

Practical consensus recommendations regarding the management of hormone receptor positive early breast cancer in elderly women

Govind Babu, A. Goel¹, S. Agarwal², S. Gupta³, P. Kumar⁴, B. K. Smruti⁵, V. Goel², R. Sarangi⁶, M. Gairola⁷, S. Aggarwal⁸, Purvish M. Parikh⁹

Abstract

Breast cancer is a leading cause of death among women, and its incidence increases with age. Currently the treatment of breast cancer in older patients is almost identical to their younger counterparts. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at these practical consensus recommendations for the benefit of community oncologists regarding the management of early breast cancer specifically in elderly women.

Key words: Axillary node, biomarkers, breast conservation surgery, Ki67, radiotherapy

Introduction

In India, we are now witnessing more and more number of patients being diagnosed with breast cancer in the younger age groups. Still, 22% of the patients diagnosed with breast cancer are in the age group of above 60 years.^[1,2] The primary treatments for early breast cancer are surgery, adjuvant radiotherapy and adjuvant systemic therapy. The purpose of this manuscript is to help the community oncologist optimise the management of early breast cancer in the elderly.

Expert oncologists from all over India met to discuss and reach a consensus statement to provide community oncologists practical guidelines on the management of early breast cancer in elderly women. The discussion was based on published evidence and practical experience in real life management of such patients. The expert group discussions were moderated by Dr Govind Babu. The core expert group consisted of Dr Ashish Goel, Dr Sandeep Agarwal, Dr Sachin Gupta, Dr Piyush Kumar, Dr B.K Smruti and Dr Vineeta Goel. Members of the panel were also allowed to share their personal experiences and make comments. This manuscript is the outcome of the expert group discussion and consensus arrived at in 2017.

Defining Clinical Cohort and Practice of Expert Group Panel Members

The primary objective was to provide a consensus statement for community oncologists that could be applicable as ready-to-use practical recommendations. Hence, the applicable setting was outlined by defining the clinical cohort and current practice of the participating delegates and expert group panel members – on the basis of which this document was prepared. The experts discussed a case of a 75 years old normotensive, non-diabetic fit woman who developed a 2.8 cm lump in OUQ left breast with clinically non palpable axillary lymph nodes. Trucut biopsy showed invasive duct carcinoma, ER/PR 80% positive and Her 2 neu negative. Metastatic workup came out to be negative. Based on

this case, a series of questions were put up for poll upon which the expert group discussed and aimed to reach a consensus. Each question had multiple choice options from which participants were to select the one most appropriate for their clinical practice setting. The expert group then formed the practical consensus recommendations for the community oncologists.

Treatment - Surgery

When asked which surgery they would recommend, a total of 71.3% polled oncologists were in support of recommending BCS with sentinel lymph node dissection [Table 1]. The experts recommended that breast conservation surgery (BCS) with sentinel lymph node dissection is to be offered as standard of care for all patients irrespective of age and that the physiological age of the patient, rather than the chronological age should be considered while planning treatment in elderly patients. The experts added that the management of breast cancer in older women is not different to that in younger patients. There are no standard guidelines set for older patients, and the management is different from one country to another and from one centre to another. An international study comparing local treatments (surgery and radiotherapy) for operable breast cancer in older women showed that in many countries, most patients had undergone conservative surgery.^[3] Two randomized controlled trials^[4,5] showed better locoregional control in favour of the surgical group as compared to the tamoxifen group. The panelists concluded that BCS with sentinel node dissection should be offered as the standard of care in elderly patients. The group also added that it is possible to avoid axillary dissection in women aged 60 or older with hormone receptor positive early breast cancer and clinically node negative disease, provided that the patients receive endocrine therapy following surgery.^[6] While some studies have shown longer survival for patients undergoing axillary dissection,^[7] others have failed to show any benefit.^[8]

Treatment - Radiotherapy

In women with early breast cancer undergoing BCS, radiation treatment to the preserved breast is standard practice.^[9]

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Babu G, Goel A, Agarwal S, Gupta S, Kumar P, Smruti BK, *et al.* Practical consensus recommendations regarding the management of Hormone Receptor positive early breast cancer in elderly women. *South Asian J Cancer* 2018;7:123-6.

<p>Access this article online</p> <p>Quick Response Code:</p> 
<p>Website: www.sajc.org</p>
<p>DOI: 10.4103/sajc.sajc_117_18</p>

Department of Medical Oncology, KMIO, Bengaluru, Karnataka, Department of ¹Surgical Oncology and ²Radiation Oncology, Max Hospital, Departments of ⁴Surgery and ⁸Medical Oncology, Sir Ganga Ram Hospital, ⁷Department of Radiation Oncology, RGCI, New Delhi, ³Department of Medical Oncology, Sarvodaya Hospital, Faridabad, Haryana, ⁴Department of Radiation Oncology, Ram Murti Medical College, Bareilly, Uttar Pradesh, ⁵Department of Medical Oncology, Bombay Hospital, Mumbai, ⁹Department of Oncology, Shalby Cancer and Research Institute, Mumbai, Maharashtra, India

Correspondence to: Dr. Govind Babu,
E-mail: kgblaugh@gmail.com

Majority of the polled oncologists (71.3%) were in support of recommending radiation therapy to elderly patients [Table 2]. In older women, it has been suggested that whole-breast radiation given per guidelines following surgery decreases in-breast recurrences and lengthens disease-specific and overall survival as well.^[10-13] A study by Truong *et al.*^[14] enrolled 4,836 patients aged 50–89 with early stage breast cancer who were treated with BCS. After a median follow-up of 7.5 years, radiation omission was associated with significantly increased relapse rates as well as poorer disease-specific and all-cause survival. However, the expert panel noted that survival benefits usually are not noted until 5 to 10 years after diagnosis, which makes such a treatment of marginal or no benefit in those with life expectancies lesser than 5 years.^[15] The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published an updated analysis using individual patient data from 10,801 patients included in 17 randomized trials of radiation after breast-conserving surgery.^[16] This publication revealed that the addition of radiation therapy was associated with a highly significant absolute benefit of 15.7% in any first recurrence (local, regional, or distant recurrence) at 10 years. The expert panel concluded that radiation therapy should be offered to elderly patients, especially to those with longer life expectancies.

Treatment – Chemotherapy

To the question whether they would recommend chemotherapy, a total of 50% of the polled oncologists gave a negative answer. Thirty percent of the polled oncologists were in support of recommending chemotherapy while the remaining 20% opined that they will opt to go for more tests on biopsy before proceeding further [Table 3]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, which included 3,700 women, confirmed that tamoxifen reduced the relapse rate by 28% and mortality by 21% in women aged 70 years or more.^[17] The experts concluded that hormonal therapy should be offered to all older patients with hormone receptor positive breast cancer.^[18-20] The expert panel suggested that adjuvant chemotherapy has been shown to be consistently beneficial only for younger patients.^[21-23] Studies have also suggested that adjuvant chemotherapy is most beneficial for patients over 65 years of age when their tumor is estrogen receptor negative or positive lymph nodes.^[24-26] Considering the available evidence, the expert panel consensus was that chemotherapy in patients older than 70 years of age should be offered when the tumour is hormone receptor negative.

Molecular Tests Required for Decision Making

To the final question as to what other tests would they recommend in case the patient is unable to afford Oncotype Dx, a total of 50% of the polled oncologist were in favour of recommending Ki67 testing. Additional 30% of the polled oncologists were in support of recommending Prosigna test while the remaining 20% voted testing for the grade of tumour [Table 4]. Ki-67 protein expression plays an important role in predicting the proliferative status of tumour cells and deciding the future course of therapy in breast cancer.^[27] Its potential uses include prognosis, prediction of relative responsiveness or resistance to chemotherapy or endocrine therapy and as a dynamic biomarker of treatment efficacy

Table 1: Question 1 - What is your advice to the patient regarding surgery?

Options	BCS with sentinel lymph node dissection	BCS with axillary nodes dissection	Modified radical mastectomy	Any other
Percentage of polled oncologists	71.4	0	28.6	0

Expert group consensus: BCS with sentinel lymph node dissection should be offered as standard of care for all patients irrespective of age. Axillary node dissection is not always necessary. BCS=Breast conservation surgery

Table 2: Question 2 - What is your advice to the patient regarding radiotherapy?

Options	Yes	No
Percentage of polled oncologists	71.4	28.6

Expert group consensus: Radiation therapy should be offered to elderly patients, especially when the life expectancy is more than 5 years

Table 3: Question 3 - What is your opinion on giving chemotherapy?

Options	Yes	No	Will do more tests before deciding
Percentage of polled oncologists	30	50	20

Expert group consensus: Chemotherapy in patients older than 70 years of age should be offered when the tumour is hormone receptor negative. Hormonal therapy may be considered in older patients with hormone receptor positive breast cancer

Table 4: Question 4 - What tests will you do if patient is unable to afford oncotype?

Options	Ki67	Grade of tumour	Prosigna
Percentage of polled oncologists	50	30	20

Expert group consensus: Ki67 bio-marker testing and Prosigna assay are useful predictive and prognostic markers and should be used as appropriate

in samples taken before, during, and after neoadjuvant therapy.^[28]

It is known that breast cancer is truly heterogeneous disease.^[29,30] Late relapses occur even after 20 years. Significant percent of elderly women with breast cancer still die of their cancer as opposed to age. Aggressiveness of disease needs to be matched with aggressiveness of the health-care programme implemented. Low risk patients should be spared unnecessary prescriptions. Multi-gene signature assays are now proven to be of prognostic and predictive significance.^[31,32] Although the largest data is available with Oncotype Dx, there are a few limitations such as cost, lack of data in Indian patients, change in cut off score and applicability only in subset of patients. Hence, a search for additional biomarkers is ongoing. Some possibilities are Ki67, PAM50, and Mammprint. The focus for this discussion was Ki67 and PAM50. A meta-analysis by de Azambuja *et al.*^[33] evaluated 46 studies including 12155 patients who were considered to present positive tumours for the expression of Ki-67 according to the cut-off points defined by the authors. The analysis found that Ki-67 positivity was associated with higher probability of relapse in all patients. Furthermore, Ki-67 positivity was also associated with worse survival in all patients. Some studies have demonstrated a reduction in Ki-67 index after chemotherapy,^[34-37] tamoxifen therapy,^[38,39] and chemo-endocrine therapy.^[40,41]

The expert panel concluded that significant evidence exists to justify the use of Ki67 testing to help decision making.

Looking at the evidence on the prognostic and predictive accuracy of the PAM50-based Prosigna breast cancer gene signature assay, the expert panel deemed it worth considering as well.^[42-46] Some studies have also shown that PAM50 provides a better estimate of prognosis and of prediction of treatment benefit than IHC-based surrogates.^[42-44] The expert panel concluded that Ki67 bio-marker testing and Prosigna assay, both are worth considering in helping predictive and prognostic decision making.

Take Home Message

1. Breast conservation surgery (BCS) with sentinel lymph node dissection should be offered as standard of care for all patients irrespective of age. The physiological age of the patient, rather than the chronological age should be considered while planning therapy in elderly patients. Axillary node dissection is not always necessary.
2. Radiation therapy should be offered to elderly patients, especially when the life expectancy is more than 5 years.
3. Chemotherapy in patients older than 70 years of age should be offered when their tumour is hormone receptor negative. Hormonal therapy may be considered in older patients with hormone receptor positive breast cancer.
4. Ki67 bio-marker testing and Prosigna assay are useful predictive and prognostic markers and should be used as appropriate.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. NCRP - Three Year Report of the Population Based Cancer Registries 2012 - 2014, National Cancer Registry Programme. Bangalore: Indian Council of Medical Research; 2016.
2. NNCRP - Consolidated Report of the Hospital Based Cancer Registries 2012 - 2014, National Cancer Registry Programme. Bangalore: Indian Council of Medical Research; 2016.
3. Kiderlen M, Bastiaannet E, Walsh PM, Keating NL, Schrodi S, Engel J, et al. Surgical treatment of early stage breast cancer in elderly: An international comparison. *Breast Cancer Res Treat* 2012;132:675-82.
4. Robertson JF, Todd JH, Ellis IO, Elston CW, Blamey RW. Comparison of mastectomy with tamoxifen for treating elderly patients with operable breast cancer. *BMJ* 1988;297:511-4.
5. Gazet JC, Ford HT, Coombes RC, Bland JM, Sutcliffe R, Quilliam J, et al. Prospective randomized trial of tamoxifen vs. surgery in elderly patients with breast cancer. *Eur J Surg Oncol* 1994;20:207-14.
6. International Breast Cancer Study Group, Rudenstam CM, Zahrieh D, Forbes JF, Crivellari D, Holmberg SB, et al. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: First results of International Breast Cancer Study Group Trial 10-93. *J Clin Oncol* 2006;24:337-44.
7. Martelli G, Miceli R, Daidone MG, Vetrilla G, Cerrotta AM, Piromalli D, et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: Results after 15 years of follow-up. *Ann Surg Oncol* 2011;18:125-33.
8. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs. no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial. *JAMA* 2011;305:569-75.
9. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233-41.
10. Fyles AW, McCready DR, Manchul LA, Trudeau ME, Merante P, Pintilie M, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004;351:963-70.
11. Hughes KS, Schnaper LA, Berry D, Cirincione C, McCormick B, Shank B, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004;351:971-7.
12. Smith BD, Gross CP, Smith GL, Galusha DH, Bekelman JE, Haffty BG, et al. Effectiveness of radiation therapy for older women with early breast cancer. *J Natl Cancer Inst* 2006;98:681-90.
13. Smith BD, Haffty BG, Hurria A, Galusha DH, Gross CP. Postmastectomy radiation and survival in older women with breast cancer. *J Clin Oncol* 2006;24:4901-4907.
14. Truong PT, Bernstein V, Lesperance M, Speers CH, Olivetto IA. Radiotherapy omission after breast-conserving surgery is associated with reduced breast cancer-specific survival in elderly women with breast cancer. *Am J Surg* 2006;191:749-55.
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. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707-16.
17. Tamoxifen for early breast cancer: An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998;351:1451-67.
18. VanderWalde A, Hurria A. Early breast cancer in the older woman. *Clin Geriatr Med* 2012;28:73-91.
19. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 2005;365:1687-717.
20. Crivellari D, Price K, Gelber RD, Castiglione-Gertsch M, Rudenstam CM, Lindtner J, et al. Adjuvant endocrine therapy compared with no systemic therapy for elderly women with early breast cancer: 21-year results of International Breast Cancer Study Group Trial IV. *J Clin Oncol* 2003;21:4517-23.
21. Polychemotherapy for early breast cancer: An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998;352:930-42.
22. Burdette-Radoux S, Muss HB. Adjuvant chemotherapy in the elderly: Whom to treat, what regimen? *Oncologist* 2006;11:234-42.
23. Muss HB, Berry DA, Cirincione CT, Theodoulou M, Mauer AM, Kornblith AB, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med* 2009;360:2055-65.
24. Giordano SH, Duan Z, Kuo YF, Hortobagyi GN, Goodwin JS. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. *J Clin Oncol* 2006;24:2750-6.
25. Elkin EB, Hurria A, Mitra N, Schrag D, Panageas KS. Adjuvant chemotherapy and survival in older women with hormone receptor-negative breast cancer: Assessing outcome in a population-based, observational cohort. *J Clin Oncol* 2006;24:2757-64.
26. Berry DA, Cirincione C, Henderson IC, Citron ML, Budman DR, Goldstein LJ, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. *JAMA* 2006;295:1658-67.
27. Mungle T, Tewary S, Arun I, Basak B, Agarwal S, Ahmed R, et al. Automated characterization and counting of Ki-67 protein for breast cancer prognosis: A quantitative immunohistochemistry approach. *Comput Methods Programs Biomed* 2017;139:149-61.
28. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, et al. Assessment of Ki67 in breast cancer: Recommendations from the international Ki67 in breast cancer working group. *J Natl Cancer Inst* 2011;103:1656-64.
29. Bertucci F, Birnbaum D. Reasons for breast cancer heterogeneity. *J Biol* 2008;7:6.
30. Polyak K. Heterogeneity in breast cancer. *J Clin Invest* 2011;121:3786-8.
31. Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. *World J Clin Oncol* 2014;5:412-24.
32. Munkácsy G, Szász MA, Menyhárt O. Gene expression-based prognostic and predictive tools in breast cancer. *Breast Cancer* 2015;22:245-52.
33. de Azambuja E, Cardoso F, de Castro G Jr., Colozza M, Mano MS, Durbecq V, et al. Ki-67 as prognostic marker in early breast cancer: A meta-analysis of published studies involving 12,155 patients. *Br J Cancer* 2007;96:1504-13.
34. Sharma S, Hiran KR, Pavithran K, Vijaykumar DK. A pilot study to assess the feasibility of evaluation of markers of response to chemotherapy at one day and 21 days after first cycle of chemotherapy in carcinoma of breast: A prospective non-randomized observational study. *World J Surg Oncol* 2009;7:35.

35. Bottini A, Berruti A, Bersiga A, Brizzi MP, Bruzzi P, Aguggini S, *et al.* Relationship between tumour shrinkage and reduction in Ki67 expression after primary chemotherapy in human breast cancer. *Br J Cancer* 2001;85:1106-12.
36. Bottini A, Berruti A, Bersiga A, Brunelli A, Brizzi MP, Marco BD, *et al.* Effect of neoadjuvant chemotherapy on Ki67 labelling index, c-erbB-2 expression and steroid hormone receptor status in human breast tumours. *Anticancer Res* 1996;16:3105-10.
37. Ellis PA, Smith IE, Detre S, Burton SA, Salter J, A'Hern R, *et al.* Reduced apoptosis and proliferation and increased Bcl-2 in residual breast cancer following preoperative chemotherapy. *Breast Cancer Res Treat* 1998;48:107-16.
38. Clarke RB, Laidlaw IJ, Jones LJ, Howell A, Anderson E. Effect of tamoxifen on Ki67 labelling index in human breast tumours and its relationship to oestrogen and progesterone receptor status. *Br J Cancer* 1993;67:606-11.
39. Dardes RD, Horiguchi J, Jordan VC. A pilot study of the effects of short-term tamoxifen therapy on Ki-67 labelling index in women with primary breast cancer. *Int J Oncol* 2000;16:25-30.
40. Makris A, Powles TJ, Allred DC, Ashley S, Ormerod MG, Titley JC, *et al.* Changes in hormone receptors and proliferation markers in tamoxifen treated breast cancer patients and the relationship with response. *Breast Cancer Res Treat* 1998;48:11-20.
41. Chang J, Powles TJ, Allred DC, Ashley SE, Clark GM, Makris A, *et al.* Biologic markers as predictors of clinical outcome from systemic therapy for primary operable breast cancer. *J Clin Oncol* 1999;17:3058-63.
42. Nielsen TO, Parker JS, Leung S, Voduc D, Ebbert M, Vickery T, *et al.* A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. *Clin Cancer Res* 2010;16:5222-32.
43. Chia SK, Bramwell VH, Tu D, Shepherd LE, Jiang S, Vickery T, *et al.* A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. *Clin Cancer Res* 2012;18:4465-72.
44. Martín M, Prat A, Rodríguez-Lescure A, Caballero R, Ebbert MT, Munárriz B, *et al.* PAM50 proliferation score as a predictor of weekly paclitaxel benefit in breast cancer. *Breast Cancer Res Treat* 2013;138:457-66.
45. Cheang MC, Voduc KD, Tu D, Jiang S, Leung S, Chia SK, *et al.* Responsiveness of intrinsic subtypes to adjuvant anthracycline substitution in the NCIC.CTG MA.5 randomized trial. *Clin Cancer Res* 2012;18:2402-12.
46. Jørgensen CL, Nielsen TO, Bjerre KD, Liu S, Wallden B, Balslev E, *et al.* PAM50 breast cancer intrinsic subtypes and effect of gemcitabine in advanced breast cancer patients. *Acta Oncol* 2014;53:776-87.

Best of ASCO India

6-8 July 2018, Coimbatore

Dr R Bharath - bharath37@gmail.com

www.BestOfASCO.in

Conference Organizer : Kashish Parikh

+91-98190-25850 and kashishparikh@gmail.com

4th AMMO Conference

11-12 August 2018, Nashik

Dr Shailesh Bondarde - shaileshbondarde@yahoo.com

www.medintelservices.com

Conference Organizer : Kashish Parikh

+91-98190-25850 and kashishparikh@gmail.com

ICON

39th ICON Conference

8-9 Sept 2018, Indore

Dr PM Parikh - purvish1@gmail.com

www.OncologyIndia.org

Conference Organizer : Kashish Parikh

+91-98190-25850 and kashishparikh@gmail.com

4th MOSCon

16-17 Feb 2019, New Delhi

Dr Randeep Singh - drrandeep@yahoo.co.in

www.moscon.info

Conference Organizer : Kashish Parikh

+91-98190-25850 and kashishparikh@gmail.com