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"Radiotherapy for Older Women (ROW)": A Risk Calculator for Women with Early-Stage Breast Cancer

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Abstract

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Objective: Among older adult women with early-stage breast cancer who undergo lumpectomy, the benefits of radiotherapy vary according to tumor characteristics and life expectancy. We aimed to develop a risk calculator to predict individualized probability of long-term survival and local recurrence, accounting for these factors.

Methods—We developed a simulation model to estimate an individual patient's risk of local recurrence and all-cause mortality according to age, comorbidities, functional status, tumor characteristics, and radiotherapy status. We integrated two existing prediction models, the Early Breast Cancer Trialist's Collaborative Group prediction model for breast cancer specific outcomes and ePrognosis for life expectancy. An online risk calculator "Radiotherapy for Older Women (ROW)" was developed through an iterative multi-stage process, that included individual consultation and group meetings with an advisory committee (AC) comprised of patients, advocates, clinicians, and researchers.

Results—We developed the tool over 40 months and had 15 group meetings. The risk calculator developed as a simulation model with 16 factors (5 tumor-related, 3 demographic, 4 comorbidities, and 4 functional statuses). Across 56,700 simulated scenarios, the benefit of RT in terms of absolute 10-year local recurrence reduction, ranged from 0% to 34%, depending on individual characteristics. Based on feedback from the AC, overall survival and local recurrence were chosen as the output for ROW, with these outcomes displayed numerically (percentages and natural frequencies) and graphically (pictographs).

Conclusions—This tool "ROW" could facilitate shared decision making regarding receipt of radiotherapy for older women with early breast cancer. Additional studies to examine usability testing are underway.

Introduction

For older adult women with early-stage, estrogen receptor (ER) positive breast cancer who undergo breast-conserving surgery (BCS), two randomized controlled trials have demonstrated that adjuvant whole breast radiation therapy (WBRT, hereafter as RT) reduces local recurrence but does not improve overall survival. (1, 2) Based on these data, consensus guidelines recommend that omission of RT can safely be considered for women aged 70 or older with stage I disease who receive endocrine therapy (ET).(3) However, more than two-thirds of these women undergo RT.(4, 5) While RT does reduce local recurrence, it also requires travel to receive daily radiation for several weeks and poses risks of side effects, such as fatigue, breast pain, and pneumonitis.(6–10) Therefore, it is critical that women are well-informed when considering the receipt of RT.

Risk of local recurrence can vary significantly. Tumor size, tumor grade, margin width, ER status, and number of positive axillary nodes, for example, have all been associated with local recurrence.(11–13) Several risk calculators or nomograms have been developed to help RT decision-making by predicting outcomes with and without adjuvant RT.(12) However, these programs do not focus on older women, and do not incorporate competing mortality. It is well known that the benefits of an intervention decrease as life expectancy decreases.(14, 15) Older patients are more likely to have multiple comorbidities or impaired functional status, and to die of non-breast-cancer-related causes, and therefore might be less likely to

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benefit from RT. To our knowledge, there is no RT risk calculator that incorporates life expectancy into its prediction model, despite the substantive relationship between life expectancy and recurrence in this population.

Accordingly, we sought to develop an interactive, individualized, automated risk calculator "Radiotherapy for Older Women (ROW)." Our objective was to promote patient-centered treatment decisions by providing personalized risk estimates for older women with early-stage breast cancer. We proposed a novel model that integrates two published predictive models, ePrognosis (a survival prediction tool frequently used in geriatric assessment)(16, 17) and the Early Breast Cancer Trialist's Collaborative Group (EBCTCG) prediction models.(13) We also convened an advisory committee (AC) to help develop ROW to be patient-centered and user-friendly. Through collaborative discussions, we presented individualized outcome estimates in an electronic format to facilitate provider-patient communication.

Methods

Study Design

The Human Investigation Committee of the authors' institution approved this study. A synopsis of the study design is shown in Figure 1. In brief, this was a two-part study: (1) development of simulation models to estimate personalized outcomes, with and without RT; and (2) development of a risk calculator for older adult women deciding whether or not to undergo RT for early-stage breast cancer. As stakeholder engagement is a crucial component to the success of decision support development, patient clinician and researcher partners have been involved since inception. We organized an AC (Appendix A for detailed information about the committee members),(18) which included breast cancer survivors (n=6), advocates of breast cancer care and aging (n=7), oncology clinicians (n=4), and researchers (n=4). Our clinician partners consist of a multidisciplinary team, including a radiation oncologist, a medical oncologist, a surgical oncologist, and a geriatric oncologist. While researchers are from one single institute, the patient committee members were recruited from eight organizations across the state of Connecticut. Our patient committee members were also racially/ethnically diverse; five are African Americans and two are Hispanics. The AC plays a central role in guiding the calculator development, including but not limited to overviewing the assumptions of the simulation models and designing the layouts of the risk calculator. The iterative staged process occurred over 40 months through 15 group meetings and numerous individual consults. For instance, committee members served as a focus group in which the members' perceptions, opinions, and attitudes toward the risk calculator were discussed during group meetings.

Simulation models

We constructed a prediction model that incorporated two main elements. First, we estimated 10-year mortality risks for older women without breast cancer by using ePrognosis, a validated prediction tool used by physicians to estimate life expectancy.(16) Based on patient age, sex, body mass index (BMI), smoking, functional status, and comorbidities, ePrognosis categorizes patients by the Lee index (ranging from 0 to 26) and predicts the risk

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of 10-year mortality for each stratum. Second, we estimated breast cancer specific outcomes using the EBCTCG prediction model regarding the efficacy of RT.(13) The EBCTCG model uses age, tumor size, tumor grade, and ER status to predict 10-year recurrence rates, with and without RT among women with lymph node (LN)-negative breast cancer. Using these two inputs, we constructed a Markov model, integrating the 10-year mortality from ePrognosis as the background mortality into the EBCTCG model. We incorporated the relative risks of recurrence attributed to LN status and margin status to estimate risks for the scenarios beyond the EBCTCG model.(19–21) This new model yielded individualized outcome estimates, including local breast cancer recurrence and overall survival, taking into account individual comorbidities, functional status, and tumor characteristics.

Our Markov model consisted of five health states, including no recurrence, local recurrence, distant metastasis, death due to other causes, and death due to breast cancer (Appendix B). Background mortality, the transition probability from state ‘no recurrence’, as well as state “local recurrence” and state “distant metastasis”, to state ‘death due to other disease’ was derived from the 10-year mortality based on the Lee index.(16) Our simulation was limited to female gender, and breast cancer mortality was excluded in the background mortality calculation (as we estimated breast cancer mortality separately).

The EBCTCG report provides the 10-year risks of any first recurrence (including both local recurrence and distant metastasis) according to age, tumor grade, tumor size, ER status, and RT status among LN-negative women who underwent BCS.(13) Using the proportion of local-regional recurrence vs. distant recurrence from the Cancer and Leukemia Group B (CALGB) C9343 trial,(22) we estimated the 10-year local-regional recurrence rate and distant metastasis rate separately. We incorporated the relative risks of LN positivity to estimate risks of recurrence for patients with LN-positive breast cancer (0–3 and ≥4).(23) Patients with local-regional recurrence were modeled with a higher probability of developing distant metastasis than those without local-regional recurrence.(24, 25) We assumed the annual rate of death due to metastatic breast cancer to be 0.243.(26) With the use of complementary data (19–21), we extended the risk estimations beyond the EBCTCGgroups to more specific subgroups by age, tumor size, and margin status. The detailed information of model assumptions and parameters are presented in Appendix C (online only).

We acknowledged that providers might have had other prognostic information beyond the variables included in our simulation models, such as factors related to overall health (other comorbidities or conditions) and tumor characteristics (Ki-67, lymphovascular invasion, potential size uncertainties, or genomic profiling results). Taking this into account, we conducted additional simulations which allowed adjustment of the risk estimates (more favorable, neutral [default], and less favorable for both health conditions and breast cancer characteristics). For example, when providers select a “less favorable” health condition because the patient has end-stage renal disease and undergoes maintenance hemodialysis, the tool will increase the Lee index by one to reflect the projected increase in mortality risk. Similarly, we assumed women with less favorable tumor characteristics were more likely to have recurrence than women with “neutral” tumor characteristics, with relative risk of 1.1. This was necessary because the current EBCTCG prediction did not include genomic

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profiling information or HER2 status. Thus, the final model considered 18 parameters (Table 1). We conducted 56,700 model simulations using each combination of 18 input parameters.

User-interface development

Employing a user-centered approach, we designed the ROW web-based risk calculator. The development involved (1) integrating the risk calculator with the routine workflow, (2) specifying and designing input entries and output reports, and (3) designing and testing the user interface. To reduce clinical workload and engage patients, the ROW risk calculator allows patients to input demographics, comorbidities, and functional status independently before clinic visits. We require providers to input tumor characteristics. After entering tumor characteristics, providers and patients review the input summary together (see Figure 2). ROW allows physicians to correct any inaccuracies or “unknown” input. This final check can be completed directly from the summary screen; that is, providers do not need to return back to previous screens.

To communicate the outcomes generated by our simulation modeling, we reviewed several mockups with the AC to determine the final design. ROW is designed to first provide the estimates of absolute risk for overall mortality, with and without undergoing RT. It then compares the risk of local breast cancer recurrence between RT and no RT. Additionally, ROW provides risk estimates in 5-year and 10-year intervals. The visual presentation of the calculated risk is described using both numerical (percentages and natural frequencies) and graphical (pictographs) presentations.

Results

Simulation results

Among 56,700 simulations, the mean 10-year local recurrence was 22.2% (range: 1–73%) for patients not undergoing RT, compared to 8.6% (range: 0–41%) for patients undergoing RT. The average absolute benefit of RT in 10-year local recurrence reduction across all scenarios was 13.5%, ranging from 0% to 34%. The mean 10-year all-cause mortality was 53.4% (range: 597%) for those not undergoing RT and 52.3% (range: 5–97%) if undergoing RT. The absolute mortality reduction attributable to the receipt of RT in our simulation was therefore 1.2% (range: 0–5%). Based on our estimation, RT reduces overall mortality when it reduces 10-year local recurrence risk by 6%.

The projected outcome estimates were consistent with clinically expected benefits of RT, as illustrated in four scenarios (Table 2). Each scenario represents a combination of two sets of ePrognosis variables (short vs. long life expectancy) and two sets of tumor characteristics (aggressive vs. non-aggressive breast cancer). Our simulation projected that RT would not improve overall survival except for women who had aggressive breast cancer and long life expectancy. Additionally, the model demonstrated that RT reduces local recurrence, especially for women with aggressive breast cancer and long life expectancy. For instance, the absolute risk reduction in 10-year local recurrence attributed to RT was 30% for patients with aggressive breast cancer and long life expectancy. However, the magnitude decreased to 17% for patients with same tumor characteristics but having multiple comorbidities and low

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functional status. Similarly, among patients with non-aggressive breast cancer, the projected absolute risk reduction was larger for patients with long life expectancy, compared with those with short life expectancy.

The ROW risk calculator

There are several important features of the interface: First, because our population is limited to women over age 65, each question is shown on one screen, enabling a large font size. Second, ROW has an audio function to and includes voice overs of all content. Third, the time to complete the task is short so as not to disrupt workflow. Patients can enter the required information within 10 minutes while waiting to be called. Finally, once all parameters are entered, ROW shows the projections of outcomes in numerical and graphical format (Figures 3A and 3B, details below). A beta-version of this risk calculator can be accessed online at https://rtbreastcancer.org.

Pictographs are used to visually present the risks and benefits of RT. We provided both 5-year and 10-year estimates, reporting the frequencies of outcomes. First, we show the estimated overall survival with and without RT (Figure 3A). Based on our simulation, the estimates between two treatment strategies are identical, except in the setting of high risk breast cancer. Second, we show the estimated proportion of local recurrence with and without RT, as well as the frequencies of local recurrence (Figure 3B).

ROW development

During our development phase, the risk calculator evolved as stakeholders provide feedback. Their suggestions led to changes in several interface elements such as font size, color, wording, and layout. At one point, ROW used two different ways to show the estimates of four outcomes, including survival without recurrence, survival with recurrence, breast cancer mortality, and other cause mortality (Appendix D). While the layout was comprehensive, it increased the complexity of the pictograph. Additionally, demonstrating the rates of distant metastasis and death from breast cancer in the radiation oncology encounter was felt to have the potential to undermine information given by other members of the multidisciplinary team. Because prognostication for distant metastasis and breast cancer-specific survival is best estimated by medical oncologist when making systematic therapy decisions, we removed these outcomes and redesigned the presentation format. Specifically, we included one screen for overall survival and one for local recurrence. Clinician stakeholders indicated that the revision was better aligned to how they communicate outcomes in clinical practice and patient stakeholders reported that graphical risk presentations facilitated understanding of radiotherapy benefits.

Discussion

Approximately half of all breast cancers in the United States occur in women over the age of 65.(27) For those with early disease, understanding the risks and benefits of RT is critical for treatment decision-making. There is, however, no risk calculator specific for the older adult population. As a majority of older adult women undergo RT despite a lack of survival

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benefit,(28) developing a patient-centered risk calculator to provide individualized risk estimates could help facilitate provider-patient communications.

The risk calculator not only can be used in clinical practice by itself but also could be integrated into a larger decision-support tool. The ability of ROW to present individualized benefits of RT has a unique advantage in decision aid development. Many decision aids have been developed to support shared decision-making processes: one of the major limitations of most existing decision aids is that they are often generic in nature, providing information on risk estimates by aggregating the patient outcomes. In practice, however, patients and providers need information that is individualized.(29) Prior literature has shown the benefits of individualized health information for patients and providers.(30–32) Compared with generic information, individualized information improved patient satisfaction and was more likely to lead to behavior change.(30) Additionally, lack of applicability due to patient characteristics has been identified as one of the most often reported barriers to implement shared decision-making in clinical practice,(33, 34) reflecting the importance to take individual situation into consideration.

Using simulation modeling, we were able to project outcome estimates, which were then used as the output of our risk calculator. The EBCTCG model has demonstrated that the benefit of RT in recurrence risk reduction varied across groups with different age and tumor characteristics. The model, however, does not include comorbidities and functional impairment, which are more prevalent in older adults and associated with decreased life expectancy. Building upon the EBCTCG model, we demonstrated that the benefit of RT in local recurrence reduction also differed greatly by individual life expectancy (as illustrated in Table 2). Thus, even if a radiation oncologist was able to use ePrognosis to estimate patient life expectancy, the RT benefit estimates derived from EBCTCG model for a patient with comorbidities or functional impairment could not be directly used. The provider needs to make some qualitative adjustment, which may be difficult for providers to discuss with patients. Availability of quantitative and personalized risk estimates as provided by ROW can help physicians communicate with their patients effectively, and empower patients to make an informed decision. The tool also has the potential to promote the use of geriatric assessments because information regarding comorbidities and functional status is required for risk estimation.

ROW was developed using early and consistent stakeholder engagement. Meeting with patients, advocates for breast cancer and aging care, and clinicians allowed us to integrate the simulation results into the risk calculator in a user-friendly fashion. The benefits of an iterative staged process ensured that the contents of ROW, such as information and layout, are responsive to the complexities of the decision context.

Our study has several limitations. First, our simulation applied a number of simplifying approximations to produce the estimates. For instance, the local recurrence estimates were derived from the EBCTCG data, which contains trials from decades ago. The estimates may not be generalizable to contemporary populations. Additionally, the estimates have not yet been validated. However, to validate the results presented by ROW is challenging because there are no population-based databases that have all information regarding comorbidities,

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functional status, tumor characteristic, and outcomes. We are planning to analyze patients in our institution to validate our estimates. Second, we did not account for compliance with endocrine therapy, as our risk calculator, based on the EBCTCG model, assumed that all ER-positive patients would receive endocrine therapy. Thus, for patients with ER-positive breast cancer, ROW indicates that the risk estimates apply to those who are taking hormone therapy. Given that non-compliance with endocrine therapy could definitively impact local control and survival, developing a risk calculator which can take endocrine therapy compliance into consideration is needed.

Additionally, the intervention strategy in our risk calculator was limited to whole breast RT, and therefore this tool is not appropriate for women making a decision about partial breast radiation. Fourth, a usability/feasibility study is still in progress: We are recruiting eligible patients from radiation oncology clinics and health volunteers from community to understand the experiences of using this tool. The findings from the ongoing usability and feasibility study could further improve the functionality of the risk calculator. Finally, we acknowledge that not all prognostic factors are included in our calculator. For example, HER2-receptor status and 21-gene assay result can provide important prognostic information. Although the tool has categories (such as “more favorable” and “less favorable”) for providers to modify the risk estimates, the magnitude of this adjustment has been clinically decided. Future research is needed to incorporate these factors in the prediction model.

In conclusion, we used simulation modeling to estimate local recurrence and overall survival for older women with early stage breast cancer, accounting for life expectancy and tumor characteristics. We used a patient-centered approach to design the user interface that presents individualized outcome estimates. Our study highlights the strength of multidisciplinary collaboration and stakeholder engagement. Our risk assessment tool could be ready for dissemination and implementation testing and has potential to help facilitate patient-specific RT decision-making.

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Appendix A

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Breast cancer survivor; Patient advocate, Breast Cancer Alliance & National Lymphedema Network

Ms. Fedus

Gerontologist & Founder, Borrow My Glasses, LLC

Dr. Evans

Radiation oncologist, Associate Professor of Therapeutic Radiology, Yale University

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Appendix B

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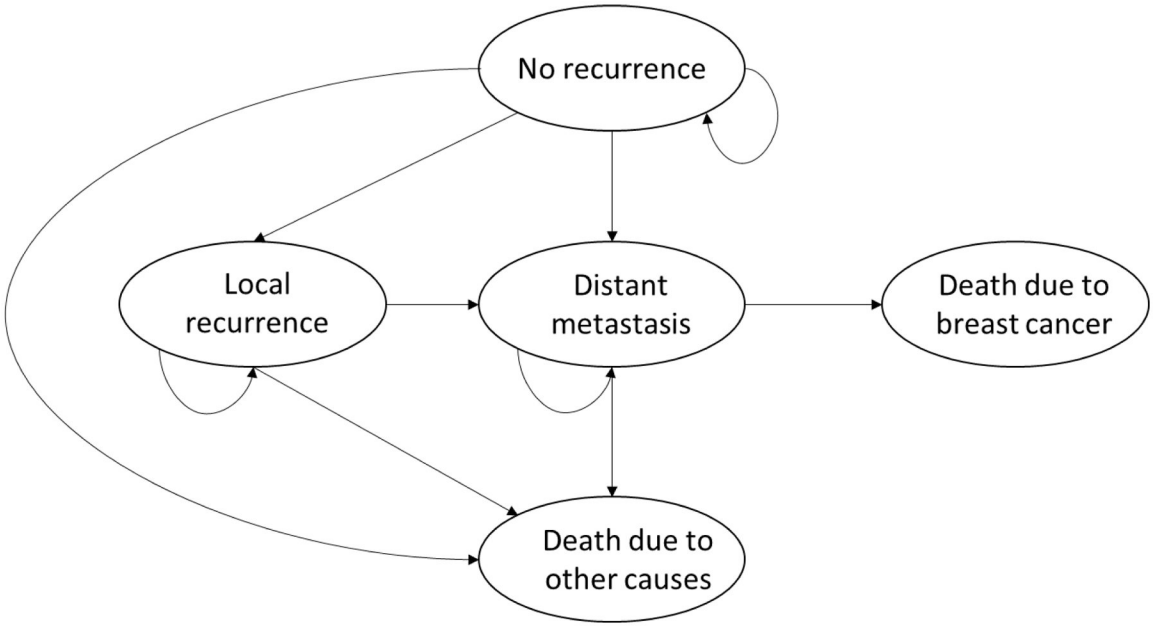

Schematic view of Markov model

Appendix C

Simulation Methods

We constructed a Markov model (Appendix B) to estimate individual outcomes, including breast cancer local recurrence, breast cancer specific mortality, and death due to other diseases, taking account for individual comorbidities, functional status, and tumor characteristics.

Input parameters

Background mortality rate—The transition probability from state ‘no recurrence’, as well as state “local recurrence” and state “distant metastasis”, to state ‘death due to other disease’ was derived from the 10-year mortality based on the Lee index.[1] Based on patient age, sex, BMI, smoking, general health condition, functional status, and a variety of important comorbidities, the Lee index (ranging from 0 to 26) has been validated in predicting 10-year mortality rate (Appendix Table 1). To reflect our population, our tool was limited to female, and breast cancer mortality was excluded in background mortality calculation (we estimated breast cancer mortality separately, see below).

Local recurrence and distant metastasis rates—The EBCTCG report provides the 10-year risks of any first recurrence (including both local recurrence and distant metastasis) according to prognostic and other factors among node negative women allocated to BCS without RT.[2] With this information, we obtained 10-year any recurrence rates for prognostic groups defined by combination of the factors including age (60–70, or 70+), tumor grade (low, intermediate, or high), tumor size (1–20 mm or 21–50 mm), and estrogen receptor status (“Lumpectomy, ER-poor” in original table as ER negative, “Lumpectomy, ER+ tam+”

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as ER positive) for the BCS alone group (Appendix Table 2). Note that the categorization of tumor grade and ER status fits in with our model.

We calibrated the risks by tumor size and age using 1) literature review reporting risk estimates of age and tumor size; and 2) distributions of age and tumor size. We first assumed the relative risk (RR) of recurrence for patients aged 70, compared to those aged 65 is equal to RR of recurrence for patients aged 75, compared to those aged 70. Using RR between age above 70 vs age 60–69 = 1.18[3] and the age distributions in the SEER-Medicare who received BCS, the RR of age 65 vs 70 was estimated at 1.07. Similarly, using the RR of tumor size from prior literature,[4] we estimated the risks for tumor size 0–0.5cm, 0.6–1.0cm, 1.1–1.5cm, 1.6–2.0cm, and >2cm. Because some of the EBCTCG trials might include participants with positive margin, which would have a higher risk of recurrence, we applied the ECBTCG risk estimates to patients who had a close margin (0–2mm). Using estimates from a previous literature review,[5] we estimated the 10-year any recurrence rates for other margin groups (positive margin and margin ≥2mm).

We incorporate the RRs of LN positivity to estimate risks of recurrence for patients with LN positive breast cancer (0–3 and ≥4).[6] Lastly, we separated 10-year any recurrence rate to local-regional recurrence and distant metastasis using the information from the C9343 trial;[7] that is, among patients with any recurrence, the proportion of local recurrence was estimated as 76.2%, and the proportion of distant metastasis was 23.8%.

To estimate risks for patients who received RT, we assumed RT is able to reduce local recurrence but not “distant metastasis only” recurrence. The RR of RT on local recurrence was estimated as 0.33, based on prior literature.[8] We allowed that patients with local recurrence with higher probability of developing distant metastasis, depending on lymph node involvement.[9,10] For instance, among patients with nodal negative breast cancer, annual probability of distant metastasis after local recurrence was 11% if local recurrence occurred less than 4 years, and was 6% if local recurrence occurred longer than 4 years.(12) The annual rate of death due to metastatic breast cancer is 0.243.[11] The detailed information of relative risks we used were reported in Appendix Table 3.

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Appendix Table 1.

Lee index to predict mortality due to other diseases

Point score	10-year mortality
0	2.80%
1	4.00%
2	6.00%
3	9.10%
4	14%

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Point score	10-year mortality
5	21%
6	30%
7	40%
8	52%
9	62%
10	71%
11	81%
12	85%
13	89%
14	95%

Appendix Table 2.

10-year risk of recurrence, women with nodal negative breast cancer receiving BCS without RT

Tumor Size	ER	Tumor Grade	Age	10-year risk of recurrence (local or distant metastasis)
1–20 mm	Negative	1	60–70	25%
1–20 mm	Negative	1	>70	23%
1–20 mm	Positive	1	60–70	11%
1–20 mm	Positive	1	>70	10%
1–20 mm	Negative	2	60–70	37%
1–20 mm	Negative	2	>70	34%
1–20 mm	Positive	2	60–70	19%
1–20 mm	Positive	2	>70	16%
1–20 mm	Negative	3	60–70	45%
1–20 mm	Negative	3	>70	40%
1–20 mm	Positive	3	60–70	32%
1–20 mm	Positive	3	>70	27%
21–50 mm	Negative	1	60–70	37%
21–50 mm	Negative	1	>70	34%
21–50 mm	Positive	1	60–70	17%
21–50 mm	Positive	1	>70	15%
21–50 mm	Negative	2	60–70	53%
21–50 mm	Negative	2	>70	49%
21–50 mm	Positive	2	60–70	28%
21–50 mm	Positive	2	>70	24%
21–50 mm	Negative	3	60–70	61%
21–50 mm	Negative	3	>70	56%
21–50 mm	Positive	3	60–70	45%

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Tumor Size	ER	Tumor Grade	Age	10-year risk of recurrence (local or distant metastasis)
21–50 mm	Positive	3	>70	38%

Appendix Table 3.

Relative risks

	Reference Group	Comparison Group	Relative Risk	Source
Age	for each 5-year increase		1.07	Calibration; [3]
Tumor size	<=0.5cm	0.6–1.0cm	1.70	Calibration; [4]
	<=0.5cm	1.1–1.5cm	1.90	
	<=0.5cm	1.6–2.0cm	2.09	
	<=0.5cm	>2.0cm	3.16	
Surgical margin	Close	Positive	1.34	[5]
	Close	Negative	0.56	
Lymph nodes	negative	1–3	1.85	[6]
	negative	≥4	2	
RT	No RT	RT	0.33	[8]

Appendix D.

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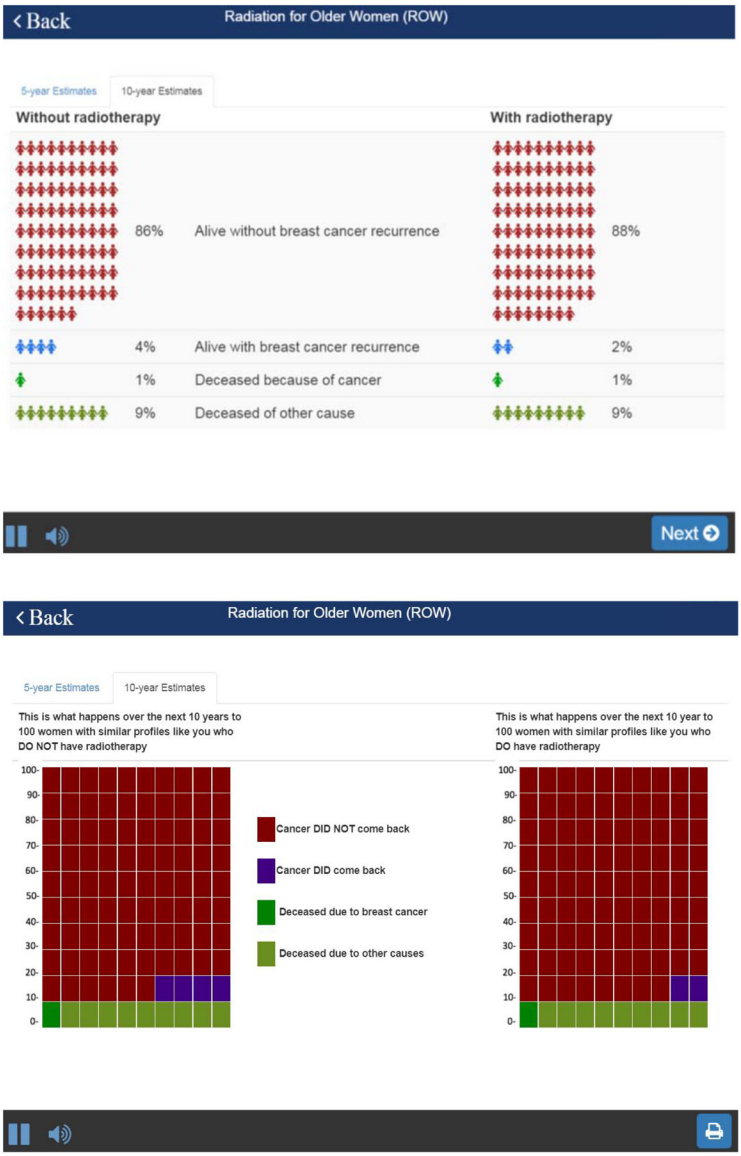

Examples of early output during the development phase

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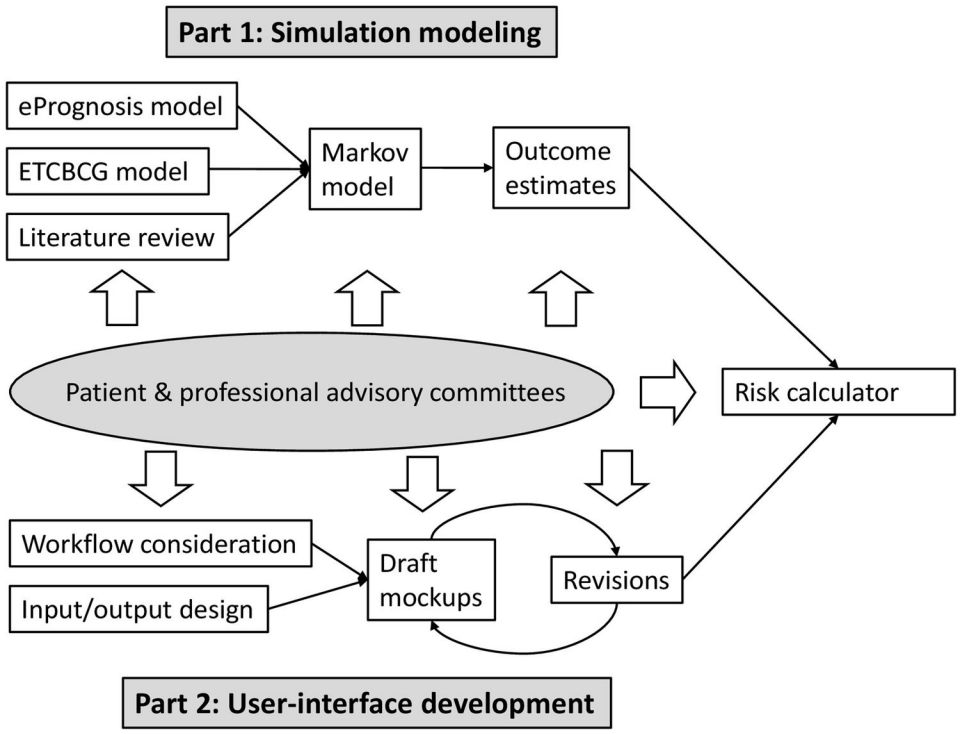

Figure 1.
Overview of the development process

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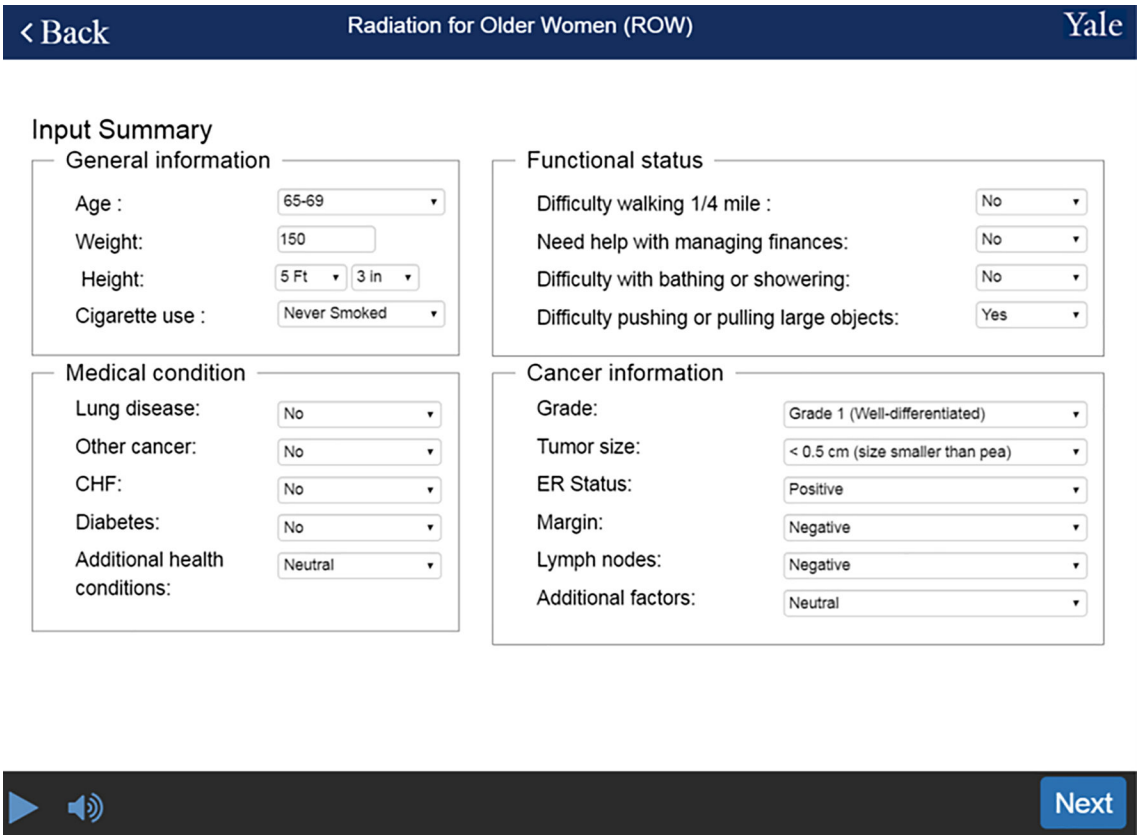

Figure 2.
Input summary

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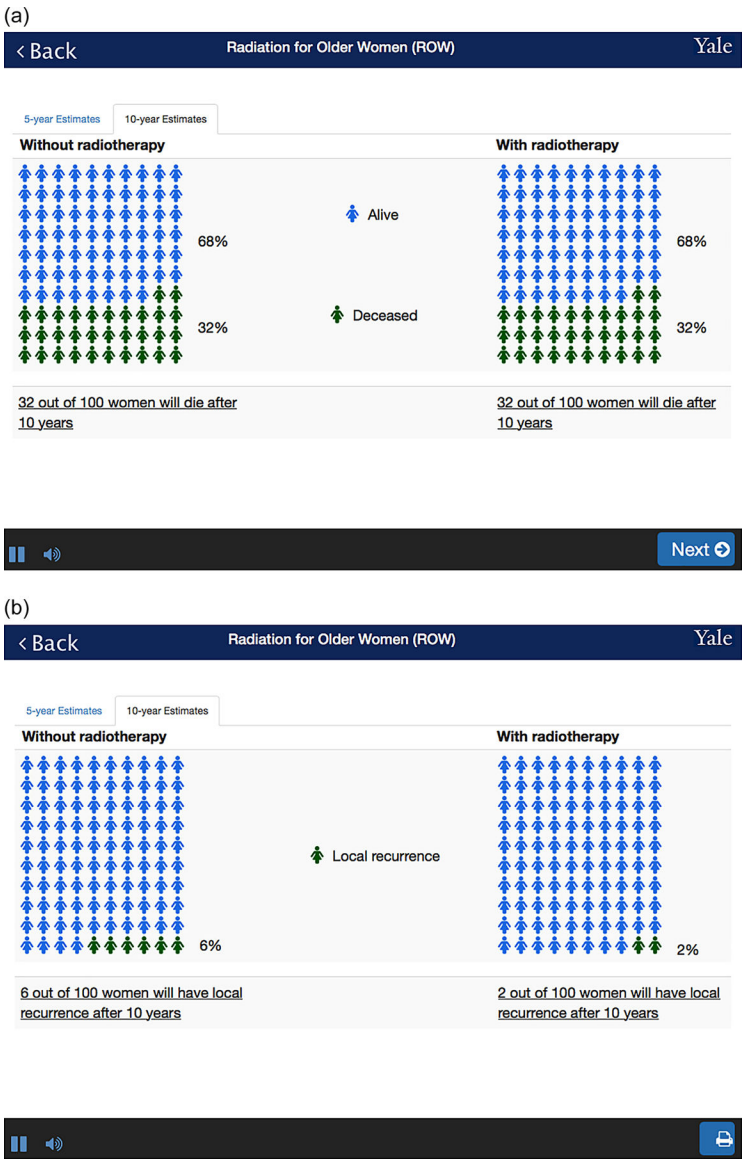

Figure 3.
An output example: A. Overall survival; and B. Local recurrence

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Table 1.

Model inputs

Input parameter	Possible values
Age	65–69, 70–74, 75–79, 80–84, and ≥85
Body mass index	<25 vs. ≥25
Cigarette use	current user vs. former user or non-smoker
Chronic obstructive pulmonary disease	yes vs. no
Other cancer	yes vs. no
Congestive heart failure	yes vs. no
Diabetes	yes vs. no
Difficulty walking several blocks	yes vs. no
Difficulty managing finances	yes vs. no
Difficulty bathing	yes vs. no
Difficulty pushing/pulling large objects	yes vs. no
Tumor grade	low, intermediate, and high
Tumor size	0–0.5cm, 0.6–1.0cm, 1.1–1.5cm, 1.6–2.0cm, and >2.0cm
Estrogen receptor status	positive vs. negative
Margin	positive, close, and negative
Lymph nodes	0, 1–3, and ≥4
Additional health conditions	neutral, more favorable, and less favorable
Additional breast cancer factors	neutral, more favorable, and less favorable

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Table 2.

Projected benefits of radiotherapy, by life expectancy and breast cancer aggressiveness

	Aggressive breast cancer		Non-aggressive breast cancer	
	No RT	**RT**	**No RT**	**RT**
10-year overall survival				
Short life expectancy	24%	24%	29%	29%
Long life expectancy	72%	77%	92%	92%
10-year local recurrence				
Short life expectancy	28%	11%	3%	1%
Long life expectancy	52%	22%	7%	2%

Aggressive breast cancer: high grade, ≥2cm, estrogen receptor-negative, positive margin, ≥4 lymph node involvement

Non-aggressive breast cancer: low grade, 0.5–0.99cm, estrogen receptor-positive, negative margin, no lymph node involvement

Short life expectancy: age ≥85, BMI>25, never smoked, comorbidities of congestive heart failure and diabetes, and difficulty pushing or pulling large objects

Long life expectancy: age 65–69, BMI>25, never smoked, no comorbidities, and no functional impairment