

BRACHYTHERAPY IN TREATMENT OF VAGINAL CANCER

Kaprin A.D.¹, Galkin V.N.¹, Ivanov S.A.¹, Solodkiy V.A.², Titova V.A.²

¹National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Moscow, Russia

²Russian Scientific Center of Roentgeno-Radiology, Moscow, Russia

Abstract

Characteristics of diagnosis and treatment of different types of primary vaginal cancer are highlighted, the role and place of brachytherapy as independent method or combined treatment modality for this pathology is shown in the review. Epidemiological data on incidence of vaginal cancer in Russia are represented, presumptive mechanisms for development of the disease, risk factors, histological types, features of the course, clinical presentation, diagnostic algorithm are described. Treatment methods for primary vaginal cancer according to world standards such as surgery, radiotherapy and systemic drug therapy are covered. Specifics of radiological methods of treatment (low-dose rate and high-dose rate brachytherapy, including the combination with external beam radiotherapy) according to the stage of the disease, are shown in details. The results of several large foreign clinical trials for efficiency of different methods of radiotherapy are discussed. The combination of brachytherapy on primary tumor with external radiation therapy to the lymph nodes was confirmed to be the most effective modality. The conclusion on opportunities of different methods of radiotherapy in treatment of vaginal cancer was made.

Keywords: radiotherapy, brachytherapy, microspheres, vaginal cancer.

For citations: Kaprin A.D., Galkin V.N., Ivanov S.A., Solodkiy V.A., Titova V.A. Brachytherapy in treatment of vaginal cancer, *Biomedical Photonics*, 2016, T. 5, No. 1, pp. 22–27.

Contacts: Titova V.A., e-mail: mailbox@rncrr.rssi.ru

Introduction

Primary tumors of vagina are encountered rarely and make up 1-2% of all malignant tumors of female genital organs. Secondary (metastatic) tumors of vagina are several times more frequent. Metastatic tumors of vagina are very often caused by cervical cancer, endometrial cancer, trophoblastoma and uterine sarcoma, rarely – by ovarian cancer and hypernephroma. According to the regulations accepted by FIGO, in case of simultaneous diagnosis of squamous cervical cancer (SCC) and vagina

cancer (VC), they are regarded as a vaginal variant of SCC. In case of malignant damage of vulva and vagina, “vulvar cancer” is diagnosed. Taking into consideration the same embryogenesis of vulva, vagina and uterine cervix from urogenital sinus, it is assumed that tumors of these localizations have common etiology and pathogenesis. However, one should not consider these tumors to be similar, as VC occurs 30-40 times less frequently than SCC.

The tumors originating in the vaginal part of uterine cervix and passing on to the vagina wall

must be regarded as cervical tumors. Tumors involving the vulva must be classified as vulvar cancers. Vagina cancer occurring 5 and more years after a successful treatment (complete regression) of cervical cancer is considered to be a primary vagina cancer [2].

Vagina tumors have three age-related incidence peaks. Primary tumors in children of up to 5 years of age are represented by botryoid foetal rhabdomyosarcomas, in patients of 14-20 years of age – by a clear cell adenocarcinoma with transplacental diethylstilbestrol carcinogenesis (in the majority of researches the mothers of these patients took diethylstilbestrol or similar nonsteroidal estrogens during pregnancy), while elder age groups suffer mostly from squamous cancer. Cases of diagnosing adults with non-epithelial malignant tumors, such as sarcoma and melanoma, are extremely rare. 30% of patients with primary vagina cancer have a preinvasive or invasive stage of cervical cancer in antecedent anamnesis [1, 3].

The risk factors for VC development are:

- contamination of a woman, during her life, with HPV, HSV-2 and HIV viruses with manifestation into pointed condyloma;
- post-menopausal hypogonadism, serious chronic senile colpites, involute or dystrophic post-castration and age-related processes, chronic nonspecific vaginitis.
- irradiation or immunodepression (of local and general character) in patients who underwent combined radiotherapy for cancer of other pelvic organs, or immunodepressive treatment after transplantation of organs;
- mechanical damages of the vagina mucous tunic in patients with complete falling of womb due to the use of pessaries ;
- relative predilection to development of squamous cancer in young women who underwent reconstructive-plastic surgeries of vagina in antecedent anamnesis;
- use of oral contraceptives (synthetic estrogens);
- smoking in combination with other etiopathogenetic factors.

Many authors consider that the cycle of VC development includes dysplasia, preinvasive and invasive types of cancer. The duration of invasive cancer development from its preinvasive stage is 12-15 years in average. In case of dysplasia or intraepithelial VC, it is quite sufficient to perform a surgery with excision of the pathologic focus, cryodestruction by laser, contact radiotherapy. Henceforth, it is necessary to perform cytologic

and colposcopic monitoring of the vagina mucous tunic [4].

Most frequently, primary VC is represented by squamous cancer or its types. There occur differentiated (cornific) and non-differentiated (non-cornific) types of tumors. Other types of malignant vaginal epithelial neoplasms (rare types) include the verrucose basal-cellular vaginal tumors and adenocarcinomas [5, 6]. Adenocarcinoma development is related to focal points of vaginal adenosis. At that, depending on its histologic type, a mucic-, endometriotic- and clear-cell carcinomas can develop. In the treatment of histologic types of vaginal neoplasms, preference shall be given to surgical and combined methods.

The predominant type of primary VC dissemination is a lymphogenous one. Dissemination pathways and topography of lymphogenous metastases are determined by the tumor localization. In case of a cancer of the vagina top third part, metastases develop in the same lymphatic basins, as in the case with SCC: outer-, inner iliac- and obturator lymph nodes. Tumors of the vagina top third part metastasize, like in the case with vulvar cancer, into femoroinguinal lymph nodes. Comparatively rare tumors of the vagina middle third part can metastasize into the lymph nodes of the pelvis (including the lower cluneal ones), interfacial lymph nodes and deep inguinal ones [4].

The tumor progression is accompanied by dissemination into the soft tissues of the perineum, parametrium, bladder, and rectum; at late stages, dissemination of tumor occurs in bones and lungs [2, 4].

The clinical presentation of VC is rather multiform, which, undoubtedly, leads to certain peculiarities and difficulties of diagnosing. In particular, they become evident during the analysis of symptoms at different stages of the disease. Thus, the frequency of blood-tinged discharges and the ratio of pain significantly increase in line with the degree of tumor dissemination. At the same time, the frequency of an asymptomatic clinical course decreases threefold, and the transfer from the first stage to the second one happens abruptly. Consequently, presence of pain in a patient with a vaginal neoplasm practically testifies the process expansion over the organ limits; at early stages of carcinoma development, it is often detected accidentally [7].

At an attentive pelvic examination, the diagnosis of VC does not cause any difficulties. Examination should be done with the help of speculums; it is necessary to attentively examine

the vaginal fornix and not to forget that most vaginal tumors, especially at early stages of their development, localize in its top third part. Taking into consideration the fact that vaginal tumors refer to "visual" localization, successively performed colposcopy, cytological examination and biopsy ensure a definite diagnosis. An extrinsic value in this row belongs to the biopsy of suspicious areas, which allows to confirm or exclude a tumor with high accuracy (up to 95%) [2, 8]. The following types of examinations are performed in order to specify the degree of the process dissemination: ultrasonography of small pelvis- and abdominal space organs, cystoscopy, proctosigmoidoscopy, chest X-ray study, isotopic examination of the skeleton bones, etc. Hi-technology examination methods, including MRI, CT and PET-CT with fluorodeoxyglucose radiopharmaceutical (FDG-PET), appear to be rather useful but not strictly obligatory, taking into consideration their high cost.

Thus, C. Lopez et.al (2005) note that, in case of vagina cancer, MRI is used for diagnosis of metastases into regional lymph nodes, but the MRI picture of a primary tumor is not specific [9].

The research of W.T. Lamoreaux (2005) compared the results of CT and FDG-PET studies in 23 patients with stages II – IV of vagina cancer. Primary vagina cancer was diagnosed in 43% of cases via CT, and in 100% of cases via FDG-PET. Presence of metastases in inguinal and pelvic lymph nodes was detected in 17% of patients with CT, and in 35% of patients with FDG-PET. The authors make a conclusion about a higher diagnostic effectiveness of FDG-PET compared with CT for tumors with this localization [10].

According to worldwide standards, VC treatment includes surgical- and radiotherapy, as well as systemic drug therapy. Choice of a treatment method mainly depends on the disease stage, taking into account the histologic type of the tumor, the patient's age and her somatic status.

Taking into consideration anatomic-topographic peculiarities of VC dissemination, the preferable way of treatment in modern standards is radiotherapy: teletherapy and brachytherapy.

Brachytherapy is treatment of malignant tumors with radioactive sources located very closely to or inside the target [11]. Along with this, the term "contact irradiation" is also used.

The brachytherapy dose rate within the limits of 0,4-2 Gy/h is defined as a low one (low dose rate – LDR), the dose rate between 2 and 12 Gy/h is called a middle one (middle dose rate – MDR), and

the dose rate above 12 Gy/h is called a high one (high dose rate – HDR) [12].

Methods of vaginal tumors brachytherapy are largely variable. There are interstitial, intracavitary and contact methods. The most widespread method is intracavitary radiation using cylindrical colpostats with different location of sources Co^{60} , Cs^{137} and Ir^{192} [13, 14]. Contact irradiation of tumors localized in the top third part of the vagina is performed with the same applicators, as in cases of cervical cancer brachytherapy. If a neoplasm is located in the middle and lower third of the vagina, vaginal cylinders of different modifications are used. Besides, it is most reasonable to take vaginal cylinders with big diameters in order to improve the ratio between radiation action on the tumor and mucous tunic. Along with one-channel vaginal cylinders, there exist vaginal cylinders with a few channels that contribute to creation of optimal isodose distribution around the cylinder.

There are no principal differences between teleirradiation and brachytherapy in terms of radiation effect mechanism that causes destruction of cells, damage of normal tissues and elimination of the tumor. Radiobiological principles of both radiotherapy variants have much in common. At the same time, the physical features of the spatial and temporal distribution of the absorbed dose differ significantly. The conceptual issues to define brachytherapy effectiveness are as follows: the value of a teleirradiation dose rate (in case of low dose rate application) and the model of functioning (in case of high dose rate application).

The scheduling of primary VC treatment depends on the disease stage. At stages TisNOMO and T1NOMO, only young patients with tumors localized in the top third part of the vagina undergo operative therapy: extensive hysterectomy with removal of one half of the vagina is performed. In other clinical groups, patients with stage TisNOMO undergo only intracavitary irradiation of cumulative basic dose (CBD) reaching 60 Gy with LDR, and CBD 35 Gy with HDR. In the case when the tumor size is up to 1 cm and the infiltration of the vagina wall is up 0.5 cm, they undergo only intracavitary irradiation with CBD reaching 60 Gy with LDR, and CBD 35 with HDR. In the cases of the same T1NOMO stage and a large size of tumor or a low degree of differentiation, there is additionally performed tumor teleirradiation with CBD 20 Gy and regional lymphatic outflow zones irradiation with CBD of up to 40 Gy. At stage T2NOMO, use is made of a complex radiation treatment: intracavitary irradiation with CBD of up to 70 Gy

with LDR and with CBD of up to 35-40 Gy with HDR, and teleirradiation of tumor with CBD 20 Gy and of regional lymphatic outflow zones – with CBD of up to 45 Gy. At stages T1–3N1M0 and T4N0M0, based on individual indications, the radiation treatment is also complex: intracavitary or interstitial irradiation with CBD reaching 70 Gy with LDR and CBD of up to 40 Gy with HDR, and teleirradiation of tumor with CBD 30 Gy and of regional lymphatic outflow zones – with CBD of up to 50 Gy [12].

One of the first big reports, which was based on the results of primary VC treatment in 434 patients who underwent treatment from 1952 till 1984, was submitted by H. Kucera et.al [15]. The biggest part of the women underwent standard LDR brachytherapy with use of radium sources. Data on the five-year survival rate was presented according to the disease stages: stage I – 76,7%, stage II – 44,5%, stage III – 31,0%, stage IV – 18,2%. This data was later presented with comparison to HDR brachytherapy. No significant differences were noted in the results of radiotherapy by the two brachytherapy methods [16].

In another study, R. Perez et.al estimated the role of prognostic and technical radiotherapy factors in 212 patients with VC. The size of the primary vaginal tumor was acknowledged as the most important prognostic factor. The actuarial ten-year survival rate of patients with the disease of stage 0 was 94%, stage I – 80%, stage II – 55%, stage III – 35%, stage IV – 0%. Among patients with stage I of VC (treated only with brachytherapy), the result was similar to the result of the complex radiotherapy. The incidence of complications at stages 2 and 3 was 7% [17].

The results of another massive study of VC patients' treatment were submitted by Gustav Russi Institute. 103 patients were treated in the period from 1970 till 1998. The biggest part of the patients (82%) underwent complex radiotherapy. The average CBD was 50 Gy. The average CBD of the brachytherapy was 10 Gy. The general five-year survival rate was as follows: at stage I – 67%, at stage II – 61%, at stage III – 35%, at stage IV – 20% [18].

The role of interstitial brachytherapy in treatment of primary VC remains rather contradictory. 10 (14%) patients was diagnosed stage I of the disease, 14 (20%) patients – stage IIa, 25 (35%) patients – stage IIb, 15 (21%) patients – stage III, and 7 (10%) patients – stage IV. Complex radiotherapy was applied to 88% of women (CBD – up to 50,4 Gy, with central block settings beyond 40 Gy). The cumulative dose of interstitial brachytherapy was

within the limits of 16,5-22 Gy and depended on the disease stage. The general ten-year survival rate was 58%. Severe radial complications were observed in 13% of patients [19].

Until recently, VC treatment with chemotherapy was conducted only for mitigation of incurable cases. At present, in case of an extensive process, radiotherapy is supplemented by drug therapy with Cisplatinum in the mode similar to the one used in SCC treatment – 40 mg/m² once a week. B. Panici et.al published the results of the neoadjuvant chemotherapy (NJCT) and a subsequent radical surgery on the survival rate of patients with vagina cancer of stage II. After neoadjuvant treatment, partial or complete resorption of the tumor was observed in more than 90% of patients. At the second treatment stage, all patients underwent surgeries. Depending on the process extent, the patients underwent radical hysterectomy of type III, radical vaginectomy or double-sided extra-peritoneal lymph dissection. If the lower third part of the vagina was involved into the neoplastic process prior to NJCT, inguinal lymph nodes were also removed.

Important criteria to evaluate treatment efficiency are the general and relapse-free survival rates of the patients. The information on the relapse rate after the primary VC treatment is rather discrepant. In literature, there are data on the disease relapses in 23-83% of patients. The fact that, in 67% of cases, the only localizations of relapses are small pelvis organs and lymph nodes is considered to be important. The occurrence periods are also different – from 7 to 56 months. For a number of authors, this circumstance makes it possible to make a practical conclusion that, after the treatment termination, close control over the patients with obligatory cytologic screening every 6-12 months is obligatory [5].

Conclusion

The anatomic and topographic peculiarities of the vagina limit the use of the surgical method in the treatment of malignant tumors with this localization. Scientific data allow making a conclusion about advantages of the surgical method against radiotherapy only at stage I of vagina cancer. In the cases with bigger dissemination of the neoplastic process, the method of choice should be radiotherapy or chemoradiotherapy. Here, the biggest effectiveness is achieved after a combination of brachytherapy of the primary tumor with teleirradiation of lymph nodes zones.

REFERENCES

1. Bokhman Ya.V. Rukovodstvo po onkoginekologii (Guide-line for oncogynecology). Leningrad, Meditsina Publ., 1989. pp. 1–464.
2. Poddubnaya I.V. Onkologiya: Spravochnik prakticheskogo vracha (Oncology: A Handbook for practitioners). Moscow, MEDpress-inform Publ., 2009, pp. 1–768.
3. Vol'fon N.I. Vliyaniye testosteron-propionata na vozniknovenie eksperimental'nykh opukholei sheiki matki i vlagalishcha u myshei (Impact of testosterone propionate on development of experimental cervical and vaginal tumors in mice), *Voprosy onkologii*, 1960, No. 9, p. 15.
4. Gritsai A.A., Korzhenskaya E.V., Kravets O.A., Kuznetsov V.V., Khokhlova S.V. Klinicheskie rekomendatsii po diagnostike i lecheniyu bol'nykh rakom vlagalishcha (Clinical guidelines for diagnosis and treatment of patients with vaginal cancer). Moscow, 2014, pp. 1–11.
5. Chistova N.M. Vliyaniye ekstrakta ostrokonechnykh kondilom cheloveka na tkanevye kul'tury vaginal'nogo epiteliya (Effect of human condyloma acuminatum extract on tissue cultures of the vaginal epithelium). *Voprosy onkologii*, 1962, No. 6, pp. 118–125.
6. Levine D.A., De Los Santos J. Handbook for Principles and Practice of Gynecologic oncology. New York, Wolters Kluwer health Publ., 2010, pp. 1–288.
7. Filatova E.I. Pervichnyi rak vlagalishcha. Diagnostika i lechenaya taktika (Primary vaginal cancer: diagnosis and management), *Prakticheskaya onkologiya*, 2006, T.7, No. 4, pp. 228–234.
8. Genadry R., Olson E.J., Parmley T., Woodruff J.D. The morphology of the earliest invasive cell in low genital tract epidermoid neoplasia, *Obstetrics and gynecology*, 1978, Vol. 51 (7), pp. 718–722.
9. Lopez C., Balogun M., Ganesan R., Olliff J.F. MRI of vaginal conditions, *Clinical Radiology*, 2005, Vol. 60, pp. 648–662.
10. Lamoreaux W.T., Grigsby P. W., Dehdashti F., Zoberi I., Powell M.A., Gibb R.K., Rader J.S., Mutch D.G., Siegel B.A. FDG-PET evaluation of vaginal carcinoma. *International Journal of Radiation Oncology, Biology, Physics*, 2005, Vol. 62 (3), pp. 733–737.
11. Basil S.H., Dattatreya N., Anderson L.L. *An Atlas of Brachytherapy*. New York, Macmillan Publishing Company, 1988. 326 p..
12. Turkevich V.G. Luchevoye lechenie pervichnogo i metastaticheskogo raka vlagalishcha (Radiation therapy for primary and metastatic vaginal cancer), *Prakticheskaya onkologiya*, 2006, T. 7, No. 4, pp. 236–245.
13. Perez C.A., Madoc-Jones H. *Carcinoma of the vagina*. Philadelphia, J.B. Lippincott Publ., 1998, Chapter 53, pp. 1023–1035.
14. Stock R.G. *Vaginal Cancer Textbook of radiation oncology*. Philadelphia, W.B.Saunders company, 1998, Chapter 47, pp. 891–906.
15. Kucera H., Vavra N. Radiation management of primary carcinoma of the vagina: clinical and histopathological variables associated with survival, *Gynecological Oncology*, 1991, Vol. 40, pp. 12–16.
16. Kucera H., Mock U., Knocke T.H., Kucera E., Potter R. Radiotherapy alone for invasive vaginal cancer: outcome with intracavitary high dose rate brachytherapy versus conventional low dose rate brachytherapy, *Acta Obstetrica et Gynecologica Scandinavica*, 2001, Vol. 80, pp. 355–360.
17. Perez C., Slessinger E., Grigsby P.W. Design of an afterloading vaginal applicator (MIRALVA), *International Journal of Radiation Oncology, Biology, Physics*, 1990, Vol. 18, pp. 1503–1508.
18. De Crevoisier R., Breton-Callu C., Morice P. et al. Primary squamous cell carcinoma of the vagina / experience at the Gustave-Roussy Institute, *Radiotherapy and oncology*, 2001, Vol. 60 (Abstr. 7).
19. Tewari K.S., Cappuccini F., Puthawala A.A., Kuo J.V., Burger R.A., Monk B.J., Manetta A., Berman M.L., Disaia P.J., Nisar A.M. Primary invasive carcinoma of the vagina: treatment with interstitial brachytherapy, *Cancer*, 2001, Vol. 91, pp. 758–770.