Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. Arriagada R, Rutqvist LE, Mattsson A, Kramar A, Rotstein S. Adequate locoregional treatment for early breast cancer may prevent secondary dissemination. *J Clin Oncol* 1995; 13(12):2869-2878.	1	960 patients	Randomized trial to analyze different events that determine event-free survival in a randomized trial on adjuvant RT in early breast cancer patients with more than 15 years of follow-up evaluation.	RT produced a fivefold decrease of the risk of local recurrence (P<.0001). In N(+) patients, postoperative RT decreased the risk of distant dissemination (RR, 0.63). When local recurrence was introduced in the model as a time-dependent covariate, this factor was predictive of distant dissemination (P<.0001) and nullified the effect of postoperative RT. This finding suggests that the decrease of distant metastases was related to the prevention of local recurrence. A similar effect was found in models that used OS as an end point. This study shows that PMRT in N(+) breast cancer patients may decrease the distant metastasis rate by preventing local recurrences and thus avoiding secondary dissemination.	1
2. Arriagada R, Rutqvist LE, Le MG. Postmastectomy radiotherapy: randomized trials. *Semin Radiat Oncol* 1999; 9(3):275-286.	7 (meta-analysis)	13 different trials	Meta-analysis of large unconfounded randomized trials (at least 500 patients) evaluating PMRT.	Results strongly suggest that PMRT may give a beneficial effect in terms of OS. This effect could be explained by prevention of secondary dissemination from residual tumor left in the tumor bed. Moreover, this effect would be independent of the use of adjuvant chemotherapy, as shown in two published trials. Evidence shows that an improved locoregional control after total mastectomy may have a significant impact on OS by decreasing the risk of secondary dissemination. The exact definition of subgroups to be treated by PMRT and the LN volumes to be irradiated are currently matters of clinical research. The main practical guideline should be the actual risk of LRR in each category of patients.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
3. Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. *J Clin Oncol* 2006; 24(15):2268-2275.	3a	3,083 patients	To examine the overall disease recurrence pattern among patients randomly assigned to receive treatment with or without RT.	The 18-year probability of any first breast cancer event was 73% and 59% (P<.001) after no RT and RT, respectively (RR, 0.68; 95% CI, 0.63 to 0.75). The 18-year probability of LRR (with or without distant metastases) was 49% and 14% (P<.001) after no RT and RT, respectively (RR, 0.23; 95% CI, 0.19 to 0.27). The 18-year probability of distant metastases subsequent to LRR was 35% and 6% (P<.001) after no RT and RT, respectively (RR, 0.15; 95% CI, 0.11 to 0.20), whereas the probability of any distant metastases was 64% and 53% (P<.001) after no RT vs RT, respectively (RR, 0.78; 95% CI, 0.71 to 0.86). PMRT changes the disease recurrence pattern in high-risk breast cancer patients; fewer patients have LRR as first site of recurrence, and overall fewer patients have distant metastases.	2
4. 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. *J Clin Oncol* 1999; 17(6):1689-1700.	15	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 LRF 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 LRF, 254 (13%); LRF with simultaneous distant failure, 166 (8%); and distant only, 679 (34%). The risk of LRF with or without simultaneous distant failure at 10 years was 12.9% in patients with one to three positive nodes and 28.7% for patients with four 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 LRF with or without simultaneous distant failure. LRF 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.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
5. Cheng JC, Chen CM, Liu MC, et al. Locoregional failure of postmastectomy patients with 1-3 positive axillary lymph nodes without adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 2002; 52(4):980-988.	3a	125 patients	To analyze the incidence and risk factors for LRR in patients with breast cancer who had T1 or T2 primary tumor and 1-3 histologically involved axillary LNs treated with MRM without adjuvant RT.	Of 110 patients without RT, 17 had LRR during follow-up. The 4-year LRR rate was 16.1% (95% CI, 9.1-23.1%). All but one LRR were isolated LRR without preceding or simultaneous distant metastasis. According to univariate analysis, age <40 years (P=0.006), T2 classification (P=0.04), tumor size ≥3 cm (P=0.002), negative ER protein status (P=0.02), presence of LVI (P=0.02), and no tamoxifen therapy (P=0.0006) were associated with a significantly higher rate of LRR. Tumor size (P=0.006) was the only risk factor for LRR with statistical significance in the multivariate analysis. On the basis of the 4 patient-related factors (age <40 years, tumor≥3 cm, negative ER protein, and LVI), the high-risk group (with 3 or 4 factors) had a 4-year LRR rate of 66.7% (95% CI 42.8-90.5%) compared with 7.8% (95% CI 2.2-13.3%) for the low-risk group (with 0-2 factors; P=0.0001). For the 110 patients who received no adjuvant RT, LRR was associated with a 4-year distant metastasis rate of 49.0% (9/17, 95% CI 24.6-73.4%). For patients without LRR, it was 13.3% (15/93, 95% CI 6.3-20.3%; P=0.0001). The 4-year survival rate for patients with and without LRR was 75.1% (95% CI 53.8-96.4%) and 88.7% (95% CI 82.1-95.4%; P=0.049), respectively. LRR was independently associated with a higher risk of distant metastasis and worse survival in multivariate analysis. Patients with risk factors for LRR may need adjuvant RT. Randomized trials are warranted to determine the potential benefit of PMRT on the survival of patients with a T1 or T2 primary tumor and 1-3 positive nodes.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
6. 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.	1	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.	1
7. Truong PT, Lee J, Kader HA, Speers CH, Olivotto IA. Locoregional recurrence risks in elderly breast cancer patients treated with mastectomy without adjuvant radiotherapy. *Eur J Cancer* 2005; 41(9):1267-1277.	3a	2,362 total women: Age 50-69 (n = 1,423); Age 70+ (n = 939)	To examine tumor and treatment characteristics in elderly women treated with mastectomy without RT and compare their outcomes to younger counterparts.	Median follow-up was 8.3 years. The distribution of nodal stage was similar in the two age cohorts but older women were more likely to have fewer axillary nodes removed (P=0.009). Fewer women aged 70+ had grade III histology (P=0.002) and ER-negative status (P<0.001). The rates of systemic therapy use were comparable in the two age groups. With tumors >5 cm, LRR were 13.7% and 30.0% in women aged 50-69 and 70+, respectively. With 1-3 positive nodes, LRR were 14.8% and 13.0% in women aged 50-69 and 70+. In the presence of 4 positive nodes, LRR were 16.8% and 30.8% in women aged 50-69 and 70+. - Independent prognostic factors for LRR were grade III histology, LVI and positive nodal status. This study suggests that despite more favorable tumor characteristics and comparable systemic therapy use, women aged 70+ years have similar or higher postmastectomy LRR risks compared to younger women. Chronologic age alone should not preclude these women from consideration of adjuvant RT.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
8. Truong PT, Yong CM, Abnousi F, et al. Lymphovascular invasion is associated with reduced locoregional control and survival in women with node-negative breast cancer treated with mastectomy and systemic therapy. *J Am Coll Surg* 2005; 200(6):912-921.	3a	763 patients	To evaluate the association of LVI with relapse and survival in a cohort of women with early-stage breast cancer.	Median follow-up was 7.0 years (range 0.34 to 14.9 years). LVI was present in 210 (27.5%) patients. In log-rank comparisons of Kaplan-Meier curves stratified by LVI status, LVI-positive disease was associated with significantly higher risks of LRR (P=0.006), distant relapse (P=0.04), and lower OS (P=0.02). In the multivariable Cox regression analysis, LVI was significantly associated with LRR (RR = 2.32; 95% CI, 1.26-4.27; P=0.007), distance relapse (RR = 1.53; 95% CI, 1.00-2.35; P=0.05), and OS (RR = 1.46; 95% CI, 1.04-2.07; P=0.03). In patients with one of the following characteristics: age younger than 50 years, premenopausal status, grade III histology, or ER-negative disease, 7-year LRR risks increased threefold from 3% to 5% when LVI was absent, to 15% to 20% in the presence of LVI.	2
9. Abi-Raad R, Boutrus R, Wang R, et al. Patterns and risk factors of locoregional recurrence in T1-T2 node negative breast cancer patients treated with mastectomy: implications for postmastectomy radiotherapy. *Int J Radiat Oncol Biol Phys* 2011; 81(3):e151-157.	4	1,136 node-negative T1-T2 breast cancer cases	To retrospectively review and identify a subgroup of T1-T2 breast cancer patients with LN- who might benefit from PMRT.	Median follow-up was 9 years. The 10-year cumulative incidence of LRR was 5.2% (95% CI: 3.9%-6.7%). Chest wall was the most common (73%) site of LRR. Tumor size, margin, patient age, systemic therapy, and LVI were significantly associated with LRR on multivariate analysis. These five variables were subsequently used as risk factors for stratified analysis. The 10-year cumulative incidence of LRR for patients with no risk factors was 2.0% (95% CI: 0.5%-5.2%), whereas the incidence for patients with three or more risk factors was 19.7% (95% CI: 12.2%-28.6%). It has been suggested that patients with T1-T2N0 breast cancer who undergo mastectomy represent a favorable group for which PMRT renders little benefit. However, this study suggests that select patients with multiple risk factors including LVI, tumor size ≥2 cm, close or positive margin, age ≤50, and no systemic therapy are at higher risk of LRR and may benefit from PMRT.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
10. Truong PT, Olivotto IA, Speers CH, Wai ES, Berthelet E, Kader HA. A positive margin is not always an indication for radiotherapy after mastectomy in early breast cancer. *Int J Radiat Oncol Biol Phys* 2004; 58(3):797-804.	3a	2,570 total women	To examine relapse and survival among women with node-negative breast cancer and positive surgical margins after mastectomy.	Median follow-up time was 7.7 years. The distributions of age, histologic grade, LVI, ER status, and number of axillary nodes removed were similar between the two treatment groups. 6 local chest wall recurrences (6.4%), 4 regional recurrences (4.3%), and 11 distant recurrences (11.7%) were identified. Local relapse rates were 2.4% vs 9.4% (P=0.23), and regional relapse rates were 2.4% vs 5.7% (P=0.63), with and without PMRT, respectively. Trends for higher cumulative LRR rates without PMRT were identified in the presence of age ≤50 years (LRR 20% without vs 0% with PMRT), T2 tumor size (19.2% vs 6.9%), grade III disease (23.1% vs 6.7%), and LVI (16.7% vs 9.1%). Statistical significance was not demonstrated in these differences (P>0.10), possibly because of the small number of events. In patients with age >50 years, T1 tumors, grade I/II disease, and absence of LVI, no locoregional relapse occurred even with positive margins. PMRT did not improve distant relapse, 8-year breast cancer-specific and OS rates. This study suggests that not all patients with node-negative breast cancer with positive margins after mastectomy require RT. LRF rates approximating 20% were observed in women with positive margins plus at least one of the following factors: age ≤50 years, T2 tumor size, grade III histology, or LVI. The absolute and relative improvements in locoregional control with RT in these situations support the judicious, but not routine, use of PMRT for positive margins after mastectomy in patients with node-negative breast cancer.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
11. Hetelekidis S, Schnitt SJ, Silver B, et al. The significance of extracapsular extension of axillary lymph node metastases in early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2000; 46(1):31-34.	3a	368 patients	To investigate if ECE of axillary LN metastases predicts for a decreased rate of DFS or an increased rate of regional recurrence of breast carcinoma.	122 patients (33%) had ECE and 246 patients did not. The median number of LN with ECE was 1 (range 1-10) and 20% of patients had ECE in ≥4 LN. Patients with ECE tended to be older (median age 51 vs 47, P=0.01), and had a higher number of involved LN (median 3 vs 2, P=0.005) than patients without ECE. 43% of patients with ECE had ≥4 involved LN compared to 15% of patients without ECE (P<0.0001). Models of ECE and the above factors revealed no significant correlation between ECE and either DFS or OS. There was no statistically significant increase in local, regional nodal, or distant failures in patients with ECE as compared to patients without ECE. In this population of patients with nodal involvement, the presence of ECE correlates with the number of involved LN but does not appear to add predictive power to models of local, regional, or distant recurrence when the number of positive LN is included.	2
12. Gruber G, Cole BF, Castiglione-Gertsch M, et al. Extracapsular tumor spread and the risk of local, axillary and supraclavicular recurrence in node-positive, premenopausal patients with breast cancer. *Ann Oncol* 2008; 19(8):1393-1401.	1	1,475 patients	Randomized trial to evaluate ECS as a predictor of local, axillary, and supraclavicular recurrence.	The median follow-up was 14 years. In univariable analysis, ECS was significantly associated with supraclavicular recurrence (HR = 1.96; 95% CI 1.23-3.13; P=0.005). HRs for local and axillary recurrence were 1.38 (P=0.06) and 1.81 (P=0.11), respectively. Following adjustment for number of LN metastases and other baseline prognostic factors, ECS was not significantly associated with any of the three recurrence types studied. The results indicate that the decision for additional regional RT should not be based solely on the presence of ECS.	1

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
13. Recht A, Pierce SM, Abner A, et al. Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. *J Clin Oncol* 1991; 9(6):988-996.	3a	1,624 patients	To retrospectively analyze the likelihood of regional nodal failure for patients with stage I or II invasive breast carcinoma treated with conservative surgery and RT.	The median follow-up time was 77 months. Regional nodal failure was the first site of failure for 38/1,624 patients (2.3%). The incidence of axillary failure for patients undergoing axillary dissection who were irradiated to the breast only was 2.1% (9/420) for patients with negative nodes and 2.1% (1/47) for patients with one to three positive nodes. The incidence of supraclavicular failure in these two groups was 1.9% (8/420) and 0% (0/47), respectively. The incidences of axillary and supraclavicular failure in patients without clinically suspicious axillary involvement who did not have axillary dissection but were treated with RT were 0.8% (3/355) and 0.3% (1/364), respectively. Despite various combinations of salvage surgery, RT, and systemic therapy, only 47% of patients (18/38) achieved complete regional control after nodal relapse. It is concluded that regional nodal failure is uncommon in patients treated to the breast alone following an adequate axillary dissection when the axillary nodes are negative or when one to three nodes are positive. Regional nodal failure is also uncommon in patients with a clinically uninvolved axilla treated with nodal RT without axillary dissection. Symptoms of regional nodal failure can be controlled in most but not all patients. Further study is needed to determine if the benefits of RT in preventing a small number of symptomatic regional nodal failure outweigh the potential toxicity for any subgroup of patients.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
14. Strom EA, Woodward WA, Katz A, et al. Clinical investigation: regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. *Int J Radiat Oncol Biol Phys* 2005; 63(5):1508-1513.	3a	1,031 patients	To describe regional nodal failure patterns in patients who had undergone mastectomy with axillary dissection to define subgroups of patients who might benefit from supplemental regional nodal radiation to the axilla or supraclavicular fossa/axillary apex.	21 patients recurred within the low-mid axilla (10-year actuarial rate 3%). Of these, 16 were isolated regional failures. 3/100 patients with <10 nodes examined recurred in the low-mid axilla. 77 patients had a recurrence in the supraclavicular fossa/axillary apex (10-year actuarial rate 8%). 49 were isolated regional recurrences. Significant predictors of failures in this region included ≥4 involved axillary LNs, >20% involved axillary nodes, and the presence of gross extranodal extension (10-year actuarial rates 15%, 14%, and 19%, respectively, P<0.0005). The extent of axillary dissection and the size of the largest involved node were not predictive of failure within the supraclavicular fossa/axillary apex.	2
15. Albert JM, Gonzalez-Angulo AM, Guray M, et al. Patients with only 1 positive hormone receptor have increased locoregional recurrence compared with patients with estrogen receptor-positive progesterone receptor-positive disease in very early stage breast cancer. *Cancer* 2011; 117(8):1595-1601.	3a	635 patients	To retrospectively evaluate whether patients with only 1 positive hormone receptor have increase LRR compared with patients with ER-positive PR-positive disease in very early stage breast cancer.	LRR rates were higher in patients with 1 receptor positive compared with ER(+)/PR(+) (7-year rate: 8.8% vs 2.5%, P=.024). There was no difference between the 2 groups in the rates of distant metastasis (P=.531) or OS (P=.491). One positive receptor predicted for LRR in patients who did not receive hormonal therapy (P = .046), but not in patients who received hormonal therapy (P = .296). On multivariate analysis, 1 positive receptor predicted for LRR in the overall group (HR, 2.81; 95% CI, 1.06-7.48; P=.038). Patients with T1a,bN0 breast cancer with only 1 positive hormone receptor have increased rates of LRR compared with patients with ER(+)/PR(+) disease, although this difference may be reduced or eliminated with systemic treatment.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
16. Wang SL, Li YX, Song YW, et al. Triple-negative or HER2-positive status predicts higher rates of locoregional recurrence in node-positive breast cancer patients after mastectomy. *Int J Radiat Oncol Biol Phys* 2011; 80(4):1095-1101.	4	835 patients	To evaluate the prognostic value of determining ER, PR, and HER2 expression in node-positive breast cancer patients treated with mastectomy.	Patients with triple-negative, Rec-/HER2+, and Rec+/HER2+ expression profiles had a significantly lower 5-year LRR-free survival than those with Rec+/HER2- profiles (86.5% vs 93.6%, P=0.002). Compared with those with Rec+/HER2+ and Rec+/HER2- profiles, patients with Rec-/HER2- and Rec-/HER2+ profiles had significantly lower 5-year distant metastasis-free survival (69.1% vs 78.5%, P=0.000), lower DFS (66.6% vs 75.6%, P=0.000), and lower OS (71.4% vs 84.2%, P=0.000). Triple-negative or Rec-/HER2+ breast cancers had an increased likelihood of relapse and death within the first 3 years after treatment. Triple-negative and HER2+ profiles are useful markers of prognosis for LRR and survival in node-positive breast cancer patients treated with mastectomy.	2
17. 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.	4	768 patients	To evaluate the risk of LRR associated with locoregional treatment of women with primary breast cancer tumors negative for ER, PR, and HER2 (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), LVI and LN 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). Women with T1-2N0 triple-negative breast cancer treated with MRM without RT have a significant increased risk of LRR compared with those treated with BCT. Prospective studies are warranted to investigate the benefit of adjuvant RT after MRM in triple-negative breast cancer.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
18. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997; 337(14):949-955.	1	1,708 women 852 randomized to receive 8 cycles of CMF plus RT of the chest wall and regional LNs or 9 cycles of CMF alone (856 women)	Randomized trial of RT after mastectomy in high-risk premenopausal women, all of whom also received adjuvant systemic chemotherapy with CMF.	The frequency of LRR alone or with distant metastases was 9% among the women who received RT plus CMF and 32% among those who received CMF alone (P<0.001). The probability of survival free of disease after 10 years was 48% among the women assigned to RT plus CMF and 34% among those treated only with CMF (P<0.001). OS at 10 years was 54 % among those given RT and CMF and 45 % among those who received CMF alone (P<0.001). Multivariate analysis demonstrated that RT after mastectomy significantly improved DFS and OS, irrespective of tumor size, the number of positive nodes, or the histopathological grade. The addition of postoperative RT to mastectomy and adjuvant chemotherapy reduces LRR and prolongs survival in high-risk premenopausal women with breast cancer.	1
19. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997; 337(14):956-962.	1	318 patients randomized to chemotherapy–RT group (n=164), chemotherapy group (n=154)	To prospectively test the efficacy of combining RT with chemotherapy in a randomized study.	After 15 years of follow-up, the women assigned to chemotherapy plus RT had a 33% reduction in the rate of recurrence (RR, 0.67; 95 % CI, 0.50 to 0.90) and a 29% reduction in mortality from breast cancer (RR, 0.71; 95% CI, 0.51 to 0.99), as compared with the women treated with chemotherapy alone. RT combined with chemotherapy after MRM decreases rates of locoregional and systemic relapse and reduces mortality from breast cancer.	1
20. 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.	1	318 patients randomly assigned to receive no further therapy or RT	To determine the survival impact of locoregional RT in premenopausal LN + 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

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
21. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999; 353(9165):1641-1648.	1	1,375 patients randomized to adjuvant tamoxifen: (30 mg daily for 1 year) alone (689) or with postoperative RT to the chest wall and regional LNs (686)	To compare adjuvant tamoxifen alone with tamoxifen plus postoperative RT in a randomized trial among postmenopausal women who had undergone mastectomy.	Median follow-up 123 months. LRR occurred in 52 (8%) of RT plus tamoxifen group and 242 (35%) of tamoxifen only group (P<0.001). DFS: 36% RT plus tamoxifen, 24% tamoxifen alone (P<0.001). OS: higher in RT group (385 vs 434 deaths; survival 45% vs 36% at 10 years, P=0.03). Postoperative RT decreased risk of LRR and was associated with improved survival in high-risk postmenopausal breast-cancer patients after mastectomy and limited axillary dissection. Improved survival in high-risk breast cancer is best achieved by strategy of both loco-regional and systemic tumor control.	1
22. 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.	1	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

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
23. 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.	1	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
24. 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.	7 (meta-analysis)	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.	2
25. The NCCN Clinical Practice Guidelines in Oncology™ Breast Cancer Version 2.2011 © 2011 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.	15	N/A	To provide treatment summaries for breast cancer to the general public.	N/A	4

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
26. Smith BD, Smith GL, Haffty BG. Postmastectomy radiation and mortality in women with T1-2 node-positive breast cancer. *J Clin Oncol* 2005; 23(7):1409-1419.	3a	18,038 women	To determine the relationship between PMRT and mortality in a population-based cohort of women with T1-2 node-positive breast cancer.	Median follow-up was 8.1 years. Only 2,648 women (15%) received PMRT. After adjusting for covariates, PMRT use was not associated with mortality (HR = 0.96; 95% CI, 0.90 to 1.03). However, the interaction term for PMRT use and number of involved regional LNs was significant (P=.002), suggesting that, above a certain threshold of involved nodes; a mortality benefit from PMRT may exist. Adjusted analysis stratified by number of involved nodes revealed that patients with seven or more involved nodes treated with PMRT experienced a significant reduction in all-cause (HR = 0.84; 95% CI, 0.76 to 0.93) and cause-specific mortality (HR = 0.86; 95% CI, 0.77 to 0.96). Propensity score matched case-control analysis confirmed that PMRT was associated with reduced mortality only in the subset of patients with seven or more involved nodes (HR = 0.81; 95% CI, 0.73 to 0.91 for all-cause mortality; and HR = 0.82; 95% CI, 0.72 to 0.93 for cause-specific mortality). For women with T1-2 breast cancer, PMRT is associated with a 15% to 20% relative reduction in mortality for patients with seven or more involved regional LNs.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
27. Cheng SH, Horng CF, West M, et al. Genomic prediction of locoregional recurrence after mastectomy in breast cancer. *J Clin Oncol* 2006; 24(28):4594-4602.	3a	94 patients	To explore gene expression profiles that is associated with LRR in breast cancer after mastectomy.	Our study demonstrates two sets of gene expression profiles (one with 258 genes and the other 34 genes) to be of predictive value with respect to LRR. The overall accuracy of the prediction tree model in validation sets is estimated 75% to 78%. Of patients in validation data set, the 3-year LR control rate with predictive index more than 0.8 derived from 34-gene prediction models is 91%, and predictive index 0.8 or less is 40% (P=.008). Multivariate analysis of all patients reveals that ER and genomic predictive index are independent prognostic factors that affect LR control. Using gene expression profiles to develop prediction tree models effectively identifies breast cancer patients who are at higher risk for LRR. This gene expression-based predictive index can be used to select patients for PMRT.	2
28. Jagsi R, Raad RA, Goldberg S, et al. Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. *Int J Radiat Oncol Biol Phys* 2005; 62(4):1035-1039.	3a	877 cases	To retrospectively assess whether subsets of node-negative patients with sufficiently high risk of LRR might benefit from PMRT.	Median follow-up was 100 months. 10 year cumulative incidence of LRR as first event was 6.0%. Size >2 cm, margin <2 mm, premenopausal status, and LVI were independently significant prognostic factors. 10 year LRR was 1.2% for those with 0 risk factors, 10.0% for those with 1 risk factor, 17.9% for those with 2 risk factors, and 40.6% for those with 3 risk factors. The chest wall was the site of failure in 80% of patients. PMRT has not been recommended for node-negative patients because the LRR rate is low in that population overall. This study suggests, however, that node-negative patients with multiple risk factors, including close margins, T2 or larger tumors, premenopausal status, and LVI, are at higher risk for LRR and might benefit from PMRT. Because the chest wall is the most common site of failure, treating the chest wall alone in these patients to minimize toxicity is reasonable.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
29. 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. *J Clin Oncol* 2010; 28(10):1677-1683.	3a	895 tamoxifen-treated patients; 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 two 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). There were also significant associations between recurrence score and LRR in placebo-treated patients from B-14 (P=.022) and in chemotherapy plus tamoxifen-treated patients from B-20 (P=.028). 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

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
30. 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. *Ann Surg Oncol* 2010; 17(11):2899-2908.	3a	1,019 total patients with pT1 or pT2 tumors and zero positive LNs n=753; 1 positive LN n=176; 2 positive LNs n=69; 3 positive LNs n=21	To determine present-day LRR rates to better understand the role of postmastectomy RT in women with 0 to 3 positive LNs.	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 ≤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 one positive node had a similar 10-year LRR risk (3.3%; P>0.5), and patients with two 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 ≤40 years old.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
31. Wallgren A, Bonetti M, Gelber RD, et al. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. *J Clin Oncol* 2003; 21(7):1205-1213.	1	5,352 women 1,275 received either no adjuvant therapy or a single cycle of perioperative chemotherapy: 4,077 received adjuvant chemotherapy of at least 3 months' duration and/or tamoxifen	To explore prognostic factors for LRF among women treated for invasive breast cancer within clinical trials of adjuvant therapies.	Median follow-up of 12 to 15.5 years. In women with node-negative disease, factors associated with increased risk of LRF were vascular invasion and tumor size >2 cm for premenopausal and vascular invasion for postmenopausal patients. Of the 1,275 patients, 345 (27%) met criteria for the highest risk groups, and the 10-year cumulative incidences of LRF with or without distant metastases were 16% for premenopausal and 19% for postmenopausal women. For the node-positive cohort, number of nodes and tumor grade were factors for both menopausal groups, with additional prediction provided by vascular invasion for premenopausal and tumor size for postmenopausal patients. Of the 4,077 patients, 815 (20%) met criteria for the highest risk groups, and 10-year cumulative incidences were 35% for premenopausal and 34% for postmenopausal women. LRF are a significant problem after mastectomy alone even for some patients with node-negative breast cancer, as well as after mastectomy and adjuvant treatment for some subgroups of patients with node-positive disease. In addition to number of positive LNs, predictors of LRF include tumor-related factors, such as vascular invasion, higher grade, and larger size.	1

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
32. Yang PS, Chen CM, Liu MC, et al. Radiotherapy can decrease locoregional recurrence and increase survival in mastectomy patients with T1 to T2 breast cancer and one to three positive nodes with negative estrogen receptor and positive lymphovascular invasion status. *Int J Radiat Oncol Biol Phys* 2010; 77(2):516-522.	2	544 patients 383 patients had no RT 161 received RT	To retrospectively define a subgroup of patients at high risk of LRR who might benefit from PMRT in invasive breast cancer and tumor size <5 cm with one to three involved axillary LNs (T1-2 N1).	With a median follow-up of 40.3 months, LRR occurred in 40 (7.4%) of 544 patients. On univariate analysis, high nuclear grade (P=0.04), negative ER status (P=0.001), presence of LVI (P=0.003), and no RT (P=0.0015) were associated with a significantly higher rate of LRR. Negative ER status (HR = 5.1) and presence of LVI (HR = 2.5) were the risk factors for LRR with statistical significance in the multivariate analysis. RT reduced the LRR in patients with the following characteristics: age <40 years, T2 stage, high nuclear grade, negative ER status, and presence of LVI. For 41 patients with negative ER and positive LVI status, RT can reduce LRR from 10 of 25 (40%) to 2 of 16 (12.5%) and increase the 5-year OS from 43.7% to 87.1%. RT can reduce LRR and increase survival in T1-2 N1 breast cancer patients with negative ER status and presence of LVI.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
33. Truong PT, Woodward WA, Thames HD, Ragaz J, Olivotto IA, Buchholz TA. The ratio of positive to excised nodes identifies high-risk subsets and reduces inter-institutional differences in locoregional recurrence risk estimates in breast cancer patients with 1-3 positive nodes: an analysis of prospective data from British Columbia and the M. D. Anderson Cancer Center. *Int J Radiat Oncol Biol Phys* 2007; 68(1):59-65.	3a	82 patients	To examine the power of the nodal ratio of positive/excised nodes in predicting postmastectomy LRR in patients with 1-3 positive nodes (N+) and in identifying cohorts at similar risk across independent data sets.	The median number of excised nodes was 10 in British Columbia (BC) and 16 in M. D. Anderson Cancer Center (MDACC) (P<0.001). Examining LRR by number of N+, the 10-year LRR rate for patients with 1-3 N+ was higher in BC compared with MDACC (21.5% vs 12.6%; P=0.02). However, when examining LRR using nodal ratio, no differences were found between institutions. In patients with nodal ratio ≤0.20, the 10-year LRR rate was 17.7% BC vs 10.9% MDACC (P=0.27). In patients with nodal ratio ≥0.20, the 10-year LRR rate was 28.7% BC vs 22.7% MDACC (P=0.32). On Cox regression analysis, nodal ratio was a stronger prognostic factor compared with number of N+. In patients with 1-3 N+, evaluating nodal positivity using nodal ratio reduced inter-institutional differences in LRR estimates that may exist due to variations in numbers of nodes excised. Nodal ratio >0.20 was associated with LRR >20%, warranting PMRT consideration. Nodal ratio may be useful for extrapolating data from prospective trials to clinical practices in which axillary staging extent vary.	2
34. Kunkler IH, Canney P, van Tienhoven G, Russell NS. Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial. *Clin Oncol (R Coll Radiol)* 2008; 20(1):31-34.	4	N/A	Editorial.	A fuller understanding of the biological basis of radioresistance in breast cancer is needed to underpin the rationale design of therapeutic strategies to overcome it. At present there are no reliable molecular tumor markers to identify individuals likely to benefit from RT. In addition, specific drug therapies are required to target radioresistant stem cells. These should be priorities for translational research in breast cancer. Given the high proportion of patients requiring RT for breast cancer, the clinical dividends of progress in this field could be enormous.	4

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
35. Ahmann DL, O'Fallon JR, Scanlon PW, et al. A preliminary assessment of factors associated with recurrent disease in a surgical adjuvant clinical trial for patients with breast cancer with special emphasis on the aggressiveness of therapy. *Am J Clin Oncol* 1982; 5(4):371-381.	1	293 patients	Randomized trial to assess factors associated with recurrent disease in a surgical adjuvant clinical trial for patients with breast cancer.	For premenopausal patients, increased risk of recurrence was associated with presence of unfavorable local signs, large number of LNs involved, greater body weight, younger age, and L-PAM treatment. For postmenopausal patients, only 3 factors were associated with an increased risk of recurrent disease: large tumor size, large number of LNs involved and inner/central location of the primary lesion. Although patients who experience little or no myelosuppression have significantly worse disease-free intervals than patients who experience moderate or severe myelosuppression, there is no benefit for severe myelosuppression over moderate, myelosuppression.	1
36. Klefstrom P, Grohn P, Heinonen E, Holsti L, Holsti P. Adjuvant postoperative radiotherapy, chemotherapy, and immunotherapy in stage III breast cancer. II. 5-year results and influence of levamisole. *Cancer* 1987; 60(5):936-942.	1	120 patients	Randomized trial to present 5-year results and influence of levamisole from randomized trial studying preoperative RT, chemotherapy, and immunotherapy in stage III breast cancer patients.	RT provided local and chemotherapy systemic control over the tumor, but the best patient-saving results were achieved with a combination of RT and chemotherapy. Levamisole seemed to increase DFS and OS in all 3 treatment arms (RT, chemotherapy, combined treatment). Significance was reached in DFS (P=0.035) and OS, adjusted for all other treatment modalities (P=0.019).	1
37. Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. *J Clin Oncol* 2004; 22(23):4691-4699.	3a	676 patients	Retrospective analysis to evaluate the efficacy of radiation in patients treated with neoadjuvant chemotherapy and mastectomy.	Median follow-up: Irradiated, 73 months; nonirradiated, 66 months. Irradiated patients had lower rate of LRR (10-year rates: 11% vs 22%, P=.0001). Radiation reduced LRR for patients with clinical T3 or T4 tumors, stage ≥IIB disease, pathological tumor size >2 cm, or ≥4 positive nodes (P≤.002 for all comparisons). Radiation improved CSS in the following subsets: stage ≥IIIB disease, clinical T4 tumors, and ≥4 positive nodes (P≤.007 for all comparisons). After neoadjuvant chemotherapy and mastectomy, radiation benefited both local control and survival for patients with clinical T3 tumors or stage III-IV disease and for patients with ≥4 positive nodes. Radiation should be considered for these patients regardless of their response to initial chemotherapy.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
38. Helinto M, Blomqvist C, Heikkila P, Joensuu H. Post-mastectomy radiotherapy in pT3N0M0 breast cancer: is it needed? *Radiother Oncol* 1999; 52(3):213-217.	4	81 patients with T3N0M0 breast cancer	To review the records of patients treated with post-mastectomy RT in pT3N0m0 breast cancer to evaluate its effects.	Only 38/81 patients had true pT3N0M0 breast cancer after the review (0.9% of the 4,190 new breast cancer patients registered in the department from 1987 to 1994). 3/5 (60%) patients who were not treated with postoperative RT developed LRR of breast cancer as compared with only three (9%) of the 33 patients who were given postoperative RT during a median follow-up of 58 months (P=0.0003). Patients who were given postoperative RT had a better distant DFS rate (P=0.04) and OS rate (P=0.03) than the ones who were not treated with RT after surgery. Of the 29 patients who had chest wall irradiation only, one had in-field recurrence at the surgical scar, one both at the scar and the unirradiated axilla, and only one (3%) solely in the axilla. Patients with true pT3N0M0 breast cancer are rare. The results suggest that women with pT3N0M0 breast cancer benefit from postoperative RT, but the value of irradiating the dissected ipsilateral axilla remains unsettled.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
39. Floyd SR, Buchholz TA, Haffty BG, et al. Low local recurrence rate without postmastectomy radiation in node-negative breast cancer patients with tumors 5 cm and larger. *Int J Radiat Oncol Biol Phys* 2006; 66(2):358-364.	3a	70 patients	To assess the need for adjuvant RT following mastectomy for patients with node-negative breast tumors ≥5 cm and to retrospectively assess the rates and risk factors for LRF, OS, and DFS in these patients.	With a median follow-up of 85 months, the 5-year actuarial LRF rate was 7.6% (95% CI, 3%-16%). LRF was primarily in the chest wall (4/5 local failures), and LVI was statistically significantly associated with LRF risk by the log-rank test (P=0.017) and in Cox proportional hazards analysis (P=0.038). The 5-year OS and DFS rates were 83% and 86% respectively. LVI was also significantly associated with OS and DFS in both univariate and multivariate analysis. This series demonstrates a low LRF rate of 7.6% among breast cancer patients with node-negative tumors ≥5 cm after mastectomy and adjuvant systemic therapy. The data indicate that further adjuvant RT to increase local control may not be indicated by tumor size alone in the absence of positive LNs. LVI was significantly associated with LRF in the series, indicating that patients with this risk factor require careful consideration with regard to further local therapy.	2
40. Taghian AG, Jeong JH, Mamounas EP, et al. Low locoregional recurrence rate among node-negative breast cancer patients with tumors 5 cm or larger treated by mastectomy, with or without adjuvant systemic therapy and without radiotherapy: results from five national surgical adjuvant breast and bowel project randomized clinical trials. *J Clin Oncol* 2006; 24(24):3927-3932.	7 (meta-analysis)	N/A	To assess patterns of LRF in LN-negative patients who underwent mastectomy, either with or without adjuvant chemotherapy or hormonal therapy and without PMRT.	28 patients experienced LRF. The overall 10-year cumulative incidences of isolated LRF, LRF with and without distant failure, and distant failure alone as first event were 7.1%, 10.0%, and 23.6%, respectively. Cumulative incidences for isolated LRF as first event for patients with tumors of ≥5 cm were 7.0% and 7.2%, respectively (P=.9). For patients who underwent no systemic treatment, chemotherapy alone, tamoxifen alone, or chemotherapy plus tamoxifen, the incidences were 12.6%, 5.6%, 4.6%, and 5.3%, respectively (P=.2). The majority of failures occurred on the chest wall (24/28 patients). Multivariate analysis did not identify significant prognostic factors for LRF. In patients with LN-negative tumors ≥5 cm who are treated by mastectomy with or without adjuvant systemic therapy and no PMRT, LRF as first event remains low. PMRT should not be routinely used for these patients.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
41. Mignano JE, Gage I, Piantadosi S, Ye X, Henderson G, Dooley WC. Local recurrence after mastectomy in patients with T3pN0 breast carcinoma treated without postoperative radiation therapy. *Am J Clin Oncol* 2007; 30(5):466-472.	4	2,362 patients	Retrospective analysis to assess the frequency of local and distant recurrence in patients treated with mastectomy without postoperative RT.	The median follow-up time was 93 months. 22 T3N0 patients developed recurrent disease. Site of first recurrence was isolated local recurrence in 11 patients and distant in 11 patients. Four patients had simultaneous local and distant recurrences. Site of isolated local recurrence was chest wall failure in 5 patients and regional LNs failure in 6 patients. Median tumor size was 6 cm (range, 5-10.5 cm). There was no difference in local recurrence for tumor sizes ≤7 cm vs >7 cm (P=0.07). The crude recurrence rate for T3pN0 patients treated by mastectomy was similar to T2pN0 patients treated in similar fashion (P=0.3). The risk of isolated local recurrence in patients with T3pN0 breast cancer and negative margins is moderately low and similar to T2pN0 patients. These results suggest that routine use of postoperative chest wall and nodal irradiation in all T3pN0 patients may not be required.	2
42. Goulart J, Truong P, Woods R, Speers CH, Kennecke H, Nichol A. Outcomes of node-negative breast cancer 5 centimeters and larger treated with and without postmastectomy radiotherapy. *Int J Radiat Oncol Biol Phys* 2011; 80(3):758-764.	4	100 patients	To examine LRR and breast cancer-specific survival in pT2 = 5.0 cm and pT3 >5.0 cm tumors treated with mastectomy, stratified by PMRT use.	The PMRT group contained significantly more pT3 >5 cm cases (P=0.001) and margin-positive cases (P=.03). With a median follow-up of 10 years, the cumulative 10-year LRR rate was 2.3% (95% CI, 0.2-10.5) in the PMRT group vs 8.9% (95% CI, 3.2-18.2) in the no-PMRT group (P=.2). Regarding LRR in the no-PMRT group, all patients had Grade 3 histologic features (LRR 17%, 5/29) and had not received hormonal therapy (LRR 15%, 5/34). The 10-year breast cancer-specific survival rate was 85.8% (95% CI 71.0-93.4) in the PMRT group vs 74.6% (95% CI 59.9-84.5) in the no-PMRT group (P=.2). On multivariate analysis, adjusted for the prognostic and predictive variables, PMRT did not significantly improve the LRR or breast cancer-specific survival rates. The present study demonstrated a low LRR rate for node-negative breast cancer ≥5 cm. The results indicate that PMRT should be considered for Grade 3 histologic features and patients not undergoing hormonal therapy.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
43. Yu JB, Wilson LD, Dasgupta T, Castrucci WA, Weidhaas JB. Postmastectomy radiation therapy for lymph node-negative, locally advanced breast cancer after modified radical mastectomy: analysis of the NCI Surveillance, Epidemiology, and End Results database. *Cancer* 2008; 113(1):38-47.	3a	1,777 patients	To evaluate the role of PMRT for LN-negative locally advanced breast carcinoma (T3N0M0) after MRM with regard to improvement in survival remains an area of controversy.	Median tumor size was 6.3 cm. The median number of LNs examined was 14 (range, 1-49). Propensity score matched case-control analysis showed no improvement in OS with the delivery of PMRT in this group. Older patients, patients with ER– disease (compared with ER+), and patients with high-grade tumors (compared with well differentiated) had increased mortality. The use of PMRT for T3N0M0 breast carcinoma after MRM is not associated with an increase in OS. It was not possible to analyze local control in this study given the limitations of the SEER database. The impact of potential improvement in local control as it relates to OS should be the subject of further investigation.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
44. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998; 16(8):2672-2685.	1	1,523 patients	To determine, in women with primary operable breast cancer, if preoperative AC therapy yields a better outcome than postoperative AC therapy, if a relationship exists between outcome and tumor response to preoperative chemotherapy, and if such therapy results in the performance of more lumpectomies.	There was no significant difference in DFS, distant DFS, or survival (P=.99, .70, and .83, respectively) among patients in either group. More patients treated preoperatively than postoperatively underwent lumpectomy and RT (67.8% vs 59.8%, respectively). Rates of IBTR after lumpectomy were similar in both groups (7.9% and 5.8%, respectively; P=.23). Outcome was better in women whose tumors showed a partial response than in those with a pathologic invasive cells, partial response, or no response (RFS rates, 85.7%, 76.9%, 68.1%, and 63.9%, respectively; P<.0001), even when baseline prognostic variables were controlled. When prognostic models were compared for each treatment group, the preoperative model, which included breast tumor response as a variable, discriminated outcome among patients to about the same degree as the postoperative model. Preoperative chemotherapy is as effective as postoperative chemotherapy, permits more lumpectomies, is appropriate for the treatment of certain patients with stages I and II disease, and can be used to study breast cancer biology. Tumor response to preoperative chemotherapy correlates with outcome and could be a surrogate for evaluating the effect of chemotherapy on micrometastases; however, knowledge of such a response provided little prognostic information beyond that which resulted from postoperative therapy.	1

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
45. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst* 2005; 97(3):188-194.	7 (meta-analysis)	9 randomized studies with a total of 3,946 patients	To compare the clinical end points of patients with breast cancer treated preoperatively with systemic therapy (neoadjuvant therapy) and of those treated postoperatively with the same regimen (adjuvant therapy) in a meta-analysis of randomized trials.	No statistically or clinically significant difference was found between neoadjuvant therapy and adjuvant therapy arms associated with death (summary RR = 1.00, 95% CI = 0.90 to 1.12), disease progression (summary RR = 0.99, 95% CI = 0.91 to 1.07), or distant disease recurrence (summary RR = 0.94, 95% CI = 0.83 to 1.06). However, neoadjuvant therapy was statistically significantly associated with an increased risk of loco-regional disease recurrences (RR = 1.22, 95% CI = 1.04 to 1.43), compared with adjuvant therapy, especially in trials where more patients in the neoadjuvant, than the adjuvant, arm received RT without surgery (RR = 1.53, 95% CI = 1.11 to 2.10). Across trials, heterogeneity was observed in the rates of complete clinical response (range = 7%-65%; P for heterogeneity of <.001), pathologic response (range = 4%-29%; P for heterogeneity of <.001), and adoption of conservative local treatment (range = 28%-89% in neoadjuvant arms, P for heterogeneity of <.001). Neoadjuvant therapy was apparently equivalent to adjuvant therapy in terms of survival and overall disease progression. Neoadjuvant therapy, compared with adjuvant therapy, was associated with a statistically significant increased risk of loco-regional recurrence when RT without surgery was adopted.	1

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
46. Buchholz TA, Katz A, Strom EA, et al. Pathologic tumor size and lymph node status predict for different rates of locoregional recurrence after mastectomy for breast cancer patients treated with neoadjuvant versus adjuvant chemotherapy. *Int J Radiat Oncol Biol Phys* 2002; 53(4):880-888.	3a	1,081 total patients: 50 patients in the neoadjuvant chemotherapy group and 1,031 patients in the adjuvant chemotherapy group	To retrospectively analyze and compare the pathologic factors associated with postmastectomy LRR in breast cancer patients not receiving radiation who were treated with neoadjuvant chemotherapy vs adjuvant chemotherapy.	Despite the more advanced clinical stage in the neoadjuvant chemotherapy group, the pathologic size of the primary tumor and the number of positive LNs (+LNs) were significantly less in the neoadjuvant chemotherapy group than in the adjuvant chemotherapy group (P<0.001 for both comparisons). However, the 5-year actuarial LRR rate was 27% for the neoadjuvant chemotherapy group vs 15% for the adjuvant chemotherapy group (P=0.001, log-rank). The 5-year risk for LRR was higher in the neoadjuvant chemotherapy patients for all pathologic tumor sizes: 0-2 cm (18% vs 8%, P=0.011), 2.1-5 cm (36% vs 15%, P<0.001), and >5 cm (46% vs 28%, P=0.028). The rates of postmastectomy LRR for any pathologic tumor size are higher for patients treated with initial chemotherapy than for patients treated with initial surgery. RT should be offered to all patients with ≥4 +LNs, tumor size >5 cm, or clinical Stage IIIA or greater disease, regardless of whether they receive neoadjuvant or postoperative chemotherapy. The information assessing LRR rates in patients with clinical Stage II disease who receive neoadjuvant chemotherapy, particularly if 1-3 LNs remain pathologically involved, is insufficient to determine whether these patients should receive RT.	2
47. Buchholz TA, Tucker SL, Masullo L, et al. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. *J Clin Oncol* 2002; 20(1):17-23.	3a	150 breast cancer cases	Retrospective analysis to define clinical and pathologic predictors of LRR for patients treated with neoadjuvant chemotherapy and mastectomy without radiation.	Median follow-up 4.1 years. 5- and 10-year LRR both 27%. Pathologic and treatment factors that positively correlated with LRR were size of residual primary tumor (P=.0048), increasing number of involved LNs (P<.0001), and no use of tamoxifen (P=.0013). In Cox analysis, clinical stage IIIB or greater (HR of 4.5, P<.001), pathologic involvement of ≥4 LNs (HR 2.7, P=.008), and no use of tamoxifen (HR 3.9, P=.027) independently predicted for LRR. Advanced disease and positive LNs after chemotherapy predict for clinically significant rates of LRR.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
48. Garg AK, Strom EA, McNeese MD, et al. T3 disease at presentation or pathologic involvement of four or more lymph nodes predict for locoregional recurrence in stage II breast cancer treated with neoadjuvant chemotherapy and mastectomy without radiotherapy. *Int J Radiat Oncol Biol Phys* 2004; 59(1):138-145.	4	132 patients with Stage I or II breast cancer	To retrospectively review outcomes to help define the clinical and pathologic predictors of LRR in breast cancer patients treated with neoadjuvant chemotherapy and mastectomy without RT for early-stage disease.	The actuarial LRR rate at both 5 and 10 years was 10%. Factors that correlated positively with LRR included clinical Stage T3N0 (P=0.0057), four or more positive LNs at surgery (P=0.0001), age ≤40 years at diagnosis (P=0.0001), and no use of tamoxifen. In the patients who did not receive tamoxifen, ER-positive disease correlated positively with LRR (P=0.0067). The 5-year LRR rate for the 42 patients with clinical Stage T1 or T2 disease and one to three positive LNs at surgery was 5% (only two events). For patients with clinical Stage II breast cancer, T3 primary disease, four or more positive LNs after chemotherapy, and age ≤40 years old predicted for LRR. For most patients with clinical T1 or T2 disease and one to three positive LNs, the 5-year risk for LRR was low, and the routine inclusion of PMRT does not appear to be justified.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
49. Nagar H, Mittendorf EA, Strom EA, et al. Local-regional recurrence with and without radiation therapy after neoadjuvant chemotherapy and mastectomy for clinically staged T3N0 breast cancer. *Int J Radiat Oncol Biol Phys* 2011; 81(3):782-787.	4	162 patients	To determine LRR risk according to whether PMRT was used to treat breast cancer patients with clinical T3N0 disease who received neoadjuvant chemotherapy and mastectomy.	At a median follow-up of 75 months, 15/162 patients developed LRR. For all patients, the 5-year LRR rate was 9% (95% CI, 4%-14%). The 5-year LRR rate for those who received PMRT was 4% (95% CI, 1%-9%) vs 24% (95% CI, 10%-39%) for those who did not receive PMRT (P<0.001). A significantly higher proportion of irradiated patients had pathology involved LNs and were ≤40 years old. Among patients who had pathology involved LNs, the LRR rate was lower in those who received PMRT (P<0.001). A similar trend was observed for those who did not have pathology involved LN disease. Among nonirradiated patients, the appearance of pathologic LN disease after neoadjuvant chemotherapy was the only clinicopathologic factor examined that significantly correlated with the risk of LRR. Breast cancer patients with clinical T3N0 disease treated with neoadjuvant chemotherapy and mastectomy but without PMRT had a significant risk of LRR, even when there was no pathologic evidence of LN involvement present after neoadjuvant chemotherapy. PMRT was effective in reducing the LRR rate. We suggest PMRT should be considered for patients with clinical T3N0 disease.	2
50. Garg AK, Oh JL, Oswald MJ, et al. Effect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. *Int J Radiat Oncol Biol Phys* 2007; 69(5):1478-1483.	4	107 consecutive patients	To retrospectively assess the benefits of PMRT in patients <35 years old treated with doxorubicin-based neoadjuvant chemotherapy for stage II-III breast cancer.	Despite more advanced disease stages, the patients who received PMRT (n = 80) had greater rates of LRC (5-year rate, 88% vs 63%, P=0.001) and better OS (5-year rate, 67% vs 48%, P=0.03) than patients who did not receive PMRT (n = 27). Among breast cancer patients <35 years old at diagnosis, the use of PMRT after doxorubicin-based neoadjuvant chemotherapy and mastectomy led to a statistically greater rate of LRC and OS compared with patients without PMRT. The benefit seen for PMRT in young patients provides valuable data to better tailor adjuvant, age-specific treatment decisions after mastectomy.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
51. McGuire SE, Gonzalez-Angulo AM, Huang EH, et al. Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. *Int J Radiat Oncol Biol Phys* 2007; 68(4):1004-1009.	3a	226 patients	To retrospectively investigate the role of PMRT in women with breast cancer who achieved a pathologic complete response to neoadjuvant chemotherapy.	The median follow-up of surviving patients was 62 months. Use of RT did not affect the 10-year rates of LRR for patients with stage I or II disease (the 10-year LRR rates were 0% for both groups). However, the 10-year LRR rate for patients with stage III disease was significantly improved with RT (7.3% +/- 3.5% with vs 33.3% +/- 15.7% without; P=0.040). Within this cohort, use of RT was also associated with improved disease-specific and OS. PMRT provides a significant clinical benefit for breast cancer patients who present with clinical stage III disease and achieve a pathologic complete response after neoadjuvant chemotherapy.	2
52. Le Scodan R, Selz J, Stevens D, et al. Radiotherapy for stage II and stage III breast cancer patients with negative lymph nodes after preoperative chemotherapy and mastectomy. *Int J Radiat Oncol Biol Phys* 2012; 82(1):e1-7.	3a	134 patients	To evaluate the effect of PMRT in stage II-III breast cancer patients with negative LNs (pN0) after neoadjuvant chemotherapy.	At a median follow-up time of 91.4 months, the 5-year LRR-free survival and OS rate was 96.2% and 88.3% with PMRT and 92.5% and 94.3% without PMRT, respectively (P=NS). The corresponding values at 10 years were 96.2% and 77.2% with PMRT and 86.8% and 87.7% without PMRT (P=NS). On multivariate analysis, PMRT had no effect on either LRR-free survival (HR, 0.37; 95% CI, 0.09-1.61; P=.18) or OS (HR, 2.06; 95% CI, 0.71-6; P=.18). This remained true in the subgroups of patients with clinical stage II or III disease at diagnosis. A trend was seen toward poorer OS among patients who had not had a pathologic complete in-breast tumor response after neoadjuvant chemotherapy (HR, 6.65; 95% CI, 0.82-54.12; P=.076). The results from the present retrospective study showed no increase in the risk of distant metastasis, LRR, or death when PMRT was omitted in breast cancer patients with pN0 status after neoadjuvant chemotherapy and mastectomy. Whether the omission of PMRT is acceptable for these patients should be addressed prospectively.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
53. Buchholz TA, Lehman CD, Harris JR, et al. Statement of the science concerning locoregional treatments after preoperative chemotherapy for breast cancer: a National Cancer Institute conference. *J Clin Oncol* 2008; 26(5):791-797.	7	N/A	To review the state of the science with respect to diagnostic imaging and locoregional therapy for patients with breast cancer receiving preoperative chemotherapy.	Loco-regional therapy decisions should be based on the pretreatment clinical extent of disease and the pathologic extent of the disease after chemotherapy. Physical examination and imaging studies that accurately define the initial extent of disease are required before treatment. Increased use of preoperative chemotherapy has raised questions concerning optimal methods to stage and monitor disease response to treatment and how to optimize loco-regional treatment. Multidisciplinary approach improves outcomes.	4
54. Rashtian A, Iganej S. 195 Close or Positive Margins Following Mastectomy for Ductal Carcinoma in Situ (DCIS): Patterns of Relapse and Potential Indications for Radiotherapy. *Int J Radiat Oncol Biol Phys* 2006; 66(3 Suppl 1):S108-S109.	3a	574 patients	To retrospectively review close or positive margins following mastectomy for DCIS.	With a median follow-up of 61 months, 6 (7.5%) of the 80 patients developed local recurrence. Of the 31 patients with a margin of ≤2 mm, 5 (16%) developed local recurrence vs only 1 (2%) of 49 patients with a margin of 2.1-10 mm (P=0.0356). Of the 6 patients with local recurrence, 5 had high-grade disease and/or comedonecrosis. All six recurrences were noted in patients <60 years old. The findings of this review suggest that patients with pure DCIS who undergo mastectomy with a margin of <2 mm have a greater-than-expected incidence of local recurrence. Patients with additional unfavorable features such as high-grade disease, comedonecrosis, and age <60 years are particularly at risk of local recurrence. These patients might benefit from PMRT.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
55. Carlson GW, Page A, Johnson E, Nicholson K, Styblo TM, Wood WC. Local recurrence of ductal carcinoma in situ after skin-sparing mastectomy. *J Am Coll Surg* 2007; 204(5):1074-1078; discussion 1078-1080.	3a	223 consecutive patients	To examine the risk factors for local recurrence after skin-sparing mastectomy for DCIS.	Mean follow-up was 82.3 months (range 4.9-123.2 months). Recurrences developed in 11 patients (5.1%), including: local (n = 7; 3.3%), regional (n = 2; 0.9%), and distant (n = 2; 0.9%). All 7 local recurrences were detected by physical examination. No patients received adjuvant RT. Two of 19 patients with surgical margins <1 mm developed LR (10.5%). Univariate analysis showed high tumor grade (P=.019) to influence LR. The incidence of local recurrence of DCIS after skin-sparing mastectomy is similar to conventional total mastectomy. Reexcision of close margins should be performed if possible and adjuvant RT should be considered.	2
56. Chan LW, Rabban J, Hwang ES, et al. Is radiation indicated in patients with ductal carcinoma in situ and close or positive mastectomy margins? *Int J Radiat Oncol Biol Phys* 2011; 80(1):25-30.	3a	193 women	To determine chest wall recurrence rates in women with DCIS and close (<5 mm) or positive mastectomy margins in order to evaluate the potential role of RT.	Median follow-up was 8 years. Median pathologic size of the DCIS in the mastectomy specimen was 4.5 cm. 22 patients had DCIS of >5 cm or diffuse disease. Median width of the close final margin was 2 mm. 19 patients had margins of <1 mm. The DCIS was high-grade, 4 cm, with a 5-mm deep margin. A second patient developed an invasive cancer in the chest wall 20 years after her mastectomy for DCIS. This cancer was considered a new primary site arising in residual breast tissue. The risk of chest wall recurrence in this series of patients is 1.7% for all patients and 3.3% for high-grade DCIS. One out of 20 (5%) patients undergoing skin sparing or total skin-sparing mastectomy experienced a chest wall recurrence. This risk of a chest wall recurrence appears sufficiently low not to warrant a recommendation for PMRT for patients with margins of <5 mm. There were too few patients with positive margins to draw any firm conclusions.	2

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
57. Kim JH, Tavassoli F, Haffty BG. Chest wall relapse after mastectomy for ductal carcinoma in situ: a report of 10 cases with a review of the literature. *Cancer J* 2006; 12(2):92-101.	4	10 patients	To report chest wall relapse after mastectomy for DCIS.	Of the 10 cases, 9 patients remain alive without evidence of disease. Young patient age, multiquadrant disease, and the presence of residual normal breast tissue were common features among these chest wall relapses. Pathological features of the original mastectomies and chest wall relapses are presented and discussed. Postmastectomy chest wall relapses in patients with DCIS are an uncommon event. Patients treated aggressively with resection of the lesion followed by RT to the chest wall have a favorable prognosis.	4
58. Romestaing P, Belot A, Hennequin C, et al. Ten-year Results of a Randomized Trial of Internal Mammary Chain Irradiation after Mastectomy. *International Journal of Radiation Oncology*Biology*Physics* 2009; 75(3, Supplement 1):S1-S1.	1	1,334 total patients	Randomized, phase III trial to evaluate the impact of internal mammary chain RT on long-term survival in breast cancer patients treated with mastectomy.	With a median follow-up of 10 years, we observed 535 deaths. Ten-year survival was 62.57% in case of internal mammary chain RT and 59.55% without internal mammary chain RT (P=0.8762 by log–rank test). No difference was obtained in the different subgroups: positive or negative axillary nodes, external vs central/internal tumors, or according to the different histologic subtypes, adjuvant chemotherapy, or hormonotherapy. Causes of death are known in 422 patients: most of these deaths were due to breast cancer (371); no increase in cardiac toxicity was observed in the internal mammary chain RT group. Using internal mammary chain RT did not improve OS in this large randomized study.	1

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
59. Whelan TJ, Olivotto I, Ackerman I, et al. NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. *ASCO Meeting Abstracts* 2011; 29(18_suppl):LBA1003.	1	1,832 women	To evaluate the addition of regional nodal irradiation to whole breast irradiation following BCS.	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%. Whole breast irradiation + regional nodal irradiation in comparison to whole breast irradiation 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). Whole breast irradiation + regional nodal irradiation in comparison to whole breast irradiation 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). The majority of women with node positive breast cancer are now managed by BCS followed by whole breast irradiation and adjuvant systemic therapy. Results from MA.20 demonstrate that additional regional nodal irradiation reduces the risk of locoregional and distant recurrence, and improves DFS with a trend in improved OS.	1

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
60. Macdonald SM, Abi-Raad RF, Alm El-Din MA, et al. Chest wall radiotherapy: middle ground for treatment of patients with one to three positive lymph nodes after mastectomy. *Int J Radiat Oncol Biol Phys* 2009; 75(5):1297-1303.	3a	238 total patients	To retrospectively evaluate the outcomes for patients with Stage II breast cancer and one to three positive LNs after mastectomy who were treated with observation or adjuvant RT to the chest wall with or without the regional lymphatics.	LRR and DFS were significantly improved by PMRT, with a 5- and 10-year LRR rate without PMRT of 6% and 11%, respectively and, with PMRT, of 0% at both 5 and 10 years (P=.02). The 5- and 10-year DFS rate without PMRT was 85% and 75%, respectively, and, with PMRT, was 93% at both 5 and 10 years (P=.03). A similar benefit was found for patients treated with RT to the chest wall alone. The LRR, DFS, and OS rate for patients treated to the chest wall only was 0%, 96%, and 95% at 10 years, respectively. The data suggest that adjuvant PMRT to the chest wall alone provides excellent disease control for patients with breast cancer <5 cm with one to three positive LNs.	2
61. Li XA, Tai A, Arthur DW, et al. Variability of target and normal structure delineation for breast cancer radiotherapy: an RTOG Multi-Institutional and Multiobserver Study. *Int J Radiat Oncol Biol Phys* 2009; 73(3):944-951.	4	N/A	To quantify the multi-institutional and multiobserver variability of target and organ-at-risk delineation for breast-cancer RT and its dosimetric impact as the first step of a Radiation Therapy Oncology Group effort to establish a breast cancer atlas.	Variability in contouring the targets and organs-at-risk between the institutions and observers was substantial. Structure overlaps were as low as 10%, and volume variations had standard deviations up to 60%. The large variability was related both to differences in opinion regarding target and organ-at-risk boundaries and approach to incorporation of setup uncertainty and dosimetric limitations in target delineation. These interobserver differences result in substantial variations in dosimetric planning for breast RT. Differences in target and organ-at-risk delineation for breast irradiation between institutions/observers appear to be clinically and dosimetrically significant. A systematic consensus is highly desirable, particularly in the era of intensity-modulated and image-guided RT.	3
62. Radiation Therapy Oncology Group. Breast cancer atlas for radiation therapy planning: consensus definitions. http://www.rtog.org/LinkClick.aspx?fileticket=vzJFhPaBipE%3D&tabid=236. Accessed 5 December 2011.	15	N/A	RTOG atlas for Breast Cancer Radiation Therapy planning based on consensus based definitions.	Definitions include: Breast clinical target volume-Considers referenced clinical breast at time of CT. Chest Wall clinical target volume - Includes the mastectomy scar. Defines regional nodal contours and anatomical boundaries.	4

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
63. Moran MS, Haffty BG. Radiation techniques and toxicities for locally advanced breast cancer. *Semin Radiat Oncol* 2009; 19(4):244-255.	7	N/A	To review radiation techniques and toxicities for locally advanced breast cancer.	RT is an important component of the multidisciplinary management of locally advanced breast cancer. The treatment units and techniques have evolved significantly over the years, with a subsequent decrease in the long-term cardiac complications and cardiac-related deaths and improvements in OS. The current technology mandates an in-depth knowledge of the anatomy and treatment techniques to improve homogeneity in the treatment field while minimizing the dose to organs at risk. Only with optimal radiation treatment planning and delivery can the survival benefit with adjuvant RT for locally advanced breast cancer continue to be achieved.	4

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
64. Pierce LJ, Butler JB, Martel MK, et al. Postmastectomy radiotherapy of the chest wall: dosimetric comparison of common techniques. *Int J Radiat Oncol Biol Phys* 2002; 52(5):1220-1230.	4	20 cases	To compare 7 techniques for irradiation of the postmastectomy chest wall using normal tissue complication probability predictions for pneumonitis and ischemic heart disease and dose-volume histogram analyses for normal and target tissues.	Overlap in the distributions of the chest wall mean dose for all plans was found, except cobalt, which was significantly less than the remaining techniques (global F test, F = 21.90, P<0.0001). Standard tangents produced a significantly lower internal mammary node mean dose than all other methods, as expected (F = 59.55, P< 0.0001); the reverse hockey stick and cobalt techniques were lower than the other methods, which were statistically similar. Cobalt produced a significantly higher percentage of the heart that received >30 Gy (V30) than the other methods (F = 49.76, P<0.0001). Use of partially wide tangent fields resulted in the smallest heart V30. Use of cobalt fields resulted in a significantly greater normal tissue complication probability estimate for ischemic heart disease than all the remaining techniques (F = 70.39, P<0.0001). Standard tangents resulted in a percentage of the lung receiving >20 Gy (V20) significantly less than with partially wide tangent fields, 30/70 and 20/80 photon/electron mix, and reverse hockey stick techniques. Normal tissue complication probability estimates for pneumonitis revealed significantly better results with standard tangents (F = 6.57, P<0.0001). No one technique studied combines the best chest wall and internal mammary node coverage with minimal lung and heart complication probabilities. The choice of technique should be based on clinical discretion and the technical expertise available to implement these complex plans. Of the 7 techniques studied, this analysis supports partially wide tangent fields as the most appropriate balance of target coverage and normal tissue sparing when irradiating the chest wall and internal mammary node.	3

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
65. Shelley W, Brundage M, Hayter C, Paszat L, Zhou S, Mackillop W. A shorter fractionation schedule for postlumpectomy breast cancer patients. *Int J Radiat Oncol Biol Phys* 2000; 47(5):1219-1228.	4	294 patients	To determine the effectiveness of 40 Gy in 16 daily fractions in preventing local recurrence in postlumpectomy invasive breast cancer patients whose margins of resection were clear of tumor by at least 2 mm.	The 5-year actuarial breast-relapse rate was 3.5%, with an overall 5-year survival and disease-specific survival of 87.8% and 92.1%, respectively. In response to the cosmesis questionnaire, 77% of patients stated they were either extremely or very satisfied with the overall appearance of the breast, 19.5% moderately satisfied, and 3.5% either slightly or not at all satisfied. The corresponding responses for overall level of comfort of the breast were 79%, 16.5%, and 4.5% respectively. This regimen is very effective at preventing recurrent breast cancer in this group of patients, and it provides a high level of patient satisfaction with cosmetic outcome. Its short duration offers the added advantage of a more efficient use of resources and greater patient convenience.	2
66. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; 362(6):513-520.	1	1,234 total patients: 612 women assigned to standard RT; 622 women assigned to the hypofractionated regimen	Randomized study to determine whether a hypofractionated 3-week schedule of whole-breast RT 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 RT 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). Ten years after treatment, accelerated, hypofractionated whole-breast RT was not inferior to standard radiation treatment in women who had undergone BCS for invasive breast cancer with clear surgical margins and negative axillary nodes.	1

Postmastectomy Radiotherapy
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
67. Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008; 371(9618):1098-1107.	1	2,215 patients: 1,105; 50 Gy group 1,110; 40 Gy group	To test the benefits of RT schedules using fraction sizes larger than 2.0 Gy in terms of local-regional tumor control, normal tissue responses, quality of life, and economic consequences in women prescribed post-operative RT.	After a median follow up of 6.0 years (IQR 5.0-6.2) the rate of local-regional tumor relapse at 5 years was 2.2% (95% CI, 1.3-3.1) in the 40 Gy group and 3.3% (95% CI, 2.2 to 4.5) in the 50 Gy group, representing an absolute difference of -0.7% (95% CI, -1.7% to 0.9%) — ie, the absolute difference in local-regional relapse could be up to 1.7% better and at most 1% worse after 40 Gy than after 50 Gy. Photographic and patient self-assessments indicated lower rates of late adverse effects after 40 Gy than after 50 Gy. A radiation schedule delivering 40 Gy in 15 fractions seems to offer rates of local-regional tumor relapse and late adverse effects at least as favorable as the standard schedule of 50 Gy in 25 fractions.	1
68. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 2005; 6(8):557-565.	3a	308,861 women with early breast cancer of known laterality	Prospective cohort study of women in US Surveillance Epidemiology and End Results (SEER) cancer registries to assess the long-term heart disease risks associated with RT for early breast cancer.	Increased cardiac related mortality was seen for breast cancer patients irradiated before 1980. However, since that time there is no discernable increase in cardiac-related mortality for breast patients treated with RT.	2

Evidence Table Key

Study Type Key

Numbers 1-7 are for studies of therapies while numbers 8-15 are used to describe studies of diagnostics.

1. Randomized Controlled Trial — Treatment
2. Controlled Trial
3. Observation Study
    a. Cohort
    b. Cross-sectional
    c. Case-control
4. Clinical Series
5. Case reviews
6. Anecdotes
7. Reviews
8. Randomized Controlled Trial — Diagnostic
9. Comparative Assessment
10. Clinical Assessment
11. Quantitative Review
12. Qualitative Review
13. Descriptive Study
14. Case Report
15. Other (Described in text)

Strength of Evidence Key

- Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.
- Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.
- Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.
- Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Abbreviations Key

AC = Doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan)
BCS = Breast-conserving surgery
BCT = Breast-conserving therapy
CI = Confidence interval
CMF = Cyclophosphamide, methotrexate, and fluorouracil
DCIS = Ductal carcinoma in situ
DFS = Disease-free survival
ECE = Extracapsular extension
ER = Estrogen receptor
HER2 = Human epidermal growth factor 2
HR = Hazard ratio
IBTRs = Ipsilateral breast tumor recurrences
LN = Lymph node
L-PAM = L-phenylalanine mustard
LRF = Locoregional failure
LRR = Locoregional recurrence
LVI = Lymphovascular invasion
MRM = Modified radical mastectomy
OS = Overall survival
PMRT = Postmastectomy radiotherapy
PR = Progesterone receptor
RFS = Relapse-free survival
RT = Radiation therapy