International Journal of Medical and Pharmaceutical Research
Website: https://ijmpr.in/ | Print ISSN: 2958-3675 | Online ISSN: 2958-3683
NLM ID: 9918523075206676
Volume: 4 Issue:3 (May-June 2023); Page No: 585-592

Original Article

IJMPR

Recurrence Patterns of Breast Cancer in Elderly Women Following Breast Conservation Surgery or Mastectomy without Adjuvant Radiotherapy or Chemotherapy

Dr E. Govindaraja[1], Dr Prasad H Upase[*2]

[1] *Professor and Surgical Oncologist, Dept of General Surgery, VIMS, Ballari*
[2] *3rd year Post Graduate, Dept of General Surgery, VIMS, Ballari*

ABSTRACT

Background: This research aims to investigate the recurrence patterns of breast cancers in elderly women (>65 years) treated with breast-conserving surgery (BCS) or mastectomy alone, and compare the treatment outcomes with those having BCS/mastectomy plus adjuvant radio or chemotherapy.

Methods: The study was conducted on 75 patients divided into two groups: Group-1 consisted of 50 patients who underwent BCS/MRM without adjuvant chemotherapy or radiotherapy, only receiving adjuvant hormonal therapy, while Group-2 was comprised of 25 patients who underwent BCS/MRM and received adjuvant chemo and/or radiotherapy, with or without hormonal therapy.

Results: The recurrence rates were 10% and 8% in Group-1 and Group-2 respectively. The risk ratio was 1.07, indicating a minor difference in the risk of recurrence between the two groups, which was not statistically significant (p>0.05). The mean time to recurrence was marginally higher in Group-1 (15.25 +/- 3.77 months) compared to Group-2 (14.33 +/- 3.05 months).

Conclusion: The study reveals no significant difference in breast cancer recurrence rates in elderly women post BCS/mastectomy whether adjuvant therapy was administered or not. This challenges traditional protocols and argues for the reconsideration of the necessity and benefits of adjuvant therapies in this demographic.

Key Words: *Breast Cancer, Elderly Women, Recurrence, Adjuvant Therapy, BCS/Mastectomy, Hormonal Therapy*

***Corresponding Author**
Dr Prasad H Upase
3rd year Post Graduate, Dept of General Surgery, VIMS, Ballari

INTRODUCTION

Breast cancer stands as the most prevalent cancer among women globally, accounting for a quarter (25%) of all cancer cases. In India, while cervical cancer continues to hold prominence in rural regions, breast cancer has taken the lead among women overall [1].

Despite the increasing incidence of breast cancer correlating directly with age – with a mean diagnosis age of 61 and over 40% of cases occurring in women aged 65 or older [2] – there is a research bias towards younger women. This has resulted in a notable data gap regarding treatment efficacy and associated toxicity in elderly patients, presenting significant therapeutic challenges [3].

Standard treatment protocol for invasive breast cancer typically includes breast conservation surgery (BCS) or modified radical mastectomy (MRM) followed by adjuvant therapies like radiotherapy, chemotherapy, or endocrine therapy to decrease the risk of recurrence and potential mortality [4, 5 & 6]. However, the appropriateness and benefit of these adjuvant treatments are influenced by several factors such as risk of recurrence, tumor biology, potential side effects, and patient tolerance [7].

Intriguingly, there is evidence to suggest that breast cancer in elderly women may exhibit distinct biological characteristics and clinical behaviour, potentially following a less aggressive course. This highlights the need for a re-evaluation of standard treatment practices for breast cancer in older patients.

Recent studies support this view, reporting no significant impact on tumor recurrence rates or mortality upon the omission of adjuvant radiotherapy from standard treatment [8, 9 & 10]. This has led certain institutions to revise their treatment policy to exclude routine adjuvant radiotherapy and chemotherapy [3].

Adjuvant hormonal therapies, on the other hand, have shown clear benefits in improving overall survival rates, and current guidelines also endorse the consideration of endocrine therapy for patients who undergo BCS or mastectomy without radiotherapy [11].

In India, factors such as limited access to radiotherapy, ER/PR testing, loss to follow-up, side effects, non-compliance due to cost, and overall low acceptance rate for adjuvant therapy suggest that a therapy limited to surgery with hormonal therapy might be a more practical approach for women over 65 with breast cancer.

This study is therefore designed to examine early recurrence patterns in patients treated under this approach, with the aim of determining its efficacy and making appropriate recommendations based on the findings.

OBJECTIVES OF THE STUDY:

1) To study recurrence patterns of breast cancers in elderly women (>65 years) treated with BCS or mastectomy alone.
2) To compare treatment outcomes of BCS/mastectomy-alone approach with BCS/mastectomy + adjuvant radio or chemotherapy.

MATERIALS AND METHODS

Study Design:

This research was a prospective analytical study carried out between January 1st, 2019, and June 30th, 2020. The study was conducted at the General Surgical Outpatient Department (OPD) in a tertiary care hospital, VIMS, Bellary.

Study Participants:

The target population for this study included women aged over 65 years diagnosed with breast cancer who presented at the OPD during the study period. The patients who refused adjuvant radio or chemotherapy, were unfit for such therapies, or were irrespective of their hormonal receptor status were included in the study.

However, women who were already post-treatment for breast cancer, unwilling to give consent for participation, presented with recurrent breast cancer at the time of presentation, had inflammatory or Stage 4A (inoperable) tumours, or diagnosed with male breast cancer were excluded from the study.

Hypothesis:

The research hypothesis was that Breast Conserving Surgery (BCS) or mastectomy with hormonal therapy alone, omitting adjuvant radio or chemotherapy, may be an acceptable treatment strategy for breast cancer in elderly women.

Data Collection:

Data was collected prospectively over an 18-month period. Mean age, mean tumour size, stage at diagnosis, tumour grade, and adjuvant therapy received were assessed. Participants were categorized into two groups - those who received treatment with BCS or mastectomy alone, and those who received adjuvant therapy following BCS or mastectomy. Clinical assessments were periodically conducted for all participants. Features suggestive of recurrence were documented and confirmed by biopsy.

Sample Size:

The sample size was estimated using the formula n=4pq/l2, with a level of significance of 5% and a 95% confidence interval. The average admission rates for elderly women with breast cancer at the institution, fitting the inclusion criteria, was 2.86 +/- 0.74 per month. Consequently, the sample size for the group without adjuvant chemo or radiotherapy (study group) was determined to be 50, while the control group consisted of 25 participants.

Sampling Technique:

Convenience sampling was utilized to gather the participants for the study.

Statistical Analysis:

The collected data was tabulated using MS Excel 2016 and analysed using SPSS version 18. Continuous variables were expressed as mean +/- standard deviation (SD), and percentages were used where appropriate. The Chi-square test was used to generate P-values where relevant. Survival analysis with regard to recurrence was done by generating Kaplan-Meier curves.

RESULTS

This study was conducted on 75 patients of breast cancer aged 65 years and above, operated at Vijayanagar Institute of Medical Sciences, Ballari within the study period.

These patients were divided into two groups –

1) **Group-1** - Those who underwent BCS/MRM, and did not opt for, or were not advised, adjuvant chemotherapy or radiotherapy. These patients had only adjuvant hormonal therapy.
   This constitutes the Study Group.
   Number of patients (x) = 50
2) **Group-2** - Those who underwent BCS/MRM and received adjuvant chemo and/or radiotherapy, with or without hormonal therapy.
   This served as our Control Group.

Number of patients (y) = 25

Demographic and Clinical profile of patients –

The patients were compared on the various factors at presentation across both groups.

Age: Patients older than 65 years were included in the study. Majority of the patients were within the 65-70-year category among members of both the groups. Maximum number of patients were aged 68 years, with mean age of patients being 69.88 +/- 4.93 years in Group-1 and 68 +/- 3.32 years in Group-2.

Table 1: Age distribution of patients in Group-1 and Group-2

AGE (in years)	Group-1		Group-2	
	Frequency	Percent	Frequency	Percent
65	13	26%	9	36%
66	4	8%	2	8%
67	3	6%	2	8%
68	8	16%	3	12%
69	1	2%	0	0
70	5	10%	4	16%
71	0	0	1	4%
72	1	2%	3	12%
73	2	4%	0	0
75	5	10%	0	0
76	2	4%	0	0
78	1	2%	1	4%
79	2	4%	0	0
80	3	6%	0	0
Total	50	100%	25	100%

Side of Breast:

In the study group, 31 patients (62%) had cancer of the right breast, while one patient had bilateral breast cancer.

In the control group, 15 patients (60%) had cancer of the right breast.
Side of breast had no correlation with recurrence risk. (p = 0.1394)

Table 2: Side of tumour in Group-1 and Group-2

SIDE	Group-1		Group-2	
	Frequency	Percent	Frequency	Percent
Left Breast	18	36%	10	40%
Right Breast	31	62%	15	60%
Bilateral	1	2%	0	0
Total	50	100%	25	100%

Family History:

In Group-1, only 5 patients (10%) had a significant family history of breast cancer, involving the first- or second-degree relatives.

In Group-2, only 3 patients (12%) had a significant family history.
No significant association noted between family history and risk of recurrence. (p = 0.6173)

Table 3: Family history of breast cancer among Group-1 and Group-2

FAMILY HISTORY	Group-1		Group-2	
	Frequency	Percent	Frequency	Percent
No	45	90%	22	88%
Yes	5	10%	3	12%
Total	50	100%	25	100%

Neoadjuvant Treatment:

In Group-1, 12 patients (24%) had received neoadjuvant treatment in the form of neoadjuvant chemotherapy, prior to undergoing surgery. All of them received 4 cycles of AC (anthracycline-cyclophosphamide) as part of chemotherapy regimen.In Group-2, 32% of patients had received neoadjuvant chemotherapy with 4 cycles of AC regimen.No significant difference is noted in between the two groups. (p = 0.0687).

Table 4: Patients in Group-1 and Group-2 who received neoadjuvant chemotherapy

NACT	Group-1		Group-2	
	Frequency	Percent	Frequency	Percent
No	38	76%	17	68%
Yes	12	24%	8	32%
Total	50	100%	25	100%

Stage of tumour:

Tumours of various clinical stage were noted in the both groups, with similar incidences. 28% of tumours were of T2N0M0 while 20% were T2N1M0 tumours in both groups, indicating that majority of the cases were of early breast cancer.

No significant differences are noted in the stage distribution of tumours within the two groups, with p value insignificant.

Table 5: Distribution of tumour stage in Group-1 and Group-2

STAGE	Group-1		Group-2	
	Frequency	Percent	Frequency	Percent
T1N0M0	4	8%	1	4%
T1N1M0	1	2%	1	4%
T2N0M0	14	28%	7	28%
T2N1M0	10	20%	5	20%
T3N0M0	7	14%	2	8%
T3N1M0	5	10%	6	24%
T3N2M0	1	2%	0	0
T4bN0M0	2	4%	0	0
T4bN1M0	5	10%	3	12%
T4bN2M0	1	2%	0	0
Total	50	100%	25	100%

Type of Surgery:

A majority of patients (n=41), 82%, in Group-1 underwent modified radical mastectomy while the remaining (n=8) 16% underwent breast conservation surgery (lumpectomy + ALND). One patient underwent bilateral MRM owing to bilateral breast cancer. In group-2 rate of MRM was 56% while BCS was 44%.No significant relation was noted between the two groups with respect to type of surgery. (p=1.21)

Table 6: Type of surgery done in Group-1 and Group-2

SURGERY	Group-1		Group-2	
	Frequency	Percent	Frequency	Percent
B/L MRM	1	2%	0	0
BCS	8	16%	11	44%
MRM	41	82%	14	56%
Total	50	100%	25	100%

Tumour Histopathology:

Post-operative histopathology report was found to be infiltrating ductal carcinoma of no special type in 35 patients (70%) in Group-1 and 60% in Group 2, with largely similar profiles seen between the two groups. Next most common type was infiltrating ductal carcinoma with DCIS component, in 4 patients (8%) in Group-1 and 5 patients (20%) in Group-2.The two groups no significant differences in terms of histopathology, with insignificant p-value.

Table 7: Tumour histopathology in Group-1 and Group-2

HPE	Group-1		Group-2	
	Frequency	Percent	Frequency	Percent
Carcinosarcoma	2	4%	0	0
Cribriform Ca	1	2%	0	0
DCIS	1	2%	0	0
IDC+DCIS	4	8%	5	20%
IDC-NOS	35	70%	15	60%
Mucinous Ca	3	6%	2	8%
Neuroendocrine differentiation	2	4%	0	0
Papillary Ca	1	2%	1	4%
Sebaceous Ca	1	2%	0	0

Micropapillary Ca	0	0	1	4%
Total	50	100%	25	100%

Grade of tumour:

In Group-1, 48% of tumours were low grade, i.e., Grade 1 tumours. 44% were intermediate grade, i.e., Grade 2 tumours and remaining 8% were high grade, i.e., Grade 3 tumours, as classified by the Nottingham Classification [12]. In Group-2, 36% of tumours were low grade, 44% were intermediate grade and 20% high grade.The two groups are comparable in terms of tumour grade, with no significant p-value.

Table 8: Grade of tumour among Group-1 and Group-2

GRADE	Group-1		Group-2	
	Frequency	**Percent**	**Frequency**	**Percent**
1	24	48%	9	36%
2	22	44%	11	44%
3	4	8%	5	20%
Total	50	100%	25	100%

Reason for not receiving adjuvant Chemotherapy/RT:

This group of patients has not received any adjuvant chemo or radiotherapy, but only hormonal therapy, and forms our study group. However, 26 (52%) of these patients were advised adjuvant therapies but were not willing for the same, for various personal reasons. The remaining 24 patients (48%) decided to pursue a course of only hormonal therapy following appropriate counselling regarding risks and benefits by the treating doctors.

Table 9: Reason for not receiving adjuvant therapy

ADJUVANT CT/RT	Frequency	Percent
Advised for	26	52%
Counselled against	24	48%
Total	50	100%

Type of adjuvant therapy:

The first-choice hormonal therapy agent used was Anastrozole, as single agent therapy for 1 year post-operatively, and 25 patients (50%) received the same. Due to cost considerations, 19 patients (38%) opted for Tamoxifen, while 6 (12%) patients were put on Letrozole.

Table 10: Drug used for hormonal therapy

HORMONAL THERAPY	Frequency	Percent
Anastrozole	25	50.00%
Letrozole	6	12.00%
Tamoxifen	19	38.00%
Total	50	100.00%

Follow-up:

Patients were followed up from the time of surgery at monthly intervals. 17 patients have been followed up for more than 18 months (18-20 months). 31 patients have been followed up for a period of 13-18 months. Hence cumulatively, 48 patients (33 from Group-1 and 15 from Group-2) have been followed up beyond a period of one year. The mean period of follow-up was 13.44 +/- 4.76 months among patients in Group 1 and 12.52+/- 3.98 months among patients in Group-2.

Table 11: Duration of follow-up among Group-1 and Group-2

FOLLOW UP PERIOD (in months)	Group-1	Group-2	TOTAL
Less than 6	3	1	4
6 to 12	14	9	23
13 to 18	19	12	31
More than 18	14	3	17
TOTAL	50	25	75

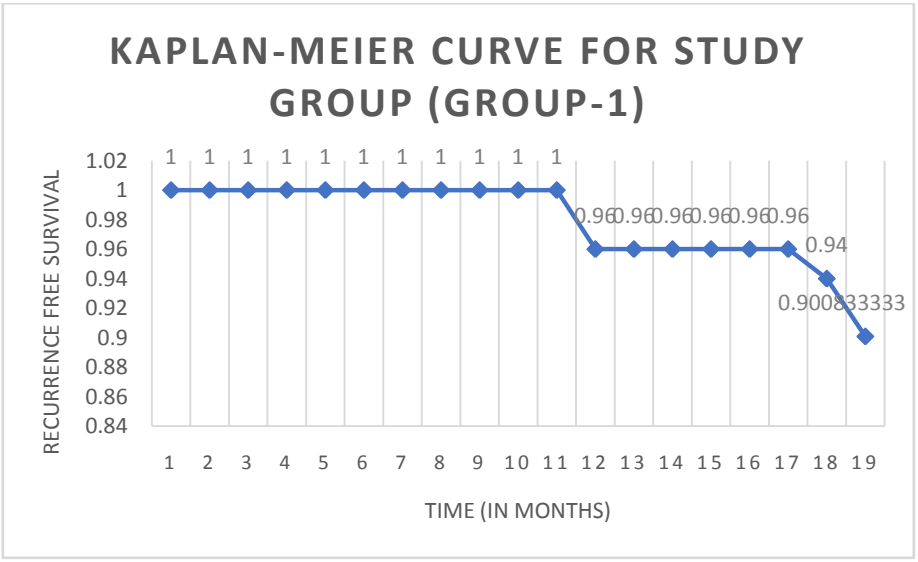
OUTCOME VARIABLES

Recurrence: Recurrence was defined as either ipsilateral local recurrence or regional recurrence to the axilla. Among the Group-1 patients, 5 patients developed a recurrence, translating to a recurrence rate of 10%.Among the Group-2 patients who received adjuvant therapy, recurrence was noted in 2 patients, translating to a recurrence rate of 8%.The mean time to recurrence among Group-1 patients was 15.25 +/- 3.77 months.However, it was noted that the mean time to recurrence among Group-2 patients was shorter, at 14.33 +/- 3.05 months.

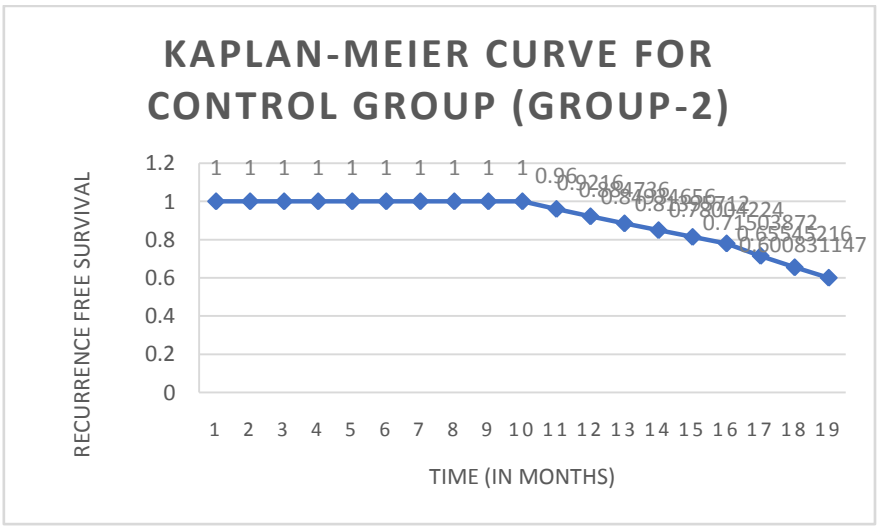
Table 12: Incidence of recurrence among Group-1 and Group-2

Recurrence	Group-1		Group-2		Total	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Yes	5	10%	2	8%	7	9.33%
No	45	90%	23	92%	68	90.67%
Total	50	100%	25	100%	75	100%

The Risk Ratio (RR) between the groups is 1.07, indicating that there exists only a very small difference in the risk of recurrence between the groups of patients who received no adjuvant therapy versus those who received adjuvant chemotherapy and/or radiotherapy. This difference in recurrence is not statistically significant, with $p>0.05$, and is suggestive of the fact that treatment protocols in the two groups are comparable in their outcomes.



Graph 1: Kaplan-Meier curve indicating survival among Group-1



Graph 2: Kaplan-Meier curve indicating survival among Group-2

DISCUSSION

BCS or mastectomy is routinely recommended for patients with small, early-stage tumors. Various randomized control studies, such as the one by Wyld et al. [13], have shown that BCS and mastectomy provide comparable efficacy in elderly patients with early-stage breast cancer, additionally affording improved quality of life.

The necessity of adjuvant radiotherapy in managing early-stage breast cancers in elderly patients is a subject of ongoing debate, with numerous studies and reviews examining this topic. Valassiadou et al. [3] discovered an annual recurrence rate of 2.4%, with the median time to local recurrence being 17 months (ranging from 3 – 96 months). Factors such as margins of excision, ER status, and tumor size significantly correlated with local recurrence.

Conversely, Vincent et al. [10] argue that the omission of radiotherapy may result in a substantial increase in the risk of ipsilateral breast tumor recurrence and a minor rise in the risk of patient mortality. Interestingly, in women aged 55

years or older, the aging process appears to be linked with more favorabletumor biology. Consequently, irrespective of disease status, breast cancer survival in older women mirrors survival rates in the general population.

According to Wickberg [9], concurrent morbidity surpasses breast cancer as the primary cause of death in elderly women with low-risk breast tumors. Sami et al. [14] demonstrated favorable 8-year survival rates relative to age-matched women from the general population, suggesting that other competing causes of mortality become more prominent in determining survival in older patients. Consequently, breast cancer mortality decreases as patients age.

Hormonal therapy (HT) benefits are linked to long-term adherence [15]. HT has a significant effect on survival rates in all patients, and a 5-year therapy regimen with Tamoxifen in HR-positive women older than 50 has a more positive impact on survival and relapse rate than CT [16]. Hershman et al. [17] found that women who continued HT had a 10-year survival rate of 80.7%, compared to 73.6% in those who discontinued HT.

These benefits were also observed in older patients with early cancers treated by BCS alone, where local recurrence (LR) rates saw a substantial reduction of 23% after the widespread use of tamoxifen [18].

However, a trial by Fyles et al. [19] concluded that the risk from omitting radiotherapy was too significant, despite some larger studies advocating for more conservative approaches.

The Cancer and Leukemia Group B (CALGB) 9343 trial [20] and the Postoperative Radiotherapy in Minimum Risk Elderly (PRIME) II study [21] presented evidence that the differences in recurrence parameters of breast cancers in elderly patients were marginal and not statistically significant, aligning with our study findings.

Lastly, a study by Liu et al. [22] suggested that patients with luminal subtypes benefited less from adjuvant therapy and that immunohistochemistry (IHC) for common markers could identify a subset of patients where adjuvant therapy could be safely omitted.

In conclusion, the above studies consistently suggest that the therapeutic strategy of BCS or mastectomy with hormonal therapy, while omitting adjuvant radiotherapy and chemotherapy, deserves further exploration in the treatment of breast cancer in elderly women.

CONCLUSION

In our investigation, we compared breast cancer recurrence rates in elderly patients across two groups. The first group received adjuvant chemotherapy and/or radiotherapy, while the second group only received hormonal therapy in the adjuvant setting, abstaining from adjuvant chemo and radiotherapy.

Although the absolute recurrence rates were slightly higher in the group excluding hormonal therapy (10% vs. 8%), the risk ratio between the two groups (1.07) indicates that there is no increased recurrence risk associated with forgoing adjuvant radio and chemotherapy. The Kaplan-Meier curves corroborate this finding, and p-values reveal no significant differences in recurrence rates between the two groups.

These findings have significant implications in clinical practice. Traditional adjuvant therapies, such as chemotherapy and radiotherapy, are time-consuming, expensive, and often lead to significant patient morbidity. These considerations are particularly relevant in the context of treating elderly patients.

Given that the benefits to patients appear equivocal, and the risks could potentially outweigh the benefits, there is a compelling argument to reconsider the use of such adjuvant therapies in certain elderly breast cancer patients. This study aligns with other trials and studies suggesting the need for a more measured approach to managing breast cancer in elderly patients and the importance of a cost-benefit analysis.

Future research could potentially stratify patients with more favorable prognostic factors, in whom adjuvant therapy could be safely omitted. This study is critical in addressing a major controversy in managing breast cancer in the elderly and calls for a paradigm shift in treatment strategy.

However, our study does have limitations:

Firstly, the sample size of our study is relatively small, which can potentially limit the generalization of our results to a wider population. To extrapolate the results more confidently, future studies may need to consider larger sample sizes. Secondly, the follow-up period for a subset of patients within our study is less than 6 months (5%), mainly due to their late entry into the study. This shorter follow-up duration necessitates longer monitoring to effectively identify potential future recurrences. This aspect can be addressed in further investigations, ensuring a more comprehensive understanding of the long-term recurrence risks.

REFERENCES

1. Malvia S, Bagadi SA, Dubey US, Saxena S. (2017). Epidemiology of breast cancer in Indian women. Asia Pacific J Clin Oncol. 13:289–295.
2. Shlomit Strulov Shachar, Arti Hurria, Hyman B. (2016). Muss; Breast Cancer in Women Older Than 80 Years, Journal of Oncology Practice 12, no. 2, 123-132.
3. Valassiadou, K, Morgan, DA, Robertson, JF, Pinder, SE, Cheung, KL. (2007). Successful management of elderly breast cancer patients treated without radiotherapy. World J. Surg. Oncol. 5, 62.
4. Arun C, Cheung KL: (2003). Management of elderly primary breast cancer. Current medical literature. Breast Cancer. 15: 31-39.
5. DeVita, Vincent T., Jr., Theodore S. Lawrence, and Steven A. (2015). Rosenberg. Devita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. 10th edition. Philadelphia: Wolters Kluwer.
6. Townsend, Courtney M., R. Daniel Beauchamp, B. Mark Evers, and Kenneth L. Mattox. Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practic. 20th edition. Philadelphia, PA: Elsevier Saunders, (2017).
7. Soyder A, Özbaş S, Koçak S. (2013). Locoregional Recurrence and Survival Rates after Breast-Conserving Surgery and Hormonal Therapy in 70-Year-Old or Older Patients with Stage I or IIA Breast Carcinoma. Breast Care. 8(2):134-137.
8. Yamada, K. Narui, S. Sugae, et al. (2016). Operation with less adjuvant therapy for elderly breast cancer, J. Surg. Res., 204, pp. 410-417
9. Wickberg A, Liljegren G, (2018). Omitting radiotherapy in women ≥ 65 years with low-risk early breast cancer after breast-conserving surgery and adjuvant endocrine therapy is safe; Eur J Surg Oncol. 44(7):951-956
10. Vincent Vinh-Hung, Claire Verschraegen, For The Breast Conserving Surgery Project; Breast-Conserving Surgery With or Without Radiotherapy: Pooled-Analysis for Risks of Ipsilateral Breast Tumor Recurrence and Mortality, JNCI: Journal of the National Cancer Institute, Volume 96, Issue 2, (2004), Pages 115–121.
11. Hsu T, Sud S (2017) Endocrine Therapy in Older Women with Early- Stage Hormone Sensitive Breast Cancer. J Gerontol Geriatr Res 6: 440.
12. Elston CW, Ellis IO. (1998). Assessment of histologic grade. In: Elston CW, Ellis IO, eds. The Breast. Edinburgh: Churchill Livingstone; 356–384.
13. Wyld L, Reed M. (2007). The role of surgery in the management of older women with breast cancer. Eur J Cancer. 43:2253–2263.
14. Sami G. Diab, Richard M. Elledge, Gary M. Clark; (2000). Tumor Characteristics and Clinical Outcome of Elderly Women with Breast Cancer; J Natl Cancer Inst. 92:550–6.
15. Chelsea Anderson, Aaron N. Winn, Stacie B. Dusetzina, Hazel B. (2017). Nichols Endocrine Therapy Initiation among Older Women with Ductal Carcinoma in Situ; Journal of Cancer Epidemiology, Article ID 6091709, 6 pages
16. National Comprehensive Cancer Network, (2016). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Version 1.
17. Hershman, D.L., Shao, T., Kushi, L.H. et al. (2011). Breast Cancer Res Treat. 126: 529.
18. Lim M, Bellon JR, Gelman R, et al. (2006). A prospective study of conservative surgery without radiation therapy in select patients with stage I breast cancer. Int J Radiat Oncol Biol Phys. 65(4):1149–1154.
19. Fyles AW, McCready DR, Manchul LA, et al. (2004). Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 351(10):963–970.
20. Hughes KS, Schnaper LA, Bellon JR, et al. (2013). Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 31(19):2382–2387.
21. Kunkler IH, Williams LJ, Jack WJ, et al. (2015). Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 16(3):266–273.
22. Liu FF, Shi W, Done SJ, et al. (2015). Identification of a low-risk luminal a breast cancer cohort that may not benefit from breast radiotherapy. J Clin Oncol. 33(18):2035–2040.