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Ways to improve the diagnostics and detection of cervical cancer development and recurrence risk

Relevance: Cervical cancer is the fourth leading cause of female death and the third most common female cancer worldwide.

The purpose of the study was to determine risk factors and time to progression and recurrence in patients with cervical cancer after complex treatment (neoadjuvant chemotherapy + radical hysterectomy + combined radiation therapy).

Materials and methods: This retrospective study involved female patients with stage IB-IIA cervical cancer registered at Shymkent city oncological dispensary in 2011-2021 (n=883). All patients underwent radical hysterectomy with pelvic lymph node dissection. The patients were selected who underwent radiation therapy of the lower pelvis at a dose of ≥ 40 Gy. The age-, stage-, and tumor morphological structure-dependent survival factors and recurrence risk were analyzed during the research decade.

Results: Direct correlation of the disease stage and the recurrence period was established. The progression was most often 5 to 6 months after treatment. 68.7% of progression and 63.1% of recurrences occurred in the first year and a half after the end of treatment, so this period is considered the most "dangerous" regarding the recurrence risk. 5.3% of patients had a recurrence 19 to 24 months after treatment, 31.5% – after more than two years.

Conclusions: In this research, cervical cancer progressed in 74 (10.6%) out of 883 women and recurred in 19 (3.0%). The recurrence was most frequent in women aged 45-50 years (28.4%) and 50-60 years (26.3%).

Keywords: cervical cancer, risk factor, progression, recurrence.

Introduction: Cervical cancer is the fourth leading cause of death among women and the third leading cause of cancer among women worldwide [1].

According to 2012 global cancer statistics, 528,000 new cases of cervical cancer were diagnosed and 266,000 patients died from cervical cancer during the year [2, 3]. As reported in previous studies, most patients with early-onset cervical cancer (IA-IV) who received appropriate treatment had a positive outcome, and only 10-15% of patients with risk factors experienced recurrence [3]. Therefore, timely and accurate diagnostics, as well as appropriate treatment, are very important to reduce the risk of cervical cancer recurrence [4].

According to proven studies, most cervical cancer recurrences occur in the first two years after treatment [5]. The recurrence rate is 0.7% in stage IA, 9.8% in stage I after combined treatment, 24.0% in stage IIB, and 9.5% after combined and integrated treatment. In stage IIA-II local cervical cancer, the recurrence rate reaches 20%. In ongoing cervical cancer, it is important to investigate early diagnostic factors that influence recurrence and progression [6].

The purpose of the study was to determine risk factors and time to progression and recurrence in patients with cervical cancer after complex treatment (neoadjuvant chemotherapy + radical hysterectomy + combined radiation therapy).

Materials and methods: This retrospective study involved female patients with stage IB-IIA cervical cancer who underwent radical hysterectomy with excision

of pelvic lymph nodes and received radiotherapy of the lower pelvis in the dose ≥ 40 Gy. The patients enrolled (n=883) were registered at Shymkent city oncological dispensary from 2011 to 2021. Such factors as quality of life and risk of recurrence depending on the disease stage and the patient age were analyzed over the ten years [7-8].

All patients were planned and prescribed treatment following the protocol of the joint committee on quality of care of the Ministry of Healthcare of the Republic of Kazakhstan No. 56 dated March 01, 2019).

After radical hysterectomy with dissection of pelvic lymph nodes, the patients underwent dual radiation therapy (DRT) by remote gamma therapy (RGT) using the Teregam apparatus with two opposing radiation fields. Size of the field – 16x18 cm, SD (single dose) – 2 Gy, total average dose – 44 Gy, boost dose – 20 Gy; ICGT (intracellular gamma-therapy) single dose – 5 Gy, total average dose on the "Multisource" apparatus – 45-50 Gy at point A. Radiation treatment was accompanied by the procedures aimed to improve the overall condition and combat anemia. Blood and urine parameters were monitored. According to the decision of the MDG (Multidisciplinary Group), 18 out of 94 patients underwent DRT [9-10].

Statistical analysis. The study aimed to determine the time interval and the appropriateness of complex and combined treatment. Recurrences were detected in the pelvis, including the vaginal cavity and aortic bifurcation area; metastases in the pelvic lymph nodes were quite frequent.

Specific χ^2 or Fisher's tests were used to compare clinical and pathological characteristics and complications associated with adjuvant treatment. Survival rates were estimated by Kaplan-Meier and compared with log-rank tests. Cox proportional hazards regression analysis was used to identify independent predictive factors; $p \leq 0.05$ was considered statistically significant for the two-sided test. Statistical analysis was performed using SPSS software, 23 (IBMSPSSInc23, Chicago, IL, USA)[11].

Selection criteria: patients with histological diagnostics, squamous cell, adenocarcinoma, or squamous cell cervical cancer; stages IB-IIA of the FIGO cervical cancer classification; history of neoadjuvant chemotherapy + radical hysterectomy followed by pelvic radiotherapy at ≥ 40 Gy.

Exclusion criteria: patients with stage IV cervical cancer, patients with metastases to other organs, and

patients with a history of not receiving radiotherapy were excluded.

A total of 1,117 medical histories were selected. Patients with incomplete medical histories, unclear histological analyses, or those who had moved to another city were not enrolled.

Finally, 697 out of 883 patients meeting the selection criteria were included in the study.

Results:

Patient characteristics: The clinical and pathological characteristics of the patients included in the study are presented in Table 1. The average age was 50 years (range: 18-76 years). Most patients (35.1%) had stage IIa cervical cancer. According to histological examination, squamous cell carcinoma accounted for 76.3% of cases.

Median follow-up was 78 months (3 to 124 months). The survival rate associated with cervical cancer recurrence in different age groups of patients are provided in Table 1.

Table 1 – Cervical cancer recurrence rate in different age groups of patients (over the ten-years follow-up)

Age groups	Patients per age group (n=697)		Patients with pro-gression per age group (n=74)		Patients with recur-rece per age group (n=19)	
	abs.	%	abs.	%	abs.	%
18-29	19	2.1	1	1.4	0	0.0
30-39	105	20.7	6	8.1	1	5.3
40-49	135	21.9	16	21.6	3	15.8
50-59	187	26.6	21	28.4	5	26.3
60-69	177	20.0	20	27.0	6	31.6
≥ 70	74	8.5	10	13.5	4	21.1
Total:	697	100%	74	100%	19	100%

The disease has exacerbated in 57 patients (77.0%), involving vaginal metastases, regional lymph nodes, and IIaSt in each patient. Distant metastases were detected in 17 patients (22.9%), most frequently affecting the lungs (n=14) and paracentric lymph nodes (n=3). Exacerbations were reported in 19 patients. The most frequent progression and recurrence occurred in the age range of 50 to 59 years.

In the group of patients with progressing cervical cancer (within 6 months), the histological form of squamous cell cancer was registered in 60.8% of cases (n=74 patients), often occurring in patients with stage I disease (10.6%).

The proportion of patients with adenocarcinoma was 31.0%. Glandular squamous cell carcinoma (2.7%) was more common in patients with stage II disease; low-grade cancer was detected in 5.6% (Table 2).

Table 2 – Recurrence development and frequency depending on the primary tumor morphological structure

Tumor structure morphological type	Patients with tumor progression (n=74)		Patients with recur-rent tumors (n=19)	
	abs.	%	abs.	%
Squamous cell carcinoma	45	60.8	1	5.4
Adenocarcinoma	23	31.0	5	26.3
Glandular squamous cell	2	2.5	0	0.0
Poorly differentiated cancer	4	5.6	13	68.4

Table 3 – Progression and recurrence periods

Period of exacerbation and recurrence (months)	Cervical cancer progression (n = 74)		Patients with recur-rece (n = 19)	
	abs. number	%	abs. number	%
Within 3	23	21.2	-	-
5-6	51	68.7	-	-
7-12	-	-	6	-
13-18	-	-	12	63.1
19-24	-	-	1	5.2
After 24	-	-	-	31.5

The higher the stage of the disease was, the shorter was the recurrence period. Progression was most often (68.7%) between the 5th and 6th months. In 63.1% of

cases, cervical cancer recurred within 18 months after treatment, so this period may be the most likely time for recurrence.

Table 4 – Average life expectancy

Development and recurrence of cervical cancer	Average			
	Control	Standard error	Confidence interval 95%	
			Lower confidence limit	Upper confidence limit
Progress	3.390	0.114	3.166	3.615
Recurrence	3.529	0.206	3.126	3.933
Total	3.412	0.101	3.213	3.611

The most “dangerous” period with an increased risk of recurrence is between 19 and 24 months. During this period, recurrence was registered in 5.3% of patients. Within 2 years, recurrence was reported in 31.5% of patients with cervical cancer.

Discussion: Most recurrences occur within 2 years of diagnostics, the prognosis is severe, and most patients die of untreated disease. In a retrospective review of over 500 patients treated at the University of Kentucky, recurrence was found in 31% of patients, of whom 58% recurred within a year and 76% within 2 years. In this trial, only 6% of patients with recurrent tumors lived without an exacerbation for 3 years. Patients with recurrent cervical cancer can be divided into subgroups by prognosis and therapeutic goal. In 50-60% of patients, the disease is located outside the pelvis; such cases are mostly untreatable. The treatment will be palliative, as in most patients with recurrent pelvic wall lesions of cervical cancer.

Treatment decisions should be based on the patient's condition, the location of recurrence and/or metastasis, the extent of metastatic lesions, and previous treatment.

Patients with recurrent/metastatic cervical cancer may experience a variety of symptoms, including pain, anorexia, vaginal bleeding, cachexia, and psychological problems. The exact treatment of these symptoms is described later in this guideline [12]. Treatment of these symptoms is the main concern of physicians treating patients with recurrent cervical cancer.

There were several limitations in our study. First, a retrospective nature of the study could lead to a distortion of the sample. Second, adjuvant treatment could be changed by decision of the physician. There is still a debate in clinical practice about whether CT and chemotherapy are more effective in patients with cervical cancer with a risk factor compared to CT therapy only.

Conclusions: Out of 697 cervical cancer patients, 74 (10.6%) women had progression, and 19 (3.0%) had a recurrence in our study. Cervical cancer recurrence was more common in women aged 45-50 years (28.4%) and 50-60 years (26.3%).

The higher was the stage of the disease, the shorter was the period of recurrence. In most cases, progression occurred within 5-6 months after treatment. 68.7% of progressions and 63.1% of recurrences occurred within a year and a half after treatment, which

is considered the most “dangerous” period for cervical cancer recurrence. The most “dangerous” period in terms of recurrence was between 19 and 24 months (recurrence rate of 5.3%) and after two years (31.5% of patients with cervical cancer).

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ТҰЖЫРЫМ

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Қатерлі ісікті диагностикалауды жақсарту жолдары және жатыр мойны обырының дамуы мен қайталануының қауіпін анықтау

Өзектілігі: Жатыр мойны обыры (КК) дүние жүзінде әйелдер арасында өлім себептері арасында төртінші және қатерлі ісіктердің даму құрылымында үшінші орында.

Мақсаты: күрделі емнен (неоадьювантты химиотерапия + ради-калды гистерэктомия + аралас сәулелік терапия) жатыр мойны обыры бар науқастарда асқыну және қайталану басталғанға дейінгі қауіп факторларын және уақыт аралығын анықтау.

Әдістер: 2011-2021 жылдар аралығында Шымкент қаласындағы қалалық онкологиялық диспансерде есепте тұрған жатыр мойны обырының ІВ-IIА сатысы бар науқастарға ретроспективті жағдай-бақылау зерттеуі жүргізілді (n=883). Барлық науқастарға ≥40 г дозада жамбас лимфа түйіндерін кесу және кіші жамбастың сәулелік терапиясымен радикалды гистерэктомия жасалды. Зерттеудің 10 жылында жасына, аурудың сатысына және ісіктің морфологиялық құрылымына байланысты өмір сүрудің қауіп факторлары және қайталану қауіпін талданған.

Нәтижелері: Аурудың сатысы неғұрлым жоғары болса, қайталану кезеңі соғұрлым қысқа болады. Көбінесе прогрессияның кезеңі 5 айдан 6 айға дейін созылады. Жатыр мойны обырының асқыну жағдайларының 68,7% және қайталану жағдайларының 63,1% емдеу аяқталғаннан кейін бір жарым жыл ішінде орын алды, сондықтан бұл кезең қайталану қауіпін жоғарылаған кезде ең «қауіпті» болып саналады. 19 айдан 24 айға дейінгі кезеңде рецидив 5,3%-да, ал 2 жылдан астам - жатыр мойны обыры бар науқастардың 31,5%-ында байқалды.

Қорытынды: Жатыр мойны обыры бар 883 науқастың 74 (10,6%) әйелде асқыну, 19-ында (3,0%) қайталану болды. Жатыр мойны обырының қайталануы 45-50 жас (28,4%) және 50-60 жас (26,3%) жастағы әйелдерде жиі байқалды.

Түйінді сөздер: жатыр мойны обыры (КК), қауіп факторы, прогрессия, рецидив.

АННОТАЦИЯ

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Способы улучшения диагностики и выявления риска развития и рецидива рака шейки матки

Актуальность: Рак шейки матки (РШМ) занимает четвертое место среди причин смертности и третье место в структуре заболеваемости злокачественными опухолями у женщин во всем мире.

Цель: определить факторы риска и промежуток времени до прогрессирования и рецидива у больных раком шейки матки после комплексного лечения (неоадьювантная химиотерапия + радикальная гистерэктомия + комбинированная лучевая терапия).

Методы: Проведено ретроспективное исследование случай-контроль у больных РШМ ІВ-IIА стадии, состоявших на учете в городском онкологическом диспансере г. Шымкента с 2011 по 2021 год (n=883). Все пациентки перенесли радикальную гистерэктомию с иссечением тазовых лимфатических узлов и лучевую терапию нижнего таза в дозе ≥40 гр. За 10 лет исследования были проанализированы факторы выживаемости и риск рецидива в зависимости от возраста пациенток, стадии заболевания и морфологической структуры опухоли.

Результаты: Чем выше стадия заболевания, тем короче период рецидива. Чаще всего прогрессирование составляло от 5 до 6 месяцев. 68,7% случаев прогрессирования и 63,1% случаев рецидива РШМ имели место в первые полтора года после окончания лечения, поэтому этот период считается наиболее «опасным», когда увеличивается риск рецидива. В период от 19 до 24 месяцев рецидивы наблюдались у 5,3%, а более 2 лет – у 31,5% больных РШМ.

Заключение: Из 883 больных РШМ, у 74 (10,6%) женщин наблюдалось прогрессирование, а у 19 (3,0%) – рецидив. Рецидивы РШМ чаще отмечались у женщин в возрасте 45-50 лет (28,4%) и 50-60 лет (26,3%).

Ключевые слова: рак шейки матки (РШМ), фактор риска, прогрессирование, рецидив.

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