

**Conservative Surgery and Radiation-Stage I and II Breast Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. <i>CA Cancer J Clin.</i> 2015;65(1):5-29.	Review/Other-Tx	N/A	To provide the expected numbers of new cancer cases and deaths in 2015 nationally and for each state, as well as a comprehensive overview of cancer incidence, mortality, and survival rates and trends using the most current population-based data. The article also estimates the total number of deaths averted nationally during the past 2 decades and by state in 2011 as a result of the continual decline in cancer death rates and present actual number of deaths reported in 2011 by age for the 10 leading causes of death and for the 5 leading causes of cancer death.	Cancer death rates have been continuously declining for the past 2 decades. Overall, the risk of dying from cancer decreased by 22% between 1991 and 2011. Regionally, progress has been most rapid for residents of the Northeast, among whom death rates have declined by 25% to 30%, and slowest in the South, where rates declined by about 15%. Further reductions in cancer death rates can be accelerated by applying existing cancer control knowledge across all segments of the population, with an emphasis on those in the lowest socioeconomic bracket and other disadvantaged populations.	4
2. Parviz M, Cassel JB, Kaplan BJ, et al. Breast conservation therapy rates are no different in medically indigent versus insured patients with early stage breast cancer. <i>J Surg Oncol.</i> 2003;84(2):57-62.	Observational-Tx	928 patients with early stage breast cancer (stages 0, I, and II)	To compare BCT rates in the medically indigent vs insured patients. Data collected from the institutional tumor registry and hospital's claims records were analyzed.	Patient age, race, surgeon, or insurance status did not significantly affect the rate of mastectomy. Stage I patients ( $P<0.001$ ) and those treated after 1995 had higher BCT rates (54.9% in 1993-1995 vs 70.7% in 1996-2000; $P<0.001$ ). Travel distance to a RT center had no significant impact on BCT rates, except for patients >40 miles distant. Data refute the hypothesis that socioeconomic status, as reflected by medical insurance, is a determinant of BCT in women with early stage breast cancer. Distance of <40 miles to a RT facility, stage I disease, and diagnosis after 1995 were factors associated with higher BCT rates.	2
3. Greenberg CC, Lipsitz SR, Hughes ME, et al. Institutional variation in the surgical treatment of breast cancer: a study of the NCCN. <i>Ann Surg.</i> 2011;254(2):339-345.	Review/Other-Tx	10,607 patients	To investigate the relationship between supply of subspecialty care and type of procedure preferentially performed for early stage breast cancer.	Among 10,607 patients, 19% had mastectomy alone, 60% BCS, and 21% reconstruction. The institutional rate of BCS and reconstruction were strongly correlated ( $r = -0.80$ , $P=0.02$ ). Institution was more important than all patient factors except age in predicting receipt of reconstruction or BCS. Reconstruction was more likely for patients treated at an institution with a greater supply of reconstructive surgeons or where patients live further from radiation facilities. Reconstruction was less likely at institutions with longer waiting times for surgery with reconstruction.	4

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4. NIH consensus conference. Treatment of early-stage breast cancer. <i>JAMA</i> . 1991;265(3):391-395.	Review/Other-Tx	N/A	To evaluate the treatment of early stage breast cancer by a consensus panel.	BCT preferable among eligible early stage breast cancer patients.	4
5. Arriagada R, Le MG, Guinebretiere JM, Dunant A, Rochard F, Tursz T. Late local recurrences in a randomised trial comparing conservative treatment with total mastectomy in early breast cancer patients. <i>Ann Oncol</i> . 2003;14(11):1617-1622.	Experimental-Tx	179 total patients: 88 with BCS; 91 mastectomy	A randomized trial to compare wide lumpectomy and breast RT with MRM, analyzing the variation in the effect of treatment over time.	Mean follow-up of 22 years. The risk of LR was lower during the first 5 years for the BCS group as compared with the mastectomy group, but higher after 5 years ( $P=10^{-4}$ ) for a different treatment effect over time). Late breast recurrences were more frequently observed in younger patients treated with breast-conserving treatment compared with those submitted to mastectomy. These results require confirmation in other randomized studies so that younger patients with early breast cancer can receive adequate counseling and so that a more stringent long-term follow-up policy can be adopted when breast-conserving treatment is planned.	1
6. Blichert-Toft M, Nielsen M, Duing M, et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. <i>Acta Oncol</i> . 2008;47(4):672-681.	Experimental-Tx	793 patients	A randomized study comparing the long-term efficacy of BCS vs mastectomy.	Median follow-up time of 19.6 years. The main analyses focus on the subgroup of 793 correctly randomized patients representing 70% of the complete series. 10-year recurrence free survival and 20-year OS based on intent to treat did not reveal significant differences in outcome between BCS vs mastectomy, $P=0.95$ and $P=0.10$ , respectively. Long-term data indicate that BCS in eligible patients proves as effective as mastectomy both regarding local tumor control, recurrence free survival and OS. Local failures as a first event consistent with new primaries are strongly associated with BCS, whereas true recurrence predominates after mastectomy.	1

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7. 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. <i>N Engl J Med.</i> 2002;347(16):1233-1241.	Experimental-Tx	1,851 patients assigned to: total mastectomy, lumpectomy alone, or lumpectomy and breast RT	A randomized trial to determine whether lumpectomy with or without radiation was as effective as total mastectomy in the treatment of breast cancer.	No significant differences were observed among the 3 groups of women with respect to DFS, distant-DFS, or OS. Among the lumpectomy-treated women whose surgical specimens had tumor-free margins, the HR for death among the women who underwent postoperative breast RT, as compared with those who did not, was 0.91 (95% CI, 0.77 to 1.06; $P=0.23$ ). RT was associated with a marginally significant decrease in deaths due to breast cancer. This decrease was partially offset by an increase in deaths from other causes. Lumpectomy followed by breast RT continues to be appropriate therapy for women with breast cancer, provided that the margins of resected specimens are free of tumor and an acceptable cosmetic result can be obtained.	1
8. 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. <i>N Engl J Med.</i> 2002;347(16):1227-1232.	Experimental-Tx	701 women: (349 underwent a radical (Halsted) mastectomy and 352 underwent BCS)	To compare the efficacy of radical (Halsted) mastectomy with that of BCS in a 20-year follow-up of women enrolled in a randomized study.	30 women in the group that underwent BCT had a recurrence of tumor in the same breast, whereas 8 women in the radical-mastectomy group had LRs ( $P<0.001$ ). The crude cumulative incidence of these events was 8.8% and 2.3%, respectively, after 20 years. In contrast, there was no significant difference between the 2 groups in the rates of contralateral-breast carcinomas, distant metastases, or second primary cancers. After a median follow-up of 20 years, the rate of death from all causes was 41.7% in the group that underwent BCS and 41.2% in the radical-mastectomy group ( $P=1.0$ ). The respective rates of death from breast cancer were 26.1% and 24.3% ( $P=0.8$ ).	1

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9. Litiere S, Werutsky G, Fentiman IS, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. <i>Lancet Oncol</i> . 2012;13(4):412-419.	Experimental-Tx	868 patients; 448 patients were randomized to BCT and 420 to MRM	20 year follow-up of the EORTC 10801 phase 3 randomized trial. The EORTC 10801 trial compared BCT with MRM in patients with tumors ≤5 cm and axillary node negative or positive disease.	After a median follow-up of 22.1 years (IQR 18.5–23.8), 175 patients (42%) had distant metastases in the MRM group vs 207 (46%) in the BCT group. Furthermore, 506 patients (58%) died (232 [55%] in the MRM group and 274 [61%] in the BCT group). No significant difference was observed between BCT and MRM for time to distant metastases (HR 1.13, 95% CI, 0.92–1.38; <i>P</i> =0.23) or for time to death (1.11, 0.94–1.33; 0.23). Cumulative incidence of distant metastases at 20 years was 42.6% (95% CI, 37.8–47.5) in the MRM group and 46.9% (42.2–51.6) in the BCT group. 20-year OS was estimated to be 44.5% (95% CI, 39.3–49.5) in the MRM group and 39.1% (34.4–43.9) in the BCT group. There was no difference between the groups in time to distant metastases or OS by age (time to distant metastases: <50 years 1.09 [95% CI, 0.79–1.51] vs ≥50 years 1.16 [0.90–1.50]; OS <50 years 1.17 [0.86–1.59] vs ≥50 years 1.10 [0.89–1.37]).	1
10. Simone NL, Dan T, Shih J, et al. Twenty-five year results of the national cancer institute randomized breast conservation trial. <i>Breast Cancer Res Treat</i> . 2012;132(1):197-203.	Experimental-Tx	237 women	To report the 25 year outcomes of a single institution, prospective, randomized clinical trial at the National Cancer Institute.	At a median follow-up of 25.7 years, OS was 43.8% for the MRM group and 37.9% for BCT ( <i>P</i> =0.38). Although the cumulative incidence of a DFS event was higher in BCT patients (29.0% MRM vs 56.4% BCT, <i>P</i> =0.0017), the additional treatment failures were primarily isolated IBTRs requiring salvage mastectomy. 22.3% of BCT patients experienced an IBTR. Distant disease and second cancers were similar in both arms. After 25 years, long term survival between BCT and MRM continues to be similar in patients treated for early stage breast cancer. Patients receiving BCT may be at risk for additional treatment-related morbidity, which may occur as a late event.	1

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11. Vicini FA, Antonucci JV, Goldstein N, et al. The use of molecular assays to establish definitively the clonality of ipsilateral breast tumor recurrences and patterns of in-breast failure in patients with early-stage breast cancer treated with breast-conserving therapy. <i>Cancer</i> . 2007;109(7):1264-1272.	Observational-Tx	29 patients	To evaluate BCT outcomes compared to those produced by mastectomy.	Clonally related IBTRs were more frequently higher grade (72.2% vs 14.3%; $P=0.009$ ) and developed sooner after initial treatment (mean time to IBTR, 4.04 years in clonally related IBTRs vs 9.25 years in clonally different IBTRs; $P=0.002$ ). Clinical IBTR classification and molecular clonality assay results differed in 30% of all patients. The proportion of IBTRs that were related clonally at 5 years, 10 years, and 15 years after BCT were 93%, 67%, and 33%, respectively. Clinical classifications of IBTRs were unreliable methods for determining clonality in many patients. Molecular clonality assays provided a reliable means of identifying patients who may benefit from aggressive systemic therapy at the time of IBTR and also provided a more accurate assessment of the efficacy of various forms of local therapy.	2
12. Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. <i>J Clin Oncol</i> . 2002;20(20):4141-4149.	Experimental-Tx	1,009 total women: 336 tamoxifen; 336 RT and placebo; 337 RT and tamoxifen	Randomized trial to determine whether tamoxifen, RT or both are needed for breast RT after lumpectomy in node-negative women with invasive breast cancers.	RT and placebo resulted in a 49% lower hazard rate of IBTR than did tamoxifen alone; RT and tamoxifen resulted in a 63% lower rate than did RT and placebo. When compared with tamoxifen alone, RT plus tamoxifen resulted in an 81% reduction in hazard rate of IBTR. Cumulative incidence of IBTR through 8 years was 16.5% with tamoxifen, 9.3% with RT and placebo, and 2.8% with RT and tamoxifen. RT reduced IBTR below the level achieved with tamoxifen alone, regardless of ER status. Distant treatment failures were infrequent and not significantly different among the groups ( $P=.28$ ). When tamoxifen-treated women were compared with those who received RT and placebo, there was a significant reduction in CBC (HR, 0.45; 95% CI, 0.21–0.95; $P=.039$ ). Survival in the 3 groups was 93%, 94%, and 93%, respectively ( $P=.93$ ). In women with tumors $\leq 1$ cm, IBTR occurs with enough frequency after lumpectomy to justify considering RT, regardless of tumor ER status, and tamoxifen plus RT when tumors are ER positive.	1

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13. Fyles AW, McCreedy DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. <i>N Engl J Med.</i> 2004;351(10):963-970.	Experimental-Tx	769 total women with early breast cancer randomized to receive: 386 breast RT plus tamoxifen; 383 tamoxifen alone	Randomized study to determine the effect of breast RT plus tamoxifen on DFS and local relapse in women 50 years of age or older who had T1 or T2 node-negative breast cancer.	The rate of local relapse at 5 years was 7.7 % in the tamoxifen group and 0.6 % in the group given tamoxifen plus RT (HR, 8.3; 95% CI, 3.3–21.2; $P < 0.001$ ), with corresponding 5-year DFS rates of 84% and 91% ( $P = 0.004$ ). A planned subgroup analysis of 611 women with T1, receptor-positive tumors indicated a benefit from RT (5-year rates of local relapse, 0.4% with tamoxifen plus RT and 5.9% with tamoxifen alone; $P < 0.001$ ). Overall, there was a significant difference in the rate of axillary relapse at 5- years (2.5% in the tamoxifen group and 0.5% in the group given tamoxifen plus RT, $P = 0.049$ ), but no significant difference in the rates of distant relapse or OS. As compared with tamoxifen alone, RT plus tamoxifen significantly reduces the risk of breast and axillary recurrence after lumpectomy in women with small, node-negative, hormone-receptor-positive breast cancers.	1
14. Liljegren G, Holmberg L, Bergh J, et al. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. <i>J Clin Oncol.</i> 1999;17(8):2326-2333.	Experimental-Tx	381 total women: 184 randomized to receive postoperative RT to the breast (RT group); 197 women received no further treatment (non-RT group)	To study the long-term effectiveness of postoperative RT after sector resection for breast cancer in a randomized trial in which mammography is a major pathway to diagnosis.	The LR rate was 8.5% (95% CI, 3.9%–13.1%) in the RT group and 24.0% (95% CI, 17.6%–30.4%) in the non-RT group ( $P = .0001$ ). Survival free from regional and distant recurrence was 83.3% in the RT group (95% CI, 77.5%–89.1%) and 80.0% in the non-RT group (95% CI, 73.9%–86.1%) ( $P = .23$ ). OS was 77.5% in the RT group (95% CI, 70.9%–84.1%) and 78% in the non-RT group (95% CI, 71.7%–84.3%) ( $P = .99$ ). A subgroup analysis suggested that women >55 years of age without comedo or lobular carcinomas had a low-risk of LR of 6.1% (95% CI, 0.1%–9.1%) in the RT-group and 11.0% (4.0%–18.0%) in the non-RT group ( $P = .16$ ). Sector resection plus RT resulted in an absolute reduction in LR of 16% at 10 years compared with surgery alone. Women >55 years of age without comedo or lobular carcinomas may have a low-risk of LR. Postoperative RT was not shown to reduce distant recurrences or improve OS.	1

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15. Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. <i>Ann Oncol.</i> 2001;12(7):997-1003.	Experimental-Tx	579 total patients: 299 quadrantectomy, axillary dissection and RT; 280 quadrantectomy with axillary dissection without RT	A randomized trial to compare quadrantectomy followed by RT to same surgical procedure without RT.	The number of IBTR was significantly higher in patients treated with surgery alone than in patients treated with surgery plus RT. The difference in IBTR frequency between the 2 treatments appeared to be particularly high in women up to 45 years of age, tending to decrease with increasing age up to no apparent difference in women >65 years. OS curves for the 2 groups, did not differ significantly ( $P=0.326$ ). However, a limited survival advantage was evident after RT for node-positive women. After BCS, RT appears indicated in all patients up to 55 years of age, in patients with positive axillary nodes, and in patients with extensive intraductal component at histology. The data suggest that RT may be avoided in patients >65, and may be optional in women aged 56-65 years with negative nodes.	1
16. Holli K, Hietanen P, Saaristo R, Huhtala H, Hakama M, Joensuu H. Radiotherapy after segmental resection of breast cancer with favorable prognostic features: 12-year follow-up results of a randomized trial. <i>J Clin Oncol.</i> 2009;27(6):927-932.	Experimental-Tx	264 patients	To evaluate the efficacy of RT in the prevention of LR in a patient population that had small-size breast cancer with features that suggested low biologic aggressiveness.	16 (11.6%) and 34 (27.2%) cancers recurred locally in the RT and the control arms, respectively ( $P=.0013$ ). Time to LR was longer in the RT arm (HR, 0.36; 95% CI, 0.20 to 0.65; $P=.00071$ ). 21 patients assigned to RT and 26 assigned to control died during the follow-up. There were no differences in OS time (HR, 0.63; 95% CI, 0.35 to 1.12; $P=.11$ ), distant DFS ( $P=.94$ ), or breast cancer-specific survival ( $P=.56$ ) between the RT and control groups.	1
17. Stewart HJ, Prescott RJ, Forrest AP. Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. <i>J Natl Cancer Inst.</i> 2001;93(6):456-462.	Experimental-Tx	1,323 patients randomized; (667 to the adjuvant arm and 656 to the control arm)	To report updated results of the Scottish adjuvant tamoxifen trial after a median follow-up of 15 years. The purpose of this trial was to assess the effect of tamoxifen given to patients with breast cancer immediately after mastectomy (or mastectomy + RT) (adjuvant arm) or only after the patients had had a relapse (control arm).	The beneficial effect of adjuvant tamoxifen given for 5 years on the probability of total survival ( $P=.006$ ), systemic relapse ( $P=.007$ ), and death from breast cancer ( $P=.002$ ) has been maintained through 15 years. No additional benefit was observed in those randomly assigned to continue taking tamoxifen beyond 5 years.	1

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18. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. <i>J Clin Oncol.</i> 2013;31(19):2382-2387.	Observational-Tx	711 patients	To determine the risk of IBEs in patients with DFS treated with local excision without irradiation.	With a median follow-up of 6.2 years, the 5-year rate of IBEs in the 565 eligible patients in the low/intermediate grade stratum was 6.1% (95% CI, 4.1% to 8.2%). With a median follow-up of 6.7 years, this incidence for the 105 eligible patients in the high-grade stratum was 15.3% (95% CI, 8.2% to 22.5%).	1
19. Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. <i>J Natl Cancer Inst.</i> 2004;96(2):115-121.	Review/Other-Tx	15 trials with a pooled total of 9,422 patients	Pooled analysis of randomized clinical trials to determine whether RT or its omission after BCS has measurable consequences on local tumor growth and patient survival.	The relative risk of IBTR after BCS, comparing patients treated with no RT or RT, was 3.00 (95% CI, 2.65–3.40). Mortality data were available for 13 trials with a pooled total of 8,206 patients. The RR of mortality was 1.086 (95% CI, 1.003–1.175), corresponding to an estimated 8.6% (95% CI, 0.3%–17.5%) relative excess mortality if RT was omitted. Omission of RT is associated with a large increase in risk of IBTR and with a small increase in the risk of patient mortality.	4

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<p>20. Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. <i>Lancet</i>. 2011;378(9804):1707-1716.</p>	<p>Review/Other-Tx</p>	<p>10,801 women in 17 randomized trials</p>	<p>Meta-analysis was performed to determine the effect of RT after BCS on 10-year recurrence and 15-year breast cancer death.</p>	<p>Overall, RT reduced the 10-year risk of any (ie, locoregional or distant) first recurrence from 35.0% to 19.3% (absolute reduction 15.7%, 95% CI, 13.7–17.7, <math>2P &lt; 0.00001</math>) and reduced the 15-year risk of breast cancer death from 25.2% to 21.4% (absolute reduction 3.8%, 1.6–6.0, <math>2P = 0.00005</math>). In women with pN0 disease (n=7287), RT reduced these risks from 31.0% to 15.6% (absolute recurrence reduction 15.4%, 13.2–17.6, <math>2P &lt; 0.00001</math>) and from 20.5% to 17.2% (absolute mortality reduction 3.3%, 0.8–5.8, <math>2P = 0.005</math>), respectively. In these women with pN0 disease, the absolute recurrence reduction varied according to age, grade, ER status, tamoxifen use, and extent of surgery, and these characteristics were used to predict large (<math>\geq 20\%</math>), intermediate (10%–19%), or lower (<math>&lt; 10\%</math>) absolute reductions in the 10-year recurrence risk. Absolute reductions in 15-year risk of breast cancer death in these 3 prediction categories were 7.8% (95% CI, 3.1–12.5), 1.1% (-2.0 to 4.2), and 0.1% (-7.5 to 7.7) respectively (trend in absolute mortality reduction <math>2P = 0.03</math>). In the few women with pN+ disease (n=1050), RT reduced the 10-year recurrence risk from 63.7% to 42.5% (absolute reduction 21.2%, 95% CI, 14.5–27.9, <math>2P &lt; 0.00001</math>) and the 15-year risk of breast cancer death from 51.3% to 42.8% (absolute reduction 8.5%, 1.8–15.2, <math>2P = 0.01</math>). Overall, about 1 breast cancer death was avoided by year 15 for every 4 recurrences avoided by year 10, and the mortality reduction did not differ significantly from this overall relationship in any of the 3 prediction categories for pN0 disease or for pN+ disease.</p>	<p>4</p>

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21. 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. <i>Lancet</i> . 2005;366(9503):2087-2106.	Review/Other-Tx	42,000 patients in 78 randomized studies	To determine the variations in local treatment that affects the risk of LRR through a meta-analysis of previous studies.	About three-quarters of the eventual LR risk occurred during the first 5-years. In the comparisons that involved little (<10%) difference in 5-year LR risk there was little difference in 15-year breast cancer mortality. Among the 25,000 women in the comparisons that involved substantial (>10%) differences, however, 5-year LR risks were 7% active vs 26% control (absolute reduction 19%), and 15-year breast cancer mortality risks were 44.6% vs 49.5%. Improved local control may lead to decrease in breast cancer-specific mortality. Avoidance of a LR in a conserved breast (after BCT and radiation) and avoidance of a LR elsewhere (ie, the chest wall or regional nodes) after mastectomy are of comparable relevance to 15 year breast cancer mortality.	4
22. Berrington de Gonzalez A, Curtis RE, Gilbert E, et al. Second solid cancers after radiotherapy for breast cancer in SEER cancer registries. <i>Br J Cancer</i> . 2010;102(1):220-226.	Observational-Tx	182,057 survivors of breast cancer	To evaluate long-term second cancer risks among 182,057 5-year survivors of locoregional invasive breast cancer diagnosed between 1973 and 2000 and reported to U.S. NCI-SEER Program cancer registries.	By the end of 2005 (median follow-up=13.0 years), 15 498 second solid cancers had occurred, including 6,491 CBCs. The RRs for RT were 1.45 (95% CI=1.33–1.58) for high-dose second cancer sites (1+ Gy: lung, esophagus, pleura, bone and soft tissue) and 1.09 (1.04–1.15) for CBC (approximately 1 Gy). These risks decreased with increasing age and year of treatment. There was no evidence of elevated risks for sites receiving medium (0.5–0.99 Gy, RR=0.89 (0.74–1.06)) or low doses (<0.5 Gy, RR=1.01 (0.95–1.07)). The estimated excess cases of cancer in women treated with RT were as follows: 176 (95% CI=69–284) CBCs or 5% (2%–8%) of the total in all 1+ year survivors, and 292 (222–362) other solid cancers or 6% (4%–7%) of the total.	2

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23. Zhang W, Becciolini A, Biggeri A, Pacini P, Muirhead CR. Second malignancies in breast cancer patients following radiotherapy: a study in Florence, Italy. <i>Breast Cancer Res.</i> 2011;13(2):R38.	Observational-Tx	5,248 women	To evaluate the effect that RT may have had on the subsequent risk of second malignancies, including the possible influences of age at treatment and menopausal status.	This study indicated an increased relative risk of all second cancers combined following RT (1.22, 95% CI: 0.88 to 1.69). The increased relative risk appeared 5 or more years after RT and appeared to be highest amongst women treated after the menopause (1.61, 95% CI: 1.13 to 2.29). Increased relative risks were observed specifically for leukemia (8.13, 95% CI: 0.96 to 69.1) and other solid cancers (1.84, 95% CI: 1.06 to 3.16), excluding CBC. For CBC, no raised relative risk was observed during the period more than 5 years after RT.	2
24. Meric F, Buchholz TA, Mirza NQ, et al. Long-term complications associated with breast-conservation surgery and radiotherapy. <i>Ann Surg Oncol.</i> 2002;9(6):543-549.	Observational-Tx	294 patients	To evaluate the long-term complications of BCS plus RT.	BCS plus RT was associated with grade 2 or higher complications in only 9.9% of patients. Half of these complications were attributable to axillary dissection, it is hoped that lower complication rates can be achieved with SLN biopsy. BCS and RT are associated with grade 2 or greater complications in only 9.9% of patients. Nearly half of these complications are attributable to axillary dissection.	2
25. Coen JJ, Taghian AG, Kachnic LA, Assaad SI, Powell SN. Risk of lymphedema after regional nodal irradiation with breast conservation therapy. <i>Int J Radiat Oncol Biol Phys.</i> 2003;55(5):1209-1215.	Observational-Tx	727 stage I-II patients	To retrospectively evaluate the risk factors for lymphedema in patients receiving BCT for early-stage breast cancer.	Median follow-up was 72 months. The 10-year actuarial incidence for persistent arm lymphedema was 4.1%. The median time to edema was 39 months. The 10-year risk was 1.8% for breast RT alone vs 8.9% for breast and regional nodal RT ( $P=0.001$ ). Most patients underwent Level I or II dissection. In this subgroup, the lymphedema risk at 10 years was 10.7% for breast and regional nodal RT vs 1.0% for breast RT alone ( $P=0.0003$ ). Nodal RT was the only significant risk factor for arm lymphedema in patients receiving BCT for early-stage breast cancer. The data suggest that this risk is low with Level I/II dissection and breast RT. However, even after the addition of RT to the axilla and supraclavicular fossa, the development of lymphedema was only 1 in 10, lower than generally recognized.	2

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26. Hill-Kayser CE, Vachani C, Hampshire MK, Di Lullo GA, Metz JM. Cosmetic outcomes and complications reported by patients having undergone breast-conserving treatment. <i>Int J Radiat Oncol Biol Phys.</i> 2012;83(3):839-844.	Review/Other-Tx	1,763 breast cancer survivorship care plans	Report on breast cancer survivors who voluntarily used an anonymous, internet-based tool for creation of survivorship care plans with regard to their own cosmetic outcomes and perceived complications after BCT.	354 breast cancer survivors having undergone BCT and voluntarily using this tool were queried with regard to breast cosmesis and perceived late effects. Median diagnosis age was 48 years, and median current age 52 years. "Excellent" cosmesis was reported by 27% (n = 88), "Good" by 44% (n = 144), "Fair" by 24% (n = 81), and "Poor" by 5% (n = 18). Of the queries posted to survivors after BCT, late effects most commonly reported were cognitive changes (62%); sexual concerns (52%); changes in texture and color of irradiated skin (48%); chronic pain, numbness, or tingling (35%); and loss of flexibility in the irradiated area (30%). Survivors also described osteopenia/osteoporosis (35%), cardiopulmonary problems (12%), and lymphedema (19%).	4
27. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. <i>N Engl J Med.</i> 2010;362(6):513-520.	Experimental-Tx	1,234 patients	To determine whether a hypofractionated 3-week schedule of WBI is as effective as a 5-week schedule.	The risk of LR at 10 years was 6.7% among the 612 women assigned to standard irradiation as compared with 6.2% among the 622 women assigned to the hypofractionated regimen (absolute difference, 0.5 percentage points; 95% CI, -2.5 to 3.5). At 10 years, 71.3% of women in the control group as compared with 69.8% of the women in the hypofractionated-radiation group had a good or excellent cosmetic outcome (absolute difference, 1.5 percentage points; 95% CI, -6.9 to 9.8).	1

Conservative Surgery and Radiation-Stage I and II Breast Cancer  
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
28. Lazovich D, Solomon CC, Thomas DB, Moe RE, White E. Breast conservation therapy in the United States following the 1990 National Institutes of Health Consensus Development Conference on the treatment of patients with early stage invasive breast carcinoma. <i>Cancer</i> . 1999;86(4):628-637.	Observational-Tx	10,9880 women	To evaluate the national use of breast conservation therapy before and after the National Institutes of Health (NIH) Consensus Development Conference to determine whether the conference had had an impact on utilization.	From 1985 (the year that the U.S. randomized controlled trial demonstrating equivalent efficacy between BCT and mastectomy was published) through 1989, approximately 35% of women with stage I and 19% of women with stage II breast carcinoma underwent BCS; these percentages remained constant throughout this period. Beginning in 1990, the year of the NIH Consensus Development Conference, the use of BCS increased in each subsequent year; by 1995, 60% of women with stage I and 39% of women with stage II breast carcinoma received such treatment. However, regional variation in use was observed (stage I, range 41.4%–71.4% for 1995) and no registry reported BCT for the majority of women with stage II disease (range, 23.8%–48.0%). The use of postoperative RT for women who underwent BCS was similar in the periods before and after the conference.	3
29. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. <i>Ann Surg</i> . 2013;257(2):249-255.	Review/Other-Tx	9 studies	Meta-analysis was performed to examine the effect of preoperative MRI compared with standard preoperative assessment on surgical outcomes, focusing on studies that used a controlled design.	There were 9 eligible studies (2 randomized trials; 7 comparative cohorts). Outcomes in 3,112 patients with breast cancer (any histological tumor type) for MRI vs no-MRI (referent) were as follows: initial mastectomy 16.4% vs 8.1% [OR, 2.22 ( $P<0.001$ ); adjusted OR, 3.06 ( $P<0.001$ ); re-excision after initial breast conservation 11.6% vs 11.4% [OR, 1.02 ( $P=0.87$ ); adjusted OR, 0.95 ( $P=0.71$ )]; overall mastectomy 25.5% vs 18.2% [OR, 1.54 ( $P<0.001$ ); adjusted OR, 1.51 ( $P<0.001$ )]. In 766 patients with ILC, outcomes were as follows: initial mastectomy 31.1% vs 24.9% [OR, 1.36 ( $P=0.056$ ); adjusted OR, 2.12 ( $P=0.008$ )]; re-excision after initial breast conservation 10.9% vs 18.0% [OR, 0.56 ( $P=0.031$ ); adjusted OR, 0.56 ( $P=0.09$ )]; overall mastectomy 43.0% vs 40.2% [OR, 1.12 ( $P=0.45$ ); adjusted OR, 1.64 ( $P=0.034$ )].	4

**Conservative Surgery and Radiation-Stage I and II Breast Cancer  
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Hylton N. Magnetic resonance imaging of the breast: opportunities to improve breast cancer management. <i>J Clin Oncol.</i> 2005;23(8):1678-1684.	Review/Other-Dx	N/A	Review the current clinical applications for breast MRI and emerging areas where MRI has the potential to change and improve breast cancer management.	As an adjunct to mammography and US, MRI can be a valuable addition to the workup of a breast abnormality or biopsy-proven cancer. MRI has the advantages of providing a 3-D view of the breast, performing with high sensitivity in dense breast tissue and using nonionizing radiation. MRI has significant disadvantages as well, including its high cost, variability in performance, and moderate specificity that, in combination with high sensitivity, often leads to unnecessary workup.	4
31. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. <i>CA Cancer J Clin.</i> 2007;57(2):75-89.	Review/Other-Dx	N/A	Guidelines for breast screening with MRI as an adjunct to mammography.	Screening MRI is recommended for women with an approximately 20%–25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease. There are several risk subgroups for which the available data are insufficient to recommend for or against screening, including women with a personal history of breast cancer, carcinoma in situ, atypical hyperplasia, and extremely dense breasts on mammography.	4

Conservative Surgery and Radiation-Stage I and II Breast Cancer  
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. <i>J Clin Oncol.</i> 2008;26(19):3248-3258.	Review/Other-Dx	19 studies	Systematic review and meta-analysis of the accuracy of MRI in detection of multifocal and/or multicentric cancer not identified on conventional imaging.	Results data studies showed MRI detects additional disease in 16% of women with breast cancer (n=2,610). MRI incremental accuracy differed according to the reference standard ( $P=.016$ ) decreasing from 99% to 86% as the quality of the reference standard increased. Summary positive predictive value was 66% (95% CI, 52%–77%) and true-positive: false positive ratio was 1.91 (95% CI, 1.09-3.34). Conversion from wide local excision to mastectomy was 8.1% (95% CI, 5.9-11.3), from wide local excision to more extensive surgery was 11.3% in multifocal/multicentric disease (95% CI, 6.8–18.3). Due to MRI-detected lesions (in women who did not have additional malignancy on histology) conversion from wide local excision to mastectomy was 1.1% (95% CI, 0.3–3.6) and from wide local excision to more extensive surgery was 5.5% (95% CI, 3.1–9.5).	4
33. Sorbero ME, Dick AW, Beckjord EB, Ahrendt G. Diagnostic breast magnetic resonance imaging and contralateral prophylactic mastectomy. <i>Ann Surg Oncol.</i> 2009;16(6):1597-1605.	Observational-Dx	3,606 total women diagnosed with stage 0-III breast cancer: 1,743 from 1998–2000 (early period); 1,863 from 2003–2005 (late period)	To examine the relationships between breast MRI and therapeutic and contralateral prophylactic mastectomy in women with breast cancer. Women were retrospectively identified.	14.2% of women underwent MRI, 29.0% had mastectomy, and 5.3% had contralateral prophylactic mastectomy. Use of breast MRI increased substantially between the 2 time periods (4.1%–23.7%, $P<0.001$ ). Mastectomy rates increased from 28%–30% ( $P>0.05$ ). The rate of contralateral prophylactic mastectomy increased by >50% from the early-late period (4.1%–6.4%, $P<0.002$ ). Women who underwent MRI were nearly twice as likely to have contralateral prophylactic mastectomy (9.2 vs 4.7%, $P<0.001$ ). Multivariate models found MRI was associated with increased rates of contralateral prophylactic mastectomy for women with stage I or II disease (OR 2.04, $P=0.001$ ). MRI changes the surgical treatment of breast cancer among subsets of women diagnosed with breast cancer, suggesting there are hidden monetary and nonmonetary costs associated with its use.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Bleicher RJ, Ciocca RM, Egleston BL, et al. Association of routine pretreatment magnetic resonance imaging with time to surgery, mastectomy rate, and margin status. <i>J Am Coll Surg.</i> 2009;209(2):180-187; quiz 294-185.	Observational-Tx	577 patients	To retrospectively characterize breast cancer patients receiving MRI vs those who did not, and report on their short-term surgical outcomes, including time to operation, margin status, and mastectomy rate.	The OR for mastectomy, controlling for T size and stage, was 1.80 after MRI vs no MRI ( $P=0.024$ ). Breast MRI use was not confined to any particular patient group. MRI use was not associated with improved margin status or BCT attempts, but was associated with a treatment delay and increased mastectomy rate. Without evidence of improved oncologic outcomes as a result, the study does not support the routine use of MRI to select patients or facilitate the performance of BCT.	2
35. Houssami N, Turner R, Macaskill P, et al. An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence. <i>J Clin Oncol.</i> 2014;32(5):392-401.	Review/Other-Tx	4 studies	To examine the association between preoperative MRI and LR as primary outcome, as well as distant recurrence, in patients with breast cancer.	4 eligible studies contributed individual person data on 3,180 affected breasts in 3,169 subjects (median age, 56.2 years). 8-year LR-free survival did not differ between the MRI (97%) and no-MRI (95%) groups ( $P=.87$ ), and the multivariable model showed no significant effect of MRI on LR-free survival: HR for MRI (vs no-MRI) was 0.88 (95% CI, 0.52 to 1.51; $P=.65$ ); age, margin status, and tumor grade were associated with LR-free survival (all $P<.05$ ). HR for MRI was 0.96 (95% CI, 0.52 to 1.77; $P=.90$ ) in sensitivity analysis. 8-year distant recurrence-free survival did not differ between the MRI (89%) and no-MRI (93%) groups ( $P=.37$ ), and the multivariable model showed no significant effect of MRI on distant recurrence-free survival: HR for MRI (vs no-MRI) was 1.18 (95% CI, 0.76 to 2.27; $P=.48$ ) or 1.31 (95% CI, 0.76 to 2.27; $P=.34$ ) in sensitivity analysis.	4

**Conservative Surgery and Radiation-Stage I and II Breast Cancer  
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Cutuli B, Kanoun S, Tunon De Lara C, et al. Breast cancer occurred after Hodgkin's disease: clinico-pathological features, treatments and outcome: analysis of 214 cases. <i>Crit Rev Oncol Hematol</i> . 2012;81(1):29-37.	Observational-Tx	189 women	To describe the largest series on detailed clinical and histological features of breast cancer occurring after Hodgkin disease treatment.	With a 50-month median follow-up, LR occurred in 12% of the tumors (9% after mastectomy, 21% after lumpectomy alone and 13.7% after lumpectomy with RT). Metastasis occurred in 47 (26%) patients. The risk factors were pN+, pT, high SBR grade and young age (<50 years). The 10-year OS and specific survival rates were 53% and 63.5%, respectively. The 10-year specific survival rates were 79% for pT0T1T2, 48% for pT3T4 ( $P=0.0002$ ) and 79% for pN0 vs 38.5% for pN+ ( $P=0.00026$ ). Among 67 deaths, 43 (73%) were due to breast cancer.	2
37. Haberer S, Belin L, Le Scodan R, et al. Locoregional treatment for breast carcinoma after Hodgkin's lymphoma: the breast conservation option. <i>Int J Radiat Oncol Biol Phys</i> . 2012;82(2):e145-152.	Observational-Tx	72 women	To report clinical and pathologic characteristics and outcome of breast cancer after irradiation for Hodgkin's lymphoma in women treated at the Institut Curie, with a special focus on the breast-conserving option.	With a median follow-up of 7 years, 5-year OS rate and locoregional control rate were, respectively, 74.5% (95% CI, 64%–88%) and 82% (95% CI, 72%–93%) for invasive carcinoma and 100% (95% CI, 100%–100%) and 92% (95% CI, 79%–100%) for in situ carcinoma. In patients with invasive tumors, the 5-year distant DFS rate was 79% (95% CI, 69%–91%), and 13 patients died of progressive breast cancer. CBC was diagnosed in 10 patients (14%).	2
38. Lin A, Abu-Isa E, Griffith KA, Ben-Josef E. Toxicity of radiotherapy in patients with collagen vascular disease. <i>Cancer</i> . 2008;113(3):648-653.	Observational-Tx	86 RT courses for 73 patients	To identify factors that influence RT toxicity in the setting of collagen vascular disease.	There was no significant difference between collagen vascular disease patients (65.1%) and controls (72.5%) experiencing any acute toxicity. Collagen vascular disease patients had a higher incidence of any late toxicity (29.1% vs 14%; $P=.001$ ), and a trend toward an increased rate of severe late toxicity (9.3% vs 3.7%; $P=.079$ ). RT delivered to the breast had increased risk of severe acute toxicity, whereas RT to the pelvis had increased risk of severe acute and late toxicity. RT administered in the setting of scleroderma carried a higher risk of severe late toxicity, whereas RT to systemic lupus erythematosus patients carried a higher risk of severe acute and late toxicity.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. Chen AM, Obedian E, Haffty BG. Breast-conserving therapy in the setting of collagen vascular disease. <i>Cancer J.</i> 2001;7(6):480-491.	Observational-Tx	36 patients	To determine whether women with pre-existing collagen vascular disease have an increased incidence of complications after BCT.	With a median clinical follow-up time of 12.5 years (range, 3.0–22.5 years), no significant difference was detected between the collagen vascular disease and control groups with respect to acute complications (14% vs 8%). With respect to late complications, a significant difference was observed (17% vs 3%) between the 2 groups. However, when patients in the collagen vascular disease group were analyzed by specific disease, this significance disappeared in all but the scleroderma group.	2
40. Yerushalmi R, Tyldesley S, Woods R, Kennecke HF, Speers C, Gelmon KA. Is breast-conserving therapy a safe option for patients with tumor multicentricity and multifocality? <i>Ann Oncol.</i> 2012;23(4):876-881.	Observational-Tx	19,754 women	To compare outcomes after BCT and mastectomy in multicentric/multifocal vs unifocal breast cancer.	Median follow-up was 7.9 years, 11,983 having BCT (unifocal: 11,683, multicentric/multifocal: 300) and 7,771 having mastectomy (unifocal: 6884, multicentric/multifocal: 887). Multicentric/multifocal patients treated with BCT were 50-69 years old, free of extensive ductal carcinoma in situ, and had smaller tumors. The cumulative 10-year LR rates among unifocal and multicentric/multifocal disease were 4.6% [95% CI, 4.1% to 5.0%] vs 5.5% (95% CI, 2.6% to 9.9%) for the BCT group, $P=0.76$ and 5.8% (95% CI, 5.2% to 6.5%) vs 6.5% (95% CI, 4.7% to 8.7%) for the mastectomy group, $P=0.77$ . Multicentric/multifocal was not a significant factor for relapse or survival on multivariate analyses. In the matched analysis, relapse rates were similar in the unifocal and multicentric/multifocal groups, $P=0.60$ .	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. Carpenter S, Fraser J, Fleming M, Gray R, Halyard M, Pockaj B. Optimal treatment of multiple ipsilateral primary breast cancers. <i>Am J Surg.</i> 2008;196(4):530-536.	Observational-Tx	149 patients	A retrospective review to evaluate the success of BCT for patients with multiple ipsilateral invasive breast cancers.	Preoperatively, multiple tumors were suspected in more mastectomy patients than BCT patients (75% vs 62%). 55% of patients with tumors within 1 quadrant underwent BCT vs 10% of patients with tumors in more than 1 quadrant. 108 patients underwent SLN biopsy. 27% percent (34) were SLN positive. There were no regional recurrences among the SLN-negative patients. The locoregional BCT recurrence rate was 3.4%. Multiple ipsilateral invasive breast cancers patients can safely undergo BCT with low recurrence risk. SLN biopsy can be performed with minimal risk of regional recurrence.	3
42. Stegman LD, Beal KP, Hunt MA, Fornier MN, McCormick B. Long-term clinical outcomes of whole-breast irradiation delivered in the prone position. <i>Int J Radiat Oncol Biol Phys.</i> 2007;68(1):73-81.	Observational-Tx	245 total patients with 248 early-stage or in situ cancers	To evaluate retrospectively the effectiveness and toxicity of post-lumpectomy WBI delivered with prone positioning.	Median follow-up of 4.9 years. 5 year actuarial true local and elsewhere IBTR rates were 4.8% and 1.3%, respectively. The 5-year actuarial rates of regional nodal recurrence and distant metastases were 1.6% and 7.4%. Actuarial DFS, disease-specific, and OS rates at 5 years were 89.4%, 97.3%, and 93%, respectively. Treatment breaks were required by 2.4% of patients. Grade 3 acute dermatitis and edema were each limited to 2% of patients. Only 4.9% of patients complained of acute chest wall discomfort. Chronic Grade 2 to 3 skin and subcutaneous tissue toxicities were reported in 4.4% and 13.7% of patients, respectively. Prone position breast radiation results in similar long-term disease control with a favorable toxicity profile compared with standard supine tangents. The anatomic advantages of prone positioning may contribute to improving the therapeutic ratio of post-lumpectomy radiation by improving dose homogeneity and minimizing incidental cardiac and lung dose.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
43. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. <i>J Clin Oncol.</i> 2008;26(5):778-785.	Experimental-Tx	1,493 total patients: 751 preoperative doxorubicin and cyclophosphamide; 742 postoperative doxorubicin and cyclophosphamide	To determine whether 4 cycles of doxorubicin and cyclophosphamide administered preoperatively improved breast cancer DFS and OS compared with doxorubicin and cyclophosphamide administered postoperatively.	There were trends in favor of preoperative chemotherapy for DFS and OS in women <50 years old (HR = 0.85, $P=.09$ for DFS; HR = 0.81, $P=.06$ for OS). DFS conditional on being event free for 5 years also demonstrated a strong trend in favor of the preoperative group (HR = 0.81, $P=.053$ ). Protocol B-27 results demonstrated that the addition of docetaxel to doxorubicin and cyclophosphamide did not significantly impact DFS or OS. Preoperative docetaxel added to doxorubicin and cyclophosphamide significantly increased the proportion of patients having pathologic complete responses compared with preoperative doxorubicin and cyclophosphamide alone (26% vs 13%, respectively; $P<.0001$ ). In both studies, patients who achieved a pathologic complete response continue to have significantly superior DFS and OS outcomes compared with patients who did not. Protocols B-18 and B-27 demonstrate that preoperative therapy is equivalent to adjuvant therapy. B-27 also showed that the addition of preoperative taxanes to doxorubicin and cyclophosphamide improves response.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
44. Arvold ND, Taghian AG, Niemierko A, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. <i>J Clin Oncol.</i> 2011;29(29):3885-3891.	Observational-Tx	1,434 consecutive patients	To characterize the risk of LR after BCT in the current era according to both age and breast cancer subtype.	Median follow-up was 85 months. Overall 5-year cumulative incidence of LR was 2.1% (95% CI, 1.4% to 3.0%). The 5-year cumulative incidence of LR was 5.0% (95% CI, 3.0% to 8.3%) for age quartile 23 to 46 years; 2.2% (95% CI, 1.0% to 4.6%) for ages 47 to 54 years; 0.9% (95% CI, 0.3% to 2.6%) for ages 55 to 63 years; and 0.6% (95% CI, 0.1% to 2.2%) for ages 64 to 88 years. The 5-year cumulative incidence of LR was 0.8% (95% CI, 0.4% to 1.8%) for luminal A; 2.3% (95% CI, 0.8% to 5.9%) for luminal B; 1.1% (95% CI, 0.2% to 7.4%) for luminal HER2; 10.8% (95% CI, 4.6% to 24.4%) for HER2; and 6.7% (95% CI, 3.6% to 12.2%) for triple negative. On multivariable analysis, increasing age was associated with decreased risk of LR (adjusted HR, 0.97; 95% CI, 0.94 to 0.99; $P=0.009$ ).	2
45. 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. <i>J Clin Oncol.</i> 2007;25(22):3259-3265.	Experimental-Tx	5,318 patients: 2,661 boost dose of 16 Gy; 2,657 no boost dose	A randomized trial to investigate the long-term impact of a boost radiation dose of 16 Gy on local control, fibrosis, and OS for patients with stage I and II breast cancer who underwent BCT.	Boost with improved LR but there was no difference in OS. The 10 year LRR risk in patient's $\leq 40$ years old after RT with boost was 13.5% vs 3.8% for those greater than 60 years old.	1

Conservative Surgery and Radiation-Stage I and II Breast Cancer  
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
46. Sharma R, Bedrosian I, Lucci A, et al. Present-day locoregional control in patients with t1 or t2 breast cancer with 0 and 1 to 3 positive lymph nodes after mastectomy without radiotherapy. <i>Ann Surg Oncol</i> . 2010;17(11):2899-2908.	Observational-Tx	1,019 total patients with pT1 or pT2 tumors and zero positive lymph nodes n=753; 1 positive lymph node n=176; 2 positive lymph nodes n=69; 3 positive lymph nodes n=21	To determine present-day LRR rates to better understand the role of postmastectomy RT in women with 0 to 3 positive lymph nodes.	After a median follow-up of 7.47 years, the overall 10-year LRR rate was 2.7%. The only independent predictor of LRR was younger age ( $P=0.004$ ). Patient's $\leq 40$ years old had a 10-year LRR rate of 11.3% vs 1.5% for older patients ( $P<0.0001$ ). The 10-year rate of LRR in patients with 1 to 3 positive nodes was 4.3% (94.4% had systemic therapy), which was not significantly different from the 10-year risk of CBC development (6.5%; $P>0.5$ ). Compared with the 10-year LRR rate among patients with node-negative disease (2.1%), patients with 1 positive node had a similar 10-year LRR risk (3.3%; $P>0.5$ ), and patients with 2 positive nodes had a 10-year LRR risk of 7.9% ( $P=0.0003$ ). Patients with T2 tumors with 1 to 3 positive nodes had a 10-year LRR rate of 9.7%. In patients with T1 and T2 breast cancer with 0 to 3 positive nodes, LRR rates after mastectomy are low, with the exception of patient's $\leq 40$ years old.	2
47. Cao JQ, Truong PT, Olivotto IA, et al. Should women younger than 40 years of age with invasive breast cancer have a mastectomy?: 15-year outcomes in a population-based cohort. <i>Int J Radiat Oncol Biol Phys</i> . 2014;90(3):509-517.	Observational-Tx	965 patients	To examine 15-year outcomes among women younger than 40 years treated with BCS plus WBI compared with those treated with MRM.	965 patients were identified; 616 had WBI and 349 had MRM. The median follow-up time was 14.4 years (range, 8.4–23.3 years). Overall, 15-year rates of breast cancer-specific survival (76.0% vs 74.1%, $P=.62$ ), OS (74.2% vs 73.0%, $P=.75$ ), local relapse-free survival (85.4% vs 86.5%, $P=.95$ ), locoregional relapse-free survival (82.2% vs 81.6%, $P=.61$ ), and distant relapse-free survival (74.4% vs 71.6%, $P=.40$ ) were similar between the WBI and MRM cohorts. In the "ideal" for WBI subgroup, there were 219 WBI and 67 MRM patients with a median follow-up time of 15.5 years. The 15-year breast cancer-specific survival (86.1% vs 82.9%, $P=.57$ ), OS (82.6% vs 82.9%, $P=.89$ ), local relapse-free survival (86.2% vs 84.2%, $P=.50$ ), locoregional relapse-free survival (83.1% vs 78.3%, $P=.24$ ), and distant relapse-free survival (84.8% vs 79.1%, $P=.17$ ) were similar in the WBI and MRM cohorts.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Mahmood U, Morris C, Neuner G, et al. Similar survival with breast conservation therapy or mastectomy in the management of young women with early-stage breast cancer. <i>Int J Radiat Oncol Biol Phys.</i> 2012;83(5):1387-1393.	Observational-Tx	14,764 women	To evaluate survival outcomes of young women with early-stage breast cancer treated with BCT or mastectomy, using a large, population-based database.	A total of 14,764 women were identified, of whom 45% received BCT and 55% received mastectomy. Median follow-up was 5.7 years (range, 0.5–17.9 years). After authors accounted for all patient and tumor characteristics, multivariable analysis found that BCT resulted in OS (HR, 0.93; 95% CI, 0.83–1.04; $P=0.16$ ) and CSS (HR, 0.93; CI, 0.83–1.05; $P=0.26$ ) similar to that of mastectomy. Matched pair analysis, including 4,644 BCT and mastectomy patients, confirmed no difference in OS or CSS: the 5-, 10-, and 15-year OS rates for BCT and mastectomy were 92.5%, 83.5%, and 77.0% and 91.9%, 83.6%, and 79.1%, respectively ( $P=0.99$ ), and the 5-, 10-, and 15-year CSS rates for BCT and mastectomy were 93.3%, 85.5%, and 79.9% and 92.5%, 85.5%, and 81.9%, respectively ( $P=0.88$ ).	2
49. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. <i>Lancet Oncol.</i> 2015;16(3):266-273.	Experimental-Tx	1,326 patients	To assess the effect omission of WBI would have on local control in older women at low risk of local recurrence at 5 years.	658 women who had undergone BCS and who were receiving adjuvant endocrine treatment were randomly assigned to receive WBI and 668 were allocated to no further treatment. After median follow-up of 5 years (IQR 3.84–6.05), IBTR was 1.3% (95% CI, 0.2–2.3; $n=5$ ) in women assigned to WBI and 4.1% (2.4–5.7; $n=26$ ) in those assigned no RT ( $P=0.0002$ ). Compared with women allocated to WBI, the univariate HR for IBTR in women assigned to no RT was 5.19 (95% CI, 1.99–13.52; $P=0.0007$ ). No differences in regional recurrence, distant metastases, contralateral breast cancers, or new breast cancers were noted between groups. 5-year OS was 93.9% (95% CI, 91.8–96.0) in both groups ( $P=0.34$ ). 89 women died; 8 of 49 patients allocated to no RT and 4 of 40 assigned to RT died from breast cancer.	1
50. Alpert TE, Haffty BG. Conservative management of breast cancer in BRCA1/2 mutation carriers. <i>Clin Breast Cancer.</i> 2004;5(1):37-42.	Review/Other-Tx	N/A	To review the published literature on conservative management of patients with BRCA1/2 mutations.	N/A	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
51. Robson M, Svahn T, McCormick B, et al. Appropriateness of breast-conserving treatment of breast carcinoma in women with germline mutations in BRCA1 or BRCA2: a clinic-based series. <i>Cancer</i> . 2005;103(1):44-51.	Observational-Tx	87 female participants in genetic testing protocols	To evaluate the appropriateness of BCT in women with BRCA mutations. Clinical records were reviewed and follow-up was updated.	In all 95 treated breasts, the 5-year and 10-year probabilities of metachronous ipsilateral breast carcinoma were 11.2% and 13.6%, respectively. Among the 87 subjects, the 5-year and 10-year probabilities of metachronous CBC after treatment of the index tumor were 11.9% and 37.6%. No clinical factors were identified that were associated with either multiple ipsilateral invasive breast cancers or CBC, including the use of tamoxifen or chemotherapy. Women with BRCA-associated breast carcinoma who undergo BCT appear to have risks of multiple ipsilateral invasive breast cancers that are similar to those reported for young women without known mutations.	2
52. Pierce LJ, Levin AM, Rebbeck TR, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. <i>J Clin Oncol</i> . 2006;24(16):2437-2443.	Observational-Tx	160 BRCA1/2 mutation carriers with breast cancer; 445 controls	To compare the outcome of BCS and RT in BRCA1/2 mutation carriers with breast cancer vs that of matched sporadic controls.	Median follow-up was 7.9 years for mutation carriers and 6.7 years for controls. 10- and 15-year estimates were 12% and 24% for carriers and 9% and 17% for controls, respectively (HR, 1.37; $P=.19$ ). Multivariate analyses for IBTR found BRCA1/2 mutation status to be an independent predictor of IBTR when carriers who had undergone oophorectomy were removed from analysis (HR, 1.99; $P=.04$ ). CBC were significantly greater in carriers vs controls, with 10- and 15-year estimates of 26% and 39% for carriers and 3% and 7% for controls, respectively (HR, 10.43; $P<.0001$ ). Tamoxifen use significantly reduced risk of CBC in mutation carriers (HR, 0.31; $P=.05$ ). IBTR risk at 10 years is similar in BRCA1/2 carriers treated with BCS who undergo oophorectomy vs sporadic controls. As expected, CBC is significantly increased in carriers. Although the incidence of CBC was significantly reduced in mutation carriers who received tamoxifen, this rate remained significantly greater than in controls. Additional strategies are needed to reduce contralateral cancers in these high-risk women.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. Pierce LJ, Phillips KA, Griffith KA, et al. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. <i>Breast Cancer Res Treat.</i> 2010;121(2):389-398.	Observational-Tx	655 women	To compare long-term outcome following BCT and mastectomy in BRCA1/2 carriers.	Local failure as first failure was significantly more likely in those treated with BCT compared to mastectomy, with a cumulative estimated risk of 23.5% vs 5.5%, respectively, at 15 years ( $P<0.0001$ ); 15-year estimates in carriers treated with BCT and chemotherapy was 11.9% ( $P=0.08$ when compared to mastectomy). Most events appeared to be second primary cancers rather than failure to control the primary tumor. The risk of CBC was high in all groups, exceeding 40%, but was not statistically significantly different by use of adjuvant RT or not, suggesting no added risk from scatter RT at 10 and 15 years. There were no differences seen in regional or systemic recurrences between the BCT and mastectomy groups, and no difference in OS.	2
54. Pierce LJ, Haffty BG. Radiotherapy in the treatment of hereditary breast cancer. <i>Semin Radiat Oncol.</i> 2011;21(1):43-50.	Review/Other-Tx	N/A	To review literature describing treatment and toxicity outcomes in patients undergoing RT after BCS and after mastectomy for breast cancer patients who have BRCA1 and BRCA2 mutations.	No results stated in abstract.	4
55. Gray RJ, Forstner-Barthell AW, Pockaj BA, Schild SE, Halyard MY. Breast-conserving therapy and sentinel lymph node biopsy are feasible in cancer patients with previous implant breast augmentation. <i>Am J Surg.</i> 2004;188(2):122-125.	Observational-Tx	39 total patients: 18 were treated with BCT; 11 patients had SLN mapping and biopsy	Retrospective review of patients with prior breast augmentation treated with BCT or SLN.	During follow-up (median 3 years), 1 LR (5.3%) occurred in a patient who refused adjuvant RT and systemic therapy. 11 patients underwent SLN biopsy with an identification rate of 100% and a false-negative rate of 0%. BCT inclusive of RT after implant breast augmentation produced acceptable cosmetic results in nearly two-thirds of patients. SLN mapping in the setting of prior implant augmentation was highly successful and accurate.	2
56. Karanas YL, Leong DS, Da Lio A, et al. Surgical treatment of breast cancer in previously augmented patients. <i>Plast Reconstr Surg.</i> 2003;111(3):1078-1083; discussion 1084-1076.	Review/Other-Tx	58 patients	To examine the usefulness of surgical treatment of breast cancer in previously augmented patients.	Data illustrate that BCT with maintenance of the implant is not ideal for the majority of augmented patients. BCT with explanation and mastopexy might be appropriate for rare patients with large volumes of native breast tissue. Mastectomy with immediate reconstruction might be a more suitable choice for these patients.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
57. Demirci S, Broadwater G, Marks LB, Clough R, Prosnitz LR. Breast conservation therapy: the influence of molecular subtype and margins. <i>Int J Radiat Oncol Biol Phys.</i> 2012;83(3):814-820.	Observational-Tx	1,058 stage I or II breast cancer patients	To evaluate treatment results and prognostic factors, especially margin status and molecular subtype, in early-stage breast cancer patients treated with BCT.	Of the patients, 80% had T1 disease and 66% N0 disease pathologically. With a median follow-up of 9.8 years, an in-breast recurrence developed in 53 patients and 10 patients had nodal failure. For all patients, the 10-year CSS rate was 94%; LRC rate, 94%; and failure-free survival rate, 88%. Luminal A patients had a CSS rate of 95% and LRC rate of 99%. Basal-type patients appeared to do worse, with regard to both CSS rate (74%) and LRC rate (76%), but the numbers were small and the difference was not statistically significant. LRC rates of patients with negative margins (widely negative, close, and extent of margin not known) were virtually identical (93%, 96%, and 94%, respectively). Those with positive margins appeared to fare slightly worse based on LRC rate (88%), but again, the numbers were small and the difference was not statistically significant.	2
58. Russo AL, Arvold ND, Niemierko A, et al. Margin status and the risk of local recurrence in patients with early-stage breast cancer treated with breast-conserving therapy. <i>Breast Cancer Res Treat.</i> 2013;140(2):353-361.	Observational-Tx	906 women	To assess whether a close surgical margin (>0 and <2 mm) after BCT confers an increased risk of LR compared with a widely negative margin (≥2 mm).	With a median follow-up of 87.5 months, the 5-year cumulative incidence of LR was 2.5%. The 5-year cumulative incidence of LR by margin status was 2.3% (95% CI 1.4%-3.8%) for widely negative, 0% for close, and 6.4% (95% CI 2.7%-14.6%) for no additional tissue, <i>P</i> =0.3. On multivariate analysis, margin status was not associated with LR; however, triple-negative subtype (AHR 3.7; 95% CI 1.6-8.8; <i>P</i> =0.003) and increasing number of positive LNs (AHR 1.6; 95% CI 1.1-2.3; <i>P</i> =0.025) were associated.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
59. 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. <i>J Clin Oncol.</i> 2008;26(14):2373-2378.	Observational-Tx	793 consecutive patients with invasive breast cancer who received BCT	To determine whether breast cancer subtype is associated with outcome after BCT consisting of lumpectomy and RT.	Overall 5-year cumulative incidence of LR was 1.8% (95% CI, 1.0 to 3.1); 0.8% (0.3, 2.2) for luminal A, 1.5% (0.2, 10) for luminal B, 8.4% (2.2, 30) for HER-2, and 7.1% (3.0, 16) for basal. On multivariable analysis with luminal A as baseline, HER-2 (adjusted HR = 9.2; 95% CI, 1.6-51; <i>P</i> =.012) and basal (adjusted HR = 7.1; 95% CI, 1.6-31; <i>P</i> =.009) subtypes were associated with increased LR. On multivariable analysis, luminal B (adjusted HR = 2.9; 95% CI, 1.3-6.5; <i>P</i> =.007) and basal (adjusted HR = 2.3; 95% CI, 1.1-5.2; <i>P</i> =.035) were associated with increased distant metastases. Overall, the 5-year LR rate after BCT was low, but varied by subtype as approximated using ER, PR, and HER-2 status. LR was particularly low for the luminal A subtype, but was <10% at 5 years for all subtypes.	1
60. Santiago RJ, Wu L, Harris E, et al. Fifteen-year results of breast-conserving surgery and definitive irradiation for Stage I and II breast carcinoma: the University of Pennsylvania experience. <i>Int J Radiat Oncol Biol Phys.</i> 2004;58(1):233-240.	Observational-Tx	937 total patients	To determine the 15-year outcomes for women with early stage breast cancer after BCT.	Median follow-up was 10.1 years. For the overall group, the 15-year OS rate was 71%, and the rate of freedom from distant metastases was 76%. The 15-year local failure rate was 19%. The 15-year CBC rate was 12%. The local failure rate at 10 years for favorable subsets of tumors characterized by mammographic detection, resection with negative margins, treatment with chemotherapy, and treatment with hormones was 8%, 10%, 10%, and 7%, respectively. Local failures were most commonly observed within (true recurrence), or just outside (marginal miss), the primary tumor bed (66%, 85/128). The rate of true recurrence or marginal miss at 5, 10, and 15 years was 5%, 10%, and 12%, respectively. These high rates of survival and local control confirm that breast conservation therapy yields favorable results in women with early breast cancer into the second decade after treatment.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
61. Ali AN, Vapiwala N, Guo M, Hwang WT, Harris EE, Solin LJ. The impact of re-excision and residual disease on local recurrence after breast conservation treatment for patients with early stage breast cancer. <i>Clin Breast Cancer</i> . 2011;11(6):400-405.	Observational-Tx	902 patients	To examine the impact of re-excision and residual disease on LR after breast conservation treatment for patients with negative margins.	At 15 years, the rates of local failure were 10% for patients with a single excision, 10% for patients with a re-excision without residual disease, and 16% for patients with a re-excision with residual disease ( $P=.033$ ). There were no significant differences between the 3 groups for OS, CSS, relapse-free survival, or freedom from distant metastases (all $P\geq.082$ ). Multivariate analysis demonstrated an increased risk of local failure for patients with residual disease in the re-excision specimen that was borderline statistically significant (HR, 2.16; $P=.061$ ).	2
62. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. <i>Ann Surg Oncol</i> . 2014;21(3):717-730.	Review/Other-Tx	33 studies (LR in 1,506 of 28,162)	To systematically review the evidence on surgical margins in BCT for invasive breast cancer to support the development of clinical guidelines.	Based on 33 studies (LR in 1,506 of 28,162), the odds of LR were associated with margin status [model 1: OR 1.96 for positive/close vs negative; model 2: OR 1.74 for close vs negative, 2.44 for positive vs negative; ( $P<0.001$ both models)] but not with margin distance [model 1: $>0$ mm vs. 1 mm (referent) vs. 2 mm vs. 5 mm ( $P=0.12$ ); and model 2: 1 mm (referent) vs. 2 mm vs. 5 mm ( $P=0.90$ )], adjusting for study median follow-up time. There was little to no statistical evidence that the odds of LR decreased as the distance for declaring negative margins increased, adjusting for follow-up time [model 1: 1 mm (OR 1.0, referent), 2 mm (OR 0.95), 5 mm (OR 0.65), $P=0.21$ for trend; and model 2: 1 mm (OR 1.0, referent), 2 mm (OR 0.91), 5 mm (OR 0.77), $P=0.58$ for trend]. Adjustment for covariates, such as use of endocrine therapy or median-year of recruitment, did not change the findings.	4

**Conservative Surgery and Radiation-Stage I and II Breast Cancer  
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
63. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. <i>Int J Radiat Oncol Biol Phys.</i> 2014;88(3):553-564.	Review/Other-Tx	33 studies; 28,162 patients	To convene a multidisciplinary panel of breast experts to examine the relationship between margin width and IBTR and develop a guideline for defining adequate margins in the setting of BCS and adjuvant RT.	Positive margins (ink on invasive carcinoma or ductal carcinoma in situ) are associated with a 2-fold increase in the risk of IBTR compared with negative margins. This increased risk is not mitigated by favorable biology, endocrine therapy, or a radiation boost. More widely clear margins than no ink on tumor do not significantly decrease the rate of IBTR compared with no ink on tumor. There is no evidence that more widely clear margins reduce IBTR for young patients or for those with unfavorable biology, lobular cancers, or cancers with an extensive intraductal component.	4
64. Delpach Y, Coutant C, Hsu L, et al. Clinical benefit from neoadjuvant chemotherapy in oestrogen receptor-positive invasive ductal and lobular carcinomas. <i>Br J Cancer.</i> 2013;108(2):285-291.	Observational-Tx	1,895 patients (n=177 ILC; n=1,718 IDC)	To compare clinical and pathological outcomes after neoadjuvant chemotherapy between ER-positive ILC and IDC.	There was a trend for fewer good clinical responses in ILC compared with IDC. Tumor downstaging was significantly less frequent in ILC. Positive or close surgical resection margins were more frequent in ILC, and BCS was less common ( $P<0.001$ ). These outcome differences remained significant in multivariate analysis, including tumor size, nodal status, age, grade and type of chemotherapy. Invasive pure lobular carcinoma was also associated with a significantly lower pathological complete response rate in univariate analysis, but this was no longer significant after adjusting for tumor size and grade.	2
65. Vo TN, Meric-Bernstam F, Yi M, et al. Outcomes of breast-conservation therapy for invasive lobular carcinoma are equivalent to those for invasive ductal carcinoma. <i>Am J Surg.</i> 2006;192(4):552-555.	Observational-Tx	84 patients with ILC and 1,126 with IDC	The authors evaluated their institutional experience with BCT and compared treatment outcomes for ILC with those for IDC.	The 5- and 10-year local-regional recurrence rates for the ILC group were 1% and 7%, respectively, and 4% and 9%, respectively, for the IDC group ( $P=.70$ ). There were no significant differences in the 5- and 10-year disease-specific survival rates between the groups. CBC occurred in 11.3% of patients with IDC and 11.9% of patients with ILC.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Moran MS, Yang Q, Haffty BG. The Yale University experience of early-stage invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC) treated with breast conservation treatment (BCT): analysis of clinical-pathologic features, long-term outcomes, and molecular expression of COX-2, Bcl-2, and p53 as a function of histology. <i>Breast J.</i> 2009;15(6):571-578.	Observational-Tx	142 ILC and 1,760 IDC patients	To evaluate clinical-pathologic features and outcomes of early-stage ILC vs ID) carcinoma treated with BCT.	Median follow-up was 6.8 years. A higher percentage of ILC patients presented at >40 years of age (94% ILC vs 89% IDC, $P=0.0353$ ) and had more mammographically occult tumors ( $P<0.002$ ). There were no significant differences in T stage, nodal status, family history, final margin, ER/PR/HER-2 status or triple negative tumors (all $P$ -values>0.05). From the immunohistochemical analysis, expression of p53, COX-2, and Bcl-2 did not differ significantly (all $P$ -values>0.05) between the 2 cohorts. At 10 years, there was no difference in breast relapse (20% vs 13%, $P=0.25$ ), distant relapse (26% vs 20%, $P=0.28$ ), CSS (72% vs 84%, $P=0.09$ ) and OS (68% vs 78%, $P=0.08$ ). Patients with ILC had higher contralateral breast relapses (26% vs 12%, $P=0.0006$ ).	2
67. Santiago RJ, Harris EE, Qin L, Hwang WT, Solin LJ. Similar long-term results of breast-conservation treatment for Stage I and II invasive lobular carcinoma compared with invasive ductal carcinoma of the breast: The University of Pennsylvania experience. <i>Cancer.</i> 2005;103(12):2447-2454.	Observational-Tx	1,093 women with stage I and II IDC of the breast and 55 women with ILC of the breast	To determine the long-term results of breast-conservation treatment in women with early-stage, ILC of the breast.	The median follow-up was 8.7 years and 10.2 years for patients in the IDC and ILC groups, respectively. A comparison of patients who had ILC with patients who had IDC showed no difference in the 10-year actuarial rates of OS (85% vs 79%, respectively; $P=0.73$ ), CSS (93% vs 84%, respectively; $P=0.85$ ), or freedom from distant metastases (81% vs 80%, respectively; $P=0.76$ ). The 10-year rates of local failure were 18% for patients with ILC and 12% for patients with IDC ( $P=0.24$ ), and the 10-year rates of CBC development for the 2 groups were 12% and 8%, respectively ( $P=0.40$ ).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
68. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. <i>Nature</i> . 2000;406(6797):747-752.	Review/Other-Tx	65 surgical specimens	The authors characterized variation in gene expression patterns in a set of 65 surgical specimens of human breast tumors from 42 different individuals, using complementary DNA microarrays representing 8,102 human genes.	These patterns provided a distinctive molecular portrait of each tumor. 20 of the tumors were sampled twice, before and after a 16-week course of doxorubicin chemotherapy, and 2 tumors were paired with a lymph node metastasis from the same patient. Gene expression patterns in 2 tumor samples from the same individual were almost always more similar to each other than either was to any other sample. Sets of co-expressed genes were identified for which variation in messenger RNA levels could be related to specific features of physiological variation.	4
69. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. <i>Proc Natl Acad Sci U S A</i> . 2001;98(19):10869-10874.	Review/Other-Tx	85 cDNA microarray experiments	To classify breast carcinomas based on variations in gene expression patterns derived from cDNA microarrays and to correlate tumor characteristics to clinical outcome.	A novel finding was that the previously characterized luminal epithelial/ER-positive group could be divided into at least 2 subgroups, each with a distinctive expression profile. These subtypes proved to be reasonably robust by clustering using 2 different gene sets: first, a set of 456 cDNA clones previously selected to reflect intrinsic properties of the tumors and, second, a gene set that highly correlated with patient outcome.	4
70. Millar EK, Graham PH, O'Toole SA, et al. Prediction of local recurrence, distant metastases, and death after breast-conserving therapy in early-stage invasive breast cancer using a five-biomarker panel. <i>J Clin Oncol</i> . 2009;27(28):4701-4708.	Experimental-Tx	498 total patients treated with or without a cavity boost	A randomized trial to determine the clinical utility of intrinsic molecular phenotype after BCT with lumpectomy and WBI with or without a cavity boost.	Median follow-up was 84 months. The overall 5-year disease-free rates for the whole cohort were: IBTR 97.4%, LRR 95.6%, distant DFS 92.9%, and breast cancer-specific death 96.3%. A significant difference was observed for survival between subtypes for LRR ( $P=.012$ ), distant DFS ( $P=.0035$ ), and breast cancer-specific death ( $P=.0482$ ), but not for IBTR ( $P=.346$ ).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
71. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. <i>J Clin Oncol.</i> 2010;28(10):1684-1691.	Observational-Tx	2,985 patients with early invasive breast cancer	To determine the risk of local and regional relapse associated with each breast cancer molecular subtype in a large cohort of patients with breast cancer.	Luminal A tumors (ER or PR positive, HER-2 negative, Ki-67 <1%) had the best prognosis and the lowest rate of local or regional relapse. For patients undergoing breast conservation, HER-2-enriched and basal subtypes demonstrated an increased risk of regional recurrence, and this was statistically significant on multivariable analysis. After mastectomy, luminal B, luminal-HER-2, HER-2-enriched, and basal subtypes were all associated with an increased risk of local and regional relapse on multivariable analysis. Luminal A tumors are associated with a low risk of local or regional recurrence. Molecular subtyping of breast tumors using a 6-marker immunohistochemical panel can identify patients at increased risk of local and regional recurrence.	2
72. Mamounas EP, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. <i>J Clin Oncol.</i> 2010;28(10):1677-1683.	Observational-Tx	895 tamoxifen-treated patients (from both trials): 355 placebo-treated patients (from B-14); 424 chemotherapy plus tamoxifen-treated patients (from B-20)	To investigate the association between recurrence score and risk for LRR in patients with node-negative, ER-positive breast cancer from 2 National Surgical Adjuvant Breast and Bowel Project (NSABP) trials (NSABP B-14 and B-20).	In tamoxifen-treated patients, LRR was significantly associated with recurrence score risk groups ( $P < .001$ ). The 10-year Kaplan-Meier estimate of LRR was 4.0% (95% CI, 2.3% to 6.3%) for patients with a low recurrence score (<18), 7.2% (95% CI, 3.4% to 11.0%) for those with intermediate recurrence score (18-30), and 15.8% (95% CI, 10.4% to 21.2%) for those with a high recurrence score (>30). In multivariate analysis, recurrence score was an independent significant predictor of LRR along with age and type of initial treatment. Similar to the association between recurrence score and risk for distant recurrence, a significant association exists between recurrence score and risk for LRR. This information has biologic consequences and potential clinical implications relative to locoregional therapy decisions for patients with node-negative and ER-positive breast cancer.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
73. Rose MA, Olivotto I, Cady B, et al. Conservative surgery and radiation therapy for early breast cancer. Long-term cosmetic results. <i>Arch Surg.</i> 1989;124(2):153-157.	Observational-Tx	593 patients	To evaluate the cosmetic outcome of conservative surgery and RT for early-stage breast cancer and its stability over time.	Median follow-up was 76 months. Cosmetic results were generally excellent or good. The percent's of excellent, good, fair, and poor results at 3 years were 65%, 25%, 7%, and 3%, respectively. Patients not receiving adjuvant chemotherapy were more likely than those receiving chemotherapy to have excellent scores at 5 years (71% vs 40%). Tumor size also influenced cosmetic outcome: 73% of patients with T1 tumors vs 55% with T2 tumors had excellent scores at 5 years. The cosmetic results achieved with conservative surgery and RT are good to excellent in approximately 90% of patients and these results remain stable for at least 7 years.	2
74. Vrieling C, Collette L, Fourquet A, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. <i>Radiother Oncol.</i> 2000;55(3):219-232.	Review/Other-Tx	5,569 patients	To analyze the influence of different patient, tumor, and treatment parameters on the cosmetic outcome after BCT at 3-year follow-up.	The factors associated with a worsened cosmesis according to the panel evaluation were: an inferior tumor location, a large excision volume, the presence of postoperative breast complications, and the RT boost. According to the digitizer measurements, a central/superior tumor location, a large excision volume, an increased pathological tumor size, an increased radiation dose inhomogeneity, and an increased bra cup size resulted in an increased asymmetry in nipple position. It appeared that the evaluation of the nipple position (whether by panel or by digitizer) is only moderately representative of the overall cosmetic outcome.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
75. 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. <i>Radiother Oncol.</i> 2007;82(3):254-264.	Experimental-Tx	306 total women: 156 randomized to standard 2D; 150 randomized to 3D IMRT	Prospective randomized trial with the aim of testing improved radiation dosimetry after 3D IMRT in terms of external assessments of change in breast appearance and patient self-assessments of breast discomfort, breast hardness and quality of life.	240 (79%) patients with 5-year photographs were available for analysis. Change in breast appearance was identified in 71/122 (58%) allocated standard 2D treatment compared to only 47/118 (40%) patients allocated 3D IMRT. The control arm patients were 1.7 times more likely to have a change in breast appearance than the IMRT arm patients after adjustment for year of photographic assessment (95% CI, 1.2–2.5, $P=0.008$ ). Significantly fewer patients in the 3D IMRT group developed palpable induration assessed clinically in the center of the breast, pectoral fold, infra-mammary fold, and at the boost site. No significant differences between treatment groups were found in patient reported breast discomfort, breast hardness or quality of life.	1
76. Pignol JP, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. <i>J Clin Oncol.</i> 2008;26(13):2085-2092.	Experimental-Tx	331 patients	A multicenter, double-blind, randomized clinical trial to test if breast IMRT would reduce the rate of acute skin reaction (notably moist desquamation), decrease pain, and improve quality of life compared with standard RT using wedges.	A lower proportion of patients experienced moist desquamation during or up to 6 weeks after their radiation treatment; 31.2% with IMRT compared with 47.8% with standard treatment ( $P=.002$ ). A multivariate analysis found the use of breast IMRT ( $P=.003$ ) and smaller breast size ( $P<.001$ ) were significantly associated with a decreased risk of moist desquamation. The use of IMRT did not correlate with pain and quality of life, but the presence of moist desquamation did significantly correlate with pain ( $P=.002$ ) and a reduced quality of life ( $P=.003$ ). Breast IMRT significantly reduced the occurrence of moist desquamation compared with a standard wedged technique. Moist desquamation was correlated with increased pain and reduction in the quality of life.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
77. Barnett GC, Wilkinson JS, Moody AM, et al. Randomized controlled trial of forward-planned intensity modulated radiotherapy for early breast cancer: interim results at 2 years. <i>Int J Radiat Oncol Biol Phys.</i> 2012;82(2):715-723.	Experimental-Tx	1,145 patients	To investigate whether IMRT reduces late toxicity in patients with early-stage breast cancer.	At 2 years, no significant difference was found in the development of any photographically assessed breast shrinkage between the patients randomized to the interventional or control group (OR, 1.51; 95% CI, 0.83–1.58; $P= .41$ ). The patients in the control group were more likely to develop telangiectasia than those in the IMRT group (OR, 1.68; 95% CI, 1.13–2.40; $P= .009$ ). Poor baseline surgical cosmesis resulted in poor overall cosmesis at 2 years after RT. In patients who had good surgical cosmesis, those randomized to IMRT were less likely to deteriorate to a moderate or poor overall cosmesis than those in the control group (OR, 0.63; 95% CI, 0.39–1.03, $P= .061$ ).	1
78. Remouchamps VM, Letts N, Vicini FA, et al. Initial clinical experience with moderate deep-inspiration breath hold using an active breathing control device in the treatment of patients with left-sided breast cancer using external beam radiation therapy. <i>Int J Radiat Oncol Biol Phys.</i> 2003;56(3):704-715.	Review/Other-Tx	5 patients with stages I/II left-sided breast cancer	To describe the clinical experience using moderate deep-inspiration breath hold with an active breathing control device to reduce heart dose in the treatment of patients with early-stage, left-sided breast cancer using EBRT limited to the whole breast.	Active breathing control treatments achieved a mean absolute reduction of 3.6% in heart volume receiving 30 Gy (heart V(30)) and 1.5% in the heart normal tissue complication probability. The average number of breath holds required per beam direction was 2.5 (4-6 per treatment) with a median duration of 22 s per breath hold (range: 10-26 s). Patients tolerated moderate deep-inspiration breath hold well. The median treatment time was 18.2 min (range: 13-32 min), which was progressively shortened with increasing experience. Reduction in heart V(30) can be achieved in patients with left-sided breast cancer using moderate deep-inspiration breath hold assisted with an active breathing control device. With increasing experience, active breathing control treatments were streamlined and could be performed within a 15-min treatment slot. Our results suggest that moderate deep-inspiration breath hold using an active breathing control device may provide 1 of the most promising methods of improving the efficacy of EBRT in patients with left-sided breast cancer, particularly when wide tangential beams are employed.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
79. Vikstrom J, Hjelstuen MH, Mjaaland I, Dybvik KI. Cardiac and pulmonary dose reduction for tangentially irradiated breast cancer, utilizing deep inspiration breath-hold with audio-visual guidance, without compromising target coverage. <i>Acta Oncol.</i> 2011;50(1):42-50.	Review/Other-Tx	17 patients	To quantify the reduction of radiation doses to the heart and lung, using deep inspiration breath-hold.	Compared to free breathing, the deep inspiration breath-hold-plans obtained lower cardiac and pulmonary doses, with equal coverage of planning target volume. The average mean heart dose was reduced from 3.7 to 1.7 Gy and the number of patients with >5% heart volume receiving 25 Gy or more was reduced from 4 to 1 of the 17 patients. With deep inspiration breath-hold the heart was completely out of the beam portals for 10 patients, with free breathing this could not be achieved for any of the 17 patients. The average mean dose to the left anterior descending coronary artery was reduced from 18.1 to 6.4 Gy. The average ipsilateral lung volume receiving more than 20 Gy was reduced from 12.2% to 10.0%. Respiratory gating with deep inspiration breath-hold, utilizing audio-visual guidance, reduces cardiac and pulmonary doses for tangentially treated left sided breast cancer patients without compromising the target coverage.	4
80. Zellars R, Bravo PE, Tryggestad E, et al. SPECT analysis of cardiac perfusion changes after whole-breast/chest wall radiation therapy with or without active breathing coordinator: results of a randomized phase 3 trial. <i>Int J Radiat Oncol Biol Phys.</i> 2014;88(4):778-785.	Experimental-Tx	43 patients	The authors hypothesized that active breathing coordinator would prevent radiation-induced cardiac toxicity and conducted a randomized controlled trial evaluating myocardial perfusion changes after radiation for left-sided breast cancer with or without active breathing coordinator.	Between 2006 and 2010, 57 patients were enrolled and 43 were available for analysis. The cohorts were well matched. The apical and left anterior descending coronary artery segments had significant decreases in perfusion on SPECT scans in both active breathing coordinator and No-active breathing coordinator cohorts. In unadjusted and adjusted analyses, controlling for pretreatment perfusion score, age, and chemotherapy, active breathing coordinator was not significantly associated with prevention of perfusion deficits.	1

**Conservative Surgery and Radiation-Stage I and II Breast Cancer  
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
81. Borger JH, Hooning MJ, Boersma LJ, et al. Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: the role of irradiated heart volume. <i>Int J Radiat Oncol Biol Phys.</i> 2007;69(4):1131-1138.	Observational-Tx	1,601 patients	To assess the risk of cardiovascular disease after postlumpectomy irradiation restricted to tangential fields.	Follow-up was complete for 94% of the patients, and median follow-up was 16 years. The incidence of cardiovascular disease overall was 14.1%, of ischemic heart disease 7.3%, and for other types of heart disease 9.2%, with a median time to event of 10 to 11 years. The incidence of cardiovascular disease was 11.6% in patients with right-sided breast cancer, compared with 16.0% in left-sided cases. The HR associated with left-sided vs right-sided breast cancer was 1.38 (95% CI, 1.05–1.81) for cardiovascular disease overall, 1.35 (95% CI, 0.93–1.98) for ischemic heart disease, and 1.53 (95% CI, 1.09–2.15) for other heart disease, adjusted for age, diabetes, and history of cardiovascular disease. The risk of cardiovascular disease did not significantly increase with increasing maximum heart distance.	2
82. Lymberis SC, deWyngaert JK, Parhar P, et al. Prospective assessment of optimal individual position (prone versus supine) for breast radiotherapy: volumetric and dosimetric correlations in 100 patients. <i>Int J Radiat Oncol Biol Phys.</i> 2012;84(4):902-909.	Observational-Tx	100 patients	To evaluate which position is best to spare lung and heart from RT exposure. The authors report the dosimetric analysis of the first 100 patients accrued to trial 05-181: 53 left and 47 right breast cancer patients.	53 left and 47 right breast cancer patients were consecutively accrued to the trial. In all patients, the prone position was optimal for sparing lung volume compared to the supine setup (mean lung volume reduction was 93.5 cc for right and 103.6 cc for left breast cancer patients). In 46/53 (87%) left breast cancer patients best treated prone, in-field heart volume was reduced by a mean of 12 cc and by 1.8 cc for the other 7/53 (13%) patients best treated supine. As predicted, supine-prone differences in in-field volume and mean dose of heart and lung were highly correlated (Spearman's correlation coefficient for left breast cancer patients was 0.90 for heart and 0.94 for lung and 0.92 for right breast cancer patients for lung).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
83. Mulliez T, Veldeman L, van Greveling A, et al. Hypofractionated whole breast irradiation for patients with large breasts: a randomized trial comparing prone and supine positions. <i>Radiother Oncol.</i> 2013;108(2):203-208.	Experimental-Tx	100 patients	To compare acute toxicity of WBI in prone and supine positions.	Prone treatment resulted in: improved dose coverage ( $P<0.001$ ); better homogeneity ( $P<0.001$ ); less volumes of over-dosage ( $P=0.001$ ); reduced acute skin desquamation ( $P<0.001$ ); a 3-fold decrease of moist desquamation $P=0.04$ (chi-square), $P=0.07$ (Fisher's exact test)); lower incidence of dermatitis ( $P<0.001$ ), edema ( $P=0.005$ ), pruritus ( $P=0.06$ ) and pain ( $P=0.06$ ); 2- to 4-fold reduction of grades 2-3 toxicity; lower ipsilateral lung ( $P<0.001$ ) and mean left anterior descending ( $P=0.007$ ) dose; lower, though statistically non-significant heart and maximum left anterior descending.	1
84. Mitchell J, Formenti SC, DeWyngaert JK. Interfraction and intrafraction setup variability for prone breast radiation therapy. <i>Int J Radiat Oncol Biol Phys.</i> 2010;76(5):1571-1577.	Experimental-Tx	10 patients	To report the interfraction and intrafraction setup variation for prone breast RT and to determine an appropriate clinical tumor volume to planning target volume margin to account for motion and positional uncertainties.	The mean interfraction setup variability for the fiducial was 0.08 cm (CI: 0.02–0.14) in the anterior to posterior direction and -0.04 cm (CI: -0.07-0.00) in the superior to inferior direction. The mean interfraction variability of the breast surface was -0.14 cm (CI: -0.24 to -0.04) in the anterior to posterior direction. The mean intrafraction displacements of the fiducial and the breast surface were 0.13 cm (CI: 0.12–0.15) and 0.15 cm (CI: 0.14–0.17), respectively. Using the systematic and random errors for the external fiducial, the calculated clinical tumor volume to planning target volume expansion was 1.4 cm. Acceptable interfraction and intrafraction variability were demonstrated. The findings resulted in a clinical tumor volume to planning target volume expansion of 1.4 cm.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
85. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. <i>Lancet Oncol.</i> 2013;14(11):1086-1094.	Experimental-Tx	START-A – 2,236 women; START-B – 2,215 women	To report the 10-year update of START-A and START-B, including assessment of long-term efficacy and adverse effects.	START-A: Median follow-up was 9.3 years (IQR 8.0–10.0), after which 139 local regional relapses had occurred. 10-year rates of local-regional relapse did not differ significantly between the 41.6 Gy and 50 Gy regimen groups (6.3%, 95% CI, 4.7–8.5 vs 7.4%, 5.5–10.0; HR 0.91, 95% CI, 0.59–1.38; <i>P</i> =0.65) or the 39 Gy (8.8%, 95% CI, 6.7–11.4) and 50 Gy regimen groups (HR 1.18, 95% CI, 0.79–1.76; <i>P</i> =0.41). In START-A, moderate or marked breast induration, telangiectasia, and breast edema were significantly less common normal tissue effects in the 39 Gy group than in the 50 Gy group. Normal tissue effects did not differ significantly between 41.6 Gy and 50 Gy groups. START-B: Median follow-up was 9.9 years (IQR 7.5–10.1), after which 95 local-regional relapses had occurred. The proportion of patients with local-regional relapse at 10 years did not differ significantly between the 40 Gy group (4.3%, 95% CI, 3.2–5.9) and the 50 Gy group (5.5%, 95% CI, 4.2–7.2; HR 0.77, 95% CI, 0.51–1.16; <i>P</i> =0.21). In START-B, breast shrinkage, telangiectasia, and breast edema were significantly less common normal tissue effects in the 40 Gy group than in the 50 Gy group.	1
86. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. <i>Int J Radiat Oncol Biol Phys.</i> 2011;81(1):59-68.	Review/Other-Tx	N/A	To develop an evidence-based guideline to provide direction for clinical practice.	The majority of patients in randomized trials were aged 50 years or older, had disease stage pT1-2 pN0, did not receive chemotherapy, and were treated with a radiation dose homogeneity within +/-7% in the central axis plane. Data were sufficient to support the use of hypofractionated-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 hypofractionated-WBI, which nevertheless should not be interpreted as a contraindication to its use.	4

Conservative Surgery and Radiation-Stage I and II Breast Cancer  
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
87. Benda RK, Yasuda G, Sethi A, Gabram SG, Hinerman RW, Mendenhall NP. Breast boost: are we missing the target? <i>Cancer</i> . 2003;97(4):905-909.	Experimental-Tx	30 patients	To evaluate, by means of 3D computer treatment planning tools, the accuracy of 2 techniques for volume definition and dose coverage: the commonly used clinical technique and a technique based on CT imaging of surgical clips in the tumor bed.	The isocenter differed more than 1 cm in the medial-lateral direction in 5 patients and in the cephalocaudal direction in 12 patients. The en face gantry angle differed for most patients. On average, only 51% (range, 27%–79%) of the planning target volume received 90% or more of the prescribed dose when the electron plan was generated using the electron boost volume ( $P<0.0001$ ). 10 patients received the prescription dose to <50% of the planning target volume. Mean volume of normal tissue receiving more than 50% of prescribed dose was 64.5 cm (3) (range, 24-119 cm (3)). Authors recommend the use of surgical clips to delineate the target volume, followed by CT-based treatment planning, accounting for not only microscopic disease, but also organ motion and daily setup error.	2
88. Recht A, Gray R, Davidson NE, et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. <i>J Clin Oncol</i> . 1999;17(6):1689-1700.	Review/Other-Tx	2,016 patients entered onto 4 randomized prospective trials	To assess patterns of failure and how selected prognostic and treatment factors affect the risks of locoregional failure after mastectomy in breast cancer patients with histologically involved axillary nodes treated with chemotherapy with or without tamoxifen without RT.	1,099 patients (55%) experienced disease recurrence. The first sites of failure were as follows: isolated locoregional failure, 254 (13%); locoregional failure with simultaneous distant failure, 166 (8%); and distant only, 679 (34%). The risk of locoregional failure with or without simultaneous distant failure at 10 years was 12.9% in patients with 1 to 3 positive nodes and 28.7% for patients with 4 or more positive nodes. Multivariate analysis showed that increasing tumor size, increasing numbers of involved nodes, negative ER protein status, and decreasing number of nodes examined were significant for increasing the rate of locoregional failure with or without simultaneous distant failure. Locoregional failure after mastectomy is a substantial clinical problem, despite the use of chemotherapy with or without tamoxifen. Prospective randomized trials will be necessary to estimate accurately the potential disease-free and OS benefits of PMRT for patient's in particular prognostic subgroups treated with presently used and future systemic therapy regimens.	4

\* See Last Page for Key

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
89. Whelan T, Olivotto I, Ackerman I, et al. NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. <i>J Clin Oncol.</i> 2011;29:(suppl; abstr LBA1003).	Experimental-Tx	1,832 women randomized to WBI + regional nodal irradiation (916) or WBI (916)	An intergroup trial of regional nodal irradiation in early breast cancer. Women with high risk node-negative or node-positive breast cancer treated with BCS and adjuvant chemotherapy and/or endocrine therapy were stratified by positive nodes, axillary nodes removed, chemo- and endocrine therapy and randomized to WBI (50 Gy in 25 fractions +/- boost irradiation) or WBI + regional nodal irradiation (45 Gy in 25 fractions) to the internal mammary, supraclavicular, and high axillary lymph nodes.	Median follow-up was 62 months. Characteristics of the study population were: mean age, 53.3 years; node negative, 10%; 1-3 positive nodes, 85%; >4 positive nodes, 5%; adjuvant chemotherapy, 91%; and adjuvant endocrine therapy, 71%. WBI + regional nodal irradiation in comparison to WBI alone was associated with an improvement in isolated locoregional disease free survival (DFS; HR=.59, $P=.02$ , 5 year risk: 96.8% and 94.5% respectively), distant DFS (HR=.64, $P=.002$ , 5 year risk: 92.4% and 87.0% respectively), DFS (HR=.68, $P=.003$ , 5 year risk: 89.7% and 84.0% respectively) and OS (HR=.76, $P=.07$ , 5 year risk: 92.3% and 90.7% respectively). WBI + regional nodal irradiation in comparison to WBI was associated with an increase in grade 2 or greater pneumonitis (1.3% and 0.2% respectively, $P=.01$ ), and lymphedema (7.3% and 4.1% respectively, $P=.004$ ).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
<p>90. Jagsi R, Ballman K, Chadha M, et al. Radiation field design on the ACOSOG Z0011 trial [P5-14-19]. Paper presented at: San Antonio Breast Cancer Symposium 2013; San Antonio, Texas.</p>	<p>Observational-Tx</p>	<p>856 patients</p>	<p>To ascertain that axillary lymph node dissection is unnecessary in breast cancer patients with 1 or 2 positive SLN who undergo lumpectomy, RT and systemic therapy.</p>	<p>Of the 891 patients enrolled on Z0011, 35 withdrew consent prior to surgery, leaving 856 who were analyzed in the primary report on trial outcomes. Among the 605 of these patients with a completed adjuvant RT form, 89% were noted to receive WBI. Of these, 89 patients (15%) were recorded as also receiving treatment to the supraclavicular region. Detailed RT records were received on 228 patients: 104/389 (26.7%) and 124/404 (30.7%) on the axillary lymph node dissection and SLN dissection arms, respectively. Of the 228 patients, 185 patients (81.1%) received tangent-only treatment. Among these 185 patients, there was sufficient data to evaluate tangent field height in 142 (76.8%). High tangent RT fields (with cranial tangent border within 2 cm of the humeral head) were used in 52.6% (40/76) patients randomized to the axillary lymph node dissection arm and 50% (33/66) patients randomized to the SLN dissection arm. Of the 228 patients with records reviewed, 43 (18.9%) received directed regional nodal RT using ≥3 fields: 22 in the axillary lymph node dissection and 21 in the SLN dissection arm. Those receiving directed nodal RT tended to have greater nodal involvement (<math>P&lt;0.001</math>).</p>	<p>2</p>

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
91. Hindie E, Groheux D, Hennequin C, et al. Lymphoscintigraphy can select breast cancer patients for internal mammary chain radiotherapy. <i>Int J Radiat Oncol Biol Phys.</i> 2012;83(4):1081-1088.	Review/Other-Tx	6 studies; 3,876 patients	To determine whether lymphoscintigraphy for axillary sentinel node biopsy might help in selecting patients for prophylactic internal mammary radiation.	Parasternal drainage was present in 792 patients (20.4%). Internal mammary biopsy was performed in 644 patients and was positive in 111 (17.2%). Of the positive internal mammary biopsies, 40% were associated with tumors in the lateral breast quadrants. A major difference in the internal mammary positivity rate was found according to the axilla sentinel node status. In patients with negative axilla, the internal mammary biopsy was positive in 7.8% of cases. In patients with positive axilla, however, the internal mammary biopsy was positive in 41% ( $P<.00001$ ). Because biopsy of multiple internal mammary hot nodes is difficult, the true risk could be even greater, probably close to 50%.	4
92. Yu JT, Provenzano E, Forouhi P, Malata CM. An evaluation of incidental metastases to internal mammary lymph nodes detected during microvascular abdominal free flap breast reconstruction. <i>J Plast Reconstr Aesthet Surg.</i> 2011;64(6):716-721.	Review/Other-Tx	43 patients	The authors report their experience with opportunistic internal mammary lymph node biopsy and its impact on the oncological management of the patients.	Of the 293 free flap breast reconstructions, 43 patients had 46 internal mammary lymph nodes harvested during 20 immediate and 26 delayed free flap breast reconstructions. 6 patients had positive nodes (4 immediate breast reconstruction and 2 delayed breast reconstruction), and were offered postoperative chemotherapy. 4 received radiotherapy to the internal mammary chain. 3 of the 4 internal mammary lymph node+ve immediate breast reconstruction patients have died of metastatic disease at 23, 33 and 55 months after reconstruction. The 2 internal mammary lymph node+ve delayed breast reconstruction patients were alive at 4 and 20 months.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
93. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. <i>Radiat Oncol.</i> 2013;8:267.	Review/Other-Tx	7,170 breast cancer patients from 3 randomized trials	To review 3 randomized trials to examine adjuvant radiotherapy of regional lymph nodes in breast cancer patients.	Regional radiation therapy of the medial supraclavicular lymph nodes and the internal mammary lymph nodes (MA.20 and EORTC) resulted in a significant improvement of OS (HR 0.85 (95% CL 0.75 - 0.96)). Adding the results of the French trial and using the random effects model to respect the different design of the French trial, the effect on OS of regional radiotherapy was still significant (HR 0.88 (95% CL 0.80–0.97)). The absolute benefits in OS were 1.6% in the MA.20 trial at 5 years, 1.6% in the EORTC trial at 10 years, and 3.3% in the French trial at 10 years (not significant in single trials). Regional radiotherapy of the medial supraclavicular lymph nodes and the internal mammary lymph nodes (MA.20 and EORTC) was associated with a significant improvement of DFS (HR 0.85 (95% CL 0.77 - 0.94)) and distant metastasis free survival (HR 0.82 (95% CL 0.73–0.92)). The effect sizes were not significantly different between trials for any end point.	4
94. Poortmans PM, Bollet M, Van Limbergen E. Infiltrating lobular breast cancer: truly a separate entity! Consequences for radiation therapy. <i>Radiother Oncol.</i> 2013;106(1):1-4.	Review/Other-Tx	N/A	To review the particular aspects of locoregional treatment for patients with the lobular variant of breast cancer.	Infiltrating lobular cancer patients do not have a higher local recurrence risk after breast conserving therapy. Lobular histology should also be considered as a separate prognostic factor in favor of referral for radiotherapy after mastectomy.	4
95. Matzinger O, Heimsoth I, Poortmans P, et al. Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925). <i>Acta Oncol.</i> 2010;49(1):24-34.	Experimental-Tx	3,866 patients	Phase III study to investigate the potential survival benefit and toxicity of elective irradiation of the internal mammary and medial supraclavicular nodes.	Only lung (fibrosis; dyspnoea; pneumonitis; any lung toxicities) (4.3% vs 1.3%; P<0.0001) but not cardiac toxicity (0.3% vs 0.4%; P=0.55) significantly increased with internal mammary and medial supraclavicular treatment. Internal mammary and medial supraclavicular irradiation seems well tolerated and does not significantly impair WHO performance status at 3 years. A follow-up period of at least 10 years is needed to determine whether cardiac toxicity is increased after RT.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
96. Hayes SB, Freedman GM, Li T, Anderson PR, Ross E. Does axillary boost increase lymphedema compared with supraclavicular radiation alone after breast conservation? <i>Int J Radiat Oncol Biol Phys.</i> 2008;72(5):1449-1455.	Observational-Tx	2,579 total women with T1-2, N0-3, M0 breast cancer treated with breast conservation: 2,169 (84%) received RT to the breast; 226 (8.8%); to the breast and supraclavicular lymph nodes; 184 (7.1%) to the breast, supraclavicular lymph nodes, and a posterior axillary boost	To determine independent predictors of lymphedema after breast RT and to quantify added risks of lymphedema from regional node irradiation.	Median follow-up was 81 months. 18% of patients developed lymphedema. Lymphedema risks were as follows: 16% breast, 23% breast and supraclavicular, and 31% breast, supraclavicular, and a posterior axillary boost ( $P<0.0001$ ). Lymphedema severity was greater in patients who had regional node irradiation ( $P=0.0002$ ). On multivariate analysis, RT field ( $P<0.0001$ ), obesity index ( $P=0.0157$ ), systemic therapy ( $P=0.0013$ ), and number of lymph nodes dissected ( $P<0.0001$ ) independently predicted for lymphedema. In N1 patients, the addition of a supraclavicular to tangents ( $P<0.0001$ ) and the addition of a posterior axillary boost to tangents ( $P=0.0017$ ) conferred greater risks of lymphedema, but adding a posterior axillary boost to breast and supraclavicular RT did not ( $P=0.8002$ ). In the N2 patients, adding a posterior axillary boost increased the risk of lymphedema 4.5-fold over breast and supraclavicular RT ( $P=0.0011$ ). Lymphedema predictors included number of lymph nodes dissected, regional node irradiation, obesity index, and systemic therapy. Lymphedema risk increased when a supraclavicular or posterior axillary boost were added in the N1 subgroup. In the N2 patients, a posterior axillary boost increased the risk over breast and supraclavicular. The decision to boost the axilla must be weighed against the increased risk of lymphedema that it imposes.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
97. Polgar C, Major T, Fodor J, et al. Accelerated partial-breast irradiation using high-dose-rate interstitial brachytherapy: 12-year update of a prospective clinical study. <i>Radiother Oncol.</i> 2010;94(3):274-279.	Experimental-Tx	45 total patients: 8 patients 30.3 Gy; 37 patients 36.4 Gy	To prospectively report the 12-year updated results of APBI using multicatheter interstitial high-dose-rate brachytherapy.	Median follow-up time was 133 months. 4 (8.9%) IBTR were observed, for a 5-, 10-, and 12-year actuarial rate of 4.4%, 9.3%, and 9.3%, respectively. A total of 2 regional nodal failures were observed for a 12-year actuarial rate of 4.4%. The 12-year DFS, CSS, and OS were 75.3%, 91.1%, and 88.9%, respectively. 12 year results with APBI using high-dose-rate multicatheter interstitial implants continue to demonstrate excellent long-term local tumor control, survival, and cosmetic results with a low-rate of late side effects.	2
98. Vicini FA, Antonucci JV, Wallace M, et al. Long-term efficacy and patterns of failure after accelerated partial breast irradiation: a molecular assay-based clonality evaluation. <i>Int J Radiat Oncol Biol Phys.</i> 2007;68(2):341-346.	Observational-Tx	199 total patients	To prospectively determine the long-term efficacy and cosmetic results of APBI.	The median follow-up for surviving patients was 8.6 years. 6 IBTR were observed, for a 5-year and 10-year actuarial rate of 1.6% and 3.8%, respectively. 3 regional nodal failures were observed, for a 10-year actuarial rate of 1.6%. 5 CBC developed, for a 5- and 10-year actuarial rate of 2.2% and 5.2%, respectively. 83 % of IBTRs (n=5) were classified as clonally related. Cosmetic results were rated as excellent/good in 99% of patients. Long-term results with APBI using interstitial brachytherapy continue to demonstrate excellent long-term local and regional control rates and cosmetic results. According to a polymerase chain reaction-based loss of heterozygosity assay, 83% of recurrences were classified as clonally related.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
99. Shaitelman SF, Vicini FA, Beitsch P, Haffty B, Keisch M, Lyden M. Five-year outcome of patients classified using the American Society for Radiation Oncology consensus statement guidelines for the application of accelerated partial breast irradiation: an analysis of patients treated on the American Society of Breast Surgeons MammoSite Registry Trial. <i>Cancer</i> . 2010;116(20):4677-4685.	Observational-Tx	1,449 breasts in 1,440 patients	ASTRO consensus statement for the application of APBI was applied to patients who were treated with this technique on the American Society of Breast Surgeons MammoSite Registry Trial to determine potential differences in clinical outcome based on classification group.	Of the 1,449 cases who were treated, 1,025 patients (71%) could be classified according to the consensus statement groupings, including 419 patients (41%) who fit the “suitable” criteria, 430 patients (42%) who fit the “cautionary” criteria, and 176 patients (17%) who fit the “unsuitable” criteria. At a median follow-up of 53.5 months, the 5-year actuarial rates of IBTR for the “suitable,” “cautionary,” and “unsuitable” groups were 2.59%, 5.43%, and 5.28%, respectively ( $P=.1884$ ). Univariate analysis of factors potentially associated with IBTR indicated that negative ER status was the only variable associated with IBTR among patients with invasive breast cancer (OR, 4.01; $P=.0003$ ). Larger tumor size was associated with a greater risk of distant metastasis (OR, 3.05; $P=.0001$ ). Among patients with ductal carcinoma in situ, only age <50 years and close-positive margins were associated with IBTR (OR, 1.12 [ $P=.0079$ ] and OR, 7.81 [ $P=.0131$ ], respectively).	2
100. Formenti SC, Hsu H, Fenton-Kerimian M, et al. Prone accelerated partial breast irradiation after breast-conserving surgery: five-year results of 100 patients. <i>Int J Radiat Oncol Biol Phys</i> . 2012;84(3):606-611.	Experimental-Tx	100 patients	To report the 5-year results of a prospective trial of 3D-CRT to deliver APBI in the prone position.	At a median follow-up of 64 months (range, 2-125 months), there was 1 LR (1%) and 1 CBC (1%). There were no deaths due to breast cancer by 5 years. Grade 3 late toxicities occurred in 2 patients (1 breast edema, 1 transient breast pain). Cosmesis was rated good/excellent in 89% of patients with at least 36 months follow-up.	2
101. Pashtan IM, Recht A, Ancukiewicz M, et al. External beam accelerated partial-breast irradiation using 32 Gy in 8 twice-daily fractions: 5-year results of a prospective study. <i>Int J Radiat Oncol Biol Phys</i> . 2012;84(3):e271-277.	Experimental-Tx	98 patients	To present 5-year results of a study involving external beam APBI using 32 Gy in 8 twice-daily fractions.	5 patients developed IBTR, for a 5-year actuarial IBTR rate of 5% (95% CI, 1%–10%). 3 of these cases occurred in patients with triple-negative disease and 2 in nontriple-negative patients, for 5-year actuarial IBTR rates of 33% (95% CI, 0%–57%) and 2% (95% CI, 0%–6%; $P<.0001$ ), respectively. On multivariable analysis, triple-negative phenotype was the only predictor of IBTR, with borderline statistical significance after adjusting for tumor grade ( $P=.0537$ ).	2

Conservative Surgery and Radiation-Stage I and II Breast Cancer  
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
102. Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. <i>J Clin Oncol.</i> 2013;31(32):4038-4045.	Experimental-Tx	2,135 women	To report interim cosmetic and toxicity results of a multicenter randomized trial comparing APBI using 3D-CRT with WBI.	Between 2006 and 2011, 2,135 women were randomly assigned to 3D-CRT, APBI, or WBI. Median follow-up was 36 months. Adverse cosmesis at 3 years was increased among those treated with APBI compared with WBI as assessed by trained nurses (29% vs 17%; $P<.001$ ), by patients (26% vs 18%; $P=.0022$ ), and by physicians reviewing digital photographs (35% vs 17%; $P<.001$ ). Grade 3 toxicities were rare in both treatment arms (1.4% vs 0%), but grade 1 and 2 toxicities were increased among those who received APBI compared with WBI ( $P<.001$ ).	1
103. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. <i>Lancet.</i> 2010;376(9735):91-102.	Experimental-Tx	2,232 total patients	Randomized, prospective trial to compare targeted intraoperative RT with the conventional policy of whole breast EBRT.	The Kaplan-Meier estimate of LR in the conserved breast at 4 years was 1.20% (95% CI, 0.53–2.71) in the targeted intraoperative RT and 0.95% (0.39–2.31) in the EBRT group (difference between groups 0.25%, –1.04 to 1.54; $P=0.41$ ). The frequency of any complications and major toxicity was similar in the 2 groups (for major toxicity, targeted intraoperative RT, 37 [3.3%] of 1,113 vs EBRT, 44 [3.9%] of 1,119; $P=0.44$ ). RT toxicity (RTOG grade 3) was lower in the targeted intraoperative RT group (6 patients [0.5%]) than in the EBRT group (23 patients [2.1%]; $P=0.002$ ). For selected patients with early breast cancer, a single dose of RT delivered at the time of surgery by use of targeted intraoperative RT should be considered as an alternative to EBRT delivered over several weeks.	1

**Conservative Surgery and Radiation-Stage I and II Breast Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
104. Veronesi U, Orecchia R, Luini A, et al. Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. <i>Breast Cancer Res Treat.</i> 2010;124(1):141-151.	Experimental-Tx	1,822 total patients	To evaluate the effects of intraoperative RT with electrons after conservative surgery for breast carcinoma.	Local side effects of intraoperative RT with electrons were mainly liponecrosis (4.2%) and fibrosis (1.8%). After a mean follow-up of 36.1 months, 42 women (2.3%) developed a LR, 24 (1.3%) a new primary ipsilateral carcinomas and 26 (1.4%) distant metastases as first event. 46 women died (2.5%), 28 for breast carcinoma and 18 for other causes. 5- and 10-year survivals were, respectively, 97.4 and 89.7%. Intraoperative RT with electrons appears a promising feature in early breast cancer treated with BCS, reducing the exposure of normal tissues to radiations and shortening the radiation course from 6 weeks to 1 single session.	1

Conservative Surgery and Radiation-Stage I and II Breast Cancer  
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
105. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. <i>Lancet</i> . 2014;383(9917):603-613.	Experimental-Tx	3,451 patients: 1,721 patients were randomized to targeted intraoperative RT and 1,730 to EBRT	To compare risk-adapted RT using single-dose targeted intraoperative RT with fractionated EBRT for breast cancer. The authors report 5-year results for LR and the first analysis of OS.	Supplemental EBRT after targeted intraoperative RT was necessary in 15.2% [239/1,571] of patients who received targeted intraoperative RT (21.6% prepathology, 3.6% postpathology). 3,451 patients had a median follow-up of 2 years and 5 months (IQR 12–52 months), 2,020 of 4 years, and 1,222 of 5 years. The 5-year risk for LR in the conserved breast was 3.3% (95% CI, 2.1–5.1) for targeted intraoperative RT vs 1.3% (0.7–2.5) for EBRT ( $P=0.042$ ). Targeted intraoperative RT concurrently with lumpectomy (prepathology, $n=2,298$ ) had much the same results as EBRT: 2.1% (1.1–4.2) vs 1.1% (0.5–2.5; $P=0.31$ ). With delayed targeted intraoperative RT (postpathology, $n=1,153$ ) the between-group difference was larger than 2.5% (targeted intraoperative RT 5.4% [3.0–9.7] vs EBRT 1.7% [0.6–4.9]; $P=0.069$ ). Overall, breast cancer mortality was much the same between groups (2.6% [1.5–4.3] for targeted intraoperative RT vs 1.9% [1.1–3.2] for EBRT; $P=0.56$ ) but there were significantly fewer non-breast-cancer deaths with targeted intraoperative RT (1.4% [0.8–2.5] vs 3.5% [2.3–5.2]; $P=0.0086$ ), attributable to fewer deaths from cardiovascular causes and other cancers. Overall mortality was 3.9% (2.7–5.8) for targeted intraoperative RT vs 5.3% (3.9–7.3) for EBRT ( $P=0.099$ ). Wound-related complications were much the same between groups but grade 3 or 4 skin complications were significantly reduced with targeted intraoperative RT (4/1,720 vs 13/1,731, $P=0.029$ ).	1

**Conservative Surgery and Radiation-Stage I and II Breast Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
106. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. <i>Lancet Oncol.</i> 2013;14(13):1269-1277.	Experimental-Tx	1,305 patients randomized (654 to EBRT and 651 to intraoperative RT)	The results of a randomized equivalence study comparing LR and OS after electron intraoperative RT with postoperative EBRT is presented.	After a medium follow-up of 5.8 years (IQR 4.1–7.7), 35 patients in the intraoperative RT group and 4 patients in the EBRT group had had an IBTR ( $P<0.0001$ ). The 5-year event rate for IBTR was 4.4% (95% CI, 2.7–6.1) in the intraoperative RT group and 0.4% (0.0–1.0) in the EBRT group (HR 9.3 [95% CI, 3.3–26.3]). During the same period, 34 women allocated to intraoperative RT and 31 to EBRT died ( $P=0.59$ ). 5-year OS was 96.8% (95% CI, 95.3–98.3) in the intraoperative RT group and 96.9% (95.5–98.3) in the EBRT group. In patients with data available (n=464 for intraoperative RT; n=412 for EBRT) we noted significantly fewer skin side-effects in women in the intraoperative RT group than in those in the EBRT group ( $P=0.0002$ ).	1
107. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). <i>Int J Radiat Oncol Biol Phys.</i> 2009;74(4):987-1001.	Review/Other-Tx	645 original research articles; 4 published randomized clinical trials and 38 prospective single-arm studies	To present guidance for patients and physicians regarding the use of APBI based on current published evidence complemented by expert opinion.	Task Force proposed 3 patient groups: a “suitable” group, for whom APBI outside of a clinical trial is acceptable, a “cautionary” group, for whom caution and concern should be applied when considering APBI outside of a clinical trial, and an “unsuitable” group, for whom APBI outside of a clinical trial is not generally considered warranted. RT is a new technology that may ultimately demonstrate long-term effectiveness and safety comparable to that of WBI for selected patients with early breast cancer.	4

Conservative Surgery and Radiation-Stage I and II Breast Cancer  
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
108. Formenti SC, Volm M, Skinner KA, et al. Preoperative twice-weekly paclitaxel with concurrent radiation therapy followed by surgery and postoperative doxorubicin-based chemotherapy in locally advanced breast cancer: a phase I/II trial. <i>J Clin Oncol.</i> 2003;21(5):864-870.	Experimental-Tx	44 patients	Phase I/II trial to examine the safety and efficacy of primary twice-weekly paclitaxel and concurrent RT before MRM followed by adjuvant doxorubicin-based chemotherapy.	Toxicity from paclitaxel/RT included grade 3 skin desquamation (7%), hypersensitivity (2%), and stomatitis (2%). Postsurgery complications occurred in 6 patients (14%). The only grade 4 toxicity of postmastectomy chemotherapy was hematologic (10%). Grade 3 toxicities were leukopenia (24%), infection (22%), peripheral neuropathy (17%), arthralgia and pain (17%), stomatitis (12%), fatigue (10%), esophagitis (5%), and nausea (2%). Overall clinical response rate to preoperative paclitaxel and RT was 91%. 34% of patients achieved a pathologic response in the mastectomy specimen: 16% pathologic complete responses (clearance of invasive cancer in the breast and axillary contents) and 18% pathologic partial responses (<10 residual microscopic foci of invasive breast cancer). Twice-weekly paclitaxel with concurrent RT is a feasible and effective primary treatment for locally advanced breast cancer.	1
109. Burstein HJ, Bellon JR, Galper S, et al. Prospective evaluation of concurrent paclitaxel and radiation therapy after adjuvant doxorubicin and cyclophosphamide chemotherapy for Stage II or III breast cancer. <i>Int J Radiat Oncol Biol Phys.</i> 2006;64(2):496-504.	Experimental-Tx	40 patients	To evaluate the safety and feasibility of concurrent RT and paclitaxel-based adjuvant chemotherapy, given either weekly or every 3 weeks, after adjuvant doxorubicin and cyclophosphamide.	Weekly paclitaxel treatment at 60 mg/m <sup>2</sup> per week with concurrent radiation led to dose-limiting toxicity in 4/16 patients (25%), including 3 who developed pneumonitis (either Grade 2 [1 patient] or Grade 3 [2 patients]) requiring steroids. Efforts to eliminate this toxicity in combination with weekly paclitaxel through treatment scheduling and computed tomography-based RT simulation were not successful. By contrast, dose-limiting toxicity was not encountered among patients receiving concurrent radiation with paclitaxel given every 3 weeks at 135-175 mg/m <sup>2</sup> . However, Grade 2 radiation pneumonitis not requiring steroid therapy was seen in 2/24 patients (8%) treated in such a fashion. Excessive radiation dermatitis was not observed with either paclitaxel schedule.	2

Conservative Surgery and Radiation-Stage I and II Breast Cancer  
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
110. Bellon JR, Come SE, Gelman RS, et al. Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: updated results of a prospective randomized trial. <i>J Clin Oncol.</i> 2005;23(9):1934-1940.	Experimental-Tx	244 total patients: 122 chemotherapy followed by RT (chemotherapy-first arm); 122 RT followed by the same chemotherapy regimen (designated as the RT-first arm)	Updated results of a prospective randomized trial to determine the optimal integration of chemotherapy with RT for patients with early-stage breast cancer.	Median follow-up for surviving patients was 135 months. There were no significant differences between the chemotherapy-first and RT-first arms in time to any event, distant metastasis, or death. Sites of first failure were also not significantly different. Among breast cancer patients treated with conservative surgery, there is no advantage to giving RT before adjuvant chemotherapy. However, this study does not have enough statistical power to rule out a clinically important survival benefit for either sequence.	1
111. Pierce LJ, Moughan J, White J, Winchester DP, Owen J, Wilson JF. 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. <i>Int J Radiat Oncol Biol Phys.</i> 2005;62(1):183-192.	Review/Other-Tx	71,877 patient records obtained from a stratified 2-stage sampling of 353 patient records	A 1998-1999 patterns of care study process survey of national practice patterns using BCS and RT in the management of stage I-II breast cancer.	Improved quantification of an intraductal component from 7.0% in 1993–1994 to 20.4% in 1998–1999 ( $P=0.01$ ). Tumor characteristics were better defined, with estrogen and PR measurement performed in 91.4% and 91.3% in the 1998–1999 survey vs 83.7% and 80.3% in the 1989 survey, respectively ( $P=0.03$ and $P=0.002$ , respectively). Axillary dissection was performed in 82.2% in the present survey compared with 93.6% in the 1993–1994 survey ( $P=0.0004$ ); sentinel node biopsy was performed in 20.1% of the present cases. Use of CT for planning was increased in the current survey, with 22.9% cases CT planned vs 9% in 1993–1994 ( $P=0.10$ ). In the present survey, 100% had received WBI. When a supraclavicular field was added, the dose was prescribed to a specified depth in 67.5% of cases, most commonly 3 cm. Chemotherapy and tamoxifen was used in 36% and 55.8% of patients, respectively, in the 1998–1999 survey, representing a statistically significant increase compared with the 1993–1994 survey, despite comparable pathologic tumor size and nodal involvement.	4

Conservative Surgery and Radiation-Stage I and II Breast Cancer  
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
112. Pierce LJ, Hutchins LF, Green SR, et al. Sequencing of tamoxifen and radiotherapy after breast-conserving surgery in early-stage breast cancer. <i>J Clin Oncol.</i> 2005;23(1):24-29.	Observational-Tx	2,690 patients	Retrospective study to evaluate the optimal sequencing of tamoxifen and RT after BCS. Southwest Oncology Group trial 8897 (Intergroup 0102) was reviewed. For this analysis, data are reported only in the tamoxifen groups. RT was allowed either before adjuvant therapy (sequential RT; 107 patients) or after chemotherapy but concurrent with tamoxifen (concurrent RT; 202 patients).	With a median follow-up of 10.3 years, 10-year disease free status values were 83% and 83% for concurrent vs sequential RT groups (log-rank $P=.73$ ; $P=.76$ adjusted for patient characteristics), and 10-year OS were 88% and 90%, respectively (log-rank $P=.59$ ; adjusted $P=.65$ ). Patterns of failure showed no increase in in-breast recurrence rates between concurrent RT and sequential RT groups, with 10-year LR rates of 7% for concurrent RT and 5% for sequential RT (HR, 0.73; 95% CI, 0.26-2.04; $P=.54$ ). Current analysis does not suggest an adverse effect on local or systemic control with concurrent vs sequential tamoxifen and RT in node-negative breast cancer. A randomized trial is encouraged to validate these results.	1
113. Ahn PH, Vu HT, Lannin D, et al. Sequence of radiotherapy with tamoxifen in conservatively managed breast cancer does not affect local relapse rates. <i>J Clin Oncol.</i> 2005;23(1):17-23.	Observational-Tx	1,649 total patients with stage I or II breast cancer; 500 received tamoxifen	To evaluate whether the sequencing of tamoxifen relative to RT affects outcome in breast cancer patients treated with conservative surgery plus RT (lumpectomy with RT).	At a median follow-up of 10 years, there were no significant differences between the concurrent-tamoxifen and sequential-tamoxifen groups in OS (84% vs 82%; HR, 1.234; 95% CI, 0.42 to 2.05; $P=.45$ ), distant-metastasis-free rate (82% vs 78%; HR, 1.55; 95% CI, 0.89 to 2.68; $P=.12$ ), ipsilateral breast-relapse-free rate (90% vs 86%; HR, 0.932; 95% CI, 0.42 to 2.05; $P=.86$ ), or contralateral breast-relapse-free rate (95% vs 93%; HR, 0.892; 95% CI, 0.53 to 1.48; $P=.66$ ). Although the concurrent use of tamoxifen with RT may theoretically render cancer cells less responsive to RT, this retrospective study suggests that in practical application, concurrent administration of tamoxifen with RT does not compromise local control.	2

**Conservative Surgery and Radiation-Stage I and II Breast Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
114. Harris EE, Christensen VJ, Hwang WT, Fox K, Solin LJ. Impact of concurrent versus sequential tamoxifen with radiation therapy in early-stage breast cancer patients undergoing breast conservation treatment. <i>J Clin Oncol.</i> 2005;23(1):11-16.	Observational-Tx	174 tamoxifen given during RT followed by continued tamoxifen (concurrent); 104 RT followed by tamoxifen (sequential)	To retrospectively assess the impact of sequencing of tamoxifen and RT on outcomes in early-stage breast cancer.	Median follow-up after RT was 8.6 years for both groups. The pathologic T and N stage, race, estrogen and progesterone status, number of positive nodes, and RT were comparable between the 2 groups (all $P \geq .08$ ). More women age $\leq 49$ years of age and women who received chemotherapy were in the sequential group than the concurrent group (6% and 25%, respectively; $P < .0001$ ). The sequence of tamoxifen therapy did not influence 10-year LR rates (sequential, 7%; concurrent, 3%; $P = .52$ ), OS (sequential, 86%; concurrent, 81%; $P = .64$ ), or relapse-free survival (sequential, 76%; concurrent, 85%; $P = .35$ ). When adjusting age and chemotherapy use in the multivariable Cox model, HR comparing sequential vs concurrent tamoxifen therapy were 1.56 (95% CI, 0.87 to 2.79), 1.23 (95% CI, 0.63 to 2.41), and 1.22 (95% CI, 0.33 to 4.49) for the OS, relapse-free survival, and LR, respectively. The therapeutic regimens of tamoxifen given concurrently or sequentially with RT both appear to be reasonable options for patients treated with BCT.	2
115. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. <i>N Engl J Med.</i> 2005;353(16):1659-1672.	Experimental-Tx	5,081 total patients: 1,694 2-years with trastuzumab; 1,694 1-year with trastuzumab; 1,693 assigned to observation	A randomized trial to investigate the efficacy and safety of trastuzumab after excision of early-stage breast cancer and completion of chemotherapy.	Median follow-up of 1-year. The unadjusted HR for an event in the trastuzumab group, as compared with the observation group, was 0.54 (95% CI, 0.43 to 0.67; $P < 0.0001$ by the log-rank test, crossing the interim analysis boundary), representing an absolute benefit in terms of DFS at 2 years of 8.4 percentage points. OS in the 2 groups was not significantly different. Severe cardiotoxicity developed in 0.5% of the women who were treated with trastuzumab. 1 year of treatment with trastuzumab after adjuvant chemotherapy significantly improves DFS among women with HER-2-positive breast cancer.	1

Conservative Surgery and Radiation-Stage I and II Breast Cancer  
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
116. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. <i>N Engl J Med.</i> 2005;353(16):1673-1684.	Review/Other-Tx	394 reported events; 133 in the trastuzumab group; 261 controls	2 randomized trials that compared adjuvant chemotherapy with or without concurrent trastuzumab in women with surgically removed HER-2-positive breast cancer.	The absolute difference in DFS between the trastuzumab group and the control group was 12% at 3 years. Trastuzumab therapy was associated with a 33% reduction in the risk of death (P=0.015). The 3-year cumulative incidence of class III or IV congestive heart failure or death from cardiac causes in the trastuzumab group was 4.1% in trial B-31 and 2.9% in trial N9831. Trastuzumab combined with paclitaxel after doxorubicin and cyclophosphamide improves outcomes among women with surgically removed HER-2-positive breast cancer.	4
117. Halyard MY, Pisansky TM, Dueck AC, et al. Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831. <i>J Clin Oncol.</i> 2009;27(16):2638-2644.	Experimental-Tx	1,503 irradiated patients for RT-associated adverse events across treatment arms: 1,418 (73.2%) received adjuvant RT; 450 (23.2%) received no RT; 70 (3.6%) had unknown RT status	To assess whether trastuzumab with RT increases adverse events after BCS or mastectomy.	No significant differences among arms were found in incidence of acute skin reaction, pneumonitis, dyspnea, cough, dysphagia, or neutropenia. A significant difference occurred in incidence of leukopenia, with higher rates for doxorubicin and cyclophosphamide-paclitaxel-trastuzumab vs doxorubicin and cyclophosphamide-paclitaxel (OR = 1.89; 95% CI, 1.25 to 2.88). At a median follow-up of 3.7 years (range, 0 to 6.5 years), RT with trastuzumab did not increase relative frequency of cardiac events regardless of treatment side. The cumulative incidence of cardiac events with doxorubicin and cyclophosphamide-paclitaxel-trastuzumab was 2.7% with or without RT. With doxorubicin and cyclophosphamide-paclitaxel-trastuzumab, the cumulative incidence was 1.7% vs 5.9% with or without RT, respectively. Concurrent adjuvant RT and trastuzumab for early-stage breast cancer was not associated with increased acute adverse events. Further follow-up is required to assess late adverse events.	1

## Evidence Table Key

### Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  - a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  - b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  - c) the study is an expert opinion or consensus document.
- M = Meta-analysis

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Dx = Diagnostic

Tx = Treatment

## Abbreviations Key

3D-CRT = 3D conformal external beam radiotherapy

APBI = Accelerated partial-breast irradiation

BCS = Breast-conserving surgery

BCT = Breast-conserving therapy

CBC = Contralateral breast cancer

CSS = Cause-specific survival

DFS = Disease-free survival

EBRT = External beam radiation therapy

ER = Estrogen receptor

HR = Hazard ratio

IBE = Ipsilateral breast event

IBTRs = Ipsilateral breast tumor recurrences

IDC = Invasive ductal carcinoma

ILC = Invasive lobular carcinoma

IMRT = Intensity-modulated radiotherapy

LR = Local recurrence

LRR = Locoregional relapse

MRI = Magnetic resonance imaging

MRM = Modified radical mastectomy

OR = Odds ratio

OS = Overall survival

PR = Progesterone receptor

RT = Radiation therapy

SLN = Sentinel lymph node

US = Ultrasound

WBI = Whole-breast irradiation