

REVIEW

## MODERN DIAGNOSTIC AND TREATMENT METHODS IN PARANASAL SINUS MALIGNANT TUMORS

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### ABSTRACT

Malignant tumors of the head and neck are still one of the most challenging problems of treatment in modern oncology. The disease affects mainly the capable people (from 30 to 60 years old). Tumor lesions of the paranasal sinuses lead to disability and have a high mortality rate. Head and neck tumors comprise of 20–30 % of all cancer cases. People with early paranasal sinus cancer have minor complaints, their general condition doesn't get affected so they don't seek for medical care in a while. As a result, patients start on treatment at tumor grades III–IV. This article provides the most complete information about the causes, frequency and special features of the course of paranasal sinus cancer, as well as about modern methods of its diagnosis and combination treatment. Despite the great advances in the treatment of these malignant tumors the three and five year survival rates remain unsatisfactory, which requires a research for new effective treatments. Currently the main treatment methods for these malignant tumors are combination and complex (involving surgery, radiotherapy and chemotherapy) treatments. The standard treatment approach includes radical surgical removal of the primary tumor and metastatic lymph nodes followed by radiation or chemoradiation therapy. Chemotherapy as monotherapy is administered in non-resectable primary or recurrent tumors, distant metastases or when a patient refuses the radical surgery. Improvement of existing treatment methods and development of new ones are an essential need. Earlier detection of the disease requires primary care physicians to be trained to diagnose tumor lesions of the paranasal sinuses, and highly specialized physicians (dentists, otorhinolaryngologists, maxillofacial surgeons, dermatologists) to express their cancer alertness.

### Keywords:

malignant neoplasms of the paranasal sinuses, diagnostics of tumors of the malignant nature of the paranasal sinuses, etiological factors of development, methods of treating malignant formations of the paranasal sinuses, chronic inflammatory diseases of the paranasal sinuses, benign neoplasms of the paranasal sinuses

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## СОВРЕМЕННЫЕ МЕТОДЫ ДИАГНОСТИКИ И ЛЕЧЕНИЯ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ ОКОЛОНОСОВЫХ ПАЗУХ

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### РЕЗЮМЕ

Опухоли злокачественной природы, локализующиеся в области головы и шеи, остаются одной из сложнейших проблем при лечении в современной онкологии. Заболеванию подвержена преимущественно трудоспособная часть населения (от 30 до 60 лет). Опухолевые поражения околоносовых пазух приводят к инвалидизации, а также к высокой смертности населения. В общей структуре онкологической заболеваемости опухоли головы и шеи составляют 20–30 %. Жалобы при наличии злокачественной опухоли околоносовых пазух в начальных стадиях незначительные, общее состояние больных не страдает и продолжительное время они не обращаются к врачу. В итоге, пациенты начинают лечение, когда опухолевый процесс достигает III–IV стадии заболевания. В нашей статье представлена наиболее полная информация о причинах возникновения, частоте встречаемости, особенностях течения злокачественных новообразований околоносовых пазух, современных методах диагностики и комплексного лечения этой категории пациентов. Несмотря на большие достижения в лечении злокачественных опухолей представленной локализации, показатели трех- и пятилетней выживаемости остаются неудовлетворительными, в связи с чем, необходим поиск новых эффективных методов лечения. В настоящее время основными методами лечения злокачественных образований данной локализации являются комбинированный и комплексный (сочетание хирургических вмешательств, лучевой терапии и химиотерапии). Стандартным подходом в лечении является радикальное хирургическое удаление первичной опухоли и метастатически-измененных лимфоузлов с последующей лучевой или одномоментной химиолучевой терапией. Химиотерапия в моноварианте используется при наличии нерезектабельных первичных или рецидивных опухолей, отдаленных метастазов или отказе пациента от радикальной хирургической операции. Неоспоримой является необходимость поиска путей совершенствования существующих и разработки новых методов лечения. Также с целью повышения выявляемости болезни на ранних стадиях необходимо обучение врачей первичного звена диагностике опухолевого поражения околоносовых пазух, проявлению онконастороженности узких специалистов (стоматологов, оториноларингологов, челюстно-лицевых хирургов, дерматологов).

### Ключевые слова:

злокачественные новообразования придаточных пазух носа, диагностика опухолей злокачественной природы околоносовых пазух, этиологические факторы развития, методы лечения злокачественных образований околоносовых пазух, хронические воспалительные заболевания околоносовых пазух, доброкачественные новообразования придаточных пазух носа

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## RELEVANCE

Approximately 8.8 million people die a year from malignant neoplasms (World Health Organization). The incidence in Russia per 100,000 population in 2020 was 0.65 people [1].

Tumors of the nasal cavity and paranasal sinuses account for 0.2 to 1.4 % of cancerous tumors of other organs and 10 to 20 % of neoplasms of ENT organs [2; 3]. Women get sick with a frequency of 42.9 %, men – 57.1 % [2–4]. Tumors with epithelial origin account for 70–80 %. Esthesioneuroblastoma (as a non-epithelial tumor) accounts for 50–60 % [2]. The asymptomatic course in the early stages of the development of tumors of this localization is the reason for patients to go to an oncologist with advanced processes [5].

Chronic inflammatory diseases such as sinusitis, ethmoiditis, frontitis, rhinosinusitis (catarrhal, polypous) play an important role in the etiology of the development of tumor processes in the nasal cavity and paranasal sinuses. Adverse natural factors, chemical and physical carcinogenic substances also have a great influence on changes in the mucous membrane [6–8].

Inflammatory diseases that occur for a long time, with periodic remissions and exacerbations, lead to various hyperplastic processes in the epithelium of the paranasal sinuses, which may precede the onset of malignancy.

A complex of specific and non-specific mechanisms of local and general immunity provides protection of the mucous membrane of the paranasal sinuses and nasal cavity. Factors of local protection play a leading role. Non-specific factors are the primary link in the protection of the epithelium of the mucous membrane. The secretion of products with bactericidal properties, such as interferon, lysozyme, etc., as well as mucociliary transport carried out by macrophages and monocytes phagocytosis are non-specific protection factors. Lymphocytes of the pharyngeal tonsil and its own epithelial plate provide specific protection of the mucous membrane [9–12]. Secretory immunoglobulin A (SIg A) is the main component of the immune protection of the nasal mucosa and paranasal sinuses from foreign influences. It's production is provided by mucosa-associated lymphoid tissue, which participates in the formation and ensures the functioning of mucosal immunity.

Damage to the epithelium contributes to the penetration of pathogens into the mucous membrane and disrupts the constant immune regulation. Venous congestion, swelling and thickening of the mucous membrane, leading to a violation of blood supply, are constant companions of inflammatory processes in the paranasal sinuses and nasal cavity [12]. Under conditions of oxygen starvation, anaerobic processes begin to prevail in the mucous membrane, which leads to the accumulation of under-oxidized metabolic products. Due to changes in the acid-base balance and slowing of mucociliary clearance, mucosal secretion stagnates. Also, due to the products of metabolic acidosis, the protective effect of lysozyme stops. All these processes provide the most favorable conditions for the suppression of obligate non-pathogenic microflora of the upper respiratory tract and the development of pathogenic anaerobes.

Chronic minor injuries of the mucous membrane play a great role in the etiology of malignant neoplasms of the sinuses. They can occur due to the impact of sharp edges of destroyed teeth, improperly installed fillings or dentures. In the area of chronic minor injuries of the mucous membrane, tumors develop in 5.2–5.7 %.

The source of tumor development may be dysplastic foci formed as a result of embryonic disorders during the fusion of various tissue rudiments, which is accompanied by the formation of teeth and the transition of the flat outer epithelium to the atrial fibrillation. Sometimes epithelial rudiments associated with the formation of teeth are preserved in the area of the alveolar process of the upper jaw, which can also give rise to tumor degeneration.

Leukoplakia of the mucous membrane, as one of the types of dyskeratosis, is an optional precancerous disease. According to that, patients are subject to dynamic monitoring and active treatment of foci of leukoplakia. Tumors can develop against the background of polypous rhinosinusitis and various sinus papillomas (especially inverted papilloma). Oncological alertness of primary care physicians, timely histological examination of pathological formations of the paranasal sinuses allows to identify malignant degeneration and to begin timely treatment in the early stages of the disease.

Tumors of the paranasal sinuses can originate from the mucous membrane of the alveolar and

palatine processes of the upper jaw, nasal cavity and sinuses, as well as from cartilage and bone tissue. Most often (70–80 %) there are tumors of epithelial origin, up to 50 % are squamous cell carcinoma, 10 % are transitional cell carcinoma, 5–7 % of patients are diagnosed with adenocarcinomas.

As a result of prolonged inflammatory processes, metaplasia of the cylindrical epithelium occurs. This explains the development in most cases of squamous cell cancers from the mucous membrane lining the oral cavity, sinuses, and nasal cavity. Adenocarcinomas, adenocystic cancers, and cylindrical cell cancers are associated with malignant degeneration of the glandular epithelium.

The most common representative of non-epithelial sinus tumors, occurring in 15–20 %, is esthesioneuroblastoma or neuroendocrine tumor (50–60 %), which develops from the neuroepithelium of olfactory bulbs. The tumor has a high potential for malignancy, intensive growth (often into the cranial cavity), and often recurs after treatment [13; 14].

Sarcomas of the upper jaw, which are connective tissue tumors that originate mainly from the maxillary bone (especially in the area of connective tissue sutures) and are much less common than epithelial neoplasms [14–16].

Also, tumors of the upper jaw in 0.9 % of cases may be secondary or metastatic in thyroid, breast, kidney, and melanoma cancers [14]. The clinical picture of metastatic tumors has no specific signs, the diagnosis is made with a comprehensive examination and histological examination of the biopsy material.

**According to the international histological classification of malignant tumors of the nose and sinuses, the following types of formations are distinguished:**

Epithelial tumors, which include cancers – squamous, verrucous (squamous), spinocellular, transitional cell, adenocystic, mucoepidermoid, undifferentiated, adenocarcinoma, mucosal adenocarcinoma, others.

II. Soft tissue tumors, which include malignant hemangiopericytoma, fibrosarcoma, rhabdomyosarcoma, neurogenic sarcoma, malignant fibroxanthoma and others.

III. Bone and cartilage tumors are isolated separately, which include chondrosarcomas, osteogenic sarcomas and others.

IV. Tumors of hematopoietic and lymphoid tissue include lymphomas (lymphosarcomas; reticulosarcomas; plasmocytomas; Hodgkin's disease).

V. There are mixed tumors, which include malignant melanoma, esthesioneuroblastoma and others.

Also in this classification, secondary tumors (metastatic) and unclassifiable tumors are singled out separately.

Treatment and diagnosis (especially early) of tumors of the nasal cavity and sinuses is a complex task and does not depend on the histological structure. To date, the search for ways to improve the unsatisfactory results of diagnosis and treatment has not stopped [17–19].

**The purpose of the study:** was to highlight the relevance of the problem of treating tumors of the paranasal sinuses, the need to develop clear algorithms for diagnosis (especially early), treatment and rehabilitation.

Despite the huge achievements in the field of radiation therapy, surgical technologies, chemotherapy, the prognosis for the treatment of tumors of the paranasal sinuses and nasal cavity remains unfavorable. This is due to the fact that mostly patients with advanced tumor processes get to the oncologist. In the initial stages, the clinical manifestations of these tumors are extremely scarce and, for a long time, patients do not attach importance to them and do not seek medical help. The reasons for the neglect of cancer of these localizations are the late treatment of patients, insufficient oncological alertness of primary care doctors, and, accordingly, incorrect diagnosis and incorrect treatment tactics. Symptoms such as toothache, bleeding from the nasal cavity, purulent discharge, unilateral nasal congestion do not alarm doctors in terms of tumor development. As a result, long-term treatment with antibacterial drugs, physiotherapy, etc. is prescribed [2; 6]. The patient goes to the oncologist when the tumor reaches a large size, deforms the face and there is no doubt about the diagnosis of a malignant tumor.

In the early stages of the development of the disease, it is possible to establish the primary affected area. Most often, tumors begin their development in the area of the ethmoidal labyrinth or the maxil-

lary sinus. It is extremely rare that the primary and frontal sinuses are affected. Unilateral difficulty in nasal breathing may be one of the first symptoms of damage to the maxillary sinus, then local pain, bulging of the eyeball, purulent discharge, repeated bleeding may join. The asymptomatic or latent period of the course of the disease can last up to one year [2; 20; 21].

In the course of clinical observations, the frequency of occurrence of certain symptoms of cancer of the paranasal sinuses and nasal cavity was established. Unilateral difficulty breathing through the nose is noted in 21 % of cases. Discharge from the nasal cavity, which can be mucous, purulent and hemorrhagic, is observed in 14.3 % of cases. Recurrent and non-severe nosebleeds occur in approximately 5 % of patients. Localized in the area of teeth, jaws, ears and eyes, pain of varying intensity is noted by 20.4 % of patients. In 1.1 % of cases, manifestations of paresthesia, anesthesia of individual areas of the face are possible. As the first sign of the disease, 21 % of patients report facial deformity (swelling in the cheeks, eyelids, cheekbones, alveolar and palatine processes of the jaws). 6.9 % of patients have symptoms such as loss, displacement or loosening of teeth. On the part of the organ of vision, symptoms such as lacrimation, swelling of the eyelids, protrusion of the eyeball and its displacement in various directions, impaired mobility of the eyeball and decreased visual acuity are also possible (6.3 % of cases) [2].

Metastatic lesion of the lymph nodes of the neck occurs in 20 % of cases. Mainly the postaryngeal lymph nodes and nodes under the base of the skull are affected, then metastases are found in the submandibular and deep cervical lymph nodes. Distant metastasis to other organs (lungs, brain, liver) is not typical for tumors of these localizations and manifests late [22].

The algorithm of examination of patients with malignant tumors of the paranasal sinuses has been developed. It includes physical examination, X-ray examination of the facial skeleton and chest organs, video endoscopic examination of the nasal cavity and pharynx, tumor biopsy with histological examination, fine needle aspiration biopsy of enlarged lymph nodes, ultrasound examination of the lymph nodes of the neck and abdominal organs, computed tomography of the head with contrast enhancement, etc. [2; 23].

Various types of X-ray examinations (radiography, computed tomography) are the main diagnostic measures that allow to establish the localization and prevalence of the pathological process [24; 25]. SCT and MRI are used for differential diagnosis of inflammatory and cancerous diseases of the adnexal sinuses. During these studies, a detailed assessment of the zone of perifocal edema, the density and size of the tumor in anatomically complex structures of the skull is possible. It is possible to accurately assess destructive processes in the bones of the facial skeleton, the presence or absence of tumor germination into the cranial cavity, damage to vital structures. Magnetic resonance imaging allows you to optimally determine the size of the soft tissue component of the tumor, and computed tomography allows you to more accurately assess the integrity of bone structures. Also, with small-sized neoplasms, it is possible to use positron emission tomography for diagnosis [20; 26].

A necessary and mandatory stage of diagnosis is a biopsy of the pathological formation of the paranasal sinuses. In the histological conclusion, it is necessary to indicate the histotype and the degree of differentiation of tumor cells, which largely affects the choice of the optimal treatment method.

A fine needle aspiration biopsy of enlarged neck lymph nodes under ultrasound control is also a mandatory diagnostic measure. The presence of a metastatic lesion of the cervical lymphocollector largely determines the tactics and choice of treatment method.

Due to the presence of a number of reasons, the treatment of malignant neoplasms of the paranasal sinuses and nasal cavity is considered difficult for both the doctor and the patient. Anatomically complex area, the occurrence of extensive post-operative defects and functional disorders, are the reason for the refusal of patients from active surgical treatment. The surgical method in the monovariant provides a five-year survival rate of 18–35 %, a combination of surgical and radiation methods – 77.5 %. Most often (in 50 % of patients), the disease recurs within the first 2 years from the start of treatment [2].

The leading component of the combined and complex treatment of cancer of the paranasal sinuses is surgical [2; 23]. According to historical sources, one of the first operations in oncology is



resection of the upper jaw for a tumor. There are many options for surgical interventions for neoplasms of the upper jaw (including rhinotomy). Contraindications and indications for surgical interventions on the upper jaw are described in the literature, the disadvantages and advantages of certain approaches are identified, and complications are also analyzed [2; 27–30]. The volume and types of operations depend on the prevalence and localization of the tumor process, the general status of the patient, and the predicted complications. Due to the high risk of recurrence, the surgical method in monovariant is not used in stage 3–4 tumor processes. To date, the search for ways to optimize surgical interventions, increase their radicality, plastic elimination of postoperative defects, complex prosthetics, as well as professional and social rehabilitation has not stopped.

Radiation monotherapy is also ineffective in the treatment of tumors of the paranasal sinuses [31]. A permanent cure is possible in rare cases in the early stages of tumor development. However, if there are contraindications to surgical treatment, radiation therapy is the leading method of treatment. Radiation therapy helps to reduce the size of the tumor, the disappearance of pain, the restoration of nasal breathing, which accordingly leads to an improvement in the patient's well-being. Unfortunately, radiation therapy does not lead to a complete cure, but only helps to slow down the growth of the tumor.

The combined method, which consists in a combination of surgical and radiation methods, is the gold standard in the treatment of locally common tumors of the paranasal sinuses [2; 22; 30]. Postoperative irradiation is more effective than preoperative due to significantly greater targeting, based on determining the true size and prevalence of the tumor during surgery [32]. However, even the use of a combination of radiation and surgical methods in the treatment of malignant tumors of the paranasal sinuses and cavities does not prevent the development of relapses of the disease at a relatively early time, which occur in 30–60 % of cases.

Since the mid-70s of the last century, systemic chemotherapy has been actively used in the treatment of common tumors. Chemotherapy is used as a component of complex treatment (including chemoradiotherapy). It is also possible to use polychemotherapy as an independent palliative

method when the possibilities of surgical and radiation treatment have already been exhausted. The most effective use of chemotherapy is for tumors of epithelial origin (squamous cell cancers). Most often, stabilization of the tumor process is achieved. At the same time, tumor regression of varying severity is observed in 10–75 % of cases. Analyzing the experience of our department, the use of chemotherapy as a neoadjuvant component has not been widely used in the treatment of cancer of the paranasal sinuses. Currently, thanks to advances in the study of biology and immunology of malignant tumors, cellular technologies, pharmacodynamics and pharmacokinetics of drugs, as well as a detailed study of the mechanisms of their action, the possibilities of chemotherapy are significantly expanding. However, polychemotherapy in a monovariant never leads to the cure of patients and is mainly used as a palliative effect on the tumor in the late stages of the development of the malignant process.

Currently, the treatment of cancer of the paranasal sinuses depends on the size of the primary focus (symbol T), the sequence of therapeutic measures is reflected in clinical recommendations [23].

Surgical intervention or independent radiation treatment is indicated for patients with cancer of the nasal cavity and the trellis labyrinth T1-T2N0. If the histological examination of the surgical material determines unfavorable prognostic factors, such as intracranial spread and tumor cells at the edges of resection, patients are prescribed postoperative radiation or chemoradiotherapy. This tactic aims to increase overall survival and reduce the number of relapses of the disease.

With the prevalence of the tumor corresponding to the symbols T3-T4a, surgical intervention is also recommended as the first stage of treatment. In case of refusal of the operation, the use of chemoradiotherapy is possible. Radiation or competitive chemoradiotherapy is used as an adjuvant component of treatment.

If there are unresectable tumors (T4b) or if the patient refuses to perform extensive surgery, chemoradiotherapy or independent radiation therapy is performed. With non-radical surgical treatment and the presence of a residual tumor of the lattice labyrinth, patients undergo surgery or chemoradiotherapy. With the prevalence of the primary tumor corresponding to the T1 symbol, the

presence of negative resection edges, high differentiation of tumor cells, dynamic observation is shown in the postoperative period. Dynamic observation in the postoperative period is also indicated for cancer of the maxillary sinus (T1-T2, N0). Adjuvant radiation treatment is indicated in the case of determining unfavorable prognostic factors, such as perivascular, perineural and lymphatic invasion, as well as in the detection of adenocystic cancer. If tumor cells are detected at the edges of the resection, a repeated surgical operation is performed, followed by radiation or chemoradiotherapy.

Patients with locally advanced cancers of the maxillary sinus corresponding to T3-T4a undergo radical surgery with a postoperative course of radiation therapy. In case of detection of tumor cells in the edges of resection, simultaneous chemoradiotherapy is performed, and repeated surgical intervention may also be recommended.

In case of unresectable tumors (T4b) of the maxillary sinus, chemoradiotherapy or independent radiation therapy is performed.

If patients are diagnosed with metastatic lesion of the lymph nodes of the neck, cervical lymph dissection is performed simultaneously with the operation on the primary focus. The volume of surgical intervention in this case is determined by the number and size of metastatic foci. If the histological examination reveals unfavorable prognostic factors, such as extracapsular spread of metastases, positive resection margins, perineural, perivascular, lymphatic invasion, adjuvant radiation or simultaneous chemoradiotherapy is indicated.

Radical surgical intervention is performed in patients with local recurrences of maxillary sinus cancer, the presence of a residual tumor after non-radical removal. Subsequently, the issue of the expediency of adjuvant radiation treatment or competitive chemoradiotherapy is being resolved.

In case of detection of unresectable tumors, repeated radiation therapy, simultaneous chemoradiotherapy, or symptomatic treatment is possible.

Modes of independent radiation therapy for cancer of the paranasal sinuses have been developed: a dose of 66–70 Gy is applied daily to the area of the primary focus and clinically determined metastases to the lymph nodes of the neck in fractions of 1.8–2.0 Gy for 6–7 weeks.

Independent simultaneous chemoradiotherapy is also performed daily for 7 weeks. A dose of 70

Gy is applied to the area of the primary focus and lymphatic collector. At the same time, on the 1st, 22nd and 43rd days of radiation therapy, cisplatin is administered at a dose of 100 mg/m<sup>2</sup> against the background of hyperhydration and forced diuresis. The total dose of cisplatin for the entire period of treatment is 300 mg/m<sup>2</sup>. It is possible to replace cisplatin with carboplatin in the AUC 1.5–2.0 mode in the form of weekly injections from the first day of radiation treatment.

After performing surgical interventions, adjuvant radiation (chemoradiotherapy) should be carried out in the interval from 6 weeks to 3 months. Prolongation of this interval is unfavorable in terms of the appearance of continued tumor growth or relapse of the disease. The total radiation dose during postoperative radiation therapy is 66 Gy per primary focus area and 50–54 Gy per regional lymphatic collector area. In the presence of recurrent unresectable tumors, as well as with the appearance of distant metastases, mono- or polychemotherapy with first-line drugs, which include cisplatin (carboplatin), paclitaxel, cetuximab, is used to increase overall survival [22; 31].

The results of treatment of malignant tumors of the paranasal sinuses and nasal cavity, despite great achievements in oncology, remain unsatisfactory. Combined treatment (a combination of surgical and radiological methods) allows achieving five-year survival in stage I–II cancer in 73.6 % of patients, stage III – in 54.9 % of patients, stage IV – in 24.2 % of patients. When regional metastases to the neck lymph nodes are detected, the five-year survival rate decreases to 37.5 %. In the presence of a widespread tumor lesion with a low degree of cell differentiation, chemoradiotherapy will be used, which allows achieving a positive clinical result in 74 % of patients. However, the stabilization of the tumor process is not long-term. The use of surgical or radiation method in monovariants allows to achieve a five-year survival rate in 18–35 % of patients, which demonstrates the need for combined treatment. If the tumor is detected early and combined treatment is started in a timely manner, it is possible to achieve the values of the overall three- and five-year survival of 87.3 % and 83.5 %, respectively. With the complex treatment of locally widespread tumor processes of the paranasal sinuses, the three-year survival rate is 37.1 %.

## CONCLUSION

Our analysis of the literature data, as well as our own experience in the treatment of limited and widespread tumors of the paranasal sinuses and nasal cavity, indicate the need to improve existing and develop new methods of treatment. The training of primary care physicians in the di-

agnosis of tumor lesions of the paranasal sinuses in the early stages, the oncological alertness of narrow specialists (dentists, otorhinolaryngologists, maxillofacial surgeons, dermatologists) will contribute to the early and timely detection, and accordingly the timely treatment of malignant neoplasms of tumors of the head and neck organs.

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