Original Article

Identifying the Risk Factors of Local Recurrence of Early-Stage Breast Cancer after Surgery and Adjuvant Treatment

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Abstract

Background: Local recurrence of breast cancer after treatment remains a major challenge that affects survival and quality of life. Identifying the risk factors for locoregional recurrence (LRR) may change our strategies in the treatment of those patients to let them enjoy long survival. **Aim of the Study:** To identify the risk factors associated with high rate of local recurrence of early breast cancer and its impaction on time of recurrence. **Materials and Methods:** In this retrospective study, we evaluated 225 patients with early breast cancer (T1–2, N0–1) with a mean age of 46.178 years and a median of 45 years, who treated by surgery and adjuvant treatment (chemotherapy and/or hormonal therapy) without radiotherapy in Babylon Oncology Center from 2012 to 2014 and followed for next 5 years. We collected data to identify the risk factors; we used files from archive and follow-up program in this center. We used SPSS version 23 in our calculation; $P \leq 0.05$ was considered statistically significant. **Results:** From a total of 225 patients, the mean age was 46.178 years and the median was 45 years; we found that 31 (13.8%) patients developed local recurrence after surgery. The median time for follow-up was 40.2 months, and the median time to recurrence was 30 months. From 31 recurred patients, 58.1% were recurred after 2 years and 41.9% recurred within 2 years and less after surgery. In univariate analyses, tumor size more than 20 mm, lymph nodes (LNs) <10 removed by surgery, positive (1–3) LNs, high-grade tumor, presence of lymphovascular invasion, extracapsular extension, and estrogen receptor (ER) negative appeared significant for local recurrence. In multivariate analyses, all significant factors did not change except number of LNs removed and ER negative. No single factor appears significant for early recurrence (2 years and less after surgery). **Conclusion:** Our study showed many factors can affect locoregional recurrence after initial treatment with surgery and chemotherapy with (58.1%) of cases recur after 2 years of surgery, so we recommend

1) offering a post mastectomy radiotherapy (PMRT) for those patients with significant clinical and pathological risk factors.
2) establish a close follow up program to diagnose early LRR to deal with those patient early in order to prevent more serious event that affect quality of life and patient survival.

Keywords: Breast cancer, recurrence, risk factors

Introduction

Breast cancer is the most common cancer all over the world. The annual report of Iraqi Cancer Registry in 2018 reported that breast cancer constitutes 36.7% of new female cases and 20.3% in both sexes diagnosed annually. It is the second leading cause of cancer death (11.9%) after lung cancer in both sexes.[1]

Early breast cancer patients enjoy good survival, but still, there are large percentage of patients suffer failure after treatment; many studies show locoregional recurrence (LRR) rate of around 20% in early breast cancer patients after treatment.[2]

Local recurrence and distant metastases represent main challenge, which affects disease-free survival, overall survival (OS), and quality of life of patients. Microscopically, residual disease after surgery may lead to local and regional recurrence as well as distant metastases.[3-7] Many guidelines and large studies recommend postmastectomy radiotherapy (PMRT) for those patients after surgery and chemotherapy.[8]

Results from the Danish trials,[9] the Vancouver British Columbia trial,[10] and the National Comprehensive Cancer Network guideline recommendation[11] suggested that patients with <4 positive lymph nodes (LNs) get benefit from adjuvant

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radiotherapy and recommend offering of radiotherapy for early breast cancer, especially if one or more risk factors are present such as lymphovascular invasion (LVI), high grade, triple negative, and others.

Meanwhile there are many trials revealed lower risk of recurrence without PMRT.[12] Therefore, the analysis of clinical and histopathological factors of patients with early breast cancer (pT1-2, N0-1) can identifying the high-risk patient for local recurrence and the significant risk factors that contribute to recurrence. And this is crucial to derive a risk classification and establish a perfect plan for treatment to offer the post mastectomy radiotherapy (PMRT) for those patients in high risk group and follow them aggressively.[12]

Materials and Methods

In this retrospective study, we evaluated 225 patients with early breast cancer, tumor size <5 cm (T_{1-2}), and <4 LNs positive for tumor (N_{0-1}), who were staged according to 7th American Joint Committee on Cancer, treated in Babylon Oncology Center (BOC) from 2012 to 2014, and monitored for further 5 years.

We used files of patients and follow-up program registered in BOC to collect informations and to fill our questionnaire. All patients included in study treated by surgery (mastectomy) with negative margins (R0) and received adjuvant chemotherapy and/or hormonal therapy with tamoxifen or aromatase inhibitor according to menopausal state. Trastuzumab added according to human epidermal growth factor receptor 2 (HER2/neu) results. And all cases not received radiotherapy. We found that 31 cases recurred locally and 194 free from disease after adjuvant treatment.

We considered any recurrence in the remaining breast tissue or chest wall after mastectomy, scar and skin around scar as local recurrence and any recurrence occur in ipsilateral axillary, internal mammary, and supraclavicular LNs as regional. We considered recurrence in any of these sites as LRR and we named it as recurrence.

We evaluated 10 risk factors (clinical and pathological) for recurrence. We considered age as 40 years and less as risk factor versus more than 40 years, Grade 3 and 4 as high grade and high risk for recurrence versus 1 and 2 (low grade), and size of tumor more than 20 mm as high risk factor versus 20 mm and less.

We evaluated positive LNs (1–3) versus negative, inadequate LNs dissection (as <10) versus 10 and more (adequate) also LVI and extracapsular extension (ECE) Presence versus absence, and negative estrogen , progesterone receptor (PR) versus positive. We considered 3 plus results of HER/2neu by immunohistochemistry study and equivocal results confirmed by fluorescence in situ hybridization as positive scored according the CAP/ASCO guidelines.[13,14]

Statistical analysis

Univariate and multivariate analyses for our data were carried out using Statistical package for the social sciences version 23 (SPSS, IBMCompany, Chicago, USA). Categorical variables were presented as frequencies and percentages. Pearson's Chi-square and Fisher's exact tests were used to find the association between categorical variables. $P \leq 0.05$ was considered statistically significant.

We evaluated these factors for association with early and late recurrence, 2 years and less taken as early and more than 2 years as late recurrence.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patient's verbal and analytical approval before the sample was taken. The study protocol and the subject information and consent form were reviewed and approved by the local ethics committee.

Results

From a total of 225 patients, 31 (13.8%) patients revealed local recurrence [Figure 1]. The median time for follow-up

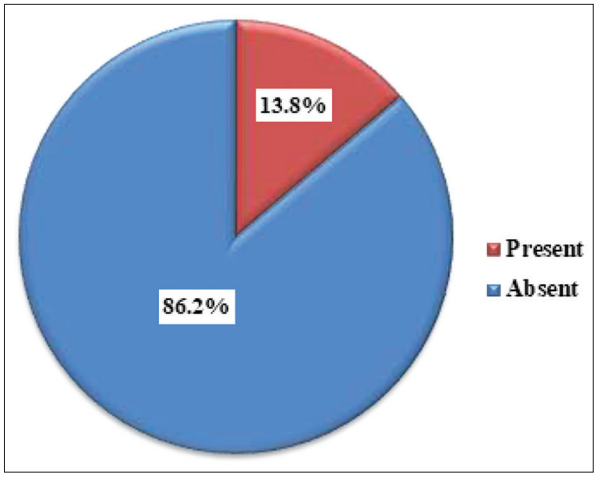

Figure 1: Percent of local recurrence from 225 patients

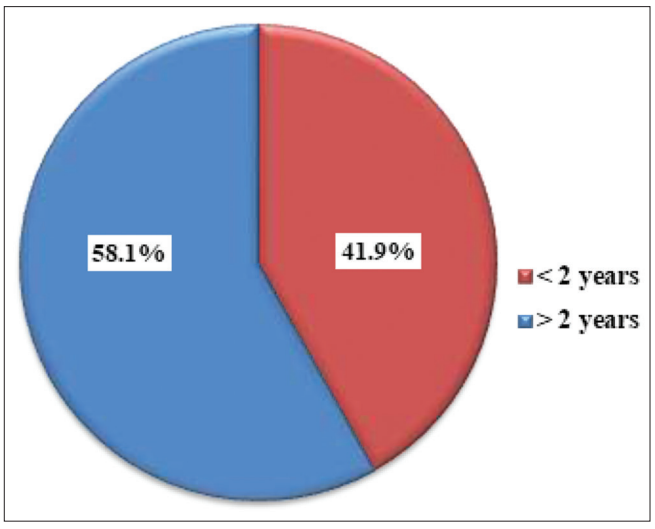

Figure 2: Percent of recurred patients before and after 2 year of surgery

Table 1: Association between local recurrence and study variables among the study patients

Study variables	Local recurrence		Total	χ^2	*P*	OR	95% CI
	Present	Absent					
Age (years)							
≤40	15 (48.4)	71 (36.6)	86 (38.2)	1.573	0.21	1.624	0.758-3.482
>40	16 (51.6)	123 (63.4)	139 (61.8)				
Total	31 (100.0)	194 (100.0)	225 (100.0)				
Tumor size (cm)							
≤2	6 (19.4)	102 (52.6)	108 (48.0)	11.82	0.001*	0.216	0.085-0.551
>2	25 (80.6)	92 (47.4)	117 (52.0)				
Total	31 (100.0)	194 (100.0)	225 (100.0)				
Number of LN							
<10	19 (61.3)	64 (33.0)	83 (36.9)	9.195	0.002*	3.216	1.471-7.032
≥10	12 (38.7)	130 (67.0)	142 (63.1)				
Total	31 (100.0)	194 (100.0)	225 (100.0)				
Positive LN							
Yes	26 (83.9)	57 (29.4)	83 (36.9)	34.08	<0.001*	12.49	4.57-34.16
No	5 (16.1)	137 (70.6)	142 (63.1)				
Total	31 (100.0)	194 (100.0)	225 (100.0)				
LVI							
Present	19 (61.3)	18 (9.3)	37 (16.4)	52.62	<0.001*	15.48	6.48-36.96
Absent	12 (38.7)	176 (90.7)	188 (83.6)				
Total	31 (100.0)	194 (100.0)	225 (100.0)				
Grade							
Grade 3	23 (74.2)	59 (30.4)	82 (36.4)	22.11	<0.001*	6.57	2.78-15.55
Grade 2	8 (25.8)	135 (69.6)	143 (63.6)				
Total	31 (100.0)	194 (100.0)	225 (100.0)				
ECE							
Present	6 (19.4)	8 (4.1)	14 (6.2)		0.006* (*f*)	5.58	1.78-17.41
Absent	25 (80.6)	186 (95.9)	211 (93.8)				
Total	31 (100.0)	194 (100.0)	225 (100.0)				
ER							
Negative	13 (41.9)	40 (20.6)	53 (23.6)	6.74	0.009*	2.78	1.25-6.14
Positive	18 (58.1)	154 (79.4)	172 (76.4)				
Total	31 (100.0)	194 (100.0)	225 (100.0)				
PR							
Negative	11 (35.5)	44 (22.7)	55 (24.4)	2.37	0.123	1.875	0.835-4.21
Positive	20 (64.5)	150 (77.3)	170 (75.6)				
Total	31 (100.0)	194 (100.0)	225 (100.0)				
HER2/neu							
Negative	18 (58.1)	99 (51.0)	117 (52.0)	0.53	0.467	1.329	0.61-2.86
Positive	13 (41.9)	95 (49.0)	188 (48.0)				
Total	31 (100.0)	194 (100.0)	225 (100.0)				

*$P \leq 0.05$ was significant. *f*: Fisher's exact test, OR: Odds ratio, HER2/neu: Human epidermal growth factor receptor 2, CI: Confidence interval, LN: Lymph node, LVI: Lymphovascular invasion, ECE: Extracapsular extension, ER: Estrogen receptor, PR: Progesterone receptor

Table 2: Logistic regression for risk factors of local recurrence of tumor

Study variables	*B*	SE	Wald	df	*P*	OR	95% CI
Tumor size (mm)	-2.940-	0.970	9.175	1	0.002*	0.053	0.008-0.354
Number of LN	-0.929-	0.850	1.194	1	0.275	0.395	0.075-2.09
Grade of tumor	1.896	0.699	7.353	1	0.007*	6.658	1.691-26.20
Positive LN	2.777	0.722	14.793	1	<0.001*	16.076	3.904-66.19
LVI	4.297	1.125	14.598	1	<0.001*	73.457	8.105-665.71
ECE	2.798	1.257	4.957	1	0.026*	16.407	1.39-192.58
ER	0.701	0.703	0.993	1	0.319	2.015	0.508-7.996

OR: Odds ratio, CI: Confidence interval, LN: Lymph node, LVI: Lymphovascular invasion, ECE: Extracapsular extension, ER: Estrogen receptor

Table 3: Association between time of local recurrence and study variables among the study patients

Study variables	Time of local recurrence		Total	χ^2	*P*	OR	95% CI
	≤2 years	>2 years					
Age (years)							
≤40	7 (53.8)	8 (44.4)	15 (48.4)	0.267	0.605	1.458	0.348-6.112
>40	6 (46.2)	10 (55.6)	16 (51.6)				
Total	13 (100.0)	18 (100.0)	31 (100.0)				
Tumor size (cm)							
≤2	2 (15.4)	4 (22.2)	6 (19.4)		0.226 (*f*)	0.634	0.098-4.138
>2	11 (84.6)	14 (77.8)	25 (80.6)				
Total	13 (100.0)	18 (100.0)	31 (100.0)				
Number of LN							
<10	8 (61.5)	11 (61.1)	19 (61.3)	0.001	0.981	1.018	0.235-4.407
≥10	5 (38.5)	7 (38.9)	12 (38.7)				
Total	13 (100.0)	18 (100.0)	31 (100.0)				
Positive LN							
Yes	10 (76.9)	16 (88.9)	26 (83.9)		0.625 (*f*)	0.417	0.059-2.946
No	3 (23.1)	2 (11.1)	5 (16.1)				
Total	13 (100.0)	18 (100.0)	31 (100.0)				
LVI							
Present	8 (61.5)	11 (61.1)	19 (61.3)	0.001	0.981	1.018	0.235-4.407
Absent	5 (38.5)	7 (38.9)	12 (38.7)				
Total	13 (100.0)	18 (100.0)	31 (100.0)				
Grade							
Grade 3	10 (76.9)	13 (72.2)	23 (74.2)		1.000 (*f*)	1.28	0.24-6.68
Grade 2	3 (23.1)	5 (27.8)	8 (25.8)				
Total	13 (100.0)	18 (100.0)	31 (100.0)				
ECE							
Present	1 (7.7)	5 (27.8)	6 (19.4)		0.359 (*f*)	0.217	0.022-2.131
Absent	12 (92.3)	13 (72.2)	25 (80.6)				
Total	13 (100.0)	18 (100.0)	31 (100.0)				
ER							
Negative	8 (61.5)	5 (27.8)	13 (41.9)	3.53	0.06	4.16	0.909-19.03
Positive	5 (38.5)	13 (72.2)	18 (58.1)				
Total	13 (100.0)	18 (100.0)	31 (100.0)				
PR							
Negative	5 (38.5)	6 (33.3)	11 (35.5)		1.000 (*f*)	1.25	0.283-5.525
Positive	8 (61.5)	12 (66.7)	20 (64.5)				
Total	13 (100.0)	18 (100.0)	31 (100.0)				
HER2/neu							
Negative	8 (61.5)	10 (55.6)	18 (58.1)	0.11	0.739	1.28	0.299-5.47
Positive	5 (38.5)	8 (44.4)	13 (41.9)				
Total	13 (100.0)	18 (100.0)	31 (100.0)				

*$P \leq 0.05$ was significant. *f*: Fisher' exact test, OR: Odds ratio, HER2/neu: Human epidermal growth factor receptor 2, CI: Confidence interval, LN: Lymph node, LVI: Lymphovascular invasion, ECE: Extracapsular extension, ER: Estrogen receptor, PR: Progesterone receptor

was 40.2 months. The mean age was 40.178 years, median age was 45 years, minimum age was 22 years, and maximum age was 77 years.

Table 1 shows the association between local recurrence and studied variables including (age, tumor size, number of LNs removed by surgery, positive LN, presence of LVI, grade of tumor, extracapsular extension, estrogen receptor [ER], PR, and Her 2neu) among the study patients. Seven factors appeared significant for recurrence as shown in Table 1.

In multivariate analyses, all seven risk factors remain significant except the number of LNs removed and ER-negative patients where $P > 0.05$ [Table 2].

Impaction on time of recurrence

The median time to recurrence was 30 months, and the mean time was 29.61 months; 58.1% of patients developed local recurrence after 2 year of treatment and 41.9% developed recurrence in 2 years and less after surgery [Figure 2]. Table 3 shows the association between time of local recurrence and

study variables (age, tumor size, number of LNs removed by surgery, positive LN, presence of lymphovascular invasion, grade of tumor, extracapsular extension, ER, PR, and Her 2neu) among the study patients. No single risk factor appeared significant to cause recurrence in 2 years and less.

Discussion

In Table 1, we found that 7 factors were significant for local recurrence from 10 factors evaluated and 2 of these significant factors were changed in multivariate analyses [Table 2]. Moreover, most of these recurrences occurred after 2 years of surgery [Table 3]; the median time for recurrence was 30 months.

These factors may affect recurrence and compressed survival in early breast cancer, so identifying of these factors considered important to highlights risk patients for recurrence to put a perfect plan for treatment to overcome serious events.

Meta-analysis in 2005 had revealed that the OS rate can benefit from the reduction of LRR for early (T1–2, N0–1) breast cancer.[15] Many trials from Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have revealed statistically significant reduction in LRR for early breast cancer patients with post-PMRT (6.7% vs. 19.6%, $P < 0.001$);[16] another trials revealed that many of early cancer with negative LNs with specific risk factors carry higher risk of local recurrence.[17] The 10-year local recurrence rate for this group was about 14% or may be higher than those with <4 nodes metastasis.[18]

Offer radiotherapy after surgery decrease occurrence of local failure and this is crucial for good quality of life and prolong survival.

Tumor size may be associated with increased LRR in breast cancer. The cutoff point of the tumor size in multiple investigations is variable; larger size tumors showed worse prognosis.[19]

Our study showed that patients with tumor size <20 mm is protective from local recurrence $P = 0.001$ and not changed in multivariate analyses.

Number of LN dissection has prognostic value for breast cancer patients. Inadequate LN dissection in early breast cancer stage may lead to miss of LN stage after mastectomy.[20] Inadequate LN dissection carry poor prognosis,[21] local recurrence higher in patients with axillary LN dissection number <10 than 10 and more (24% vs. 11%, $P < 0.02$).[18] Meanwhile, from 22 EBCTCG meta-analysis of data randomized trials showed that radiotherapy reduced LRR and breast cancer mortality in patients with 1–3 positive nodes.[22]

In our study, we found positive LNs (1–3) significant factor for local recurrence. Inadequate LNs dissection (removal of <10) appear as significant factors for local recurrence, although its not stay strong in multivariate analyses but still crucial for recurrence as evident by many studies and this change may be largely due to small sample of patient Included in our study. Hence, we agree with EBCTCG meta-analyses to offer radiotherapy for those patients.

Young patients carry strong invasiveness than older,[23] 10-year local recurrence of age ≤40 years was significantly higher than more 40 years (11.3% vs. 1.5%, $P < 0.001$) Sharma *et al*.[24]

In our study, age <40 appear not significant for recurrence, but it is still important factor especially if associated with other risk factors such as high grade and large tumor size in addition to association of early age with genetic predisposing to cancer (BRCA) gene, and family history. Although many studies revealed poor association of age with recurrence,[12] but we thing that main cause for not significant of this factor in our study are short time for follow.up and small sample, also most of our patient may present late in addition to missing of good health education and screening program are important causes.

The use of trastuzumab, tamoxifen, or aromatase inhibitors for ER, PR, and HER2/neu receptor-positive disease may decrease breast cancer recurrence and mortality. The results from the Eastern Cooperative Oncology Group[25] and National Surgical Adjuvant Breast and Bowel Project[26] trials found a LRR rate of 13%. In our study, ER negative appear significant for local recurrence and as known worldwide its largely associated with high grade so those with positive ER receptors who's treated by hormonal therapy carry good prognosis as we seen in our practice. Many risk scoring depend on status of ER, PR and HER2neu wither positive or negative to put a risk scoring for recurrence, like Oncotype Dx scoring system and others And in spite of changing of ER negative factor in multivariate analyses to not significant still important factor widly used by these new risk scoring which used worldwide. Again small sample included may affect this result.

Truong *et al*.[17] revealed that histologic Grade 3 is a risk factor for recurrence-free survival. In our study, high grade appears as a significant risk factor for recurrence and not change in multivariate analyses.

Another study analyzed supraclavicular nodal failure in 1–3 node-positive breast cancer patients revealed that LVI and ECE were prognostic factors[27] and likewise many studies show strong association of LVI and ECE with local failure so our study proved significant of these factors in occurrence of local recurrence.

Although none of studied factors appear significant for early occurrence of local recurrence (in 2 years and less) after surgery, but we can't judge about this event in the studies of this small sample in spite of median and mean time for recurrence was (30.00) and (29.61) months respectively, which so close from this endpoint. Large sample is required to detect significant factors related with early recurrence and many patients recurred early especially if carry more than one factor as we seen in our daily practice.

Likewise, Many studies show disappointed results due to many causes, like taking a data from single center with limited

number of patients and escaping of patients from follow-up. Our study face these challenges, we evaluated 225 patents and it's really an intermediate sample but we do our best to evaluate those patients thoroughly and we touch the result of most important depended studies.

Conclusion

1) Offering of post mastectomy radiotherapy (PMRT) for patients with early breast cancer carry significant risk factors for locoregional (LLR) recurrence.
2) Establishment of good intensive follow up program for those patients.
3) Establishment of new multicenteric study with large number of patients to detect areal behavior of this disease in our patients and doing comprehensive work for evaluation of searched and other factors depending on new biological risk grouping.
4) Study survival outcome after addition of radiotherapy to show areal benefit of PMRT.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Annual Report of Iraqi Cancer Registry. Iraqi Cancer Board. Ministry of Health and Enviroment. Republic of Iraq; 2018.
2. Abi-Raad R, Boutrus R, Wang R, Niemierko A, Macdonald S, Smith B, *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:e151-7.
3. Bedwinek J. Natural history and management of isolated local-regional recurrence following mastectomy. Semin Radiat Oncol 1994;4:260-9.
4. van Tienhoven G, Voogd AC, Peterse JL, Nielsen M, Andersen KW, Mignolet F, *et al*. Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. Eur J Cancer 1999;35:32-8.
5. Fisher B, Anderson S, Fisher ER, Redmond C, Wickerham DL, Wolmark N, *et al*. Significance of ipsilateral breast tumour recurrence after lumpectomy. Lancet 1991;338:327-31.
6. Rouzier R, Extra JM, Carton M, Falcou MC, Vincent-Salomon A, Fourquet A, *et al*. Primary chemotherapy for operable breast cancer: Incidence and prognostic significance of ipsilateral breast tumor recurrence after breast-conserving surgery. J Clin Oncol 2001;19:3828-35.
7. Fortin A, Larochelle M, Laverdière J, Lavertu S, Tremblay D. Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy. J Clin Oncol 1999;17:101-9.
8. Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, *et al*. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997;337:956-62.
9. 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;82:247-53.
10. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM. 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;97:116-26.
11. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (Version 1.2018). Plymouth Meeting, PA: National Comprehensive Cancer Network; c2018. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx. [Last accessed on 2018 Nov 26].
12. McBride A, Allen P, Woodward W, Kim M, Kuerer HM, Drinka EK, *et al*. Locoregional recurrence risk for patients with T1,2 breast cancer with 1-3 positive lymph nodes treated with mastectomy and systemic treatment. Int J Radiat Oncol Biol Phys 2014;89:392-8.
13. Reisenbichler ES, Lester SC, Richardson AL, Dillon DA, Ly A, Brock JE. Interobserver concordance in implementing the 2010 ASCO/CAP recommendations for reporting ER in breast carcinomas: A demonstration of the difficulties of consistently reporting low levels of ER expression by manual quantification. Am J Clin Pathol 2013;140:487-94.
14. Rakha EA, Starczynski J, Lee AH, Ellis IO. The updated ASCO/CAP guideline recommendations for HER2 testing in the management of invasive breast cancer: A critical review of their implications for routine practice. Histopathology 2014;64:609-15.
15. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, *et al*. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. Lancet 2005;366:2087-106.
16. EBCTCG. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. N Engl J Med 1995;333:1444-55.
17. Truong PT, Lesperance M, Culhaci A, Kader HA, Speers CH, Olivotto IA. Patient subsets with T1-T2, node-negative breast cancer at high locoregional recurrence risk after mastectomy. Int J Radiat Oncol Biol Phys 2005;62:175-82.
18. Katz A, Strom EA, Buchholz TA, Thames HD, Smith CD, Jhingran A, *et al*. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: Implications for postoperative irradiation. J Clin Oncol 2000;18:2817-27.
19. Bollet MA, Kirova YM, Fourquet A, de Cremoux P, Reyal F. Prognostic factors for local recurrence following breast-conserving treatment in young women. Expert Rev Anticancer Ther 2010;10:1215-27.
20. Iyer RV, Hanlon A, Fowble B, Freedman G, Nicolaou N, Anderson P, *et al*. Accuracy of the extent of axillary nodal positivity related to primary tumor size, number of involved nodes, and number of nodes examined. Int J Radiat Oncol Biol Phys 2000;47:1177-83.
21. Cancello G, Maisonneuve P, Rotmensz N, Viale G, Mastropasqua MG, Pruneri G, *et al*. Prognosis in women with small (T1 mic, T1a, T1b) node-negative operable breast cancer by immunohistochemically selected subtypes. Breast Cancer Res Treat 2011;127:713-20.
22. Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: Meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383:2127-35.
23. Colleoni M, Rotmensz N, Robertson C, Orlando L, Viale G, Renne G, *et al*. Very young women (35 years) with operable breast cancer: Features of disease at presentation. Ann Oncol 2002;13:273-9.
24. Sharma R, Bedrosian I, Lucci A, Hwang RF, Rourke LL, Qiao W, *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;17:2899-908.
25. Recht A, Gray R, Davidson NE, Fowble BL, Solin LJ, Cummings FJ, *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;17:1689-700.
26. Taghian A, Jeong JH, Mamounas E, Anderson S, Bryant J, Deutsch M, *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;22:4247-54.
27. Yu JI, Park W, Huh SJ, Choi DH, Lim YH, Ahn JS, *et al*. Determining which patients require irradiation of the supraclavicular nodal area after surgery for N1 breast cancer. Int J Radiat Oncol Biol Phys 2010;78:1135-41.