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Radiation injuries during combined radiation treatment of locally distributed cervical cancer: A literary review

Relevance: Radiation therapy is one of the leading methods of treating malignant tumors of female genital organs. However, modern radiotherapeutic equipment technical capacity does not exclude the possibility of radiation complications from healthy organs and tissues in the radiation zone. During radiation treatment (administered independently or in combination with other methods), patients develop local radiation reactions of different intensity from related organs, such as the bladder, rectum, and vagina, which significantly deteriorate patients' quality of life. This also leads to involuntary interruptions in treatment and, finally, worsens the treatment outcome.

Purpose: To describe radiation injuries to pelvic organs in cervical cancer radiation treatment. It analyzes the frequency and evidence of early and late radiation reactions from the affected organs.

Results: Radiation injuries to the pelvic organs form the basis of radiation pathology in patients with cervical cancer and largely determine cured patients' quality of life. Radiation complications of grade II-III, less often IV, are frequent after radiation treatment for pelvic cancer, especially cervical cancer.

Conclusions: Despite the improvements in radiation treatment methods, there is still no unified system for preventing radiation reactions that would include algorithms for diagnosing and treating early and late radiation reactions using modern medications and non-pharmacological options. The development and implementation of an algorithm for the correction of radiation reactions after radiation and complex treatment for cervical cancer would timely prevent radiation and combined complications from target organs and improve patients' quality of life.

Keywords: radiation therapy (RT), cervical cancer, radiation reaction (RR), quality of life (QoL).

Introduction:

Radiation therapy (RT) remains one of the leading methods of treating patients with cancers of the female reproductive system. However, modern radiotherapeutic equipment technical capacity does not exclude the possibility of radiation complications from healthy organs and tissues in the radiation zone. During RT, patients develop local radiation reactions (RR) of different intensity from related organs, such as the bladder, rectum, and vagina; such reactions significantly deteriorate the patients' quality of life (QoL). This also leads to involuntary interruptions in treatment and, finally, worsens the treatment outcome.

Purpose: To radiation injuries to pelvic organs in cervical cancer radiation treatment. It analyzes the frequency and evidence of early and late radiation reactions from the affected organs.

Materials and methods:

A literature search was conducted in the search systems of PubMed and Google Scholar, the databases of Scopus, Web of Science, MedLine, The Cochrane Library, Global Health, CyberLeninka, and other sources by the following keywords: "radiotherapy," "cervical cancer," "radiation damage." The search covered the sources published in 2000-2020. Initially, a search period of 10 years was chosen; however, due to the limited number of publications, it was decided to expand the search to a period of 20 years.

The search by keywords was done automatically, followed by a manual search. The latter has identified sev-

eral additional literary sources. The inclusion criteria were: 1) publications in English and Russian; 2) research involving humans; 3) studies examining significant clinical outcomes of cervical cancer treatment (overall mortality, cancer-specific mortality, as well as patient survival). The publications that did not meet the inclusion criteria were excluded from the analysis.

The survey included 26 relevant articles for 2000-2020, reflecting the essence of the study problem.

Results:

Causes and types of radiation reactions

Radiation injuries occur due to errors in the planning and execution of RT when the applied single and cumulative doses exceed the tolerance of healthy tissues to ionizing radiation. Besides, the dose distribution peculiarities in the organs adjoining malignant neoplasm are often not taken into account [1]. Various authors have noted that radiation injuries are more frequent in patients with various chronic co-morbidities (70% of all cases) than in patients without chronic co-morbidities (18.1%) [2].

In terms of manifestation, RRs are divided into local and generalized. Generalized RR is the response of the whole organism to the effects of ionizing radiation, manifested by elevated temperature, dysfunction of the gastrointestinal tract, cardiovascular activity, and changes in other systems [3]. Local RRs are characterized by changes in the radiation zone itself. Most authors divide RRs into early and late. Early RRs include

pathological changes that occur during or within three months after RT. These changes are functional and often reversible. Most of them pass within the next four months.

According to various authors, early radiation injuries occur in 69-83.6% of cases [4]. Radiation injuries of different degrees of severity are natural in RT or combined therapy. According to WHO recommendations, their frequency shall not exceed the acceptable level of 5%. Damage to the degree of severity IV-V is not acceptable since it impairs the patient's QoL and social activity and can lead to severe disability and even death in certain cases [5].

Radial injuries of the bladder and rectum are the main manifestations of late radiation pathology in pelvic cancer patients. In many ways, they determine the QoL of patients after tumor treatment. Various authors report late radiation complications in 5-15% cases, up to 45-50% in some clinics. Radiocystitis is registered in 2-76% of cases and accounts for 2-5% of serious injuries. Radiation injuries occur in 14-63% of patients; severe (ulcerative and fistula) radiation injuries appear in 0.4-11% of patients. Radial epithets in the vagina and/or on the cervix uteri range from 4.6 to 52% of all treated CC cases. Such dispersion is primarily due to the lack of unified criteria for assessing radial injuries [6].

The frequency of radiation damage depends both on the total focal dose (TFD) and the single dose (SD). Some authors report the probability of early radial reactions from the rectum of 12% at SD 9.4 and 9.8 Gy once a week and a probability of late radiation complications of 7% at SD 9.1 and 9.3 Gy. In treating cervical cancer, an increase of TFD from 80 to 100 Gy increased the RR rate from 8.2% to 18% [7].

There are several classifications of radial cystitis and recites. At present, most radiological centers use the classification developed by the Radiotherapeutic Oncology Group, together with the European Organization for Research and Treatment of Cancer (RTOG/EORC). These injuries are assessed on a six-point scale (0-5) by the severity of manifestation, where «0» means the absence of changes, and «5» – the death of the patient as a result of radiation damage. [8].

Radial reactions from the intestine

The first clinical report of bowel damage after RT for a malignant neoplasm was made in 1917 by K. Franz and J. Orth. The number of complications increased with the expanded use of RT. RT of small pelvic malignant tumors inevitably irradiates different parts of the small or large intestine [9]. At doses above tolerance (35 Gy for the small intestine, 40-45 Gy for the large intestine), 10-15% of patients develop early or late radiation symptomatic injuries. The course and outcome of such injuries vary depending on the dose and some other factors [10].

A review of modern literature revealed very few studies of the reasons for developing radial damage depending on the treatment technology. The treatment of colon post-radiation complications is mainly symptomatic [11].

Radial lesions of the rectum

RT of the pelvic region is connected with colon and rectum dysfunction. According to the literature, complications from the colon are more common than those from the rectum and occur in 10 to 32% of cases [12, 13].

Lesions on the bladder

The assessment of combined intracavity RT effectiveness for patients with stages II-III cervical cancer confirmed the dose-dependence of the frequency and severity of radiative lesions of the bladder and rectum. For example, the late radial cystitis occurred in 11.2% of cases at a high dose rate and 7.1% of cases at a low dose rate. However, the lower dose rate was associated with a higher frequency of vesicovaginal fistulas – 0.9% and late injuries met in 8.5% cases [14, 15].

The most common urological complication is post-radiation cystitis, which occurs in the RT background at the end of treatment, or several years after [7]. Some researchers report the bladder irradiation at a focal dose of 35 Gy, the others – at a dose above 40 Gy. A dose increase to achieve a better treatment outcome with malignant pelvic tumors can lead to more severe bladder irradiation [16].

Late radial injuries are more common than early ones. The clinical courses of early and late bladder lesions have a lot in common [17, 18]. Thus, the probability of late radiation complications in the form of disruption of the structure and function of the bladder and rectum depends on many factors such as the total absorbed dose, the fractionation and planning methods, the amount of irradiated tissue, the contagious diseases of irradiated organs. The risk of radiation damage depends on the total absorbed or single focal dose, the intervals between exposure sessions, and dose rates [19, 20]. The use of remote radiation from two contrasting open fields significantly increases the frequency of bladder and rectum irradiation compared to the RT in which the uterus and neighboring organs are shielded from remote action (irradiation from 4 fields or using forming blocks, rotational irradiation method). The advent of conformal RT allows extending the therapeutic range of radiation action without increasing the frequency of radiation complications. Non-traditional hypofractionation regimes used since recently to treat cervical cancer reduce the total duration of treatment and result in rapid tumor regression and reoxygenation [21].

Lesions of the ureters

Another serious complication of pelvic organ RT is the lower third of the ureters post-radiation strictures, which can significantly deform the upper urinary tract. The literature reports a scar narrowing the urinary tract in 23-29% of women after RT [22].

The genesis of strictures of the ureters like lymphatic edema in these patients is caused by the development of pronounced intrapelvic radiation fibrosis. Such lesions of the urinary tract can occur up to two years after RT, especially after repeated RT [23].

The upper urinary tract's retinal complications are important for the prognosis of disease and QoL of patients with cervical cancer. Hydronephrotic changes are the consequence of the tumor growth in the parameter cell and the metastasizing into the regional lymph nodes with post-radiation fibrosis changes of the ureters [24, 25]. Hydronephrosis accounts for 1.4-2% of postoperative complications and about 4-9% of post-radiation complications. Hydronephrosis is most often (~59%) caused by tumor growth progression or is related to radiation and combination therapies (~32%) [25].

Radial lesions to the vagina

Errors related to excessive doses of radiation, the deficiencies in radiation planning and implementation, individual sensitivity, and the lack of protective therapy contribute to the development of extensive post-radiation vaginal damage. Urinary fistula is the most problematic in treatment. Bladder-vaginal fistula is one of the most difficult conditions. It causes physical and mental suffering to the female patient and disturbs the entire urinary tract anatomical functioning [26].

Conclusions

The body reactions to radiation are very diverse and depend on both the radiation and body conditions. The biological effect is dose-dependent. The irradiation effect is also associated with the time distribution of the dose, i.e., the rate of energy absorption. The separation of the same total dose into separate fractions and the intermittent conduct of irradiation reduces the irradiation rate since the recovery processes that start immediately after irradiation can partially compensate for the resulting disruptions. The most lethal effect occurs when the whole body is irradiated (total irradiation), while the same dose affecting single parts of the body causes smaller changes (local exposure).

To sum up, despite the improvements in RT methods, there is still no unified system for preventing RRs that would include algorithms for diagnosing and treating early and late RRs using modern medications and non-pharmacological options. As a result, when RR is used for treating pelvic cancer, especially cervical cancer, the incidence of radiation complications of grade II-III, less often IV, is still quite high. No preventive recommendations have been developed for the use of modern RT methods; no new therapeutic methods have been proposed for the treatment of developing complications that would improve the QoL of patients.

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ТҰЖЫРЫМ

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Жергілікті кең таралған жатыр мойны қатерлі ісігінің біріктірілген радиациялық терапиясы кезіндегі сәулелік зақымданулар: Әдеби шолу

Өзектілігі: Сәулелік терапия әйелдер арасындағы жыныс мүшелерде болатын қатерлі ісіктері бар науқастарды емдеуде жетекші орындардың бірін алатын ем. Алайда, қазіргі сәулелік терапия жабдықтарының ең жоғары техникалық мүмкіндіктері де сәулелену аймағындағы сау мүшелер мен тініндегі сәулелік асқынулардың дамуын жоққа шығара алмайды. Сәулелік терапияны жүргізу кезінде (тәуелсіз түрде де, басқа да әдістермен бірге) пациенттер тік ішектен, қуықтан және қынаптан әртүрлі қарқындылықтағы жергілікті сәулелік реакцияларды дамытады, бұл пациенттердің өмір сүру сапасын нашарлатады, емдеудегі мәжбүрлі үзілістерге және қорыта келгенде, қатерлі ісік ауруының нәтижелерін төмендетеді.

Зерттеудің мақсаты: Оқырманға жатыр мойны қатерлі ісігіне жасалған сәулелік терапия кезінде жамбас мүшелеріне радиациялық зақымдану жағдайына егжей-тегжейлі шолу жасауды, зардап шеккен пациенттердің сәулелік реакцияларының ерте және кеш жиілігі мен ауырлығын талдауды ұсыну.

Нәтижелер: Жамбас мүшелерінің сәулелік реакциясы жатыр мойны қатерлі ісігі бар пациенттерде радиациялық патологияның негізін құрайды және көбінесе ісікті емдеген пациенттердің өмір сүру сапасын анықтайды. Нәтижесінде, жамбас ағзаларының қатерлі ісігін емдеуде сәулелік терапияны қолданған кезде II - III дәрежелі радиациялық асқынулар жиі кездеседі, ал IV дәрежелі асқынулар сирек болады.

Қорытынды: Сәулелік терапияның заманауи әдістерінің жетілдірілгеніне қарамастан, қазіргі кезде сәулелік реакциялардың асқынуларының алдын-алудың бірыңғай жүйесі жоқ, оның ішінде қазіргі заманғы медициналық пен медициналық емес мүмкіндіктерді қолдана отырып, ерте және кеш сәулелік реакцияларды диагностикалау және емдеу алгоритмдері жоқ.

Сәулелік реакцияларды түзету алгоритмін қолдану және жатыр мойны қатерлі ісігін кешенді емдеу тәжірибеде мақсатты органдардан сәулеленуді және аралас асқынуларды уақтылы болдырмауға және пациенттердің өмір сүру сапасын жақсартуға мүмкіндік береді.

Түйінді сөздер: радиациялық терапия, жатыр мойны обыры, сәулелік жарақаттар.

АННОТАЦИЯ

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Радиационные повреждения при комбинированной лучевой терапии местно-распространенного рака шейки матки: Обзор литературы

Актуальность: Лучевая терапия занимает одно из ведущих мест в лечении больных со злокачественными опухолями женских половых органов. Однако даже самые высокие технические возможности современной радиотерапевтической аппаратуры не исключают развития лучевых осложнений со стороны здоровых органов и тканей в зоне облучения. При проведении лучевой терапии (как самостоятельного вида лечения, так и в комбинации с другими методами) у большинства пациенток развиваются местные лучевые реакции различной степени интенсивности со стороны смежных органов, таких как мочевого пузыря, прямая кишка, влагалище. Эти реакции ухудшают качество жизни пациенток, приводят к вынужденным перерывам в лечении и, в конечном итоге, ухудшают онкологические результаты.

Цель исследования: представить читателю подробный обзор ситуации по радиационным повреждениям органов малого таза при лучевой терапии рака шейки матки, проанализировать частоту и выраженность ранних и поздних лучевых реакций со стороны поражаемых органов.

Результаты: Лучевые повреждения органов малого таза составляют основу лучевой патологии у больных раком шейки матки и во многом определяют качество жизни излеченных больных. При использовании радиационной терапии в лечении рака органов малого таза, в частности рака шейки матки, высокая частота лучевых осложнений степени II – III, реже IV.

Выводы: Несмотря на совершенствование современных методов лучевой терапии, на сегодняшний день не сложилась единая система профилактики лучевых реакций, включающая в себя алгоритмы диагностики и лечения ранних и поздних лучевых реакций с использованием современных медикаментозных и немедикаментозных возможностей. Разработка и внедрение в практическую деятельность алгоритма коррекции лучевых реакций лучевого и комплексного лечения РШМ позволяет своевременно предупредить лучевые и комбинированные осложнения со стороны органов таза и улучшить качество жизни больных.

Ключевые слова: лучевая терапия (РТ), рак шейки матки (РШМ), лучевая реакция (ЛР), качество жизни (КЖ).

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