

Multimodality Treatment of Locally-Advanced Breast Cancer Using 6.3 MeV Fast Neutrons and Quality of Life in Patients in Long-term Follow-up

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Abstract. The purpose of the study is to present the 10-year results of the combined modality treatment with the use of neutron-photon therapy for patients with $T_{2-4}N_{0-2}M_0$ locally advanced breast cancer (LABC). The study involved 246 LABC patients ($T_{2-4}N_{0-2}M_0$). Analysis of long-term results of multimodality treatment of patients with primary LABC has shown that preoperative neutron therapy is the most effective in the presence of multicentric tumors, radioresistance to neoadjuvant chemotherapy and other adverse prognostic factors.

Introduction

Currently, most Russian and foreign oncology scientists agree on the advisability of an integrated approach to the treatment of patients with locally advanced breast cancer ($T_{2-4}N_{0-2}M_0$) including systemic chemotherapy, surgery and radiotherapy. Preoperative radiotherapy to the breast, contributing to the reduction in the incidence of local recurrence and lymph node micrometastases plays an important role in multimodality treatment of these patients [1, 2].

The objective of this paper was to carry out analysis of long-term results of multimodality treatment with preoperative neutron therapy and assessment of quality of life of patients with locally advanced breast cancer (LABC).

Materials and Methods

In cyclotron U-120 is using as source of accelerated deuterons to initiate reaction where therapeutic bunch of fast neutrons with average energy $\sim 6.3\text{MeV}$ is obtained during bombardment of Be target with deuterons (13.6 MeV). For medical application complex collimator is using. Irradiation field aperture can be adjusted by removable polyethylene collimator and could be varying from 6×6 to $5 \times 15 \text{ cm}^2$. Dosimetry and radiobiological planning of irradiation regimes for all patients was carried out by the way described in [3].

The study involved 246 LABC patients ($T_{2-4}N_{0-2}M_0$). Patients of the study group (n-103) received multimodality treatment consisting of neo-and adjuvant chemotherapy with CMF, CAF/FAC regimens, preoperative neutron therapy to the breast area at a single dose of 2.4 Gy, 3 sessions to the total dose of 7.2 Gy (38-40 Gy photon-equivalent dose), radical mastectomy, hormone therapy (if indicated) and external beam radiotherapy (EBRT) to the regions of metastasis at the total dose of 40-44 Gy. Eligibility criteria for neutron therapy included: tumor with extensive local spread; multicentric tumor growth; location of the tumor in the internal quadrants and/or central parts of the breast; resistance to neoadjuvant chemotherapy (according to findings of ultrasound, mammography and ^{99m}Tc -MIBI mammoscintigraphy). Two comparison groups (n-78) received similar treatment but with preoperative hyperfractionated EBRT at a total dose of 35-40 isoGy (n-40) and standard fractionated EBRT at a total dose of 40-44 Gy (n-38). The control group (n-83) received no preoperative radiotherapy. The follow-up period was 10 ± 1.3 years.

Results

Preoperative neutron therapy was well tolerated by all patients. After the first session of neutron therapy, 32 patients ($31 \pm 4.4\%$) had slight indisposition, nausea. Peripheral blood indices during the period of radiation therapy remained stable. Complete tumor regression was recorded in 9 ($9 \pm 2.5\%$) of 103 patients, the tumor sizes did not exceed 5 cm in diameter and were originally designated as T₂ index. Considering that most patients had T₃₋₄ tumor, partial regressions (reduction in tumor size $> 50\%$) were mainly registered ($65 \pm 4.8\%$). Stable disease was observed in 27 patients. There was no evidence of disease progression in any case. Immediate tumor response was assessed 3-7 days after the last session of neutron therapy. A small percentage of complete tumor regression can be explained by the lack of time to show the effect of chemoradiotherapy.

Local disease progression was observed 2 and 6 years after completion of multimodality treatment in 2 ($2 \pm 1.4\%$) patients of the study group. In the comparison groups, the rate of local recurrence was 7-12 times higher than that in the study group, being $15 \pm 5.6\%$ in patients receiving hyperfractionated photon radiation therapy and $23.7 \pm 6.9\%$ in patients receiving EBRT in a standard mode ($p = 0.008$ and $p = 0.0002$, respectively). The control group had the highest rate of tumor recurrence ($31.3 \pm 5.1\%$, $p < 0.01$). The recurrence-free survival rate was $96.0 \pm 3.0\%$ in the study group patients, $74.4 \pm 10\%$ and $69.8 \pm 8.9\%$ in the comparison groups and $57.9 \pm 7.4\%$ in the control group ($p < 0.05$).

Analysis of distant metastases showed the lowest rates in the study group ($27.8 \pm 4.5\%$) compared with the control group ($50.6 \pm 5.5\%$) ($p = 0.001$), in the comparison groups: I - $45 \pm 7.9\%$, and II - $42.1 \pm 8.0\%$ ($p = 0.04$). In the study group patients receiving neutron therapy, the 10-year metastasis-free survival rate was $63.6 \pm 6.1\%$ compared with $40.1 \pm 9.6\%$ in patients with preoperative hyperfractionated EBRT and $49.6 \pm 9.4\%$ in patients with standard radiotherapy fractionation ($p < 0.05$). In the control group, the corresponding value was $37.0 \pm 7.1\%$ ($p < 0.05$).

In the neutron therapy group, the 10-year survival rate was $70.8 \pm 5.8\%$, while in the hyperfractionated EBRT group, in standard fractionated photon therapy group and in the control group, the corresponding values were $42.4 \pm 10.7\%$, $54.2 \pm 9.6\%$ and $40.6 \pm 7.5\%$, respectively ($p < 0.05$).

Despite the increasing interest to the problem of the effect of various treatment modalities (chemotherapy, hormone therapy, surgery) on the health of breast cancer patients, few studies are reported on the role of radiotherapy, especially densely ionizing radiation (neutron therapy). Unfavorable effect of neutron therapy, especially in long-term follow-up is debated. However, these facts do not have direct evidence and require additional researches.

Changes in the main functional symptoms were noticed in all patients 6 months after treatment.

Thus, the patient's physical status in the study group reduced to 84 ± 3.7 points (initial index: 93 ± 2.6 points), in the comparison group to 77 ± 6.7 points (89 ± 4.9 points) and in the control group to 80 ± 6.3 points (88 ± 3.6 points). Changes in the cognitive function towards decrease to 83.4 points (90 points) were observed in the experimental group and to 73.4 points (76.7 points) in the control group. Changing in role functions and social status was more evident in the control group (75 points) than in the study group (80 points) and comparison group (81 points) (initial indexes: 92 , 94 and 90 points, respectively). Multimodality treatment resulted in decrease in sexual function of patients of all groups to 2-3 points, compared with the initial indexes. In 6 months after multimodality treatment, there was a positive trend showing the recovery of physical status of patients.

In addition to functional parameters, the study evaluated such symptoms as fatigue, nausea/vomiting, pain, insomnia and appetite. Thus, fatigue was observed in all patients before treatment. After completion of treatment, the studied levels slightly exceeded the initial index being 35 ± 4.8 points (initial index: 33 ± 4.7) in the study group, 36 ± 7.6 (initial index: 34 ± 7.5) in the comparison group and 34 ± 5.2 (initial index: 32 ± 5.1) in the control group. Recovery of general and physical status of patients was observed in 6 months after treatment, therefore fatigue complaints were recorded mainly in elderly patients aged over 60 years. After 1 year of follow-up, no significant changes were observed.

In all patients, pain syndrome was observed before starting the specific treatment and was caused by locally advanced disease. Pain relief was noted after completion of treatment, but complaints of discomfort in the region of the postoperative scar still kept. In long-term follow-up period, there was no pain syndrome in patients having no evidence of disease progression. There were no complaints of dyspnea in all patients. Early and late radiation-induced reactions in lung tissue after neutron and photon therapy were not observed, that was confirmed by the findings of the chest X-ray.

Limited movement in the arm after radical mastectomy and radiotherapy was observed in all patients with LABC. One year after treatment, all patients noted an increase in range of motion of the arm on the side of the affected breast.

Prior to treatment, the general health status was 58.3 ± 5.0 points in the study group, 52.7 ± 7.9 points in the comparison group and 49.8 ± 5.5 points in the control group. After completion of multimodality treatment, all patients, regardless of the type of ionizing radiation, noted the decrease in the general health status by 6% in the study group, by 8% and 10% in the comparison group and control groups, respectively. The rise of general health status was observed in all 3 groups of LABC patients 6 months after treatment (66.2 ± 4.8 points, 64.8 ± 7.6 and 61.7 ± 5.3 points, respectively). The maximum values of the general health status in all 264 patients were recorded 1 year after the completion of multimodality treatment.

Conclusion

Analysis of long-term results of multimodality treatment of patients with primary LABC has shown that preoperative neutron therapy is the most effective in the presence of multicentric tumors, radioresistance to neoadjuvant chemotherapy and other adverse prognostic factors.

Neutron therapy contributed to the reduction in the frequency of tumor local recurrence to 2% and increase in the recurrence-free survival rate. In addition, the tendency towards increased overall survival and metastasis-free survival was observed in the group of patients with neutron-photon therapy. No increase in the incidence of complications was noted in LABC patients having no the evidence of distant metastases.

References

- [1] V.V. Velikaya, L.I. Musabaeva, Zh.A. Zhogina, V.A. Lisin, Efficacy of neutron and neutron-photon therapy in multimodality treatment of local breast cancer recurrence, *Siberian J. of Oncology*. 1 (2008) 11-16 (in Russian)
- [2] L.I. Musabaeva, V.A. Lisin, Zh.A. Zhogina, V.V. Velikaya, Neutron and neutron-photon therapy in the treatment of locally advanced breast cancer and local recurrences, *Practical medicine*. 36 (2009) 45-46 (in Russian)
- [3] V.A. Lisin, Dosimetry gamma - neutron therapy planning of malignant neoplasms using U-120 cyclotron. *Medical radiology and radiation safety*. 5 (1994) 53-57 (in Russian)