

## **Fractionation for whole breast irradiation: An American Society for Radiation**

### **Oncology (ASTRO) evidence-based guideline**

Benjamin D. Smith, M.D., Department of Radiation Oncology, University of Texas MD Anderson Cancer Center

Soren M. Bentzen, Ph.D, D.Sc., Department of Human Oncology, University of Wisconsin School of Medicine and Public Health

Candace R. Correa, M.D., Department of Radiation Oncology, University of Michigan

Carol A. Hahn, M.D., Department of Radiation Oncology, Duke University Medical Center

Patricia H. Hardenbergh, M.D., Shaw Regional Cancer Center

Geoffrey S. Ibbott, Ph.D., Department of Radiation Physics, University of Texas MD Anderson Cancer Center

Beryl McCormick, M.D., FACR, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center

Julie R. McQueen, CHES, RHEd, Oncology Patient Navigator, Duke Raleigh Cancer Center

Lori J. Pierce, M.D., Department of Radiation Oncology, University of Michigan Comprehensive Cancer Center

Simon N. Powell, M.D., Ph.D., Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center

Abram Recht, M.D., Harvard Medical School and Beth Israel Deaconess Medical Center

Alphonse G. Taghian, M.D., Ph.D., Department of Radiation Oncology, Massachusetts General Hospital

Frank A. Vicini, M.D., FACR, Department of Radiation Oncology, Beaumont Cancer Institute

Julia R. White, M.D., Department of Radiation Oncology, Medical College of Wisconsin

Bruce G. Haffty, M.D., Department of Radiation Oncology, Cancer Institute of New Jersey

Acknowledgments: The authors would like to thank the following individuals who served as expert reviewers of the manuscript: Alain Fourquet, Barbara Fowble, Gary Freedman, Jay Harris, and Lawrence Solin. The authors would also like to thank ASTRO staff members Barbara Muth, Shari Siuta, and Morgan Honeycutt for their assistance with the systematic literature review and administrative support. The authors would also like to thank the Department of Scientific Publications at The University of Texas M. D. Anderson Cancer Center for their assistance in editing the manuscript.

**Conflicts of interest: None**

Expiration Date: December 31, 2015

## **Abstract**

*Purpose:* In patients with early-stage breast cancer treated with breast-conserving surgery, randomized trials have found little difference in local control and survival outcomes between patients treated with conventionally fractionated (CF-) whole-breast irradiation (WBI) and those receiving hypofractionated (HF)-WBI. However, it remains controversial whether these results apply to all subgroups of patients. We therefore developed an evidence-based guideline to provide direction for clinical practice.

*Methods and Materials:* A task force authorized by ASTRO weighed evidence from a systematic literature review and produced the recommendations contained herein.

*Results:* The majority of patients in randomized trials were 50 years of age or older, had disease stage pT1-2 pN0, did not receive chemotherapy, and were treated with a radiation dose homogeneity within  $\pm 7\%$  in the central axis plane. Such patients experienced equivalent outcomes with either HF-WBI or CF-WBI. Patients not meeting the above criteria were relatively underrepresented, and few of the trials reported subgroup analyses. For patients not receiving a radiation boost, the task force favored a dose schedule of 42.5 Gy in 16 fractions when HF-WBI is planned. The task force also recommended that the heart should be excluded from the primary treatment fields (when HF-WBI is used).

*Conclusion:* Data were sufficient to support the use of HF-WBI for patients with early-stage breast cancer who met all the aforementioned criteria. For other patients, the task force could not reach agreement either for or against the use of HF-WBI, which nevertheless should not be interpreted as a contraindication to its use.

## Introduction

Randomized clinical trials in patients with early-stage breast cancer have demonstrated that following breast-conserving surgery, adjuvant whole breast irradiation (WBI) lowers the relative risk of ipsilateral breast tumor recurrence (IBTR) by approximately 70% at 5 years and produces a 5% absolute improvement in 15-year overall survival.<sup>1</sup> Most of these studies used “conventionally fractionated” (CF) radiation schemes, such as 1.8 Gy to 2.0 Gy per fraction for a total dose of 45 to 50 Gy in 25 to 28 daily fractions<sup>2-5</sup> with or without a subsequent radiation boost to the tumor bed. Recent patterns-of-care studies have indicated that the vast majority of radiation oncologists in both the United States and Continental Europe mainly use CF-WBI, often with a subsequent boost to the tumor bed.<sup>6-9</sup> Historically, CF-WBI has been recommended based upon the theory that small, as opposed to large, daily fraction sizes lower the risk of late normal tissue toxicity without compromising cancer control due to the differential sensitivity of normal tissues and cancer cells to fraction size.<sup>10</sup>

Despite its proven effectiveness and safety, CF-WBI has certain shortcomings, including the inconvenience to patients associated with undergoing daily treatment for 6 to 7 weeks and the cost of treatment (both direct health care expenditures and opportunity costs to the patient and society due to time away from home and work).<sup>11,12</sup> In the United Kingdom and countries heavily influenced by British practices, physicians have long used adjuvant hypofractionated whole breast irradiation (HF-WBI), in which both the total dose and the number of fractions are decreased compared to CF-WBI schemes, with excellent results.<sup>13-15</sup> Such HF-WBI shortens total treatment time, enhances convenience, and lowers costs.<sup>11</sup>

In the past several years, results from four randomized clinical trials conducted in Canada and the United Kingdom comparing CF-WBI with HF-WBI as adjuvant therapy for surgically treated early-stage breast cancer have yielded sufficient data to allow an evidence-based comparison of the two treatment approaches.<sup>10,16-20</sup> Accordingly, the American Society for Radiation Oncology (ASTRO) Health Services Research Committee (HSRC) convened a task force to formulate clinically useful evidence-based guidelines on WBI fractionation. The task force conducted a systematic review of the literature, which, supplemented by the expertise and clinical experience of the task force members, provided the rationale for the following recommendations.

### **Materials and Methods**

In 2008, the ASTRO HSRC identified WBI fractionation as a high-priority topic needing evidence-based guidelines. Accordingly, the HSRC submitted a project proposal to the ASTRO Board of Directors, which was approved in January 2009. The Board of Directors authorized creation of a task force to study WBI fractionation and approved its membership which included eight recognized experts in breast cancer radiation oncology, one in radiobiology (SB), one in radiation physics (GI), two representatives from the HSRC (BDS, CH), one radiation oncologist in private practice (PH), one radiation oncology resident (CC), and one patient advocate (JM). We were charged with using currently available evidence to develop a clinically practical, evidence-based guideline to help radiation oncologists and breast cancer patients determine the appropriate use of HF-WBI as adjuvant treatment of breast cancer following breast-conserving surgery. In addition, the task force was asked to provide relevant background on the clinical radiobiology of breast cancer to increase

understanding of recent clinical trial findings. Potential conflicts of interest were identified prospectively at the outset of guideline development. Through a series of conference calls, the task force completed the systematic literature review, reviewed evidence tables, and formulated the guidelines contained herein. The initial draft of the manuscript was reviewed by five expert reviewers and ASTRO legal counsel and was subsequently placed on the ASTRO website in January 2010 for a period of public comment. Upon integration of all feedback, the document was submitted to the *International Journal of Radiation Oncology, Biology, and Physics* for additional peer review and, finally, to the ASTRO Board of Directors for their review and approval in March 2010.

During the formulation of this evidence-based guideline, the task force sought to adhere to the American Medical Association's Physician Consortium for Performance Improvement guidance for measure development<sup>21</sup> and recent calls for reform of the guideline process.<sup>22</sup> It was noted that although this guideline strives to be firmly evidence-based, the opinions of the individual task force members inevitably inform their interpretation and application of the available evidence. As a result, it has been recommended that guidelines include "alternate interpretations and viewpoints" along with the majority opinion to ensure that the final guideline is representative of all task force members' input.<sup>22</sup> In this guideline, unanimous recommendations based firmly on evidence are specified with a "**(U-evidence)**" and unanimous recommendations based on expert opinion are specified with a "**(U-opinion)**". When unanimity could not be reached, majority and minority opinions are presented and specified.

*Systematic Literature Review.* For the purposes of this literature review, we defined HF as a daily dose exceeding 2 Gy and CF as a daily dose of 2 Gy or less. WBI was defined as radiation intended to treat all clinically detectable breast tissue ipsilateral to the index cancer. Studies pertinent to the guideline topic were identified by searching the National Library of Medicine's PubMed database for articles published from January 1, 1990 through February 28, 2009. For the initial screen, we selected English-language studies categorized under the Medical Subject Heading (MeSH) "Breast neoplasms/radiotherapy" with any of the following key words: hypofractionation, hypofractionated, fractionation, fraction, accelerated, short, or shorter. Of 558 candidate abstracts screened, we sought to identify randomized trials that compared HF-WBI with other treatments and also nonrandomized clinical studies whose primary purpose was to evaluate any aspect of HF-WBI. We identified six randomized clinical trials that compared HF-WBI with CF-WBI (Hôpital Necker,<sup>23</sup> Queen Elizabeth,<sup>24</sup> Canadian,<sup>18,19</sup> Royal Marsden Hospital/Gloucester Oncology Center (RMH/GOC),<sup>17,20</sup> and Standardization of Breast Radiotherapy (START) A and B.<sup>10,16</sup> We also identified two randomized clinical trials that compared HF-WBI with partial breast irradiation (PBI),<sup>25-27</sup> two randomized clinical trials that compared HF-WBI with no irradiation,<sup>12,28-30</sup> and one randomized trial that compared HF-WBI alone with HF-WBI followed by a boost to the tumor bed.<sup>31</sup> Additionally, 34 nonrandomized clinical studies met inclusion criteria (Supplementary Table 1).<sup>13-15,32-63</sup> Articles whose sole focus was postmastectomy radiation or concurrent chemoradiation were excluded. Bibliographies of candidate articles were also reviewed to ensure that all relevant articles were included. Studies published in abstract form only were not included, with the exception of the updated

results of the Canadian trial presented at the 2008 ASTRO Annual Meeting.<sup>19</sup> Based upon results of the systematic literature review, evidence tables were constructed to summarize tumor control (local control, local-regional control, disease-free survival, overall survival) and toxicity (cosmesis, skin, soft tissue, pulmonary, cardiac, brachial plexus, rib) endpoints.

The quality of randomized clinical trials was evaluated using criteria adapted from the United States Preventive Services Task Force Procedure Manual.<sup>64</sup> The Queen Elizabeth trial reported psychological outcomes only and thus was not included in the evidence tables or formally scored for quality.<sup>24</sup> The recommendations contained herein will expire on December 31, 2015. The ASTRO Guidelines Subcommittee will monitor this guideline and initiate an update when so indicated.

## Results

### **Clinical Question #1: Which patients obtain equivalent results from HF-WBI and CF-WBI?**

*Guideline:* Evidence from randomized clinical trials has demonstrated that HF-WBI and CF-WBI are equally effective for in-breast tumor control and comparable in long-term side effects for patients meeting all the criteria listed in Table 1 (**U-evidence**).<sup>10,16-20,64</sup>

The task force was unable to reach agreement as to the equivalence of HF-WBI to CF-WBI for patients who do not satisfy all these criteria, and thus, we could not make a recommendation either for or against the use of HF-WBI in such patients.

*Narrative:* We identified one “fair” and three “good” quality randomized trials including 7,095 patients and approximately 45,000 patient-years worth of follow-up time that compared HF-WBI with CF-WBI (Tables 2-4).<sup>10,16-20,64</sup> Published length of follow-up ranged from 5.1 to 9.7 years, and extended to 12 years in abstract form<sup>19</sup> (Tables 5-6). Collectively, these trials demonstrated that several HF-WBI regimens produced IBTR rates and toxicity profiles comparable with those for CF-WBI (50 Gy in 25 fractions). In addition, two randomized clinical trials that compared HF-WBI with PBI<sup>25-27</sup> and two randomized clinical trials that compared HF-WBI with no irradiation<sup>12,28-30</sup> demonstrated a lower risk of IBTR with HF-WBI than with regimens in the other arms of these trials. The subsequent discussion will focus exclusively on trials that compared CF-WBI with HF-WBI.<sup>10,16-20,64</sup>

Although eligibility criteria for these trials were rather broad, the majority of enrolled patients fulfilled the characteristics outlined in Table 1. The effectiveness and toxicity of WBI are known to vary with patient-, tumor-, and treatment-related factors

such as age at diagnosis, status of the surgical margins, molecular classification of the index cancer, the use of a boost, and the use of systemic therapy.<sup>65-68</sup> The intrinsic radiosensitivity of individual breast cancers might also vary in relation to these factors. Therefore, it is critical to assess these trials' selection criteria, characteristics of the study populations, potential use of additional therapies, and whether results were analyzed in relation to these factors to determine whether the trials' findings apply to all patient subgroups. Unfortunately, few subgroup analyses were reported for these trials, as discussed below.

**AGE:** The risk of IBTR after breast-conserving surgery followed by adjuvant WBI decreases as age increases, and is particularly high for younger women ages 40 and under.<sup>69</sup> The reasons for this discrepancy are not fully understood, but one possibility is that the sensitivity of breast cancer to radiation therapy may vary with age. Thus, it may be necessary to consider younger and older women as two distinct patient populations when evaluating the appropriateness of HF-WBI. The vast majority (about 70% to 79%) of patients enrolled in clinical trials comparing HF-WBI with CF-WBI were age 50 years or older at diagnosis (Table 4).<sup>10,16-20</sup> The effect of age on outcome has only been reported for the Canadian trial, which stratified entry by age (younger than 50 years versus 50 years or older).<sup>18</sup> A preplanned analysis found that HF-WBI was equivalent to CF-WBI in both groups.<sup>18,19</sup> However, the Canadian trial included only 305 women under 50, and no further division of results by age was performed within this group (eg, age 40 years or younger versus age 41 to 49 years). Thus, the task force unanimously agreed that the available data supported the equivalence of HF-WBI with CF-WBI for patients age 50 years or older at diagnosis. Although the available data did appear to

support the equivalence of CF- and HF-WBI for patients under 50, a minority of the task force believed that the data were insufficient to support a guideline recommending routine implementation of HF-WBI in younger women.

**T STAGE:** The majority of patients treated on these trials had stages pT1 or pT2 invasive breast cancer (Table 4).<sup>70</sup> Given the published results, the task force believed that HF-WBI has been proven equivalent to CF-WBI in this patient population. Patients with ductal carcinoma in situ (DCIS) were excluded from the randomized trials, and although a small phase II study has shown favorable early results using HF-WBI to treat DCIS,<sup>40</sup> at this time the task force thought that data were insufficient to allow an evidence-based recommendation for or against HF-WBI for women with DCIS. Patients with stage pT3 or pT4 disease are primarily treated with mastectomy, and thus there was little data from the randomized trials to determine the appropriateness of HF-WBI for this patient group.

**N STAGE:** The majority of women treated on these trials had node-negative disease as confirmed by pathologic evaluation of axillary lymph nodes, and thus the evidence most supports the use of HF-WBI in women with stage pN0 breast cancer. Although a minority of patients treated on the RMH/GOC, START A, and START B trials received hypofractionated regional nodal irradiation, at this time the task force believed that the small number of patients treated with this approach precluded a firm evidence-based recommendation on the effectiveness and toxicity of HF-WBI for preventing regional lymph node failure. Certain hypofractionated approaches have resulted in an increased risk of late brachial plexopathy,<sup>48,52,53,71</sup> and although this risk has yet to been seen in the RMH/GOC, START A, and START B trials, the follow-up in those studies

was not considered sufficient to exclude such late toxicity.<sup>10,16-20</sup> It is also possible that hypofractionated regional nodal irradiation could increase the risk of pulmonary toxicity. Finally, although the strong majority of task force members thought that HF-WBI could be used in patients with pN1 breast cancer for whom regional nodal irradiation is not indicated, the scarcity of this population in the randomized trials provided insufficient data to permit a firm evidence-based endorsement of HF-WBI in this setting.

**SYSTEMIC THERAPY:** Approximately 65% to 90% of patients in these trials did not receive chemotherapy (Table 4), and thus there was consensus among the task force that the evidence supported the equivalence of HF-WBI to CF-WBI in patients not receiving chemotherapy. Anthracycline-containing and taxane-containing regimens were used in 25% and 1%, respectively, of patients in the START A trial and in 13% and 0.4%, respectively, of patients in the START B trial.<sup>10,16</sup> The types of chemotherapy used in the Canadian and RMH/GOC trials were not reported, although it is likely that anthracyclines and taxanes were used very infrequently during the era in which those trials were conducted.<sup>17,18,20</sup> None of the patients in those trials received trastuzumab or newer targeted agents. Toxicity in each study arm was not reported separately for patients receiving or not receiving chemotherapy in these trials.<sup>10,16-20,64</sup> Retrospective studies have not shown that chemotherapy increased the risk of side effects attributable to HF-WBI, but the numbers of patients in these studies was small and follow-up limited.<sup>32,72</sup> The majority of the task force members reported that they commonly use HF-WBI following anthracycline- or taxane-based chemotherapy in their clinical practice, but a strong minority thought that the toxicity profile of HF-WBI in patients receiving currently-used systemic agents and regimens has not been studied sufficiently to

ensure its safety and therefore should not merit routine endorsement. No recommendation can be rendered with respect to use of HF-WBI for women treated with neoadjuvant chemotherapy, as such patients were not included in these trials.<sup>10,16-20,64</sup> Further, as a measure of caution, the task force members would generally recommend against use of HF-WBI concurrently with systemic therapy to include cytotoxic chemotherapy or targeted agents given lack of data at the present time.<sup>10,16-20,64</sup> With regard to endocrine therapy, tamoxifen was used in 41%, 64%, 79%, and 87% of patients in the Canadian, RMH/GOC, START A, and START B trials, respectively,<sup>10,16-20,64</sup> and very few patients received other endocrine therapies such as aromatase inhibitors. Outcomes stratified by receipt of tamoxifen or sequencing of tamoxifen with radiation were not generally reported, though it appears that the majority of patients in the START trials were receiving endocrine therapy during their course of radiation.<sup>10,16-20,64</sup>

**DOSE HOMOGENEITY:** All these trials required that the maximum dose to the breast on the central axis plane be no greater than 105% to 107% and no less than 93% to 95% of the prescription dose (Table 3). No stipulations were placed on the homogeneity of the dose distribution outside of the central axis plane. The majority of patients on these trials were treated with two-dimensional planning techniques without inhomogeneity corrections (Table 3). Because inhomogeneity of the radiation dose increases with increasing patient chest wall separation, the Canadian trial excluded patients whose separation along the central axis exceeded 25 cm.<sup>18</sup> In contrast, the other trials used higher energies for patients with larger breasts in an effort to ensure acceptable dose homogeneity and did not explicitly exclude patients with larger breasts,

although it remains possible that women with larger breasts could have been underrepresented.<sup>10,16,17,20</sup> Optimizing the homogeneity of dose in the off-axis planes as well as the central-axis plane reduces acute and late toxicities.<sup>73,74</sup> Therefore, the task force recommended that the minimum dose should be no less than 93% and that the maximum dose should be no greater than 107% of the prescription dose ( $\pm 7\%$ ) in the central-axis plane, as calculated using two-dimensional treatment planning without heterogeneity corrections, in accordance with planning guidelines from the published randomized trials (Table 3).<sup>10,16-20,64</sup> However, the task force encourages the use of three-dimensional planning techniques in all patients to reduce toxicity (see below).

In summary, the task force could not reach agreement as to whether the demonstrated equivalence of HF-WBI to CF-WBI should be considered to hold true broadly (for all patients who would have been eligible for these trials) as well as narrowly (for only the patient groups that were well-represented in these trials). As a result, the task force could not agree on the appropriateness of HF-WBI for those patient groups that were underrepresented in these trials.<sup>10,16-20,64</sup>

### **Clinical Question #2: What is the role of a tumor-bed radiation boost in patients treated with HF-WBI?**

*Guideline:* There were few data to define the indications for and toxicity of a tumor bed boost in patients treated with HF-WBI (**U-evidence**). The task force agreed that the use of HF-WBI alone (without a boost) is not appropriate when a tumor bed boost is thought to be indicated (**U-opinion**). When a boost is indicated, there was lack of consensus regarding the appropriateness of HF-WBI. While the majority of the task force members

thought that there were sufficient data showing the safety of HF-WBI followed by a tumor bed boost to recommend its use in otherwise suitable patients, a minority believed that CF-WBI should be used instead when a tumor bed boost is indicated.

*Narrative:* There is limited evidence from prospective randomized trials to define the toxicity and efficacy of a tumor-bed boost in patients treated with HF-WBI (Table 3). In the Canadian study, none of the patients received a tumor bed boost, but the risk of IBTR at 5 years was very low (approximately 3%), suggesting that potential benefit of a tumor-bed boost is likely to be small.<sup>18</sup> Sixty-one percent of patients in the START A trial and 43% of those in the START B trial undergoing breast-conserving surgery received the optional tumor-bed boost of 10 Gy in 5 fractions.<sup>10,16</sup> Entry into the START trials was stratified by intention to give a tumor-bed boost, but the outcomes for whether a boost was actually used have not yet been reported.<sup>10,16</sup> The RMH/GOC trial included a substudy in which 723 patients were randomized to receive no boost or a boost of 14 Gy in 7 fractions to the tumor bed.<sup>17,20</sup> The rates of IBTR in relation to the use of a boost have not been reported. Patients allocated to receive a boost had a higher risk of breast induration and telangiectasia than those who received no boost, but there was no difference between these groups in breast appearance (assessed photographically by a blinded observer), proportion of fair or poor cosmetic results, or risks of breast shrinkage, breast distortion, breast edema, arm swelling, or shoulder stiffness. However, results were not further divided according to whether patients received HF-WBI or CF-WBI, so it is not possible to determine whether one regimen was preferable when a boost was used. Further, the risk of a fair or poor cosmetic outcome in this trial

was high (58-74% at 10 years), raising concern that the overall treatment plan did not result in optimal cosmesis, irrespective of assigned dose and use of a boost.

Two randomized trials have specifically sought to evaluate the role of a tumor-bed boost following WBI. In the Lyon trial, 1,024 women with invasive breast cancer 3 cm or smaller and negative surgical margins treated with HF-WBI (50 Gy in 20 fractions of 2.5 Gy) were randomized to receive a tumor-bed boost of 10 Gy in 4 fractions or no boost.<sup>31</sup> With a median follow-up duration of 3.3 years, receipt of a tumor-bed boost was associated with a lower risk of IBTR, a higher risk of telangiectasia, and no difference in patient-reported cosmetic outcome. However, the relatively short length of follow-up in this trial precluded firm conclusions as to the long-term toxicity profile of a tumor-bed boost in patients receiving HF-WBI. In addition, the effective biologic dose of the HF-WBI regimen used in this trial was higher than that of the HF-WBI arms of the Canadian and START B trials.<sup>16,18,19</sup>

The European Organization for the Research and Treatment of Cancer (EORTC) enrolled 5,318 women with stages I and II breast cancer who were treated with CF-WBI, randomized to a tumor-bed boost or no boost, and followed for over 10 years.<sup>65,69</sup> The large size and comprehensive follow up of this trial have helped to define the indications for and toxicity profile of a tumor-bed boost in patients treated with CF-WBI; however, it is unclear whether these results apply also to patients treated with HF-WBI.

Given the limitations of these data, the task force was unable to reach consensus on the integration of a tumor-bed boost and HF-WBI in clinical practice. There was general agreement that the indications for when to use a boost are likely to be similar regardless of the WBI fractionation scheme employed. The majority of the task force

membership supported using a tumor-bed boost in conjunction with HF-WBI when a boost is indicated, but a minority favored using only CF-WBI in this setting.

**Clinical Question #3: What are appropriate regimens for HF-WBI and a tumor-bed boost?**

*Guideline:* For patients not receiving a tumor-bed boost, the task force favored a dose of 42.5 Gy in 16 fractions over approximately 22 days when HF-WBI is planned (**U-evidence**). The optimal HF-WBI regimen to use when a boost is given and the optimal tumor-bed boost dose-fractionation to use in conjunction with HF-WBI have not been determined (**U-evidence**).

*Narrative:* The dose-fractionation schemes used in the Canadian trial (42.5 Gy in 16 fractions over 22 days),<sup>18,19</sup> START A trial (41.6 Gy in 13 fractions over 35 days),<sup>10</sup> and START B trial (40 Gy in 15 fractions over 21 days)<sup>16</sup> appear equivalent in efficacy to 50 Gy in 25 fractions over 5 weeks (Tables 5-6). The HF-WBI doses used in the RMH/GOC trial were not recommended because of concern that compared with the 50-Gy arm, the 42.9-Gy arm yielded excessive toxicity and the 39-Gy arm yielded a higher risk of IBTR (Tables 5-6).<sup>17,20</sup> Further, the 39-Gy arm of the START A trial was not recommended due to its numerical inferiority with respect to risk of IBTR, which may reach statistical significance with further follow-up (Tables 5-6).<sup>10</sup> Since the Canadian trial had both the longest follow-up time and was the only trial in which no patients received a boost, the task force recommended that its regimen should be preferred in patients who do not receive a tumor-bed boost.<sup>18,19</sup> For patients who do receive a tumor-bed boost, the

optimal dose to the whole breast with HF-WBI is not known, although any of the three regimens shown to be equivalent to 50 Gy in 25 fractions appear reasonable.

The tumor-bed boost doses used in published clinical trials that compared HF-WBI with CF-WBI are listed in Table 3. In the absence of strong evidence, the task force could not endorse a specific dose-fractionation scheme to use for the tumor bed when given in conjunction with HF-WBI. However, based on the published data and the collective expert opinion of the panel, boost doses of 10-16 Gy in 2-Gy fractions or 10 Gy in 2.5-Gy fractions<sup>31</sup> were considered acceptable.

**Clinical Question #4: What are the characteristics of an acceptable radiotherapy plan for patients treated with HF-WBI?**

*Guideline:* Two-dimensional treatment planning with optimization of dose homogeneity in the central axis is the minimum acceptable standard for HF-WBI treatment planning **(U-evidence)**. However, computed tomography (CT)-guided treatment planning using three-dimensional dose compensation is strongly recommended to optimize dose homogeneity throughout the entire breast **(U-opinion)**. As a conservative measure, the task force recommended exclusion of the heart from the primary treatment fields provided that coverage of the primary tumor site is not compromised **(U-opinion)**.

*Narrative:* The clinical trials comparing HF-WBI with CF-WBI primarily utilized two-dimensional treatment planning with optimization of dose homogeneity in the central-axis plane (Table 3).<sup>10,16-20,64</sup> This therefore represents the minimum acceptable standard for HF-WBI treatment planning. However, more recent randomized trials have demonstrated that for patients treated with CF-WBI, CT-guided treatment planning with

three-dimensional dose compensation resulted in lower risks of acute skin toxicity<sup>73</sup> and late breast induration<sup>74</sup> and also improved cosmetic outcome.<sup>74</sup> It is reasonable, although as yet unproven, to expect that similar benefits will be realized in patients treated with HF-WBI. There was thus consensus that meticulous care to optimize dose homogeneity within the target volume and to minimize the dose to normal tissues is strongly recommended for patients treated with either HF-WBI or CF-WBI.

A critical concern for the use of HF-WBI has been whether exposure of the heart to larger fraction sizes could lead to an increased risk of late cardiac events over the risk with CF-WBI.<sup>55,75</sup> Even though the available clinical trials did not specifically require use of a cardiac block or shield, to date, reports have not suggested increased risks of ischemic heart disease or cardiovascular mortality attributable to HF-WBI, with follow up ranging from 5 to 12 years (Table 6).<sup>10,16-20</sup> The largest non-randomized study of the effect of fraction size on risk of cardiac death included 1,140 breast cancer patients treated with CF-WBI and 6,307 breast cancer patients treated with HF-WBI in British Columbia, Canada, with a median follow-up of 7.9 years and maximal follow-up exceeding 20 years (Supplementary Table 1).<sup>46</sup> This study concluded that receipt of HF-WBI, as compared to CF-WBI, was not associated with a statistically significantly increased risk of cardiac mortality in multivariate analysis, although it should be noted that close inspection of the survival curves suggested that receipt of HF-WBI was associated with an increased risk of cardiac death after more than 10 years follow up had elapsed. A recent systematic review also suggested that follow up exceeding 10 years is needed to demonstrate a deleterious effect of WBI on cardiac outcomes.<sup>76</sup> Thus, although the available literature does not indicate a deleterious effect of HF-WBI

on cardiovascular health, the task force members believed that a small but potentially clinically significant effect could not be ruled out at this time. Because of this lingering uncertainty, the task force recommended that HF-WBI be used primarily when the heart can be excluded from the treatment fields without compromising coverage of the primary tumor site.

The optimum dose-volume parameters for the ipsilateral lung and heart are not known for patients treated with either HF-WBI or CF-WBI. The task force recommended that the doses to these organs should, when possible, be minimized provided that coverage of the breast is not compromised. Toward this end, the task force noted that novel techniques for delivery of WBI as reported in small studies, such as intensity modulated radiation therapy,<sup>32,77,78</sup> treatment in the prone position<sup>32,44,45</sup> or gating of treatment to the deep inspiratory phase of the respiratory cycle,<sup>79,80</sup> have shown promise in decreasing the radiation dose to the lung and/or heart without compromising coverage of the breast.

**Clinical Question #5: What insights relevant to the radiobiology of breast cancer can be gained from recently published clinical trials comparing CF-WBI with HF-WBI?**

*Guideline:* The randomized trials comparing CF-WBI with HF-WBI have suggested that the extent of both local control of subclinical breast cancer and late change in breast appearance exhibit similar sensitivity to fraction size as modeled by the  $\alpha/\beta$  ratio in the linear-quadratic (LQ) formulation (**U-evidence**). Additional clinical data are needed to

quantify the effects of overall treatment time, dose homogeneity, and systemic agents on tumor control and normal tissue toxicity (**U-evidence**).

*Narrative:* The randomized trials comparing CF-WBI with HF-WBI were unusual in that they were designed in part based on radiobiological considerations rather than simply as pragmatic comparisons of dose-fractionation schemes used in various centers.

These trials have produced novel data regarding the dose-fractionation response of both breast cancer and irradiated normal tissues.

In modeling clinical dose-fractionation-response data, the most widely used metric for the steepness of the dose-response curve is the  $\gamma$ -value, interpreted as the absolute percent change in risk of a given endpoint (tumor or normal tissue) for a 1% relative increase in dose. The local-regional control data in the START A trial yielded an estimate of 0.2% for the  $\gamma$ -value for subclinical breast cancer control.<sup>10</sup> This modest gain occurred in part because local-regional control after surgery alone is achieved in approximately 70% of patients, and thus WBI can affect only about 30% of all patients.<sup>81</sup> This phenomenon also limits the precision of estimates of parameters related to local-regional control in trials of altered dose fractionation. In contrast, the isoeffective dose for normal tissue toxicity endpoints can be determined with greater precision because the dose-response curves are steeper for normal tissue toxicity than for local-regional control, since all patients can be affected by differences between regimens vis a vis normal tissue.

Fractionation sensitivity, as quantified by the  $\alpha/\beta$ -ratio of the linear-quadratic model, has been estimated for both normal tissue toxicity and local-regional control

following WBI. The most accurate estimate currently known for late changes is that for breast appearance (determined from serial photographs), where  $\alpha/\beta$  is estimated at 3.4 Gy (95% confidence interval (CI), 2.3 to 4.5 Gy).<sup>10</sup> For local-regional control,  $\alpha/\beta$  is estimated at 4.6 Gy (95% CI, 1.1 to 8.1 Gy).<sup>10</sup> These point estimates are quite close and the differences are not statistically significant. The similarity in the measured fractionation sensitivity of both subclinical breast cancer and irradiated normal tissue strongly suggests that regimens for HF-WBI can be identified that will provide tumor control and in-breast normal tissue toxicity comparable to CF-WBI, as illustrated in Table 7.

Overall treatment time is shorter with many HF-WBI schedules than with CF-WBI, although the RMH/GOC and START A trials deliberately kept this factor constant.<sup>10,17,20</sup> This allowed a decoupling of the  $\alpha/\beta$  estimate and the overall time factor. More data from short schedules will be needed to arrive at a more precise estimate of the influence of overall treatment time on tumor control. For late effects, the available evidence suggests that variation in overall treatment time in the ranges studied (3 to 6 weeks) did not affect risk of normal tissue toxicity in a substantive manner.

Multiple daily fractions are used with some accelerated partial-breast irradiation schedules, but not for WBI. Accurate estimates of the effect of the time interval between fractions on recovery kinetics are lacking. Thus, multiple WBI fractions per day should not be used outside controlled clinical trials.

Concern has been raised that different effects between CF-WBI and HF-WBI might be seen clinically due to differences in dose-distribution homogeneity. Withers et al noted with conventionally fractionated doses of 2 Gy per fraction, a subvolume receiving, for example, 110% of the prescribed target dose will receive both a higher total dose as well as a higher dose per fraction.<sup>82</sup> When using hypofractionated doses in excess of 2 Gy per fraction, such a subvolume not only will receive a higher total dose and higher dose per fraction but also (due to the mathematical form of the linear quadratic formula), the effect on the biologically equivalent dose will be larger than for conventionally fractionated doses of 2 Gy per fraction.<sup>83</sup> In practice, however, if the prescribed total dose delivered with hypofractionation is isoeffective with a conventionally fractionated plan, this effect is relatively small. For example, if 50 Gy is delivered in 2 Gy per fraction to the 100% isodose line, then a 110% hotspot will receive an biologically equivalent dose in 2-Gy fractions of 57.2 Gy, estimated for an endpoint with  $\alpha/\beta=3$  Gy. If instead, a dose biologically equivalent to 50 Gy in 2 Gy per fraction is delivered at 3 Gy per fraction to the 100% isodose line, then a 110% hotspot will receive a biologically equivalent dose in 2-Gy fractions of 57.8 Gy, nearly identical to the effect of the 110% hotspot with conventional fractionation. This suggests that the requirements for dose homogeneity should be similar for both conventional fractionation and moderate hypofractionation with an appropriate reduction in total dose.

Chemotherapy has been shown to affect the incidence of normal tissue toxicity following WBI.<sup>84,85</sup> However, it is not clear whether chemotherapy exerts a larger or smaller effect on normal tissue toxicity following HF-WBI than it does following CF-WBI. Although many hypothetical mechanisms of interaction between chemotherapy and

fraction size have been proposed based on preclinical data (for example, inhibition of repair), clinical data on the specific mechanisms are still lacking.

## **Conclusion**

Randomized clinical trials comparing CF-WBI with HF-WBI have provided a wealth of information about the radiobiology of breast cancer and acceptable fractionation schemes following breast-conserving surgery. Widespread adoption of HF-WBI for appropriately selected patients has the potential to enhance the convenience of treatment and lower the costs of WBI. It is important to note that this guideline should not be interpreted to prohibit or oppose the use of HF-WBI for patients not meeting all the criteria listed in Table 1 but rather that the evidence was not sufficient to reach consensus for such patients. Many task force members themselves use HF-WBI for many such patients, although their own patterns of practice often differ substantially from one another. Finally, we hope that this guideline will encourage the additional research needed to resolve the remaining issues we have identified regarding the promise and limitations of HF-WBI for specific patient groups.

**Table 1. Evidence Supports the Equivalence of HF-WBI with CF-WBI for Patients****Who Satisfy All of These Criteria\***

1. Age 50 years or older
2. Pathologic stage T1-2 N0 treated with breast conserving surgery
3. Not treated with systemic chemotherapy
4. Within the breast along the central axis, minimum dose no less than 93% and maximum dose no greater than 107% of the prescription dose ( $\pm 7\%$ ) (as calculated with 2-dimensional treatment planning without heterogeneity corrections)

\* Patients should also be otherwise suitable for breast-conserving therapy with regards to standard selection rules (e.g., not pregnant, no history of certain collagen-vascular diseases, no evidence of multicentric disease, no prior radiotherapy to the breast). For patients who do not satisfy all of these criteria, the task force could not reach consensus and therefore chose not to render a recommendation either for or against HF-WBI in this setting.

**Table 2. Design and Quality of Randomized Clinical Trials**

	<b>Hôpital Necker<sup>23</sup></b>	<b>Canada<sup>18,19</sup></b>	<b>RMH/GOC<sup>17,20</sup></b>	<b>START A<sup>10</sup></b>	<b>START B<sup>16</sup></b>
Intention to treat analysis?	---	Yes	Yes	Yes	Yes
Stratification variables	None	Age Tumor size Systemic therapy	Treatment center Margin status	Treatment center Type of surgery Intention to boost	Treatment center Type of surgery Intention to boost
Equal distribution of potential confounders	No*	Yes	---	Yes	Yes
Power	---	90% power to exclude an increase of 5% in the absolute risk of IBTR in the experimental as compared to control arm.	---	80% power to detect a difference of 5% in the absolute risk of IBTR between the control and either of the experimental arms.	95% power to exclude an increase of 5% in the absolute risk of local-regional recurrence in experimental as compared to control arm.
% attrition	---	0.3%	0.2%	0.2%	0.3%
% crossover	---	1.0%	0.1%	0.8%	0.5%
% non-adherent	---	0.3%	0.7%	0.3%	0.2%
% lost to follow up	0%	0%	1.3%	0.4%	0.9%
Overall rating‡	Poor	Good	Fair†	Good	Good

\* More mastectomies were performed for experimental arm.

† No data presented to demonstrate equal distribution of potential confounders across treatment groups.

‡ Evaluation criteria adapted from U.S. Preventive Services Task Force Procedure Manual.<sup>64</sup>

'---' indicates not reported.

Because the Hôpital Necker trial was rated as poor for our purposes, it is not included in subsequent tables.

#### Abbreviations:

IBTR: ipsilateral breast tumor recurrence

RMH/GOC: Royal Marsden Hospital/Gloucester Oncology Center

START: Standardization of Breast Radiotherapy

**Table 3. Radiotherapy Parameters for Randomized Clinical Trials Comparing HF-WBI to CF-WBI**

	Canada <sup>18,19</sup>	RMH/GOC <sup>17,20</sup>	START A <sup>10</sup>	START B <sup>16</sup>
Energy	Co-60, 4 MV or 6 MV	6 MV*	6 MV*	6 MV*
Wedges	yes	yes	yes	Yes
Inhomogeneity Corrections	---	GOC only	Variable	Variable
Planning	2D	2D - RMH 3D - GOC	2D or 3D	2D or 3D
Central Axis Dose Homogeneity	-7% to +7%	-5% to +7%	-5% to +5%	-5% to +5%
Separation	≤ 25 cm	---	---	---
% receiving boost	0%	75%†	61%	39%
Boost dose	---	14 Gy, 7 fr	10 Gy, 5 fr	10 Gy, 5 fr
Boost modality	---	Electrons	Electrons	Electrons
% receiving regional nodal irradiation	0%	21%	14%	7%
Target for nodal irradiation	---	SCV +/- Ax	SCV +/- Ax	SCV +/- Ax
Use of PAS	---	Yes	.	.
Dose to regional nodes	---	Same as breast	Same as breast	Same as breast

\* Energies ranging from Co-60 or 10 MV were used for a minority of patients depending on breast size.

† 364 were randomized to receive a boost, 359 were randomized to not receive a boost, and 687 received a non-randomized boost.

'---' indicates not reported or not applicable.

Abbreviations (see also prior tables):

Ax: axilla.

fr: number of fractions.

MV: megavoltage.

PAS: posterior axillary supplement.

SCV: supraclavicular lymph nodes.

2D: two-dimensional.

3D: three-dimensional.

**Table 4. Characteristics of Patients Enrolled on Clinical Trials Comparing HF-WBI to CF-WBI**

	<b>Canada<sup>18,19</sup></b>		<b>RMH/GOC<sup>17,20</sup></b>		<b>START A<sup>10</sup></b>		<b>START B<sup>16</sup></b>	
	n	%	n	%	n	%	n	%
Treated with breast-conserving surgery	1234	100%	1410	100%	1900	85%	2038	92%
Age ≥50 years	929	75%	987	70%	1727	77%	1758	79%
pT1-2	1234	100%	1324	94%	Majority	.	Majority	.
pN0	1234	100%	564	40%	1547	69%	1635	74%
Chemotherapy not used	1098	89%	1214	86%	1443	65%	1724	78%
Central axis inhomogeneity -7% to +7%	1234	100%	1410	100%	2236	100%	2215	100%

Abbreviations (see also prior tables):

CF: conventional fractionation.

HF: hypofractionation.

WBI: whole-breast irradiation.

Table 5. Oncologic Outcomes for Randomized Clinical Trials Comparing HF-WBI to CF-WBI

Trial	Median Follow up (years)	Timepoint for outcome reporting (years)	Arm			N	IBTR		Local-Regional Recurrence		Disease-Free Survival		Overall Survival	
			Dose (Gy)	# Fr	# Days		%	P	%	P	%	P	%	P
Canada <sup>18,19</sup>	5.8	5	50	25	35	612	3.2	.	.	.	.	.	.	.
			42.5	16	22	622	2.8	<.001*	.	.	.	0.37	.	0.78
RMH/GOC <sup>17,20</sup>	9.7	10	50	25	35	470	12	†	.	.	.	.	.	.
			42.9	13	35	466	9.6	†	.	.	.	.	.	.
			39	13	35	474	15	†	.	.	.	.	.	.
START A <sup>10</sup>	5.1	5	50	25	35	749	3.2	.	3.6 <sup>‡</sup>	.	86	.	89	.
			41.6	13	35	750	3.2	0.74	3.5 <sup>‡</sup>	0.86 <sup>§</sup>	88	0.33 <sup>§</sup>	89	0.81 <sup>§</sup>
			39	13	35	737	4.6	0.40	5.2 <sup>‡</sup>	0.35 <sup>§</sup>	85	0.33 <sup>§</sup>	89	0.99 <sup>§</sup>
START B <sup>16</sup>	6.0	5	50	25	35	1105	3.3	.	3.3 <sup>‡</sup>	.	86	.	89	.
			40	15	21	1110	2.0	0.21	2.2 <sup>‡</sup>	0.35	89	0.02	92	0.03

\* The hypothesis that the 42.5 Gy arm is worse than the 50 Gy arm is rejected at P<.001.

† P-value for the comparison of 42.9 Gy to 39 Gy was significant at P=0.027. P-values were > 0.05 for the comparisons of 42.9 Gy to 50 Gy arm, and 39 Gy to 50 Gy.

‡ Only local or regional relapses inside the irradiated volume were included in this outcome.

§ P-values as compared to control arm of 50 Gy in 25 fractions.

Abbreviations: see tables above.

Table 6. Toxicity Outcomes for Randomized Clinical Trials Comparing HF-WBI to CF-WBI

Trial	Toxicity	Assessor	Blinded	Assessment Scale	Severity Reported	Timepoint Assessed	Arm			P
<b>Canada<sup>18,19</sup></b>										
	Late						<b>50 Gy</b>	<b>42.5 Gy</b>		
	Cosmesis	Nurse	no	EORTC	Fair/Poor	5 years	23%	23%		>0.05
	Skin changes	Nurse	no	RTOG/EORTC	Grade 1-3	5 years	18%	13%		>0.05
	Subcutaneous tissue changes	Nurse	no	RTOG/EORTC	Grade 1-3	5 years	40%	34%		>0.05
	Pneumonitis	Nurse	no	RTOG/EORTC	Any	Crude	0.3%	0.3%		>0.05
	Rib fracture	Nurse	no	RTOG/EORTC	Any	Crude	0.2%	0%		>0.05
<b>RMH/GOC<sup>17,20</sup></b>										
	Late						<b>50 Gy</b>	<b>42.9 Gy</b>	<b>39 Gy</b>	
	Change in breast appearance	Photo	yes	3-pt scale	Mild/Marked	10 years	53%	58%	56%	<0.001
	Change in breast appearance	Photo	yes	3-pt scale	Marked	10 years	10%	16%	7%	<0.001
	Cosmesis	MD	no	4-pt scale	Fair/Poor	10 years	71%	74%	58%	<0.001
	Breast shrinkage	MD	no	4-pt scale	Mod/Marked	10 years	64%	66%	56%	0.03
	Breast distortion	MD	no	4-pt scale	Mod/Marked	10 years	58%	62%	49%	0.005
	Breast edema	MD	no	4-pt scale	Mod/Marked	10 years	14%	21%	11%	0.004
	Induration	MD	no	4-pt scale	Mod/Marked	10 years	36%	51%	28%	<0.001
	Telangiectasia	MD	no	4-pt scale	Mod/Marked	10 years	18%	18%	12%	0.07
	Arm edema	MD	no	4-pt scale	Mod/Marked	10 years	8%	10%	7%	0.49
	Shoulder stiffness	MD	no	4-pt scale	Mod/Marked	10 years	10%	22%	10%	<0.001
<b>START A<sup>10</sup></b>										
	Early						<b>50</b>	<b>41.6</b>	<b>39</b>	

							<b>Gy</b>	<b>Gy</b>	<b>Gy</b>	
	Severe acute reaction	MD	no	---	.	.	0.3%	0%	0%	>0.05
<b>Late</b>	Breast shrinkage	Patient	no	---	Mod/Marked	5 years	20%	23%	22%	>0.05; >0.05 <sup>+</sup>
	Breast hardness	Patient	no	---	Mod/Marked	5 years	43%	45%	35%	>0.05; >0.05 <sup>+</sup>
	Change in skin appearance	Patient	no	---	Mod/Marked	5 years	31%	25%	22%	>0.05; 0.004 <sup>+</sup>
	Breast swelling	Patient	no	---	Mod/Marked	5 years	15%	12%	12%	>0.05; >0.05 <sup>+</sup>
	Change in breast appearance	Patient	no	---	Mod/Marked	5 years	40%	42%	34%	>0.05; >0.05 <sup>+</sup>
	Change in breast appearance	Photo	yes	3-pt scale	Mild/Marked	5 years	43%	44%	32%	0.62; 0.01 <sup>+</sup>
	Brachial plexopathy	MD	no	---	---	Crude	0%	0.1%	0%	>0.05
	Ischemic heart disease	MD	no	---	---	Crude	1.6%	0.9%	1.1%	>0.05
	Symptomatic rib fracture	MD	no	---	---	Crude	1.1%	1.2%	1.4%	>0.05
	Symptomatic lung fibrosis	MD	no	---	---	Crude	0.7%	0.8%	0.9%	>0.05
	Contralateral breast cancer	Path	no	---	---	Crude	1.7%	0.7%	1.1%	>0.05
<b>START B<sup>16</sup></b>										
<b>Early</b>							<b>50 Gy</b>	<b>40 Gy</b>		
	Severe acute reaction	MD	no	---	---	---	1.2%	0.3%		.
<b>Late</b>	Breast shrinkage	Patient	no	---	Mod/Marked	5 years	24%	23%		>0.05
	Breast hardness	Patient	no	---	Mod/Marked	5 years	42%	38%		>0.05
	Change in skin appearance	Patient	no	---	Mod/Marked	5 years	28%	23%		0.02
	Breast swelling	Patient	no	---	Mod/Marked	5 years	12%	11%		>0.05
	Change in breast appearance	Patient	no	---	Mod/Marked	5 years	39%	24%		>0.05
	Change in breast appearance	Photo	yes	3-point scale	Mild/Marked	5 years	42%	37%		0.06
	Brachial plexopathy	MD	no	---	---	Crude	0%	0%		>0.05
	Ischemic heart disease	MD	no	---	---	Crude	1.7%	1.3%		>0.05
	Symptomatic rib fracture	MD	no	---	---	Crude	1.5%	1.4%		>0.05
	Symptomatic lung fibrosis	MD	no	---	---	Crude	1.4%	1.4%		>0.05
	Contralateral breast cancer	Path	no	---	---	Crude	1.7%	1.5%		>0.05

\* First P-value for comparison of 42.9 Gy to 50 Gy, second P-value for comparison of 39 Gy in 50 Gy.

'---' indicates not reported.

Abbreviations: see tables above.

**Table 7. Equivalent Doses in 2-Gy Fractions for Local-Regional Control of SubClinical Breast Cancer and Breast Appearance for the Experimental Arms of the Phase III Whole-Breast Irradiation Fractionation Trials**

	Total dose (Gy)	Dose per fraction (Gy)	# Fractions	Overall time (days)	NTD-breast cancer (Gy)*	NTD-Breast appearance (Gy)*
Standard	50	2	25	35	50	50
Canada <sup>18,19</sup>	42.5	2.66	16	22	46.7 <sup>†</sup>	47.7
RMH/GOC high <sup>‡</sup> <sup>17,20</sup>	42.9	3.3	13	35	51.4	53.2
START A high <sup>‡</sup> <sup>10</sup>	41.6	3.2	13	35	49.2	50.8
START A low <sup>‡</sup> <sup>10</sup>	39	3	13	35	44.9	46.2
START B <sup>16</sup>	40	2.67	15	21	44.0 <sup>†</sup>	44.9

\*NTD: Normalized Total Dose in 2-Gy fractions (also often denoted EQD<sub>2</sub>).  $\alpha/\beta$  for subclinical breast cancer: 4.6 Gy, for changes in breast appearance: 3.4 Gy

<sup>†</sup>Assuming that the dose recovered per day for subclinical breast cancer is zero in the interval from 21 to 35 days

<sup>‡</sup>The RMH/GOC and START A trials had a low and a high dose experimental arm. The low dose arms of the two trials were identical.

Supplementary Table 1. Summary of Non-Randomized Studies of HF-WBI

Topic	Subtopic	First author	Year	Study Design	N	Key Finding
<b>Early invasive</b>						
	<b>Modest Hypofractionation</b>					
		Croog <sup>32</sup>	2009	Retrospective	128	42.5 Gy in 16 fractions using prone intensity modulated radiation therapy technique produced only 1 in-breast recurrence and acceptable toxicity profile with median follow up 18 months.
		McBain <sup>16</sup>	2003	Retrospective	2159	40 Gy in 15 fractions conferred 6.3% risk of in-breast recurrence at 5 years.
		Magee <sup>13</sup>	1999	Retrospective		
		Livi <sup>72</sup>	2007	Retrospective	539	44 Gy in 16 fractions conferred 2.1% risk of local-regional recurrence at five years (median follow up 4.3 years). Risk of late grade 3 toxicity was 2.5%. Association between young age and higher risk of local-regional

recurrence.

Shelley <sup>37</sup>	2000	Retrospective	294	40 Gy in 16 fractions resulted in a 3.5% five-year risk of in-breast recurrence with median follow up of 5.5 years (all patients had negative margins at a minimum of 2 mm). 77% of patients were either 'extremely' or 'very' satisfied with the appearance of the treated breast.
Yamada <sup>38</sup>	1999	Retrospective	118 matched pairs	40 Gy in 16 fractions resulted in trend toward higher risk of in-breast recurrence at five-years compared to 50 Gy in 25 fractions (12.7% vs 6.8%) in matched pair analysis.

Olivotto <sup>15</sup>	1996	Prospective	186	44 Gy in 16 fractions conferred 6% risk of in-breast recurrence at 5 years with 6.7 years median follow up. Cosmetic result at 5 years was reported as good/excellent by 89% of physicians and 96% of patients. At 5 years, risks were as follows: breast discomfort - 20%, induration - 18%, inframammary telangiectasia - 13%, erythema - 6%, and breast edema - 3%.
Ash <sup>39</sup>	1995	Prospective	334	40 Gy in 15 fractions conferred in-breast recurrence rate of 13.8% with median follow up 8 years. Toxicity included pneumonitis (7%) and severe acute dermatitis (5%). At 1 year, excellent/good cosmesis was 62% as assessed by physicians and 80% as assessed by patients.

### Marked Hypofractionation

Martin <sup>33</sup>	2008	Prospective	30	30 Gy in 5 fractions over 15 days conferred 100% in-breast tumor control and no major changes in breast appearance with median follow up 3.1 years.
Ortholan <sup>36</sup>	2005	Prospective	150	32.5 Gy in 5 fractions (one fraction per week) resulted in 2.3% risk of local-regional recurrence with median follow up of 5.4 years. Toxicity was deemed acceptable.

### Ductal Carcinoma in Situ

Constantine <sup>40</sup>	2008	Prospective	59	42 Gy in 15 fractions for mammographically-detected ductal carcinoma in situ resulted in 100% in-breast tumor control and mild toxicity profile with 3 years median follow up.
---------------------------	------	-------------	----	--

### Treatment toxicity

#### Brachial Plexus

Galecki <sup>48</sup>	2006	Review	.	Doses ranging from 34 - 40 Gy in fraction sizes ranging from 2.2 - 2.5 Gy appear to be associated with a low risk of radiation-induced brachial plexopathy comparable to the risk associated with 50 Gy in 25 fractions.
Bajrovic <sup>52</sup>	2004	Retrospective	140	Supraclavicular radiation to a dose of 52 Gy in 20 fractions to a depth of 3 cm using Co-60 resulted in a 56% risk of grade $\geq 1$ brachial plexopathy at 20 years, with the annualized risk relatively constant throughout the follow up period. Median follow up was 8.2 years in surviving patients.
Johansson <sup>53</sup>	2000	Retrospective	71	57 Gy in 16-17 fractions Co-60 resulted in brachial plexopathy and upper extremity paralysis in 11 of 12 long-term survivors.

**Breast**

Inomata <sup>43</sup>	2008	Retrospective	196 - 50 Gy 154 - 44 Gy	Patient-reported sense of breast hardness was greater in 44 Gy in 16 fraction group (33%) compared to 50 Gy in 25 fraction group (22%). No other significant differences in patient-reported acute or late toxicity.
Fehlauer <sup>50</sup>	2005	Retrospective	65 - 2.5 Gy/fx 64 - 2 Gy/fx	55 Gy in 22 fractions (4 days per week) was associated with significantly increased risks of fibrosis, telangiectasia, atrophy, and poor cosmesis as compared to 55 Gy in 28 fractions.
Brierley <sup>57</sup>	1991	Prospective	133	For patients treated to 48.75 Gy in 15 fractions over 39 days, there was a significant correlation between higher risk of adverse breast late effects and both larger bust size and larger bra cup size (median follow up 4.2 years).

**Heart**

	Marhin <sup>46</sup>	2007	Population-based	1140 ( $\leq 2$ Gy) 6307 ( $> 2$ Gy)	With median follow up 7.9 years, neither tumor laterality nor fraction size were associated with an increased risk of cardiac mortality.
	Paszat <sup>55</sup>	1999	Population-based	25,570	Receipt of left breast irradiation associated with higher risk of death from myocardial infarction, but no effect of fraction size $> 2$ Gy on risk of myocardial infarction.
<b>Lung</b>	Plataniotis <sup>49</sup>	2005	Prospective	30	50% of patients treated with 42.5 Gy in 16 fractions experienced minor radiographic lung parenchyma changes on high resolution computed tomography scan 6 month after completion of radiation. Larger separation was associated with a higher risk of radiographic changes.
<b>Skin</b>					

Osako <sup>41</sup>	2008	Retrospective	377 - 50 Gy 66 - 40 Gy	Lower risk of grade 2-3 dermatitis with 40 Gy in 16 fractions (9%) compared to 50 Gy in 25 fractions (22%)
Ivaldi <sup>42</sup>	2008	Prospective	204	12 Gy intraoperative electron therapy to tumor bed followed by 37.05 Gy in 13 fractions conferred a 27% risk of acute grade 2-3 skin toxicity.
DeWyngaert <sup>44</sup> Formenti <sup>45</sup>	2007	Prospective	91	40.5 Gy in 15 fractions prone whole breast irradiation (with simultaneous integrated tumor-bed boost of 7.5 Gy in 15 fractions) conferred 67% risk of grade 1-2 dermatitis and allowed significant sparing of heart and lung.
Freedman <sup>47</sup>	2007	Prospective	75	45 Gy in 20 fractions whole breast IMRT (56 Gy in 20 fractions to tumor bed with simultaneous integrated boost) produced 23% risk of acute grade 2 skin toxicity and 0% risk of grade 3 skin toxicity.

				7% of patients developed infection in breast or adjacent extremity.
Marcenaro <sup>51</sup>	2004	Retrospective	29 - 50 Gy 29 - 45 Gy	50 Gy in 25 fractions over five weeks and 45 Gy in 15 fractions over five weeks conferred similar late toxicity including quantitative measurement of skin elasticity with median follow up of 15 months.
Gorodetsky <sup>54</sup>	1999	Retrospective	110	50 Gy in 20 fxs resulted in greater impairment of skin viscoelasticity in the treated breast as compared to 45-50.4 Gy in 25-28 fxs. Fraction size, rather than total dose, appeared to be the primary determinant of skin viscoelasticity.
Dodwell <sup>56</sup>	1995	Retrospective	34 - 40 Gy 28 - 45 Gy	40 Gy in 15 fractions conferred 71% risk of any telangiectasia compared to 7% risk with 45 Gy in 25

fractions (median follow up 32 months).

## Other

Pierquin <sup>58</sup>	2007	Prospective	21	Treatment with low dose rate external beam radiation to 45 Gy in 5 fractions over five days resulted in severe late effects and no in-breast recurrence of advanced breast cancer. 35 Gy in 5 fractions over five days resulted in 18% risk of in-breast recurrence and acceptable normal tissue toxicity.
Manavis <sup>59</sup>	2006	Prospective	32	35 Gy in 10 fractions followed by boost of 8 Gy in 2 fx with amifostine showed no evidence of lung changes on computed tomography 2 years post-treatment.
Koukourakis <sup>60</sup>	2002	Prospective	15	42-48 Gy in 12 fractions with amifostine resulted in 73% complete response rate for women with locally

				advanced breast cancer with minimal acute toxicity.
Palazzoni <sup>61</sup>	2004	Prospective	9	Dose escalation study of 1.8 Gy twice daily for 20, 22, or 24 fractions led to conclusion that 36 Gy in 20 fractions over 12 days was optimal alternative fractionation scheme for breast cancer.
Fehlauer <sup>62</sup>	2003	Retrospective	45 - 60 Gy, 24 fx 345 - 55 Gy, 22 fx 200 - 55 Gy, 28 fx	The feasibility of the Late Effects Normal Tissue - Subjective Objective Management Analytic (LENT-SOMA) scale was demonstrated in the assessment of late toxicity from breast irradiation, and results supported the hypothesis that a lower fraction size is associated with a lower risk of late toxicity.

Maier <sup>63</sup>	1995	Prospective	70	32.5 Gy in 5 fractions (one fraction per week) to whole breast plus 13 Gy in 2 fractions (one fraction per week) to tumor bed and tamoxifen without breast surgery resulted in 3-yr local control of 86% with median follow up 3 years in cohort of elderly patients (median age 81 years).
---------------------	------	-------------	----	---

---

Abbreviations:

HF-WBI: hypofractionated whole breast irradiation.

## References

1. Clarke M, Collins R, Darby S, *et al.* 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* 2005;366:2087-2106.
2. Fisher B, Anderson S, Bryant J, *et al.* Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233-1241.
3. Veronesi U, Cascinelli N, Mariani L, *et al.* Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227-1232.
4. Overgaard M, Hansen PS, Overgaard J, *et al.* Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997;337:949-955.
5. Overgaard M, Jensen MB, Overgaard J, *et al.* Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999;353:1641-1648.
6. Pierce LJ, Moughan J, White J, *et al.* 1998-1999 patterns of care study process survey of national practice patterns using breast-conserving surgery and radiotherapy in the management of stage I-II breast cancer. *Int J Radiat Oncol Biol Phys* 2005;62:183-192.
7. Ceilley E, Jagsi R, Goldberg S, *et al.* Radiotherapy for invasive breast cancer in North America and Europe: results of a survey. *Int J Radiat Oncol Biol Phys* 2005;61:365-373.
8. White J, Moughan J, Pierce LJ, *et al.* Status of postmastectomy radiotherapy in the United States: a patterns of care study. *Int J Radiat Oncol Biol Phys* 2004;60:77-85.
9. Srokowski TP, Fang S, Duan Z, *et al.* Completion of adjuvant radiation therapy among women with breast cancer. *Cancer* 2008;113:22-29.
10. Bentzen SM, Agrawal RK, Aird EG, *et al.* The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008;9:331-341.
11. Suh WW, Pierce LJ, Vicini FA, *et al.* A cost comparison analysis of partial versus whole-breast irradiation after breast-conserving surgery for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2005;62:790-796.
12. Whelan TJ, Levine M, Julian J, *et al.* The effects of radiation therapy on quality of life of women with breast carcinoma: results of a randomized trial. Ontario Clinical Oncology Group. *Cancer* 2000;88:2260-2266.
13. Magee B, Stewart AL, Swindell R. Outcome of radiotherapy after breast conserving surgery in screen detected breast cancers. *Clin Oncol (R Coll Radiol)* 1999;11:40-45.
14. McBain CA, Young EA, Swindell R, *et al.* Local recurrence of breast cancer following surgery and radiotherapy: incidence and outcome. *Clin Oncol (R Coll Radiol)* 2003;15:25-31.
15. Olivetto IA, Weir LM, Kim-Sing C, *et al.* Late cosmetic results of short fractionation for breast conservation. *Radiother Oncol* 1996;41:7-13.
16. Bentzen SM, Agrawal RK, Aird EG, *et al.* The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008;371:1098-1107.
17. Owen JR, Ashton A, Bliss JM, *et al.* Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* 2006;7:467-471.

18. Whelan T, MacKenzie R, Julian J, *et al.* Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002;94:1143-1150.
19. Whelan TJ, Pignol JP, Julian J, *et al.* Long-term results of a randomized trial of accelerated hypofractionated whole breast irradiation following breast conserving surgery in women with node-negative breast cancer. *Int J Radiat Oncol Biol Phys* 2008;72 (Suppl):A60, S28.
20. Yarnold J, Ashton A, Bliss J, *et al.* Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. *Radiother Oncol* 2005;75:9-17.
21. Physician Consortium for Performance Improvement: The Evidence Base Required for Measure Development. <http://www.ama-assn.org/ama/pub/physician-resources/clinical-practice-improvement/clinical-quality/physician-consortium-performance-improvement/position-papers.shtml>. Accessed December 1,, 2009.
22. Sniderman AD, Furberg CD. Why guideline-making requires reform. *Jama* 2009;301:429-431.
23. Baillet F, Housset M, Maylin C, *et al.* The use of a specific hypofractionated radiation therapy regimen versus classical fractionation in the treatment of breast cancer: a randomized study of 230 patients. *Int J Radiat Oncol Biol Phys* 1990;19:1131-1133.
24. Wallace LM, Priestman SG, Dunn JA, *et al.* The quality of life of early breast cancer patients treated by two different radiotherapy regimens. *Clin Oncol (R Coll Radiol)* 1993;5:228-233.
25. Dodwell DJ, Dyker K, Brown J, *et al.* A randomised study of whole-breast vs tumour-bed irradiation after local excision and axillary dissection for early breast cancer. *Clin Oncol (R Coll Radiol)* 2005;17:618-622.
26. Ribeiro GG, Dunn G, Swindell R, *et al.* Conservation of the breast using two different radiotherapy techniques: interim report of a clinical trial. *Clin Oncol (R Coll Radiol)* 1990;2:27-34.
27. Ribeiro GG, Magee B, Swindell R, *et al.* The Christie Hospital breast conservation trial: an update at 8 years from inception. *Clin Oncol (R Coll Radiol)* 1993;5:278-283.
28. Fyles AW, McCready DR, Manchul LA, *et al.* Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004;351:963-970.
29. Clark RM, McCulloch PB, Levine MN, *et al.* Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. *J Natl Cancer Inst* 1992;84:683-689.
30. Clark RM, Whelan T, Levine M, *et al.* Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. *J Natl Cancer Inst* 1996;88:1659-1664.
31. Romestaing P, Lehingue Y, Carrie C, *et al.* Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997;15:963-968.
32. Croog VJ, Wu AJ, McCormick B, *et al.* Accelerated whole breast irradiation with intensity-modulated radiotherapy to the prone breast. *Int J Radiat Oncol Biol Phys* 2009;73:88-93.
33. Martin S, Mannino M, Rostom A, *et al.* Acute toxicity and 2-year adverse effects of 30 Gy in five fractions over 15 days to whole breast after local excision of early breast cancer. *Clin Oncol (R Coll Radiol)* 2008;20:502-505.
34. Fujii O, Hiratsuka J, Nagase N, *et al.* Whole-breast radiotherapy with shorter fractionation schedules following breast-conserving surgery: short-term morbidity and preliminary outcomes. *Breast Cancer* 2008;15:86-92.

35. Livi L, Paiar F, Buonamici FB, *et al.* Accelerated intensity-modulated external radiotherapy as a new technical approach to treat the index quadrant after conserving surgery in early breast cancer: a preliminary study. *Tumori* 2005;91:227-232.
36. Ortholan C, Hannoun-Levi JM, Ferrero JM, *et al.* Long-term results of adjuvant hypofractionated radiotherapy for breast cancer in elderly patients. *Int J Radiat Oncol Biol Phys* 2005;61:154-162.
37. Shelley W, Brundage M, Hayter C, *et al.* A shorter fractionation schedule for postlumpectomy breast cancer patients. *Int J Radiat Oncol Biol Phys* 2000;47:1219-1228.
38. Yamada Y, Ackerman I, Franssen E, *et al.* Does the dose fractionation schedule influence local control of adjuvant radiotherapy for early stage breast cancer? *Int J Radiat Oncol Biol Phys* 1999;44:99-104.
39. Ash DV, Benson EA, Sainsbury JR, *et al.* Seven-year follow-up on 334 patients treated by breast conserving surgery and short course radical postoperative radiotherapy: a report of the Yorkshire Breast Cancer Group. *Clin Oncol (R Coll Radiol)* 1995;7:93-96.
40. Constantine C, Parhar P, Lymberis S, *et al.* Feasibility of accelerated whole-breast radiation in the treatment of patients with ductal carcinoma in situ of the breast. *Clin Breast Cancer* 2008;8:269-274.
41. Osako T, Oguchi M, Kumada M, *et al.* Acute radiation dermatitis and pneumonitis in Japanese breast cancer patients with whole breast hypofractionated radiotherapy compared to conventional radiotherapy. *Jpn J Clin Oncol* 2008;38:334-338.
42. Ivaldi GB, Leonardi MC, Orecchia R, *et al.* Preliminary results of electron intraoperative therapy boost and hypofractionated external beam radiotherapy after breast-conserving surgery in premenopausal women. *Int J Radiat Oncol Biol Phys* 2008;72:485-493.
43. Inomata T, Narabayashi I, Inada Y, *et al.* Patients' subjective evaluation of early and late sequelae in patients with breast cancer irradiated with short fractionation for breast conservation therapy: comparison with conventional fractionation. *Breast Cancer* 2008;15:93-100.
44. DeWyngaert JK, Jozsef G, Mitchell J, *et al.* Accelerated intensity-modulated radiotherapy to breast in prone position: dosimetric results. *Int J Radiat Oncol Biol Phys* 2007;68:1251-1259.
45. Formenti SC, Gidea-Addeo D, Goldberg JD, *et al.* Phase I-II trial of prone accelerated intensity modulated radiation therapy to the breast to optimally spare normal tissue. *J Clin Oncol* 2007;25:2236-2242.
46. Marhin W, Wai E, Tyldesley S. Impact of fraction size on cardiac mortality in women treated with tangential radiotherapy for localized breast cancer. *Int J Radiat Oncol Biol Phys* 2007;69:483-489.
47. Freedman GM, Anderson PR, Goldstein LJ, *et al.* Four-week course of radiation for breast cancer using hypofractionated intensity modulated radiation therapy with an incorporated boost. *Int J Radiat Oncol Biol Phys* 2007;68:347-353.
48. Galecki J, Hicer-Grzenkowicz J, Grudzien-Kowalska M, *et al.* Radiation-induced brachial plexopathy and hypofractionated regimens in adjuvant irradiation of patients with breast cancer--a review. *Acta Oncol* 2006;45:280-284.
49. Plataniotis GA, Theofanopoulou ME, Sotiriadou K, *et al.* High resolution computed tomography findings on the lung of early breast-cancer patients treated by postoperative breast irradiation with a hypofractionated radiotherapy schedule. *Indian J Cancer* 2005;42:191-196.
50. Fehlaue F, Tribius S, Alberti W, *et al.* Late effects and cosmetic results of conventional versus hypofractionated irradiation in breast-conserving therapy. *Strahlenther Onkol* 2005;181:625-631.

51. Marcenaro M, Sacco S, Pentimalli S, *et al.* Measures of late effects in conservative treatment of breast cancer with standard or hypofractionated radiotherapy. *Tumori* 2004;90:586-591.
52. Bajrovic A, Rades D, Fehlauer F, *et al.* Is there a life-long risk of brachial plexopathy after radiotherapy of supraclavicular lymph nodes in breast cancer patients? *Radiother Oncol* 2004;71:297-301.
53. Johansson S, Svensson H, Larsson LG, *et al.* Brachial plexopathy after postoperative radiotherapy of breast cancer patients--a long-term follow-up. *Acta Oncol* 2000;39:373-382.
54. Gorodetsky R, Lotan C, Piggot K, *et al.* Late effects of dose fractionation on the mechanical properties of breast skin following post-lumpectomy radiotherapy. *Int J Radiat Oncol Biol Phys* 1999;45:893-900.
55. Paszat LF, Mackillop WJ, Groome PA, *et al.* Mortality from myocardial infarction following postlumpectomy radiotherapy for breast cancer: a population-based study in Ontario, Canada. *Int J Radiat Oncol Biol Phys* 1999;43:755-762.
56. Dodwell DJ, Povall J, Gerrard G, *et al.* Skin telangiectasia: the influence of radiation dose delivery parameters in the conservative management of early breast cancer. *Clin Oncol (R Coll Radiol)* 1995;7:248-250.
57. Brierley JD, Paterson IC, Lallemand RC, *et al.* The influence of breast size on late radiation reaction following excision and radiotherapy for early breast cancer. *Clin Oncol (R Coll Radiol)* 1991;3:6-9.
58. Pierquin B, Tubiana M, Pan C, *et al.* Long-term results of breast cancer irradiation treatment with low-dose-rate external irradiation. *Int J Radiat Oncol Biol Phys* 2007;67:117-121.
59. Manavis J, Ambatzoglou J, Sismanidou K, *et al.* Computed tomography (CT) scan evaluation of late toxicity following hypofractionated/accelerated radiotherapy with cytoprotection (HypoARC) in breast cancer patients treated with conservative surgery. *Am J Clin Oncol* 2006;29:479-483.
60. Koukourakis MI, Giatromanolaki A, Kouroussis C, *et al.* Hypofractionated and accelerated radiotherapy with cytoprotection (HypoARC): a short, safe, and effective postoperative regimen for high-risk breast cancer patients. *Int J Radiat Oncol Biol Phys* 2002;52:144-155.
61. Palazzoni G, Nardone L, Cianciulli M, *et al.* Dose fractionation and biological optimization in breast cancer. *Rays* 2004;29:333-338.
62. Fehlauer F, Tribius S, Holler U, *et al.* Long-term radiation sequelae after breast-conserving therapy in women with early-stage breast cancer: an observational study using the LENT-SOMA scoring system. *Int J Radiat Oncol Biol Phys* 2003;55:651-658.
63. Maher M, Campana F, Mosseri V, *et al.* Breast cancer in elderly women: a retrospective analysis of combined treatment with tamoxifen and once-weekly irradiation. *Int J Radiat Oncol Biol Phys* 1995;31:783-789.
64. U.S. Preventive Services Task Force Procedure Manual, AHRQ Publication No. 08-05118-EF, July 2008. <http://www.ahrq.gov/clinic/uspstf08/methods/procmmanual.htm>. Accessed April 15, 2009.
65. Bartelink H, Horiot JC, Poortmans PM, *et al.* Impact of a Higher Radiation Dose on Local Control and Survival in Breast-Conserving Therapy of Early Breast Cancer: 10-Year Results of the Randomized Boost Versus No Boost EORTC 22881-10882 Trial. *J Clin Oncol* 2007;25:3259-3265.
66. Buchholz TA, Tucker SL, Erwin J, *et al.* Impact of systemic treatment on local control for patients with lymph node-negative breast cancer treated with breast-conservation therapy. *J Clin Oncol* 2001;19:2240-2246.
67. Nguyen PL, Taghian AG, Katz MS, *et al.* Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. *J Clin Oncol* 2008;26:2373-2378.

68. Buccholz TA, Strom EA, McNeese MD. The Breast. In: Cox JD, Ang KK, editors. Radiation Oncology: Rationale, Technique, Results. St Louis: Mosby; 2003.
69. Bartelink H, Horiot JC, Poortmans P, *et al.* Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001;345:1378-1387.
70. Greene FL, Page DL, Fleming ID, *et al.* AJCC Cancer Staging Handbook, Sixth Edition. New York: Springer; 2002.
71. Recht A. Brachial Plexus. In: Shrieve DC, Loeffler JS, editors. Radiation Injury. Philadelphia: Lippincott Williams and Wilkins; in press.
72. Livi L, Stefanacci M, Scocciati S, *et al.* Adjuvant hypofractionated radiation therapy for breast cancer after conserving surgery. *Clin Oncol (R Coll Radiol)* 2007;19:120-124.
73. Pignol JP, Olivetto I, Rakovitch E, *et al.* A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol* 2008;26:2085-2092.
74. Donovan E, Bleakley N, Denholm E, *et al.* Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. *Radiother Oncol* 2007;82:254-264.
75. Host H, Brennhovd IO, Loeb M. Postoperative radiotherapy in breast cancer--long-term results from the Oslo study. *Int J Radiat Oncol Biol Phys* 1986;12:727-732.
76. Demirci S, Nam J, Hubbs JL, *et al.* Radiation-induced cardiac toxicity after therapy for breast cancer: interaction between treatment era and follow-up duration. *Int J Radiat Oncol Biol Phys* 2009;73:980-987.
77. Freedman GM, Li T, Nicolaou N, *et al.* Breast intensity-modulated radiation therapy reduces time spent with acute dermatitis for women of all breast sizes during radiation. *Int J Radiat Oncol Biol Phys* 2009;74:689-694.
78. Harsolia A, Kestin L, Grills I, *et al.* Intensity-modulated radiotherapy results in significant decrease in clinical toxicities compared with conventional wedge-based breast radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;68:1375-1380.
79. Krauss DJ, Kestin LL, Raff G, *et al.* MRI-based volumetric assessment of cardiac anatomy and dose reduction via active breathing control during irradiation for left-sided breast cancer. *Int J Radiat Oncol Biol Phys* 2005;61:1243-1250.
80. Remouchamps VM, Vicini FA, Sharpe MB, *et al.* Significant reductions in heart and lung doses using deep inspiration breath hold with active breathing control and intensity-modulated radiation therapy for patients treated with locoregional breast irradiation. *Int J Radiat Oncol Biol Phys* 2003;55:392-406.
81. Bentzen SM. High-tech in radiation oncology: should there be a ceiling? *Int J Radiat Oncol Biol Phys* 2004;58:320-330.
82. Lee SP, Leu MY, Smathers JB, *et al.* Biologically effective dose distribution based on the linear quadratic model and its clinical relevance. *Int J Radiat Oncol Biol Phys* 1995;33:375-389.
83. Jones B, Dale RG, Finst P, *et al.* Biological equivalent dose assessment of the consequences of hypofractionated radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;47:1379-1384.
84. Munshi A, Kakkar S, Bhutani R, *et al.* Factors influencing cosmetic outcome in breast conservation. *Clin Oncol (R Coll Radiol)* 2009;21:285-293.
85. Rose MA, Olivetto I, Cady B, *et al.* Conservative surgery and radiation therapy for early breast cancer. Long-term cosmetic results. *Arch Surg* 1989;124:153-157.