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## ABSTRACT

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## PRIMARY FALLOPIAN TUBE CANCER: A LITERATURE REVIEW

**Introduction.** This literature review presents an analysis of diagnostic methods and treatment of a relatively rare and highly malignant tumor – primary fallopian tube cancer, which is poorly studied and difficult to diagnose. The study of the fallopian tube disorder is very relevant, as the fallopian tube mucosa can be a source of "serous carcinogenesis" for serous ovarian and peritoneal cancer.

**Methods.** The author selected more than 50 scientific works from the world literature on the problems of incidence, diagnosis, and treatment of primary fallopian tube cancer and conducted a detailed analysis of them.

**Results and Discussion.** The author draws attention to the risk group for primary fallopian tube cancer. Women with BRCA-1 and BRCA-2 mutations are more likely to develop FTC, especially in families with a history of breast and (or) ovarian cancer. Approximately 30% of women with FTC have a BRCA-1 or BRCA-2 mutation. All patients with a burdened history and pathologic mutations should be considered candidates for routine rehabilitation. The author analyzes options for improving preoperative diagnosis using modern methods of additional examination, such as tumor markers, vacuum suction biopsy, transvaginal ultrasound, CT and MRI, and diagnostic laparoscopy. The author emphasizes that it is possible to avoid diagnostic errors during operations using a detailed examination of the affected fallopian tube mucosa on a longitudinal section and suboperative methods of morphological diagnosis. In addition, the author points out the prognostic importance of adequate staging and complete courses of adjuvant polychemotherapy according to modern clinical protocols. The author also draws attention to the interdependence of prevention methods, diagnosis, and treatment of FTC and ovarian cancer.

**Keywords:** primary fallopian tube cancer, incidence, clinical features, diagnosis, treatment.

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## РЕЗЮМЕ

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## ПЕРВИННИЙ РАК МАТКОВИХ ТРУБ: ОГЛЯД ЛІТЕРАТУРИ

**Вступ.** У даному огляді літератури представлено аналіз стану діагностики та лікування порівняно рідкої, недостатньо вивченої, трудно діагностованої та дуже злоякісної пухлини – первинного раку маткових труб. Вивчення патології маткових труб є дуже актуальним, так як їх слизова оболонка може бути джерелом «серозного канцерогенезу» для виникнення серозного раку яєчників та очеревини.

**Методи.** Зі світової літератури автором вибрані більше 50 наукових праць з проблем захворюваності, діагностики та лікування первинного раку маткових труб та проведений їх детальний аналіз.

**Результати аналізу та їх обговорення.** Автор звертає увагу на групу ризику первинного раку маткових труб. Велика ймовірність виникнення даної патології у жінок з мутаціями BRCA -1 та BRCA-2, особливо в тих родинах, де були хворі на рак молочної залози та (або) яєчників. Приблизно 30% жінок хворих РМТ мають мутацію BRCA-1 або BRCA-2. Усі пацієнтки з обтяженим анамнезом та патологічними мутаціями повинні розглядатися як кандидати на планове оздоровлення. Автор аналізує можливості покращення доопераційної діагностики за допомогою сучасних додаткових методів обстеження, таких як онкомаркери, пайпель біопсія, трансвагінальна сонографія, КТ і МРТ та діагностична лапароскопія. Він також підкреслює, що можна не припуститися діагностичних помилок під час операцій шляхом детального вивчення на повздожньому розрізі слизової оболонки ураженої маткової труби і застосуванням субопераційних методів морфологічної діагностики. Крім того, автор указує на прогностичну важливість адекватного стадіювання та повноцінних курсів ад'ювантної поліхіміотерапії згідно сучасних клінічних протоколів. Також звертає увагу на взаємозалежність методів профілактики, діагностики та лікування РМТ та яєчників.

**Ключові слова:** первинний рак маткових труб, захворюваність, особливості клініки, діагностика, лікування.

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## Abbreviations:

PCT – polychemotherapy;

FTC – fallopian tube cancer

## INTRODUCTION / ВСТУП

For a long time, gynecologists and pathologists considered fallopian tube cancer a non-existent thing. In 1888, K. Orthman was the first to describe

in detail and confirm a case of primary fallopian tube cancer (FTC) by histological findings. He analyzed the literature sources of that time and proved that the cases of fallopian tube cancer previously described

by Raymond (1847), Rokitanski (1861), Renault (1861), and other authors were secondary to uterine or ovarian tumors. In the same 1888 year, at a meeting of the Kharkiv doctors' union, doctor N. P. Fedorov made a report on the fallopian tube tumor that developed in the hydrosalpinx [1]. Nowadays, no doubts arise concerning the FTC, which is known to have an incidence of at least 1.8% among malignant tumors of the female genital tract and 4 to 6% – among uterine adnexa cancers [2, 3]. According to the reports of a number of authors, the incidence of FTC is increasing. For example, in North America, this indicator increased from 0.22 per 1 million women in 1999–2001 to 0.62 per 1 million in 2011–2012, while from 2001 to 2014, according to the reports of other authors, the incidence of FTC increased up to 4 times [4, 5]. The issues of FTC diagnosis and the features of fallopian tube pathology associated with its role in the occurrence of serous ovarian and peritoneal cancers remain relevant.

Based on world literature data and our own experience, we conducted a concise analysis of the up-to-date methods of FTC diagnosis and treatment and the possibilities for their improvement.

#### **Causes of FTC**

The etiology of FTC remains unclear, but a number of diseases and conditions were documented that often precede FTC. The age of patients with FTC ranges mainly from 40 to 60 years, but several cases were described in patients between 17 and 89 [6, 7]. Up to 35–70% of patients with FTC suffer from infertility and have a history of inflammatory diseases of the uterine adnexa [8, 9, 10]. The role of inflammation in the development of FTC was proved by the unique observation of H. I. Thompson (1904) on the development of FTC in the hydrosalpinx 8 years after the operation. During the first operation, they could not remove hydrosalpinx, and thus, it was sutured into the colpotomy wound for drainage and possible atresia [1]. Women with BRCA-1 and BRCA-2 mutations are more likely to develop FTC, especially in families with a history of breast and (or) ovarian cancer [1, 11, 12]. Approximately 30% of women with FTC have a BRCA-1 or BRCA-2 mutation. The highest frequency of BRCA mutations was observed in women with FTC diagnosed before the age of 60, as well as in Jewish women, women with a family history of cancer, and women with a personal history of breast cancer. All patients with a burdened history and an FTC diagnosis should be considered candidates for

genetic testing and adequate routine rehabilitation [13].

After the discovery of "serous carcinogenesis" of the fallopian tube mucosa and its role in the occurrence of serous ovarian and peritoneal cancers, the study of the causes, features of diagnosis, and treatment of FTC became even more relevant [14, 15, 16, 17]. This discovery provided a practical opportunity to effectively prevent ovarian and peritoneal cancer by opportunistic salpingectomy in post-reproductive age. It is now known that timely tubal ligations or tube removal reduces the incidence of serous ovarian cancer by 30 to 90% [17, 18, 19].

#### **Clinical features of FTC**

Clinical manifestations of FTC are not always specific, but at a doctor's appointment, they are found in more than 90% of patients. Discomfort or pain, sometimes paroxysmal, in the lower abdomen, is registered in 70% of women; pathological vaginal discharge – in 65 to 75% of patients. The most characteristic symptom is watery or chyliform discharge, often with opalescence or blood impurities. Bleeding of varying intensity or yellowish purulent discharge is less common. A typical feature of FTC is the correlation between pain and discharge: increased pathological discharge after an episode of pain. Bimanually, at the time of consulting a gynecologist, 70 to 76% of patients already present with anatomical changes in the internal genital organs, mainly the uterine adnexa, which is often a sign of an old disease [1, 20].

The most characteristic signs of FTC are the Latzko's triad, when all three symptoms are present (pain, discharge, neoplasms in the uterine adnexa), and hydrops tubae profluens. In hydrops, tubae profluens (hydrosalpinx), along with paroxysmal pain syndrome, a large amount of watery discharge appears, the pain decreases, and the previously observed cyst-like mass in the uterine adnexa decreases or completely disappears. Such clinical picture is reported in 15 to 20% of cases; in the remaining cases, FTC disguises as hydro- or hematosalpinx, cysts or ovarian cancer, endometrial cancer, uterine leiomyoma, inflammatory process, acute abdomen, and other diseases that greatly complicate FTC diagnosis [1, 3, 19]. To date, even in specialized oncology hospitals, reliable preoperative diagnoses range from 0 to 10–15% [21, 22, 23], and errors during laparotomies and laparoscopies reach 50% [24, 25].

#### **Problems and capabilities of FTC diagnosis**

It is almost impossible to establish a reliable FTC diagnosis before surgery without additional

diagnostic methods. For the first time, E. Antonowitch used hysterosalpingography to diagnose FTC in 1950 and made the correct diagnoses before surgery in two patients [1]. In the following years, this technique, especially bicontrast methods of examination, made it possible to recognize FTC before surgery in  $\geq 50\%$  of cases [1, 3]. Nowadays, sonography and magnetic resonance imaging (MRI) are successfully replacing radiocontrast diagnostic methods in gynecologic oncology [25, 27, 28]. Transvaginal 3D and Doppler ultrasonography allow to detect not only the anatomical changes characteristic of FTC (sausage-shaped mass, thickening of the walls, papillary projections, infiltrates), but also the changes in the vascular geometry characteristic of cancer. In a tumor lesion, the chaotic vascular pattern, disproportionate calibration of vessels, arteriovenous shunts, microaneurysms, tumoral lakes, blind ends, and even the signs characteristic of borderline tumors are revealed [29, 30].

In contrast to sonography, MRI, in addition to anatomical features, allows recognition of fine details of contrast, hydrophilicity, and chemical features of the tumor and detection of metastases in the lymph nodes. Some authors consider it necessary to include MRI in FIGO clinical protocols as a mandatory method of examination when FTC is suspected [31].

In some cases, cytological analysis of pathological uterine discharge, which is observed in 60–75% of patients, plays a decisive role in diagnosing FTC. According to the reports of some authors, tumor cell findings range from 0 to 40%, but a lot depends on the amount and quality of the collected material. For example, smears from the vagina and cervical canal present no more than 6–11% of reliable results, while vacuum suction biopsy brings about 65% of reliable results [3, 32, 33].

Ca125 and HE4 tumor markers are important in FTC diagnosis, treatment, and prognosis, although their diagnostic capabilities are contradictory [1, 9]. Before the operation, Ca125 antigen is positive in 60 to 80% of cases, mainly with a pronounced tumor process. In the early stages, Ca125 is within the normal range or questionable, especially in accompanying inflammatory processes, endometriosis, and early pregnancy. The prognosis for patients with FTC largely depends on the initial level of Ca125. Almost always, after radical operations and chemotherapy, the level of Ca125 normalizes; when the tumor process is activated, the Ca125 level increases rapidly. Ca125 level

monitoring makes it possible to recognize the activation of the disease and start treatment on average 3 months earlier than with other methods of diagnosis [22, 34].

In the diagnosis of FTC, laparoscopy is considered very promising, but, unfortunately, the results are not encouraging yet. For example, over the past 4 years, 3 laparoscopic operations for FTC were performed in the hospitals of the Sumy region. In all the cases, the operations were non-radical, and the diagnosis of FTC was made only after a routine histological examination. In addition, in the available literature, we found 21 cases of the use of diagnostic laparoscopy in FTC. The analysis of their results revealed that out of 24 patients with early stages of FTC who underwent diagnostic laparoscopy, 17 (70.8%) patients were misdiagnosed with benign cystic masses of the uterine adnexa [21, 35, 36]. The diagnosis of FTC in these patients was established only by routine histological postoperative examination. The errors were probably caused by the lack of the following: developed laparoscopic semiotics of FTC, proper examination of the longitudinal section of the removed fallopian tube in the operating room, and suboperative morphological diagnosis. Despite the complexity of preoperative diagnosis of FTC, clinical manifestations and comprehensive use of additional modern examination methods make it possible to avoid mistakes in most cases [20, 21, 32, 37].

Due to errors in preoperative diagnosis, patients with FTC are often operated on by other surgeons rather than oncologists. It is recommended to remember that fallopian tube tumors are associated with various sacosalpinges, and thus, a thorough examination of the removed tube on a longitudinal section in the operating room is necessary. Suboperative morphological analysis is often required to confirm suspected cancer. In cases of significant lesions when the ovaries or uterus are involved, it is necessary to follow the criteria for FTC diagnosis, proposed by S. Hu et al. (1950) and modified by A. Sedlis (1951) and M. Yoonessi (1979), in order to determine the primary site [9, 21, 38]. The final diagnosis of FTC is made only after a routine histological analysis.

Morphological studies have shown that over 80–85% of fallopian tube neoplasias are serous adenocarcinomas of various malignancy level. Among them, up to 90% of tumors are moderately and poorly differentiated, which characterizes FTC as a very aggressive tumor [38, 39, 40]. In fallopian

tubes, along with serous masses, tumors of the endometrioid structure, carcinosarcomas, and other rare neoplasms of an equally malignant nature can be found [42, 43]. Progression of FTC occurs by lymphogenous, hematogenous, and implantation metastasis or invasion into the neighboring organs [34, 42, 46]. FTC is characterized by significant lymphotropicity. Lymph node metastases are found in almost a third of operated patients, even at the very early clinical and surgical stages, while in severe tumor processes, this value reaches more than 40% [40, 46, 47, 48].

#### **FTC treatment features and outcomes**

Treatment of FTC has evolved from purely surgical to combined with the use of various types of radiation therapy in the early days, then chemotherapy, and currently – adjuvant PCT with modern medications according to clinical protocols [49]. Most authors are unanimous that the results of treatment primarily depend on optimal cytoreduction [50, 51]. Surgical intervention with tumor remnants of more than 1 cm is considered suboptimal [8, 22]. Even accidental entry of tumor cells into the abdominal cavity during puncture or biopsy of “hydrosalpinges” can reduce the survival rate of patients by up to 8 times [52]. In FTC, it is recommended to perform panhysterectomy with resection of the omentum and removal of pelvic and para-aortic lymph nodes [49]. Organ-preserving operations in the early stages of FTC (stage 1A according to FIGO) may be permitted only in certain cases, namely, for well-differentiated forms

of tumors and on the responsibility of the patient and the doctor [22, 23]. Adjuvant polychemotherapy in patients with FTC largely complies with the standards of treatment of ovarian cancer with the use of platinum and taxane medications. Three to six courses of polychemotherapy are recommended for stage 1A to 1C FTC, and six to eight courses – for stage II to IV FTC. The calculation of chemotherapeutic agent dosage is based on the Calvert formula. The maximum dose is determined based on the maximum glomerular filtration rate [49].

Currently, with the relatively effective use of polychemotherapy, radiation therapy can be used in the treatment of FTC only as an auxiliary method for local recurrences and individual metastases. The possibility of using hormone therapy in FTC is based on the fact that the tube epithelium changes due to hormone fluctuations during the menstrual cycle. Since the vast majority of patients with FTC are postmenopausal women and there have been no randomized studies on this problem, hormone therapy is not recommended [49].

A comparative analysis of FTC treatment results published in the world literature reveals a tendency towards their improvement. For example, before 2000, the overall five-year survival rate of patients with FTC ranged from 22% to 57%, while in 2015–2021, this value reached 57–80% (for the early stages, the overall five-year survival rate was more than 80–90%) [50, 51, 53, 54].

#### **CONCLUSIONS / ВИСНОВКИ**

Based on the above, we currently have real opportunities to improve FTC detection and preoperative diagnosis, prevent diagnostic errors during operations, and save many women from life-threatening diseases – primary cancers of fallopian tubes and ovaries. It is necessary to remember that methods of prevention, diagnosis, and treatment of FTC and ovarian cancer are closely interconnected.

We consider it necessary to give the following recommendations to medical practitioners:

- pay special attention to patients from the FTC risk group;
- consider women as high-risk patients if suspected of familial breast or ovarian cancer; they should be offered an examination for BRCA-1 and BRCA-2 mutations in order to provide timely treatment and rehabilitation.

#### **CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ**

The authors declare no conflict of interest.

#### **FUNDING / ДЖЕРЕЛА ФІНАНСУВАННЯ**

None.

#### **AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ**

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.



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