

TITLE: Hypofractionation as the Primary Radiation Therapy Following Surgery for Localized Breast Cancer

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HYPOFRACTIONATION AS THE PRIMARY RADIATION THERAPY FOLLOWING SURGERY FOR LOCALIZED BREAST CANCER

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) has been asked to review the scientific literature on the safety and efficacy of hypofractionation as the primary radiation therapy for localized breast cancer. The goal of hypofractionation is to reduce the length of time required for radiation therapy following breast conserving surgery from the five to six weeks required for standard external beam radiation (EBR) therapy to three weeks or less while preserving the benefits of radiation therapy. Theoretically, higher dose fractions may be more effective at treating breast cancer, but these are limited by the potential toxicity to normal tissue including skin, bone, lung, and heart. Given the extensive literature demonstrating the effectiveness of standard dosing in the prevention of local breast cancer recurrence and eventually breast cancer mortality, a high level of evidence is required in order to demonstrate equivalence or superiority of a new dosing strategy.

BACKGROUND

Breast Cancer

Cancer of the breast is the most common form of cancer in women. Every American woman is estimated to have a one in nine chance of developing breast cancer at some time during her life. In 2008, there will be an estimated 184,450 new cases of invasive breast cancer in the United States and an estimated 40,930 deaths from this cancer.¹ In addition to invasive breast cancer, 67,770 new cases of breast carcinoma *in situ*, a condition also often treated with radiation therapy, will be diagnosed in women in 2008.

Radiation Therapy

Radiation therapy (as part of breast-conserving local therapy) most commonly consists of postoperative external-beam radiation to the entire breast with a total dose of 50 Grey (Gy) given in 25 daily fractions of 2.0 Gy over a five-week period. A further radiation boost of 10 to 16 Gy is commonly given to the tumor bed. Large randomized trials with more than 15 years of follow-up have demonstrated that treatment of breast cancer with breast conserving surgery (BCS) plus radiation therapy has equivalent outcomes to mastectomy.²⁻⁹ Despite the strong evidence of the effectiveness of BCS plus whole breast irradiation (WBI),

many eligible women in the United States opt for mastectomy.¹⁰ For some women, fears about local recurrence affect the decision. For others, fears about the radiation therapy that is required after partial mastectomy affects their decision-making. Finally, the conventional postoperative course of radiation requires daily attendance (Monday to Friday) for five to six weeks and is perceived as a major inconvenience.¹¹⁻¹³ This last concern may disproportionately affect patients with limited economic means or patients who have to travel large distances to reach a center offering radiation therapy.

Hypofractionation

Initial experiments with radiation therapy for cancer used large doses of radiation during each treatment session or fraction. This approach had only limited success at controlling tumor growth and caused significant damage to surrounding normal tissue. Investigators found that they could achieve better control of tumors with less toxicity if they delivered radiation therapy in many fractions (treatment sessions) over weeks to months. Several different fractionation schedules were used in the pivotal clinical trials and there is significant heterogeneity in the treatment approach used at different cancer centers.¹⁴⁻¹⁶ However, all of the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials used 50 Gy in 25 fractions and it has become the most commonly used schedule. Hypofractionation is a form of radiation therapy that uses a lower number of fractions to treat women than the conventional 25 fractions of 2 Gy each. Each fraction will be at a higher dose to give approximately the same total radiation dose.

The optimal fractionation schedule differs for each type of tumor. A given radiation dose results in nonrepairable and repairable damage to tissue. The ratio of these two measures differs by tumor type. If the ratio of non-repairable to repairable damage for a tumor is greater than the ratio for surrounding normal tissue, then lower doses per fraction delivered in many fractions to a high total dose should most effectively balance tumor control and damage to normal tissue. This is thought to be true for head and neck squamous cell tumors. On the other hand, if the ratio for a tumor is similar to or less than that of the surrounding normal tissue, then a larger dose per fraction (hypofractionation) to a lower total dose should be the most effective balance of benefits and harms. Until recently, there have been no published randomized trials comparing different fractionation schedules for adjuvant radiation therapy for breast cancer. Years of clinical experience support the use of the conventional fractionation schedule. However, studies of the response of breast cancer tissue cultures to radiation suggest that fractions larger than 2 Gy may be more effective.¹⁷⁻²⁰ Until recently, concerns about toxicity in normal tissue has limited the use of hypofractionation in clinical practice, particularly in the United States.

The principle advantage of hypofractionation is the delivery of effective radiation therapy in fewer sessions. This may make radiation therapy more convenient for women, increasing the use of BCS and adherence to the recommended treatment schedule. It would also increase the efficiency of delivery of radiation therapy services in regions with limited access to the highly trained staff and expensive machines required to deliver radiation therapy. Finally, hypofractionation may be more effective at preventing local recurrence.

Technology Assessment (TA)

TA Criterion 1: The technology must have the appropriate regulatory approval.

There are several manufacturers of linear accelerators, the primary device for delivering whole breast irradiation. Two of these include Varian and Siemens. These devices have been approved through the FDA 510(k) process. Specialized computer software is used with these devices to plan and deliver the radiation used in hypofractionation.

TA Criterion 1 is met.

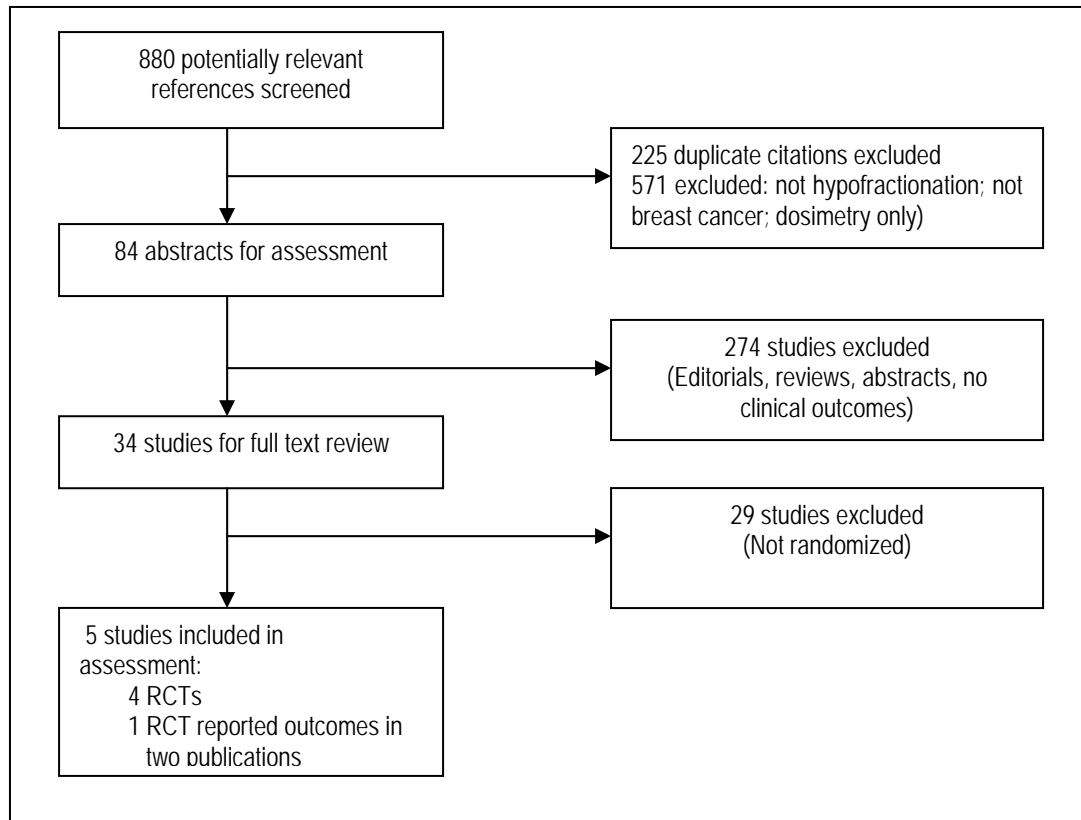
TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE), and Embase were searched using the key words hypofractionation or breast irradiation. These were cross-referenced with the keywords breast neoplasms and human. The search was performed on January 30, 2009. The bibliographies of review articles and other key references were manually searched for additional references and the manufacturers were contacted for reference lists. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

Full details of the search terms are included in the Appendix. The Figure describes the search results. In brief, a total of 880 references were reviewed (421 from Embase, 333 from PubMed, and 126 from the combined Cochrane databases). Because of the strong evidence base for whole breast irradiation as an essential component of breast cancer treatment following lumpectomy, the large differences in expected outcomes based on patient characteristics, and known cohort effects from improvements in screening and

treatment over the past decade, we included only randomized trials with at least five years follow-up in this assessment.

Figure: Selection of studies for inclusion in review



The most important health outcome of breast cancer treatment is survival. Most authorities agree that the long natural history of breast cancer means that 10- to 15-year follow-up is required for meaningful survival data.²¹ However, local control is an important intermediate outcome both because local control appears to predict long-term mortality²² and because the primary goal of BCS with radiation is to prevent local recurrences and to preserve the breast. Most patients with recurrent local disease are treated with mastectomy. The majority of local recurrences occur within the first five years, although additional recurrences continue to accrue through at least fifteen years of follow-up.²² A minimum of five to seven years follow-up should be required to adequately evaluate differences in local recurrence rates. Because local recurrence rates vary significantly by patient age, tumor histology, nodal status, and adjuvant therapy, comparative studies should be randomized in order to have confidence in the results.

Breast preservation is a key goal of therapy. Thus, cosmetic outcomes are also of high importance. If local recurrence rates with hypofractionation are equivalent to the standard fractionation schedule, but cosmetic outcomes are significantly worse, hypofractionation would not be considered equivalent to standard dosing. Late radiation effects on normal tissue are the major concern with the higher dose fractions used in hypofractionation. Adverse effects include breast edema, erythema, fibrosis, hyperpigmentation, hypopigmentation, telangiectasias, and fibrosis. Late radiation effects of particular concern include damage to the coronary arteries leading to coronary artery disease, lung fibrosis, and rib fractures.

For the purposes of this review, we will focus on local recurrence rates at five years as the primary outcome with cosmetic outcomes being an important secondary outcome if local recurrence rates are found to be equivalent. Data from four large, multi-center randomized trials provide a good evidence base for the assessment.²³⁻²⁷

Level of Evidence: 1

TA Criterion 2 is met.

TA Criterion 3: The technology must improve the net health outcomes.

Randomized controlled trials (Table)

Five-year results from the four randomized trials are summarized in the Table.²³⁻²⁷ All four trials used a fractionation schedule of 50 Gy divided into 25 fractions of 2.0 Gy as the comparison group. More detailed information about the individual trials including the ten year results from one study is described below. The major differences between the trials are the patient population enrolled and the fractionation schedules. The Canadian trial only included lymph node negative women who were treated with breast-conserving surgery.²⁶ The three trials in the United Kingdom (UK) randomized all women with operable breast cancer (T1-3, N0-1, M0) including women with up to three positive lymph nodes and women who were treated with mastectomy.^{23-25, 27} Most women in the UK trials were treated with BCS and the cosmetic results are presented in this subgroup of women, allowing for conclusions to be drawn about the cosmetic outcomes in this important subgroup.

Table 1: Randomized Trials of Hypofractionation for Whole Breast Irradiation

Study	Patients (n)	Median follow-up (years)	Fractionation schedule (Total / F / D / weeks)	Local recurrence At 5 years (%)	Disease-free survival at 5 years	Overall survival at 5 years	Cosmetic outcome (% good / excellent)
Whelan 2002	1234	5.8	50.0 / 25 / 2.0 / 5	3.2	ND p 0.37	ND p 0.78	77.4
			42.5 / 16 / 2.66 / 3	2.8	~ 88%	~ 93%	76.2
Yarnold 2005	1410	9.7	50.0 / 25 / 2.0 / 5	7.9	NR	NR	44.1
Owen 2006*			42.9 / 13 / 3.3 / 5	7.1			37.9
			39.0 / 13 / 3.0 / 5	9.1			54.6
START A 2008	2236	5.1	50.0 / 25 / 2.0 / 5	3.2	86.4	88.9	57.1
			41.6 / 13 / 3.2 / 5	3.2	88.0	88.7	56.4
			39.0 / 13 / 3.0 / 5	4.6	84.8	89.3	67.9
START B 2008	2215	6.0	50.0 / 25 / 2.0 / 5	3.3	85.9	89.0	57.8
			40.0 / 15 / 2.67 / 3	2.0	89.4	92.0	63.5

* See the body of the assessment under TA3 for the 10-year local recurrence rates

Gy: Grey
 F: Number of fractions
 D: Fraction size or dose (Gy)
 Wks: Weeks
 ND: No difference
 NR: Not reported
 START: United Kingdom Standardization of Breast Radiotherapy Trials

Whelan 2002

Whelan et al published the first randomized trial comparing hypofractionation to standard radiation therapy for breast cancer.²⁶ The study included all women with invasive breast cancer and no lymph node involvement after axillary lymph node dissection (pN0) who had negative surgical margins and a tumor size less than 5 cm in diameter (T1-2). The primary outcome measure was local recurrence of invasive breast cancer. An important secondary outcome was the cosmetic result evaluated using the standard European Organization for Research and Treatment of Cancer (EORTC) Cosmetic Rating System. A treatment that has equivalent local recurrence rates, but worse cosmetic outcomes would not be acceptable. Other secondary outcomes included disease free survival and overall survival.

The investigators randomized 1234 Canadian women to radiation therapy after lumpectomy using either the standard fractionation schedule of 50 Gy delivered in 25 fractions of 2 Gy over 35 days or to a shorter, hypofractionation schedule of 42.5 Gy delivered in 16 fractions of 2.7 Gy over 22 days. A total of 622 women were randomized to the hypofractionation group and 612 to the standard group. A few women did not complete their treatment as randomized (eight in the hypofractionation group and 12 in the standard group), but all patients were analyzed as they were randomized. Patient age, tumor size, tumor grade, estrogen receptor status, chemotherapy and endocrine therapy were nearly identical in the two groups. The median follow-up was 69 months at the time of the analysis included in this assessment. Ten-year follow-up results were reported in 2008, but have not yet been published.

At five years the rate of local recurrence was 2.8% in the hypofractionation group and 3.2% in the standard group (absolute difference 0.4%, 95% CI -1.5% to 2.4%). The five year disease free survival (approximately 88% estimated from graphs, $p=0.37$) and overall survival (approximately 93% estimated from graphs, $p=0.78$) did not differ between the two groups. Cosmetic outcomes were also almost identical with 77% of subjects in both groups judged to have good or excellent cosmetic outcomes at three and five years. Similarly there were no important differences in radiation toxicity. No grade 4 toxicities occurred in either group. Grade 2 or 3 skin toxicity occurred in two patients in each group at three years and in three patients in each group at five years. Similarly, grade 2 or 3 subcutaneous toxicity occurred in four patients in the hypofractionation group and five patients in the standard group at three years and five patients in the hypofractionation group and seven patients in the standard group at five years. Overall there was a trend towards less skin and subcutaneous tissue toxicity in the hypofractionation group and no differences in radiation pneumonitis (two in each group).

In this large, high quality, multi-center study, a shorter course of radiation therapy produced results that were equivalent to a standard fractionation schedule with no increase in radiation induced toxicity to the skin or lungs. This fractionation schedule is less burdensome on women and would allow more efficient use of health care personnel and equipment. If the results remain consistent with longer follow-up and are confirmed in a second trial, hypofractionation should become the standard radiation therapy for women

Yarnold 2005 and Owen 2006

Four years later, Owen and Yarnold published the five and ten year results from a second randomized trial comparing three different fractionation schedules for breast cancer.^{25, 27} The study included all women with invasive breast cancer not invading the skin or chest wall (T1-3) and a maximum of three lymph nodes positive (N0-1). Visual, but not pathological surgical margins were required to be negative. The primary outcome measure was radiation toxicity. The investigators hypothesized that the incidence of late radiation effects would be less than 10%, assuming that the incidence in the standard therapy group would be less than five percent. Radiation effects and other cosmetic outcomes were assessed by comparing photographs of the breasts that were taken prior to radiation therapy with those taken at each annual follow-up visit. Local recurrence of invasive breast cancer was a secondary outcome.

The investigators randomized 1410 women in the UK to radiation therapy after breast surgery using either the standard fractionation schedule of 50 Gy delivered in 25 fractions of 2 Gy or to one of two hypofractionation schedules: 42.9 Gy delivered in 13 fractions of 3.3 Gy or 39 Gy delivered in 13 fractions of 3.0 Gy. All three fractionation schedules were delivered over a five week period. The study randomized 470 women to the standard 50 Gy group, 466 women to the 42.9 Gy group, and 474 to the 39 Gy group. During a median of 9.7 years follow-up (maximum 18.4 years), only 18 women were lost to follow-up.

At five years the local recurrence rate was 7.9% (95% CI 5.4-10.4) in the standard 50 Gy group, 7.1% (95% CI 4.6-9.5) in the 42.9 Gy group, and 9.1% (95% CI 6.4-11.7) in the 39 Gy group. Similarly, the ten year local recurrence rate was 12.1% (95% CI 8.8-15.5) in the standard 50 Gy group, 9.6% (95% CI 6.7-12.6) in the 42.9 Gy group, and 14.8% (95% CI 11.2-18.3) in the 39 Gy group. None of the differences between the hypofractionation groups and the standard 50 Gy group were statistically significant. The authors performed survival analysis as well: through five years the relative risk for local recurrence was 0.90 (95% CI 0.55-1.46) in the 42.9 Gy group and 1.14 (95% CI 0.72 – 1.79) in the 39 Gy group compared with the 50 Gy

group. However, the cosmetic outcomes differed between groups, with the outcomes for the standard 50 Gy consistently falling in between those of the 42.9 and 39 Gy groups. The p-values for differences between the three groups were less than 0.001 for any change in breast appearance, marked change in breast appearance, the cosmetic outcome being good / excellent, induration, and shoulder stiffness. For example, the percentage of women at five years with no apparent changes in the breast was 60% in the 50 Gy group, 54% in the 42.9 Gy group, and 70% in the 39 Gy group. Similarly, the percentage of women at five years with good or excellent cosmetic outcomes was 44% in the 50 Gy group, 38% in the 42.9 Gy group, and 55% in the 39 Gy group. Overall the 39 Gy group had significantly better cosmetic outcomes, but there was a trend towards more frequent local recurrence in that group. The early results of this trial were used to inform the choice of dosing schedules in the START A and START B trials described below.

START A 2008

The design of the UK START trials was based on the initial results of the study of Owen and Yarnold described above.^{25, 27} Trial A retained the design of the original trial with a plan to combine the data in order to generate data to model the optimal fraction schedule for radiotherapy for breast cancer.²³ The only change was a reduction in the total dose and fraction size for one of the groups in the trial from 42.9 Gy in 3.3 Gy fractions to 41.6 Gy in 3.2 Gy fractions based on evidence for an increase in late radiation damage to normal tissue in patients randomized to the original fractionation schedule. Trial B, on the other hand, was a pragmatic trial that compared the standard 50 Gy in 25 fractions of 2 Gy to a fractionation schedule commonly in use in the UK: 40 Gy in 15 fractions over three weeks.²⁴ Both trials randomized women with T1-3, N0-1, M0 tumors, the same inclusion criteria used in the pilot trial of Owen and Yarnold.^{25, 27}

In the START A trial, the investigators randomized 2236 women in the UK to radiation therapy after breast surgery.²³ The study randomized 749 women to the standard 50 Gy group, 750 women to the 41.6 Gy group, and 737 to the 39 Gy group. During a median of 5.1 years follow-up (maximum 8.0 years), only nine women were lost to follow-up. Baseline demographic and clinical characteristics were similar in all three groups. The mean age of the participants was 57.2 years. Fifteen percent of the participants underwent total mastectomy, while the remainder had BCS. There were positive axillary lymph nodes in 28.8% of the women.

At five years the local recurrence rate was 3.2% (95% CI 1.9-4.6) in the standard 50 Gy group, 3.2% (95% CI 1.9-4.5) in the 41.6 Gy group, and 4.6% (95% CI 3.0-6.2) in the 39 Gy group. The disease free survival

rates (86.4%, 88.0%, and 84.8%) and overall survival rates (88.9%, 88.7%, and 89.3%) were similar in all three groups. None of the differences between the hypofractionation groups and the standard 50 Gy group were statistically significant. The estimated absolute difference in locoregional recurrence rates between the 41.6 Gy group and the 50 Gy group was 0.2% (95% CI -1.3% to 2.6%); the absolute difference in locoregional recurrence rates between the 39 Gy group and the 50 Gy group was 0.9% (95% CI -0.8% to 3.7%). The cosmetic outcomes were similar across the groups, although the outcomes for the standard 50 Gy tended to fall between those of the 41.6 and 39 Gy groups. The only significant differences favored the 39 Gy group compared with the 50 Gy group: there were fewer changes in skin appearance (21.6% vs. 31.1%; RR 0.65, 95% CI 0.49-0.87) and fewer poor cosmetic outcomes (32.1% vs. 42.9%; RR 0.69, 95% CI 0.52-0.91). The investigators also reported the incidence of other potentially significant late adverse effects of radiation therapy that are of concern when using the larger doses of radiation required for hypofractionation. The reported incidence of ischemic heart disease (1.6% in 50 Gy; 0.9% in 41.6 Gy; 1.1% in 39 Gy), symptomatic rib fracture (1.1% in 50 Gy; 1.2% in 41.6 Gy; 1.4% in 39 Gy), and symptomatic lung fibrosis (0.7% in 50 Gy; 0.8% in 41.6 Gy; 0.9% in 39 Gy) did not differ significantly between groups. However, the length of follow-up may be too short to detect meaningful differences in these potentially important outcomes.

START B 2008

In the START B trial, the investigators randomized 2215 women in the UK to radiation therapy after breast surgery.²⁴ The study randomized 1105 women to the standard 50 Gy group and 1110 women to the 40 Gy group. During a median of 6.0 years follow-up (maximum 8.0 years), 19 women were lost to follow-up. Baseline demographic and clinical characteristics were similar in all three groups. The mean age of the participants was 57.4 years. Eight percent of the participants underwent total mastectomy, while the remainder had breast-conserving surgery. There were positive axillary lymph nodes in 22.8% of the women.

At five years the local recurrence rate was 3.3% (95% CI 2.2-4.4) in the standard 50 Gy group and 2.0% (95% CI 1.1-2.8) in the 40 Gy group. The disease free survival rates (85.9% in 50 Gy, 89.4% in 40 Gy) and overall survival rates (89.0% in 50 Gy, 92.0% in 40 Gy) were similar in both groups. None of the differences were statistically significant, but all trends favored the 40 Gy hypofractionation group. The estimated absolute difference in locoregional recurrence rates between the 40 Gy group and the 50 Gy group was -0.7% (95% CI -1.7% to 0.9%). The cosmetic outcomes all favored the 40 Gy group. The only significant difference was fewer changes in skin appearance (22.9% vs. 27.8%; RR 0.77, 95% CI 0.61-0.98). There

was a trend towards fewer changes in breast appearance by self-report (39.4% vs. 34.4%; RR 0.86, 95% CI 0.70-1.05) and by comparison of photographs from baseline to five years (42.2% vs. 36.5%; RR 0.83, 95% CI 0.66-1.04). The investigators also reported the incidence of other potentially significant late adverse effects of radiation therapy that are of concern when using the larger doses of radiation required for hypofractionation. The reported incidence of ischemic heart disease (1.7% in 50 Gy; 1.3% in 40 Gy), symptomatic rib fracture (1.5% in 50 Gy; 1.4% in 40 Gy), and symptomatic lung fibrosis (1.4% in 50 Gy; 1.4% in 40 Gy) did not differ significantly between groups. As in START A, the length of follow-up may be too short to detect meaningful differences in these potentially important outcomes.

Systematic reviews

The Cochrane collaboration published a review of hypofractionation in radiation treatment of breast cancer in 2008.²⁸ Their review focused on the first two trials included in this assessment. They concluded that there was “evidence from two high quality randomized trials that the use of unconventional fractionation regimes (greater than 2 Gy per fraction) does not affect breast appearance or toxicity and does not seem to affect local recurrence for selected women treated with breast conserving surgery.”

Summary

Four high quality trials randomizing 7095 women convincingly demonstrated that hypofraction can be performed with low morbidity rates and low local recurrence rates when used as adjuvant therapy following surgical treatment of breast cancer. The five-year local recurrence rates reported in these studies (2.0% to 9.1% in the new series) are much lower than those reported by randomized clinical trials for patients treated with BCS without radiation (24% to 37%). These large differences are unlikely to be due to selection bias given that the results appear comparable to the standard fractionation schedule in all of the randomized comparisons. In general the cosmetic outcomes were similar with standard fraction sizes and the larger fraction sizes used in the trials. Fraction sizes above 3.0 Gy appeared to give worse cosmetic outcomes, although they also tended to result in lower local recurrence rates. Late radiation damage to other normal structures (heart, lung, ribs) was rare and did not occur more frequently in women treated with the hypofractionation schedules studied in these trials. However, longer follow-up is needed to adequately rule out increases in these uncommon late adverse events.

TA Criterion 3 is met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

Because of the strong evidence base and extensive clinical experience demonstrating the efficacy of standard radiation therapy for breast cancer, large phase III trials with a minimum of five years of follow-up are needed to assess novel approaches to the delivery of adjuvant radiation therapy. It had been hypothesized that breast cancer could be more effectively treated using large dose fraction sizes than the standard 2.0 Gy, but early evidence suggested that there would be an unacceptable level of late radiation toxicity to normal tissues including skin, lung, heart, and bone. However observational data from centers using larger fraction sizes suggested that late toxicity may not be as large an issue as previously thought.²⁹⁻

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There are now four large trials with at least five years follow-up that compare hypofractionation to the established alternative of 50 Gy total delivered in 25 fractions of 2.0 Gy (see Table).²³⁻²⁷ These are the only published randomized data comparing radiation fractionation schedules used as adjuvant therapy following breast surgery for breast cancer. The results of these trials should be used as the primary data for practice guidelines regarding fractionation schedules. In both trials with only two groups (Whelan 2002; START B), a three week hypofractionation schedule with fraction sizes of approximately 2.67 Gy had lower local recurrence rates at five years (not statistically significant) and similar cosmetic outcomes compared with 25 fractions of 2.0 Gy over five weeks.^{24, 26} There were no differences in disease-free and overall survival as well as late radiation toxicity to the lung, heart, or bone. Indeed, the trend favored hypofractionation over the standard 2.0 Gy fraction size. In the other two trials (Owen 2006; START A), the groups randomized to the largest fraction sizes (3.2 or 3.3 Gy in 13 fractions over five weeks) tended to have lower local recurrence rates than the standard schedule, but had worse cosmetic outcomes.^{23, 25, 27} Again there was no difference in survival or late radiation toxicity except to the skin. The lower total dose fractionation schedule used in both of these trials (39 Gy in 13 fractions of 3.0 Gy over five weeks) tended to have slightly higher local recurrence rates, although they had better cosmetic outcomes. Again, hypofractionation did not result in higher rates of late toxicity to the skin, lung, heart, or bone.

Overall, the data suggest that fractionation schedules using dose fractions greater than 2.0 Gy have equivalent breast cancer outcomes, cosmetic outcomes and late radiation toxicities compared to the standard 2.0 Gy fraction size. Current evidence favors 15 or 16 fractions of 2.67 Gy over three weeks as the optimal regimen for minimizing local recurrence and late toxicity while optimizing cosmetic outcomes.

However, the groups in these clinical trials should continue to be monitored out to at least 15 years to ensure that current trends continue to hold.

TA Criterion 4 is met.

TA Criterion 5: The improvement must be attainable outside the investigational setting.

Hypofractionation schedules for the delivery of adjuvant radiation therapy have been in use at many clinical centers around the world for several decades. However, until recently there have not been clinical trials demonstrating equivalent outcomes for fractionation schedules using more than 2.0 Gy per fraction compared to those using 2.0 Gy or less. The four randomized trials discussed in this assessment were all multicenter trials, thus providing additional evidence that this approach to breast radiation therapy can be extended beyond the investigational setting.

TA Criterion 5 is met.

CONCLUSION

Because of the strong evidence base and extensive clinical experience demonstrating the efficacy of standard radiation therapy for breast cancer, large phase III trials with a minimum of five years of follow-up are needed to assess novel approaches to the delivery of adjuvant radiation therapy. Accelerated partial breast irradiation has the potential to dramatically shorten the time required to delivery of effective radiation therapy, but there are no large clinical trials with mature data demonstrating the safety and efficacy of this approach. In the interim, hypofractionation may provide an alternative approach that shortens the time required for women to receive effective radiation therapy and decreases the health care resources needed to deliver optimal therapy. The primary goal of radiation therapy after breast conserving therapy to prevent local recurrences. Four large, multicenter trials randomizing 7095 women to the standard 50 Gy regimen or alternative hypofractionation schedules have published their five-year, and in one case 10-year results. The results consistently demonstrate equivalence in local recurrence rates with relatively tight confidence intervals around the absolute difference in recurrence rates between hypofractionation and standard fractionation with 50 Gy in 25 fractions. The fraction schedules using 15 or 16 fractions of approximately 2.67 Gy over a three week period had lower recurrence rates than the 50 Gy schedule and better cosmetic

outcomes in two different trial performed in different countries. This hypofractionation schedule also had a trend towards better disease free survival and overall survival with lower rates of serious late radiation complications in the lung, heart, and bone. The length of follow-up in these trials is not long enough to fully assess survival and late adverse effects, but the trends are promising. Current randomized trial evidence suggests that one of these two fractionation schedules should be the standard against which all other forms of adjuvant radiation therapy to the breast are judged.

DRAFT RECOMMENDATION

It is recommended that the use of hypofractionation meets Technology Assessment Criteria 1 through 5 for safety, effectiveness and improvement in health outcomes when used as adjuvant radiation therapy following breast surgery for localized breast cancer.

March 11, 2009

This is the first time this technology has been reviewed by the CTAF panel.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not conducted a formal review of this technology.

Centers for Medicare and Medicaid Services (CMS)

A search of the CMS web site did not reveal a specific NCD regarding this technology.

California Radiological Society (CRS)

The CRS has been invited to provide an opinion and to have a representative provide testimony at the CTAF meeting.

American Society for Therapeutic Radiology and Oncology (ASTRO)

ASTRO has been invited to provide an opinion and to have a representative provide testimony at the CTAF meeting.

American Cancer Society (ACS)

The ACS has been invited to provide an opinion and to have a representative provide testimony at the CTAF meeting.

Association of Northern California Oncologists (ANCO)

ANCO has been invited to provide an opinion and to have a representative provide testimony at the CTAF meeting.

Medical Oncology Association of Southern California (MOASC)

MOASC has been invited to provide an opinion and to have a representative provide testimony at the CTAF meeting.

American College of Radiation Oncology (ACRO)

The ACRO has been invited to provide an opinion and to have a representative provide testimony at the CTAF meeting.

American Society of Breast Surgeons (ASBrS)

The ASBrS has been invited to provide an opinion and to have a representative provide testimony at the CTAF meeting.

ABBREVIATIONS USED IN THIS ASSESSMENT

CTAF	California Technology Assessment Forum
EBR	External beam radiation
GY	Grey
BCS	Breast conserving surgery
WBI	Whole breast irradiation
NSABP	National Surgical Adjuvant Breast and Bowel Project
DARE	Database of Abstracts of Reviews of Effects
UK	United Kingdom
F	Number of fractions
D	Fraction size or dose (Gy)
Wks	Weeks
ND	No difference
NR	Not reported
START	United Kingdom Standardization of Breast Radiotherapy Trials
EORTC	European Organization for Research and Treatment of Cancer

APPENDIX: Detailed search criteria

Pubmed Search

PubMed, dates of coverage 1966 to present, run date 1/30/09

Search	Most Recent Queries	Time	Result
#11	Search #9 OR #10	17:48:54	333
#10	Search #8 AND (systematic review* OR meta-analysis[mh])	17:48:35	7
#9	Search #8 NOT (editorial[pt] OR letter[pt] OR review[pt] OR news[pt]) Limits: English	17:47:30	328
#8	Search #7 NOT (murine[ti] OR rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti]) Limits: English	17:46:21	406
#7	Search #3 OR #4 OR #5 Limits: English	17:45:29	413
#6	Search #3 OR #4 OR #5	17:45:17	481
#5	Search (hypofraction*[ti] OR fraction*[ti]) AND breast AND (cancer OR cancers OR tumor OR tumors OR tumour OR tumours OR carcinoma OR carcinomas OR adenocarcinom*) AND (radiotherap*[tiab] OR radiation[tiab] OR irradiat* OR lumpectom* OR breast conserv* OR breast preserv* OR early breast cancer* OR "early stage")	17:44:56	207
#4	Search breast neoplasms/rt AND (hypofraction*[ti] OR fraction*[ti]) AND radiotherapy dosage[mh:noexp]	17:44:33	93
#3	Search #1 AND #2	17:43:01	352
#2	Search dose fractionation[mh] OR hypofraction* or fractionat*	17:42:48	74705
#1	Search breast neoplasms/rt[majr]	17:42:15	5238

Embase Search



Dates of coverage for EMBASE, 1974 to present

No.	Query	Results	Date
#1	'breast tumor'/exp/dm_rt/mj	10,470	30 Jan 2009
#2	'breast cancer'/exp/mj	119,463	30 Jan 2009
#3	'radiotherapy'/mj OR 'cancer radiotherapy'/mj	42,786	30 Jan 2009
#4	#2 AND #3	3,392	30 Jan 2009
#5	#1 OR #4	12,483	30 Jan 2009
#6	'radiation dose fractionation'/exp OR fractionat* OR hypofraction*	75,455	30 Jan 2009
#7	#5 AND #6	511	30 Jan 2009
#13	'breast tumor'/exp/dm_rt AND ('radiation dose fractionation'/mj OR hypofraction*:ti OR fraction*:ti)	184	30 Jan 2009
#14	#7 OR #13	580	30 Jan 2009
#15	#7 OR #13 AND [english]/lim	511	30 Jan 2009
#16	#15 NOT (murine:ti OR rat:ti OR rats:ti OR mouse:ti OR mice:ti)	478	30 Jan 2009
#18	#16 AND ([editorial]/lim OR [letter]/lim)	36	30 Jan 2009
#19	#16 NOT #18	442	30 Jan 2009
#20	#19 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)	59	30 Jan 2009
#21	#19 AND ([review]/lim OR [short survey]/lim)	51	30 Jan 2009
#22	#19 NOT #21	391	30 Jan 2009
#23	#20 OR #22	412	30 Jan 2009

Cochrane Search:

ID	Search	Hits
#1	MeSH descriptor Breast Neoplasms explode all trees with qualifier: RT	610
#2	(hypofraction* or fraction*):ti	1020
#3	(#1 AND #2)	19
#4	(hypofraction* or fraction*):ti,ab,kw and (breast or mammary):ti and (radiotherap* or irradiat* or radiation):ti,ab,kw	121
#5	(#3 OR #4)	127

Search Results

[Cochrane Reviews \[1\]](#) | [Other Reviews \[1\]](#) | **Clinical Trials [125]** | [Methods Studies \[0\]](#) | [Technology Assessments \[0\]](#) | [Economic Evaluations \[0\]](#) | [Cochrane Groups \[0\]](#)

Search Results

Show Results in:

Cochrane Reviews [3] | [Other Reviews \[0\]](#) | [Clinical Trials \[10\]](#) | [Methods Studies \[0\]](#) | [Technology Assessments \[2\]](#) | [Economic Evaluations \[1\]](#) | [Cochrane Groups \[0\]](#)

[Eit Search](#)

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin.* Mar-Apr 2006;56(2):106-130.
2. Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr.* 1992(11):19-25.
3. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med.* Nov 30 1995;333(22):1456-1461.
4. Jacobson JA, Danforth DN, Cowan KH, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med.* Apr 6 1995;332(14):907-911.
5. Sarrazin D, Le MG, Arriagada R, et al. Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiother Oncol.* Mar 1989;14(3):177-184.
6. van Dongen JA, Bartelink H, Fentiman IS, et al. Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. *J Natl Cancer Inst Monogr.* 1992(11):15-18.
7. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst.* Jul 19 2000;92(14):1143-1150.
8. Veronesi U, Banfi A, Salvadori B, et al. Breast conservation is the treatment of choice in small breast cancer: long-term results of a randomized trial. *Eur J Cancer.* 1990;26(6):668-670.
9. Veronesi U, Salvadori B, Luini A, et al. Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomised trials on 1,973 patients. *Eur J Cancer.* Sep 1995;31A(10):1574-1579.
10. Morrow M, White J, Moughan J, et al. Factors predicting the use of breast-conserving therapy in stage I and II breast carcinoma. *J Clin Oncol.* Apr 15 2001;19(8):2254-2262.
11. Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR. Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. *J Natl Cancer Inst.* Feb 2 2000;92(3):269-271.
12. Farrow DC, Hunt WC, Samet JM. Geographic variation in the treatment of localized breast cancer. *N Engl J Med.* Apr 23 1992;326(17):1097-1101.
13. Hebert-Croteau N, Brisson J, Latreille J, Blanchette C, Deschenes L. Compliance with consensus recommendations for the treatment of early stage breast carcinoma in elderly women. *Cancer.* Mar 1 1999;85(5):1104-1113.

14. Langlois D. [A survey on breast conservation modalities in cancer institutes]. *Bull Cancer*. 1990;77(8):793-797.
15. Whelan T, Marcellus D, Clark R, Levine M. Adjuvant radiotherapy for early breast cancer: patterns of practice in Ontario. *CMAJ*. Nov 1 1993;149(9):1273-1277.
16. Williams MV, James ND, Summers ET, Barrett A, Ash DV. National survey of radiotherapy fractionation practice in 2003. *Clin Oncol (R Coll Radiol)*. Feb 2006;18(1):3-14.
17. Hall EJ, Marchese M, Hei TK, Zaider M. Radiation response characteristics of human cells in vitro. *Radiat Res*. Jun 1988;114(3):415-424.
18. Steel GG, Deacon JM, Duchesne GM, Horwich A, Kelland LR, Peacock JH. The dose-rate effect in human tumour cells. *Radiother Oncol*. Aug 1987;9(4):299-310.
19. Williams JR, Zhang Y, Zhou H, et al. A quantitative overview of radiosensitivity of human tumor cells across histological type and TP53 status. *Int J Radiat Biol*. Apr 2008;84(4):253-264.
20. Williams MV, Denekamp J, Fowler JF. A review of alpha/beta ratios for experimental tumors: implications for clinical studies of altered fractionation. *Int J Radiat Oncol Biol Phys*. Jan 1985;11(1):87-96.
21. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. May 20 2000;355(9217):1757-1770.
22. 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*. Dec 17 2005;366(9503):2087-2106.
23. 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*. Apr 2008;9(4):331-341.
24. 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*. Mar 29 2008;371(9618):1098-1107.
25. 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*. Jun 2006;7(6):467-471.
26. 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*. Aug 7 2002;94(15):1143-1150.
27. 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*. Apr 2005;75(1):9-17.

28. James ML, Lehman M, Hider PN, Jeffery M, Francis DP, Hickey BE. Fraction size in radiation treatment for breast conservation in early breast cancer. *Cochrane Database Syst Rev.* 2008(3):CD003860.
29. Ash DV, Benson EA, Sainsbury JR, Round C, Head C. 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(2):93-96.
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.* Nov 20 1996;88(22):1659-1664.
31. 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(1):86-92.
32. 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(1):93-100.
33. Kirova YM, Campana F, Savignoni A, et al. Breast-Conserving Treatment in the Elderly: Long-Term Results of Adjuvant Hypofractionated and Normofractionated Radiotherapy. *Int J Radiat Oncol Biol Phys.* Jan 23 2009.
34. Koukourakis MI, Tsoutsou PG, Abatzoglou IM, Sismanidou K, Giatromanolaki A, Sivridis E. Hypofractionated and Accelerated Radiotherapy with Subcutaneous Amifostine Cytoprotection as Short Adjuvant Regimen After Breast-Conserving Surgery: Interim Report. *Int J Radiat Oncol Biol Phys.* Dec 4 2008.
35. 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.* Oct 1 2007;69(2):483-489.
36. Olivotto IA, Weir LM, Kim-Sing C, et al. Late cosmetic results of short fractionation for breast conservation. *Radiother Oncol.* Oct 1996;41(1):7-13.
37. Shelley W, Brundage M, Hayter C, Paszat L, Zhou S, Mackillop W. A shorter fractionation schedule for postlumpectomy breast cancer patients. *Int J Radiat Oncol Biol Phys.* Jul 15 2000;47(5):1219-1228.
38. Yamada Y, Ackerman I, Franssen E, MacKenzie RG, Thomas G. Does the dose fractionation schedule influence local control of adjuvant radiotherapy for early stage breast cancer? *Int J Radiat Oncol Biol Phys.* Apr 1 1999;44(1):99-104.