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Clinical Investigation

Preoperative Single-Fraction Partial Breast Radiation Therapy: A Novel Phase 1, Dose-Escalation Protocol With Radiation Response Biomarkers

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Summary

This phase 1, dose-escalation trial evaluated the feasibility

Purpose: Women with biologically favorable early-stage breast cancer are increasingly treated with accelerated partial breast radiation (PBI). However, treatment-related morbidities have been linked to the large postoperative treatment volumes

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of single-dose preoperative partial breast irradiation delivered with external beam techniques in early-stage breast cancer patients. No acute dose-limiting toxicity was observed at 15, 18, or 21 Gy. Paired pre- and post-radiation imaging and tumor biopsies offer unique insight into the biology of breast cancer radiation response.

required for external beam PBI. Relative to external beam delivery, alternative PBI techniques require equipment that is not universally available. To address these issues, we designed a phase 1 trial utilizing widely available technology to 1) evaluate the safety of a single radiation treatment delivered preoperatively to the small-volume, intact breast tumor and 2) identify imaging and genomic markers of radiation response.

Methods and Materials: Women aged ≥55 years with clinically node-negative, estrogen receptor−positive, and/or progesterone receptor−positive HER2−, T1 invasive carcinomas, or low- to intermediate-grade in situ disease ≤2 cm were enrolled (n=32). Intensity modulated radiation therapy was used to deliver 15 Gy (n=8), 18 Gy (n=8), or 21 Gy (n=16) to the tumor with a 1.5-cm margin. Lumpectomy was performed within 10 days. Paired pre- and postradiation magnetic resonance images and patient tumor samples were analyzed.

Results: No dose-limiting toxicity was observed. At a median follow-up of 23 months, there have been no recurrences. Physician-rated cosmetic outcomes were good/excellent, and chronic toxicities were grade 1 to 2 (fibrosis, hyperpigmentation) in patients receiving preoperative radiation only. Evidence of dose-dependent changes in vascular permeability, cell density, and expression of genes regulating immunity and cell death were seen in response to radiation.

Conclusions: Preoperative single-dose radiation therapy to intact breast tumors is well tolerated. Radiation response is marked by early indicators of cell death in this biologically favorable patient cohort. This study represents a first step toward a novel partial breast radiation approach. Preoperative radiation should be tested in future clinical trials because it has the potential to challenge the current treatment paradigm and provide a path forward to identify radiation response biomarkers.

Introduction

Partial breast irradiation (PBI) is increasingly utilized in the treatment of early-stage breast cancer. As data supporting the efficacy and tolerability of PBI continue to accumulate, this conceptual approach has been incorporated into national radiation guidelines and deemed acceptable for use outside of a clinical trial in carefully selected patients (1). A number of techniques are available for treatment delivery, ranging from a single intraoperative treatment to 1 week of twice-daily treatments. In fact, a phase 3 trial focused only on brachytherapy PBI delivery techniques completed enrollment in 2009 with 1300 patients (Groupe Européen de Curiethérapie−European Society for Radiotherapy and Oncology; NCT00402519). In addition, early reports are emerging from 2 randomized trials (Electron Intraoperative Radiotherapy [ELIOT] and TARGeted Intraoperative radioTherapy [TARGIT]) testing a single fraction of radiation delivered in the operating suite directly to the tumor bed (2, 3). However, with the exception of external beam PBI, every technique requires specialized training or equipment that, relative to linear accelerator−based options, are not as widely available to all radiation oncology practitioners. As a result, in a recent interim analysis of the phase 3 National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413 partial breast trial, external beam PBI was used in 72.9% of patients randomized to the PBI arm (4).

However, suboptimal outcomes have been reported with postoperative external beam PBI. Hepel et al (5) reported high rates of grade 3 to 4 soft-tissue fibrosis (8.3%) in 60 patients treated with external beam techniques. Jagsi et al (6) closed their study after only 34 patients secondary to high rates of unacceptable cosmesis after only 2.5 years. Both groups linked these adverse outcomes to the sizeable treatment volumes required to target a postoperative surgical seroma plus appropriate margin. Although other institutional series and phase 2 trials (7-10), as well as the randomized NSABP B-39/RTOG 0413 trial (4), have reported low rates of long-term toxicity, the Canadian phase 3 Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) also noted adverse cosmetic outcomes (29% PBI vs 17% whole breast, $P<.001$) at 3 years (11), suggesting that the results of external beam PBI could be improved upon.

To address these issues, we designed a novel, phase 1, dose-escalation trial of single-dose preoperative radiation treatment in carefully selected, favorable-risk patients. This technique has numerous potential advantages: (*1*) it can be delivered with widely available radiation techniques; (*2*) the target volume is a small intact breast tumor and its adjacent tissue rather than a large postoperative seroma, which significantly decreases the uninvolved breast tissue