Patient Study Spotlight

Intraoperative radiotherapy in elderly patients with breast cancer: long-term follow-up results of the prospective phase II trial TARGIT-E

Seeing beyond

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Introduction:

Breast cancer (BC) is becoming more common in elderly patients, partly because people are living longer (1). However, these patients are often not included in clinical trials, even though their unique health conditions, like other illnesses and medications, need special attention (2). Radiation therapy (RT) for the whole breast can cause side effects like fibrosis and edema and might affect the heart, lungs, and thyroid, which can lower the quality of life (3 - 6).

Studies show that the side effects of RT in elderly patients are similar to those in the general population (7). However, some research suggests that skipping RT after breast-conserving surgery (BCS) in elderly patients can lead to worse outcomes, such as higher rates of local recurrence and lower overall survival. RT is sometimes skipped due to concerns about toxicity, other health conditions, or the presence of pacemakers (2, 8 - 11).
One way to reduce potential side effects is to use targeted RT, which only irradiates part of the breast (12). This method can still effectively control cancer using techniques like brachytherapy, external beam irradiation, or intraoperative radiotherapy (IORT) (13–15).

Methods:

- **Participants:** 591 patients included, at a median age of 74 years
- **Design:** prospective, multi-center, phase-II
- **Inclusion Period:** February 2011 - September 2014
- **Inclusion Criteria:** low-risk breast cancer, ≥70 years, cT1 - 2, cN0, cM0, invasive carcinoma of no special type
- **Treatment:** IORT alone: one single dose of 20 Gy; IORT + WBRT: Additional postoperative WBRT (46 - 50 Gy) in case of risk factors in the final histopathology report

Endpoints:

- **Primary:** local recurrence rate after 2.5, 5 and 7.5 years using Kaplan-Meier-estimates
- **Secondary:** overall survival, ipsilateral recurrence (= on the same side) and contralateral (= on the other side) breast cancer, lymph node recurrence, distant metastases, toxicities, and cosmetic results

Results:

- **Groups**: 383 patients (65%) received IORT alone; 132 pts (22%) received IORT + WBRT; 36 patients (6%) received WBRT alone (due to large tumor cavity or the tumor being very close to the skin); 40 patients were (7%) not specific
- **Median follow-up time:** 65 months (5.4 years)
- **Recurrences: total:** 18 local recurrences (LR), 13 in the exclusive IORT group (13/383; 3.4%), 4 in the IORT + WBI group (4/132; 3.0%), 1 in non-IORT group (1/36; 2.8%)

- **Local recurrence-free survival:**

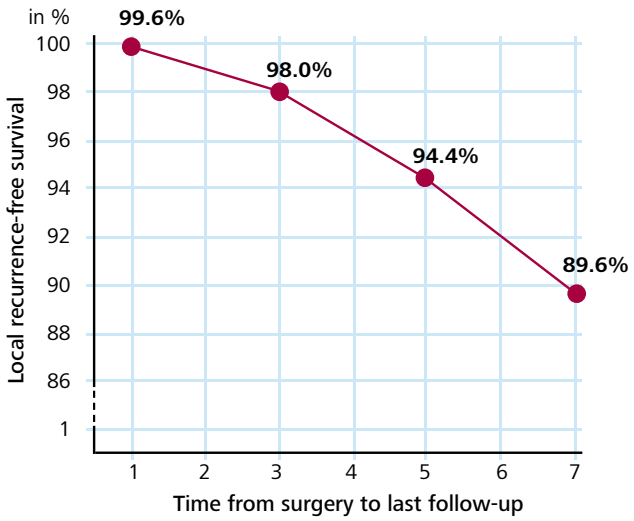

Fig. 1: Local recurrence-free survival (local recurrences and death counted as an event, whatever occurs first).

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- **Toxicity:** Most patients experienced no (grade 0) or mild toxicities (grade I)
  - **Ulcerations and lymph edemas** were very rare, with serious toxicities (grade II–III) occurring <1% during the follow-up period
  - **Hyperpigmentation (= skin darkening)** grade II only occurred within the first 3 years (2.6 % after 1 year, 0.3 % after 3 years)
  - The most common late side effects were **fibrosis (= tissue hardening), retractions (= inward pulling of skin), pain, and teleangiectasia (= visible blood vessels)**
  - **Chronic serious fibrosis** was seen in 10 % and chronic pain (grade II or III) in 2 % after 5 and 7 years in patients treated with IORT only. After 7 years, 97 % had no **teleangiectasia** and 84 % no **retraction** with IORT only.
  - **Fibrosis:** patients receiving both IORT + WBRT showed significantly lower toxicity-free rates after 5 and 7 years than the patients receiving either IORT or WBRT only (free from fibrosis: IORT after 5 and 7 years: 90 %, WBRT after 5 and 7 years: 93 % vs. IORT + WBRT after 5 and 7 years: 66 %; $p<0.001$). The same trend was seen for pain (IORT after 5 and 7 years: 98 %, WBRT after 5 and 7 years: 93 % vs. IORT + WBRT after 5 years: 89 % and after 7 years: 85 %; $p<0.05$).

- **Cosmetic outcome:**

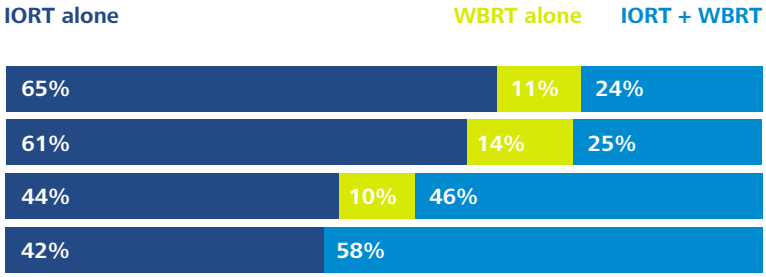

Fig. 2: Cosmetic outcome according to RT treatment over the whole study period.

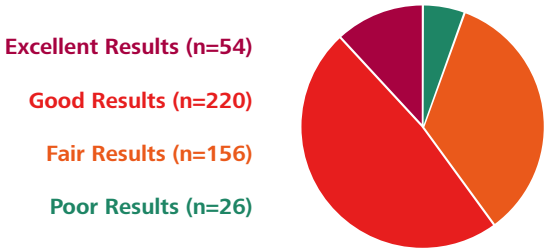

Fig. 3: Cosmetic outcome.

Discussion:

For low-risk elderly patients who have undergone breast-conserving surgery with IORT, recurrence rates were low after more than 7 years and more than 90 % of the patients experienced good local control and survival rates. Side effects (= toxicities) were generally mild, especially when only IORT was used, and cosmetic results were mostly good to excellent, suggesting an advantage of IORT over traditional whole-breast radiotherapy (WBRT).

Other studies in elderly patients have shown that skipping radiation therapy (RT) after surgery leads to lower local recurrence-free rates (= preventing cancer from returning in the same area) compared to using RT after surgery. For example, two studies, PRIME II and CALGB 9343, reported similar 5-year rates of keeping cancer from coming back locally, with PRIME II at 98.7 % and CALGB 9343 at 99 % (8, 10). However, these rates were noticeably lower when RT was not used. In the long-term follow-ups of these studies (median follow-up PRIME: 9.1 years; CALGB 9343: 12.6 years) the advantage of using WBRT after breast-conserving surgery was even clearer and significantly in favor of WBRT. Regarding survival rates, the PRIME II study found that both groups had roughly the same overall survival rate of about 80 %, which is 10 % lower than the roughly 90 % survival rate seen in the TARGIT-E group. This aligns with data from the TARGIT-A study and other analyses showing consistently high survival rates for patients treated with IORT (16, 17).

When it comes to side effects, targeted intraoperative radiation therapy (IORT) can help protect healthy tissues from unnecessary radiation, which reduces the risk of radiation-related toxicities (12). In TARGIT-E, we observed either no late toxicities or mild ones for most patients. Freedom from chronic toxicity was remarkable high when IORT was used alone and less when IORT was given in combination with WBRT. As people age, their skin becomes less elastic and heals slower, which can lead to more frequent skin tightening or retractions (18). However, we did not find a clear trend, and all reported retractions were mild (grade I).

This study has some limitations. It only looked at one group of patients without comparing them to another group (= single-arm design). Although the study used standardized methods to measure long-term toxicities and cosmetic outcomes, these evaluations were still based on the doctors' personal evaluation and photos analyzed with software. Additionally, over time, many patients didn't continue with follow-up assessments for long-term side effects and cosmetic results, which affects the completeness of the data.

Conclusion:

Our findings indicate that targeted IORT is an effective, fast and feasible method for radiation treatment during breast-conserving surgery, especially for elderly patients. Over a follow-up period of more than 7 years, the rates of preventing cancer from returning locally and overall survival were very high. Long-term side effects, measured by the so-called LENT-SOMA score, were mostly non-existent or mild and comparable to the rates seen in younger breast cancer patients. The cosmetic results were generally excellent or good, also comparable to those in younger patients. Therefore, IORT is a very interesting single-treatment option for elderly patients with early-stage breast cancer.

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