Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; 347(16):1227-1232.	Observational-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 two 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
2. Blichert-Toft M, Nielsen M, During 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. *Acta Oncol* 2008; 47(4):672-681.	Experimental-Tx	793 patients	To compare the long-term efficacy of BCS vs mastectomy based on a randomized design.	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. Including the complete series comprising 1,133 eligible patients based on treatment in fact given similarly no significant difference between surgical options could be traced in outcome of 10-year recurrence free survival and 20-year OS, P=0.94 and P=0.24, respectively. The pattern of recurrences as a first event in breast conservation vs mastectomy did not differ significantly irrespective of site, P=0.27. Looking into the type of local relapse, viz., new primaries vs true recurrences, it appeared that new primaries were significantly associated to BCS, while true recurrences dominated among mastectomy treated patients (P<0.001).	1

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3. Moran MS, Haffty BG. Local-regional breast cancer recurrence: prognostic groups based on patterns of failure. *Breast J* 2002; 8(2):81-87.	Observational-Tx	213: 68 relapsed in the ipsilateral breast following CS + RT within 5 years of original diagnosis (EARLYBR); 51 relapsed in the ipsilateral breast after 5 years from original diagnosis (LATEBR); 35 relapsed in the chest wall within 5 years following mastectomy (EARLCW); 18 relapsed in the chest wall later than 5 years following mastectomy, and 41 failed in the regional lymphatics following mastectomy or CS + RT (REGREC)	To determine the outcome of breast cancer patients sustaining local-regional failure as their first site of relapse in an effort to group patients into prognostic categories.	Overall 10-year survival for all 213 patients was 61%, and the 10-year distant metastasis-free rate was 59%. Patients with a LATEBR had a relatively favorable prognosis with a 5-year postrelapse distant metastasis rate of 80%. Patients with EARLYBR and LATECW had a similar prognosis, with a 5-year postrelapse distant metastasis rate of 61% and 65%, respectively. Patients with an EARLCW had a 5-year distant recurrence-free rate following a local relapse of 42%. 10-year survivals from original diagnosis were 62% and 50%, respectively, and distant metastasis-free survival rates were 56% and 52%, respectively. Patients suffering REGREC following mastectomy or CS + RT carried a poor prognosis with a 10-year survival of 33% and a 10-year distant metastasis-free rate of 30%. Placing patients with breast cancer and local-regional relapse into these prognostic categories may be helpful in decision making regarding the role of systemic therapy at the time of local-regional relapse.	1

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4. van Tienhoven G, Voogd AC, Peterse JL, et al. Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. *Eur J Cancer* 1999; 35(1):32-38.	Experimental-Tx	1,807 patients with stage I and II breast cancer randomized to receive either MRM or BCT	To investigate and compare the prognosis after treatment for LRR after MRM or BCT, in terms of OS and time to subsequent LRR, in patients originally treated in two European randomized trials.	The 5-year survival rates were 58% and 59% and the 5-year subsequent loco-regional control rates 62% and 63%, respectively. pN category, pT category and vascular invasion (P=0.02) of the primary tumor were the only independent prognostic factors for survival, whereas extensive LRR (P<0.001), interval ≤2 years (P<0.002) and pN+ at primary treatment (P=0.004) were significant predictive factors for time to subsequent LRR. The type of original treatment (MRM or BCT) did not have any prognostic impact. The survival and time to subsequent LRR after treatment for an early LRR after MRM or BCT was similar. This suggests that both after MRM and BCT an early LRR is an indicator of a biologically aggressive tumor; early loco-regional relapse carries a poor prognosis and salvage treatment only cures a limited number of patients, whether treated by MRM or BCT originally.	1
5. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 366(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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
6. Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Loco-regional recurrence after mastectomy in high-risk breast cancer--risk and prognosis. An analysis of patients from the DBCG 82 b&c randomization trials. *Radiother Oncol* 2006; 79(2):147-155.	Experimental-Tx	3,083 patients with stage I and II breast cancer randomized to receive post-mastectomy RT or no RT	A randomized study to compare the efficacy of post-mastectomy RT vs no RT in addition to systemic therapy and to identify risk factors for LRR, to evaluate the treatment of LRR and to examine the prognosis after LRR.	In univariate analyses, large primary tumor size, ductal carcinoma, high malignancy grade, fascia invasion, few removed nodes, many positive nodes and extracapsular invasion were all risk factors for developing LRR. Combined treatment with surgery and RT at the time of LRR increased the persistent loco-regional control. In multivariate analysis, large primary tumor size, many positive nodes, extracapsular invasion, supra/infraclavicular failures, multiple LRR and a short-interval <2 years to first LRR were poor prognostic factors for survival. 28% of LRR patients had no distant metastases 5 years after failure. Initial randomization group did not alter the prognosis after LRR. Combined treatment of the LRR with surgery and RT improved persistent loco-regional control compared with surgery or RT alone.	1
7. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst* 2005; 97(2):116-126.	Observational-Tx	318 patients randomly assigned to receive no further therapy or RT	To determine the survival impact of locoregional RT in premenopausal LN positive patients treated by MRM and adjuvant chemotherapy through a randomized study.	Chemotherapy and RT, compared with chemotherapy alone, were associated with a statistically significant improvement in all end points analyzed, including survival free of isolated LRR (74% vs 90%), systemic relapse-free survival (31% vs 48%); OS (47% vs 37%). For patients with high-risk breast cancer treated with MRM, treatment with RT (schedule of 16 fractions) and adjuvant chemotherapy leads to better survival outcomes than chemotherapy alone, and it is well tolerated, with acceptable long-term toxicity.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
8. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. *Radiother Oncol* 2007; 82(3):247-253.	Experimental-Tx	1,152 patients randomized to postoperative RT in addition to adjuvant systemic therapy	A randomized study to evaluate the 15-year LRR rate and survival in relation to number of positive nodes.	The overall 15-year survival rate in the subgroup was 39% and 29% (P=0.015) after RT and no RT, respectively. RT reduced LRF rate from 51% to 10% (P<0.001) in 4+ positive node patients and from 27% to 4% (P<0.001) in patients with 1–3 positive nodes. Survival benefit after RT was significantly improved in 1–3 positive nodes (57% vs 48%, P=0.03) 4+ positive nodes (21% vs 12%, P=0.03). The survival benefit after postmastectomy RT was substantial and similar in patients with 1-3 and 4+ positive LN. Furthermore, it was not strictly associated with the risk of LRR, which was most pronounced in patients with 4+ positive nodes. The indication for RT seems therefore to be at least equally beneficial in patients with 1-3 positive nodes, and future consensus should be modified accordingly.	1
9. Whelan TJ, Olivotto I, Ackerman I, et al. NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. *J Clin Oncol* 2011; 29:(suppl; abstr LBA1003).	Experimental-Tx	1,832 women randomly assigned to WBI + regional nodal irradiation (916) or WBI alone (916)	To evaluate the addition of regional nodal irradiation to WBI following BCS.	WBI + regional nodal irradiation in comparison to WBI alone was associated with an improvement in isolated locoregional 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 alone 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
10. Arriagada R, Le MG, Contesso G, Guinebretiere JM, Rochard F, Spielmann M. Predictive factors for local recurrence in 2006 patients with surgically resected small breast cancer. *Ann Oncol* 2002; 13(9):1404-1413.	Observational-Tx	2,006 patients: 717 treated with lumpectomy and breast RT; 1,289 treated with total mastectomy	To investigate whether factors predictive of LR differ between patients treated with CS or radical surgery.	Statistically significant predictive factors for mastectomized patients were histological grade, extensive axillary node involvement (10 nodes or more), and inner quadrant tumors, which were of borderline significance. Young age, however, was not a prognostic indicator for LR. The main statistically significant factor for patients treated with a conservative approach was young age (≤40 years). Young age (≤40) was predictive for LR in patients treated with BCT. Extensive axillary node involvement (10+ nodes) was predictive for LR in patients treated with mastectomy.	2
11. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007; 25(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 ≤40 years old after RT with boost was 13.5% vs 3.8% for those greater than 60 years old.	1
12. de Bock GH, van der Hage JA, Putter H, Bonnema J, Bartelink H, van de Velde CJ. Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. *Eur J Cancer* 2006; 42(3):351-356.	Review/Other-Tx	3,602 patients	To evaluate prognostic factors for isolated LRR in stage I or II breast cancer.	Young age and BCT are both independent predictors for isolated LRR. As an isolated LRR is a potentially curable condition, women treated with breast conservation or diagnosed with breast cancer at a young age should be monitored closely to detect LR at an early stage.	4
13. Voogd AC, Nielsen M, Peterse JL, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol* 2001; 19(6):1688-1697.	Observational-Tx	1,772 patients: 879 underwent BCT; 893 MRM	To evaluate risk factors for local and distant recurrence after BCT and mastectomy, using pooled data of two randomized clinical trials.	Age ≤35 years and the presence of extensive intraductal component were significantly associated with an increased risk of LR after BCT. Vascular invasion causes a higher risk of LRR after mastectomy and BCT.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. Freedman GM, Hanlon AL, Fowble BL, Anderson PR, Nicolaou N. Recursive partitioning identifies patients at high and low risk for ipsilateral tumor recurrence after breast-conserving surgery and radiation. *J Clin Oncol* 2002; 20(19):4015-4021.	Observational-Tx	912 patients; 32% chemotherapy with or without tamoxifen 27% tamoxifen 41% none	To determine subgroups at significantly different risk for IBTR in early-stage breast cancer by using recursive partitioning analysis.	Age ≤55 vs >55 years was the most significant factor for IBTR (age >55 had 4% 10-year IBTR). Extensive intraductal component was an independent risk factor for IBTR for age's ≤55 years. Tamoxifen use was the most significant factor in patients >55 years, but resulted in greater absolute decrease in risk of IBTR for patients age 36-55.	2
15. Kreike B, Hart AA, van de Velde T, et al. Continuing risk of ipsilateral breast relapse after breast-conserving therapy at long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008; 71(4):1014-1021.	Observational-Tx	1,026 patients	To evaluate the IBTR incidence and the risk factors for IBTR after BCT	The IBTR rate was 9.3% and 13.8%, respectively, at 10 and 15 years. Also, the increase in IBTR was continuous without reaching a plateau, even after 15 years. Univariate analysis showed that involved surgical resection margins, young age, vascular invasion, and the presence and quantity of an in situ component are risk factors for IBTR. Multivariate analysis showed that tumor-positive surgical resection margins or the presence of vascular invasion is the major independent risk factor for IBTR. The data from long-term follow-up showed a constant increase in IBTR among patients treated by BCT, even after 15 years, without reaching a plateau. Involved surgical resection margins and vascular invasion were the most important risk factors for IBTR.	2

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16. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. *J Clin Oncol* 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 six-marker immunohistochemical panel can identify patients at increased risk of local and regional recurrence.	2
17. Solin LJ, Hwang WT, Vapiwala N. Outcome after breast conservation treatment with radiation for women with triple-negative early-stage invasive breast carcinoma. *Clin Breast Cancer* 2009; 9(2):96-100.	Observational-Tx	519 women	To determine the relationship of triple-negative tumor status to outcome after breast conservation treatment with radiation.	Compared with the patients without a triple-negative tumor, the patients with a triple-negative tumor had a higher 8-year rate of any local failure (8% vs 4%, respectively; P=.041) and a lower 8-year rate of freedom from distant metastases (81% vs 92%, respectively; P=.0066). There were no differences between the 2 groups for local-only first failure, OS, or contralateral breast cancer (all P≥.3). On multivariate analysis, triple-negative tumors had an increased risk for any local failure (HR, 2.58), although this difference was not statistically significant (P=.097).	2

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18. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; 347(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 three 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
19. Potter R, Gnant M, Kwasny W, et al. Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favorable early breast cancer. *Int J Radiat Oncol Biol Phys* 2007; 68(2):334-340.	Experimental-Tx	869 total patients: 414 breast RT +/- boost; 417 no-RT	A randomized trial to evaluate lumpectomy plus tamoxifen or anastrozole with or without WBI in women with favorable early breast cancer.	Overall, there were 21 local relapses, with 2 relapses in the RT group (5-year rate 0.4%) vs 19 in the no-RT group (5.1%), respectively (P=0.0001, HR 10.2). Overall relapses occurred in 30 patients, with 7 events in the RT group (5-year rate 2.1%) vs 23 events in the no-RT group (6.1%) (P=0.002, HR 3.5). No significant differences were found for distant metastases and OS. Breast RT +/- boost in women with favorable early breast cancer after lumpectomy combined with tamoxifen/ anastrozole leads to a significant reduction in local and overall relapse.	1

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20. Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol* 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 two 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 two 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
21. Livi L, Paiar F, Saieva C, et al. Survival and breast relapse in 3834 patients with T1-T2 breast cancer after conserving surgery and adjuvant treatment. *Radiother Oncol* 2007; 82(3):287-293.	Observational-Tx	3,834 patients	To determine the long-term results in terms of breast relapse and specific survival in patients treated with conserving surgery and adjuvant treatment for early breast cancer.	The Cox regression model by stepwise selection showed some parameters, such as chemotherapy, pT status, positive axillary LN, and local, as independent prognostic factors for breast cancer death. Moreover, we found lower rate survival among patients treated before 1991 in comparison to women treated after 1991 probably due to inadequate treatment. For local DFS, age at presentation, use of tamoxifen, surgical margins, and chemotherapy emerged by multivariate analyses as significant breast relapse predictors. BCS followed by adjuvant RT treatment gives high rates of local control in women with early breast cancer. The use of routinely adjuvant chemotherapy and hormone therapy lowered the LR and probably the modification of therapeutic approach in the last decades also improved the specific survival.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
22. Antonucci JV, Wallace M, Goldstein NS, et al. Differences in patterns of failure in patients treated with accelerated partial breast irradiation versus whole-breast irradiation: a matched-pair analysis with 10-year follow-up. *Int J Radiat Oncol Biol Phys* 2009; 74(2):447-452.	Observational-Tx	199 patients treated with APBI	To examine 10-year results of a single institution's experience with RT limited to the region of the tumor bed (ie, APBI) in selected patients treated with BCT and compare them with results of matched BCT patients who underwent WBI.	Median follow-up for surviving patients was 9.6 years (range, 0.3-13.6 years). Eight IBTR were observed in patients treated with APBI. The cumulative incidence of IBTR at 10 years was 5%. On matched-pair analysis, the rate of IBTR was not statistically significantly different between the patient groups (4%, 95% CI, 1.3%-6.7% for WBI therapy patients vs 5%, 95% CI, 1.5%-8.5% for APBI patients; P=0.48). RT limited to the region of the tumor bed (APBI) produced 10-year local control rates comparable to those from WBI in selected low-risk patients.	1
23. Arthur DW, Winter K, Kuske RR, et al. A Phase II trial of brachytherapy alone after lumpectomy for select breast cancer: tumor control and survival outcomes of RTOG 95-17. *Int J Radiat Oncol Biol Phys* 2008; 72(2):467-473.	Experimental-Tx	99: 66 treated with HDR brachytherapy; 33 treated with LDR brachytherapy	Multi-institutional phase II trial to investigate the use of multicatheter APBI as the sole method of adjuvant RT after lumpectomy.	Median follow-up in the HDR group is 6.14 years with the 5-year estimates of in-breast, regional and contralateral failure rates of 3%, 5%, and 2%, respectively. The LDR group experienced similar results with a median follow-up of 6.22 years. The 5-year estimates of in-breast, regional, and contralateral failure rates of 6%, 0%, and 6%, respectively. Patients treated with multicatheter partial breast brachytherapy in this trial experienced excellent in-breast control rates and overall outcome that compare with reports from APBI studies with similar extended follow-up.	1

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24. Polgar C, Fodor J, Major T, et al. Breast-conserving treatment with partial or whole breast irradiation for low-risk invasive breast carcinoma--5-year results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2007; 69(3):694-702.	Experimental-Tx	258 total patients: 130 - 50 Gy/25 fractions WBI; 128 partial breast irradiation	A randomized study comparing the survival and cosmetic results of breast-conserving treatment with partial breast irradiation or conventional WBI.	The 5-year actuarial rate of LR was 4.7% and 3.4% in the partial breast irradiation and WBI arms, respectively (P=0.50). There was no significant difference in the 5-year probability of OS cancer-specific survival, and DFS (88.3% vs 90.3%). The rate of excellent to good cosmetic result was 77.6% in the partial breast irradiation group (81.2% after HDR brachytherapy; 70.0% after electron beam) and 62.9% in the control group (52.2% after telecobalt; 65.6% after 6-9-MV photons; (WBI/partial breast irradiation) = 0.009). PBI using interstitial HDR implants or electron beam to deliver radiation to the tumor bed alone for a selected group of early-stage breast cancer patients produces 5-year results similar to those achieved with conventional WBI. Significantly better cosmetic outcome can be achieved with carefully designed HDR multicatheter implants compared with the outcome after WBI.	1
25. Vicini F, Winter K, Wong J, et al. Initial efficacy results of RTOG 0319: three-dimensional conformal radiation therapy (3D-CRT) confined to the region of the lumpectomy cavity for stage I/ II breast carcinoma. *Int J Radiat Oncol Biol Phys* 2010; 77(4):1120-1127.	Observational-Tx	52 patients	To examine the use of 3D conformal external beam radiotherapy to deliver APBI.	Median follow-up is 4.5 years (1.7-4.8). 4-year estimates (95% CI) of efficacy are: ipsilateral breast failure 6% (0-12%) [4% within field (0-9%)]; ipsilateral nodal failure 2% (0-6%); contralateral breast failure 0%; distant failure 8% (0-15%); mastectomy free survival 90% (78-96%); DFS 84% (71-92%); and OS 96% (85-99%). Only two (4%) Grade 3 toxicities were observed.	1

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26. 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. *Cancer* 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 estrogen receptor status was the only variable associated with IBTR among patients with invasive breast cancer (odds ratio, 4.01; P=.0003). Larger tumor size was associated with a greater risk of distant metastasis (odds ratio, 3.05; P=.0001). Among patients with ductal carcinoma in situ, only age <50 years and close-positive margins were associated with IBTR (odds ratio, 1.12 [P=.0079] and odds ratio, 7.81 [P=.0131], respectively).	1
27. Shah C, Antonucci JV, Wilkinson JB, et al. Twelve-year clinical outcomes and patterns of failure with accelerated partial breast irradiation versus whole-breast irradiation: results of a matched-pair analysis. *Radiother Oncol* 2011; 100(2):210-214.	Observational-Tx	199 patients receiving WBI and 199 patients receiving interstitial APBI	To compare 12-year outcomes of APBI vs WBI in patients treated with breast conservation.	No differences were seen in the 12-year rates of LR (3.8% vs 5.0%, P=0.40), regional recurrence (0% vs 1.1%, P=0.15), DFS (87% vs 91%, P=0.30), cause-specific survival (93% vs 95%, P=0.28), or (OS) (78% vs 71%, P=0.06) between the WBI and APBI groups, respectively. The rate of distant metastases was lower in the APBI group (10.1% vs 4.5%, P=.05). Following LR, no difference in outcome was seen between the two groups with 5year post-LR rates of DFS (80% vs 86%, P=0.55), cause-specific survival (88% vs 75%, P=0.77), and OS (88% vs 75%, P=0.77), respectively.	1

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28. Peintinger F, Symmans WF, Gonzalez-Angulo AM, et al. The safety of breast-conserving surgery in patients who achieve a complete pathologic response after neoadjuvant chemotherapy. *Cancer* 2006; 107(6):1248-1254.	Observational-Tx	109 patients	To determine the LRR rate and to evaluate the correlation between surgical resection volume and LRR in patients with breast cancer who underwent segmental mastectomy after achieving a pathologic complete response on neoadjuvant chemotherapy.	The median follow up was 6.6 years. The median resection volume was 73.12 cm^3 (range, 2.82-451.51 cm^3). Large resection volumes (>125 c cm^3) were less common than small resection volumes (up to 70 cm^3) or medium resection volumes (between 70 cm^3 and 125 cm^3. One patient with a small resection volume had an LRR at 4 years, and 2 patients with medium resection volumes had LLR at 2.3 years and 6 years, respectively. The 5-year and 10-year LRR-free survival rates were 98.1% and 96.5%, respectively, and the corresponding OS rates were 96% and 92%, respectively. Segmental mastectomy was associated with excellent locoregional control in patients who achieved a pathologic complete response after neoadjuvant chemotherapy. Prospective studies are needed to examine whether decreasing the resection volumes in this patient population leads to an increased LRR rate.	1
29. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr* 2001; (30):96-102.	Experimental-Tx	1,493 patients	Randomized trial to compare preoperative and postoperative chemotherapy in patients with operable breast cancer. The primary aim was to determine whether preoperative chemotherapy would result in improved OS and DFS relative to the same chemotherapy administered postoperatively. Secondary aims were to evaluate the response of the primary breast tumor and involved lymph nodes to preoperative chemotherapy, to correlate that response with outcome, and to determine whether preoperative chemotherapy would result in increased rates of BCS and decreased rates of IBTR.	Survival at 9 years is 70% in the postoperative group and 69% in the preoperative group (P=.80). DFS is 53% in postoperative patients and 55% in preoperative patients (P=.50). A statistically significant correlation persists between primary tumor response and outcome, and this correlation has become statistically stronger with longer follow-up. Patients assigned to preoperative chemotherapy received notably more lumpectomies than postoperative patients, especially among patients with tumors >5 cm at study entry. Although the rate of IBTR was slightly higher in the preoperative group (10.7% vs 7.6%), this difference was not statistically significant. Marginally statistically significant treatment-by age interactions appear to be emerging for survival and DFS, suggesting that younger patients may benefit from preoperative therapy, whereas the reverse may be true for older patients.	1

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Semiglazov V, Eiermann W, Zambetti M, et al. Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study. *Eur J Surg Oncol* 2011; 37(10):856-863.	Experimental-Tx	228 patients (115 received trastuzumab plus chemotherapy and 113 received chemotherapy alone)	To describe surgical outcomes in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study (ISRCTN86043495).	The addition of trastuzumab to neoadjuvant chemotherapy improved the overall, complete and pathological complete response to therapy and significantly improved event-free survival (the primary endpoint of the study). Trastuzumab also enabled more patients to have BCS (23% vs 13% respectively) without an apparent detrimental effect on local disease control (no patient treated with trastuzumab plus chemotherapy had experienced a LR after BCS at the time of analysis).	1
31. Anderson SJ, Wapnir I, Dignam JJ, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. *J Clin Oncol* 2009; 27(15):2466-2473.	Review/Other-Tx	3,799 patients randomly assigned to five National Surgical Adjuvant Breast and Bowel Project protocols	To determine incidences of IBTR, other LRR, along with distant-disease–free interval, and OS after BCT.	11% experienced LRF. 9% experienced IBTR, and 2% experienced other LRR. The 12-year cumulative incidences of IBTR and other LRR in patients treated with adjuvant systemic therapy were 6.6% and 1.8%, respectively. Overall, 37.1% of IBTR and 72.7% of other LRR occurred within 5 years of diagnosis. The 5-year OS after IBTR and other LRR were 76.6% and 34.9%, respectively. Adjusted HR for mortality associated with IBTR and other LRR were significantly higher in ER-negative patients than in ER-positive patients (P=.002 and P<.0001, respectively). Patients with early LRF had worse OS and distant-disease–free interval than those with later-occurring LRF. Although LRF is uncommon in patients with node-negative breast cancer who are treated with lumpectomy, radiation, and adjuvant systemic therapy, those who do develop LRF have substantially worse OS and distant-disease–free interval.	4

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Wapnir IL, Anderson SJ, Mamounas EP, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. *J Clin Oncol* 2006; 24(13):2028-2037.	Observational-Tx	2,669 patients randomly assigned onto five National Surgical Adjuvant Breast and Bowel Project node-positive protocols (B-15, B-16, B-18, B-22, and B-25)	To model survival using clinical and pathologic factors jointly with IBTR or other LRR as time-varying predictors.	Age, tumor size, and ER receptor status significantly associated with IBTR. LN status and ER and PR receptor status were significantly associated with other LRR.	1
33. Shah C, Vicini F, Keisch M, et al. Outcome after ipsilateral breast tumor recurrence in patients who receive accelerated partial breast irradiation. *Cancer* 2012; 118(17):4126-4131.	Observational-Tx	199 patients received WBI and 199 patients received interstitial APBI	To compare 12-year outcomes of APBI vs WBI in patients treated with breast conservation.	No differences were seen in the 12-year rates of LR (3.8% vs 5.0%, P=0.40), regional recurrence (0% vs 1.1%, P=0.15), DFS (87% vs 91%, P=0.30), cause-specific survival (93% vs 95%, P=0.28), or OS (78% vs 71%, P=0.06) between the WBI and APBI groups, respectively. The rate of distant metastases was lower in the APBI group (10.1% vs 4.5%, P=.05). Following LR, no difference in outcome was seen between the two groups with 5year post-LR rates of DFS (80% vs 86%, P=0.55), cause-specific survival (88% vs 75%, P=0.77), and OS (88% vs 75%, P=0.77), respectively.	2
34. Harris EE, Hwang WT, Seyednejad F, Solin LJ. Prognosis after regional lymph node recurrence in patients with stage I-II breast carcinoma treated with breast conservation therapy. *Cancer* 2003; 98(10):2144-2151.	Observational-Tx	1,293 patients who received BCT including lumpectomy, axillary LN dissection, and definitive breast irradiation	To evaluate the prognosis after regional LN recurrence in patients treated with BCT.	Regional LN recurrence occurred in 39 patients (3%), most commonly in the axilla (51%) and supraclavicular region (23%). OS at 10-years after regional-only disease recurrence was 44%, locoregional disease recurrence was 26% and regional with distant recurrence was 12%.	1

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Port ER, Garcia-Etienne CA, Park J, Fey J, Borgen PI, Cody HS, 3rd. Reoperative sentinel lymph node biopsy: a new frontier in the management of ipsilateral breast tumor recurrence. *Ann Surg Oncol* 2007; 14(8):2209-2214.	Observational-Tx	117 patients	To examine technical efficacy of SLN biopsy in a reoperative setting.	Reoperative SLN was successful in 64/117 (55%) patients. SLNs were identified by isotope and dye in 28/64 (44%); isotope only in 29/64 (45%); dye only in 4/64 (6%); 3/64 (5%) unknown. Success of reoperative SLN was inversely related to number of nodes removed previously, and was more likely to be successful after a previous SLN biopsy than a previous axillary LN dissection (74% vs 38%, P=.0002). There were no local or axillary recurrences at a mean follow up of 2.2 years; 6 patients developed systemic recurrence. Reoperative SLN biopsy is feasible in the setting of LRR after previous BCT/axillary surgery and deserves further study in this increasingly common clinical scenario. The added benefit of lymphoscintigraphy in identifying sites of non-axillary drainage may be greater in the setting of reoperative SLN than for the initial SLN procedure.	1
36. Wapnir IL, Aebi S, Gelber S, et al. Progress on BIG 1-02/IBCSG 27-02/NSABP B-37, a prospective randomized trial evaluating chemotherapy after local therapy for isolated locoregional recurrences of breast cancer. *Ann Surg Oncol* 2008; 15(11):3227-3231.	Review/Other-Tx	99	To determine the effectiveness of cytotoxic therapy for isolated LRR either alone or with selective use of hormonal therapy and trastuzumab.	This report describes the characteristics of the first 99 patients. Sites of recurrence at study entry were: breast (56%), mastectomy scar/chest wall (35%), and regional LNs (9%). Two-thirds of patients have ER-positive recurrences. The patient population goal is 977.This is the only trial actively investigating the question of "adjuvant" chemotherapy in locally recurrent breast cancer. The case mix of accrual to date indicates a broad representation of this patient population. Note: This trial is ongoing.	4

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. Nishimura S, Takahashi K, Akiyama F, et al. Classification of ipsilateral breast tumor recurrence after breast-conserving therapy: new primary cancer allows a good prognosis. *Breast Cancer* 2005; 12(2):112-117.	Observational-Tx	2,137 patients	To classify and assess IBTR after BCT.	Mean time to disease recurrence was 37 months for true LR (52% were within 2 years) vs 55 months for new primary cancer (19% were within 2 years) (P=0.031). Distant metastases were observed in 33% of patients with true LR and 5% of patients with new primary cancer, and cause-specific death occurred in 6 cases with true LR and in one with new primary cancer. The patients with new primary cancer had improved 5-year rates of OS (new primary cancer 91% vs true LR 76%, [P=0.0627]) and distant DFS (new primary cancer 93% vs true LR 61%, [P=0.0028]). Patients with new primary cancer more often developed CBC (new primary cancer 37% vs true LR 12%, [P=0.018]). Patients with new primary cancer had better survival rates than those with true LR. Distinguishing new primary breast carcinomas from local disease recurrences may have importance in therapeutic decisions and chemoprevention strategies.	2

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Smith TE, Lee D, Turner BC, Carter D, Haffty BG. True recurrence vs new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. *Int J Radiat Oncol Biol Phys* 2000; 48(5):1281-1289.	Observational-Tx	1,152 patients; 60 relapses classified as true LR, 70 were classified as new primary cancer and 6 were unable to be classified	To assess prognostic and therapeutic implications of classifying patients with IBRT after BCT as either new primaries or true LR.	The overall IBRT rate for all 1,152 patients was 86% at 10 years. New primary cancer patients had a longer mean time to breast relapse than true LR patients (7.3 years vs 3.7 years, $P<0.0001$) and were significantly younger than true LR patients. By 15 years following original diagnosis, the true LR rate was 6.8% compared to 13.1% for new primary cancer. Of the patients who had been previously tested for BRCA1/2 mutations, 17% had deleterious mutations. The OS following breast relapse was 64% at 10 years and 49% at 15 years. With a mean follow-up of 10.4 years following breast relapse, patients with new primary cancer had better 10-year OS. It appears that a significant portion of patients who experience ipsilateral breast tumor relapse following CS and RT have new primary tumors as opposed to true LR. True recurrence and new primary tumor ipsilateral breast tumor relapses have different natural histories, different prognoses, and, in turn, different implications for therapeutic management.	2

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. Graeser MK, Engel C, Rhiem K, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol* 2009; 27(35):5887-5892.	Observational-Tx	2,020 women with unilateral breast cancer (index patients, n=978; relatives, n=1.42) from 978 families who had a BRCA1 or BRCA2 mutation	Retrospective, multicenter, cohort study was performed to estimate the risk for CBC in members of BRCA1- and BRCA2-positive families and to determine predictive risk factors.	The cumulative risk for CBC 25 years after first breast cancer was 47.4% (95% CI, 38.8% to 56.0%) for patients from families with BRCA1 or BRCA2 mutations. Members of families with BRCA1 mutations had a 1.6-fold (95% CI, 1.2-fold to 2.3-fold) higher risk of CBC than members of families with BRCA2 mutations. Younger age at first breast cancer was associated with a significantly higher risk of CBC in patients with BRCA1 mutation, and a trend was observed in patients with BRCA2 mutation. After 25 years, 62.9% (95% CI, 50.4% to 75.4%) of patients with BRCA1 mutation who were younger than 40 years of age at first breast cancer developed CBC, compared with only 19.6% (95% CI, 5.3% to 33.9%) of those who were older than 50 years of age at first breast cancer. CBC risk depends on age at first breast cancer and on the affected BRCA gene, and this risk should be considered in treatment planning.	2

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst* 2011; 103(6):478-488.	Review/Other-Tx	NSABP B-17 trial: 818 patients: NSABP B-24 trial: 1,804 patients	To evaluate invasive-IBTR and its influence on survival among participants in two National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized trials for DCIS.	Of 490 IBTR events, 263 (53.7%) were invasive. Radiation reduced invasive-IBTR by 52% in the lumpectomy followed by RT group compared with lumpectomy only (B-17, HR of risk of invasive-IBTR = 0.48, 95% CI = 0.33 to 0.69, P<.001). Lumpectomy followed by RT + tamoxifen reduced invasive-IBTR by 32% compared with lumpectomy followed by RT + placebo (B-24, HR of risk of invasive-IBTR = 0.68, 95% CI = 0.49 to 0.95, P = .025). The 15-year cumulative incidence of invasive-IBTR was 19.4% for lumpectomy only, 8.9% for lumpectomy followed by RT (B-17), 10.0% for lumpectomy followed by RT + placebo (B-24), and 8.5% for lumpectomy followed by RT + tamoxifen. The 15-year cumulative incidence of all contralateral breast cancers was 10.3% for lumpectomy only, 10.2% for lumpectomy followed by RT (B-17), 10.8% for lumpectomy followed by RT + placebo (B-24), and 7.3% for lumpectomy followed by RT + tamoxifen. Invasive-IBTR was associated with increased mortality risk (HR of death = 1.75, 95% CI = 1.45 to 2.96, P<.001), whereas recurrence of DCIS was not. 22/39 deaths after invasive-IBTR were attributed to breast cancer. Among all patients (with or without invasive-IBTR), the 15-year cumulative incidence of breast cancer death was 3.1% for lumpectomy only, 4.7% for lumpectomy followed by RT (B-17), 2.7% for lumpectomy followed by RT + placebo (B-24), and 2.3% for lumpectomy followed by RT + tamoxifen.	4

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. Buchanan CL, Dorn PL, Fey J, et al. Locoregional recurrence after mastectomy: incidence and outcomes. *J Am Coll Surg* 2006; 203(4):469-474.	Observational-Tx	1,057 patients	To evaluate rate of LRR, identify predictive factors and examine treatment strategies and outcomes.	Overall, LRR developed in 93/1,057 (8.8%) patients. 34 (3.2%) had synchronous distant metastases. Distant recurrences developed in 31 (2.9%) during the follow-up period (median follow-up, 6 years). 28 patients with LRR (2.6%) remained free of distant disease during the study period. Despite widespread use of adjuvant therapies during the study period, we found an LRR rate after mastectomy of 9%. But for patients presenting with LRR without evidence of distant disease, aggressive multimodality therapy is warranted because many of these patients can be rendered disease free.	2
42. Taghian A, Jeong JH, Mamounas E, et al. Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. *J Clin Oncol* 2004; 22(21):4247-4254.	Observational-Tx	5,758 patients	To assess patterns of LRF in LN-positive breast cancer patients treated with mastectomy and adjuvant chemotherapy (+/- tamoxifen) and without postmastectomy RT in five National Surgical Adjuvant Breast and Bowel Project trials.	The overall 10-year cumulative incidences of isolated LRF, LRF with or without distant failure, and distant failure alone as first event were 12.2%, 19.8%, and 43.3%, respectively. Cumulative incidences for LRF as first event with or without distant failure for patients with 1-3, 4-9, and ≥10 LN-positive were 13.0%, 24.4%, and 31.9%, respectively (P<.0001). In patients with large tumors and 4 or more LN-positive, LRF as first event remains a significant problem. Although postmastectomy RT is currently recommended for patients with four or more LN-positive, it may also have value in selected patients with 1-3 LN-positive. However, in the absence of a randomized trial examining the worth of RT in this group of patients, the value of postmastectomy RT remains unknown.	2

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
43. Abdulkarim BS, Cuartero J, Hanson J, Deschenes J, Lesniak D, Sabri S. Increased risk of locoregional recurrence for women with T1-2N0 triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation therapy compared with breast-conserving therapy. *J Clin Oncol* 2011; 29(21):2852-2858.	Observational-Tx	768 patients	To evaluate the risk of LRR associated with locoregional treatment of women with primary breast cancer tumors negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (triple-negative breast cancer).	At a median follow-up of 7.2 years, 77 patients (10%) with triple-negative breast cancer developed LRR. 5-year LRR-free survival was 94%, 85%, and 87% in the BCT, MRM, and MRM + RT groups, respectively (P<.001). In multivariate analysis, MRM (compared with BCT), lymphovascular invasion and lymph node positivity were associated with increased LRR. Conversely, adjuvant chemotherapy was associated with decreased risk of LRR. For patients with T1-2N0 tumors, 5-year LRR-free survival was 96% and 90% in the BCT and MRM groups, respectively (P=.027), and MRM was the only independent prognostic factor associated with increased LRR compared with BCT (HR, 2.53; 95% CI, 1.12 to 5.75; P=.0264).	2
44. Kyndi M, Sorensen FB, Knudsen H, Overgaard M, Nielsen HM, Overgaard J. Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: the Danish Breast Cancer Cooperative Group. *J Clin Oncol* 2008; 26(9):1419-1426.	Observational-Tx	1,000 patients	To examine the importance of ER, PR, HER-2, and constructed subtypes in a large study randomly assigning patients to receive or not receive postmastectomy RT.	A significantly improved OS after postmastectomy RT was seen only among patients characterized by good prognostic markers such as hormonal receptor-positive and HER-2- patients (including the two Rec+ subtypes). No significant OS improvement after postmastectomy RT was found among patients with an a priori poor prognosis, the hormonal receptor-negative and HER-2+ patients, and in particular the Rec-/HER-2+ subtype. Hormonal receptor status, HER-2, and the constructed subtypes may be predictive of LRR and survival after postmastectomy RT.	1
45. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365(9472):1687-1717.	Review/Other-Tx	77,000 patients; 194 unconfounded randomized trials	To assess the 10-year and 15-year effects of various systemic adjuvant therapies on breast cancer recurrence and survival.	5 years of tamoxifen reduced the LR rate by about one-half in women with hormone receptor-positive disease (LR ratio 0.47), while, irrespective of hormone receptor status, polychemotherapy reduced it by about one-third (ratios 0.63 and 0.70 for women aged >50 and 50-69, respectively).	4

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
46. Schmoor C, Sauerbrei W, Bastert G, Schumacher M. Role of isolated locoregional recurrence of breast cancer: results of four prospective studies. *J Clin Oncol* 2000; 18(8):1696-1708.	Observational-Tx	2,746 patients	To evaluate the effect on future prognosis of an isolated LRR after the primary diagnosis of breast cancer, using pooled data from four studies.	Isolated LRR increased the risk with respect to distant recurrence and death. After isolated LRR, 185 events occurred with respect to the PFS end point, and 171 patients died. Primary nodal status, tumor grade, ER status of the primary tumor, and length of the disease-free interval until the time of the isolated LRR had a significant prognostic impact. Determinants of prognosis after the isolated LRR should be taken into account for designing future risk-adapted clinical studies for these patients. Risk strata can be defined by a simple classification scheme based on primary nodal status and disease-free interval.	1
47. Carlson RW, Anderson BO, Burstein HJ, et al. Breast cancer. *J Natl Compr Canc Netw* 2005; 3(3):238-289.	Review/Other-Tx	N/A	To establish breast cancer clinical practice guidelines.	Women whose disease recurs locally after initial BCT should undergo a total mastectomy.	4
48. Haffty BG, Hauser A, Choi DH, et al. Molecular markers for prognosis after isolated postmastectomy chest wall recurrence. *Cancer* 2004; 100(2):252-263.	Observational-Tx	113 patients Paraffin-embedded tumor specimens recurrences available for 43 patients	To assess the prognostic value of molecular markers at the time of LR and to compare these markers with clinical variables.	OS after chest wall recurrence was 46% at 5 years and 28% at 10 years. Distant metastasis-free survival rate was 49% at 5 years and 40% at 10 years. Local-regional control of disease was achieved in 79% of patients at 10 years. In multivariate analysis, significant factors for distant metastasis after LR were time to recurrence (<2 years from the original diagnosis to chest wall recurrence) and PR status (distant metastasis-free survival rate: 84% [PR-positive] vs 38% [PR-negative]; P=0.007). The only significant factor for local-regional disease progression was HER-2/neu status. Patients with positive HER-2/neu status had a local-regional progression-free rate of 59%, compared with 92% for patients with negative HER-2/neu status. Prognosis for patients after LRR of breast carcinoma is relatively poor. Longer time to LR and positive PR status were associated with favorable distant metastasis-free rates and long-term survival. Positive HER-2/neu status was associated with poorer local-regional control of disease.	2

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
49. Walsh N, Kiluk JV, Sun W, Khakpour N, Laronga C, Lee MC. Ipsilateral nodal recurrence after axillary dissection for breast cancer. *J Surg Res* 2012; 177(1):81-86.	Review/Other-Tx	1,612 patients	To assess the incidence of regional nodal recurrence after axillary lymph node dissection performed for definitive operative treatment for primary breast cancer.	1,614 patients had an axillary lymph node dissection for initial staging; 14/1,614 (0.9%) patients had regional nodal recurrence. Two other patients had contralateral breast/axillary recurrences and were excluded. The mean age at diagnosis for the sample group was 52.7 years (range 34-77); mean follow-up time was 47.1 months (range 12.6-114.6). The median number of nodes for axillary lymph node dissection was 16 (range 8-27). The median number of positive nodes was 2.5 (range 0-7). Nine (64.3%) cases were estrogen receptor/progesterone receptor negative. 12 (85.7%) patients had axillary recurrences, and 6/12 (50.0%) had concurrent chest wall lesions. 12 patients (85.7%) had distant metastases; 9/12 (75.0%) died; two were lost to follow-up. Mean time from regional nodal recurrence to distant recurrence was 6.0 months (range 0-29.3 months).	4
50. Kiricuta IC, Willner J, Kolbl O, Bohndorf W. The prognostic significance of the supraclavicular lymph node metastases in breast cancer patients. *Int J Radiat Oncol Biol Phys* 1994; 28(2):387-393.	Observational-Tx	795 patients	To define the patterns of failure and outcome of patients presenting supraclavicular lymph node involvement and the prognostic significance of supraclavicular lymph node involvement.	Survival from appearance of supraclavicular lymph node metastases at primary diagnosis or as a recurrence is not different from survival of patients presenting with a primary M1 stage or presenting distant metastases during the course of disease. 2- and 5-year survival rates of patients with supraclavicular lymph node involvement at primary diagnosis were 52% and 34% compared to 50% and 16% 2- and 5-year survival rate of patients with supraclavicular lymph node involvement as a recurrence. Patients who presented a primary M1-status had 2- and 5-year survival rates of 56% and 24%. Survival of patients with distant metastases calculated from the onset of metastatic disease was similar to that of the other three groups with a 46% and 16% survival rate at 2 and 5 years. There was no difference in survival rates between the four groups.	2

Local-Regional Recurrence (LRR) and Salvage Surgery — Breast Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
51. Willner J, Kiricuta IC, Kolbl O. Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis. *Int J Radiat Oncol Biol Phys* 1997; 37(4):853-863.	Observational-Tx	145 patients	To determine prognostic factors for survival after local regional recurrence and to determine subgroups of patients with favorable and unfavorable prognosis by both univariate and multivariate analysis.	Metastases-free rate was 42% at 2 years and 36% at 10 years following recurrence. With development of distant metastases, the survival rate deteriorated. Recurrences appeared within the first 2 years from primary surgery in 56% of patients, and in 89% within 5 years. Overall, 2-year and 5-year survival rates following local-regional recurrence were 67% and 42%, respectively. Univariate analysis revealed statistically significant worsening of survival rates for pT3 + 4 primary tumors, primary axillary lymph node involvement, tumor grading 3 + 4, lymphatic vessel invasion, blood vessel invasion, tumor necrosis, negative ER and PR hormonal receptor status, postmastectomy chemotherapy and hormonal therapy, short time to recurrence (<l year), combined recurrences and supraclavicular site of recurrence, non-scar recurrence, size of the largest recurrent nodule >5 cm, multiple recurrent nodules, no surgical excision of recurrence, small target volume of irradiation, chemotherapy for recurrence, and no local control within the recurrence site. The 2-year and 5-year survival rates ranged from 68% to 94%, and from 33% to 65%, respectively, in the favorable subgroups compared to 2-year and 5-year survival rates ranging from 20% to 59% and 0% to 35%, respectively, in the unfavorable subgroups. Multivariate analysis showed that site of recurrence and number of recurrent nodules have the strongest influence on postrecurrence survival, but time to recurrence, age at time of recurrence, local control in recurrent site as well as primary pT and axillary status, and the presence of tumor necrosis in the primary tumor specimen showed additional independent influences on survival.	2

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.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

APBI = Accelerated partial-breast irradiation

BCS = Breast-conserving surgery

BCT = Breast-conserving therapy

CBC = Contralateral breast cancer

CI = Confidence interval

CS = Conservative surgery

DCIS = Ductal carcinoma in situ

DFS = Disease-free survival

ER = Estrogen receptor

HDR = High-dose-rate

HR = Hazard ratio

IBTR = Ipsilateral breast tumor recurrence

LDR = Low-dose-rate

LN = Lymph node

LR = Local recurrence

LRF = Locoregional failure

LRR = Local-regional recurrence

MRM = Modified radical mastectomy

OS = Overall survival

PR = Progesterone receptor

RT = Radiation therapy

SLN = Sentinel lymph node

WBI = Whole-breast irradiation