EFFECTIVENESS OF RADIOTHERAPY TECHNIQUES AFTER BREAST-CONSERVING SURGERY IN PATIENTS WITH EARLY BREAST CANCER

UDC 618.19–006.6–039.1–089.168.1:615.831.6
Received 9.01.2014

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The improvement of early diagnostics of breast cancer has resulted in the increased proportion of early forms of the disease in women with newly diagnosed breast cancer. Enhancement of the existing and development of new breast conserving therapeutic techniques, as well as recurrence-free and total survival rate indices is of current concern. The obligatory radiotherapy for the remaining breast part has been shown to be the gold standard of such treatment.

The authors have analyzed the main current radiation techniques: boost to the tumor bed, radiation of regional metastasis areas. Particular attention is paid to a new technique, which is under study now — accelerated partial breast irradiation (APBI) in some patients. The advantages and disadvantages of these methods using the data of original studies have been presented.

There have been discussed the problems of clipping of a removed tumor bed using titanium wire clips, and the main criteria for selecting patients for accelerated partial breast irradiation.

Key words: radiotherapy; breast cancer; boost to the tumor bed.

Breast cancer continues to attract clinicians' attention due to high mortality and increasing incidence of the disease. Breast cancer gains a lead in oncologic diseases among women in Russia over the last decades. With the improvement of early diagnostics a proportion of early forms of the disease is growing [1], which calls for an active search for adequate forms of treatment.

The main concept of the work-in-progress approaches to the treatment of early forms of breast cancer is to perform breast conserving surgery in combination with radiation and drug therapy. Currently the «gold standard» of the breast-conserving therapy of these patients is obligatory radiation therapy (RT) for the remaining breast after surgery to prevent loco-regional recurrence. The necessity for RT after breast conserving surgery is confirmed by the evidence of numerous studies [2–6].

A standard dose of 50 Gy in 25 fractions over 5 weeks is recommended to deliver adjuvant RT to the breast and lymph efflux areas.

In some oncologic clinics around the world breast cancer patients receive dose-fractionated schedules different from classic ones [7–9]. In 2010, the Board of several ASTRO recognized experts analyzed the results of four largest prospective studies using RT hypofractionated schedules published over the last 5 years and demonstrating similar findings on local control and approximately equal amount of late injuries. All case histories, dose distribution schedules were thoroughly analyzed, the treatment outcomes were assessed and recommendations were drawn up, according to which a hypofractionated RT course (42.5 Gy in 16 fractions) of the mammary gland can be given to patients after breast conserving surgery on conditions that: 1) patients are over 50 years of age, 2) the stage is $pT_{1–2}N_0$, 3) no chemotherapy received, 4) when planning, dose variation within the breast should be ±7%, 5) the heart must be completely excluded from the irradiation region [10].

Boost to the tumor bed. The analysis conducted in the study [11] showed that the local recurrences often (85–95% cases) occur in the area of the primary tumor or close to it. That is why the radiation oncologists suggest reducing a local recurrence rate by delivering boost to the tumor bed, which can be called an area of high risk occurrence. The idea proved its value. Thus, the EORTC 22881–10882 trial [12] with almost 11 year follow-up of 5318 patients demonstrated a small (from 10.2 to

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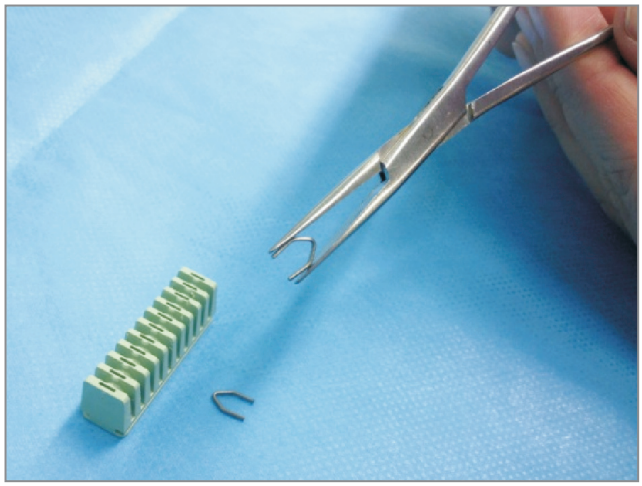

Fig. 1. Radiopaque clip

6.2%) but statistically significant (p=0.0001) reduction in the rate of local recurrence in the group with boost to the tumor bed with a 16 Gy dose. The reduction in the incidence of local recurrence was more significant in the individually investigated subgroup of young patients under 40 years of age ("Young boost trial", n=800), it amounting from 23.9 to 13.5% (p=0.0014).

Local irradiation of a removed tumor bed may be implemented with the use of various techniques:

brachytherapy, which can be intracavitary with the use of the MammoSite catheter and interstitial;

intraoperative RT with electrons, photons;

remote RT with photons or electrons (3DCRT, IMRT–RT with intensity modulating).

Boost to the tumor bed with the dose of 10–16 Gy is delivered either sequentially after irradiation of the whole breast with standard fractionation, or by the method of integrated radiation ("boost") ("field in field" technique), when a 0.35–0.4 Gy boost is delivered to the removed tumor bed after the irradiation of the remaining mammary gland with a 2 Gy dose. At this technique the total focal dose in 25 fractions of the irradiation of the tumor bed amounts 64–66 Gy. Seromas can be markers for identifying the removed tumor bed (however, they resolve with the time extension from the moment of the surgery), but most often the markers are X-ray contrast clips fixed during an operation (5–6 clips) (Fig. 1).

Boost to the tumor bed is indicated to all patients under 50 and patients of any age being at risk for tumor recurrence.

We have analyzed the results of the breast conserving treatment of 438 breast cancer patients, given in the N.N. Blokhin RCRC of the RAMS in 2000–2012. The complex of therapeutic procedures included radical resection, irradiation of the entire breast with boost to the tumor bed and without it. Systemic therapy was given when indicated. The study included patients with $T_{is-2}N_{0-2}M_0$ stage. The patients' median age was 46.7 years. The median follow up was 46 months (from 5 to 116 months).

All the cases were divided into three groups according to the volume of RT received: the patients in group 1 (n=54) were not exposed to RT after radical resection for various reasons; group 2 patients (n=113) received RT (the total dose of 50 Gy) after radical resection to the remaining breast with/without the exposure of the lymph outflow areas; in group 3 (n=72) after the irradiation of the entire breast boost to the tumor bed in the dose of 10 to 16 Gy was delivered (with a single focal dose of 2–2.5–3 Gy); the boost dose depended on the amount of the tissue removed during the surgical intervention, skin response by finishing RT of the entire breast, histological findings on the condition of the resection margin. Fig. 2 shows an example of dose distribution at the irradiation of the removed tumor bed.

Local and loco-regional recurrences were found in 14 patients (25.9%) in group 1, 18 (5.8%) in group 2, and 2 (2.7%) in group 3 over the period from 19 to 53 months. The earliest local recurrence developed over the period of 19 months in a patient without adjuvant RT. The difference in the recurrence rates is statistically significant (p<0.05) for groups 1 and 2, 1 and 3. Difference in the rate between groups 2 and 3 is not significant (p=0.29), which can be explained by a small number of patients in group 3.

Thus, radiation therapy is an obligatory component of breast conserving treatment of breast cancer patients, it significantly reduces the local recurrence rates; boost to the tumor bed contributes to a more significant reduction in recurrence rate.

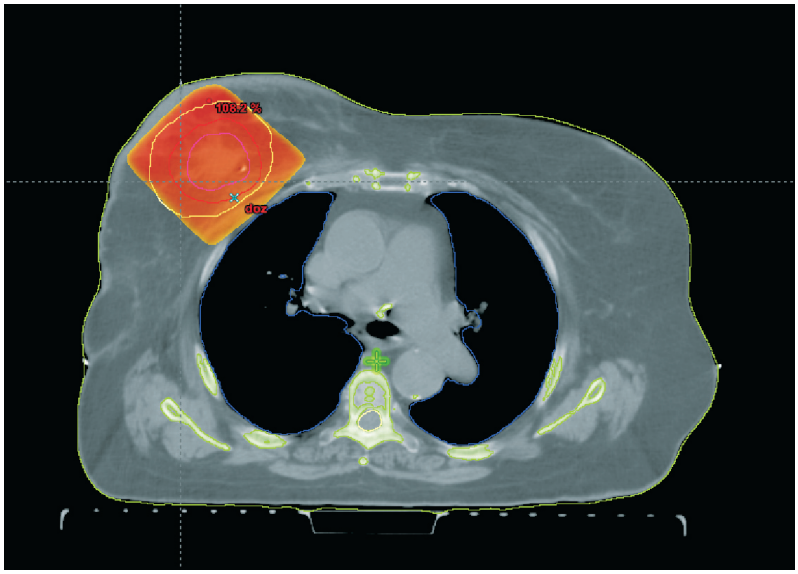

Fig. 2. Dose distribution at radiation therapy of the removed tumor bed with the photons of 6 MeV energy from three fields

Irradiation of regional metastasis areas. When performing adequate lymphadenectomy to level II (at least 10 removed lymph nodes are traditionally believed to be subject to histological investigation) in early breast cancer, adjuvant RT of the regional metastasis area is indicated if 4 or more lymph nodes are affected and it is not indicated in

case lymph nodes have no metastases. Adjuvant RT is administered individually to patients with lesions in 1–3 lymph nodes and no risk factors, since the risk of local recurrence in this group is not high [13, 14].

The expedience of the irradiation of parasternal lymph nodes is still under debate. Prospective randomized studies did not show any benefits at their removal. Even in case of clinically involved parasternal lymph nodes on implementing adjuvant chemotherapy alone recurrences are very rare. According to the NCCN guidelines parasternal lymph nodes are exposed to radiation only when their involvement is based on clinical evidence (category 2B). Currently patients have been recruited for research trials under EORTC (protocol 22922) and NCI Canada (protocol MA 20) investigating this problem [14, 15].

Accelerated partial breast irradiation. Several factors gave rise to the researchers' new concept of RT amount and dose applied to a certain group of patients: patients' desire to shorten the duration of the postoperative RT course, which usually lasts 5–7 weeks; likelihood of the development of radiation injuries of different severity in some patients as a result of the exposure of pulmonary and cardiac tissues during RT of the remaining part of the breast and the fact that local recurrence is most often localized mainly in the resection area of the primary tumor. This urged the researchers to study the potential of accelerated partial breast irradiation — APBI. In many foreign countries delivering of intraoperative RT to the removed tumor bed alone with a dose of 15–17 Gy for one session after a breast conserving surgical intervention has been actively studied since 1998. Now APBI is available with the use of the devices with an electron beam radiation energy of 3, 5, 7 and 9 MV (NOVAK 7, Italy — a mobile linear accelerator with a robotic arm and an applicator with 4–10 cm in the diameter) and a flow of photons with an energy of 50 kV (INTRABEAM, Germany); a balloon catheter MammoSite (USA); as well as brachytherapy (LDR&HDR); conformal RT; IMRT.

The main criteria for the selection of patients for accelerated partial breast irradiation are defined in the ASTRO guidelines for implementing APBI (Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology) and the guidelines of GEC-ESTRO (Groupe Européende Curiethérapie-European Society for Therapeutic Radiology and Oncology) breast cancer working group, published in 2009. The Expert team did not recommend *BRCA1* or *BRCA2* mutation carriers, patients with a family history to use APBI technique because there is no data on its implementation in this group of patients in literature. For the same reason patients with ductal carcinoma (DCIS) are also excluded from the research so far. The following criteria are applied for the selection of patients for APBI: aging (over 55 years old in Italy, over 60 years old by the USA guidelines, over 65 years old in France), occurrence of one focus of no more than 2.5 cm, intact resection margins of ⩾2 mm, no lobular cancer by histological feature, no involvement of the lymph nodes, no signs of vascular invasion, receptor positive status of a tumor [16, 17].

Errors in any of the listed provisions may lead to unsatisfactory indices on local control, development of late toxic effects and obtaining unsatisfactory cosmetic results.

Having analyzed the results of 5 studies (IRMA, IMPORT-Low, Danish Breast Cancer Group, NSABPB-39, RTOG 0413), A.M. Kirby et al. came to the conclusion that the optimum alternative to identify a removed tumor bed is surgical clips (from 3 to 12) at the CT sections, sometimes ultrasound is used to identify the location of seroma when there are no radiopaque clips. In all the five studies the "removed tumor bed — CTV (clinical treatment volume)" space equals to 15 mm and the space between the CTV and PTV (planning treatment volume) is 10 mm [18]. The stages of planning are shown in Fig. 3.

M.C. Leonardi et al. analyzed the treatment results of 1822 patients with early breast cancer, who received intraoperative RT with electrons after breast conserving surgery (Milan III ELIOT trial) [19]. In accordance with the selection criteria for implementing APBI (ASTRO) all the patients were divided into subgroups: subjects who fully meet the selection criteria (n=294), those who partially meet them (n=691), those who do not meet the criteria (n=812). 5-year incidence of loco-regional failures were 1.5, 4.4 and 8.8%, respectively (p=0.0003).

In large clinics around the world APBI after breast conserving surgery is generally implemented in two schedules: 3.4 Gy 2 times a day — 10 fractions over 5 days (brachytherapy) and 3.85 Gy 2 times a day —

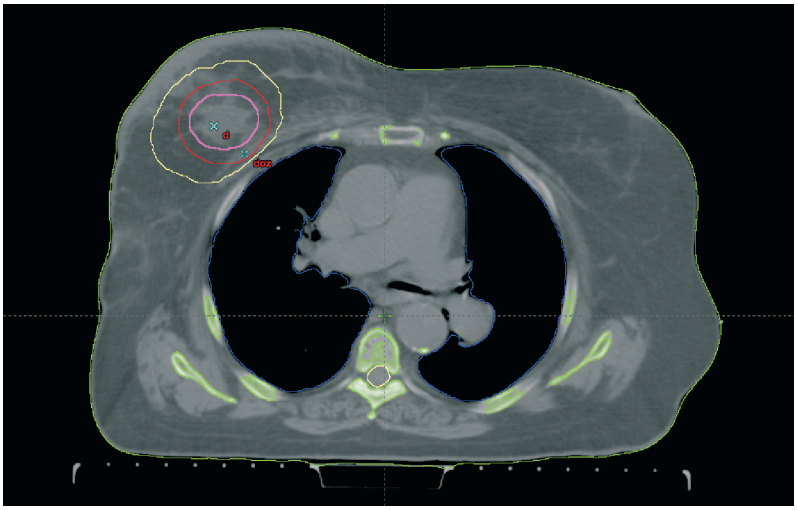

Fig. 3. Contouring stage; CT-section shows a radiopaque clip, a removed tumor bed, CTV and PTV

10 fractions (at remote RT) for 5 consecutive days (the interval between fractions is 6 h) [16].

In the N.N. Blokhin RONC of the RAMN the APBI has been administering to patients with early breast cancer ($T_{1–2}N_{0–mic}M_0$) after breast conserving surgery since 2008. When forming groups for the trial, all selection criteria listed above were carefully followed. 53 patients were treated with the use of 3D CRT technique. The age of the patients was within the range of 52 and 77 years (median 65 years). The median follow-up was 30 months (3–65 months).

The histological findings showed a tumor size up to 1 cm in 15 patients (28.3%), up to 2 cm in 25 patients (47.2%), up to 3 cm in 11 patients (20.7%), in 2 women (3.8%) the tumor size reached 3.5 cm. Infiltrative ductal cancer was diagnosed in 52 patients (98%), one patient had mixed ductal and lobular cancer. The G2 stage of malignancy was detected in 39 patients (74%) and G1 in 14 patients (26%), signs of vascular invasion in the form of isolated cancer emboli were detected in 2 women (3.8%). At histological study from 6 to 28 lymph nodes (median 10) were examined, 52 patients (98%) did not show affected lymph nodes, only one case (2%) had cancer micrometastasis in 1 lymph node. Resection margins were investigated in all 53 patients, tumor cells were not found in none of them. Single focal dose was 2.5 Gy, a daily dose was 5 Gy (with an interval of 6 h between fractions), the total focal dose throughout the course of exposure was 40 Gy. With the median follow-up of 30 months (3–60 months), local recurrence was not detected. Calculated according to the TDF tables (time-dose-fraction) the total focal dose was 56 Gy, calculated according to the linear-quadratic model at α/β=3 it was 52 Gy, at α/β=3.4 it was 50.8 Gy.

To achieve clear visualization and adequate determination of the RT volume, clipping of the removed tumor bed with the help of metal clips, made of titanium wire of specific shape was done in 92% of the patients (See Fig. 1). Titanium is used in the production of surgical clips, it is biologically inert, radiopaque and nonmagnetic material. Specifically processed, the titanium alloy has zero shape memory which enables to avoid delayed spontaneous opening of a clip and ensures reliable fixation in a previously specified area.

The selection of the area for clip fixation (pectoral muscle or mammary gland tissue) is determined by the volume of surgical intervention and location of the primary tumor. When at radical resection of the mammary gland and with the deep location of the primary tumor, clips are fixed in the area of the removed primary tumor bed projection directly to the breast muscle, which forms the bottom of the removed sector. Clipping stages are shown in Fig. 4.

On the computer section a clearly identified radiopaque clip is a landmark for selecting the volume of radiation exposure (See Fig. 3).

Accelerated partial breast gland irradiation was given with the use of 2–4 coplanar and noncoplanar photon fields or a combination of 2 photon (6–8 MeV energy) and 1 electron field (9, 12 and 18 MeV energy) ones.

Early radiation skin injuries of grade I by RTOG-EORTC classification [20] were detected in all the patients. With the median follow-up of 30 months loco-regional recurrences and distant metastases were not detected in any patient. Late radiation injuries of the skin and soft tissues were not detected in any patient.

A cosmetic effect was evaluated in 40 patients on a 4-grade scale by the Joint Center for Radiation Therapy (Boston) system [21] by both a surgeon and a radiologist (with a corresponding note in the patient's case record), photographing, and a patient's self-evaluation was also taken into account (filling out specially worked out questionnaires).

"Excellent", "good', "average" and "bad" cosmetic results were obtained in 24 (60%), 14 (35%), 2 (5%) and 0% of the patients that can be considered as a very good achievement.

Thus, the technique of accelerated partial breast irradiation of a thoroughly selected group of patients with early forms of breast cancer allows to obtain the results of the local control, similar to those at radiation exposure of the total remaining breast.

Conclusion. Irradiation of the entire breast currently remains the "gold standard" in the treatment of early breast

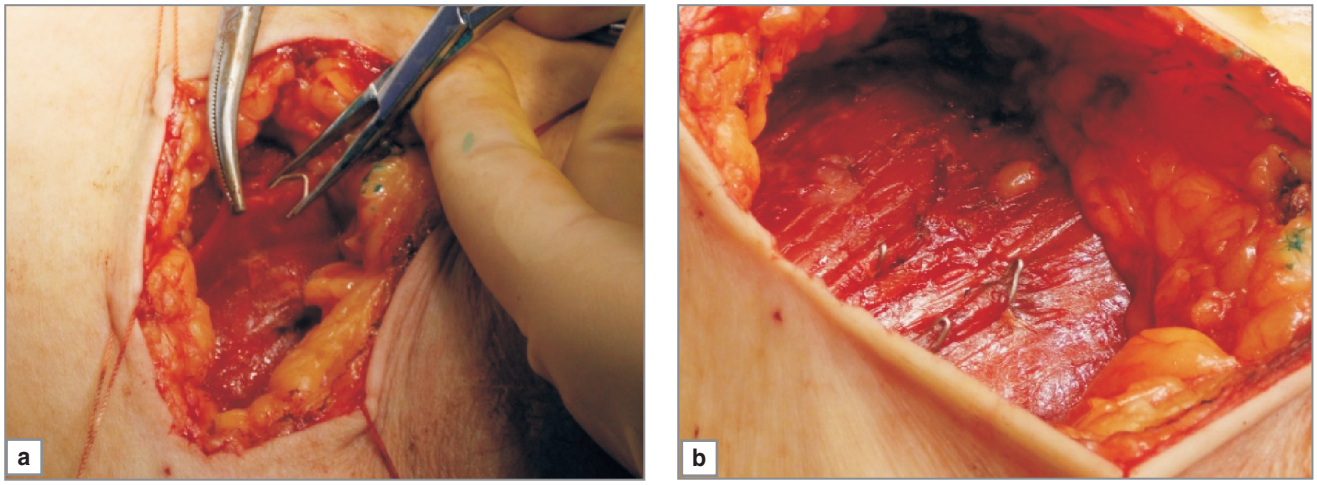

Fig. 4. Clipping of the removed tumor bed at radical resection of the mammary gland: *a* — a phase of radical resection of the mammary gland, clips are fixed to the major pectoral muscle, *b* — surgical wound after clipping with 3 clips

cancer after breast conserving surgery. Supplementary exposure of the removed tumor bed in younger patients and patients at high risk of tumor recurrence enables to reduce the incidence of local recurrences.

APBI is a new technique that provides faster, more convenient treatment after conserving surgery in a carefully selected group of patients.

Study Funding and Competing Interest. This study was not supported by any financial sources and there is no topic specific conflict of interest related to the authors of this study.

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