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CLINICAL TRIAL

# Patient preferences regarding intraoperative versus external beam radiotherapy following breast-conserving surgery

**Michael D. Alvarado · Jay Conolly · Catherine Park · Theadora Sakata · Aron J. Mohan · Brittany L. Harrison · Mitchell Hayes · Laura J. Esserman · Elissa M. Ozanne**

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**Abstract** The TARGIT-A Trial is an international randomized, prospective trial comparing intraoperative radiotherapy (IORT) for equivalence to external beam radiotherapy (EBRT) following lumpectomy for invasive breast cancer in selected low-risk patients; early results suggest that outcomes are similar. In addition to effectiveness data and cost considerations, the preferences of patients should help inform practice. This study was undertaken to explore and quantify preference in choosing between IORT and the current standard, EBRT. Eligible subjects were current or past candidates for breast-conserving surgery and radiation being seen at the University of California, San Francisco Breast Care Center. A trade-off technique varying the risk of local recurrence for IORT was used to quantify any additional accepted risk that these patients would accept to receive either treatment. Patients were first presented with a slideshow comparing EBRT with the experimental IORT option before being asked their preferences given hypothetical 10-year local recurrence risks. Patients were then given a questionnaire on demographic, social and clinical factors. Data from 81 patients were analyzed. The median additional accepted risk to have IORT was 2.3 % (−9 to 39 %), mean 3.2 %. Only 7 patients chose to accept additional risk for EBRT; 22 accepted IORT at no additional risk; and the remaining 52 chose IORT with some additional risk. Patients weigh trade-offs of risks and benefits when presented with medical treatment choices. Our results show that the majority of breast cancer patients will accept a small increment of local risk for a simpler delivery of radiation. Further studies that incorporate outcome and side effect data from the TARGIT-A trial clarify the expected consequences of a local recurrence, and include an expanded range of radiation options that could help guide clinical decision making in this area.

**Keywords** Breast-conserving surgery · Radiation · Adjuvant radiation · Intraoperative radiation · IORT · Patient preference

M. D. Alvarado (✉) · J. Conolly · M. Hayes · L. J. Esserman
Department of Surgery, UCSF Comprehensive Cancer Center, University of California, Box 1710, 1600 Divisadero, San Francisco, CA 94143-1710, USA
e-mail: Michael.Alvarado@ucsfmedctr.org

C. Park
Department of Radiation Oncology, University of California, San Francisco, CA, USA

T. Sakata
Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT, USA

A. J. Mohan
Brown University Warren Alpert School of Medicine, Providence, USA

B. L. Harrison
UCSF School of Medicine, San Francisco, USA

E. M. Ozanne
The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, USA

## Introduction

Allowing patients to choose between two non-equivalent therapeutic options is common practice in breast cancer treatment. In this setting patients are often making trade-offs between risk of recurrence and quality of life. When considering what treatment options should be offered as the field moves forward, the preferences of the patients, who are

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primary stakeholders, should be taken into consideration. These preferences, along with clinical trial data and resource considerations, should drive healthcare innovation.

In the case of early stage invasive breast cancer patients, these women routinely choose between surgical options, mastectomy or breast-conserving surgery. In the case of breast-conserving surgery, patients and their physicians now have choices about radiation therapy. For some, no radiation treatment is an option. Recent 12-year data show that radiation therapy does not reduce overall survival of patients over 70 years of age with hormone-sensitive tumors if they are treated with endocrine therapy alone [1]. However, radiation following breast-conserving surgery reduces the risk of local recurrence and for many, has a late impact on survival [2]. Most women have radiation therapy as a part of treatment. Multiple radiation modalities exist, differing by duration of treatment, side effects, cosmesis, convenience, and cost [3, 4]. When patients consider these options, the feasibility and effectiveness of radiation treatments influence their choice for radiation, and also whether or not they choose mastectomy or breast-conserving surgery [5, 6].

Currently, external beam radiotherapy (EBRT) is the standard of care for radiation therapy. Treatment requires a 3–6 week commitment from patients, who must go to a hospital or radiotherapy center for a 10–15 min treatment once every day, 5 days per week. Newer technologies, with shortened delivery times, have opened up more treatment options for patients [7–9]. One of these is intraoperative radiotherapy (IORT), which has been shown to be safe and effective in the TARGIT-A trial clinical trial [7]. This mode of radiation therapy is delivered once, in the operating room at the time of the BCS, making radiation therapy more feasible for many women.

At the time the TARGIT-A trial was initiated, a preference study was initiated to determine the trade-off results that women might make for the convenience of a single treatment delivery intraoperatively. The TARGIT-A trial results reported in Lancet 2010 showed that the local recurrence rate for IORT is 1.2 % at 4 years, as compared to 0.95 % for EBRT [7].

The purpose of this study was to explore and quantify preferences of patients using trade-off techniques if they were given a choice between IORT and the current standard, EBRT.

## Materials and methods

### Study sample

Eligible patients included women who were current and past candidates for radiation following breast-conserving surgery at the University of California, San Francisco Breast Care Center. All participants provided informed consent and ethical approval for this study was obtained through the University of California, San Francisco's Committee on Human Research.

### Study procedures

Patients were presented with a three-part presentation on the computer: an introductory educational section about EBRT and IORT; a preference elicitation section regarding the risks of recurrence for either treatment; and a brief survey about medical and personal history. The interviewer sat with the patient throughout the presentation to answer any questions that arose. Each section is described in detail below.

#### *Education section*

The introductory section compared EBRT with IORT in terms of procedures, cost to insurance, and possible side effects. The methodology used was based on that used by "decision boards" [10]. The EBRT option was presented as a regimen of 10–15 min of radiation daily, 5 days per week, lasting 5–6 weeks, plus a CT scan and planning session. The IORT option was presented as a new method of radiation, consisting of a one-time dose given during surgery and adding about 30 min to the time in the operating room. The cost of EBRT was presented as five times greater than IORT, but it was stressed that this cost would be covered by insurance. In terms of serious side effects, both EBRT and IORT listed the extremely rare side effects of damage to ribs, nerves, heart or lungs and radiation-induced cancers, while "unknown long term side effects" were used for IORT since long term results were unknown at the time that the study was initiated. Delayed surgical wound healing was also listed for IORT, in the less-frequent category, while fatigue and sensitivity to touch were listed as possible EBRT side effects.

Originally, we presented a slide explaining that some oncologists believe that a 4 % difference in the risk of local recurrence results in a 1 % difference in the risk of mortality from the cancer. The purpose was to give context for the impact of local recurrence. However, patients found this part of the presentation confusing, and after patient 68, we removed this section from the educational slides section.

#### *Preference elicitation section*

Following the educational presentation, women were asked to consider what their choice would be or would have been if they were offered IORT. A trade-off technique was used

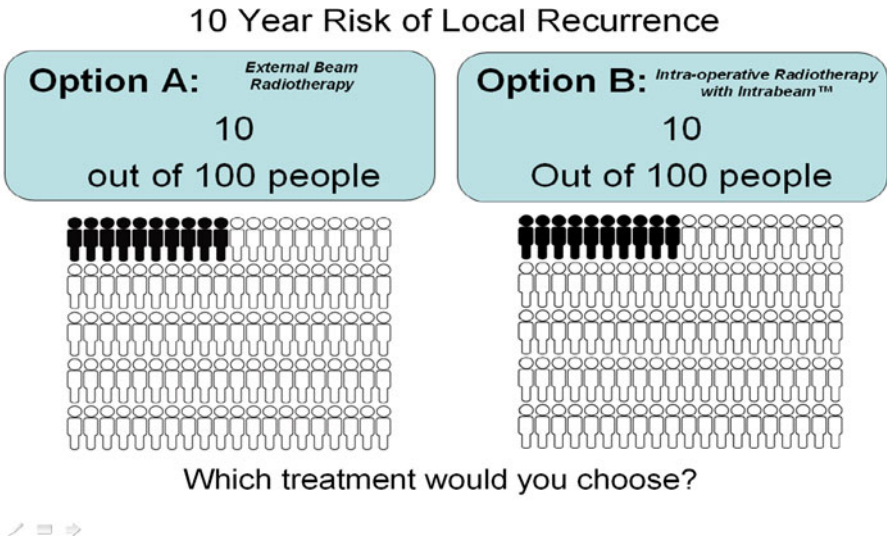


**Fig. 1** Example of an iconic graph comparing the hypothetical 10-year risk of local recurrence for option A (EBRT) and option B (IORT). In this particular slide, the risk of recurrence is equal for both options (10 %)

to quantify the additional accepted risk that patients would allow to undergo IORT instead of EBRT. Trade-off techniques have been developed as part of shared decision-making in the clinic, and to aid in assessing the distributions of patient preference for policymakers [10]. They allow quantification of preferences even when the most relevant risk probabilities are unknown [11]. The primary endpoint was the patient's switch point for when they would no longer accept an additional accepted risk for either given treatment. A hypothetical risk of 10-year local recurrence was displayed graphically. An "iconic" graph was used based on best practices for risk communication [12, 13], with shaded figures representing the number of patients out of 100 total patients who would develop a local recurrence (see Fig. 1).

Patients were initially shown one of two possible slides. The first stated that both forms of radiotherapy lead to a 10 %, 10-year risk of local recurrence, while the second stated that EBRT leads to a risk of 10 % versus IORT's risk of 20 %. These two conditions were used to assess whether the initial risk comparison had an effect on patients' switch points, in what has been described as the "shifting frame effect" among studies using trade-off technique [11]. Subsequent trade-off slides incrementally increased or decreased by 1 % the hypothetical rate of recurrence associated with IORT until the subject's preference changed—this was the switch point when the patient would no longer accept a treatment with an additional accepted risk. After three outliers (additional accepted risk 14, 34 and 39 %, respectively), the additional accepted risk was capped at 10 %, since it was felt that it approximated the absolute benefit of any radiation therapy in this scenario.

*Demographics*

After patients' switch points were recorded to determine additional accepted risk values, a brief survey was administered. Questions on the survey included age at diagnosis, time since diagnosis, race, highest education, working status (full or part time), primary caregiver status, tumor grade, types of therapy received or anticipated (chemo and/or hormone), and receptor status for estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. Patients who had already received their radiation were asked for time since diagnosis, ability to continue working, type of treatment received (IORT, EBRT, or EBRT with IORT boost), commute to radiation facility and degree of radiation tolerance. This information was gathered to analyze whether or not any of these factors were associated with additional accepted risk.

## Results and discussion

Data from 81 patients were collected. Patient characteristics are shown in Table 1. The majority of the women in the study were between the ages of 46 and 60 at diagnosis, had previously received radiation therapy, and had unknown tumor status.

Patients overwhelmingly preferred the IORT option at equivalent local recurrence risk (see Fig. 2). Only 7 patients would not choose IORT if recurrence risk were equal to that of standard EBRT; 22 accepted IORT at no additional risk, and the remaining 52 chose IORT with some additional risk of having a local recurrence within 10 years. There were two outliers who accepted 34 and

**Table 1** Selected patient data

| Characteristic | Number of patients | Percentage of patients (%) |
|---|---|---|
| Age at diagnosis | | |
| ≤45 | 18 | 22.2 |
| 46–60 | 43 | 53.1 |
| >60 | 20 | 24.7 |
| Tumor grade | | |
| Low | 15 | 18.5 |
| Intermediate | 18 | 22.2 |
| High | 6 | 7.41 |
| Unknown | 42 | 51.9 |
| Previous radiation therapy | 60 | 74 |
| Future radiation therapy planned | 16 | 20 |

39 % additional risk with IORT. The median additional accepted risk for IORT was 2.3 % (−9–39 %), the mean additional accepted risk for IORT was 3.2 %, both well over the observed additional risk IORT conferred over EBRT in the TARGIT-A trial.

Age at diagnosis, and the time since diagnosis nor the ability to continue working conclusively correlated with the additional accepted risk for IORT (see Fig. 3). In addition, there was no significant difference in additional accepted risk based on the survey arm (whether trade-off technique started with IORT 10-year local recurrence risk at 10 or 20 %).

Limited data were collected from patients regarding the following factors: commute time to the radiation facility ($n = 16$), highest education ($n = 21$), race ($n = 14$), or ER, PR, and HER2 status ($n = 59$, 37, and 47, respectively).

The results of this study show that the majority of patients would choose the presented IORT option at some increased risk of local recurrence, and the median additional accepted risk was 2.3 %. This result falls within the predefined non-inferiority margin of an absolute difference of 2.5 % for the TARGIT-A trial. It is also much higher than the observed difference in 4-year local recurrence rates between IORT and EBRT in the TARGIT-A trial, which was 0.25 %. Given the trial results and the median additional accepted risk seen in our preference study, it is clear that the majority of women would prefer the IORT option.

The trade-off techniques used in this study have been used with success in a pilot study measuring patient preference between EBRT and IORT among a largely rural population in Western Australia [10]. Trade-off techniques have also been used in several other settings where patient values are of importance, and where the effect of a treatment is yet unknown [10, 14, 15]. Treatments are, after all, for patients, and the trade-off technique can help gage attitudes toward emerging treatment options.

It is estimated that half of health care consumption is driven by physician and hospital supply, not by patient need or demand [16]. Yet, consideration of patient preferences is critical in a patient-centered healthcare delivery model. Studies show that empowered patients strongly consider effectiveness, accessibility, and cost when evaluating treatment options [5, 6]. IORT aligns with these patient preferences, and may especially appeal to particular groups of women, such as those who are unable to accept a regimen of EBRT due to physical, geographic, or psychosocial constraints, forcing them to opt for a mastectomy as a local treatment even if they are good lumpectomy candidates with a strong preference toward breast conservation. Women in this category have been offered IORT at participating TARGIT-A trial centers as well as other institutions that treat women deemed eligible for accelerated partial breast irradiation by the American Society for Radiation Oncology (ASTRO) [17]. Even among women for whom EBRT is logistically feasible, there is a significant psychological impact and fatigue associated with protracted radiotherapy [18]. This has been worsened by a relative scarcity of the resources needed to deliver EBRT and corresponding increased waiting times in the context of developed countries [11, 19]. In addition, reports also show that, from a societal point-of-view, IORT is more cost effective than EBRT [3].

Since this patient preference study closed, additional reports have provided a more refined understanding of several factors that might affect patient preference, such as side effects, cosmesis, cost effectiveness, and quality-of-life. The information presented in the trade-off technique slides during this study was relatively imprecise ("more frequent," "less frequent" and "extremely rare"). The information that has since been gathered reports a higher rate of seromas requiring more than three aspirations for IORT, and higher rate of Radiation Therapy Oncology Group grade 3 or 4 toxicities in the EBRT group [7]. Similarly, the "extremely rare" but serious side effects of damage to ribs, nerves, heart or lungs were listed as the same for both modalities in this study, even though there is now an evidence that IORT significantly decreases radiation delivered to tissue outside the breast [20]. Cosmetic outcome was largely omitted in the trade-off technique slides, even though a small TARGIT sub-study, showed cosmetic outcome to be superior for IORT [21]. These factors favor IORT over EBRT from the patient perspective.

Other studies of patient preference also indicate a preference for IORT. In one study that presented various modalities of radiation such that the side effects and

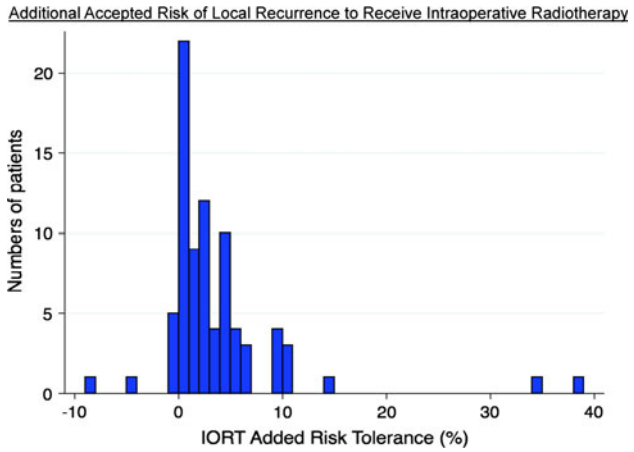


**Fig. 2** The additional risk of local recurrence patients accepted to receive IORT over EBRT

efficacy were equal for all, patients preferred options that were shorter and less invasive [22]. Another study in Western Australia evaluated the specific preference for IORT versus EBRT by querying TARGIT-A participants who were assigned to either treatment. The majority of women would choose IORT over EBRT when the risk of recurrence for IORT was equal to or greater than the risk of EBRT (98 % of patients assigned to IORT preferred IORT; 58 % of trial participants assigned to EBRT chose IORT) [21].

Still, further studies are needed to help guide policy in this area, especially to determine the most impactful factors on an individual's preferences and additional accepted risk. Investigators should consider the timing of patient's participation with respect to their overall treatment plan, as it may influence the patient-reported preferences. Corica et al. found that, when querying patients who have already been randomized to IORT or EBRT, patients tended to favor their allocated treatment [23]. Studies should be powered to determine if any social, demographic or clinical factors correlate with a higher additional accepted risk. In addition, the tools of utility analysis may be used alongside patient-level preference data as randomized trial data solidify probabilities of treatment outcomes [10].

A drawback of our study was that patients were given an ambiguous picture of the impact of local recurrence on survival, and the consequences in terms of additional treatment were not systematically discussed. Since it is likely that there will be a difference in the rate of local recurrence for at least some cohort of patients to receive IORT, a clearer explanation of how this relates to

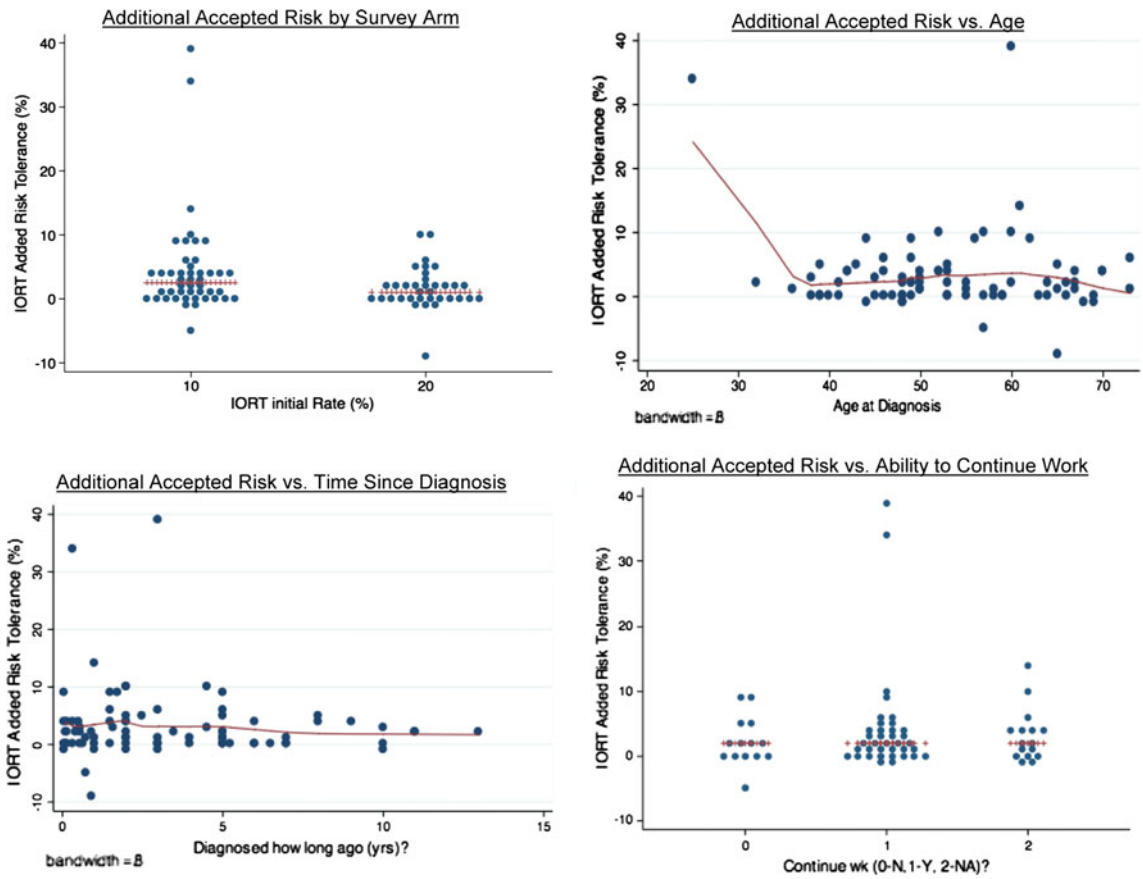


**Fig. 3** Factors that did not significantly impact additional accepted risk for IORT

probabilities of overall survival and the need for additional treatment should be systematically discussed in future preference studies, and eventually informational materials for shared decision-making.

Patients should be offered the range of appropriate options for local therapy. Radiation therapy options include modalities of radiation not discussed in this study, including 3-week delivery of EBRT as laid out in the START B regimen, IORT and EBRT, and no radiation in the case of women over 70 years old with hormone sensitive-tumors [1, 24]. The results of this study show that the majority of patients who choose to undergo radiation therapy are willing to accept some degree of uncertain side effects and elevated risk of local recurrence to receive radiation delivered as a single intraoperative dose. The degree to which different cohorts of patients would actually need to accept additional risk of local recurrence remains to be seen, but the preliminary TARGIT-A trial data show promise for IORT equivalence to EBRT in selected low-risk patients. Given this, it is reasonable to conclude that certain low-risk patients would prefer IORT if offered as an informed choice in routine practice.

**Conflict of interest** The authors declare that they have no conflict of interest.

## References


1. Hughes KS, Schnaper LA, Bellon JR et al (2013) Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol Off J Am Soc Clin Oncol 31:2382–2387. doi:10.1200/JCO.2012.45.2615
2. Clarke M, Collins R, Darby S et al (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366:2087–2106. doi:10.1016/S0140-6736(05)67887-7
3. Alvarado MD, Mohan AJ, Esserman LJ et al (2013) Cost-effectiveness analysis of intraoperative radiation therapy for early-stage breast cancer. Ann Surg Oncol 20(9):2873–2880. doi:10.1245/s10434-013-2997-3
4. Hill-Kayser CE, Vachani C, Hampshire MK et al (2012) Cosmetic outcomes and complications reported by patients having undergone breast-conserving treatment. Int J Radiat Oncol Biol Phys 83:839–844. doi:10.1016/j.ijrobp.2011.08.013
5. Herzlinger R (2007) A bold new consumer-driven health care system. The laws and their legislators. Manag care 16:34–6, 39–40
6. Herzlinger RE, Falit BP (2009) Consumer-driven health care. JAMA J Am Med Assoc 301:2093–2094. doi:10.1001/jama.2009.699 author reply 2094
7. Vaidya JS, Joseph DJ, Tobias JS et al (2010) Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet 376:91–102. doi:10.1016/S0140-6736(10)60837-9
8. Shah C, Khwaja S, Badiyan S et al (2013) Brachytherapy-based partial breast irradiation is associated with low rates of complications and excellent cosmesis. Brachytherapy 12:278–284
9. Leonardi MC, Maisonneuve P, Mastropasqua MG et al (2013) Accelerated partial breast irradiation with intraoperative electrons: using GEC-ESTRO recommendations as guidance for patient selection. Radiother Oncol J Eur Soc Ther Radiol Oncol 106:21–27. doi:10.1016/j.radonc.2012.10.018
10. Stiggelbout AM, de Haes JCJM (2001) Patient preference for cancer therapy: an overview of measurement approaches. J Clin Oncol 19:220–230
11. Palda VA, Llewellyn-Thomas HA, Mackenzie RG et al (1997) Breast cancer patients' attitudes about rationing postlumpectomy radiation therapy: applicability of trade-off methods to policy-making. J Clin Oncol Off J Am Soc Clin Oncol 15:3192–3200
12. Fagerlin A, Zikmund-Fisher BJ, Ubel PA (2011) Helping patients decide: ten steps to better risk communication. J Natl Cancer Inst 103:1436–1443. doi:10.1093/jnci/djr318
13. Brown SM, Culver JO, Osann KE et al (2011) Health literacy, numeracy, and interpretation of graphical breast cancer risk estimates. Patient Educ Couns 83:92–98. doi:10.1016/j.pec.2010.04.027
14. Llewellyn-Thomas HA (1997) Investigating patients' preferences for different treatment options. Can J Nurs Res = Revue canadienne de recherche en sciences infirmières 29:45–64
15. Llewellyn-Thomas HA, Paterson JM, Carter JA et al (2002) Primary prevention drug therapy: can it meet patients' requirements for reduced risk? Med Decis Mak 22:326–339. doi:10.1177/0272989X0202200411
16. Brownlee S (2007) Overtreated: why too much medicine is making us sicker and poorer. Bloomsbury, New York
17. Smith BD, Arthur DW, Buchholz TA et al (2009) Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). J Am Coll Surg 209:269–277. doi:10.1016/j.jamcollsurg.2009.02.066
18. Montgomery G, Kangas M, David D et al (2009) Fatigue during breast cancer radiotherapy: an initial randomized study of cognitive-behavioral therapy plus hypnosis. Health Psychol 28:317–322
19. Lehman M, Jacob S, Delaney G et al (2004) Waiting times for radiotherapy—a survey of patients' attitudes. Radiother Oncol J Eur Soc Ther Radiol Oncol 70:283–289. doi:10.1016/j.radonc.2004.01.012
20. Vaidya JS, Tobias JS, Baum M et al (2004) Intraoperative radiotherapy for breast cancer. Lancet 44:67–73
21. Mohammed R. S. Keshtgar, Norman R. Williams, Max Bulsara et al (2013) Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer: results from a randomized controlled trial. Breast Cancer Res Treat 140:519–525
22. Hoopes DJ, Kaziska D, Chapin P et al (2012) Patient preferences and physician practice patterns regarding breast radiotherapy. Int J Radiat Oncol Biol Phys 82:674–681. doi:10.1016/j.ijrobp.2010.11.077
23. Corica T, Nowak A, Saunders C et al (2012) 482 patient preferences for adjuvant radiotherapy in early breast cancer—an Australian sub-study of the international TARGIT trial. Eur J Cancer 48:S187
24. Bentzen SM, Agrawal RK, Aird EG et al (2008) The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 371:1098–1107. doi:10.1016/S0140-6736(08)60348-7