Photodynamic therapy of cervical intraepithelial neoplasia grades II and III with Photolon®

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Summary The objective of the present study was to test in clinics a previously developed novel organ-saving approach for the treatment of CIN using PDT with the photosensitizer Photolon® applied in women of a childbearing age with CIN II and III. A total number of 112 patients aged 35.2 ± 1.6 with morphologically proven diagnosis of CIN II and III were enrolled into the study. All 112 patients had been observed at least during 1-year follow-up period after PDT. Among them 53 patients (44.1%) were subjected to a dynamic observation for less than 2 years; 29 patients (24.1%) were under the observation for less than 3 years; 13 patients (10.8%) — for 3–4 years and 17 women — for more than 4 years. A complete response represented by the complete regression of neoplastic lesions, which was proved by the results of morphological examinations, was revealed in 104 (92.8%) of treated women. In 3 months after treatment a complete eradication of the HPV infection was proven by PCR-analysis in 47 (53.4%) from 88 patients who have been infected with HPV of a highly oncogenic strains before PDT. PDT with Photolon® is an alternative approach for the treatment of cervical intraepithelial neoplasia which can be recommended for women of childbearing age. The simplicity of the procedure as well as it’s high therapeutic efficacy defines the reasonability of its’ introduction into the clinical practice as a new organ-saving method for the treatment of patients with cervical intraepithelial neoplasia.

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Introduction

Cervical cancer is one of the most severe diseases among women of childbearing age. It is assumed that cervical cancer is a malignant neoplasm which is characterized by prolonged clinical behavior and clearly defined preclinical stage called cervical intraepithelial neoplasia (CIN). Several effective methods of cervical cancer diagnosis verification exist as well as effective treatment approaches. It is proven that the probability of the intraepithelial cancer development in patients with CIN is 20 times higher than in healthy women [1,2]. Moreover, the probability of the invasive cer-
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Photolon® applied in women of childbearing age with CIN

The treatment of CIN using PDT with the photosensitizer Photolon® allows to perform multiple treatment procedures in the low risk of severe systemic complications after treatment. This is due to the selective destruction of the target tissue (surgical, laser or electrosurgical excision). The most common adverse effects of such treatment are hemorrhages, endometriosis, traumatization of subjacent tissues with a formation of rough scraps, stenoses and strictures of the cervical channel. Changes in the anatomical structure of the cervix uteri lead to the loss of its’ functionality, e.g. reduction of cervical secretion resulting in decrease of successful conception probability and increase of the spontaneous abortion and the level of perinatal mortality as well as impediment of normal delivery [4,5].

Timely diagnostics and adequate treatment of CIN are major problems of oncological gynecology in prevention of cervical cancers. It requires development and introduction of novel therapeutic approaches combining the oncological radical cure and maintenance of the functional integrity of the target organ. This has not only medical but also social and economic significance saving financial resources spent on the treatment of patients.

Recently, photodynamic therapy (PDT) was proposed as a promising and highly selective therapeutic method for the treatment of CIN. PDT is based on the ability of photosensitizers to accumulate selectively in pathologic tissue and, after irradiation with the laser light of a certain wavelength (specific to the concrete photosensitizer), to provide cytotoxic effect which results in photochemically induced necrosis of the target tissue [6]. PDT has advantages relative to the conventional methods such as high selectivity of the tissue destruction, absence of the surgical interventions and low risk of severe systemic complications after treatment. PDT allows to perform multiple treatment procedures in the same patient and it is cost-effective [7].

The objective of the present study was to test in clinics a previously developed novel organ-saving approach for the treatment of CIN using PDT with the photosensitizer Photolon® applied in women of childbearing age with CIN II and III.

Materials and methods

Patients

One hundred and twelve patients aged 35.2 ± 1.6 with morphologically proven diagnosis of CIN II and III were enrolled into the study. The study protocol was approved by the local Ethical Committee and also by the Ministry of Health of the Republic of Belarus. Each patient was informed about main objectives of the study, treatment protocol and probable complications and signed an Informed Consent to participate in the clinical study. The mean Karnovsky performance index in enrolled patients was 80—100%. All 112 patients had been observed at least during 1-year follow-up period. Among them 53 patients (44.1%) were subjected to a dynamic observation for less than 2 years; 29 patients (24.1%) were under the observation for less than 3 years; 13 patients (10.8%) — for 3—4 years and 17 women — for more than 4 years (Table 1).

Initial clinical and laboratory examinations

Initial clinical examination before PDT included bacterioscopic and cytological examinations of vaginal and cervical smears, survey and extended colposcopy, Lugol’s iodine test.

Among 112 patients enrolled for this study in 24 (21.4%) women results of clinical and morphological findings corresponded to CIN II, 88 (73.3%) women had CIN III and cancer in situ (according to the WHO classification 1975 and TBS-2001 (the Bethesda System)). In 21 patients with CIN II and in 75 women with CIN III pathologic lesions localized at ectocervix. In three women with CIN II and in seven women with CIN III neoplastic lesions localized at endocervix and in the rest six patients with CIN III both ecto- and endocervixes were affected (Table 2). Five patients had recurrent CIN after previously performed surgical conization.

In all patients an identification and verification of highly oncogenic strains of the Human papilloma virus (namely, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) were performed before treatment and at different checkpoints after PDT by means of a polymerase chain reaction (PCR) using the test system ”AmpliSens HPV-VCR-screening-titre-RTF-4x” (The Central Research Institute of Epidemiology, Russia) and ”Mx3000P” analyzer (Stratagene Inc., USA). In 88 (78.6%) women among 112 patients enrolled for the study highly

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Duration of the follow-up period in treated patients.</th>
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<tbody>
<tr>
<td>Follow-up</td>
<td>CIN II</td>
</tr>
<tr>
<td>3 months—1 year</td>
<td>1</td>
</tr>
<tr>
<td>1—2 years</td>
<td>13</td>
</tr>
<tr>
<td>2—3 years</td>
<td>5</td>
</tr>
<tr>
<td>3—4 years</td>
<td>1</td>
</tr>
<tr>
<td>More than 4 years</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Localizations and severity of CIN in enrolled patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>Exocervix</td>
</tr>
<tr>
<td>CIN II</td>
<td>21 (18.7%)</td>
</tr>
<tr>
<td>CIN III</td>
<td>75 (67.0%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
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</table>


oncogenic strains of the HPV were detected in cervical smears and biopsy material from the cervix uteri before treatment.

Photosensitizer

Photolon® (RUE “Belmedpreparaty”, Belarus), a lyophilized powder for the solution for injections was utilized as a photosensitizer for PDT. Photolon® is a combination of chlorin e6 potassium salt and low-weight polyvinylpyrrolidone. Photolon® has intense absorption band between 640 and 680 nm with maximum approximately 660 nm (Fig. 1) [8]. The photosensitizer was administrated by intravenous infusion within 30 min at a dose of 1.0—2.5 mg/kg body weight. The injection was performed 3—4 h after photosensitizer administration of the drug was tolerable in all treated objective status was satisfactory in all patients and the treatment.

PDT procedure

The irradiation was performed 3—4h after photosensitizer injection using a therapeutic laser device “LD680-2000” (Biospec, Russia) with wavelength 670 nm. Regardless of the shape and localization of pathologic lesions both vaginal part of the cervix and cervical canal were irradiated.

Directly before the procedure the shape and area of pathologic lesions at cervix were estimated by means of conventional white-light and fluorescence colposcopy using upgraded colposcope EKS-1 (ECOMP, Belarus). For fluorescence images registration the mentioned colposcope was equipped by high sensitivity CCD camera and LED light source for fluorescence excitation (see LED emission and Photolon® fluorescence spectra on Fig. 1).

The number and size of irradiation fields depended on the prevalence of the pathologic lesions. In patients with CIN lesions which did not exceeded 3 cm in diameter the irradiation was performed using single irradiation field which overlapped the CIN lesion for at least 0.5 cm at any side. In case if the CIN lesion exceeded 3 cm in any direction, the irradiation was performed using two or four irradiation fields with diameter 2—3 cm each, depending of lesion shape and dimension. It was an essential condition that irradiation fields should overlap each other during the treatment procedure. Then vaginal part of the cervix was irradiated using a fiber optic catheter (Polironik, Russian Federation) equipped with a microlens for more homogeneous light distribution in irradiation field. The light dose was 100 J/cm² while the fluence rate was kept below 200 mW/cm².

At the second stage of the procedure an intraluminal irradiation along the full length of the cervical canal was performed. For this purpose a fiber optic catheter with a cylindrical diffuser (Polironik, Russian Federation) was applied. The light dose was 100 J/cm² of the diffuser length while the power of irradiation was in range 80—170 mW/cm² of the diffuser length. Irradiation time of cervical channel was 20 min.

Output power from fiber optic catheters, both with microlens and cylindrical diffuser, was controlled before every procedure by a powermeter with integration sphere.

Assessment of the PDT efficacy

Preliminary estimation of the treatment efficacy of vaginal part of cervix was estimated by Photolon® photobleaching on fluorescent images taken immediately after procedure, which were compared to fluorescence images registered before PDT. If needed, the position of treated area was corrected immediately during procedure.

The assessment of the PDT efficacy was performed by means of clinical and morphological examinations. The efficacy of the treatment was evaluated by gynecological examinations in 6 and 12 months and then every year after PDT.

The examinations included: clinical examination; bacteriologic examination of vaginal and cervical secretion; PCR-diagnostics of HPV in vaginal and cervical smears; survey and widen colposcopy; Lugol’s iodine test and cytological examination of cervical smears; morphological examination of cervical biopsy samples.

Results

During the intravenous injection of the photosensitizer the objective status was satisfactory in all patients and the administration of the drug was tolerable in all treated women. We also have not seen any allergic reactions caused by the injection of the photosensitizer.

Mild skin phototoxicity was noticed only within the first day after Photolon® injection. In 72 h after treatment content of the photosensitizer, estimated by in vivo LIFS measurements performed by fluorescence fiber optic spectrometer LESA6 (Biospec, Russian Federation), decreased to a minimal detectable level in skin.

Immediately after PDT clearly defined edema and hyperemia in the region of the performed laser irradiation at the cervix were observed in all treated patients.

In subsequent 3—4 days after irradiation a formation of the necrotic scar and fibrin films occurred in the cervical canals of all treated women (Fig. 2b). A complete healing of the cervix uteri with a normal epithelium commonly occurred 8—12 weeks after PDT (Fig. 2c).
The formation of the necrosis was correlated with photobleaching, observed immediately after PDT. This correlation was confirmed by analyze of false-colors fluorescent imaging during the colposcopic examination before PDT and immediately after treatment (Fig. 3b and c, respectively) where pixels of different fluorescence intensities were colored with different colors. Margins of the areas with a decreased (due to photobleaching) content of Photolon® revealed at fluorescent images corresponded to areas of the tissue necrosis which developed subsequently 3–5 days after PDT (Fig. 3d).

The final assessment of the treatment efficacy was made on the basis of clinical and morphological findings using the following common criteria: complete response (an absence of clinical and morphological sings of CIN); partial response (at least 50% reduction of a pathologic lesions area or absence of clinical signs of CIN but positive results of morphological examination of the cervical epithelium); stabilization (less than 50% reduction of pathologic lesions area or or stabilization of the cytological differentiation); progression (a progression of pathologic lesions or malignant transformation). The complete response rep-
represented by the complete regression of neoplastic lesions, which was proved by results of morphological examinations, was revealed in 104 (92.8%) of treated women (Table 3).

Fifteen women became pregnant after the treatment and complete convalescence. To date six of them resulted in normal delivery, two women were subjected to the cesarean operation and one woman had a still-born child. In four cases the pregnancy occurred within 1–3 months after performed treatment and was terminated according to medical indications because of the incomplete healing of the cervix uteri and the absence of objective data on patients’ recovery and prognosis for a further development of the disease. In two patients the pregnancy was terminated according to the patients’ decision. However, it should be accentuated that PDT with Photolon® did not provide either embryotoxicity or teratogenicity. Moreover, it should be also mentioned that all 15 women, who became pregnant after the performed treatment, previously have had evidences on infertility in their anamneses before the enrolment into the clinical study.

In 3 months after treatment a complete eradication of the HPV infection was proven by PCR-analysis in 47 (53.4%) from 88 patients who have been infected with HPV of a highly oncogenic strains before PDT. Later at different checkpoints within the whole follow-up period the percentage of HPV-negative patients degreased (up to 29.4% at 3-year check point) what suggests on probable reinfection with HPV or presence of the persistent strains in above mentioned patients.

HPV-DNA tests being performed at different checkpoints within the follow-up period provided the possibility to differentiate reinfection and persistence of HPV in treated patients. As far as in case of the complete recovery from the particular strain of HPV the further reinfection with the same strain was considered to be practically impossible because of the developed immunity, changes in the viral spectrum, which were revealed in treated women in 3 and 12 months after PDT, suggested for the reinfection. Otherwise, if HPV-DNA tests performed in 3 and 12 months after treatment did not revealed any changes in the viral spectrum the persistence of HPV infection was considered to be confirmed. In 3 months after PDT we revealed the reinfection with 31, 33, 45, 51, 52 and 56 strains of HPV in eight women. At the 1-year checkpoint the reinfection was additionally confirmed also in eight patients. Thus, the total number of 16 patients was re-infected with HPV within the 1-year follow-up period.

We suggest that local treatment did not provide a sufficient efficacy regarding the eradication of the HPV because of the multiple lesions and existence of a hidden component of the disease in several patients. However, there were no pathologic changes in cervical smears and biopsy samples obtained from women who became re-infected with HPV within 3 years after PDT. These results suggest that the PDT has the great therapeutic potential in HPV-positive cervical cancers and precancerous diseases.

**Discussion**

Because an adequate therapy is the most effective preventive measure for cervical cancer the problem of the early diagnostics and treatment of CIN II and III is a very important goal. High frequency of recurrences and complications after conservative therapy dictates the necessity of searching new treatment methods for CIN.

PDT is an alternative organ-saving therapeutic approach in the treatment of oncological diseases. It is based on the combination of the selective accumulation of a photosensitizer in pathologic lesions and specific damaging action of the laser light targeting malignant or pre-malignant tissue. PDT also provides an ability to perform repeated treatment and to combine the diagnostics and therapy in a single procedure.

Attempts of PDT treatment of CIN were reported by many authors within the recent decade. Thus, 24 women with CIN were treated during a phase I clinical trial of the topically applied 1% solution of Photofrin II [9]. Among those patients 13 women had CIN I; 7 — CIN II and 4 — CIN III, various light doses in a range of 100–140 J/cm² were used. A successful treatment and complete regression of neoplastic lesions achieved in 15 (68%) women was proven by clinical findings in 1 year after PDT. The other promising method was the topical application of 5-aminolevulinic acid for the treatment of CIN by PDT. However, contradictory results of such treatment were obtained in a number of studies. Hillemanns et al. [10] topically applied 20% solution of 5-ALA for PDT of CIN. In this study irradiation of the cervix uteri was performed 3–5 h after the application of the photosensitizer. In 3 months after PDT regression of neoplastic lesions was confirmed only in three (33.3%) women, remaining seven patients were subjected to surgical conization of the cervix.

In a randomized double-blind placebo-controlled clinical trial which was carried out in 26 women with CIN I and II, Barnett et al. compared the efficacy of topically applied 3% gel of 5-ALA (13 patients) versus placebo (13 patients) in the PDT treatment of CIN. Authors did not report any statistically significant difference in the treatment outcomes between two groups [11]. Morphological examination of cervical biopsy materials obtained from treated women 3 months after PDT a complete regression of neoplastic lesions was confirmed in five patients treated with 3% gel of 5-ALA; stabilization

<table>
<thead>
<tr>
<th>Severity</th>
<th>Number of patients</th>
<th>Complete regression</th>
<th>Partial regression</th>
<th>Stabilization</th>
<th>Progression</th>
</tr>
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<tbody>
<tr>
<td>CIN II</td>
<td>24 (21.4%)</td>
<td>23 (20.5%)</td>
<td>-</td>
<td>1 (0.9%)</td>
<td>-</td>
</tr>
<tr>
<td>CIN III</td>
<td>88 (78.6%)</td>
<td>81 (72.3%)</td>
<td>3 (2.7%)</td>
<td>4 (3.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>112 (100%)</td>
<td>104 (92.8%)</td>
<td>3 (2.7%)</td>
<td>5 (4.5%)</td>
<td>-</td>
</tr>
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</table>

**Table 3 Efficacy of PDT with Photolon®.**
of the pathologic process was detected in five patients and three women had a progression of the disease. In the control group (patients treated with placebo) treatment outcome was completely the same. Keefe et al. reported about results of a clinical trial performed in 40 women with CIN II and III treated by PDT with topical application of 5-ALA. Authors used various light doses (50—150 J/cm²) for irradiation of neoplastic lesions. Thirty-two women were followed-up for 1 year after PDT. Among them there were 24 patients with CIN III and 16 patients with CIN II. Colposcopy followed by morphological examination of cervical biopsy material performed in 4, 8 and 12 months after PDT a complete regression was confirmed in 15 women 4 months after treatment, in 13 women at the 8-month checkpoint and in only 9 patients in 1 year after PDT. The efficacy of PDT did not depend on the light dose used for irradiation. Three patients had a progression of the disease immediately after treatment [12].

Analogous data was reported by Soergel et al. who applied PDT with topical hexaminolevulinate in 24 women with CIN I and III. Twenty-four patients with a CIN II or III or a persistent CIN I and a positive high-risk HPV-DNA test were included. HAL-thermol was topically applied to the cervix for 3—5 h, followed by illumination with red coherent light (wavelength 633 nm) using a PDT laser and a special light catheter. In 6 months after treatment a complete regression of cervical lesions was revealed in 15 (63%) patients [13].

In another clinical trial Bodner et al. compared the efficacy of surgical conization of the cervix uteri with such for PDT with topically applied 5-ALA. In total 22 HPV-positive women with CIN II were enrolled in the study. Eight out of 11 patients in each group (73%) had an HPV remission in 3 months after performed treatment. In 12 months after treatment 11 (100%) patients in the main group and 10 (91%) women in the control had negative results of the HPV-DNA test. However, authors did not revealed any significant difference in treatment outcomes between both groups of treated patients and thus they made a conclusion that the efficacy of PDT with 5-ALA is not superior to surgical conization of the cervix uteri [14].

We think that limited success of the PDT in the treatment of CIN which was reported by a number of authors may be caused by inadequate treatment of cervical canal because mentioned authors locally applied topical forms of photosensitizers. More promising results were achieved by systemic administration of hematoporphyrine-based photosensitizers for the CIN treatment by PDT. Thus, a group of Japanese investigators reported about the successful treatment of 31 women with CIN II and III [7]. Authors used intravenous injection of a polyhematoporphyrin ether/ester (PHE) as a photosensitizer. In 12 months after PDT a complete regression of cervical intraepithelial neoplastic lesions was revealed in 100% of cases.

Two years later the same group reported about a successful treatment of 105 patients with CIN I and III by intravenous injection of Photofrin II and subsequent irradiation with the laser light (630 nm). A complete regression of CIN lesions was revealed in 3 months after PDT in 94 out of 105 (90%) women. During the procedure of PDT both vaginal part of the cervix uteri and cervical canal were irradiated with the laser light in all treated patients [15].

A group of researchers from Moscow Herzen Cancer Research Institute (Russia) reported about treatment of 44 patients with CIN III and 12 women with cervical intraepithelial cancer by PDT using PhotoGem® (Moscow Institute of High Chemical Technologies, Russian Federation) as a photosensitizer. In 26 out of 44 patients with CIN III (59%) and in 4 out 12 patients with cervical intraepithelial cancer (33%) pathologic lesions localized in endocervix. During the procedure of PDT both vaginal part of the cervix uteri and cervical canal were irradiated. The power density of the laser light used for the treatment procedure was 150—200 J/cm². A complete regression of neoplastic lesions was achieved in 37 out of 44 patients with CIN III (84%) and only in 8 out of 12 patients (60%) with cervical intraepithelial cancer [16]. Later, the same group performed PDT séances with PhotoGem® in 10 patients with CIN III and in 4 patients with cervical carcinoma in situ. In this study a complete regression was achieved in 100% and 90% of cases of carcinoma in situ and CIN III, respectively.

At present there is no published data on PDT with PhotoGem® applied for the treatment of CIN II and III. The utilized light dose of 100 J/cm² and the fluence rate below 200 mW/cm² were determined by us previously in a number of animal experiments on various models of xenograft tumors and in clinical studies regarding the application of PDT with PhotoGem® for the treatment of patients with superficial skin and mucosal tumors, including melanoma [17—19]. The problem of the optimization of the particular regimen of PDT with PhotoGem® for the treatment of CIN is still being under exploration and it is the subject of our further research.

The efficacy of PDT in the treatment of CIN is mostly dependent on the use of novel, effective and tolerable photosensitizers, which has a low systemic toxicity, rapidly eliminated from the body and at the same time accumulates in neoplastic tissues with high selectivity. The photosensitizer PhotoGem® satisfies most requirements. There were no serious adverse effects associated with PDT treatment. The most frequent reactions revealed in the clinical trial included pain syndrome at the treatment site during the PDT procedure and rise of the body temperature. In several patients a mild arterial hypertension was detected after PDT. In one (1.2%) patient with CIN III a cicatrical stenosis of cervical channel occurred after PDT. This patient was subjected to bouginage of cervical canal.

PhotoGem® in therapeutic doses provides a very weak and short time systemic phototoxicity. However, in some patients in case of violation of the recommended light regimen the administration of PhotoGem® can cause hyperemia and edema of an exposed surfaces of the body (not pigmented). It is recommended to avoid direct sunlight and UV-irradiation during first 3 days after administration of PhotoGem®. The patient should be given special instructions concerning the mandatory requirement to maintain a restricted light regimen during first days after treatment (namely, to avoid direct sunlight, watching TV, etc.). It is also recommended to perform a spectrofluorescent examination of the level of PhotoGem® content in patients’ skin in 2—3 days after treatment.

It was revealed that the process of the edge epithelization of the treated area started in 5—6 days after PDT. In 8 weeks after treatment complete healing of the cervix uteri occurred in more than 90% of patients.
Thus, high selectivity of the damaging effect of treatment versus affected tissues of the cervix, low risk of serious adverse reactions and complications, short period of systemic photosensitivity and high therapeutic efficacy beneficially distinguish the method of PDT with Photolon® from traditional destructive methods of treatment of CIN II and III. PDT is an effective and minimally invasive treatment for CIN, which also appears to eradicate HPV infection. PDT with Photolon® is also a relatively safe treatment. Among treated patients there were no cases of pathological changes in their physical state, clinical and laboratory parameters.

Conclusion

PDT with Photolon® provides several advantages in comparison with other treatment modalities widely used in gynecological practice:

- in the majority of cases there is a mild or absent pain syndrome during the treatment procedure;
- there are no hemorrhages during the treatment;
- early epithelization of the treatment site;
- a very mild leucocytic infiltration of the treated organ;
- shortening of the exudation and proliferation phases;
- absence of the severe adverse events after treatment;
- possibility to perform diagnostics and treatment during the single procedure;
- treatment provides the preservation of the anatomical integrity and architectonics of the cervix uteri and conservation of the normal menstrual cycle and reproductive function, what is extremely important for women who are planning a pregnancy;
- PDT provides the possibility to perform repeated treatment procedures in the same patient if necessary.

Photodynamic therapy with Photolon® is an alternative approach for the treatment of cervical intraepithelial neoplasia which can be recommended for women of child-bearing age. The simplicity of the procedure as well as its’ high therapeutic efficacy defines the reasonability of its’ introduction into the clinical practice as a new organ-saving method for the treatment of patients with cervical intraepithelial neoplasia.

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References


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