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Radiation-induced fibrosis

Radiation-induced fibrosis in the boost area after three-dimensional conformal radiotherapy with a simultaneous integrated boost technique for early-stage breast cancer: A multivariable prediction model

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ABSTRACT

Background and purpose: To develop a multivariable prediction model for the risk of grade ⩾ 2 fibrosis in the boost area after breast conserving surgery (BCS) followed by three-dimensional conformal radiotherapy (RT) with a simultaneous integrated photon boost (3D-CRT-SIB), five years after RT.
Material and methods: This prospective cohort study included 1,030 patients treated with RT for breast cancer (stage 0-III), after BCS. Data regarding physician-rated fibrosis and dose–volume parameters were available in 546 patients. A multivariable logistic regression model for grade ⩾ 2 fibrosis was generated.
Results: At 5 years, grade ⩾ 2 fibrosis was observed in 13.4% of the patients. The multivariable analysis resulted in a prediction model for grade ⩾ 2 fibrosis in the boost area including three independent variables: patient age, breast volume receiving ⩾ 55 Gy (V55 CTV breast) and the maximum radiation dose in the breast (D_{max}).
Conclusions: A multivariable prediction model was developed including age, V55 CTV breast and D_{max} for grade ⩾ 2 fibrosis in the boost area after breast cancer RT using a 3D-CRT-SIB technique. This model can be used to estimate the risk of fibrosis and to optimize dose distributions aiming at reducing this risk.
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Breast-conserving surgery (BCS) followed by radiotherapy (RT) is currently considered standard of care for early-stage breast cancer [1,2].

Three-dimensional conformal RT with a simultaneous integrated photon boost (3D-CRT-SIB) is a commonly applied technique as part of breast conserving therapy. In comparison to the sequential boost technique, 3D-CRT-SIB results in a higher dose homogeneity, less excessive dose outside the boost area and a higher dose per fraction to the tumor bed, resulting in an overall shorter treatment time [3].

The higher dose per fraction to the tumor bed as used in the 3D-CRT-SIB technique could however lead to more fibrosis in the boost area and subsequently to worse cosmetic outcome. In a consecutive series of breast cancer patients treated at our department, the reported local control and overall survival rate at five years was 98.9% and 93.3%, respectively [4]. Despite the higher dose per fraction to the tumor bed, the incidence of physician-rated fibrosis in the boost area was similar to that observed by other investigators using sequential boost techniques, with a cumulative incidence of grade ⩾ 2 fibrosis of 8.5% at 30 months [5].

So far, there is a lack of information on the relationship between dose distribution and fibrosis in the boost area, which applies for both sequential and simultaneous integrated boost techniques.

Therefore, the aim of this prospective cohort study was to develop a multivariable prediction model for the risk of grade ⩾ 2 fibrosis in the boost area after BCS followed by RT with 3D-CRT-SIB, five years after the end of treatment.

Methods and materials

Study population

The population of this prospective cohort study was composed of 1,030 patients consecutively treated with RT for invasive breast cancer (stage I-III) or ductal carcinoma *in situ* (DCIS), after BCS. Patients with a DCIS and free resection margins did not receive a boost dose and were not included in this study. All patients were irradiated at the department of Radiation Oncology of the University Medical Center Groningen from May 2005 to May 2009, using a 3D-CRT-SIB technique as described previously [3]. Patient, tumor and treatment-related characteristics including follow-up data

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were retrospectively analyzed from the electronic medical files. Protocols for surgery, RT and systemic treatment summarized below were described previously [4,5].

Surgery

Primary surgery was performed in nine hospitals in the Northern Netherlands. All patients were treated with lumpectomy. In case of more than focally involved resection margins, re-resection was performed if possible to obtain clear surgical margins. Axillary staging was done with sentinel node biopsy (SN) in invasive carcinoma. Axillary clearance was performed in case of positive SN or positive cytology in the clinically node-positive axilla. In selected cases of pure DCIS, SN was performed as well.

Radiotherapy

Computed tomography-planned breast irradiation and a boost dose to the tumor bed were given simultaneously. Opposing tangential beams were directed to the whole breast. In general, the boost plan consisted of three photon beams. The breast clinical target volume (CTV breast) was defined as the glandular breast tissue of the ipsilateral breast, with exclusion of ribs, skin and the major pectoral muscle. The boost clinical target volume (CTV boost) was defined as the tumor bed guided by surgical clips, hematoma, seroma and/or other surgery-induced changes and a 3D margin of 10 mm. The fractionation schemes used were 28 daily fractions of 1.8 Gy to the whole breast and a boost of 2.3 Gy or 2.4 Gy, resulting in a total dose of 64.4 or 67.2 Gy. The highest dose was administered in case of focally positive resection margins of either the invasive tumor or DCIS component after (re-)resection. Regional RT (28×1.8 Gy), including irradiation of the axillary, infra- and supraclavicular areas was applied in case of more than three positive axillary lymph nodes or a positive apical lymph node. The internal mammary nodal (IMN) areas were irradiated in case of a medially located tumor, a pathologic IMN sentinel node or positive flow to an IMN lymph node, that had not been surgically removed.

Systemic therapy

Adjuvant systemic therapy was indicated in patients with node-positive disease and high-risk node-negative tumors. Patients were classified as high risk depending on tumor size, tumor grade, hormonal receptor status, and age. In most patients with node-positive disease, RT was given after completion of chemotherapy, whereas in high-risk node-negative patients, RT was given before chemotherapy. Hormonal therapy, tamoxifen, or aromatase inhibitors were applied in case the tumor was hormonal receptor-positive, in the node-positive group and in the high-risk node-negative group. In most patients, hormonal therapy was started before or during radiotherapy. In patients receiving chemotherapy, trastuzumab was indicated in tumors positive for human Epidermal Growth Factor Receptor 2.

Toxicity assessment

After completion of RT, patients underwent routine yearly follow-up until 5 years after RT in which physician-rated toxicity was prospectively assessed according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [6].

The CTCAE criteria for fibrosis in the boost area are: grade 0 (no fibrosis), grade 1 (mild fibrosis without impairment), grade 2 (moderate fibrosis) and grade 3 (severe fibrosis with impairment). The primary endpoint was defined as fibrosis grade $\geqslant 2$ in the boost area.

Follow-up

Physician-rated toxicity data in the fifth year after treatment were available for 623 patients (60.4% of all patients treated in May 2005 to May 2009). These data were defined as the most recent follow-up in the period of 47 to 61 months after completion of RT. The reasons for the loss of follow-up of patients ($n = 407$) were: patient request for discontinuation of follow-up ($n = 236$), secondary malignancy ($n = 37$), local recurrence ($n = 10$), regional recurrence and/or distant metastases ($n = 43$), change of hospital due to migration/moving ($n = 8$), death by another cause ($n = 13$), no physician-rated toxicity data available ($n = 16$), planned follow-up visit after last inclusion date for study ($n = 29$) or unknown ($n = 15$).

Patient variables and dose–volume parameters

The following patient variables were included in the univariable analyses: patient age at start of RT (years), re-resection (no or yes), tumor size (defined as the total length x breadth x height of the tumor (cc)), axillary lymph node dissection (no or yes), adjuvant hormonal therapy (no or yes), adjuvant trastuzumab (no or yes), smoking during treatment (no or yes), treatment sequence (chemotherapy-RT; RT-chemotherapy; RT alone), weight of the lumpectomy (and eventual re-lumpectomy) specimen (g) and size of the lumpectomy (and eventual re-lumpectomy) specimen (defined as the total length $\times$ breadth $\times$ height of the lumpectomy and eventual re-lumpectomy specimen (cc)).

Physician-rated toxicity data and planning data were available for 546 patients, for 77 patients the planning data were corrupt or missing (14.1% of all patients with available follow-up data). The following dose–volume parameters were recalculated and collected from our treatment planning system (Pinnacle version 9.1; Philips Radiation Oncology, Fitchburg, WI, USA): D_{max} CTV breast (maximum dose (Gy) in CTV breast in at least one voxel), D_{mean} CTV breast (mean dose (Gy) in CTV breast), CTV boost / CTV breast ratio. The CTV boost area was always part of the CTV breast. Furthermore, for simplicity, only 4 isodoses of the CTV breast were selected for univariable analyses: volumes of CTV breast receiving $\geqslant 50$, $\geqslant 55$, $\geqslant 60$ and $\geqslant 65$ Gy (i.e. V50, V55, V60 and V65, respectively).

Statistical analysis

Univariable analyses were performed in SPSS version 20. These tests were two-sided and p-values < 0.05 were considered statistically significant. To generate a multivariable logistic regression model for grade $\geqslant 2$ fibrosis with bootstrapping and sequential forward variable selection was used, with the adaptation of consistent use of the likelihood criterion, using a dedicated MATLAB application [7]. Model performance was assessed by testing discrimination (using the area under the curve, AUC) and calibration (Hosmer–Lemeshow test).

Results

Patients

For 546 patients, treatment-related, follow-up and dosimetric data were available in the fifth year after treatment. Patient, tumor and dose distribution characteristics are listed in Table 1. The median age of the patients was 65 years (range: 40–89 years). Median follow-up time was 54 months (range 47–61 months). The majority of the patients (75.6%) received the boost dose of 64.4 Gy.

Fibrosis grade 0, 1, 2, and 3 was observed in 21.8%, 64.8%, 11.7% and 1.6%, respectively. The proportion of patients with grade $\geqslant 2$ fibrosis in the boost area was 13.4%.