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Original Article

Practical consensus recommendation on when to do BRCA testing

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Abstract

BRCA-mutation associated breast cancer and to future cancer risks and sensitivity to systemic therapies. Now that rapid genetic testing for *BRCA1* and *BRCA2* mutations is available, *BRCA* mutation status can be considered when making treatment and prevention decisions for BRCA testing, *BRCA* mutation carriers with breast cancer. Expert group used data from published literature, practical experience, and opinion of a large group of academic oncologists, to arrive at practical consensus recommendations for use by the community oncologists.

Key words: 40 years, age, extended germline mutation, family history, ovarian cancer, pancreatic, paternal history, prostate

Introduction

The update in oncology-X-2017 was organized by Sir Ganga Ram Hospital group met to discuss and arrive at a consensus statement to provide community oncologists practical guidelines for challenging common case scenarios in Breast Cancer out of these we are discus about when to go for BRCA testing in this chapter. While the discussions will take the scenario as exists in India as a representative country with limited resources, the final manuscript is applicable globally.[1,2] The discussion was based on domain expertise of the National as well as international faculty, published evidence and practical experience in real life management of breast cancer patients. Opinion of the 250 oncologist including medical oncologist, radiation oncologist, surgical oncologist, molecular oncologist and radiologist are present in the update in oncology-X-2017 was taken into consideration by the expert panel. The expert group was chaired by Dr Shsd Salim and Dr S.P.Katria whereas the discussions were moderated by Dr Jyoti Wadhwa and Dr Purvish Parikh. The core expert group consists of Dr Ashutosh Gupta, Dr Sushant Mittal, Dr Prashant Mehta, Dr Christopher Twevlves, Dr Randeep Singh and Dr Sarah P Cate. Consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations. The survey answers were used as the basis for formulating the consensus statement so that community oncologists have a ready-to-use BRCA testing in Breast cancer patients.

As part of the background work, the best existing evidence was compiled and provided to the expert group panel members for review in preparation of the expert group meeting.[3-5] The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates from the update in oncology-X-2017. Members of the panel were also allowed to share their ersonal experiences, make comments and record dissent while voting for the consensus statements. Total of five broad question categories were part of the expert group discussions [Table 1].

This manuscript is the outcome of the expert group consensus arrived at on Saturday, May 20th, 2017.

Breast cancer is the commonest cancer of urban Indian women and the second commonest in the rural women.[4] Owing to the lack of awareness of this disease and in absence of a breast cancer screening program, the majority of breast cancers are diagnosed at a relatively advanced stage. The quality of care available for breast cancer patients varies widely according to where the patient is treated. Although there are some centers of excellence providing multimodality protocol-based treatment at par with the best anywhere in the world, the vast majority of breast cancer patients undergo inadequate and inappropriate treatment due to lack of high-quality infrastructure and sometimes skills, and above all financial resources. The recent emphasis on health education, early diagnosis of cancers, and more public facilities for cancer treatment are expected to bring about the much needed improvement in breast cancer care in India. Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India.[5,6] As per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta, and Trivandrum where it constitutes >30% of all cancers in females.[7] In the rural PBCR of Barshi, breast cancer is the second commonest cancer in women after cancer of the uterine cervix.[7] The age standardized incidence rates (AARs) range from 6.2 to 39.5 per 100,000 Indian women. The rise in incidence of 0.5–2% per annum has been seen across all regions of India and in all age groups but more so in the younger age groups (<45 years).[8] In general, breast cancer has been reported to occur a decade earlier in Indian patients compared to their western counterparts.

Familial and genetic breast cancer in Indian women

Almost a third of all breast cancer patients are believed to have familial disease pattern, and some 5% are believed to be hereditary, with the BRCA1 and BRCA2 gene mutations having been identified as the major genetic causes.[2,9-18] In an Indian study on 226 breast cancer patients, 20.7% had a

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positive family history.[18] On the contrary, numerous other studies have reported a low rate of familial pattern of breast cancer in Indian patients. This is particularly interesting given the relatively young age of Indian breast cancer patients.[12,14,16,18] Genetic screening/diagnosis is not routinely performed in most Indian center due to paucity of funds and facilities. As a result, there is scarce data on the genetic composition and BRCA1/2 mutations in Indian patients. The available studies hint at a rather low incidence of BRCA mutations. In most populations, 6–10% of patients with breast cancer have mutation in BRCA gene irrespective of their family history. Though there are no robust figures, various Indian studies have reported BRCA mutations in 9–25% of familial breast cancer cases.[19-23] Hedau *et al*.[24] demonstrated 3 novel BRCA1 mutations including a founder Ashkenazi Jewish BRCA1 mutation in Indian breast cancer patients.[24]

At the present, there are no formal Indian guidelines stating which patients should be referred for genetic risk evaluation at the time of breast cancer diagnosis; however standard criteria for referral for genetic risk evaluation have been applied to this population.[25] In general, women with at least a 10% likelihood of carrying a *BRCA* mutation have been included in studies of peri-diagnostic genetic testing to date.[24,26,27] Certainly, high risk women for whom surgical treatment decisions could be impacted by genetic test results should be considered for peri-diagnostic genetic risk evaluation.

Impact of *BRCA* mutation status on local therapy for breast cancer

When considering options for local therapy for *BRCA* mutation-associated breast cancer, several issues come into play. Questions arise about the efficacy of breast conserving therapy and the possibility of excess toxicity of radiation in mutation carriers. Additionally, given the high rate of contralateral breast cancer, mutation carriers with newly diagnosed breast cancer may choose to incorporate breast cancer prevention into their surgical management and undergo mastectomy for the affected side plus contralateral prophylactic mastectomy. This section reviews issues related to management of the affected breast and options for the contralateral breast.

To the question regarding the BRCA testing in all breast cancers under age 40 years? The expert panel did not agree to be equally divided votes that are 50%-50% by the delegate shows [Table 2]. Half of the voters were in favor of BRCA testing in all breast cancers under age 40 years and remaining half do not support it, The expert panel members agreed that it is established standard of care to do BRCA testing in all patients with breast cancer diagnosed at or below the age of 40, as specified in NCCN guidelines.[25] This was followed diligently in the USA whereas in the UK the cut off age as 50 years of age. In India, factors responsible for not adhering to these guidelines include cost of testing and insufficient trained counseling professionals. Other factors discussed like reproductive history, family history and understand legality should not prevent the community oncologist from discussing or recommending BRCA testing.

A clear majority of delegates polled 66% votes in favor of BRCA testing for sporadic post menopausal triple negative breast cancer 55 years [Table 3], The expert panel also agreed on age cut off 60 years for such a scenario and commented that it's also has implication on type of treatment given to patient so it's important in such patients to advise for BRCA testing.

Absolute majority of delegates polled 100% votes and expert panel are in favor of extending germline mutation testing in triple negative 35 year old female [Table 4]. The expert panel recommending on doing such a testing as not to miss out number of other syndromes. And also suggested to chose lab wisely.

This time also a clear majority of delegates polled 71% votes in favor of BRCA testing for post menopausal breast cancer 60 years old with one maternal cousin having ovarian cancer [Table 5]. The expert panel opinion was also in favor. And one expert from US suggested for NCCN guidelines.[25] And one of expert also suggested using risk assessment calculators in such setting.

Table 1: Question categories addressed by the update in oncology-X-2017

Broad question title
Question 1 - Will you do BRCA testing in all breast cancers under age 40 years?
Question 2 - Will you do BRCA testing for sporadic postmenopauasal triple negative breast cancer 55 years?
Question 3 - Will you go for extended germline mutation testing in triple negative 35-year-old female?
Question 4 - Will you do BRCA testing for postmenopausal breast cancer 60 years old with one maternal cousin having ovarian cancer Will you do BRCA testing for postmenopausal breast cancer 60 years old with one maternal cousin having ovarian cancer?
Question 5 - Will you do BRCA testing for postmenopausal breast cancer 60 years with one paternal cousin having prostate cancer or pancreatic cancer?

Update in oncology-X-2017

Table 2: Question 1 - Will you do BRCA testing in all breast cancers under age 40 years?

Options (%)	Yes	No
Percentage of polled oncologists	50	50

Expert group consensus: The expert panel recommended not to do BRCA testing in all breast cancers under the age of 40 years

Table 3: Question 2 - Will you do BRCA testing for sporadic post menopauasal triple negative breast cancer 55 years?

Options (%)	Yes	No
Percentage of polled oncologists	66	34

Expert group consensus: BRCA testing should be done for all breast cancer patients above the age of 60 years

Table 4: Question 3 - Will you go for extended germline mutation testing in triple negative 35-year-old female?

Options (%)	Yes	No
Percentage of polled oncologists	100	0

Expert group consensus: Extended germline mutation testing (beyond BRCA) should be done fore triple negative young patients with breast cancer so as not to miss out on other syndromes

Table 5: Question 4 - Will you do BRCA testing for postmenopausal breast cancer 60 years old with one maternal cousin having ovarian cancer?

Options (%)	Yes	No
Percentage of polled oncologists	71	29

Expert group consensus: The expert panel recommended BRCA testing in breast cancer patients with maternal family history of ovarian cancer

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Table 6: Question 5 - Will you do BRCA testing for postmenopausal breast cancer 60 years with one paternal cousin having prostate cancer or pancreatic cancer?

Options (%)	Yes	No
Percentage of polled oncologists	85	15

Expert group consensus: BRCA testing is recommended in selected cases with breast cancer who have paternal family history of prostate or pancreatic cancer (based on published guidelines)

Absolute majority of delegates voted in favor of BRCA test for post menopausal breast cancer 60 years with one paternal cousin having prostate cancer or pancreatic cancer [Table 6]. The expert panelist agree if facilities are available and patient qualifies for the test based on guidelines, then it should be definitely discussed with the patient and the genetic counseling is very important for genetic testing.

Conclusion

The update in oncology-X-2017 expert group for challenging common case scenarios in Breast Cancer had the specific mandate to develop practical consensus Recommendations PCRs for easy application by the community oncologist. It took into consideration data as well as the current practices in India, in addition to international data that conventional panels look at, making it the perfect blend of evidence, clinical expertise, and real life preference.

The options for BRCA testing in breast cancer patients or the management of *BRCA* mutation-associated breast cancer is complex and multiple factors regarding the cancer at hand and future cancer risks must be weighed together when making treatment decisions. With the availability of peri-diagnostic genetic testing, care plans which incorporate *BRCA* mutation status can now be developed. Breast health specialists, genetic counselors, gynecologic oncologists, and primary health care physicians all have an important role in discussing risk-reduction strategies with women at very high risk of breast and ovarian cancer. Evaluating patient risk factors and obtaining a comprehensive family history are important steps in assessing breast and ovarian cancer risks. Genetic testing can identify individuals at very high risk for hereditary breast and ovarian cancer. Evidence is accumulating, and efficacy data are currently available for some, but not all, medical interventions for *BRCA1* and *BRCA2* mutation carriers. A coordinated team effort can provide a supportive environment and personalized approach for patients facing difficult surgical vs nonsurgical decisions related to management of hereditary breast and ovarian cancer. With time, these and other questions will be answered and we will become better able to individually tailor treatment and prevention plans for women with *BRCA* mutationassociated breast cancer.

Discussion

Traditionally, decisions regarding systemic therapy for *BRCA* mutation-associated breast cancer have been made based on the characteristics of the disease and not on the *BRCA* mutation status. However, this may change as questions exist regarding the impact of mutation status on prognosis and recent data suggesting unique patterns of sensitivity and resistance to systemic therapies in *BRCA* mutation-associated breast cancer emerges.[28-30] Notably, *BRCA* mutation-associated breast cancers appear to be particularly sensitive to a new class of drugs which inhibit poly (ADP-Ribose) polymerase (PARP).[28-30]

Since genetic testing was introduced, its use for risk assessment by health care professionals has been escalating. Hereditary *BRCA1* and *BRCA2* mutations account for about 60% of inherited breast cancer and are the only known causes of hereditary breast and ovarian cancer syndrome. Women with a germline mutation in *BRCA1* or *BRCA2* or a hereditary predisposition for breast cancer have markedly increased risk of early-onset breast cancer and ovarian cancer.

Approximately 80% of breast and 90% of ovarian cancer cases are thought to be sporadic with no associated family history. Multifactorial familial risk accounts for approximately 10% to 15% of breast cancer. In the future, testable panels of genetic variants likely will combine to subtly alter risk. Hereditary breast cancer—cancer attributable to a single hereditary gene mutation in either *BRCA1* or *BRCA2*—accounts for approximately 5% of breast cancer cases, characteristically occurring before age 50 years. Approximately 4% to 11% of ovarian cancer is attributable to a germline mutation, with the greatest proportions in cancers diagnosed before age 50 years.[31] An estimated 1 in 300 to 1 in 800 US individuals are *BRCA* carriers (1 in 50 individuals with Ashkenazi Jewish heritage).[32,33] Hereditary breast and ovarian cancer attributed to a mutation in a particular gene (ie, *BRCA1* or *BRCA2*) can be passed on to the next generation, transmitted in an autosomal dominant pattern. The gene mutation may originate from the maternal or the paternal side, and each offspring of a *BRCA* carrier has a 50% chance of inheriting the mutation.[34,35]

Take Home Messages

1	The expert panel recommended not to do BRCA testing in all breast cancers under the age of 40 years
2	BRCA testing should be done for all breast cancer patients above the age of 60 years.
3	Extended germline mutation testing (beyond BRCA) should be done fore triple negative young patients with breast cancer so as not to miss out on other syndromes.
4	The expert panel recommended BRCA testing in breast cancer patients with maternal family history of ovarian cancer.
5	BRCA testing is recommended in selected cases with breast cancer who have paternal family history of prostate or pancreatic cancer (based on published guidelines)

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Conflicts of interest

There are no conflicts of interest.

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