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Morbidity dynamics in proton–photon or photon radiation therapy for locally advanced prostate cancer

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ABSTRACT

Aim: This study evaluated the frequency and long-term dynamics of early and late post irradiation damage after proton–photon or photon therapy for locally advanced prostate cancer.

Background: The results of a randomized study of proton–photon or photon therapy using several fractionation regimes were analyzed in 272 patients with high and intermediate risk of progression.

Materials and methods: Three variants of proton boost fractionation were studied sequentially: 3.0 (8 daily fractions), 4.0 (5 fractions, 3 or 5 fractions/week), and 5.5 (3 fractions, 3 fractions/week) Gy(RBE).

Results: A significant decrease in the severity of both acute and late gastrointestinal injuries is achievable with a proton beam. The dynamics of late gastrointestinal and genitourinary toxicity over a 10-year period were generally characterized by a decrease in severity of morbidity by 30% and 15%, respectively.

Conclusions: Local irradiation with a fractional dose of 3.0–5.5 Gy(RBE) and a cumulative dose of 28.0–28.8 Gy(RBE) for protons significantly reduces the early and late rectitis severity, but does not reduce the risk of lower urinary tract injuries. Fractionation regimens do not significantly differ in toxicity levels.

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1. Background

High-dose external radiation therapy is a widely used and evolving treatment method for locally advanced prostate cancer. One of its most advanced modalities, proton therapy, is the subject of ongoing research at major centers, mainly in the USA and Japan.[1–4] At the same time, active search is being performed to increase the therapeutic interval using various hypofractionation models.[5–11] However, it is impossible to adequately determine the treatment interval without a thorough understanding of the acute and late toxicities of new treatment methods. In addition, there has been significant interest in identifying new ways to predict the frequency and severity of post irradiation injuries, including our previously applied clinical-dynamic method.[12] The unique feature of this method is the continuous monitoring of the rate of progression and the reduction of early and late post irradiation injuries.

2. Aim

We used this approach for a comparative evaluation of the quality of new hypofractionated proton–photon methods and traditional photon irradiation in prostate cancer patients with a high risk of pelvic lymph node involvement.

3. Materials and methods

The clinical efficacy of proton–photon irradiation using various methods of proton boost hypofractionation was evaluated in randomized studies.[1] Patient allocation to the main and control groups was performed according to arrival time for treatment.[2] This method of randomization was adopted due to the operating schedule of the Institute for Theoretical and Experimental Physics (ITEP) synchrotron: 3–4 cycles for 3 weeks during the calendar year, and intervals between cycles of 2–4 months. The main group was formed when the medical proton beam was operational. Patients received a preliminary photon dose of 44 Gy in 22 fractions to the small pelvis. Three variants of proton boost fractionation were studied sequentially: 3.0, 4.0, and 5.5 Gy(RBE).[3] New regimens were adopted no earlier than 3 years after initiation of a prior regimen, i.e., only after preliminary estimation of the severity of late toxicity. The control group consisted of all patients with locally advanced prostate cancer who were treated with standard conformal photon therapy.

From 2000 to 2011, 289 patients with T1-3N0-1M0 prostate cancer were included in the study. The main group consisted of 116 patients who had undergone combined proton–photon therapy and the control group consisted of 173 patients who had undergone standard conformal 8-field photon irradiation. In most cases, radiation therapy was preceded by 3–12 months of androgen deprivation.

3.1. *Methods of radiation therapy*

The main group received 4–6 field photon irradiation (1.2–6.0 MeV) to the entire volume of the small pelvis or only the prostate and seminal vesicles (this group only included those with T1-2N0-M0 disease, an initial prostate-specific antigen [PSA] level < 20 ng/ml, and a Gleason score ≤ 6), up to an overall dose of 44.0–46.0 Gy in 22–23 daily fractions. The overall dose of subsequent local proton therapy was 28.0–28.8 Gy(RBE) to the prostate in 8 daily fractions, with 3.0 Gy(RBE) in 46 patients, 5 fractions with 4.0 Gy(RBE) and 3 or 5 fractions/week in 44 patients, or 3 fractions with 5.5 Gy(RBE) and 3 fractions/week in 24 patients. Thus, considering the photon component, at $\alpha/\beta = 3$ Gy, the dose to the prostate was 72.8, 72.0, or 72.0 Gy(RBE). The prostate in the control group was irradiated with local 4-field photon boost, in 12–14 fractions at 2 Gy, up to 68.0–72.0 Gy.

Preliminary computed tomography (CT) was performed with intravenous contrast enhancement of the bladder. CT was performed from the anus to the upper border of the sacroiliac joint. Tumor volume planning was developed with a 5-mm margin from the target in the rectal zone and a 10-mm margin in the other zones. At the same time, in sagittal reconstruction, the geometrical center was established and its position was defined by the rectal marker (endostate). Three-dimensional (3D) planning was performed. Patients were irradiated with 2 lateral individual fields. Individual collimators made of Wood's lead-containing alloy were used.

The proton beam energy was 220 MeV. For 2D scanning, a water degrader with a changeable depth was used to create a spread-out Bragg peak. Dose inhomogeneity in the target generally did not exceed 5%.

To calculate equivalent doses, a linear-quadratic model was used with a modification by Withers et al.,[13] regardless of total irradiation time. The ratio α/β for a prostate tumor was defined as 3 Gy in 2000, i.e., at the beginning of the investigation, regardless of the tumor malignancy stage. RBE for protons was defined as 1.1.

Before every proton irradiation, after endostate was introduced into the rectum and the patient was immobilized on the table, X-ray positioning was performed until the desired relative positions of the marked beam center and the radiodense endostate marker were identified.

[1] According to the Decision of the Federal Service for Surveillance in Healthcare, Health Ministry of Russian Federation #NES-296(p)-06, Moscow leading medical institutions, among them P.A. Herzen Moscow Scientific and Research Oncological Institute, have a right to perform clinical investigations, among them clinical trials, at the ITEP Proton Therapy Center.

[2] According to the Federal law of the Russian Federation #323-FZ, all patients involved in the treatment gave their informed consent.

[3] Gy(RBE) – radiobiological equivalent of Gray, the unit of biological dose, previously Cobalt Gray equivalent GyE.