissues. Single focal doses were selected depending on histology, and dose prescribing was performed according to the accepted criteria of The International Commission on Radiation Units and Measurements (ICRU) (2010) Report 83. Hypofractionated stereotactic radiotherapy was performed using 2–5 fractions (FR) with an average range of 3–10 Gy.

STUDY RESULTS AND THEIR DISCUSSION

After four years of observation in the first group of SRS (184 patients), 69.8% of cases showed positive dynamics (68 patients with benign tumors, 60 with malignant brain tumors), 19.6% showed stabilization of the process (19 patients with benign tumors, 17 with malignant brain tumors), 9.8% showed negative dynamics (8 patients with malignant brain tumors).

In the SRBT group of extracranial tumors, 58.9% showed stabilization of the process (14 patients with benign lesions of the spine and 8 patients with malignant lesions of the lungs and spine), 38.5% showed positive dynamics (9 patients with vertebral body hemangiomas, 5 patients with malignant lesions of the lungs and spine), and 6.7% showed negative dynamics only for malignant formations (1 patient with metastatic lung damage).

In the SRT group, 59.3% of patients showed positive dynamics (23 patients with benign tumors and 8 patients with malignant brain lesions, respectively); 9,3% — stabilization of the process in 5 people with benign formations and 21.4% negative dynamics (11 patients with malignant brain lesions).

CONCLUSION

During the past few decades, clinical studies have provided insight into the effectiveness of stereotactic radiotherapy techniques. Initially, stereotactic methods of treatment were used as an adjunct to surgical and systemic methods of treatment. Over the past 20 years, data from clinical and scientific

studies of foreign and domestic sources have begun to use radiosurgical effects on pathological formations in the first line of treatment, pushing aside such methods of radiation exposure as total irradiation of the entire brain. Increased indications for SRS, SBRT, and SRT methods for benign intra-and extracranial formations. The analysis of our own data shows the high efficiency of SRS and SRBT methods, which allow us to achieve local control over both malignant and benign neoplasms.

Authors contribution:
Kit O.I. – research concept and design, scientific editing.
Voshedskii V.I. – data collection, analysis and interpretation, article preparation, technical editing.
Sakun P.G. – research concept and design, scientific editing.
Gusareva M.A. – scientific editing.
Vlasov S.G. – data collection, analysis and interpretation, article preparation.
Museiko K.N. – data collection, analysis and interpretation, article preparation.
Komandirov M.A. – data collection, analysis and interpretation, article preparation.
Kultysheva Yu.A. – data collection, analysis and interpretation, article preparation, technical editing.

References

1. Golanov A.V., Banov S.M., Il'yalov S.R., Vetlova E.R., Kostyuchenko V.V. Modern approaches of radiotherapy of metastatic brain lesions. Malignant tumours. 2014;(3):137–140. (In Russian). https://doi.org/10.18027/2224-5057-2014-3-137-140

2. Dunbar SF, Tarbell NJ, Kooy HM, Alexander E, Black PM, Barnes PD, et al. Stereotactic radiotherapy for pediatric and adult brain tumors: preliminary report. Int J Radiat Oncol Biol Phys. 1994 Oct 15;30(3):531–9.
https://doi.org/10.1016/0360-3016(92)90938-e

3. Lunsford LD, Niranjan A, Flickinger JC, Maitz A, Kondziolka D. Radiosurgery of vestibular schwannomas: summary of experience in 829 cases. J Neurosurg. 2005 Jan;102 Suppl:195–199.

4. Lippitz B, Lindquist C, Paddick I, Peterson D, O'Neill K, Beaney R. Stereotactic radiosurgery in the treatment of brain metastases: the current evidence. Cancer Treat Rev. 2014 Feb;40(1):48–59. https://doi.org/10.1016/j.ctrv.2013.05.002

5. Kanaev SV, Girshovich MM, Melnik YuS. Clinical experience of radiosurgical treatment for metastatic brain lesion in malignant tumors. Journal of Oncology Issues. 2016;62(2):258–264. (In Russian).

6. Golanov AV, Banov SM, Il'yalov SR, Trunin YuYu, Maryashev SA, Vetlova ER, et al. Radiosurgical treatment of brain metastases. The factors of prognosis of overall survival and intracranial recurrence rates. Journal of Neurosurgery Named after N.N.Burdenko. 2016;80(2):35–46. (In Russian).
https://doi.org/10.17116/neiro201680235-46

7. Soffietti R, Abacioglu U, Baumert B, Combs SE, Kinhult S, Kros JM, et al. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). Neuro Oncol. 2017 Feb 1;19(2):162–174.
https://doi.org/10.1093/neuonc/now241

8. Franco P, De Bari B, Ciammella P, Fiorentino A, Chiesa S, Amelio D, et al. The role of stereotactic ablative radiotherapy in oncological and non-oncological clinical settings: highlights from the 7th Meeting of AIRO-Young Members Working Group (AIRO Giovani). Tumori. 2014 Dec;100(6):e214-219. https://doi.org/10.1700/1778.19280

Information about author:
Oleg I. Kit – member of Russian Academy of Sciences, Dr. Sci. (Med.), professor, general director of National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-3061-6108, SPIN: 1728-0329, Scopus Author ID: 55994103100, Researcher ID: U-2241-2017

Vitalii I. Voshedskii – radiation oncologist, National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-1405-8329, SPIN: 4732-4005, AuthorID: 1032685, Researcher ID: Q-6122-2019

Pavel G. Sakun* – Cand. Sci. (Med.), radiation oncologist, National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. SPIN: 3790-9852, AuthorID: 734600, Scopus Author ID: 56531945400

Marina A. Gusareva – Cand. Sci. (Med.), radiation oncologist, National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. SPIN: 9040-5476, AuthorID: 705242

Stanislav G. Vlasov – graduate student, National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-4680-8991, SPIN: 3001-7426, AuthorID: 1087319

Ksenia N. Museiko – medical resident, National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation.

Maxim A. Komandirov – medical physicist, National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation. SPIN: 9331-1278, AuthorID: 843316

Yuliya A. Kultysheva – medical physicist, National Medical Research Centre of Oncology of the Russian Ministry of Health, Rostov-on-Don, Russian Federation.

South Russian Journal of Cancer 2020, v.1, №4, p. 38-46
https://doi.org/10.37748/2687-0533-2020-1-4-5
ORIGINAL ARTICLE

THE EFFECTS OF COMBINED ACTION OF LOW-INTENSITY ELECTROMAGNETIC RADIATION OF THE MILLIMETER RANGE AND COMPLEXES OF ESSENTIAL AMINO ACIDS IN TUMOR-BEARING RATS OF OLD AGE

G.V.Zhukova[1]*, A.I.Shikhlyarova[1], L.N.Loginova[2], T.P.Protasova[1]

1. National Medical Research Centre for Oncology of the Ministry of Health of Russia, 63 14 line str., Rostov-on-Don 344037, Russian Federation
2. Samara State Medical University, 89 Chapaevskaya str., Samara 443099, Russian Federation

ABSTRACT

Purpose of the study. Amplifying the effects of low-intensity modulated electromagnetic radiation (EMR) of the extremely high frequency range (EHF) on the tumor and adaptational status of old tumor-bearing rats with the help of complexes of essential amino acids enriched with vitamins and microelements (AaVM).

Materials and methods. In experiments on 50 old white outbred male rats with transplantable sarcoma 45, the effects of EMR EHF and the combined effect of EMR EHF and AaVM were studied. For exposure to EHF EHF, the "Yav-1" medical device was used. The frequency modulation with 42.2 GHz as a center frequency was applayed. The duration of treatmaent was 4 weeks. We studied the dynamics of tumor size, adaptive status (according to hematological indicators of the character and tension of the general nonspecific adaptational reactions of the body), structural and functional changes in the tumor tissue, thymus and liver. In the statistical analysis of the results, student's t test and Wilcoxon-Mann-Whitney test were used.

Results. The anti-stress effect of EMR EHF on the organism of old tumor-bearing rats, accompanied by temporary inhibition of sarcoma 45 growth was shown. The combination of EMR EHF exsposure and AaVM (as an additional metabolic factor) leaded to a persistent pronounced antitumor effect in 60% of animals. Inhibition of tumor growth in 4 times or more, as well as individual cases of its partial regression were observed. At the same time, a higher adaptational status including more numerous signs of activation of the thymus and liver than in the cases of using only EHF EMR were noted.

Conclusion. The results indicate the promise of a combination of activation electromagnetic therapy and application of complexes of essential amino acids enriched with vitamins and microelements in the development of effective methods of accompanying and supportive treatment of cancer patients.

Keywords:
accompanying and supportive treatment, antitumor effect, adaptational status, electromagnetic radiation of an extremely high frequency range, essential amino acids, activation electromagnetic therapy.

For correspondence:
Galina V. Zhukova – Dr. Sci. (Biol.), senior researcher at the testing laboratory center National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: galya_57@mail.ru
ORCID: https://orcid.org/0000-0001-8832-8219
SPIN: 1887-7415, AuthorID: 564827
Researcher ID: Y-4243-2016
Scopus Author ID: 7005456284

Information about funding: the work was supported by the National Medical Research Centre for Oncology of the Ministry of Health of Russia.
Conflict of interest: authors report no conflict of interest.

For citation:
Zhukova G.V., Shikhlyarova A.I., Loginova L.N., Protasova T.P. The effects of combined action of low-intensity electromagnetic radiation of the millimeter range and complexes of essential amino acids in tumor-bearing rats of old age. South Russian Journal of Cancer. 2020; 1(4): 38-46. https://doi.org/10.37748/2687-0533-2020-1-4-5

Received 05.06.2020, Review (1) 26.08.2020, Review (2) 22.10.2020, Accepted 01.12.2020

Южно-российский онкологический журнал 2020, т.3, №4, с. 38-46
https://doi.org/10.37748/2687-0533-2020-1-4-5
ОРИГИНАЛЬНАЯ СТАТЬЯ

ЭФФЕКТЫ КОМБИНИРОВАННОГО ВОЗДЕЙСТВИЯ НИЗКОИНТЕНСИВНОГО ЭЛЕКТРОМАГНИТНОГО ИЗЛУЧЕНИЯ МИЛЛИМЕТРОВОГО ДИАПАЗОНА И КОМПЛЕКСОВ НЕЗАМЕНИМЫХ АМИНОКИСЛОТ У КРЫС-ОПУХОЛЕНОСИТЕЛЕЙ СТАРЧЕСКОГО ВОЗРАСТА

Г.В.Жукова[1]*, А.И.Шихлярова[1], Л.Н.Логинова[2], Т.П.Протасова[1]

1. ФГБУ «НМИЦ онкологии» Минздрава России,
   344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
2. ФГБОУ ВО «Самарский государственный медицинский университет» Министерства здравоохранения Российской Федерации,
   443099, Российская Федерация, г. Самара, ул. Чапаевская, д. 89

РЕЗЮМЕ

Цель исследования. Усиление эффектов низкоинтенсивного модулированного электромагнитного излучения (ЭМИ) миллиметрового или крайне высокочастотного (КВЧ) диапазона на опухоль и адаптационный статус крыс-опухоленосителей старческого возраста с помощью комплексов незаменимых аминокислот, обогащенных витаминами и микроэлементами (АкВМ).

Материалы и методы. В экспериментах на 50 белых беспородных крысах-самцах старческого возраста с перевивной саркомой 45 изучали эффекты ЭМИ КВЧ и комбинированного воздействия ЭМИ КВЧ и АкВМ. Для воздействия ЭМИ КВЧ использовали медицинский аппарат «Явь-1». Применяли частотную модуляцию с центральной частотой 42,2 ГГц. Продолжительность воздействий — 4 недели. Изучали динамику размеров опухоли, адаптационного статуса (по гематологическим показателям характера и напряженности общих неспецифических адаптационных реакций организма), структурно-функциональные изменения в ткани опухоли, тимусе и печени. При статистическом анализе результатов использовали t-критерий Стьюдента и критерий Вилкоксона-Манна-Уитни.

Результаты. Было показано антистрессорное влияние ЭМИ КВЧ на организм старых крыс-опухоленосителей, сопровождавшееся временным торможением роста саркомы 45. При комбинированном использовании ЭМИ КВЧ и АкВМ (как дополнительного метаболического фактора) стойкий выраженный противоопухолевый эффект был получен у 60% животных. Наблюдалось торможение роста опухоли в 4 раза и более, а также отдельные случаи её частичной регрессии. При этом был отмечен более высокий адаптационный статус, в том числе, более многочисленные признаки активизации тимуса и печени, чем в случае применения только ЭМИ КВЧ.

Заключение. Полученные результаты указывают на перспективность сочетания активационной электромагнитотерапии и применения комплексов незаменимых аминокислот, обогащенных витаминами и микроэлементами, при разработке эффективных методов сопроводительного и поддерживающего лечения онкологических больных.

Ключевые слова:
сопроводительное лечение, противоопухолевый эффект, адаптационный статус, электромагнитное излучение крайне высокочастотного диапазона, незаменимые аминокислоты, активационная электромагнитотерапия.

Для корреспонденции:
Жукова Галина Витальевна – д.б.н., старший научный сотрудник испытательного лабораторного центра ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: galya_57@mail.ru
ORCID: https://orcid.org/0000-0001-8832-8219
SPIN: 1887-7415, AuthorID: 564827
Researcher ID: Y-4243-2016
Scopus Author ID: 7005456284

Информация о финансировании: работа проведена при поддержке ФГБУ «НМИЦ онкологии» Минздрава России.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Жукова Г.В., Шихлярова А.И., Логинова Л.Н., Протасова Т.П. Эффекты комбинированного воздействия низкоинтенсивного электромагнитного излучения миллиметрового диапазона и комплексов незаменимых аминокислот у крыс-опухоленосителей старческого возраста. Южно-российский онкологический журнал. 2020; 1(4): 38-46. https://doi.org/10.37748/2687-0533-2020-1-4-5

Получено 05.06.2020, Рецензия (1) 26.08.2020, Рецензия (2) 22.10.2020, Принята к печати 01.12.2020

INTRODUCTION

Systemic disorders caused by the malignant process and aggressive methods of antitumor treatment determine the relevance of the issue of developing effective technologies for supporting and accompanying therapy of cancer patients [1]. As a means of such therapy, chemical and physical factors are used, including low-intensity electromagnetic radiation (EMR) of the millimeter (or extremely high-frequency, EHF) range [2–4] and various nutraceuticals [5, 6].

Previously, in vivo experiments showed antitumor effects obtained using weak EMR of various ranges used in activation therapy modes, even without the use of special antitumor agents [7–9]. Such effects affected the regulatory centers of the neuroendocrine and immune systems, activating processes that lead to an increase in non-specific antitumor resistance of the body. It is known that the effectiveness of regulatory actions largely depends on the metabolic resources of cells, their availability of biologically active substances that play an important role in maintaining tissue homeostasis and regulating systemic processes [7, 10]. It is advisable to use preparations containing complexes of essential amino acids, vitamins and trace elements as factors of biochemical support of activation electromagnetotherapy. These drugs are designed to compensate for protein, mineral and vitamin deficiencies that are characteristic of the body in conditions of malignant growth, especially in elderly and senile patients [11, 12]. In addition, it has been shown that the use of complex preparations of essential amino acids in antitumor treatment, as well as some enzymes involved in their metabolism, contributes to inhibition of growth and reduction of tumor metastasis, potentiates the action of antitumor monoclonal antibodies, improves the condition and increases the life expectancy of cancer patients and laboratory tumor-bearing animals [13–15].

The purpose of the study: enhancing the effects of low-intensity modulated EMR EHF on the tumor and adaptational status of senile tumor-bearing rats using complexes of essential amino acids enriched with vitamins and trace elements.

MATERIALS AND METHODS

The study was performed on 60 white outbred male rats of senile age (28–30 weeks) weighing 370–410 g with a 45-graft sarcoma (C-45) in compliance with international rules for the humane treatment of laboratory animals.

The tumor was transplanted according to the standard procedure [16]. After reaching the C-45 size of 0.8–1.2 cm^3, at which its spontaneous regression is considered unlikely, the treatment began. Low-intensity (10 $mW/cm^2/s$) modulated EMR EHF, complexes of essential amino acids, vitamins and trace elements (AaVM), and combined impact of EMR EHF and AaVM were used as active factors. Frequency modulation of EMR EHF was performed in the range 42.1–42.3 GHz using a sequence of signals of low biologically significant frequencies selected based on previous experiments or close to the frequencies of Schumann resonances [8]. Frequency modulation (as opposed to amplitude modulation) in electronic shifting of the radiation frequency in the range of 42.1–42.3 GHz at a rate determined by the modulation frequency. A medical device for EHF therapy "Yav-1" was used for exposure to modulated EMR EHF, as well as a modulator designed at the Rostov research Institute of radio communications based on a special-form signal generator G6–37. In accordance with the recommendations for EHF therapy [4], the impact was performed on the occipital region of the animal's head, which was in a plexiglass chamber, through an opening covered with a radio-permeable membrane (Fig. 1). Exposure varied in the range of 15–30 min according to activation therapy algorithms [8, 9]. The modulation algorithm and other parameters of the impact were described in more detail earlier [8].

As AaVM, polyvalent biologically active additives from the company "Kordea" were used, which contained native l-amino acids in free form, as well as basic vitamins and a number of trace elements, including selenium. AaVM diluted with boiled water was administered peros through feeding tube at a dose of 260 mg/kg after exposure to EMR EHF. Three different AaVMs were used in the experiments: "L–Lysine-Active Aviton", which contained 18 amino acids with a predominance of L-lysine

(37%); "Vita Active Amiton", which included 19 amino acids with the largest amount of glutamic acid, leucine, glycine, lysine and serine (44%); "Zinc Iron Copper Aviton", which included 18 amino acids, as well as zinc, iron and copper in a dose exceeding the daily requirement of the body for these metals under normal conditions. Each of the listed AaVM also included vitamins and trace elements ("F. Hoffman-LaRoche", Switzerland). On one day, the animals received only one complex out of three. At the same time,"L–Lysine-Active Aviton "was used 2 times more often than the other two AaVMs due to the known information about the pronounced immunomodulatory and antiviral effects of L-lysine and the antitumor effects of L-lysine-α-oxidase [15, 17].

Combined impact was performed 4–6 times a week for a total duration of 4.5 weeks. The study evaluated the weekly weight of each animal, the size of the tumors (calculating the volume by the formula of Shrek for ellipsoids) and hematological parameters, including differential blood count leucocytes (on 200 cells), leucocyte count and haemoglobin level in peripheral blood. Hematological parameters were used to determine the character and tension of General non-specific adaptational reactions of the body (AR) [7, 10, 18].

At the end of the experiment, animals were over-anesthetized and fragments of tumor tissue, as well as internal organs, thymus and liver were taken for histological and histochemical study. For review purposes, hematoxylin-eosin staining was used, Brachet staining was used to identify nucleoproteins, and complex staining was used to study structures including carbohydrate — containing biopolymers using the A. L. Shabadash method with Azur I and an acidic solution of basic brown using the Shubich-Lopunova-Mogilnaya method. At the same time, morphometric study of changes in the thymus was performed with the determination of indicators that reflected the activity of lymphoproliferative processes — the width of the cortical and medullary substance in the thymus lobules, as well as the stromal-parenchymal coefficient. Also the signs of interaction between tissue basophils and thymocytes were evaluated.

Due to the old age of animals, which caused age-related thymus involution and the development of degenerative changes in the thymus and liver, which can "mask" microstructural shifts associated with the tumor process when considered separately, we find it appropriate to use generalized characteristics of the state of the studied organs based on a semi-quantitative assessment of signs that reflected various structural and functional changes. At the same time, a number of indicators that characterized both positive and negative structural and functional changes in both organs studied were ranked according to their significance in the range from - 1 to +1.These indicators were evaluated in 10 fields of view (with magnification of 10x10, 10x40 or 10x90 – depending on the feature). In addition, if the ratio of the width of the cortical and cerebral layer of the thymus, as well as the size of the lobules, corresponded to the most favorable anti-stress AR or increased activation, the maximum positive score of "+1"was added. The picture typical for AR training was evaluated with a lower score — "+0.5". In the case of severe hypoplasia of lymphoid tissue and other signs that corresponded to AR stress, the maximum negative score was assigned — "-1". The simultaneous presence of signs characteristic of the stress response and anti-stress reactions in the organ micro imaging, indicating the development of tensioned anti-stress AR of low reactivity levels, was evaluated with a zero score. In addition, positive half points were added in the following cases:

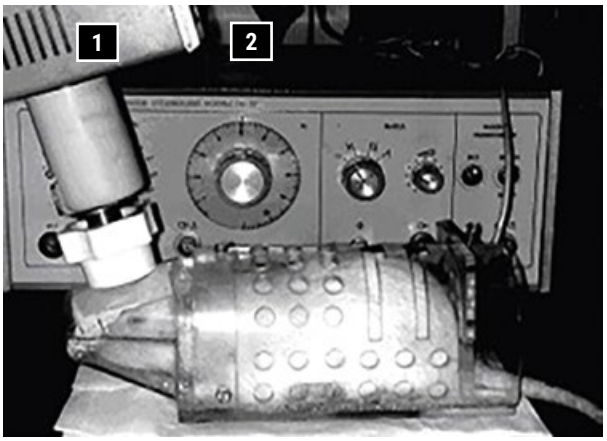


Fig. 1. Experimental setup for the impact of modulated EMR EHF on the occipital region of the head of a rat in a plexiglass chamber. Note: 1 – medical device for EHF therapy "Yav-1", 2 – frequency modulator (based on the G6-37 generator).

— in the presence of signs indicating the activation of interactions between thymocytes and tissue basophils as local regulators of tissue homeostasis, affecting the processes of maturation and differentiation of thymocytes;

— if there are signs of activation of hormone-producing epithelial-reticular complexes in the thymus (non-keratinized Gassal bodies).

In the analysis of micro imaging the liver of the experimental animals were evaluated as parenchyma and hemocirculation channel of the body. Positive points were assigned in cases of moderate fullness of the central and interlobular veins and preservation of the normal structure of the beams- "+1", uniform distribution and the absence of a pronounced decrease in the content of nucleoproteins and glycogen in hepatocytes — "+1", as well as in the presence of binuclear hepatocytes — "+0.5". Negative evaluations were carried out in cases of signs of hemostasis perivascular edema and disruption of the structure beams — –1, and in the presence of marked perivascular edema without disrupting the structure beams — "-0.5", and also in focal vacuolization of cytoplasm and lysis of chromatin in hepatocyte — "-0.5".

Statistical analysis of the experiment results was performed using the student's t-test and the Wilcoxon-Mann-Whitney test.

STUDY RESULTS AND THEIR DISCUSSION

Table 1 provides information on the dynamics of the size of sarcoma 45 within 4 weeks from the beginning of exposure. 2 weeks after the start of the treatment, tumor growth was inhibited in the group with EMR EHF and in the group with combined impact by 1.8 and 3.2 times, respectively. In the case of EMR EHF, the effect was unstable, whereas with combined impact, a marked decrease in the volume of sarcoma 45 compared to the control value was maintained until the end of the experiment. No anti-tumor effect of AaVM was observed (table 1). Therefore, the results obtained in this group were not considered in the course of further analysis.

An almost two-fold difference in the average tumor volume in the group with combined impact from the values of the indicator in the other groups after 4 weeks of treatment was obtained due to a significant antitumor effect in 60% of rats (12 out of 20). In these animals, tumor growth was inhibited by 4 times or more compared to the control group and male rats exposed to EMR EHF, and in some cases, partial regression of the tumor was noted. In the remaining 40% of the animals in the study group, the volume of the tumor at the end of the experiment did not differ statistically from the indicator in the other two groups (Fig. 2A).The impacts of the tumor tissue during inhibition of sarcoma 45 growth was characterized by a decrease in the density of growing malignated cells, a clear lymphocytic shaft, and a large amount of fibrin (Fig. 2B). In these cases, the proportion of viable tumor cells could be reduced to 1/8 of the field of view (at 10x40 magnification) ($p<0.01$). With partial regression of sarcoma 45, areas of tumor tissue replacement with connective tissue were observed. Thus, a pronounced antitumor effect was observed only with the combined action of EMR EHF and AaVM. In the future, we considered it appropriate to conduct a comparative analysis of the studied indicators in the order that only cases of effective influence of EMR EHF and AaVM (subgroup 1) should be taken into account in the group with combined exposure.

Table 2 provides information about the adaptive status of tumor-bearing rats during the entire experiment. As can be seen from the table, the effect of EMR EHF and combined impact on the growth of sarcoma 45 fully corresponded to the features of the adaptational status of animals in the studied groups. The adaptational status of rats that managed to achieve significant growth inhibition or even partial regression of sarcoma 45 was very different from the adaptational status of animals of the other two groups by the dominance of antistress AR without pronounced signs of tension. At the same time, in the case of EMR EHF, there was also a slight improvement in the AR characteristics compared to those observed in the control group. This was reflected in a more than twofold reduction in cases of AR stress (table 2).

Analysis of changes in the thymus and liver micro imagings allowed us to supplement the idea of the influence of the studied effects on

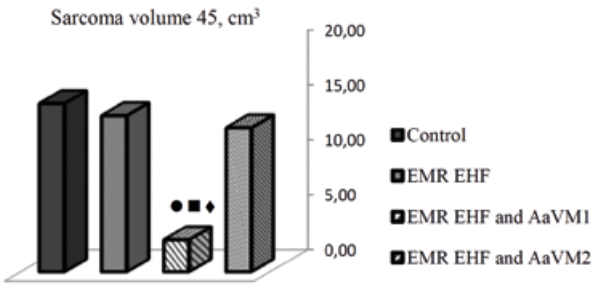
the adaptational status of senile tumor-bearing animals. Figure 3A shows the results of a score assessment of structural and functional changes in these organs, characteristic of animals of different groups. In the male rats of the control group, a clear predominance of negative changes was observed, indicating a decrease in functional activity and pronounced structural and functional disorders in the studied organs. This is reflected in the negative values of the corresponding scores (Fig. 3A). The thymus of these animals was dominated by signs of atrophy, a sharp predominance of stroma over parenchyma, cortical matter of lobules was weakly expressed, individual completely keratinized epithelial-reticular complexes were noted, and non-granulated forms of tissue basophils prevailed. The liver was characterized by a picture of hemostasis with perivascular edema and a violation of the structure of the beams, with a sharp decrease in the content of nucleoproteins and glycogen in hepatocytes and the practical absence of binuclear hepatocytes.

In contrast to the one observed in the control group, the results of morphometry and visual examination of the thymus micro imaging of animals of the two main groups even indicated some activation of lymphoproliferative processes in the majority of rats exposed to weak modulated EMR EHF (Fig. 3A).

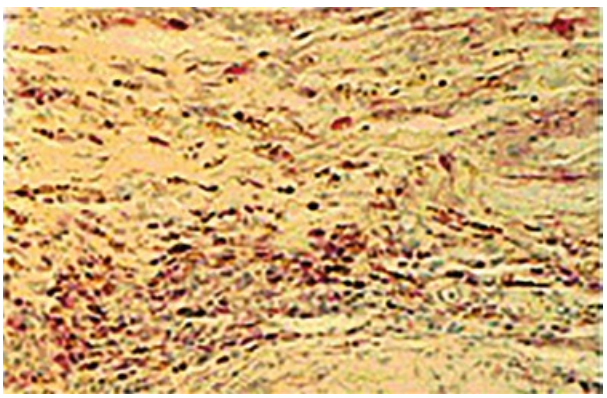
Table 1. Dynamics of sarcoma volume 45 (cm^3) under the studied impacts in white outbred male rats of senile age for 4 weeks

Stage of the study	Control *n*=15	EMR EHF *n*=15	AaVM *n*=10	EMR EHF + AaVM *n*=20
initially	1.41±0.25	1.14±0.26	1.40±0.32	1.30±0.25
week 1	2.66±0.64	2.54±0.40	2.70±0.54	1.63±0.19
week 2	6.30±1.04	3.49±0.81 ●	5.32±0.98 ■	1.98±0.24 ●▫
week 3	10.47±2.34	7.93±1.12	9.90±1.00	4.43±0.37 ●■▫
week 4	12.51±3.78	11.67±1.80	12.25±1.32	6.50±0.75 ●■▫

Note: EMR EHF – low-intensity modulated electromagnetic radiation of extremely high frequency range; AaVM-complexes of amino acids, vitamins and trace elements. Differs (p<0.05-0.01) from the control group – ●, rom EMR EHF – ■, from AaVM group – ▫. T-criteria.



A. Sarcoma volume 45 in the study groups at the end of the experiment



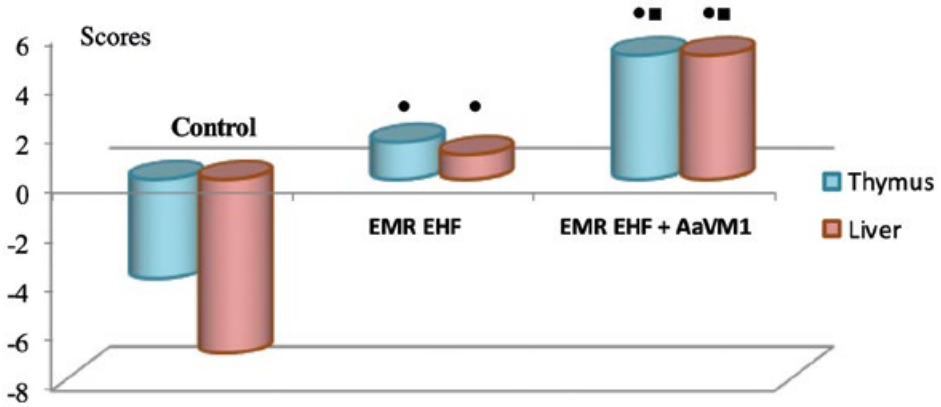
B. Changes in sarcoma tissue 45 under the influence of combined impact

Fig. 2. Antitumor effectiveness of the studied impacts.
A. sarcoma Size 45 in the studied groups of old male rats at the end of the experiment (4.5 weeks from the beginning of the effects). Notation – see table.1
Note: EMR EHF + AaVM1 and EMR EHF + AaVM2 are subgroups of animals with different severity of the combined effect of EMR EHF and AaVM.
Differs from the control group: ● – p<0.01; from the EMR EHF group: ■ – p<0.01; from the EMR EHF + AaVM2 subgroup: ♦ – p<0.05. T-test.
B. Changes in sarcoma tissue 45 under the influence of combined impact. Pronounced inhibition of tumor growth (EMR EHF + AaVM1). Reduction in the density of malignant cells. Lymphocytic shaft. Brachet. 10x6.3.

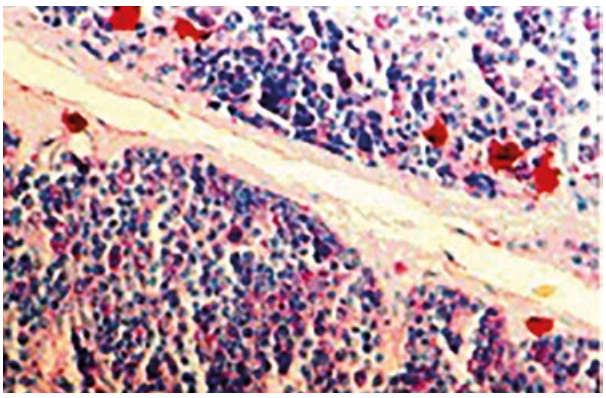
Table 2. Effects of the studied impacts on the tumor and the adaptational status of old male rats with transplanted sarcoma 45

Indicator	Control *n*=15	EMR EHF *n*=15	EMR EHF + AaVM1 *n*=12
Tumor volume, cm^3	15.3±2.6	14.2±1.8	2.9±1.3 ●■
AR stress	47	20 ●	0 ●■
Tensioned anti-stress AR	53	80	30 ■
Anti-stress AR without signs of tension	0	0	70 ●■

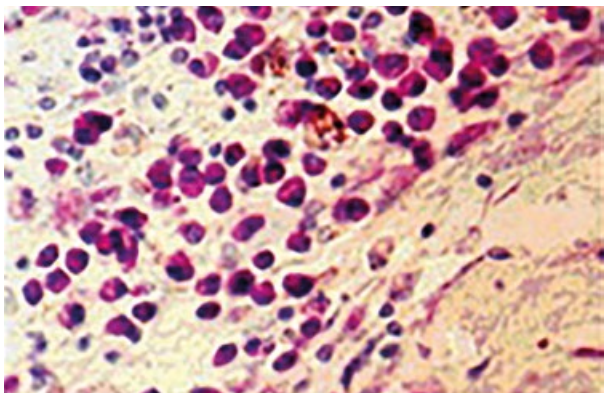
Note: AR-adaptational reactions. Differs from the control group: ● – p<0.05–0.01; from the EMR EHF group: ■ – p<0.05–0.01. T-criteria.



A. Indicators of the thymus and liver state



B. Signs of activation of interaction between thymocytes and tissue basophils.



C. Abundant infiltration of sarcoma tissue by 45 plasmocytes at pronounced inhibition of tumor growth.

Fig. 3. Changes in internal organs and tumors under effective combined action EMR EHF + AaVM1.

A. Relative (point) indicators of the morpho-functional state of the thymus and liver under the action of EMR EHF and effective combined action – EMR EHF + AaVM1. Differs from the control group: ● – p<0.05–0.01; differs from the EMR EHF group: ■ – p<0.05. Wilcoxon-Mann-Whitney Criterion.

B. An Increase in the number of degranulated tissue basophils in the immediate vicinity of thymocytes of the subcapsular zone of the cortical substance of the thymus lobes under effective combined action. Brachet. 10x40.

C. Pronounced inhibition of sarcoma 45 growth under the influence of combined impact (EMR EHF + AaVM1). Abundant infiltration of tumor tissue by plasma cells.

The severity of signs of lymphoproliferative activity was generally similar in these groups. At the same time, with effective combined use of EMR EHF + AaVM in the subcapsular zone of the thymus lobes, a more significant number of degranulating tissue basophils was observed in the immediate vicinity of thymocytes, which determined higher scores in this group (Fig. 3B). The described difference could indicate more active intercellular interactions in the organ and, as a possible consequence, a higher functional potential of T-lymphocytes under combined impact. Similarly, in the case of effective use of EMR EHF + AaVM, more pronounced signs of liver normalization were noted than with the action of EMR EHF alone (Fig. 3A). This applied both to the morphological characteristics of hemodynamics in the organ, and to the signs reflecting the level and uniformity of the distribution of nucleoproteins and glycogen in hepatocytes, as well as the number of binuclear hepatocytes in the hepatic parenchyma.

Inevitably, the question arises about the mechanisms of antitumor effect of combined impact. As a rule, when using non-specific factors that do not have a direct damaging effect on the tumor, we can talk about activation of immune processes that lead to inhibition of tumor growth or even elimination of tumor tissue [19]. In the case of inhibition of sarcoma 45 growth under the influence of combined impact, such a feature of microstructural changes in the tumor tissue as its pronounced infiltration by plasmocytes was noted (Fig. 3C). Taking into account the literature data on the fundamental possibility of changing the activity of B-lymphocytes under the influence of T-lymphocytes [20], it can be assumed that the effectiveness of combined action of EMR EHF and AaVM is associated with increased intercellular interactions in the thymus, leading to activation of T-lymphocytes, which in turn contribute to the mobilization of plasmocytes involved in the effector mechanisms of tumor cell damage. At the same time, we cannot exclude some contribution to the effects of the combined impact of direct damage of tumor tissue, due to the influence of L-lysine-α-oxidase (activated by the receipt of L-lysine), which, in particular, is associated with release of cytotoxic hydrogen peroxide effect on β-adrenergic receptors and proteins responsible for the adhesive properties of cells [15].

CONCLUSION

In contrast to the results obtained in some other experimental models [4, 8, 19], in old white outbred male rats with sarcoma 45 under the influence of low-intensity modulated EMR EHF presented in the activation therapy mode, only a temporary effect was observed — unstable inhibition of tumor growth two weeks after the start of exposure. Antistress changes caused by EMR EHF were not sufficient to activate effective antitumor mechanisms and achieve stable inhibition of tumor growth. A pronounced antitumor effect in more than half of the animals was obtained by combined use of activation electromagnetotherapy and AaVM as an additional metabolic factor. In these animals, there was a 4-fold or more inhibition of tumor growth, as well as some cases of partial regression. At the same time, a higher adaptational status was noted, including more numerous signs of activation of the thymus and liver, than in the case of using only EMR EHF. The results obtained indicate that the combination of activation electromagnetotherapy and the use of complexes of essential amino acids enriched with vitamins and trace elements is promising for the development of effective methods of accompanying treatment of elderly cancer patients.

Authors contribution:
Zhukova G.V. – concept, research design, conducting research, analyzing results, text writing.
Shikhlyarova A.I. – participation in the analysing of the results, scientific editing.
Loginova L.N. – participation in research and analysing of the results.
Protasova T.P. – participation in research, technical editing.

References

1. Recommendations for maintenance and supportive therapy RUSSCO. (In Russian). Available at: https://rosoncoweb.ru/standarts/suptherapy/2019/

2. Chissov V.I., Kabisov R.K., Pletnev S.D., Betsky O.V., Faykin V.V. A method of treating cancer patients with electromagnetic radiation of the mm range. Invention patent RU 98 102 380 A, 27.01.2000. Application: 98102380/14 from 1998.01.23. (In Russian).

3. Kolmatsui NB, Levitskii EF, Golosova OE, Pyzhova IB. The application of UHF therapy for the prevention of complications of specific antiblastoma therapy in the patients presenting with III-IV stage lung cancer. Questions of balneology, physiotherapy and therapeutic physical culture. 2013;90(2):4–7. (In Russian).

4. Betskii OV, Lebedeva NN. Biological effects of low intensity millimeter waves (Review). Biomedicinskaya radioelektronika – Biomedicine radioengineering. 2015;(1):31–47. (In Russian).

5. Heyland DK, Weijs PJM, Coss-Bu JA, Taylor B, Kristof AS, O'Keefe GE, et al. Protein Delivery in the Intensive Care Unit: Optimal or Suboptimal? Nutr Clin Pract. 2017 Apr;32(1_suppl):58S-71S. https://doi.org/10.1177/0884533617691245

6. Kostyuchenko LN, Kostyuchenko MV, Kuzmina TN, Lychkova AE. Strategy of accompanying nutritional and metabolic therapy of patients with colorectal cancer. Russian Medical Journal. 2019;(6):37-44. (In Russian).

7. Garkavi LK, Kvakina EB, Shikhliarova AI, Kuz'menko TS, Barsukova LP, Mar'ianovskaia GI, et al. Magnetic fields, adaptation reaction and self-organization of live systems. Biofizika. 1996 Aug;41(4):898–905.

8. Zhukova GV, Shikhlyarova AI, Barteneva TA, Barsukova LP, Kostrovitskiy YV, et al. Some strategies of activation therapy using radiations of microwave ranges in experiments on tumor-bearing animals. Cardiometry. 2015 Nov 27;(7):47–57. https://doi.org/10.12710/cardiometry.2015.7.4757

9. Zhukova GV, Shikhliarova AI, Soldatov AV, Barteneva TA, Goroshinskaya IA, Petrosian VI, et al. Some approaches to the activation of antitumor resistance mechanisms and functional analogs in the categories of synergetics. BIOPHYSICS. 2016 Mar 1;61(2):303–315. https://doi.org/10.1134/S0006350916020251

10. Kit Kit OI, Shikhlyarova AI, Zhukova GV, Maryanovskaya GY, Barsukova LP, et al. Activation therapy: theoretical and applied aspects. Cardiometry. 2015 Nov 27;(7):22–29. https://doi.org/10.12710/cardiometry.2015.7.2229

11. Vettore, L, Westbrook RL, Tennant DA. New aspects of amino acid metabolism in cancer. British Journal of Cancer. 2020 Jan;122(2):150–156. https://doi.org/10.1038/s41416-019-0620-5

12. Lieu, EL, Nguyen T, Rhyne S, Kim J. Amino acids in cancer. Exp Mol Med. 2020;52(1):15–30. https://doi.org/10.1038/s12276-020-0375-3

13. Al-Mahtab M, Akbar SMF, Khan MSI, Rahman S. Increased survival of patients with end-stage hepatocellular carcinoma due to intake of ONCOXIN®, a dietary supplement. Indian J Cancer. 2015 Sep;52(3):443–446. https://doi.org/10.4103/0019-509X.176699

14. Dzhugashvili M., Pokrovsky V. S., Snegovoy A. V. Novel approaches for the correction of micronutrient deficiency in patients with malignant tumors. Malignant Tumours 2016;2:55–65. https://doi.org/10.18027/2224-5057-2016-2-55-65

15. Pokrovsky VS, Lukashev EV, Chernov NN, Treshchalina EM. Experimental study of the effectiveness of L-lysine-α-oxidase Trichoderma CF. AureovirideRifai on human tumor xenografts models in bestimus mice and evaluation of synergy with cisplatin or topoisomerase inhibitors. Journal of Oncology Issues. 2017;63(3):497–505. (In Russian).

16. Konoplev VP. Perepisnye of the tumor. In: Models and methods of experimental Oncology. M: Medgiz., 1960, 144-162 p. (In Russian).

17. Zhang C, He Y, Shen Y. L-Lysine protects against sepsis-induced chronic lung injury in male albino rats. Biomed Pharmacother. 2019 Sep;117:109043. https://doi.org/10.1016/j.biopha.2019.109043

18. Selye H. Thymus and adrenals in the response of the organisms to injuries and intoxication. Brit. J. Exp. Path. 1936;(17): 234–248.

19. Zhukova GV, Shikhlyarova AI, Barteneva TA, Bragina MI, Gudtskova TN, Petrosyan VM, et al. The pattern of the immune processes during activation therapy with the use of microwave electromagnetic radiation. Cardiometry. 2017;(11):35–45. https://doi.org/10.12710/cardiometry.2017.11.3545

20. Bishop GA. B cell-T cell interaction: antigen bridge to antigen presentation. Nat Rev Immunol. 2016;16(8):467. https://doi.org/10.1038/nri.2016.82

Information about author:

Galina V. Zhukova* – Dr. Sci. (Biol.), senior researcher at the testing laboratory center National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-8832-8219, SPIN: 1887-7415, AuthorID: 564827, Researcher ID: Y-4243-2016, Scopus Author ID: 7005456284

Alla I. Shikhlyarova – Dr. Sci. (Biol.), professor, senior researcher at the laboratory for the study of malignant tumors pathogenesis National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-2943-7655, SPIN: 6271-0717, AuthorID: 482103, Scopus Author ID: 6507723229

Lyudmila N. Loginova – assistant of the department of physiology with the course of life safety and disaster medicine Samara State Medical University. ORCID: https://orcid.org/0000-0002-6309-4011, SPIN: 6288-8842, AuthorID: 682438

Tatyana P. Protasova – Cand. Sci. (Biol.), researcher at the testing laboratory center National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0001-6364-1794, SPIN: 4542-3588, AuthorID: 760427

South Russian Journal of Cancer 2020, v.1, №4, p. 47-53
https://doi.org/10.37748/2687-0533-2020-1-4-6

CLINICAL CASE REPORTS

RARE CLINICAL OBSERVATION OF PRIMARY TRACHEAL CANCER

N.A.Chertova*, Yu.V.Ulianova, M.A.Engibaryan, V.L.Volkova, I.V.Aedinova

National Medical Research Centre for Oncology of the Ministry of Health of Russia,
63 14 line str., Rostov-on-Don 344037, Russian Federation

ABSTRACT

The article describes a clinical example of primary adenoid cystic carcinoma of the trachea, characteristics of its clinical course, diagnosis and the choice of treatment. We noted the non-specificity of complaints and clinical manifestations of tracheal cancer, the period between its beginning and diagnosis, the development of severe complications in the respiratory and cardiovascular systems due to the long asymptomatic course of the disease, the need for an integrated approach by various specialists in the treatment of such a complex category of patients. An approach to the surgical treatment of tracheal cancer is described taking into account its extension to the subglottic larynx, which required laryngeal extirpation. We showed the possibility of radical treatment of patients with tracheal cancer in large medical centers with such specialists as head and neck cancer surgeons, thoracic surgeons, endoscopists, anesthesiologists and resuscitators, therapists, radiologists, and chemotherapists.

Keywords:
primary tracheal cancer, adenoid cystic carcinoma, laryngeal extirpation, malignant tracheal tumors, treatment of tracheal cancer, secondary tracheal tumors.

For correspondence:
Natalia A. Chertova – Cand. Sci. (Med.), surgeon of the head and neck tumor Department National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation.
E-mail: chertova1510@mail.ru
SPIN: 7051-4574, AuthorID: 473541

Information about funding: no funding of this work has been held.
Conflict of interest: authors report no conflict of interest.

For citation:
Chertova N.A., Ulianova Yu.V., Engibaryan M.A., Volkova V.L., Aedinova I.V. Rare clinical observation of primary tracheal cancer. South Russian Journal of Cancer. 2020; 1(4): 47-53. https://doi.org/10.37748/2687-0533-2020-1-4-6

Received 05.06.2020, Review (1) 07.07.2020, Review (2) 13.10.2020, Accepted 01.12.2020

Южно-российский онкологический журнал 2020, т.4, №2, с. 47-53
https://doi.org/10.37748/2687-0533-2020-1-4-6
КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

РЕДКОЕ КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ ПЕРВИЧНОГО РАКА ТРАХЕИ

Н.А.Чертова*, Ю.В.Ульянова, М.А.Енгибарян, В.Л.Волкова, И.В.Аединова

ФГБУ «НМИЦ онкологии» Минздрава России,
344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63

РЕЗЮМЕ

Описан клинический пример первичного аденокистозного рака трахеи, особенности клинического течения, диагностики, выбор метода лечения. Отмечена неспецифичность жалоб и клинических проявлений рака трахеи, длительность заболевания от момента его начала до постановки диагноза, развитие тяжелых осложнений со стороны дыхательной и сердечно-сосудистой системы из-за длительного бессимптомного течения заболевания, необходимость комплексного подхода различных специалистов в лечении такой сложной категории больных. Описан подход к хирургическому лечению трахеи рака, учитывающий распространённость его на подскладковый отдел гортани, что сделало необходимым выполнение экстирпации гортани. Показана возможность радикального лечения больных раком трахеи в крупных медицинских центрах, располагающих наличием специалистов: хирургов отделения опухолей головы и шеи, торакальных хирургов, эндоскопистов. анестезиологов — реаниматологов, терапевтов, радиологов, химиотерапевтов.

Ключевые слова:
первичный рак трахеи, аденокистозный рак, экстирпация гортани, злокачественные опухоли трахеи, лечение рака трахеи, вторичные опухоли трахеи.

Для корреспонденции:
Чертова Наталия Анатольевна – к.м.н., врач-хирург отделения опухолей головы и шеи ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: chertova1510@mail.ru
SPIN: 7051-4574, AuthorID: 473541

Информация о финансировании: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Чертова Н.А., Ульянова Ю.В., Енгибарян М.А., Волкова В.Л., Аединова И.В. Редкое клиническое наблюдение первичного рака трахеи. Южно-российский онкологический журнал. 2020; 1(4): 47-53. https://doi.org/10.37748/2687-0533-2020-1-4-6

Получено 05.06.2020, Рецензия (1) 07.07.2020, Рецензия (2) 13.10.2020, Принята к печати 01.12.2020

RELEVANCE

Tracheal cancer refers to rare tumors that are detected in the late stages of the disease, usually after the development of complications associated with tracheal stenosis, the development of secondary changes in the tumor, and sometimes distant metastases.

Although tracheal cancer has its place in the International classification of diseases (ICD) — C33, in the statistics of cancer care for patients with malignant neoplasms in Russia, tracheal cancer is not considered independently and is included in the trachea, bronchi, and lung group. Tracheal cancer does not have its own classification according to the TNM system. This is due to the fact that primary tracheal tumors are rare and, probably, there is not enough material for statistical processing and creating your own classification. Tracheal cancer accounts for 0.1–0.2% of all malignant tumors. This is approximately 0.2 cases per 100 thousand people, and providing highly qualified assistance to this group of people may be difficult.

Treatment of primary tracheal cancer, even in modern conditions, is a difficult task that requires coordinated collaboration of doctors of several specialties, including surgeons performing operations on various organs, as well as significant material costs.

In most cases, tracheal tumors are secondary. Wood D. E. provides data that in 65% of cases, the cause of tracheal stenosis was tumors of the lung, thyroid gland, esophagus, less often tumors and enlarged mediastinal lymph nodes, tumors of the head and neck organs [1].

The very rare occurrence of tumors in the trachea compared to the larynx and bronchi is explained by the relatively simple structure of the trachea, the lack of complex function and protection from external stimuli. The complexity of the problem is also due to the peculiarity of tumor growth in the trachea, namely, the spread of tumor cells in the submucosal layer over an extended area from its visible borders.

Among primary tracheal tumors, squamous cell carcinoma is more often detected (41%) and adenocystic cancer (28%) [2]. In most cases of detection of squamous cell carcinoma of the trachea at the time of diagnosis, it is locally common, in a third of patients metastases to the lungs and mediastinal lymph nodes are detected, making the possibility of radical treatment doubtful.

Description of a clinical case

We present a clinical case of primary tracheal cancer.

Patient E. born in 1962, 55 years old, went to the NMRCO with complaints of difficulty breathing. He has been ill for the last 2 years, was treated by a therapist for chronic obstructive bronchitis, and received constant treatment without effect. In the last two months, I had difficulty breathing, I went to the clinic of the Rostov cancer research Institute on 09.03.2018.

When examining the larynx, no tumor was found in it, the larynx is fully mobile, the glottis is wide, sufficient for breathing. The patient underwent computed tomography of the chest and neck organs from 09.03.2017 (Fig. 1). a tumor of the upper third of the trachea was detected with a transition to the subclavian larynx 4x4x4.3 cm, narrows the tracheal lumen to 0.6 cm, involves the esophagus, the lower edge of the tumor at the level of the jugular notch."

Fig. 1. Computed tomography of the chest and neck organs in the left side projection.

Ultrasound examination of the neck lymph nodes from 09.03.2017 showed no increase in the cervical lymph nodes.

09.03.2017 the esophagus and its mouth were examined. There were no endoscopic signs of involvement of the esophageal mucosa in the process.

Due to decompensated respiratory failure caused by a tracheal tumor, narrowing its lumen to 0.6 cm, the patient was given a permanent tracheostomy for urgent indications on 21.03.2017.

During the operation, after opening the trachea, a submucosal tumor of a grayish color was found between the 1st and 2nd half-rings of the posterior and left side walls of the upper third of the trachea with a spread to the subclavian larynx. A tumor biopsy was performed. Histoanalysis No. 23644–48/17 of 27.03.2017 "G2 adenocystic cancer of the bronchial glands" was obtained.

Due to the involvement of the subclavian larynx, it was decided to perform a laryngectomy with resection of the upper third of the trachea.

18.04.2017 laryngectomy with resection of the upper third of the trachea was performed.

The walls of the esophagus are not affected. Tracheal rings up to 6 semirings were isolated, the upper third of the trachea was resected between 5 and 6 semirings, after which a tumor was isolated, originating from the upper third of the trachea (1–2 semirings, posterolateral wall on the left), spreading under the left lobe of the thyroid gland, squeezing the esophagus, but not sprouting it (Fig. 3).

Resection of the left lobe of the thyroid gland was performed, in a single block the larynx with half-rings of the upper third of the trachea, the tumor and the left lobe of the thyroid gland were cut off from the pharynx (Fig. 4). A nasoesophageal feeding tube was inserted and a wide tracheostomy was formed. Given the volume of tracheal resection, tracheoesophageal bypass surgery and voice prosthetics were not performed.

Figure 5 shows the type of macropreparation: the removed larynx with the hyoid bone and the upper half-rings of the trachea with a tumor, the drug is opened, in the tracheal lumen, the tumor is 4.5 cm light yellow, in the capsule, performing the tracheal lumen.

Postoperative histoanalysis from 25.04.2017 № 34037–42 / 17 "adenocystic cancer with spread to the larynx" № 34043–4 "resection lines have a normal structure".

The wound was healed by primary tension, all sutures and the nasoesophageal probe were removed. The patient eats through natural pathways, is engaged with a speech therapist, and the esophageal voice is formed.

Fig. 2. Fibrolaryngoscopy of the larynx.

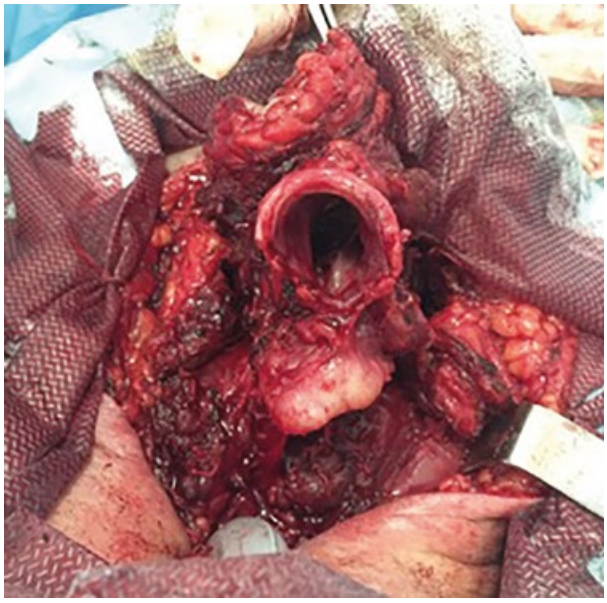


Fig. 3. Stage of separation of the upper third of the trachea with the larynx and the left lobe of the thyroid gland with a tumor.

After the operation, the patient underwent adjuvant radiation therapy on the tumor bed and lymph outflow pathway at a dose of 40g and 5 courses of adjuvant chemotherapy were performed according to the scheme: carboplatin AUC 5–6 (720 mg) intravenously drip on 1 day + etoposide 200 mg intravenously drip on 1–3 days, an interval of 3 weeks.

The patient is observed for one year after surgery without signs of relapse, regional and distant metastasis.

DISCUSSION

Among the Russian reports, the most representative is the material published in 2000. Kharchenko V. P. with co-authors who analyzed the fifty-year experience of monitoring 1062 patients with tracheal tumors, of which 46.2% are primary cancers. The authors proposed a classification of tracheal cancer and principles of diagnosis and treatment, taking into account the degree of tracheal stenosis and the presence of complications of tracheal tumors [3].

Due to the anatomical features of the trachea: the presence of sufficiently rigid cartilaginous semicircles, clinical manifestations of tracheal cancer occur at late stages and are associated with the clinic of tracheal stenosis to varying degrees of its severity.

Clinically, tracheal cancer can occur under the guise of other non-tumor diseases, such as bronchial asthma, chronic obstructive pulmonary disease. The degree of clinical manifestations is determined, for the most part, by the degree of stenosis. Often, patients with tracheal cancer complicated by stenosis of its lumen are admitted to the hospital for the first time in a state of sub — and decompensation of stenosis. This significantly complicates the possibility of diagnosis, sometimes limits the implementation of important examination methods for the patient, in particular, endoscopic. And the presence of complications of stenosis, such as purulent tracheobronchitis, pneumonia worsens the course of the disease, increases the risk of death if urgent and emergency surgical interventions are necessary.

Treatment of primary tracheal tumors can be symptomatic, aimed at restoring tracheal patency and providing breathing to the patient, which, in some cases, will allow performing radical or palliative special treatment. Depending on the level of tracheal lesion and its extent, this may be an urgent tracheostomy or various methods of endoscopic recanalization of the tracheal lumen — stenting, buging, electroexcision of the tumor, partial removal.

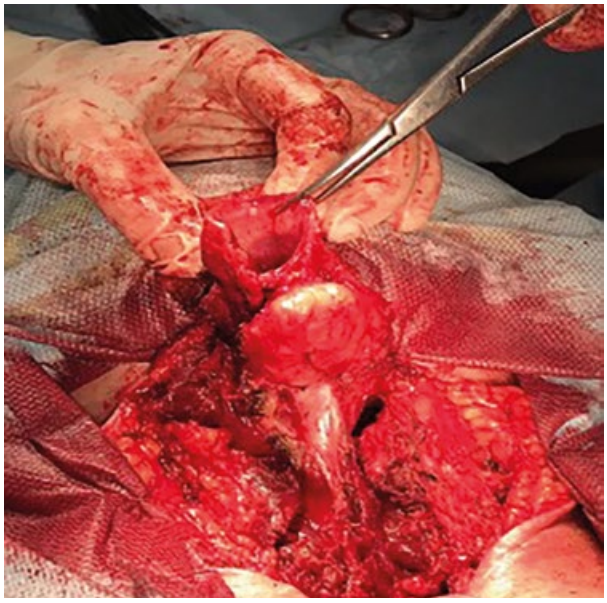


Fig. 4. Larynx with tracheal semicircles with a tumor before cutting off the preparation from the pharynx.

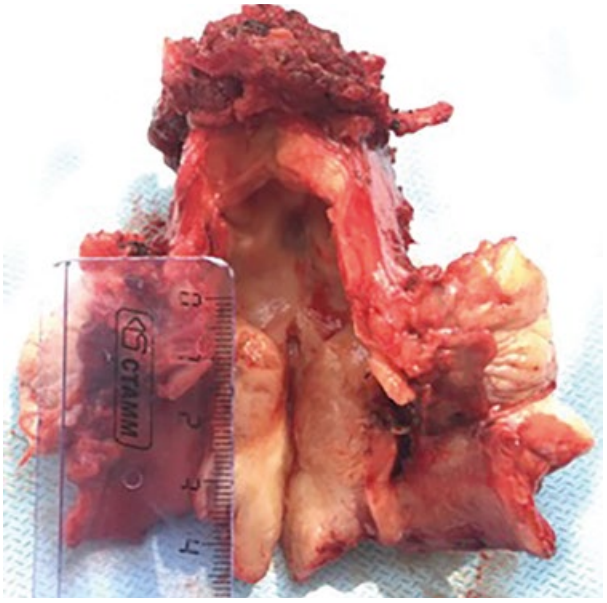


Fig. 5. The view of the removed macropreparation.

A number of authors dealing with tracheal tumors are of the opinion that the costs and efforts made for radical treatment of patients are questionable [4–7]. The trend of recent decades is the expansion of indications and opportunities for palliative care [8, 1, 5]. The possibility of recanalization of the trachea, the use of laser photocoagulation and cryodestruction of the tumor allows, in some cases, to conduct palliative radiation therapy in conditions of compensated respiration. Views on the effectiveness of radiation therapy for adenocystic tracheal cancer are different: the previous opinion about the radioresistance of adenocystic cancer is not shared by a number of authors, who provide data on five-year survival in 80% of patients treated with radiation [9, 10]. These results allowed the authors to recommend radiation treatment by the method of choice, regardless of the prevalence of the process. Proponents of surgical treatment are of the opinion that the only radical method is circular resection of the affected area of the trachea [11, 12].

There are also controversial opinions about the significance of a positive resection line and the presence of lymph node metastases. Some researchers consider them prognostic factors [13, 14, 6], but there is an opinion that the presence of tumor cells at the border of resection or metastases in regional lymph nodes does not significantly affect the long-term results of treatment in cases of adenocystic cancer [15]. When assessing the five-year survival rate of patients with adenocystic tracheal cancer, the absence of resection tumor cells and regional metastases does not significantly improve treatment results [10].

In the radical treatment of tracheal cancer, the best results are described when using a coined method of treatment with radical surgery at the first stage — the 5-year survival rate was 85.1% for adenocystic cancer and 40.9% for squamous cell carcinoma [3].

CONCLUSION

Thus, our own experience and analysis of literature data suggest that the problem of treating primary tracheal cancer is far from complete, cases of successful treatment of tracheal cancer are isolated and possible only in large multi-specialty hospitals with modern diagnostic capabilities, surgeons performing operations on areas adjacent to the trachea — the organs of the head and neck, chest, esophagus, equipped with a powerful intensive care unit, endoscopic service that owns methods of stenting the trachea and esophagus. The approach to planning the treatment of such patients should be comprehensive, involving radiotherapists, surgeons, chemotherapists, resuscitators, therapists, and in each case individual.

Authors contribution:
Chertova N.A. – research concept and design, manuscript writing, material processing, scientific editing.
Ulianova Yu.V. – surgical procedure; collection, analysis and interpretation of data.
Volkova V.L. – surgical assistance, analysis and interpretation of data.
Aedinova I.V. – scientific and technical editing

References

1. Wood DE, Liu Y-H, Vallières E, Karmy-Jones R, Mulligan MS. Airway stenting for malignant and benign tracheobronchial stenosis. Ann Thorac Surg. 2003 Jul;76(1):167–72; discussion 173–174. https://doi.org/10.1016/s0003-4975(03)00033-x

2. Kharchenko VP, Chkhikvadze VD, Gvarishvili AA, Chazova HL, Albekov RZ, Panshin GA, et al. Features of combined and radiation treatment of adenocystic tracheal cancer. Proceedings of the VII all-Russian scientific forum "Radiology 2006"; Moscow, Russia; 2006. 256–257 p. Available at: http://www.oncology.ru/events/2006/04/25/thesis.pdf. (In Russian).

3. Gvarishvili AA. Surgical, combined and radiation treatment of adenocystic tracheal cancer. Dissertation. Moscow, 2012. (In Russian).

4. Licht PB, Friis S, Pettersson G. Tracheal cancer in Denmark: a nationwide study. Eur J Cardiothorac Surg. 2001 Mar;19(3):339–345. https://doi.org/10.1016/s1010-7940(01)00597-8

5. Bolliger CT, Breitenbuecher A, Brutsche M, Heitz M, Stanzel F. Use of studded Polyflex stents in patients with neoplastic obstructions of the central airways. Respiration. 2004 Feb;71(1):83–87. https://doi.org/10.1159/000075654

6. E, Lawrie T, Harrell JH, Yi ES. Tracheobronchial adenoid cystic carcinoma: a clinicopathologic study of 14 cases. Chest. 2004 Mar;125(3):1160–1165.
https://doi.org/10.1378/chest.125.3.1160

7. Sipilä J, Pulkkinen J, Hujala K, Grenman R. Endoscopic lasersurgery in obstructive tracheal and bronchial tumors. An update. Otolaryngol Pol. 2004;58(1):187–190.

8. Gelder CM, Hetzel MR. Primary tracheal tumours: a national survey. Thorax. 1993 Jul;48(7):688–692.
https://doi.org/10.1136/thx.48.7.688

9. Cheung AY. Radiotherapy for primary carcinoma of the trachea. Radiother Oncol. 1989 Apr;14(4):279–285.
https://doi.org/10.1016/0167-8140(89)90139-4

10. Regnard JF, Fourquier P, Levasseur P. Results and prognostic factors in resections of primary tracheal tumors: a multicenter retrospective study. The French Society of Cardiovascular Surgery. J Thorac Cardiovasc Surg. 1996 Apr;111(4):808–13; discussion 813-814.
https://doi.org/10.1016/s0022-5223(96)70341-0

11. Ishihara T. Reconstruction of the trachea, carina and bronchi. Nihon Geka Gakkai Zasshi. 1985 Sep;86(9):1041–1043.

12. Kobayashi S, Kasama A, Kaya K. Anesthetic management for carinal resection. Masui. 1986 Feb;35(2):312–317.

13. Schneider P, Schirren J, Muley T, Vogt-Moykopf I. Primary tracheal tumors: experience with 14 resected patients. Eur J Cardiothorac Surg. 2001 Jul;20(1):12–18.
https://doi.org/10.1016/s1010-7940(01)00732-1

14. Hazama K, Miyoshi S, Akashi A, Yasumitsu T, Maeda H, Nakamura K, et al. Clinicopathological investigation of 20 cases of primary tracheal cancer. Eur J Cardiothorac Surg. 2003 Jan;23(1):1–5.

15. Grillo HC. Urgent Treatment of tracheal obstruction in: Grillo H.C. «Surgery of trachea and bronchi» BC Decker Inc Hamilton London; 2004, 475 p.

Information about author:

Natalia A. Chertova* – Cand. Sci. (Med.), surgeon, Department of tumors of head and neck National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 7051-4574, AuthorID: 473541

Yulia V. Ulianova – Cand. Sci. (Med.), surgeon, Department of tumors of head and neck National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 1276-9063, AuthorID: 457370

Marina A. Engibaryan – Dr. Sci. (Med.), head of the head and neck tumors Department National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 1764-0276, AuthorID: 318503

Viktoria L. Volkova – Cand. Sci. (Med.), senior researcher of the head and neck tumors Department National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 8289-6300, AuthorID: 290072

Irina V. Aedinov – Cand. Sci. (Med.), senior researcher of the head and neck tumors Department National Medical Research Centre for Oncology of the Ministry of Health of Russia, Rostov-on-Don, Russian Federation. SPIN: 9904-0539, AuthorID: 734387

South Russian Journal of Cancer 2020, v.1, №4, p. 54-60
https://doi.org/10.37748/2687-0533-2020-1-4-7

CLINICAL CASE REPORTS

PET-CT MONITORING IN THE TREATMENT OF PANCREATIC CANCER

G.E.Roitberg[1,2]*, O.Yu.Anikeeva[2]

1. N.I.Pirogov Russian National Research Medical University (RNRMU),
   1 Ostrovityanova str., Moscow 117997, Russian Federation
2. Medicina,
   10 2nd Tverskaya-Yamskaya lane, Moscow 125047, Russian Federation

ABSTRACT

Pancreatic cancer is a disease characterized by low visualization, high metastasis, and lethality. The average life expectancy for this nosology is less than 1 year. Early diagnosis of pancreatic cancer is difficult due to the lack of specific symptoms. As a rule, at the time of tumor visualization, every third patient has regional lymph nodes involved in the process, and every second patient already has distant metastases. We present a clinical case of a 73-year-old patient with a diagnosis of: cancer of the pancreatic head St IV, T4N1M1. The woman's primary positron emission tomography (PET-CT) revealed a metabolically active lesion with a size of 26x21x32 mm. After the combined multi-stage therapy under the control of PET-CT, it was possible to achieve complete leveling of the primary tumor focus and a relapse-free course of the disease for 11 months.

Our clinical observation showed the effectiveness of dynamic control (using PET-CT) treatment of metastatic pancreatic cancer, which influenced the patient's treatment strategy.

Conclusion. Patients with pancreatic adenocarcinoma ECOG ≥ 3, despite the prevalence of the process, should be offered comprehensive treatment.

Keywords:
pancreatic cancer, adenocarcinoma, positron emission tomography, chemotherapy, radiation therapy, adjuvant therapy.

For correspondence:
Grigory E. Roitberg – Dr. Sci. (Med.), professor, academician of the RAS, head of the Department of therapy, general medical practice and nuclear medicine of faculty of additional professional education of N.I.Pirogov Russian National Research Medical University (RNRMU), Moscow, Russian Federation. President of the clinic "Medicina", Moscow, Russian Federation.
Address: 1 Ostrovityanova str., Moscow 117997, Russian Federation
Address: 10 2nd Tverskaya-Yamskaya lane, Moscow 125047, Russian Federation
E-mail: jdorosh@medicina.ru
ORCID: https://orcid.org/0000-0003-0514-9114
SPIN: 1032-9122, Author ID: 218525

Information about funding: no funding of this work has been held.
Conflict of interest: authors report no conflict of interest.

For citation:
Roitberg G.E., Anikeeva O.Yu. PET-CT monitoring in the treatment of pancreatic cancer. South Russian Journal of Cancer. 2020; 1(4): 54-60.
https://doi.org/10.37748/2687-0533-2020-1-4-7

Received 18.09.2020, Review (1) 03.10.2020, Review (2) 28.10.2020, Accepted 01.12.2020

Южно-российский онкологический журнал 2020, т.3, №4, с. 54-60
https://doi.org/10.37748/2687-0533-2020-1-4-7
КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

РОЛЬ ПЭТ-КТ В ВЫБОРЕ ТАКТИКИ ЛЕЧЕНИЯ ПРИ РАКЕ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ: КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

Г.Е.Ройтберг[1,2]*, О.Ю.Аникеева[2]

1. ФГБОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И.Пирогова» Министерства здравоохранения Российской Федерации,
   117997, Российская Федерация, г. Москва, ул. Островитянова, д. 1
2. ОАО «Медицина»,
   125047, Российская Федерация, г. Москва, 2-й Тверской-Ямской пер., д. 10

РЕЗЮМЕ

Рак поджелудочной железы — злокачественное новообразование, исходящее из протоков и эпителиальной ткани железы, с высоким метастазированием и летальностью. Средняя продолжительность жизни при этой нозологии составляет менее 1 года. Ранняя диагностика рака поджелудочной железы затруднена из-за отсутствия специфичных симптомов. Как правило, на момент визуализации опухоли у каждого третьего пациента в процесс вовлечены регионарные лимфоузлы, а у каждого второго пациента уже имеются отдаленные метастазы. Мы представляем клинический случай пациентки 73 лет с диагнозом: рак головки поджелудочной железы St IV T4N1M1. У женщины при первичной позитронно-эмиссионной томографии (ПЭТ-КТ) был выявлен метаболически активный очаг размером 26x21x32 мм. После проведения комбинированной многоэтапной терапии под контролем ПЭТ-КТ удалось добиться полного нивелирования первичного очага опухоли и безрецидивного течения заболевания втечение 11 месяцев.
Наше клиническое наблюдение показало эффективность динамического контроля (с помощью ПЭТ-КТ) лечения метастатического рака поджелудочной железы, который оказал влияние на стратегию лечения пациентки.
Заключение. Пациентам с аденокарциномой поджелудочной железы ECOG ≥ 3, несмотря на распространенность процесса, следует предлагать лечение под контролем ПЭТ-КТ.

Ключевые слова:
рак поджелудочной железы, аденокарцинома, позитронно-эмиссионная томография, химиотерапия, лучевая терапия, адъювантная терапия.

Для корреспонденции:
Ройтберг Григорий Ефимович – д.м.н., профессор, академик РАН, заведующий кафедрой терапии, общей врачебной практики и ядерной медицины ФГБОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И.Пирогова» Министерства здравоохранения Российской Федерации, г. Москва, Российская Федерация. Президент клиники ОАО «Медицина», г. Москва, Российская Федерация.
Адрес: 117997, Российская Федерация, г. Москва, ул. Островитянова, д. 1
Адрес: 125047, Российская Федерация, г. Москва, 2-й Тверской-Ямской пер., д. 10
E-mail: jdorosh@medicina.ru
ORCID: https://orcid.org/0000-0003-0514-9114
SPIN: 1032-9122, Author ID: 218525

Информация о финансировании: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Ройтберг Г.Е., Аникеева О.Ю. Роль ПЭТ-КТ в выборе тактики лечения при раке поджелудочной железы: клиническое наблюдение. Южно-российский онкологический журнал. 2020; 1(4): 54-60. https://doi.org/10.37748/2687-0533-2020-1-4-7

Получено 18.09.2020, Рецензия (1) 03.10.2020, Рецензия (2) 28.10.2020, Принята к печати 01.12.2020

INTRODUCTION

The morbidity of pancreatic cancer in Russia in 2018 was 13.05 people per 100,000 population [1]. Besides, there is a steady increase in the incidence of this nosology, and the average annual growth rate reached 2.85% [1]. More than 95% of pancreatic cancer cases develop in the exocrine part of the pancreas. Adenocarcinomas are 95% of these [2]. The diagnosis of pancreatic adenocarcinoma is associated with an unfavorable prognosis of patient survival and high mortality worldwide [2–4]. In this cancer, there is still a tendency to increase mortality [2]. According to leading oncologists, pancreatic cancer will become the second leading cause of death from cancer in the next decade [4].

The clinical course of pancreatic cancer is considered aggressive, with no specific symptoms and high metastasis, which significantly reduces the patient's quality of life. At first, patients may complain of pain in the epigastric region, dyspeptic disorders, loss of appetite, weight loss. Further, as the disease progresses, obstruction of the biliary tract and functional insufficiency of the pancreas often occur, which lead to malnutrition [2].

Due to the absence of specific symptoms, more than 50% of cases of pancreatic cancer are detected at stage III–IV, where overall survival rates vary from 7 to 11 months [4, 5]. The high mortality rate from pancreatic cancer is explained by the lack of reliable screening methods for detecting the early stage of this nosology, as well as the relatively low effectiveness of systemic chemotherapy treatment [6, 7]. However, modern multicomponent chemotherapy regimens, despite their toxicity, allow us to achieve a certain increase in 5-year survival [1].

Since patients with detected pancreatic cancer in most cases already have distant metastases, radical surgical treatment of this category of patients is not always possible [4, 6, 7]. To prolong the survival period, patients with stage IV disease are recommended to undergo chemotherapy and radiation therapy with monitoring of regression of the main focus and metastases [8, 9]. Moreover, the effectiveness of treatment can be effectively evaluated using PET-CT.

Clinical case

Patient V., 73 years old, went to the clinic JCS "Medicine", Moscow with complaints of dysphagia (did not eat for 10 days), severe weakness (moved only in a chair).

From anamnesis: is registered with an oncologist since 2016, when cancer of the head of the pancreas was detected. A puncture biopsy was performed under ultrasound control of the pancreatic head tumor. Histological analysis of the biopsies revealed a low-grade adenocarcinoma. Clinical diagnosis: cancer of the pancreatic head St IV, T4N1M1. In 2016, was performed a palliative surgery — the imposition of hepatico jejuno anastomosis, cholecystectomy. Postoperative histological diagnosis — moderate differentiated adenocarcinoma with low-differentiated areas in the lymph node.

Objectively: the patient's condition is moderate, ECOG 3. Reduced power. The skin is pale, the sclera subicteric. The abdomen is soft, moderately painful in the epigastrium and right hypochondrium.

The patient was further examined at the clinic of JSC Meditsina.

According to PET-CT data from 17.02.2016 with contrast of 18F-fluorodeoxyglucose (18F-FDG), formation of 26x21x32 mm in the head of the pancreas with high metabolic activity in the tumor focus and in a few parapancreatic lymph nodes was revealed (Fig. 1). Aerobilia. Ascites. The liver is not enlarged in size. There are no foci with high FDG metabolism in the liver parenchyma.

The patient underwent EGDS, in which no tumor invasion into the duodenal wall was detected. Endoscopic stenting of the duodenum for stenosis was performed, and an infusion port was installed.

The oncological Council made to conduct chemotherapy (CT) according to the FOLFIRINOX scheme (Leucovorin, fluorouracil, irinotecan and oxaliplatin) — 7 courses, monitoring the effectiveness of treatment using PET-CT with 18F-FDG.

After the 5th course of CT, control PET-CT with 18F-FDG showed that there is still a pathological metabolically active lesion in the head of the pancreas, but there is a positive dynamics in some sorts of a decrease in the size of the

lesion and a slight decrease in its metabolism (table 1). At the end of the course of CT with PET-CT, the metabolic focus in the head of the pancreas decreased by 36.3%, and its metabolic activity by 19.8%. the Liver was not increased in size, without focal changes, and the lymph nodes were not changed (table 1, Fig. 2). The results of the dynamics of cancer markers are presented in table 2.

Taking into account the absence of pronounced positive dynamics after CT using the FOLFIRINOX scheme in July 2016 patient V. underwent palliative radiation therapy for a primary pancreatic tumor up to TTD 40 Gy against the background of xeloda radiomodification.

After the end of radiation therapy, the decision of the second meeting of the oncological Council (31.08.2016) was made to continue systemic CT (stage 2) for 2 months according to the FOLFIRINOX scheme (12 courses). After this stage of CT was completed, PET/CT data with 18F-FDG showed a marked positive dynamics in comparison, in the form of a significant decrease in the size and level of metabolism of the focus in the head of the pancreas. The liver is not enlarged, without focal changes, and the lymph nodes are not changed. There was a diffuse increase in bone marrow metabolism due to the reaction to chemotherapy.

Taking into account the almost complete regression of the pancreatic tumor, normalization of the marker level, and the presence of a minimal single node (8 mm) in the head of the pancreas, it was decided to suspend systemic treatment. Hypofractive radiation therapy (up to TTD 20g) is recommended for a residual focus in the head of the pancreas, followed by PET-CT and cancer markers.

2 months after the end of radiation therapy, PET-CT shows a pronounced positive dynamics in the form of leveling the focus of pathological metabolism in the head of the pancreas.

Taking into account the complete response of the tumor to the treatment, the consultation of oncologists of the JSC Meditsina clinic on

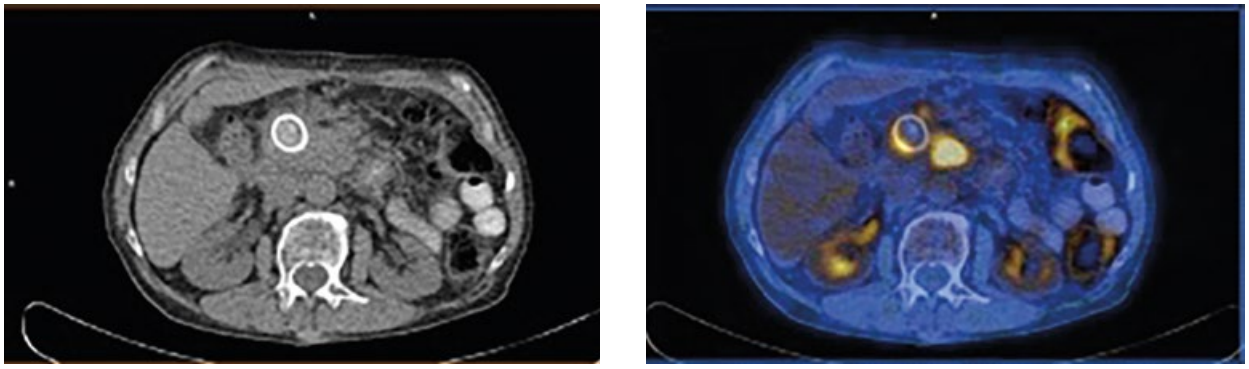


Figure 1. PET-CT with 18F-FDG without contrast enhancement is introduced here, before the treatment. The formation in the head of the pancreas with high metabolic activity SUVmax=10.77 and metabolic volume 6.53 cm^3 is visualized.

Table 1. Dynamics of PET-CT results in patient B. against the background of the ongoing treatment

PET-CT criteria	Before the treatment	After ½ of CT (1st stage)	After CT is finished (1st stage)	After CT is finished (2nd stage)	After the end of hypofractive radiation therapy
Presence of a metabolically active focus	26x21x32 mm	24x19x27 mm	17x17x22 mm	16x14x12 mm	Absent
The metabolic level in the lesion (SUVmax)	10.7	9.6	7.7	3.9	Absent

10.01.2017 decided to perform adjuvant therapy: xeloda 2000 mg / m2 / day 1–14 days of a 21-day cycle of 6 months (8 courses in the absence of progression).

Thus, in a patient with metastatic pancreatic cancer, a complete response was received against the background of complex treatment.

After 11 months, the results of PET-CT (31.10.2017) showed the progression of the disease in the form of the appearance of hypermetabolic foci in the liver (which were not previously determined by PET CT): the liver is not enlarged in size (CCS 150 mm), in S4, S6, S7, previously not visualized hypodensive foci with uneven and indistinct contours are determined, with maximum dimensions up to 12x11 mm, with hyperfixation of the RPP SUVmax up to 5.7. Also, in the right and left lobes of the liver S4, S5, S6, S7 and S8 segments, multiple hypodensive formations with uneven contours, previously not visualized, up to 19x21 (S6) mm in size without hyperfixation of the RFP are determined.

During the entire treatment period PET-CT monitoring of the treatment dynamics was performed.

DISCUSSION

Pancreatic cancer remains one of the diseases with a high mortality rate [5]. The quality of diagnosis plays a huge role in the visualization of pancreatic cancer [10]. Despite the growth of scientific and technological progress, the 5-year survival rate for this nosology has increased only by 1% (from 5 to 6%) over the past three decades [4].

For the initial examination, it is recommended to perform an ultrasound of the abdominal cavity, which allows you to detect a tumor formation in the form of hypoechoic structures, dilation of the pancreatic ducts and the biliary system [2]. The ultrasound of the abdominal cavity, head tumors are more often visualized. Cancer of the body and tail of the pancreas is difficult to diagnose by ultrasound due to the presence of gas in the stomach and transverse colon [7]. Therefore, ultrasound has a low specificity and effectiveness in the early detection of pancreatic cancer [2].

To improve the quality of diagnosis of pancreatic cancer, especially in metastases, it is recommended to perform spiral computed tomography

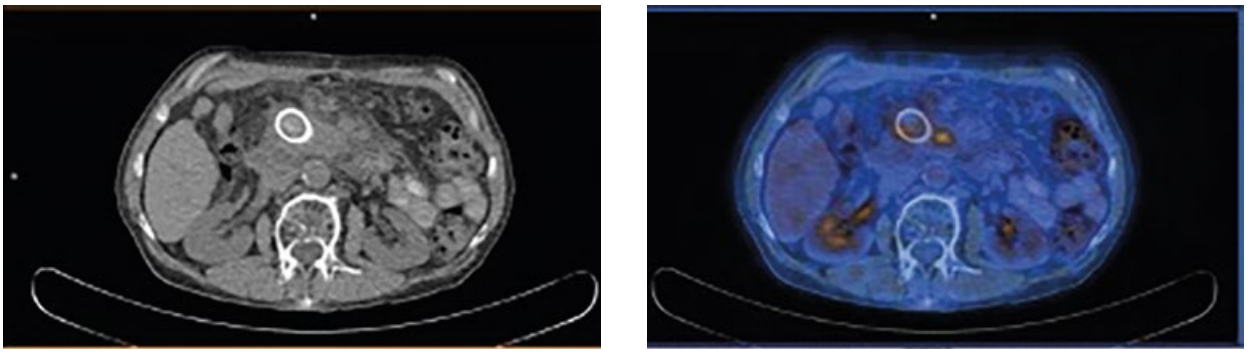


Fig. 2. PET-CT with 18F-FDG without contrast enhancement, control 14 days after the end of CT. The formation in the head of the pancreas persists with a marked decrease in metabolism and metabolic volume, SUVmax=3.98, metabolic volume 2.75 cm^3.

Table 2. Dynamics of cancer markers in the patient B

The oncomarkers	Before CT inception	After CT is finished 1st stage	After CT is finished 2nd stage	After the completion of hypofractive radiation therapy
CEA	1.12	2.8	2.5	2.1
CA125	100	18	16	12
CA19-9	171	48	25	43

(CT) with three-phase contrast [4, 12]. Most researchers believe that magnetic resonance imaging (MRI) is equivalent in sensitivity to CT in the diagnosis of pancreatic cancer [4, 12]. The accuracy of these imaging methods in the diagnosis of cancer lesions of the pancreas largely depends on the size of the tumor [12].

Positron emission tomography (PET) is not recommended for the primary diagnosis of pancreatic cancer [2]. However, according to Kauhanen SP et al. PET-CT is a more sensitive method for detecting metastases and for monitoring treatment after chemotherapy and radiation therapy [13]. The advantage of PET-CT is a wide coverage of anatomical zones, displaying metastases of any localization. Ideally, the use of contrast in PET-CT is preferable, which increases the diagnostic efficiency to 88% versus 76% without contrast [14]. Results of the study Kitajima K et al. the sensitivity, specificity, and accuracy of contrast-enhanced PET-CT in the diagnosis of pancreatic cancer were 91.7%, 95.2%, and 93.3%, respectively, compared with non-contrast PET CT — 83.3%, 90.5%, and 86.7%, and spiral CT — 66.7%, 85.7%, and 75.6%, respectively [15]. The diagnostic accuracy of contrast PET /CT in pancreatic malignancies was 89% compared to 79% in MRI [13]. Moreover, after receiving information using contrast PET-CT, the treatment strategy was changed in 26% of patients (10 out of 29) [13].

Our clinical observation showed the effectiveness of dynamic control (using PET-CT) treatment of metastatic pancreatic cancer, which influenced the patient's treatment strategy. Thanks to this tactical approach, in this clinical case, it was possible to achieve complete regression of the primary tumor focus in the head of the pancreas.

CONCLUSION

Patients with pancreatic adenocarcinoma ECOG ≥ 3 or poorly controlled comorbid conditions, despite the prevalence of the process, should be offered comprehensive treatment with monitoring of results using PET-CT. The interdisciplinary collaboration of different specialists is necessary to develop a plan for specialized treatment and follow-up of patients with pancreatic cancer.

Authors contribution:
Roitberg G.E. – research concept and design, scientific editing.
Anikeeva O.Yu. – text writing, material processing, and working on illustrations.

References

1. Khatkov IE. Modern treatment strategy for pancreatic cancer. Annals of HPB Surgery. 2019;24(3):110–114. (In Russian).
2. Strobel O, Büchler MW. Pancreatic cancer: Clinical practice guidelines – what is the evidence? Nat Rev Clin Oncol. 2016;13(10):593–594.
https://doi.org/10.1038/nrclinonc.2016.127
3. Frantsiyants EM, Kit OI, Aleynov VI, Goroshinskaya IA. Biomarkers, neoangiogenesis and growth factors in pancreatic cancer. Research and Practical Medicine Journal (Issled. prakt. med.). 2019;6(3):51–64. (In Russian).
https://doi.org/10.17709/2409-2231-2019-6-3-5
4. Sohal DPS, Kennedy EB, Khorana A, Copur MS, Crane CH, Garrido-Laguna I, et al. Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018 20;36(24):2545–2556. https://doi.org/10.1200/JCO.2018.78.9636
5. Moskvicheva LI, Petrov LO, Sidorov DV. The possibilities of modern methods of ablation in non-resectable locally advanced pancreatic cancer. Research'n Practical Medicine Journal (Issled. prakt. med.). 2018;5(2):86–99. (In Russian).
https://doi.org/10.17709/2409-2231-2018-5-2-10
6. Chiorean EG, Coveler AL. Pancreatic cancer: optimizing treatment options, new, and emerging targeted therapies. Drug Des Devel Ther. 2015;9:3529–3545.
https://doi.org/10.2147/DDDT.S60328
7. Dubtsova EA, Vinokurova LV, Nikolskaya KA, Agafonov MA. Diseases of the Pancreas - Difficulty of Differential Diagnosis. Difficult patient. 2014;12(12):18–21.
8. Gevorkyan T.G., Faynshteyn I.A. Palliative pancreatoduodenal resection in pancreatic head cancer. Research'n Practical Medicine Journal (Issled. prakt. med.). 2018;5(1):52–59. (In Rus-

sian). https://doi.org/10.17709/2409-2231-2018-5-1-6

9. Roitberg GE, Tulkina EE, Doros ZV, Filatov RE, Anikeeva OY. Organization of multidisciplinary rehabilitation of cancer patients. Bulletin of restorative medicine. 2019;5(93):14–20. (In Russian).

10. Bosetti C, Bertuccio P, Malvezzi M, Levi F, Chatenoud L, Negri E, et al. Cancer mortality in Europe, 2005-2009, and an overview of trends since 1980. Ann Oncol. 2013 Oct;24(10):2657–2671.
https://doi.org/10.1093/annonc/mdt301

11. Roitberg GE, Kondratova NV. Application of foreign screening programs experience in early cancer diagnostic improvement. Glavvrach. 2014;(2):37–46. (In Russian).

12. Zhang J, Zuo C-J, Jia N-Y, Wang J-H, Hu S-P, Yu Z-F, et al. Cross-modality PET/CT and contrast-enhanced CT imaging for pancreatic cancer. World J Gastroenterol. 2015 Mar 14;21(10):2988–2996.
https://doi.org/10.3748/wjg.v21.i10.2988

13. Kauhanen SP, Komar G, Seppänen MP, Dean KI, Minn HR, Kajander SA, et al. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. Ann Surg. 2009 Dec;250(6):957–963. https://doi.org/10.1097/SLA.0b013e3181b2fafa

14. Dibble EH, Karantanis D, Mercier G, Peller PJ, Kachnic LA, Subramaniam RM. PET/CT of cancer patients: part 1, pancreatic neoplasms. AJR Am J Roentgenol. 2012 Nov;199(5):952–967. https://doi.org/10.2214/AJR.11.8182

15. Kitajima K, Murakami K, Yamasaki E, Kaji Y, Shimoda M, Kubota K, et al. Performance of integrated FDG-PET/contrast-enhanced CT in the diagnosis of recurrent pancreatic cancer: comparison with integrated FDG-PET/non-contrast-enhanced CT and enhanced CT. Mol Imaging Biol. 2010 Aug;12(4):452–459.
https://doi.org/10.1007/s11307-009-0271-7

Information about author:

Grigory E. Roitberg – Dr. Sci. (Med.), professor, academician of the RAS, head of the Department of therapy, general medical practice and nuclear medicine of faculty of additional professional education of N.I.Pirogov Russian National Research Medical University (RNRMU), Moscow, Russian Federation. President of the clinic "Medicina", Moscow, Russian Federation. ORCID: https://orcid.org/0000-0003-0514-9114, SPIN: 1032-9122, Author ID: 218525

Olga Yu. Anikeeva – Dr. Sci. (Med.), chief of the oncological center of the clinic "Medicina", Moscow, Russian Federation. SPIN: 7581-8769, Author ID: 696308

South Russian Journal of Cancer 2020, v.1, №4, p.61-62

GUIDELINES FOR THE DESIGN OF ARTICLES (MAIN TERM)

- With a contract for the publication of articles, as well as detailed rules for authors
- examples of the bibliography design can be found on the journal's website "South Russian Journal of Cancer" www.cancersp.com
- Articles that are not designed in accordance with these rules are not accepted – they are not reviewed.
- Submit articles via the online form on the journal's website **www.cancersp.com**

The edition of the peer–reviewed scientific and practical journal "South Russian Journal of Cancer" accepts manuscripts that must meet the journal's subject matter and editorial requirements.

Only articles that have not previously been published in other publications are subject to publication in the journal.

It is not allowed to send to the editor works that have been sent to other publications.

Publication in the "South Russian Journal of Cancer" is free of charge.

The manuscript is sent to the editor in e–version via the online form of the site https://www.cancersp.com.

Along with the manuscript, the following documents are sent to the editor as scanned originals in *JPG or *PDF format:

- **A reference letter** from the organization where the first author works, signed by the scientific secretary or the head of the institution.
- **An agreement on granting the right to use the article**, filled in by the first author on behalf of the entire author's team and signed by all authors of the article.

1. The article should be submitted in e-form. Font — Times New Roman, 12, spacing — 1,0.

The text of the article, including the annotation, information about authors, references should be made in one file and each figure separate. Amount of articles. No more than 20 pages — for the heading "Original research", 25 — "literature Review", 12 — "Lecture", 10 — "Clinical observation". If more — in agreement with the edition.

2. Design of the first page (information is provided in Russian and English).

- Article title. It should be brief and informative. Abbreviations and abbreviations are not allowed in the title of the article.
- Initials and surnames of all authors. You must mention the institution where the author works.
- Full name of the institution and its address.

3. The annotation is a short and consistent presentation of the article material on the main sections. The volume of the annotation text is within **2000** characters.

The annotation of the original articles should be structured (contain the Purpose, Materials and methods, Results, Conclusion sections).

Keyword. Mention at least 6 keywords or phrases.

4. Information about the authors. The last name, the first name, patronymic, academic degree, academic title, position, and place of work of all (!) authors are indicated. The author, responsible for communication with the editorial office, should be highlighted separately (with the * icon) and the contact e–mail and mobile phone number should be indicated.

5. Additional information

- Conflict of interest. Authors must disclose financial or other existing conflicts of interest related to the manuscript.
- Funding information. If there is a source of research funding, you must provide it.
- Gratitudes. Authors can Express their gratitude to the people and organizations who

contributed to the publication of the article, but are not its authors.

6. Author's contribution

Authors are people, determined by the scientific group to be the main participants in the work described and who have agreed to take responsibility for their work. In addition to responsibility for their part of the work, the author must indicate how each of the co–authors is responsible for other parts of the work. The "South Russian Journal of Cancer" accepts the following authorship criteria:

Authors' participation:

- Research concept and design, text writing, material processing.
- Scientific editing.
- Editing, preparation of a bibliography, preparation of illustrations.
- Data collection, analysis and interpretation, assistance in operations, article preparation, etc.

The list of authors does not include people who are not the authors of the article. The names of people who are not authors, but have provided other support, are indicated in the "Thanks" section. Important! Information about the contribution of authors should be indicated before the section "References"

7. Registration of references.

References in the text of the article are placed in square brackets in the order of citation (not alphabetically!). The number of cited works: in original articles — no more than 30, in literature reviews — no more than 60, in lectures and other materials — up to 15.

- In case of referencing journal articles indicate the names and initials of authors, article title, journal title (the English title of journals should be given in accordance with the directory names of the database MedLine), year, volume, issue number, pages.
- In case of referring to a book publication — names and initials of the authors, full title of the book, place of publication, name of the publisher, year of publication.
- In case of referring to the dissertation abstracts– the authors ' last names and initials, the full title of the work, the doctor's or candidate's degree, the year and place of publication.
- In case of referring to electronic sources — the site name, e-mail address of the cited source, date of reference.

The second list of references is a complete analog of the list of references, in which sources in Russian should be presented in the Roman alphabet (Latin) in such a way that these references can be taken into account when studying the citation of publications of authors and journals.

If the article has an official translation of the title, it should be inserted instead of transliteration! Transliteration should be performed in the BSI standard (you can use the site — http://ru.translit.net/?account=bsi).

8. Illustrative materials. All tables and figures must be numbered and have a name. References to illustrative material are given in the text of the article in parentheses. Captions under the figures should explain the meaning of all curves, letters, numbers, and other symbols in Russian.

9. Abbreviations. Units of measurement are given in SI. All abbreviations in the text of the article must be fully transcribed at the first use. The use of abbreviations that are not generally accepted is not allowed.

All articles are accepted for publication free of charge.

The edition reserves the right to edit, reduce published materials and adapt them to the journal's categories.

Федеральное государственное бюджетное учреждение
НАЦИОНАЛЬНЫЙ
МЕДИЦИНСКИЙ ИССЛЕДОВАТЕЛЬСКИЙ ЦЕНТР
ОНКОЛОГИИ
Министерства здравоохранения Российской Федерации

PEER-REVIEWED SCIENTIFIC AND PRACTICAL

SOUTH RUSSIAN JOURNAL OF CANCER

РЕЦЕНЗИРУЕМЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ

ЮЖНО-РОССИЙСКИЙ ОНКОЛОГИЧЕСКИЙ ЖУРНАЛ

www.cancersp.com