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TREATMENT OF THE UTERUS CERVIX CANCER WITH THE JINR PHASOTRON PROTON BEAM

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1. Introduction

The method of the uterus cervix cancer treatment with proton-and-gamma irradiation was for the first time elaborated for the Institute of Theoretical and Experimental Physics (ITEP) in Moscow, applied to 160 patients from 1970 to 1985 [1–3] and then developed for the Joint Institute for Nuclear Research (JINR) proton beam at Dubna [4–5].

The proton accelerators of the ITEP and the JINR are very different both in design and in characteristics of the proton beams. The purpose of treating the uterus cervix cancer on a medical beam at the JINR was to reproduce the pre-operative and radical proton-and-gamma treatment methods worked out at the Cancer Research Center of the Russian Academy of Medical Science (CRC of RAMS) in Moscow and the ITEP. For this it was necessary to modify and adapt the medico-technical construction, and the methods of the radiotherapy itself to the proton beam characteristics and to the patient irradiation conditions at the medical proton beam of the JINR phasotron.

Our task was to apply two methods of proton-and-gamma treatment of the uterus cervix cancer, to study and evaluate the radiological reactions and clinical results in comparison with those as at the ITEP.

At the first step of investigations in Dubna we reproduced the method of the pre-operative proton-and-gamma irradiation of the uterus cervix cancer Stage IB. The protocol of "Pre-operative proton-and-gamma treatment of the uterus cervix cancer" has been activated since 1987.

At the second step we went on to the radical (without surgery) proton-and-gamma radiation treatment of the uterus cervix cancer Stages IB, IIAB, IIIB, according to the protocol "Radical proton-and-gamma thearapy of the uterus cervix cancer". A uniform TNM classification system of UICC (Internation Union Against Cancer), accepted by FIGO (International Federation of Gynaecology and Obstetrics) was used for all patients.

2. The technique of patient treatment at the JINR medical proton beam

The method of the proton-and-gamma irradiation of patients with cervical cancer consisted of the transvaginal proton irradiation of primary lesion (uterus) and external gamma-irradiation of the regional lymph nodes. The transvaginal proton irradiation was performed in treatment room No.2 of the clinical–physical facility with a modified horizontal 130–160 MeV proton beam. The beam of this energy is produced after deceleration of the 660 MeV proton beam from the JINR phasotron in a carbon degrader.

For transvaginal proton irradiation of the cervical cancer we use a set of cylindrical vaginal tube collimators (1, Fig.1; 1, Fig.2) with conical (2, Fig.1; 2, Fig.2) or cylindrical (3, Fig.2) plexiglass heads. A central probe (4, Fig 1; 4, Fig 2) is inserted into the cervical canal and uterus cavity. The probe, which is a 4 mm in diameter steel bulb–end rod, was introduced into a uterus without dilatation of the cervical canal. These vaginal tube collimators and the central probe are employed to fix the target volume (cervix and corpus uteri) with respect to the proton beam axis (P, Fig.1).

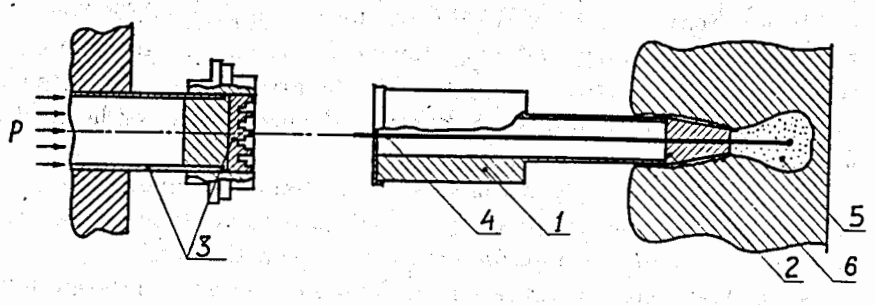


Fig.1. Schematic representation of the servical cancer proton treatment.

1 – vaginal tube-collimator;
2 – conical plexiglass head;
3 – general collimator with ridge filter;
4 – central probe;
5 – uterus;
6 – vaginal walls;
P – proton beam.

The depth-dose distribution is formed with the aid of a general collimator with a ridge filter (3, Fig.1) calculated for the nonmonoenergetic proton beam [6]. The ridge filter transforms the Bragg peak to the depth-dose distribution with a flat top and steep back slope. Extension of the flat top of the depth-dose distribution is about 8 g/cm^2.

The ridge filter is a strong scatterer, so for transvaginal proton irradiation of the cervical cancer we use a set of cylindrical vaginal tube collimators(1, Fig.1; 1, Fig.2), defined the dose field by sides.

The cylindrical and conical heads of different thickness are intended for treatment depth regulation. The conical heads also make it possible to irradiate the upper part of the vagina.

Examples of isodose distributions with cylindrical and conical heads measured with a small silicon detector in a water phantom are presented in Fig. 3a,b. Each line indicates the isodose level with an interval of 20% of the maximal dose.

The proton dose field has a cylindrical form, the diameter of which is found for individual patient's need. For this technique the diameter of the tube-collimator is taken within 30–50 mm , so that 50% isodose curve crosses point A. The proton beam range is such that 20% isodose level of the dose field includes fundus uteri. This dose distribution excludes the irradiation of critical organs (bladder and rectum), Fig. 3,c.

For absorbed dose rate measurements we use a clinical dosimeter KD-27012 with thimble ionization chambers VAK-251 and VAK-253. The dosimeter was calibrated with a ^{60}Co source of the therapeutic γ–unit placed in one of the rooms of our clinical–physical facility, and also used for patient treatment. The ^{60}Co source was calibrated against the primary standard of the Czech Republic placed in the Prague Institute of Radiation Dosimetry. The accuracy of the gamma-unit calibration is 1.3% (one standard deviation) [7].

Using the gamma-unit as a calibrated stand for ionization chambers of our clinical dosimeters was described in [8,9] and practically coincided with recommendations of the "Code of Practice for Clinical Proton Dosimetry" elaborated by the ECHED (European Clinical Heavy Particles Dosimetry) working group [10].

The full error of the JINR phasotron proton beam dosimetry is about 5%. This accuracy meets the international requirements for the therapeutic proton beams.

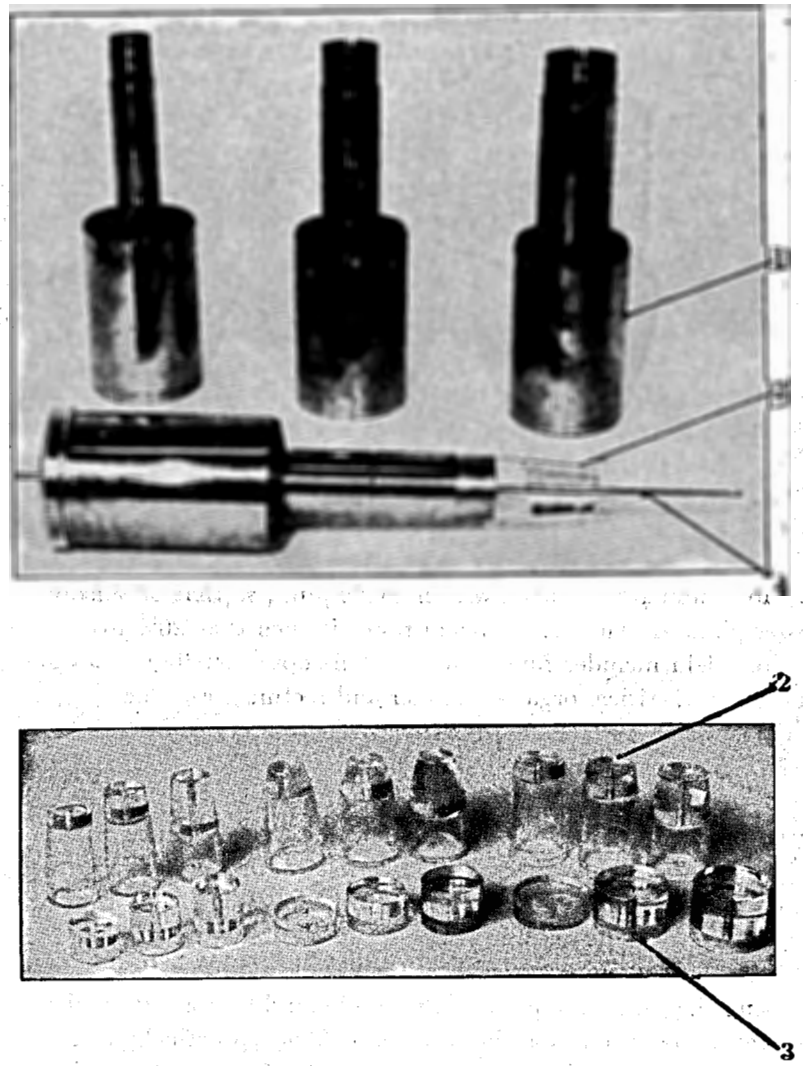


Fig.2. The collection of vaginal tube-collimators with heads.
1 – vaginal tube-collimators; 2 – conical heads;
3 – cilindrical heads; 4 – central probe.

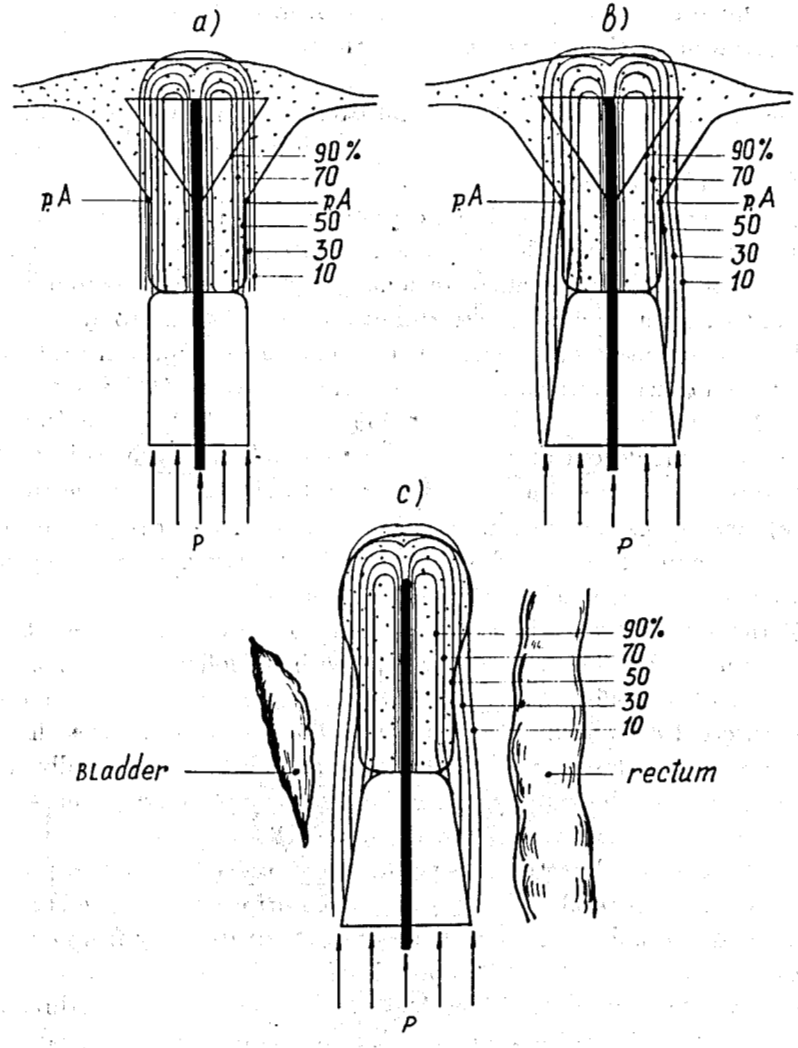


Fig.3. Proton dose distributions with:
a) – cilindrical head (frontal projection);
b) – conical head (frontal projection);
c) – conical head (sagittal projection).

3. The method of pre-operative proton-and-gamma treatment of the uterus cervix cancer

From November 1987 to December 1988 six patients were treated. The age of patients was from 30 to 50 years. All patients had the clinical Stage IB uterus cervix cancer.

The method of the pre-operative proton-and-gamma treatment of the uterus cervix cancer includes transvaginal proton irradiation of the uterus and external γ-irradiation of the regional lymphatic nodes followed by the surgical treatment: radical hysterectomy with lymphadenectomy.

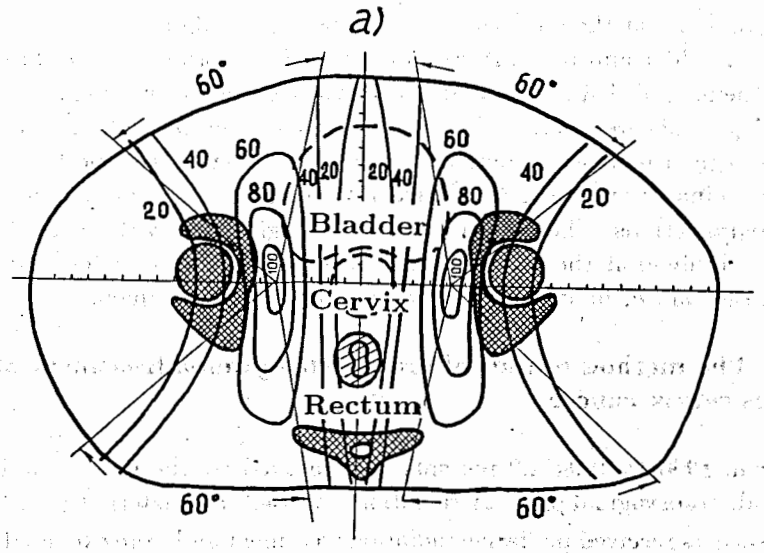
We normally used 3 fractions (treatment sessions) of proton irradiation with the following fractionation: 10 Gy tumour dose at 50% isodose level (point A) a week, the total dose at point A was 30 Gy. The diameter and depth of the dose field were chosen individually for each patient. The target dose in the maximum of the dose distribution (in the tumour centre) was 20 Gy for each fraction. The dose rate of the proton beam in the maximum of the dose field was about 2 – 5 Gy/min and the proton irradiation procedure was as long as 5 – 10 minutes.

At the same time regional lymphatic nodes were irradiated at the ^{60}Co γ-unit ROCUS-M for 3 weeks with the following fractionation: 2 Gy at 100 % isodose level (point B), five times weekly. The method of the external γ-irradiation is rotation within 4 sectors of 60° each. The dose field size was limited from (4cm*14cm) to (4cm*16cm). Usually 20–40 % isodose level of the external γ-irradiation passes through point A. The example of the dose distribution is shown in Fig.4,a.

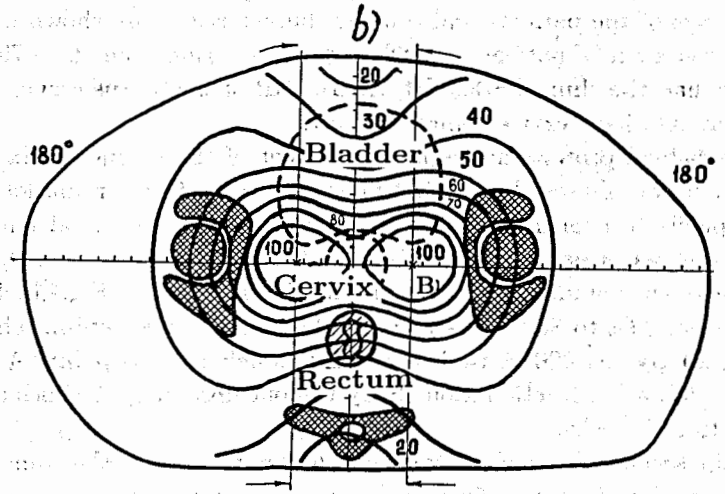
The total dose of proton-and-gamma irradiation delivered to point A was 36–42 Gy. The total dose of the external γ-irradiation applied to point B was 30 Gy. Bladder and rectum received about 6–12 Gy from external gamma-irradiation (at 20–40% isodose level).

Radical hysterectomy with lymphadenectomy was undertaken three weeks after the end of the radiation therapy at the Surgery Department of the Cancer Research Center in Moscow.

The full course of the transvaginal proton treatment was carried out for 3 patients, the other 3 patients had 1–2 transvaginal proton irradiations and additional external γ-irradiation of the whole pelvis. The total dose at point A was 30 Gy (after proton-and-gamma irradiation). All patients had



rotation within 4 sectors of 60°.



rotation within 2 sectors of 180°.

Fig.4. Dose distributions for external γ-irradiation of:
a) – the regional lymphatic nodes;
b) – the whole pelvis.

negative nodes at the operation. No any postradiation reactions to critical organs (bladder and rectum) were observed in all patients. The threshold of erythema and definite vaginal and cervical mucositis was found.

All patients were followed up over 5 years. One patient died because of the vaginal metastases outside the treatment region (in the lower part of the vagina), the other 5 (83%) are alive without recurrences, metastases and complications. These results are in good agreement with the analogous results obtained at the ITEP [3] and have become the basis for beginning of the radical (without surgery) proton-and-gamma treatment.

4. The method of radical proton-and-gamma treatment of the uterus cervix cancer

From 1990 to 1994, 22 patients were treated by the radical radiation method: transvaginal proton irradiation was used with external γ -therapy. Three others received palliative radiation treatment and were excluded from the latest analysis.

The age of the patients and tumour characteristics are shown in Table 1. The mean age of patients was 60–69 years, ranging from 50 to 79 years. Patients had the clinical Stage IB, IIA,B, IIIB of the uterus cervix cancer. Most patients had cervical cancer Stage II.

The radical proton-and-gamma treatment of the uterus cervix cancer consists of two phases. In the first phase the external γ–irradiation of the whole pelvis (the primary lesion and the zone of the regional lymphatic nodes) was performed by the biaxial bisectoral 180° rotation technique.The example of such summarized dose distribution is shown in Fig.4,b. Isodose curves from 20% to 80 % pass through the bladder and rectum. The total dose of 20 Gy (at 100 % isodose level) was delivered to points A and B with the following fractionation: 2 Gy tumour dose daily, 5 times a week, overall time 2 weeks.

In the second phase of the radical radiation treatment, the transvaginal proton irradiation was performed. It was done by the same manner as for the pre-operative approach, but the total treatment dose was increased. Four proton fractions (two of them included the upper part of the vagina) were given. The total dose of 40 Gy of the proton irradiation was delivered to point A. No dose recieved by the rectum and the bladder (Fig. 3,c).

Table 1. The age of the patients treated with a radical method and tumour characteristics

Age of patients	Number of patients	Stage I	Stage II	Stage III
50-59 years	6	-	5	1
60-69 years	12	4	7	1
70-79 years	4	2	1	1
Total	22	6	13	3

Table 2. The results of radical proton and γ–treatment of the uterus cervix cancer for patients followed up over 3 years

Stage	Number of patients	Are living over 3 year	Death from tumour	Death from other reasons
I	5	5	-	-
II	4	3	1	-
III	3	2	-	1
Total	12	10	1	1

At the same time the external γ–irradiation of the lymphatic nodes was done by the rotation technique within 4 sectors of 60^o each. The irradiation was continued for 3–4 weeks. The total dose of 30–40 Gy to point B was given. Point A received from 6 to 16 Gy.

After two phases of the proton-and-gamma irradiation the total dose of 66–76 Gy to point A and 50–60 Gy to point B were applied. The dose to the critical organs (bladder and rectum) was delivered only from external γ–irradiation. These organs received less than 18–34 Gy.

All patients achieved a complete local response just after radiation treatment, or one month after. Threshold erythema and definite vaginal and cervical mucositis were found during the radiotherapy, definite mucositis with rarely patchy – at the end, or just after radiotherapy. Cytological cancer control of cervical smears was negative with follow-up times. Slight intestinal disorders at the patients with chronical intestinal diseases were ocasional and transient, and depended only on the external γ–irradiation.

For 12 of 22 patients the follow-up is extended to over 3 years (Table 2), 2 of them died. The death of the first patient, 78 years old with Stage IIIAB, at the end of the second year after treatment was caused by cerebral thrombosis. The death of the second patient, 58 years old with Stage IIAB, was caused by the recurrence of the tumour. The others 83% are living without postradiation complications to the critical organs and without recurrences and metastases.

5. Conclusions

1. The clinical probation of the set-up for treatment of gynaecological tumours with the JINR proton beam has been done.

2. The proton irradiation technique shows advantages over other methods of the intracavitary radiation therapy, as it excludes cervical canal dilatation and reduces the treatment time (5–10 minutes instead of hours).

3. The most important advantage of the proton beam treatment is avoiding postradiation reactions and complications to the critical organs (bladder and rectum), thus in the future the planned maximal total tumour dose may be increased.

4. Up to now 31 patients with the uterus cervix cancer have been treated at the JINR phasotron.

   6 of them had the proton-and-gamma treatment combined with the surgical operation. The survival rate over 5 years was 83%.

   22 patients received the radical proton-and-gamma treatment (without surgery). The survival rate over 3 years for 12 first patients was 83%.

   Other 3 patients got palliative radiotreatment.

   112 proton treatment sessions were performed. The clinical results are in good agreement with the preceding results of the ITEP group.

5. Worked out by the CRC, the ITEP and the JINR, the proton-and-gamma methods for treatment of the uterus cervix cancer may be regarded as universal enough. After insignificant technical correction connected with characteristics of the present proton accelerator and medico-technical facility of the treatment room, our method may be adapted for proton irradiation of the uterus cervix cancer at dissimilar proton beams both in Russia and in abroad.

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Лечение рака шейки матки на медицинском протонном пучке фазотрона ОИЯИ

Методы сочетанного $p-\gamma$ лечения рака шейки матки были разработаны впервые в ИТЭФ (Москва), воспроизведены и усовершенствованы на медицинском протонном пучке ЛЯП ОИЯИ (Дубна). Результаты клинического применения методов лечения рака шейки матки подтвердили преимущество лучевого лечения протонным пучком. Наиболее важным преимуществом является отсутствие послелучевых реакций и осложнений в критических органах (мочевой пузырь и прямая кишка).

К настоящему времени на фазотроне ОИЯИ проведено лечение рака шейки матки у 31 больной. Из них 6 больным проведено комбинированное лечение ($p-\gamma$ облучение и хирургическое лечение), 22 больных получили радикальное сочетанное $p-\gamma$ лечение в самостоятельном варианте и остальным 3 больным был применен паллиативный метод лучевого лечения рака шейки матки. Клинические результаты $p-\gamma$ лечения рака шейки матки хорошо согласуются с результатами такого же лечения, проведенного в ИТЭФ. Больные, получившие $p-\gamma$ лечение рака шейки матки, живы без рецидивов, метастазов и лучевых осложнений в 83% случаев.

Работа выполнена в Лаборатории ядерных проблем ОИЯИ.

Сообщение Объединенного института ядерных исследований. Дубна, 1995

Astrakhan B.V. et al. E18-95-99

Treatment of the Uterus Cervix Cancer with the JINR Phasotron Proton Beam

The methods of the uterus cervix cancer proton-and-gamma treatment for the first time were elaborated in the CRC RAMS and ITEP in Moscow and then developed for the JINR proton beam in Dubna. The results of the clinical probation of the methods for the uterus cervix cancer treatment have confirmed the advantage of the proton irradiation.The most important advantage of the proton beam treatment is absence of postradiation reactions and complications in the critical organs (bladder and rectum).

Up to now 31 patients with the uterus cervix cancer have been treated at the JINR phasotron. 6 of them had proton-and-gamma treatment combined with surgical operation and 22 patients received a radical proton-and-gamma treatment (without surgery). The clinical results are in good agreement with the preceding results of the ITEP group. After receiving proton-and-gamma radiotherapy of the uterus cervix, 83% of the patients are alive without recurrences, metastases and complications.

The investigation has been performed at the Laboratory of Nuclear Problems, JINR.

Communication of the Joint Institute for Nuclear Research. Dubna, 1995