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## Opisthorchiasis and pancreatic cancer

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### ABSTRACT

Chronic opisthorchiasis is recognized as a precancerous condition that can present similarly to other diseases of the hepatopancreatoduodenal zone. Statistically, there is a proven correlation between the duration and intensity of parasitic invasion and the development of carcinogenesis, with the manifestations of opisthorchiasis often obscuring the early symptoms of cancer. Many researchers are working to find methods for the early diagnosis of pancreatic cancer against the background of chronic opisthorchiasis, which may enable timely treatment of the disease in the early stages.

The authors of this lecture present a literary review of the data on the incidence of pancreatic cancer in patients with chronic opisthorchiasis. Additionally, some factors contributing to cholangiocarcinoma carcinogenesis are discussed, since the exact mechanisms leading from the introduction of a trematode to the formation of a malignant process are multifunctional. Certain phenomena regarding the effect of opisthorchis on the human body currently lack explanation and require further study and clarification.

**Keywords:** cholangiocarcinoma, pancreatic cancer, cholangiogenic cancer, opisthorchiasis invasion

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## Описторхоз и рак поджелудочной железы

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## РЕЗЮМЕ

Известно, что хронический описторхоз рассматривается как предраковое заболевание, протекающее под маской других заболеваний органов гепатопанкреатодуоденальной зоны, и статистически имеется доказанная зависимость канцерогенеза от длительности и интенсивности паразитарной инвазии, а проявления описторхоза маскируют собой ранние симптомы онкологического заболевания. Многие авторы работают над поиском методов ранней диагностики рака поджелудочной железы на фоне хронического описторхоза, что может дать возможность своевременного лечения заболевания на ранних стадиях.

Авторы лекции представили литературный обзор данных заболеваемости раком поджелудочной железы у пациентов с хроническим описторхозом. Кроме того, приведены некоторые факторы канцерогенеза холангиокарциномы, поскольку точные механизмы, ведущие от внедрения трематоды до формирования злокачественного процесса, остаются не до конца ясными. Некоторые феномены действия описторхисов на организм человека в настоящее время не имеют объяснения и требуют дальнейшего изучения и детализации.

**Ключевые слова:** описторхоз, холангиокарцинома, рак поджелудочной железы, холангиогенный рак, описторхозная инвазия

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## INTRODUCTION

The increase in the incidence of pancreatic and bile duct cancer is one of the most pressing issues of modern abdominal surgery. At the same time, according to a number of authors, the 5-year survival rate in this category of patients is about 10% [1, 2]. Research in the field of surgical oncology determines a clear correlation of the development of malignant processes with a long-term parasitic infection of the biliary system. The aim of this lecture is to provide a literature overview of the data on the incidence of pancreatic cancer in patients with chronic opisthorchiasis. In addition, the lecture presents some factors in the carcinogenesis of cholangiocarcinoma, since the exact mechanisms leading from the introduction of a trematode to the formation of a malignant process remain unclear.

As is known, human infection with *Opisthorchis felinus* occurs when eating raw or undercooked freshwater fish from the carp family, which contain metacercarial cysts in the muscles [3]. After metacercariae excyst in the jejunum or duodenum, they migrate to the bile ducts, where they mature into adult worms that remain viable for more than 10 years [4]. The clinical pattern of the disease caused by the invasion of *Opisthorchis felinus* is usually

characterized by signs of damage to the hepatobiliary system, but it is often not limited to symptoms reflecting the pathology of the parasite host organs, which allows us to consider opisthorchiasis as a systemic disease [5, 6].

According to the World Health Organization, trematodosis are estimated to cause 2 million life years lost to disability and death worldwide every year, and opisthorchiasis is one of the most common helminthiases transmitted through infected fish [7]. About 40 million people in the world are infected with opisthorchiasis. At the same time, most of them are in Russia, and the incidence rate varies by region and often correlates with the level of consumption of freshwater fish, which is traditionally higher in rural areas [8].

According to the Federal Service for the Oversight of Consumer Rights and Welfare of the Russian Federation, parasitic infections in fish have been proven in 26 regions of the Russian Federation and cases of human infection are regularly recorded. The most endemic regions are located near large rivers where infected fish is caught for commercial sale. Thus, in the Ob-Irtysh river basin with the world's largest opisthorchiasis case number, up to 1,000 cases per 100,000 people are recorded, with 95% of the rural population infected [8].

In Russia, the highest incidence rate is recorded in the Tyumen and Tomsk regions, while the incidence rate is average in the rest of the regions. In her research, E.N. Ilyinskikh has established a trend toward an increase in the incidence of opisthorchiasis in Russia as a whole. During the analyzed period, opisthorchiasis was not registered only in the Pskov and Lipetsk regions. As a result of the analysis of territorial trends in the changes of morbidity growth, the authors concluded that in 22 territories there was a trend toward an increase in the number of cases, and only in two regions morbidity growth decreased. At the same time, the discussed indicators have remained at the average level for many years. Presumably, such dynamics could be explained by the fact that people in these regions do not usually eat raw or pickled fish [9].

O.S. Fedorova et al. believe that the increase in the incidence of opisthorchiasis in Russia is also influenced by the active migration of the population from Western Siberia to other territories. And if we take into account that in some areas of the Ob-Irtysh river basin, almost 100% of the population is diagnosed with opisthorchiasis, then there is a real threat of an increase in the number of patients throughout Russia. The authors draw attention to an increase in the incidence in areas where this helminthiasis was not previously detected, and in some territories of the Ob-Irtysh river basin, on the contrary, there is a decrease in the incidence rate [10].

In 2009, the International Agency for Research on Cancer (IARC) of the World Health Organization has identified *O. viverrini* among the definitive causes of bile duct cancer or cholangiocarcinoma, classifying this helminthiasis as a group 1 carcinogen [11].

A group of scientists including J.M. Banales, J.J.G. Marin, A. Lamarca, P.M. Rodrigues, S.A. Khan, L.R. Roberts and others in their study note that about 3% of all cases of malignant lesions of the gastrointestinal tract are cholangiocarcinoma, and among primary liver cancers, the incidence of this form reaches 15% [12]. Clinically, this pathology is also characterized by high mortality, which accounts for 2% of all deaths from cancer. Such statistics are explained, first of all, by the ineffectiveness of early, including non-invasive, diagnosis, and the need for histological confirmation of the diagnosis. In addition, this form of malignant liver damage is highly resistant to various treatment methods due to its properties at the genomic, epigenetic, and molecular levels. A

number of authors draw attention to the fact that in inoperable forms of the disease, the median survival is only 3–13 months. The prognosis is usually poor, after treatment there is a high risk of relapse, and the five-year survival rate does not exceed 25–43% [12, 13]. All of the above determines the need to find methods for early diagnosis of cholangiocarcinoma, which may be one of the ways to improve treatment outcomes in patients with this serious pathology.

It is believed that the combination of mechanical damage caused by the attachment and nutrition of fluke and exposure to excretory/secretory products of flukes occurs over a long period of time and ultimately leads to the development of inflammation and chronic hepatobiliary disorders [14]. These processes cause oxidative stress, lead to DNA damage and gene mutation, as well as impaired regulation of cell growth in the form of goblet cell metaplasia, adenomatous dysplasia and epithelial hyperplasia, all of which creates the basis for carcinogenesis [10, 15, 16].

G.A. Maksimova et al. studied the effect of *O. felinus* on carcinogenesis. As a result of the conducted research, the authors concluded that the effect of *O. felinus* on the development of liver pathology is comparable with that of *O. viverrini* [17]. The results obtained may indicate the need to change the group of carcinogens to which *O. felinus* belongs according to the IARC classification. M.N. Lvova et al. note that despite the similarity of these two parasites in morphology, significant differences in the timing of the histopathological profile and the very nature of these changes allow us to conclude that opisthorchiasis invasion caused by the European liver fluke *O. felinus* is more pathogenic than that caused by the Asian fluke *O. viverrini* [18].

According to the group of authors – O.A. Baykova, N.N. Nikolaeva, E.G. Grishchenko, L.V. Nikolaeva – similarity of pathogens of opisthorchiasis and the morphological identity of their damaging effects on the hepatobiliary system suggest that the model of cancer development by representatives of the Opisthorchidae family is similar [19]. The multifactorial nature of cancer development in opisthorchiasis is determined by three main components of carcinogenesis. These components include mechanical damage to the mucous membrane by parasites, toxic, anti-apoptotic, and hyperproliferative effects of secretory parasitic proteins, immunopathological processes (oxidative

stress). Mechanical damage to the epithelium of the bile ducts occurs as a result of the action of suckers, which allow the parasite to attach to the mucous membrane of the biliary system. The constant inflammatory process is accompanied by a regenerative reaction of the wound, which leads to cell proliferation and, ultimately, DNA damage, followed by the manifestation of carcinogenesis [17].

Currently, *O. felinus* is not recognized as a group 1 biological carcinogen due to insufficient evidence [20]. However, there are reports in the available literature on the results of some studies proving the role of *O. felinus* in the development of cholangiocarcinoma and carcinogenic potential in laboratory animals. A recent case-control study conducted in Western Siberia showed that people with a confirmed diagnosis (according to microscopy of fecal eggs and/or serum IgM or IgG ELISA) were at a significantly higher risk of developing cholangiocarcinoma than healthy people [21]. An increased risk of malignancy was also found in patients who were diagnosed with current or past *O. felinus* invasion [21].

O.S. Fedorova et al. analyzed the relationship between the incidence of opisthorchiasis and malignant neoplasms of the hepatobiliary system in residents of the Russian Federation using official medical reports [10]. According to the authors, the incidence of liver and intrahepatic bile duct cancer in 2011–2013 was  $4.8 \pm 0.2$  cases per 100,000 people in the population. The highest rates were recorded in the regions of the Far East, Siberia, and the Volgograd region. The authors obtained statistically significant data on the presence of a direct correlation between the incidence of opisthorchiasis (*O. felinus* invasion) in residents of endemic areas and malignant neoplasms of the duodenum, pancreas, and liver.

In their study [22], V.G. Bychkov, E.D. Khadieva, V.P. Zuevskiy, S.D. Lazarev, A.P. Baryshnikov, A.V. Simonov distinguished the following patterns of carcinogenesis in superinvasive opisthorchiasis:

1. superinvasive opisthorchiasis is a strong promoter of carcinogenesis in the parasite econiches and stomach;

2. the development of cholangiocarcinomas and adenocarcinomas in the pancreas is formed on the territory of proliferation of its own stem cells, committed cells, i.e., outside the ductal organ systems;

3. superinvasions significantly increase the mitogenic activity of tumor cells in the liver, pancreas, and stomach.

Opisthorchiasis is characterized by both local morphological changes in the parasitic organs and general, systemic, pathological processes. T.A. Khabelova et al. define acute opisthorchiasis as a hyperergic reaction to the antigens of the parasite [16]. The authors consider chronic opisthorchiasis as a systemic disease, which is accompanied by damage to the organs infected by parasites and involvement of intact organs and systems in the process. The authors note that the immunosuppressive, mutagenic effect of opisthorchis, as well as epithelial metaplasia, can collectively contribute to the development of cholangiogenic cancer.

*O. felinus* can parasitize the bile ducts of the liver for decades. In 20–40% of cases, parasites are also found in the ducts of the pancreas. The result of the presence of opisthorchis in the pancreatic ducts are papillitis, dactylitis, cholangitis, pancreatitis, and a number of other inflammatory processes of the duodenum, liver, and pancreas. The presence of parasites themselves, and obstruction of the ducts by opisthorchis detritus lead to the formation of cholangiectasis, strictures of the bile and pancreatic ducts. The mechanisms of development of these pathological processes are different. Thus, V.Yu. Rayn., V.P. Ionin, N.A. Kolmachevskiy distinguish four main components of the damaging effect of opisthorchis [23] including:

1. irritating effect of waste products of living opisthorchis and lysis of dead parasite bodies;
2. mechanical obstruction of the bile ducts by mature parasites and during egg deposition;
3. stimulation of lithogenesis;
4. translocation of bacteria during migration of opisthorchis from the duodenum to the bile ducts.

According to B.I. Alperovich et al., chronic proliferative cholangitis, stenosis of the large duodenal papilla, and extended strictures of the biliary tract contribute to the development of biliary hypertension and impaired outflow of pancreatic juice [24]. With massive invasion, the pancreatic duct can be obstructed by parasites and opisthorchiasis detritus, which leads to the development of inflammation in the pancreas, and is also often the cause of complications in the postoperative period following pancreatic cancer surgery [25].

The presence of opisthorchis invasion significantly increases the likelihood of developing ductal adenocarcinoma of the pancreas to low tumor differentiation [10]. The authors note that

a correlation has been established between the association of opisthorchiasis and the formation of foci of pancreatic intraepithelial neoplasia. The development of ductal pancreatic carcinoma is due to the progression of these processes. Interestingly, in the case of the development of highly differentiated neoplasia in opisthorchiasis, the life expectancy of patients is on average 2 months longer than without opisthorchiasis. But since low-grade forms of malignant lesions often develop in the presence of opisthorchiasis, the prognosis is less favorable.

According to the publication by N.A. Brazhnikova and M.V. Tolkaeva opisthorchiasis is a precancerous condition, which is confirmed by a number of clinical, pathomorphological, and epidemiological studies [25]. It has been statistically proven that in hyperendemic areas, the incidence of liver cancer is 2–3 times higher than average, the incidence of pancreatic cancer is 2 times higher, and that of extrahepatic bile duct cancer is 13 times higher. The urgency of the problem of earlier detection and surgical treatment of liver and pancreatic cancer in the context of chronic opisthorchiasis invasion is due to both the high incidence and the peculiarities of the clinical course of this pathology – a long asymptomatic period. Early manifestations of the malignant process mimic exacerbation of chronic opisthorchiasis, hepatocholecystitis, pancreatitis, and infectious hepatitis. Patients are admitted for surgical treatment already in the presence of complications, including jaundice more than three weeks.

When taking the medical history, in some cases, it is possible to identify changes in the nature of pain even before the clinical signs of jaundice, namely, an increase in the intensity of pain in the right hypochondrium and epigastrium, its constant nature, especially at night, the appearance of pronounced dyspeptic disorders, decreased appetite, weight loss for no particular reason, flatulence, unstable stool. In pancreatic cancer, weakness, progressive weight loss, and vomiting are more often detected, which in some patients is associated with impaired gastric emptying as a result of compression by a tumor or invasion into the wall of the duodenum. The nature of jaundice also changes, which is determined by etiopathogenetic factors.

Jaundice syndrome becomes persistent with a trend toward an increase in intensity, cholangitis may develop, which is accompanied by hyperthermia and chills, debilitating itching. All this is accompanied

by apathy, adynamia in the lack of effect from therapy. The long-term asymptomatic course of the disease is one of the most important reasons for late hospitalization of patients and, as a result, unsatisfactory outcomes of surgical treatment. The presence of opisthorchis invasion disguises the clinical picture of the malignant process, which significantly complicates timely diagnosis and radical surgical intervention. According to the authors, only 10.6% of the surgeries were radical. Palliative treatment was provided to 57.7% of patients, exploratory surgeries were performed in 13% of cases, and in 19% of cases, surgical treatment was impossible due to the prevalence of the pathological process.

O.V. Reshetnikov, T.G. Openko, and S.A. Kurilovich provide data from the pancreatic cancer registry, which is one of the deadliest types of cancer. The authors note that morbidity and mortality in this form of malignant neoplasm are almost equal. In recent years, there has been a trend towards an increase in morbidity, which leads, respectively, to an increase in mortality rates in some European countries, the Baltic States, Japan, and the USA [15].

## CONCLUSION

All of the above once again proves the need and importance of early diagnosis and prevention of opisthorchiasis, as well as deworming and medical examination of patients in order to detect opisthorchiasis and its complications earlier, including malignant progression.

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