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Archives of Surgical Research

Bringing Surgical Science and Art Closer

Archives of Surgical Research (ASR) is a double blind peer-reviewed quarterly ICMJE and COPE compliant journal dedicated to the local, national, and global advancement of surgical research, education and clinical practice. It aims to promote continued development in surgery through the dissemination of knowledge, ideas and good practice across surgical specialties. ASR provides readers with critically peer-reviewed, carefully selected and edited, and up-to-date publications about advancements in all surgery specialties.

Published by
Pakistan Endocrine & Thyroid Surgeons Association (PETSA)
537-S, Imperial Garden Homes, Paragon City, Lahore, Pakistan

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Editor in Chief: Prof Khwaja M Azim FRCS

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About Archives of Surgical Research

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The journal aims to uphold the highest standards at the cutting-edge of research, provide a focus for evidence-based medicine through the publication of review articles and special issues, and give the findings context through the publication of editorials, commentaries and letters from the surgical community. We ensure enforcement of reporting guidelines and mandate the registration of all research involving human participants in a publicly accessible research registry.

As a journal covering all surgical specialties, ASR aims to facilitate the transfer of important ideas and thought systems between and across specialties. Hence, ASR will help prevent the trend of increasing sub-specialization which leads to 'tunnel-vision' and the unfortunate concealment of important surgical advances within specific specialties.

Editor in Chief

KMA

Editorial Team

PREFACE

Shalamar Medical & Dental College has exceptionally excelled in the field of science, education and research over the last decade and has produced quality graduates who are currently serving around the world. Quality of education and research in surgery has been instrumental in this regard under the leadership of Prof Khawaja Muhammad Azim to achieve our core objective of producing quality education. Inception of Pakistan Endocrine & Thyroid Surgeons Association (PETSA) has aligned well to my vision, institutional requirements and overall rapport of the institution.

I witnessed and supported the birth of Pakistan Endocrine & Thyroid Surgeons Association here at Shalamar Medical College three years back and during this period it has evolved into a mature tree and is bearing fruits to surgical education and training here at our institution. Legacy of its founding visionary, Late Prof Syed Zafar Haider has continued. PETSA has been conducting Annual Thyroid & Parathyroid Master Class since its inception with great reception. Currently, we are the largest endocrine surgery center in Pakistan with highest volume turnover.

Now the introduction of "Archives of Surgical Research" is another feather into our institutions' cap. This journal would not only satisfy the needs of the society but would also serve to promote culture of science, education and research within our institution. This culture advocacy remains instrumental in promoting the quality of learning process of the medical graduates within our institute and is aligned with my vision about this medical college.
In the end, I am happy to write about "Archives of Surgical Research" and its inaugural issue and wish the editorial team best of luck for their endeavors for years to come.

Prof Zahid Bashir

Principal

Shalamar Medical & Dental College, Lahore

MESSAGE FROM THE PRESIDENT

Pakistan Endocrine & Thyroid Surgeons Association (PETSA)

Prof Zafar Haider was the teachers of the teachers and a great surgeon. He was the one who made thyroid and endocrine surgery safe in Pakistan and we carry the light now with aim to improve the endocrine surgery in light of modernization in the field of the surgery.

Archives of Surgical Research aims at improving the standard of surgical research and education. It would function as official Journal of Pakistan Endocrine & Thyroid Surgeons Association (PETSA).

The journal would cover endocrine, breast and surgical oncology primarily. It would also focus on the surgical education for medical students and residents to enhance the learning process through addition of technology, blended learning and modern concepts in medical education.

Prof. Khwaja M Azim FRCS
President PETSA

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Archives of Surgical Research | Editorial

Breast Cancer Care In Pakistan: Burden Of The Disease And What We Need To Do?

Muhammad Luqman Farrukh Nagi[1], Zahid Bashir[1]

IMPORTANCE Breast cancer is the most common malignancy observed in women worldwide including in Pakistan. The five-year prevalence of breast cancer was 35%, the incidence of breast cancer was 23%, and the mortality of breast cancer in Pakistan was 16% during 2017. Delayed presentation of the patients is seen to be associated with advanced-stage diagnosis, aggressive treatment, poor outcomes, poor quality of life, and higher mortality rate. Delay in effective oncological treatment could be due to patient presentation delay which results in a cumulative increase in breast cancer-associated mortality. We clearly need to identify and address the factors which mediate delay in breast cancer diagnosis and management.

KEY WORDS Breast Cancer, Delaying Factors, Pakistan, Screening, Awareness

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Editorial

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Breast cancer is the most common malignancy observed in women worldwide including Pakistan[1-3]. It is growing rapidly as 1.4 million new cases of breast cancer are diagnosed annually in Pakistan out of which almost half a million women die every year[4]. Pakistan is deficient in a national, population-based cancer registry, however few projections can be made based on the available statistics[5]. Five year prevalence of breast cancer was 35%, incidence of breast cancer was 23%, and mortality of breast cancer in Pakistan was 16% during 2017[6]. To put simply, one in every nine women in Pakistan has a lifespan threat of being detected with breast cancer, and this is corroborated in local studies as well. [7-8]

Delayed presentation of the patients is seen to be associated with advanced stage diagnosis, aggressive treatment, poor outcomes, poor quality of life and higher mortality rate[9,10]. Delay in effective oncological treatment could be due to patient presentation delay which results in cumulative increase in breast cancer associated mortality[11-12]. We clearly need to identify and address the factors which mediate delay in breast cancer diagnosis and management.

Literature suggests that certain initiatives were taken by the Federal Government for screening and early detection of breast cancer cases which included the establishment of cost-free community based Breast Care Centers in Islamabad and Lahore, and mobile mammography services for women residing in rural areas[13]. However, these efforts have not been fully integrated with the overall healthcare system, resulting in the alarming increase in breast cancer incidence in the country.

In this issue related to breast cancer management, Ashraf et al have identified various factors which could influence the delayed presentation and treatment of breast cancer in a holistic fashion[14]. The review also highlights the need for more robust quantitative and qualitative assessment of these factors specific to our cultural scenario.

Patients who present after three months of initial symptom appearance have 12% higher 5-year mortality rate than those who present earlier[9]. The 5-year survival for stage 0 and stage I cases is 100%, stage II is 93% and stage III is 72%[15]. The key lies in early detection of the cancer and managing it. Based on experience and literature review, we find three major challenges in combating breast cancer. Improving awareness about cancer, screening and provision of breast specific clinical facilities in the form of "One Stop Breast Cancer Clinics."

Ashraf et al' have laid the following recommendations:

1. Awareness about breast lumps and risk of genetic inheritance in breast cancer should be adopted as a bench mark in national healthcare program.
2. Breast self-examination (BSE) can significantly reduce delayed presentation thus improving the breast cancer care outcomes.
3. Stigmatization that breast cancer is incurable can be reduced by creating awareness about available treatment options and their effectiveness.

4. Breast-specific facilities and easy access to affordable health care facilities should be provided especially in primary healthcare setting.
5. Screening programs for early detection of breast cancer are need of the hour.
6. Multidisciplinary approach can reduce delay in chemotherapy or surgical intervention due to fear of treatment.
7. Training of clinicians about significance of triple examination, common signs and symptoms and quick referral to oncologist can reduce provider related delay.
8. Concomitant breast reconstructive surgery can reduce the delay in treatment due to fear of mastectomy.
9. Availability of health insurance can reduce the disparity seen in racial minorities of developed countries.

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Archives of Surgical Research | Original Research

Perception and Awareness of Surgical Professionals About Potential Role Of Artificial Intelligence In Surgery: A Survey Analysis

Ahmad Naeem Akhtar[1], Hamza Azhar[2], Talha Asad[3], Talat Waseem[2]

IMPORTANCE Artificial intelligence (AI) is defined as the ability of the machine to think like a human being. Since the advent of AI, there has been a major change in the medical and surgical fields. The AI-based algorithms are being incorporated into the decision-making and automation aspects of the surgical discipline. This study aims to investigate the perception and awareness of medical professionals about the role of AI in surgical fields.

METHODS A questionnaire was prepared by a panel of six experts in the field of surgery who were well-aware of the role of AI in surgery. They formulated the basic themes, and these items underwent the process of content and construct validation. The questionnaire was disseminated through Google forms. The intended participants included medical professionals interested in surgery were approached to take part in this survey. The data was collected after the approval of the ethical committee of the institute and the analysis of the data was done using IBM SPSS Statistics 23.0, for quantitative analysis, and the qualitative data were subjected to thematic analysis.

RESULTS AND DISCUSSION 197 individuals having an interest in surgery took part in this survey. Most of the participants were not familiar with the AI-based concepts and their potential role in the surgical field in the coming years. Only a limited number of participants were involved in surgical AI projects. According to the results of this survey, general acceptability towards the integration of AI in surgical practices was observed. There was a mixed opinion regarding the application of AI in surgery among medical professionals.

CONCLUSIONS Despite the limited awareness of the participants, the perception of the surgical professionals about Artificial intelligence (AI) is changing and the acceptability towards integration of AI in surgical practice is increasing.

KEYWORDS Artificial intelligence, AI, Machine learning, Surgery, neural networks, Survey,

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Original Research

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Artificial intelligence deals with training a machine to think and solve problems like a human being. Artificial intelligence is changing the outlook of every field of life. AI has been used in different fields of medicine and it has shown some outstanding results in those fields. AI is currently being used in different areas of surgery in limited capacity[1]. However, it is being speculated that in the future AI will be used as a major tool in different areas of surgery. In the surgical discipline, the role of Artificial Intelligence (AI) is evolving and is important in supporting clinical decision-making, imaging, and diagnosis, precision medicine, for risk stratification, genomics, and discovery of novel drugs[1]. The potential role of AI in imaging and navigation provides a potent notion for computer-assisted intervention both in the preoperative and intraoperative setting. Computer-aided intraoperative guidance through a minimally invasive approach provides another avenue for active exploration. Researchers are exploring four main areas in this regard: shape instantiation, endoscopic navigation, tissue tracking, and Augmented Reality (AR). The research in these areas would likely expand exponentially in the coming days and would have a significant impact on research and ultimately our surgical practice[1].

Despite the current use of AI-based technology in different surgical fields, a general skepticism is still seen among medical professionals about the integration of AI-based tools in surgical and medical practice. We conducted this survey to investigate the knowledge, acceptability, and general perception of medical professionals about artificial intelligence in surgery.

METHODS

A questionnaire was prepared by a panel of six experts in the field of surgery who were well aware of the role of AI in surgery. They formulated the basic themes, and respective items underwent the process of content and construct validation. This study was conducted after getting approval from the ethical committee of the institution. The

questionnaire was designed to get multiple choice and free-text responses from the participant. The questionnaire was disseminated through Google forms. The intended participants included medical professionals interested in surgery were approached to take part in this survey. 70.6% of the participants were medical students, 15.7% of them were consultants while the remaining 13.7% population consisted of medical professionals of varying clinical experience. The analysis of data was done using IBM SPSS Statistics 23.0 and p values were calculated using the chi-square test.

RESULTS AND DISCUSSION

Characteristics of the Participants:

A total of 197 individuals participated in this survey. A brief overview of the characteristics of the participants has been depicted in Table 1. Younger professionals in earlier phases of their careers participated more in the survey as opposed to older professionals. Most of the participants (51%) who took part in this survey belonged to the specialty of general surgery. Although the survey was circulated among the younger health professionals and the consultants alike, the professionals at earlier stages of their career responded more enthusiastically. 70.6% of the respondents were medical students, 15.7% were consultants, and 13.7% were post-graduate trainees or intern rank professionals. The research experience and experience about AI-related research experience were variable. When the participants were asked to rate their scientific experience 66.3% responded that they had been involved in some research project in the past, 23% said that they had never done any research project in their entire life while 10.7% said that they had led many research projects in the past. Similarly, the duration of the experience among the participants was also variable among the participants. 51.5% of the participants had research experience of 1 year, 12.4% had an experience of 2 years, 4.6% had an experience of 3 years, and 12.9% of them had an experience of more than four years while 18.6% had no research experience at all.

Despite a high level of enthusiasm in AI-based research, the understanding of the subject and the awareness about its potential applications still remains limited. Moreover, the surgical literature exploring the perception of medical professionals about surgical AI is even exiguous. Such a drive is probably timely and needs of the hour to stimulate the research hierarchy to focus on the subject and harness the fruits of AI in the field of surgery. A few articles exploring the attitude of medical students and medical professionals about AI in the field of medicine have been published[2,3]. A recent survey exploring the patient's perception of the use of AI in neurosurgery has been published[4]. However, there are only a limited number of surveys that have investigated the perception of surgeons and the integration of artificial intelligence in the field of surgery. In this survey, we have investigated the familiarity and acceptability of surgical AI in medical professionals who have a formal interest in the field of surgery.

Age	Percentage
The Twenties	78.06% (N = 153)
Thirties	16.32% (N = 32)
Fifties	3.57% (N = 7)
Sixties	4% (N = 8)
Gender	**Percentage**
Males	42.9%
Females	56.6%
Unidentified	0.5%
Specialty	**Percentage**
General Surgery	51%
Cardiothoracic Surgery	8.2%
Obstetrics And Gynecology	5.1%
Neurosurgery	2.6%
Ophthalmic Surgery	3.6%
Oral And Maxillofacial Surgery	2.6%
Orthopedic Surgery	3.1%
Otorhinolaryngology	2.6%
Pediatric Surgery	2.6%
Plastic Surgery	2%
Urology	1.5%
Vascular Surgery	0.5%
Radiology	0.5%
Dermatology	0.5%
Internal Medicine	0.5%

Survey Exploration and Outcomes:

The following themes were explored through the survey:

A. Familiarity and Involvement with Surgical AI-Based Research:

With the rapid growth of artificial intelligence, it has become important for physicians to develop an understanding of AI. The majority are not familiar with the basic concepts of artificial intelligence and structured data handling (which is the core of AI science), as most of them do not like to focus on complex algorithms, software languages, and engineering skills which all lead to the integrative thought process. In a recent survey conducted in 2019, it was revealed that merely 6% of the health professional participants had a good familiarity with the structured data handling, database, and AI-related concepts[3]. When the participants were asked about familiarity with the concept of surgical data science, 51.4% of them said that they didn't know what it means, 33% of them said that they have heard about it but they were not familiar with it and 14.6% of the participants said that they knew what it means but they were not working in this field. Only 1.1% of the respondents said that they were familiar

with surgical data science and they had worked in this field. This clearly shows the need for creating awareness among the hospital professionals to generate and handle the data in a more structured fashion and to train the faculty for this particular purpose. In this survey, participants were specifically asked about the procedure of surgical data collection in their institutes. More than 60% of participants believed that their institutional data handling has progressed to a more structured approach. The rest either did not have the will or the infrastructure to handle the data in a more systematic and structured way to make it more useful and good enough to be used for any research-related activity. The quality of the structured data handling however varies and only 9.7% of participants believed that their surgical data was ripe enough for use in machine learning-based projects. Awareness and practice of annotation of surgical data remain sub-optimal; 70.3% of the participants responded that they had never done it, 9.2% said that they have annotated surgical data and 20.5% of the participants were not familiar with the concept of data annotation.

Artificial Intelligence can be instrumental at many fronts in surgery starting from diagnosis, decision-making algorithms, automation, and robotic integration. For successful application of AI in these different domains needs significant in-depth knowledge of computer programming, data science, and knowledge of mechanical engineering science. The successful outcomes in this domain would depend upon the successful integration of these all domains. Therefore, a surgeon's knowledge about AI would require a significant hold of these disciplines. Participants' cognitive depth about AI was explored in this survey as well. Around 55% of them said that they have never studied anything related to artificial intelligence, 34.4% said that they have read about it, 8.2% said that they have attended seminars about it, 2.1% of them said that they had taken an online course about it and 0.5% of the participants said that they had a degree related to this subject. The survey participants were traversed about their understanding of scientific articles on artificial intelligence. 70.5% of the participants answered that they had never read any scientific article on artificial intelligence, 17.1% said that they had read AI-based articles in surgical journals but they could not understand the details dealing with artificial intelligence, 8.3% said that they had read AI-based articles in surgical journals and they were able to understand AI-related details, and 4.1% of the respondents said that they had read AI-based articles in computer science or engineering journals and they could understand the AI-related details.

The participant's familiarity with AI-related terms was scouted. The terms we used in the questionnaire were machine learning, deep learning, supervised learning, unsupervised learning, and neural networks. More than 50% of the participants were not familiar with these terms, 24.7% said that they did not understand them completely but they had heard about some of these terms, 20.6% said that they could understand some of these terms and only 2.1% said that they could understand all of these terms completely.

AI-related projects mandate a multidisciplinary research approach. On a question about collaboration with engineers in surgical AI projects, 97.8% of the participants said that they had never worked with engineers on such projects and 2.2% of the respondents said that they had worked with engineers in a surgical AI project. Participants were asked to give their opinion on leadership in surgical AI research. 11.9% of the participants said that surgeons should take lead while 9.7% said that AI researchers should take lead in researching surgical AI. 78.4% of them said that there should be a collaboration between surgeons and AI researchers in researching surgical AI. Participants were asked about their computer programming experience. 57.4% of them said that they had no experience in programming, 37.1% said that they were a little bit experienced while 5.6% said that they were somewhat experienced in computer programming. Looking at these results, it can be concluded that the involvement of participants in AI projects and their familiarity with the AI terms was limited. This clearly shows the need for an in-depth cognitive base of the surgical professionals to conduct a meaningful AI-related search and provide leadership to the research team.

B. Acceptability of AI-based technology:

Skepticism regarding the implementation of new technology is always seen in the general public. Artificial intelligence is a relatively recent concept and the understanding of this concept is limited. In this survey, we wanted to probe the adaptive and adoptive attitudes of medical professionals towards AI-based technology.

Participants of this survey were scrutinized for their reaction to new technology. 56.3% of the participants responded that they adopt technology at an average rate, 28.9% said that they accept new technology very quickly and 14.7% of the respondents said that they are usually skeptical about the new technology. Participants were asked to give their opinion about whether or not AI should be used to make an autonomous surgical robot. 23.2% of them were in favor of making AI-based autonomous surgical robots, 12.4% were against it and 47% of the participants said that it should be done only if we have solid evidence of its safety. This shows the safety remains a priority before incorporating AI-based applications into the practice. 16.2% of the participants thought that only humans should be permitted to do surgeries. Participants were also asked about their opinion about using AI for clinical decision-making. 57.3% of the respondents answered that AI should be used as a tool to help us make clinical decisions, 4.9% of the participants said that AI should replace humans and 3.8% said that AI should be used for clinical decision making because it is a more financially viable option. 34.1% of the participants said that AI should not be used for clinical decision-making. Out of these 34.1% participants,

21.1% of respondents said that AI cannot be trusted with the lives of human beings. While answering another question about willingness to use AI tools in surgical practice, 35.1% of participants answered that they would be willing to use AI tools in their surgical practice while 8.6% of the participants said that they would not use them. 56.2% of the respondents said that they would like to know more about surgical AI before using them in their surgical practice. At large, patient safety concerns remains a significant concern in the adoption of AI-based surgical solutions. The surgeons are also skeptical about the ability of the AI-based algorithms, however, they think to continue the research in this area more robustly.

Integration of AI-based solutions into the surgical practice especially in the preoperative and per-operative setting remains in infancy. Participants were asked for their opinion about the integration of AI into daily surgical practices. 25.6% of the participants said that AI will be integrated into daily surgical practices while 8.7% of respondents answered that AI will not be integrated into surgical practices. 65.6% of the participants were not sure about whether AI will be integrated into surgical practices or not. 24% of the respondents answered that AI will be integrated within five years, 34.7% said that it will be integrated within five to ten years, 37.2% said that it will be integrated in more than ten years while 4.1% of the respondents said that AI will never be integrated into daily surgical practices. Participants were asked to tell us how their jobs as surgeons will be impacted by AI. 57.4% of the respondents said that their job will be impacted for the better, 25.4% said that their job will be changed as a surgeon and 4.1% of them said that their jobs will be replaced. 13.2% of the respondents said that AI will not impact their job in any way. 54.3% of the participants said that intraoperative care will be impacted the most within the next 10 years, 17.3% said that preoperative care will be the most impacted area, 13.7% said that postoperative care will be the most affected area within the next ten years. 14.7% of the respondents said that hospital management will be the most impacted area within the next ten years. Participants were given an arbitrary scenario to investigate whether they liked explainability or accuracy in their AI-based surgical tools. 39.1% of the participants answered that they prefer accuracy, 9.6% preferred explainability while 51.3 said that their decision will depend on how much accuracy they will get at expense of explainability.

Contrary to our presupposition, there was general acceptability towards the integration of AI in surgical practice. Most of the participants were willing to use AI in their surgical practice but most of them were skeptical of AI-based autonomous surgical capacity. Most of the participants believed that AI will be integrated into general surgical practice in the future and most of them said that their jobs as surgeons will be impacted for the better.

C. Perception about the application of AI in surgery

Artificial intelligence is being used in preoperative risk assessment and prediction of post-operative complications, overall survival, and 30 day readmission[5]. AI is playing a major role in different surgical fields like ophthalmology, plastic surgery, and vascular surgery [6,7,8,9,10]. In the future, AI will be a major part of surgical practice. In this study, we wanted to know the perception of medical professionals about the application of AI in surgery.

The participants were asked to express their thoughts about what the role of AI will be in surgery within the next 10 years. Out of 197 people who answered this question on a scale of 1-5 in increasing agreement, 47 people thought that there's a 40% possibility of an increased role of AI in enhanced surgical vision (augmented reality, fusion imaging, surgical guidance system, etc.). 41 participants answered 4/5, 39 participants answered 1/5, 37 people answered 3/5 and 33 respondents answered 5/5 on the agreement scale. In response to the question about the role of AI in medical training and education 56 people answered 2/5, 45 people answered 3/5, 37 people answered 4/5, 33 respondents answered 1/5 and 26 participants answered 5/5 on an agreement scale to this question. When they were asked about the role of AI in surgical automation, 66 people answered 2/5, 44 respondents answered 3/5, 41 participants answered 1/5, 31 of them answered 4/4 and 15 people answered 5/5 on the agreement scale. 55 participants responded with 2/5 on the agreement scale to the question about the role of AI in hospital administration. 43 of them answered with 1/5, 41 participants answered with 3/5, 38 of them answered with 4/5, and 20 participants answered with 5/5 on an agreement scale. 58 participants answered 2/5, 50 participants answered 4/5, 39 people answered 1/5, 37 participants answered 3/5 and 13 people answered 5/5 on an agreement scale when they were asked about their opinion on the integration of AI in intraoperative decision support. We asked the participants to give their opinion about the role of AI in perioperative decision support on a scale of agreement from 1 to 5. 57 participants answered 2/5, 45 people answered 3/5, 40 people answered 1/5, 40 people answered 4/5 and 5 people answered 5/5 on agreement scale. Our study clearly shows that AI would significantly impact the surgical practice both in the preoperative and intraoperative setting.

D. Barriers to implementation of AI in surgical practices:

Despite the utility of AI-based tools, there are still some problems regarding the implementation of AI in surgery. In this survey, we asked the participants different questions relating to the barriers to implementing AI in surgery. They were asked to give their answer in the form of a scale of agreement from 1 to 5. When the participants were asked to give their opinion about the lack of technical infrastructure as an impediment to the integration of AI in surgical practice, 59 participants answered 5/5, 45 people

answered 4/4, 33 people answered 3/5, 31 people answered 1/5 and 29 people answered 2/5 on agreement scale. We asked the opinion of participants about the lack of trust in AI-based tools as a barrier to the implementation of AI in surgical practices. 51 participants answered 4/5, 48 people answered 3/5, 39 respondents answered 2/5, 38 people answered 5/5 and 21 people answered 1/5 on an agreement scale from 1 to 5. 51 people answered 4/5, 44 participants answered 5/5, 41 people answered 3/5, 34 participants answered 2/5 and 27 people answered 1/5 on agreement scale when they were asked about the unavailability of AI-based tools as a hurdle in implementing AI in surgery. Participants were asked about unclear legislation and ethical aspects as an impediment to the integration of AI in surgery. 51 people answered 4/5, 50 people answered 3/5, 40 people answered 5/5, 29 people answered 2/5 and 27 people answered 1/5 on the agreement scale to this statement. 51 people answered 3/5 on an agreement scale while giving their opinion about the lack of trust in AI among healthcare professionals and hospital management. 46 people answered 4/5, 44 participants answered 2/5, 32 respondents answered 5/5 and 24 people answered 1/5 on the agreement scale. Hence, the issues related to infrastructure, general trust in applications, patient safety, ethics, and legal perspectives emerged as important barriers or challenges in the expedited implementation of AI-based solutions.

CONCLUSION:

The perception of medical professionals about the role of Artificial intelligence (AI) in surgery is changing and there is a general increase in acceptability towards the integration of AI-based technology in surgical practice. In the future, the momentum of AI giant would likely influence surgical science and art significantly and our jobs and roles as surgeons would significantly be modified.

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Archives of Surgical Research | Original Research Communication

Correlation of Mammographic Breast Density (MD) And Background Parenchymal Enhancement (BPE) With Various Factors Especially Receptor Status In Pakistani Population

Muhammad Omer Altaf[1], Shahper Aqeel[1], Eisha Tahir[1], Imran Khalid Niazi[1]

IMPORTANCE Breast is one of the most common cause of malignancy related mortality all over the world accounting for more than 5 million deaths per year. Mammographic dense breast tissue is one of the most common problem in diagnosing breast CA in females. It increases the risk of breast CA up to five times and is also associated with larger tumor size, axillary lymph node involvement, higher stage of tumor owing to delay in the diagnosis.

Background parenchymal enhancement is seen on MRI breast after administration of contrast. The level of BPE is variable among different age groups being higher in young women. It is affected by several factors including age, hormone levels, and menstrual cycle phase.

OBJECTIVE This study was done to investigate the correlation between mammographic breast density (MGD) and background parenchymal enhancement (BPE) at breast MRI with receptor status in our population.

MATERIALS AND METHODS It is a retrospective study conducted at women imaging department of Shaukat Khanum Memorial Cancer Hospital from January 2013 till January 2019. All the newly diagnosed breast cancer patients aged 20 to 70 years, with dense mammogram who underwent MR imaging prior to treatment will be included. The MR imaging detection rate of additional malignant cancers occult to mammography and ultrasound will be calculated. Data will be analyzed according to the following parameters: histopathological features of the index tumor and mammographic density. The histopathological examination will be taken as gold standard. The data will be compiled and analyzed using SPSS

CONCLUSIONS High mammographic density and increased BPE are independent risk factors for the development of breast cancer. Exposure to hormones influence the BPE grade and thus is associated with increased risk of breast CA with a positive correlation between increased MGD and high BPE with both estrogen and progesterone receptors.

KEYWORDS Background parenchymal enhancement (BPE) mammographic density (MD), MRI, Breast cancer (CA)

KEYWORDS Breast Cancer, Radiology, Mammographic Breast Density, Background Parenchymal Enhancement.

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Breast carcinoma (CA) is one of the most common cause of malignancy related mortality all over the world accounting for more than 5 million deaths per year.[1] Better diagnostic modalities have been devised leading to early detection of the tumor, in which mammogram and ultrasound (USG) play initial role. The mammographic dense breast tissue, however is one of the most common problem in diagnosing breast CA in females. Almost half of the women above 50 years have high mammographic density breast tissue making the diagnosis difficult.[2] High breast density is because of increased amount of fibroglandular tissue including fibroblast, connective tissue and epithelial cells. It appears as an opaque region on mammogram.[3] In dense breasts the lesions can be masked which can lead to increases the risk of breast CA up to 5 times and is also associated with larger tumor size, axillary lymph node involvement and higher stage of tumor owing to delay in detection.[4] BIRADS guidelines are followed to describe mammographic density (MD) as four categories on mammogram ranging from extremely fatty to extremely dense.[5]

In contrary to MD, the background parenchymal enhancement (BPE) is seen on magnetic resonance imaging (MRI) of breast after administration of contrast. [6] Following the new BIRADS MRI Lexicon, this is qualitatively classified as minimal, mild, moderate and marked on the basis of degree of enhancement.[7] The level of BPE is variable among

different age groups being higher in young women. It is affected by several factors including age, hormone levels and menstrual cycle phase.[8] It has been established by recent studies that increase in BPE is associated with increased risk of cancer.[9]

Our study was done to see correlation between mammographic breast density (MD) and background parenchymal enhancement (BPE) seen on breast MRI in patients with breast CA as well as to establish their relationship with other factors like receptor status, type of tumor and stage of tumor at the time of presentation in our population.

MATERIAL AND METHODS:

It is a retrospective cross-sectional study conducted at the Women Imaging Radiology Department, Shaukat Khanum Cancer and Memorial Hospital Lahore. Our study included a total 336 patients in a study duration of 3 years, from 01-January 2015 to 31-December 2019. A total 152 patients of breast CA diagnosed on histopathology of all stages for whom preoperative mammography, ultrasound and MRI breast had been acquired were included in our study. Patient who received any treatment like chemotherapy, radiotherapy or hormonal treatment in between the imaging were excluded. Also, the patients with history of previously treated breast CA and those with incomplete or missing report or any investigation were also excluded.

Breast MRI were performed on Philips 1.5 T MRI system with a dedicated 7 channel breast coil. Bilateral Breast examination performed while patient lying in prone position. After obtaining a three plane localizer, axial fat-suppressed T2-weighted fast spin-echo sequence and T1 weighted Fast Spin Echo sequence acquired consecutively. Gadovist (Gadobutrol) contrast was injected through an automated injector by following the access of ante-cubital vein at the dose of 0.1mmol/kg of body weight with flow rate of 3ml/sec followed by 20ml saline flush. Dynamic contrast-enhanced MRI examination including one pre-contrast and five post-contrast series. Sagittal Images of Right and left breast acquired by using Fat-suppressed T1 weighted Fast Spin echo sequence consecutively. The MRI images used for analysis in this study were maximum intensity projections (MIP) of the subtracted images of the first and last post-contrast image from the stack of dynamic series.

The interpretation on MRI was done by two experienced radiologists with a minimum of 5 years expertise in breast imaging. All the patients were reviewed in detail regarding radiological imaging including USG, mammography followed by MRI and histopathological analysis. The MD were divided into 4 grades from fatty to dense according to American College of Radiology.[10] Histopathological features of the index tumor including histological grade and size of tumor and nodal metastasis status were registered. The hormone receptors status was determined by Allered score. Three receptors including estrogen receptor ER, progesterone receptor (PR) and Human epidermal growth factor receptors were identified using immunohistochemistry. The findings obtained on MRI were correlated with the conventional imaging results. Lesion description was noted and on MRI, each lesion was classified according to Breast Imaging Reporting and Data System (BI-RADS) classification system. The enhancement of normal breast parenchymal tissue on immediate post contrast acquisition was regarded as BPE and it was categorized into four grades from minimal to mark. MRI of contralateral breast was also assessed in detail for BPE. Results were formulated using SPSS. Descriptive and inferential statistical tests were applied for data analysis.

RESULTS

Out of total 152 patients, 122 (80.3%) were premenopausal and 30(19.7%) were postmenopausal. The low number of postmenopausal patients is attributed to the institutional policy in which age criteria is prioritized. The age range was 20 to 70 years with a mean age of 40.8 years SD 10.8. The histological analysis revealed 110 (72.4%) patients with ductal CA, 28 (18.4%) with lobular CA and rest 14 (9.2%) patients had both ductal and lobular histological types. Similarly infiltrating CA was present in 104 (68.4%) patients, in situ was seen in 8 (5.3%) patients and both infiltrating and insitu types were seen in 40 (26.3%) patients. The results are explained in table 1.

			Menopausal Status			
			Postmenopausal		premenopausal	
			Count	Column N %	Count	Colum n N %
Type of Breast Cancer	Infiltrating	Ductal	8	33.3%	72	90.0%
		Lobular	12	50.0%	8	10.0%
		Ductal+ Lobular	4	16.7%	0	0.0%
	In situ	Ductal	0	0.0%	6	75.0%
		Lobular	0	0.0%	2	25.0%
		Ductal+ Lobular	0	0.0%	0	0.0%
	Infiltrating + In situ	Ductal	2	33.3%	22	64.7%
		Lobular	0	0.0%	6	17.6%
		Ductal+ Lobular	4	66.7%	6	17.6%

Table 1 : Type of Breast Carcinomas in relation to menopausal status.

Among all the premenopausal and postmenopausal patients, the moderately dense category C mammographic density was observed in 70 (46.1%) patients, followed by high density category D mammographic density in 60 patients (39.5%). Similarly, minimal BPE was seen in 70 (46.1%) patients as depicted in Table 2. The categories of MD were divided in low (category A and category B) and high (category C and D). The BPE categories were also divided into high (moderate and marked) and low grade (minimal and mild).

		Count	Column N %
MD	Entirely fatty cat A	0	0.0%
	Mild fibro glandular cat B	22	14.5%
	Moderately dense cat C	70	46.1%
	Highly dense cat D	60	39.5%
BPE	Minimal	70	46.1%
	Mild	48	31.6%
	Moderate	20	13.2%
	Marked	14	9.2%

Table 2: Count and percentage of MD and BPE in study.

		MD GRADE				BPE GRADE			
		High		Low		High		Low	
		Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %
Menopausal status	Postmenopausal	18	60.0%	12	40.0%	16	53.3%	14	46.7%
	Premenopausal	112	91.8%	10	8.2%	18	14.8%	104	85.2%

Table 3: Relationship of MD and BPE with menopausal status.

MGD and BPE grading results were observed in premenopausal and post-menopausal patients as shown in Table 3. It was seen that high MGD was seen in 60 % (18/30) patients and 91.8 % (112/122) premenopausal patients. A significant correlation was observed with a p value < 0.001 in premenopausal patients and they were more likely to have high Mammographic density. For BPE, 104/120 (85.2%) premenopausal patients have low BPE showing a significant correlation p<0.05.

Variables		MD GRADE					BPE GRADE				
		High		Low		P-Value	High		Low		P-Value
		Count	N %	Count	N %		Count	N %	Count	N %	
Size Of The Index Lesion On U/S And Mammogram	Less Than 2cm	40	26.3%	6	3.9%	0.122	10	6.6%	36	23.7%	0.405
	More Than 2 Cm Less Than 5cm	88	57.9%	14	9.2%		22	14.5%	80	52.6%	
	More Than 5 Cm	2	1.3%	2	1.3%		2	1.3%	2	1.3%	
	Occult Lesion	0	0.0%	0	0.0%		0	0.0%	0	0.0%	
Lesion Location And Laterality On Mammogram And U/S	Unifocal	84	55.3%	12	7.9%	0.002	18	11.8%	78	51.3%	0.07
	Multifocal Unilateral	8	5.3%	4	2.6%		4	2.6%	8	5.3%	
	Multicentric Unilateral	30	19.7%	2	1.3%		8	5.3%	24	15.8%	
	Bilateral	8	5.3%	2	1.3%		2	1.3%	8	5.3%	
	Occult Lesion Nodes Positive	0	0.0%	2	1.3%		2	1.3%	0	0.0%	
Malignant Nodes On U/S Or Mammogram	No Nodes	58	38.2%	8	5.3%	0.619	10	6.6%	56	36.8%	0.11
	Ipsilateral Nodes	70	46.1%	14	9.2%		24	15.8%	60	39.5%	
	Contralateral Nodes	2	1.3%	0	0.0%		0	0.0%	2	1.3%	
	Ipsilateral + Contralateral	0	0.0%	0	0.0%		0	0.0%	0	0.0%	

Table 4: Correlation of MD and BPE with different variables

The correlation among variables with BPE and MGD was established (table 4)

A significant correlation was seen among location of breast CA lesion and mammographic density (p=0.002). Rest of the variables were not affected by MD. The type of CA, size of tumor, location and laterality, present of malignant nodes show no correlation with high BPE.

Table 5 explains the relationship of MD and BPE with receptor status. Among receptor status, both ER and PR

showed a significant relation with high BPE and MGD whereas HER2 (p=0.12) status was not affected by grade of BPE. The patients with high MD were most likely to have ER and PR positivity (p=<0.05).

Parameters		MD GRADE					BPE GRADE				
		High		Low		P-Value	High		Low		P-Value
		Count	N %	Count	N %		Count	N %	Count	N %	
Estrogen Receptor	Negative	90	59.2%	4	2.6%	<0.0001	2	1.3%	92	60.5%	<0.001
	Positive	38	25.0%	18	11.8%		32	21.1%	24	15.8%	
	Not Done	2	1.3%	0	0.0%		0	0.0%	2	1.3%	
Progesterone Receptor	Negative	88	57.9%	8	5.3%	0.005	4	2.6%	92	60.5%	<0.001
	Positive	42	27.6%	14	9.2%		30	19.7%	26	17.1%	
	Not Done	0	0.0%	0	0.0%		0	0.0%	0	0.0%	
Human Epidermal Growth Factor Receptor Type 2	Negative	72	47.4%	14	9.2%	0.589	16	10.5%	70	46.1%	0.083
	Positive	48	31.6%	8	5.3%		18	11.8%	38	25.0%	
	Equivocal	6	3.9%	0	0.0%		0	0.0%	6	3.9%	
	Not Done	4	2.6%	0	0.0%		0	0.0%	4	2.6%	

Table 5: Relationship of MD and BPE with Receptor status

Variables		MD GRADE					BPE GRADE				
		High		Low		P-Value	High		Low		P-Value
		Count	N %	Count	N %		Count	N %	Count	N %	
Name Of CA Ductal / Lobular	Ductal	98	64.5%	12	7.9%	0.06	16	10.5 %	94	61.8%	0.00026
	Lobular	20	13.2%	8	5.3%		14	9.2%	14	9.2%	
	Ductal+Lobular	12	7.9%	2	1.3%		4	2.6%	10	6.6%	
Type Of CA	Infiltrating	86	56.6%	18	11.8%	0.117	26	17.1 %	78	51.3%	0.241
	In Situ	6	3.9%	2	1.3%		0	0.0%	8	5.3%	
	Infilterating + In Situ	38	25.0%	2	1.3%		8	5.3%	32	21.1%	

Table 6: Correlation of MD and BPE with Breast cancer type.

POSTMENOPAUSAL PATIENTS		BPEGRADE				
		High		Low		P value
		N	Column N %	N	Column N %	
MDGRADE	High	4	25.0%	14	100.0%	<0.001
	Low	12	75.0%	0	0.0%	

PREMENOPAUSAL PATIENTS		BPEGRADE				
		High		Low		P value
		Count	Column N %	Count	Column N %	
MDGRADE	High	12	66.7%	100	96.2%	<0.001
	Low	6	33.3%	4	3.8%	

Table 7: Correlation of BPE and MD grade with Menopausal status

In Table 7 the BPE grade was compared with MD grade in pre-menopausal and post-menopausal patients, and it showed a significant correlation.

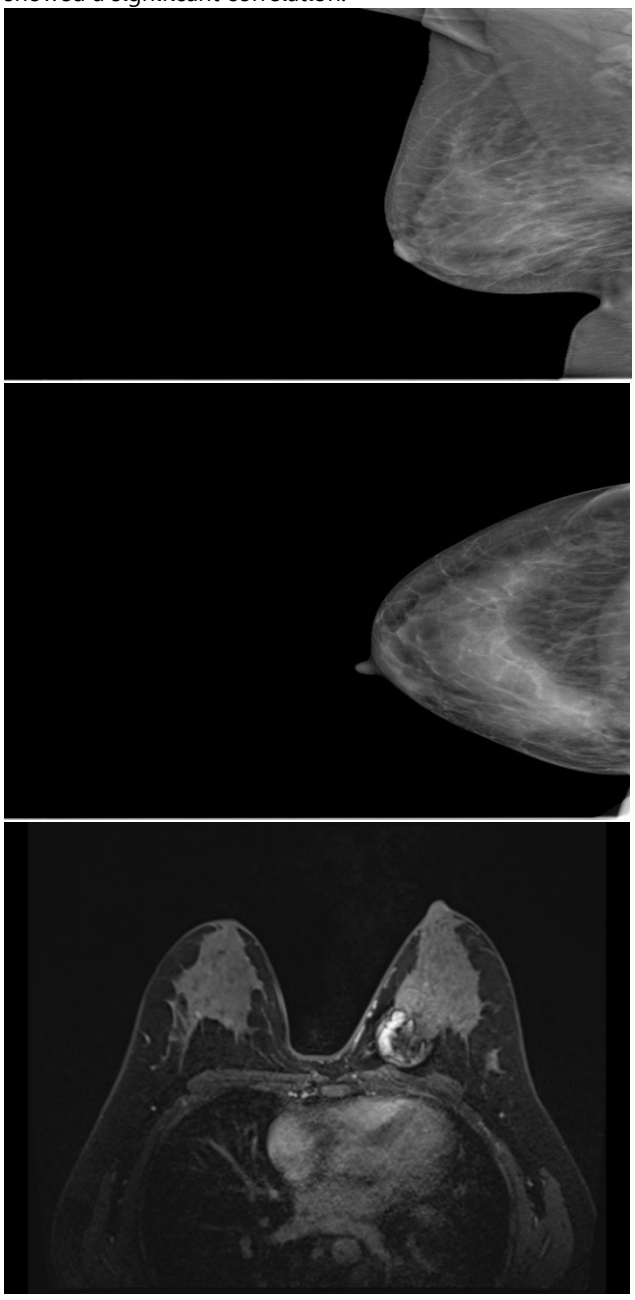

Figure 1: Image (a) and (b) Left breast mammogram CC and MLO views of a 40 year old premenopausal woman show markedly dense breast parendenchyma which leads to partial obscuration of the lesion. The lesion is difficult to visualize yet can be noticed at upper inner quadrant more appreciated on MLO view. Image (c) Show immediate post contrast T1 fat-sate axial image to look for BPE, we can appreciate that only minimal BPE is noted in this particular case.

DISCUSSION:

High Mammographic density is a major risk factor for the development of breast cancer. Also, it has a strong masking effect when it comes to the detection of small sized breast tumors.[11, 12] MRI is used to measure breast tissue density accurately. Normally BPE is increased in patients undergoing hormone replacement therapy or in lactating mothers due to increased fibroglandular tissue. However increased BPE is considered an independent risk factor for breast cancer[13] In our study we have correlated various factors with MD and BPE to determine significant difference among these. Our study revealed that menopausal status can play a significant role in developing Breast CA as it has significant association with high grade mammographic density and BPE as well. In a study done by Arsalan G, causes of raised BPE were evaluated that depicted a positive correlation with increased age hence needs to be observed closely. In premenopausal women, BPE was associates with hormonal status mainly.[14] Estrogen is considered to increase the vascularity and permeability of the blood vessels and results in BPE enhancement.[15, 16]

The type of breast CA, either ductal or lobular, has no significant correlation on mammographic density according to our study. However, the majority of patients with ductal CA have low BPE grade depicting a significant correlation. A study done by Suzaan Vreeman et al concluded that in the patients with unliteral breast CA, lower BPE in contralateral breast has direct association with high grade tumor.[17]

However, a study done by Valden V. et al investigated patients with invasive unilateral breast CA, and suggested that parenchymal enhancement in contralateral breast has significant association with the long-term outcome of the disease and has a predictive role especially when combined with receptor status.[18]

Other tumor characters including in situ or infiltrating nature of tumor and size of the lesion seems to have no direct correlation with parenchymal enhancement according to our results. Similarly, we assessed nodal status in all the patients and stratified them as patients ipsilateral, contralateral or no nodal involvement. The nodal involvement has no effect on BPE according to our study. A study done by Kim J Y et al also suggested that tumor size less than 2 cm has no correlation with BPE, however the tumors with more than 2 cm in size were associated with high BPE and may affect the size estimation of lesion.[19]

Hormonal status of receptors in the breast tissue has always been under discussion. Higher BPE and MD are associated with increased proliferative activity of the tumor. It has been postulated that exposure to hormones influence the BPE grade and thus is associated with increased risk of breast CA. Our study has depicted a positive correlation between increased MGD and high BPE with both estrogen and progesterone receptors. It explains that high estrogen and progesterone receptors are associated with increased BPE hence leading to increased risk of breast cancer. However, the Her 2 receptor has shown no significant association. Previous studies have shown variable results in this regard. Few studies have shown no association between estrogen receptor and BPE grading.[20, 21]

Interestingly one of the studies, done by Aiello EJ et al has shown that the relationship between high grade BPE and ER can be reverted by correcting the BMI.[22] This association between low grade tumor and receptor positivity has been shown in various studies. This explains the positive correlation between BPE and estrogen, progesterone receptor.[23] Contrarily, the increased expression of hormone receptor associated with increase BPE is related to increased risk of breast cancer.[24] This might explain that the pathogenesis of low grade and high-grade breast tumor is different. Positive correlation between progesterone receptor and high BPE has also been established in previous studies.[25] The expression of HER 2 in breast cancers has shown no significant correlation with BPE and MGD grade in our study. Previously many studies have shown the relation of HER-2 expression and decreased expression of BPE, however there is a need to further evaluate the relation between these entitites.[26]

In our study, there is a significant association between BPE and MD grade ($p<0.001$) regardless of the menopausal status. It implies that the patients with high MD grade should be subjected to MRI for accurate assessment. However previous studies have shown controversies in this regard. A study by Ko Es et al (2011) [13] found no significant correlation between BPE and MD. Contrarily, few studies have shown direct association between both entities.[27] Lately it has been described that high grade BPE is associated with high risk of breast cancer and can be used as an independent risk predictor of the disease.[28]

CONCLUSION:

BPE has been proved as a useful predictor of increasing risk of breast cancer. It can be used as an independent predictor of breast CA and can be combined with several other factors to enhance its predictive value. Particularly if used with hormonal expression and imagining characteristic of the tumor, it can be used as a novel entity for screening of breast cancer. This will help to choose a better treatment strategy for affected females and can also lead to adopt preventive measures before proceeding to invasive prophylactic methods.

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Archives of Surgical Research | Invited Review

Recent Advances In Treatment And Radiation Therapy Of Breast Cancer

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IMPORTANCE This review of literature will cover the recent advances in treatment of breast cancer. It will cover the molecular subtypes of breast cancer and treatment advancements in each subtype of breast cancer precisely. The role of neoadjuvant chemotherapy and advances in surgical techniques will also be discussed. One major aspect of breast cancer treatment is management of axilla, recent studies about axillary management will also be discussed. At the end there will be brief description about modern radiotherapy treatment schedules and techniques.

KEY WORDS Breast cancer, Estrogen Receptor, Progesterone receptor, Chemotherapy, human epidermal growth factor receptor 2, Radiotherapy.

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Invited review

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Worldwide, breast cancer is the most frequently diagnosed cancer and second leading cause of cancer deaths in women[1]. One of the major challenge in breast cancer treatment is its heterogeneous nature of disease each having different treatment options[2]. In last few decades treatment of breast cancer has evolved a lot mainly due to advances in surgical techniques and development of new systemic treatment options[3]. In addition to this there are also many improvements in the field of radiation oncology [4].
Previously breast cancer was considered as surgical disease but now due to recent advances in treatment options it is no longer solely a surgical disease. A better knowledge of tumor biology has led to the development of new therapeutic options resulting in better treatment outcomes. Less morbid surgery in carefully selected patients with modern conformal radiotherapy have resulted in the decreased treatment toxicity and better quality of life among breast cancer survivors.

MOLECULAR SUBTYPES OF BREAST CANCER

Breast cancer is now no longer considered as a single disease and can be classified into various molecular subtypesby evaluating few biomarkers. These biomarkers include the presence of hormone receptors mainly Estrogen receptors [ER] and Progesterone receptors [PR] and over expression of human epidermal growth factor rector 2 neu (Her2neu) receptors. This sub categorization helps to direct adjuvant therapy and also choose the patients who may get benefit maximum from neoadjuvant treatment.

Subtype	Type of treatment	Notes
Luminal A-like ER-PR +ve Her2 -ve Low proliferation rate [Ki-67]	Endocrine treatment alone in most of cases if tumor size is less than 5cm and less than 4 nodes positive.	Chemotherapy can be considered in selected cases (high 21-gene RS, high risk on 70-gene assay or high grade disease)
Luminal B-like (HER2 negative) ER-PR +ve Higher Ki-67than Luminal A	Endocrine treatment in all cases, Chemotherapy for most.	
Luminal B-like (HER2 positive) ER-PR +ve Higher Ki-67than Luminal A	Chemotherapy + anti-HER2 therapy +endocrine therapy	Better to consider for neoadjuvant treatment especially in locally advanced cases.
HER-2 positive (non-luminal) ER-PR -ve	Chemotherapy + anti-HER2 therapy	Better to consider for neoadjuvant treatment especially in locally advanced cases.
Triple negative (ductal) ER-PR-HER2 -ve	Chemotherapy	Better to consider for neoadjuvant treatment especially in locally advanced cases.
Special Histological Types		
Endocrine-responsive	Endocrine therapy	Cribriform, tubular and mucinous
Endocrine-non-responsive	Chemotherapy	Apocrine,medullary ,metaplastic, adenoid cystic

Adapted and modified from Goldhirsch et al. (2013b)

ENDOCRINE TREATMENT FOR HORMONE RECEPTOR–POSITIVE BREAST CANCER

Tomoxifen is the historical standard treatment for breast cancer .The EBCTCG Mata analysis showed data of 15 years from multiple trails including more than 80,000 patients[5]. 5 years of tomoxifen administration resulted 41% reduction in disease recurrence (Hazard Ratio (HR) 0.59) and 34% reduction in disease recurrence (HR0.66).ATLAS trail compared 10 year versus 5 year of adjuvant tomoxifen and showed better overall survival (OS) and disease free survival (DFS) with longer treatment. Based on the result of this trail 10 year tomoxifen can be considered as standard in premenopausal patients[6].

In post-menopausal patients aromatase inhibitors (AI) improved the results as compared to tomoxifen.AI treatment has been investigated as first line therapy instead of tomoxifen[7] or subsequent treatment after 2-3 years completion of tomoxifen therapy[8] and as extended treatment after 5 years completion of tomoxifen[9]. In every scenario, the use of an AI has resulted in moderate improvements in DFS by reducing incidence of distal and local failure rates.

Some of the hormone-positive breast cancer patients have progressive disease during the hormonal treatment. Combining endocrine therapy with targeted treatments inhibiting other important cell regulatory pathways has proven a useful strategy for enhancing the efficacy of endocrine treatments. Cyclin dependent kinase 4/6 (CDK4/6) inhibitors have been studied in combination either with AIs as upfront treatment for hormonal positive metastatic breast cancer or with fulvestrant as second-line treatments. In both settings, addition of CDK4/6 inhibition dramatically improved the progression-free survival compared to outcomes for endocrine therapy alone [10, 11].

GENOMIC TESTING OF BREAST CANCER TO AVOID CHEMOTHERAPY

Recently, multi-gene signatures have been used to distinguish between patients with high, intermediate or low-risk of disease recurrence. The 21-gene assay (Oncotype DX®) has been shown to estimate the likelihood of recurrence in women with early-stage hormone positive breast cancer (tumor size less than 5 cm and maximum 3 nodes positive) were treated with hormones alone without chemotherapy [12]. The 70-gene assay (MammaPrint®) is used to estimate the risk of recurrence of early breast cancer (tumor size less than 5 cm and maximum 3 nodes positive). Results from different studies using these assays have shown that subsequent subset of patients will not receive chemotherapy that otherwise may have been planned for chemotherapy on the basis of pathological findings [13].

TARGETED TREATMENT FOR HER2-NEU EXPRESSING BREAST CANCER

HER2 expression was historically considered as poor prognostic factor associated with poor outcome of this subgroup. In 2005, results from various randomized trials that examined addition of trastuzumab (Herceptin) to the chemotherapy as adjuvant treatment for HER2-expressing breast cancer it showed marked improvements in DFS (overall reduction of 50%) and OS[14]. The standard duration of trastuzumab treatment is 1 year. Although short course (9 weeks) treatment of trastuzumab given with adjuvant chemotherapy is better than omitting trastuzumab in non affording patients[15].

Women with higher risk, typically stage II or III, HER2-positive breast cancers may get benefit with additional anti-HER2 therapy. The benefit seen with dual HER2-directed therapy resulted in evaluation of pertuzumab in the neoadjuvant setting. In NeoSphere trial 417 patients were randomly assigned to receive four cycles of docetaxel combined with either trastuzumab, pertuzumab, or both agents versus combination pertuzumab and trastuzumab without docetaxel (a non chemotherapy arm). The combination pertuzumab and trastuzumab with docetaxel achieved the highest pathological complete response (pCR)rate of 39.3%, compared with the other groups[16]. This trial, as well as the TRYPHAENA study[17] combined with the survival advantage seen with pertuzumab in the metastatic setting, led the FDA to give accelerated approval of this combination for neoadjuvant treatment of HER2-expressive breast cancer[18].

TRIPLE NEGATIVE BREAST CANCER, CURRENT TREATMENT OPTIONS

Triple negative breast cancer (TNBC) is more aggressive and have less treatment options as compared to Hormonal receptor positive (HR+) and HER2+ breast cancer. For TNBC main stay of treatment is chemotherapy. TNBC has higher response rate to chemotherapy as compared to hormonal positive disease. However, their recurrence and distal failure rates are more than other subtypes[19]. The overall median survival for patients with metastatic TNBC is about 12 months with standard available chemotherapy agents. The unavailability of targeted therapies like in other subtypes is associated with this poor outcome. The widely used systemic treatment option is only chemotherapy[20] with or without bevacizumab. The immunotherapy may be the future treatment option for triple negative breast cancer. Recently Tecentriq (atezolizumab) in combination with the chemotherapy medicine Abraxane (albumin-bound paclitaxel) has been approved for the treat of unresectable locally advanced or metastatic triple-negative and PD-L1-positive breast cancer[21].

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy is day by day becoming more popular in the patients with locally advanced breast cancer[22]. Such treatment approach has resulted in more breast-conserving therapy as compared to post-operative chemotherapy[23] and may reduce the need for more aggressive axillary nodal surgeries[24]. Benefit of neoadjuvant chemotherapy includes in vivo response assessment. Neoadjuvant chemotherapy is now preferably used in HER2-positive, or triple-negative cancers due to their higher response rates and pathological complete responses. Despite of these benefits, however neoadjuvant chemotherapy has not shown survival benefit over adjuvant chemotherapy in trials[25].

LESS-EXTENSIVE SURGERY FOR SELECTED PATIENTS

With the wide-spread use of breast screening and awareness programs led to detection of early breast cancer in these cases complete mastectomy or complete axillary dissection can be avoided, hence long-term treatment morbidity is minimized[26].The follow-up results of various clinical trials have shown that breast-conserving surgery combined with radiotherapy has an outcome similar to total mastectomy in terms of survival. In modern era, nearly 40% of all breast cancer patients can receive breast-conserving treatment, which resulted in better psychological outcome in this group of patients as compared to patient undergoing complete mastectomy. The advent of sentinel node biopsy has also led its use in clinically node negative tumors and carefully selected node positive cases after neoajuvant treatment, thereby reducing incidence of lymphedema which is one of the major treatment complications in breast cancer survivors[27].

Women who have strong wish for breast conserving therapy (BCT) but are not ideal candidates for the BCT due to tumor to breast size ratio, or who have locally advanced breast cancer (LABC), can be considered for neoadjuvant therapy. The class of patients most likely converted is having unicentric, higher grade, HER2-positive, or triple-negative cancers because these cancers are excellent responders to neoadjuvant treatment. Ultrasound guided percutaneous clipping should be done before starting of treatment to localize tumor bed accurately in cases where there is adequate of clinical response.

For patients with early breast cancer who are candidates of total mastectomy due to multifocal nature of disease, total skin-sparing mastectomy with conservation of the nipple areolar complex has shown similar results in local control. This approach will result in immediate breast reconstruction and will maximize the cosmetic results. Now days this approach is gaining popularity in patients who fulfill the selection criteria for this approach[28].

MANAGEMENT OF AXILLA

Surgical management of axilla is part of the local treatment of breast cancer. Extent of axillary surgery has decreased over time due to understanding that removal of axillary nodes has more of a prognostic than a therapeutic value. Following are some basic principles guiding axillary nodal management in patients not undergoing neoadjuvant therapy.

1. Most women with clinically negative axilla are candidates of Sentinel lymph nodal biopsy (SLNB). If sentinel node is negative no more dissection is required.
2. A substantial proportion with limited axillary involvement no longer requires complete Axillary lymph nodal dissection (ALND, level l and level ll).The American College of Surgeons Oncology Group (ACOSOG) Z0011 trail showed patients with clinical T1 or T2 lesions and clinically node negative axilla, and one or two positive sentinel nodes treated with lumpectomy followed Whole breast radiation with tangents fields and adjuvant systemic treatment, SLNB was non inferior to ALND [29]. ALND should be done in patients whose tumors do not fit Z11 criteria, who will not receive radiation or sentinel lymph identification is not possible.
3. In AMAROS (After Mapping of Axilla Radiotherapy or Surgery) patients with T1-T2 tumors and clinically negative nodes but sentinel positives nodes were randomly assigned to axillary surgery or radiation. Most patients have one positive sentinel node .Both patients treated with lumpectomy and mastectomies were enrolled. In this study local control was excellent in both arm but lymphedema incidence was lower in radiation arm[30]. Therefore omission of axillary dissection can be considered if axillary radiation is in plan.
4. Patients who are candidates for neoadjuvant chemotherapy patients with clinically negative axilla can undergo sentinel nodal surgery after completion of chemotherapy[31]. If sentinel nodes are negative no more axillary surgery is required.
5. Patients will palpable nodes will require axillary nodal dissection unless they receive neoadjuvant systemic treatment[32]. About 40 % of clinically palpable nodes initially will downstage with neoadjuvant chemotherapy. The likelihood of down staging of axilla with neoadjuvant chemotherapy is higher in patients with TNBC or Her2neu positive breast cancer for which this approach is particularly favored. But this approach should be individualized after discussing in multimodality meetings.

HYPO FRACTIONATED POST-MASTECTOMY RADIOTHERAPY

Multiple randomized studies compared the normal fractionated radiotherapy protocols (25Gy in 2.0 Gy single doses) with hypo fractionated radiotherapy protocols (single doses more than 2.0Gy in 5–16 fractions). Overall, hypo fractionated radiotherapy protocols did not differ with normal fractionated radiotherapy in term of local control, toxicity profile and cosmetic results[33, 34].

ACCELERATED PARTIAL BREAST IRRADIATION

The average time of adjuvant radiation is between 4-6 weeks and for some patients from distant areas this approach is not feasible. So for this purpose, a variety of accelerated options of treatment have been developed and have been shown safe and effective in various trails [35].These approaches include interstitial implants placed around the tumor bed, a single balloon catheter that can be afterloaded with a central radiation source (MammoSite) that is placed into the excision cavity, external beam conformal partial breast irradiation, and intraoperative single-dose irradiation.

BOOST THERAPY AFTER WHOLE BREAST RADIATION

Several randomized trials have proved that an application of a localized dose escalation (boost) Of 10-16 Gy to the tumor bed after whole breast radiation improves local control but with poor cosmetic outcomes [36].Generally boost is given after breast conservation surgery and T4 or margin positive disease after Mastectomy. Boost can be omitted after breast conservation surgery for very small tumor sizes like <2cm excised with good margins >1cm particularly in old age hormonal positive cases.

HEART SPARING BREAST RADIOTHERAPY

With the advent of modern radiotherapy techniques, the knowledge for cardiac toxicity of breast cancer radiotherapy has increased significantly especially in left sided tumors .A recent guideline by the German radiation oncology society[37] recommends a dose constraint of less than 2.5Gy for the mean heart dose for chest wall radiotherapy .Modern radiotherapy techniques like intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) techniques can be used to reduce mean heart radiotherapy dose in order to minimize cardiac side effects.

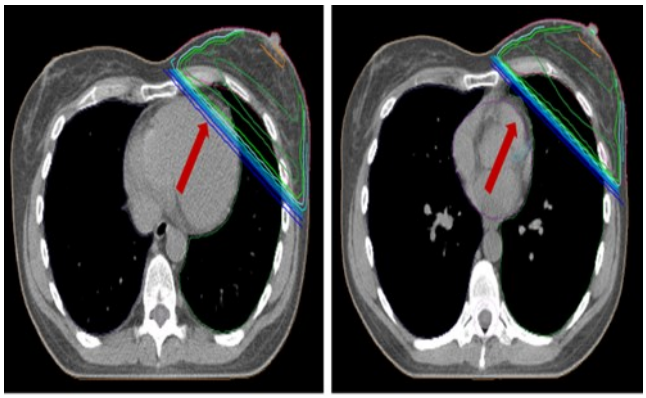

Figure: Sparing of heart volume in deep inspiration breath holding Technique (right) as compared to normal breathing (left) [38].

CONCLUSION

Over all like other cancers treatment of breast cancer needs a multidisciplinary approach. Participation of breast surgeons, medical and radiation oncologists in breast specific tumor boards can lead to much improvement in patient management. Fast growing research and with the better understanding of disease biology has given multiple treatment options even for stage 4 disease and improved overall survival in all stages of breast cancer.

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Early Breast Cancer Management following ESMO Guidelines: An Overview

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IMPORTANCE Breast cancer is the most prevalent cancer among women and rarely in the male population. With the advent of breast screening programs across the globe, early cancer detection is being done and the patients are increasingly being managed through breast conservation. National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) have provided guidelines to follow to effectively diagnose and amicably manage the cases of early breast cancer with the aim of reduction in mortality rate and enhancing disease-free survival outcomes. This review provides an overview of the management of early breast cancer in light of ESMO Guidelines and the local perspective.

KEYWORDS Early breast cancer, ESMO guidelines, mammography, mastectomy, breast conservative therapy, radiotherapy

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Review Article

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The data shown by WHO breast cancer is the most prevalent type of cancers among women, with the incidence of 25% of all female cancers in the world. According to International Agency for Research on Cancer, 2016, breast cancer is the fifth leading cause of death from cancer[1]. Incidence of breast cancer in women of early age (less than 40 years) is rather very uncommon in developed countries, it is gathered that 1 in 68 women can have breast cancer before the age of 40 years and 1 in 220 women will have breast cancer before the age of 30[2,3]. The incidence of early breast cancer in women less than age 50 years has been increased 0.2% per year since the mid-1990s[3], for women less than 40 years age there is very limited data that shows this trend[4,5]. In an analysis based on a surveillance, patients with less than 30 years age or between 30-39 years face more aggressive breast cancer and have less breast cancer specific survival than patients from age group of 40-59 years[6]. In 2018, there was around 2.1 million newly diagnosed breast cancer cases of females worldwide, approximating for one in four cancer cases among women[7].

Risk factors of early breast cancer are: positive family history causing genetic predisposition, hormone replacement therapy, and exposure to estrogens, higher breast density, low parity, ionizing radiation and history of atypical hyperplasia. Consumption of alcohol, obesity and western style food can also be the influencing factors to increased incidence of breast cancer[7].

Due to improved treatment standards and early detection of the breast cancer the mortality rate has decreased significantly especially in younger age groups, in most Western countries[8,9]. On the contrary, the prevalence of early breast cancer is rising due to improvements in treatment results and raised incidence. However, breast cancer remains one of the leading causes of cancer related deaths in women beside lung cancer, which has high mortality in women, in some countries.

Breast cancer in males is very rare, around 1% incidence rate. The important risk factors of it in males include positive family history, radiation exposure, hormonal imbalance disorders especially gynecomastia and cirrhosis and genetic predisposition[10].

METHODS

This systemic review is written according to PRISMA guidelines on early breast cancer management.

Search Strategy and Data Extraction:

All the literature was reviewed narratively for analysis. PubMed, ERIC, and Google Scholar from 1996-2021 were used as search engines for comprehensive study. Search terms were “early breast cancer” AND “ESMO guidelines for breast cancer” OR “Asian adaptations for ESMO guidelines” AND “breast cancer management”. Review of all search papers were conducted according to the selected search strategy. In addition, the reference search papers were also included for comprehensive literature review.

Selection Criteria and Quality Assessment:

450 articles were identified and their Abstracts were reviewed using the computer literature search of PubMed and Google scholars. 25 articles were excluded for duplication, remaining 425 articles were viewed and 58 articles related to the topic were included in this literature review. 9 full-text articles were assessed for eligibility and 37 articles were excluded on the basis of exclusion criteria. All papers from 2005 to 2021 were included. Exclusion criteria included duplicate articles, poster presentations, articles not related to the topic, articles on advanced breast cancer management, guidelines other than ESMO.

Data Extraction and Detailed Analysis:

Detailed analysis of each paper was done. Information about, name of the author, year of publication, country of origin, methods of study and themes are described in Table 1.

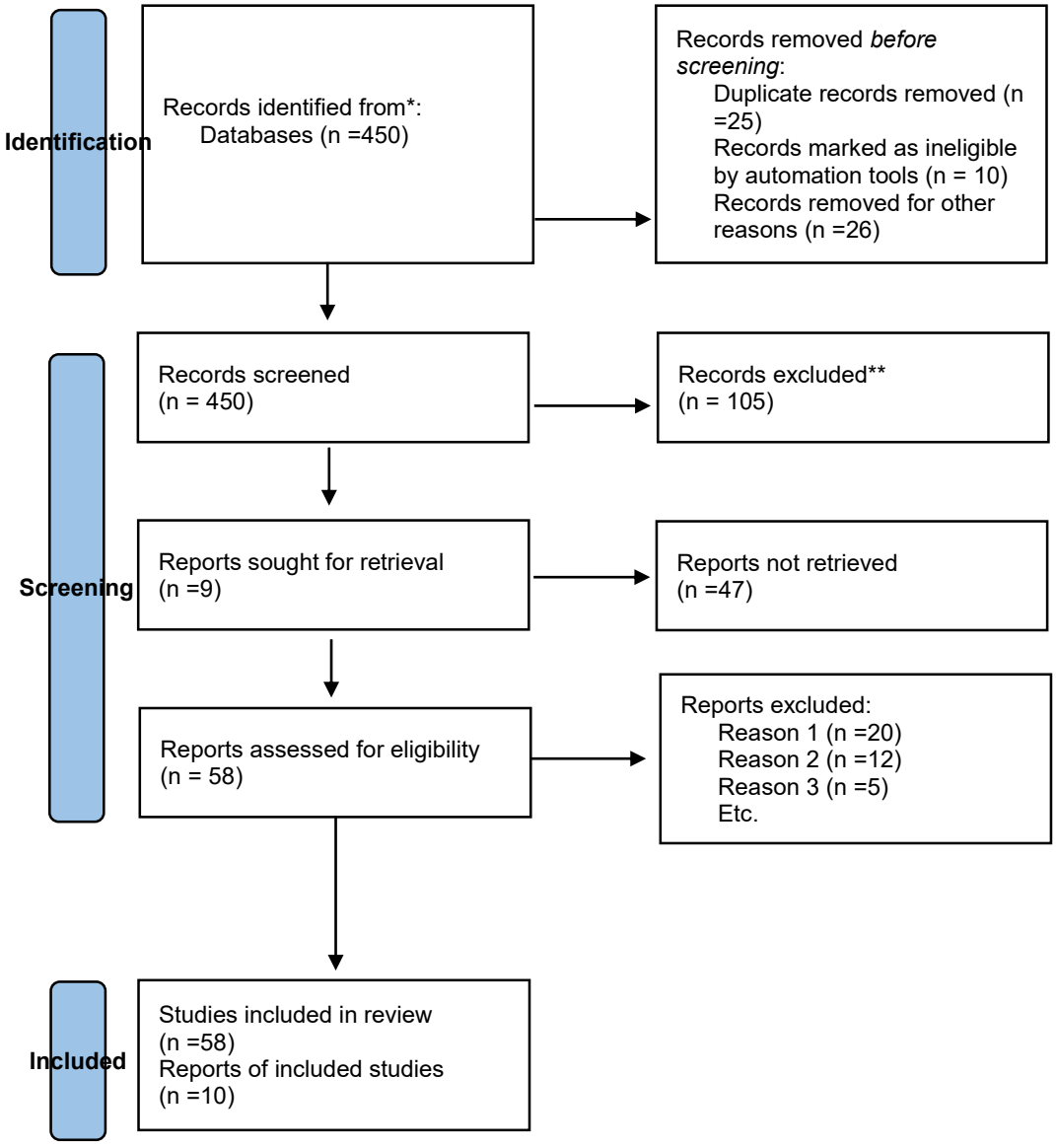

Figure 1: PRISMA Flowchart- Article selection process through computer literature search and analysis:

Year	Author	Country	Research method	Theme identified
2005	A. Goldhirsch et al.	Switzerland	Meeting highlights of primary therapy for breast cancer	Primary Therapy of Early Breast Cancer and their implications for patient care
2008	Sohee Park et al.	Korea	Systemic literature review	Breast cancer aetiology in Asia
2012	W. van de Water	Netherland	Data was obtained Netherlands Cancer Registry database between 2005 and 2008, for women with breast cancer.	Patients' adherence to breast cancer treatment
2012	Susan. harris et al.	Canada	Literature review via different data base search	Breast cancer rehabilitation need.
2011	Balman˜ a et al.	Spain	Literature review	BRACA mutation and screening in patient with breast cancer
2015	Senkus et al	Poland	Guidelines were developed in accordance with the ESMO standard operating procedures.	Early breast cancer staging and different ways for treatment.
2019	Cardoso et al.	Portugal	Literature reviews ESMO-MCBS was used to calculate scores for new indications approved by the EMA since 1 January 2016	Screening and treatment recommendations for early breast cancer
2020	Rudy Leon De Wild e et. Al	India	Literature review comparing different guidelines for invasive breast cancer	Restricted comparison of latest guidelines for different breast cancer guidelines
2020	Y.H Park	Korea	Operating guidelines for Asian women with early breast cancer	Pan Asian adaptations for early breast cancer management, ESMO-KSMO initiative
2021	Morgan et al.	United Kingdom	prospective, longitudinal, multicentre observational cohort study	Impact of omission of breast cancer surgery in older women with oestrogen receptor-positive early breast cancer on quality-of-life outcomes

Table 1: Various early breast cancer guidelines documents and their overview.

SCREENING OF BREAST CANCER ACCORDING TO ESMO GUIDELINES

For the detection of breast cancers at pre-clinical stage, population-based mammography screening needs to be introduced on national and regional level[10]. The ESMO guidelines recommend indicators and parameters that should be monitored during any screening process to ensure its quality and to reach an accurate diagnosis [11]. ECIBC (European Commission Initiative on Breast Cancer) has strongly recommended mammography screening for women aging from 50-69 years and conditional recommendations for women under this age group[11]. Effectiveness of mammography in women of 40-49 years of age is shown limited especially in age group 40-44 years but the greatest mortality reduction has been seen in the women of 50-69 years old age group[12]. IARC (International Agency for Research on Cancer) also concluded that in its breast cancer screening report in 2015[13]. There is no consensus about the effectivity of mammography on the reduction of mortality in breast cancer cases. Breast cancer mortality reduction of 20% was viewed in women of 50-70 years age group in a UK review of mammography screening trials[14]. Generalized awareness among population and mammography screening together with improved treatment contribute in overall reduction of the breast cancer. There is also controversy regarding the use of ultrasound (US) for breast cancer as a supplementary screening method.

For women with positive family history of breast cancer, with or without BRCA mutations, the recommendation is to get annual mammography with magnetic resonance imaging (MRI) as opposed to only mammography, to detect the disease at a more favorable stage. However, there is no proof showing the mortality reduction[15]. There is controversy on the use of US.

Recommendations:

• For the age group 50-69 years, annual or every 2 years mammography is recommended, it can also be done for women of age groups 40-49 and 70-74 but the evidence for benefit is less well established

• Annual MRI and annual mammography are recommendations for women with strong familial history of breast cancer, with or without BRCA mutations.

DIAGNOSIS AND PATHOLOGY

The diagnosis of breast cancer is based on history, clinical examination, imaging and further confirmed by pathological assessment after taking the biopsy. Clinical examination consists of bimanual palpation of breasts and regional lymph nodes and assessment of the distant metastasis for instance in bones, liver and lungs. A neurological examination is only done when the symptoms are present.

Imaging techniques include mammography, ultrasound and MRI. Mammography and ultrasound are always done bilaterally and regional lymph nodes are always assessed along them[16]. An MRI is not a routinely done modality but is considered only in certain circumstances which are following:

- Positive family history with positive BRCA mutations
- Lobular carcinomas
- Dense breast tissue
- Suspicion of multicentricity
- Large discrepancies between imaging and clinical examination
- Before administering neoadjuvant systemic therapy
- Inconclusive findings of conventional imaging
- In cases of breast implants

It is important to inquire the complete medical history, personal history, family history regarding any kind of carcinomas including breast or ovarian, menopausal status (if unconfirmed then measure serum estradiol and FSH levels) and complete physical examination.

After imaging, pretreatment disease evaluation consists of pathological screening of the primary tumor and histology of the lymph nodes if suspicion of their involvement is present.

Core needle biopsy should be done either by ultrasound or stereotactic guidance for the pathological diagnosis, it should be done before starting any kind of treatment. It is recommended that at least 2-3 core biopsies are collected, in case of multicentric tumors all lesions should be sampled. A marker in the form of surgical clip or carbon must be left into the tumour site at the time of biopsy, to make sure the resection of the correct site and to enable pathological assessment of the surgical specimen. The pathological report should include the histological type of the tumor, its grade, estrogen receptor (ER) status, and for invasive cancer immunohistochemistry (IHC) evaluation of PgR and HER2 expression.

In high-risk groups, genetic counselling and testing for BRCA1 and BRCA2 should be done, high risk groups would be;

- Patients with positive family history of ovarian, pancreatic and/or metastatic prostate cancer
- Breast cancer got diagnosed before 50 years of age
- Triple negative breast cancer (TNBC) diagnosed before the age of 60
- Personal history of ovarian cancer
- Male gender[17,18]

Recommendations:

- Bilateral mammogram and US of breasts and axillae should be done in all cases. MRI is recommended in certain cases following the standard imaging.
- Pathological diagnosis is based on the histology of the primary tumor and cytology of the axillary lymph nodes, if their involvement is suspected
- Histological type of the tumor, its grade, IHC evaluation of ER, PgR, HER2 and some form of proliferation markers e.g. Ki67 for invasive cancer should be present in pathological report
- TIL (Tumour-infiltrating lymphocyte) scoring is important and can be used to add information in patient's prognosis but the treatment should not be affected by it
- Genetic counselling and BRCA1 and BRCA2 germline mutations testing should be offered to high-risk group of patients

STAGING OF THE BREAST CANCER:

Breast cancer should be staged according to the eighth edition of the American Joint Committee on Cancer (AJCC) TNM (tumour, node, metastasis) staging system[19]. Asymptomatic distant metastasis is rare in case of breast cancer so most patients do not benefit from very extensive laboratory tests including tumor markers[20] and radiological staging. Recommended minimum blood work before surgery and systemic neoadjuvant therapy is complete blood count (CBC), liver function test (LFT), renal function test (RFT), alkaline phosphatase (ALP) and calcium (Ca2) levels. US, CT or MRI scan of abdomen, CT scan of chest and a bone scan are recommended for the patients of:

- Clinically suspected axillary lymph node involvement
- More than 5cm tumors
- Clinical suspicion of metastases
- Aggressive biology

In case of early breast cancer, the most important prognostic factors are expression of HER2, proliferation markers e.g. Ki67 and ER/PgR, the number of positive lymph nodes, histology of the tumor, its grade, size and presence of vascular invasion.

Clinical parameters like age, stage of the tumor, expression of HER2, PgR, and ER and histological grade have also been integrated into scoring systems for the sake of relatively accurate probability of recurrence and mortality from breast cancer. Examples of these scoring systems are NPI (Nottingham Prognostic Index), the PREDICT score and the computer program Adjuvant, which is currently unavailable[21–23].

The only validated predictive factors are ER/PgR and HER2 qualifying patients for endocrine therapy (ET) and ani HER2 therapy, respectively. Higher ER expression is usually associated with decreased absolute benefit of chemotherapy (ChT).

Recommendations:

• Staging of the breast cancer should be according to TNM staging system of AJCC.
• Extensive laboratory testing which includes tumour markers and radiological staging is not a necessity for all patients.
• Minimum blood tests including CBC, LFTs, RFTs, ALP and Ca2 levels are recommended before surgery.
• CT of chest, abdomen and bone scan is recommended only for higher-risk group patients (high tumour burden, aggressive biology, signs, symptoms or laboratory values suggesting the presence of metastases)
• Fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT scanning may be useful when conventional methods are inconclusive
• Pathological assessment of the post-operative surgical specimens is recommended to be made according to the TNM system
• Gene expression profiles may be used to complement pathological assessment and may help in decision making of adjuvant chemotherapy

TREATMENT:

1. General Rules:

Specialized units/care centers: Specialized institutions or departments that treat breast cancer patients in high volume approx. 150 new patients every year result in improved outcomes. These centers should be certified by accredited body. European Parliament and European Commission recommend the treatment of breast cancer patients in specialized units [24].

Recommendations:

• Breast cancer treatment should be in specialized centers where multidisciplinary teams should be present consisting of medical oncologists, radiation oncologists, breast surgeons, breast radiologists, breast pathologists and breast nurses and staff [24,25]
• Breast center should be able to refer patients to plastic surgeons, psychologists, physiotherapists and geneticists, upon requirement
• Breast nurse should be available to act as patient's navigator in specialized centers [24,25]

Patient's counselling and full disclosure: Upon hearing the diagnosis of breast cancer, patient finds herself/himself in gush of feelings which needs to be processed and rationally needs a plan to further move with the treatment. It generates different kinds of reaction in patients and this needs to be tailored according to each person's reaction. Patients need space to process the information about their diagnosis, so they can cope psychologically with the treatment plan.

Recommendations:

• Information on diagnosis and treatment should be provided repeatedly both verbally and in writing in easy and comprehensive language
• Reliable websites and sources of information are recommended
• All management decisions should actively involve the patient

Early breast cancer treatment is very complex and involve multiple modalities including surgery, radiotherapy, systemic anticancer therapies e.g. ChT, ET etc. Special attention should be paid to the very young or elderly patients. Younger patients should not be overtreated and older patients should not be undertreated. In younger demographic, possible fertility issues should be discussed and fertility-preservation techniques guidance should be provided [26–30].

Recommendations:

• Choice of treatment should be based on the size and location of primary tumour, number of lesions, extent of lymph node involvement and as well as the menopausal status, age, health status and treatment preference of the patient
• Age with other factors should be considered but should not be the sole determinant for withholding or recommending a treatment
• Premenopausal younger patients fertility-preservation techniques should be discussed before starting any systemic treatment

2. Local Treatment:

Surgery: Surgeons and patients both are more invested in breast conservation techniques for surgical point of view for more than 30years. Presently, in western Europe, 60-80% of cases of new breast cancers are amenable to breast conservation. For the subtypes which are highly sensitive to chemotherapy such as triple-negative and HER2 positive, a neoadjuvant approach should be preferred.
Mastectomy is still carried out in some patients due to:

• tumor size as compared to breast size
• multicentricity of tumor
• failed to get negative surgical margins even after multiple resections
• prior radiation exposure to the chest wall or breast
• oncoplastic breast conservation is not suitable
• patient's choice[31]

Breast Conserving Surgery (BCS): For breast cancer, BCS is considered the primary surgical choice. Achieving acceptable cosmesis is now emphasized and breast surgeons are trained to decrease the local impact of tumor excision on cosmetics by using tissue displacement techniques. Contrary to BCS techniques, there are rising number of breast cancer patients who are opting for bilateral mastectomy[32]. There is data showing that patients with early breast cancer who opt for BCS have better survival as compared to the ones having mastectomy [33–36].
According to the recommendations of the CAP (College of American Pathologists), status of the margin of the lesion should always be reported. In case of positive margin, the exact anatomic location of the positive margin should be specified. In case of negative margins, the distance of invasive cancer should be reported [37–39].
Tumor bed is marked with clips as a standard procedure to facilitate the accurate radiation boost, if indicated.
Recommendations:
• BCS maintain better cosmetic outcomes hence it's the preferred treatment modality in early breast cancer patients.
• It is essential to carefully assess the margins of the resection site. At the ink margin, no tumor is required and for in situ carcinoma more than 2mm resection is preferred

Mastectomy: There are three major types of mastectomy; simple mastectomy, skin sparing mastectomy (SSM) and nipple sparing mastectomy (NSM). NSM improves cosmetic outcomes for therapeutic and prophylactic surgeries also from an oncologist point of view it is considered to be safe in some patients[40,41]. In most women, the prospect of losing a breast is relatively easy when they get to know the option of immediate recnstruction[25]. Inflammatory breast cancer is the only reason to advice against the immediate reconstruction. After post-operative radiotherapy (RT), implant-based reconstruction may result in unfavorable aesthetic[42,43]. Temporary expander before RT may help post mastectomy radiotherapy (PMRT). There are multiple surgical options for breast reconstruction, among the autologous tissue flap repair, silicone gel implants are being used which are considered to be safe and have fewer problems regarding capsular rupture. Patient should be counselled regarding the risk of anaplastic large cell lymphoma in case of breast implant based reconstruction surgery. For the autologous repair, flaps can be taken from latissimus dorsi, transverse rectus abdominis or deep inferior epigastric perforator among others.
Recommendations:
• All females going through mastectomy should be informed and offered breast reconstruction.
• Except for the patients going through inflammatory carcinoma, immediate breast reconstruction should be proposed to all.
• For the optimal reconstruction, patient related factors and preferences should be taken into account

Axillary Management: In primary breast cancer, one of the strongest predictors for long term prognosis is axillary lymph node status. Axillary lymph node dissection (ALND) results in lymphedema[44,45]. Axillary clearance along wit RT to axilla increases lymphedema upto 40%. Whereas sentinel lymph node biopsy (SLNB) causes less shoulder stiffness which in turns allow less hospital stay.

Recommendations:
• In early and clinically node negative breast cancer, SLNB is considered the standard for axillary staging on the contrary to full lymph node clearance
• In case of positive SLNB, micro metastases or 1-2 positive sentinel lymph nodes, is to be treated with post-operative axillary RT instead of further axillary resection
• Irrespective the kind of breast surgery performed, radiation therapy to the axilla is recommended treatment with positive SLNB

Surgery for Intra-Epithelial Neoplasia: Intra-epithelial neoplasia or ductal carcinoma in situ (DCIS) is treated either by total mastectomy or BCS, main aim is to get clear resection margins. 2mm margin is considered adequate in case of DCIS with WBRT (whole breast radiotherapy) as the line of treatment [38], as it is associated with decreased recurrence and cosmetically improved results. SLNB is not required in case of DCIS as risk of a positive sentinel lymph node with pure DCIS is 7%–9% and most of the metastases found are micro metastases [46,47]. SLNB is only recommended in cases where risk of invasion is present.
Lobular carcinoma in situ (LCIS) unlike DCIS considered as a risk for future development of invasive cancer in both breasts and no active treatment is required.

Recommendations:
• Recommended treatment of DCIS is BCS followed by WBRT or total mastectomy
• a 2-mm margin is adequate in DCIS with WBRT after BCS
• SLNB is not a routine recommendation for DCIS apart from patients requiring mastectomy for large tumors

Management of occult breast cancer: Occult breast cancer is a tumor in absence of any primary tumor in the breast but present as a lymph node metastases. It consists of less than 0.5% of all breast cancer cases[48]. In order to exclude another primary tumour site PET-CT and MRI breast is done. Its treatment is by axillary lymph node dissection (ALND) however in case of low axillary disease burden axillary RT can be an option.

Recommendations:
• ALND and WBRT are recommended treatment options for occult breast cancer

Risk Reducing Mastectomy: BRCA1 mutation carriers have 65-90% risk of developing breast cancer with 10-year

risk of contralateral development of breast cancer is 25-31% [49].

Recommendations:
• Bilateral prophylactic mastectomy and reconstruction surgery is considered a risk reducing surgery in BRCA1and BRCA2 carriers
• Patients opting for bilateral mastectomy who fall in non-high risk group should be counselled for breast conservation as BCS has high survival outcomes

Radiotherapy:

Recommendations:
• After BCS post-operative radiotherapy is strongly recommended[50]
• In high risk of recurrence patients, boost RT is recommended to reduce the risk of relapse [51,52]
• For patients with a low risk for local recurrence, accelerated partial-breast irradiation (APBI) is recommended treatment option
• For patients having positive resection margins, involved axillary lymph nodes and T3–T4 tumours, post mastectomy radiotherapy (PMRT) is recommended[53]
• In patients with positive lymph nodes, comprehensive nodal radiotherapy is recommended line of treatment[54]
• Axillary RT is not recommended after ALND on the operation site of axilla[53]
• For routine postoperative RT for breast cancer 15–16 fractions of 3 Gy/fraction are recommended [55–57]
• DCIS diagnosed females who are treated with BCS, WBRT is recommended for them [58–60]
• Radiation therapy can be omitted in patients with low risk of DCIS, PMRT is not recommended in DCIS

3. Systemic (neo) adjuvant therapy:

General recommendations: Neoadjuvant therapy should be administered within 12 weeks post-operatively to obtain maximum benefit.

Recommendations:
• Adjuvant systemic therapy should preferably start within 3 to 6 weeks after surgery and neoadjuvant systemic therapy should begin after diagnosis and staging is completed within 2-4 weeks
• The use of chemotherapy (ChT) in luminal B-like HER2-negative patients depends on the individual risk of recurrence, the presumed response to endocrine therapy (ET) and the patient's preference.
• B-like HER2-positive light tumors should be treated with ChT, ET and anti-HER2. In some low-risk patients (T1abN0), the combination of anti-HER2 therapy and ET alone may be used, with the possible exception of selected very low risk cases, such as T1aN0 tumors
• If ChT and RT are to be used, ChT should generally precede RT. RT can be delivered safely during anti-HER2, ET and ChT treatment without anthracycline, taxane.
• Anti-HER2 treatment can be systematically combined with non-anthracycline-based ChT, ET and RT
• Patients with TNBC should receive ChT.
• ChT should not be used at the same time as ET, with the exception of gonadotropin releasing analogues (GnRH) used for ovarian protection [61]
• Tamoxifen for 5-10 years is standard of care for premenopausal women and if they become postmenopausal within the first 5 years of tamoxifen, a switch to letrozole should be considered, depending on the expected risk of late recurrence.
• Ovarian function suppression (OFS) during ChT offers some protection of ovarian function and does not negatively impact oncologic results and should be used with other methods of fertility preservation. OFS to ET should be strongly considered in patients requiring ChT who recover their periods within the first 2 years.

Chemotherapy:

• ChT is recommended in triple-negative, HER2-positive breast cancers and in high-risk HER2-negative luminal-like tumors and ER-negative tumors [62,63].
• ChT should be given in 4-8 cycles for 12-24 weeks. For low-risk patients, 4 cycles can be administered
• The sequential anthracycline / taxane regimen is the norm for the majority of patients.
• Four cycles of doxorubicin and cyclophosphamide (AC) are considered to have an effectiveness equal to 6 cycles of CMF. But should only be used if taxanes are contraindicated [64,65].
• For patients with cardiac complications, treatment regimens without anthracycline can be used.
• Non-anthracycline, taxane-based regimens (4 cycles of docetaxel and cyclophosphamide (TC)) may be used.
• read as an alternative to 4 cycles of anthracycline-based ChT but are less effective[66]
• 5 FU should not be included in anthracycline-based regimens as it increases the toxicity profile.
• Platinum compounds should not be used routinely in the adjuvant setting.
• The use of dose-dense regimens [supported by granulocyte colony stimulating factor (G-CSF)] should be considered, especially in highly proliferative tumors [67,68].

Anti-HER2 therapy:

• Trastuzumab combined with ChT is recommended in patients with positive HER2

Recommendations:
• The (neo) adjuvant trastuzumab is very effective and should be given to all patients with early HER2-positive breast cancer who have no contraindications to its use, with the possible exception of certain cases. at very low risk, such as T1aN0 tumors.
• One year of (neo) adjuvant trastuzumab remains the norm for the vast majority of HER2-positive patients. In low-risk patients who receive anthracycline / taxane-based ChT, the reduction in the duration of trastuzumab to 6 months can be discussed.

• Trastuzumab should generally not be given at the same time as anthracycline-based ChT; it can be safely combined with non-anthracycline-based ChTs (i.e. taxanes).
• Regular cardiac monitoring is mandatory before initiation and during treatment with trastuzumab.
• Double blocking with trastuzumab / lapatinib did not improve long-term results and therefore cannot be recommended.
• Double blocking with trastuzumab / pertuzumab may be considered in high-risk patients, defined as N-positive or ER-negative, for a period of 1 year, starting before or after surgery.
• If available, adjuvant trastuzumab should be replaced by adjuvant T-DM1 in the event of residual invasive disease after the end of neoadjuvant ChT associated with anti-HER2 therapy.
• Prolonged anti-HER2 treatment with neratinib may be considered in certain high-risk patients, with prophylaxis and management of diarrhea, not previously treated with double blocking.

Primary systemic therapy Or PST (neoadjuvant):

When mastectomy is necessary in locally advanced and large cancers, particularly due to the size of the tumor, PST is recommended to decrease the extent of surgery required. The timing of treatment (pre versus postoperative) has no effect on long-term results, apart from a possible small increase in locoregional recurrence in the PST group, but without impact on survival [69,70]

In selected patients with luminal tumors of type A and without indication of ChT, who are not candidates for optimal surgery, preoperative TE consisting of OFS plus an aromatase inhibitor may be considered[71]. ET is not routinely recommended in premenopausal patients.
• PST should be used to reduce the extent of surgery in locally advanced and operable cancers, especially when mastectomy is necessary due to the size of the tumor.
• In triple negative and BRCA positive patients, the platinum compound can be used.
• If PST is used, all ChT should be delivered preoperatively.
• In case of high-risk triple negative, 6 to 8 cycles of capecitabine postoperatively should be administered.
• In postmenopausal patients with ER-positive / HER2-negative cancer requiring preoperative PST TE (4-8 months or until maximal response) should be considered and continued postoperatively.

Bisphosphonates for early breast cancer:

• Prophylactic use of bisphosphonates in postmenopausal women or those undergoing SOF leads to prolonged breast cancer-specific survival [72–74].
• Bisphosphonates also decrease the risk of skeletal complications in treatment-related bone loss [75,76].

Treatment of male breast cancer:

Breast cancers in male patients are invasive ductal carcinomas of the luminal type. The indications and treatment regimens for ChT and anti-HER2 should follow the same recommendations as those for breast cancer in women.

Recommendations:

• The standard adjuvant ET for male breast cancer patients is tamoxifen. But if contraindicated, IA in combination with a luteinizing hormone releasing hormone (LHRH) agonist may be considered.
• AI alone should not be used as an adjuvant TE in men with breast cancer.

Adjuvant systemic therapy for DCIS:

In ER-positive DCIS, tamoxifen decreases the risk of non-invasive and invasive recurrence and reduce second primary (contralateral) breast cancer in conservatively treated patients. The same is true for patients who have undergone a mastectomy.

PERSONALIZED MEDICINE:

Most significant advancement in modern oncology is shift towards deep molecular analysis. The history of metastatic diseases is revolutionized by detection of gene mutations, amplification and fusions. The door to personalized medicine is opened due to focus on molecular alterations of tumor[77]. Providing best treatment is the most crucial task of personalized medicine. Use of endocrine therapy in luminal breast cancer coins it the pioneer of personalized medicine in oncology [77,78].

Systemic therapy through personalized approach requires identification of targets. Biomarkers including estrogen receptors, progesterone receptors and HER2 play a significant role as predictive factors in preparing patients for personalized treatment. Estrogen and progesterone receptors are used in selecting patients for endocrine treatment, while HER2 is used for antiHER2 therapy selection[78]. Ki67 maybe used in determination of prognosis due to its accessibility and effectiveness[79]. Breast cancer has four different molecular subtypes each one exhibiting distinct phenotypic presentations[80]. These phenotypic presentations are also used for definition of subpopulations and treatment individualization[78].

Tumor size, grade and nodal metastasis are not sufficient for treatment in early diagnosed cases. Hence, personalized medicine entails the use of molecular biomarkers [81]. Evaluation of uPA and PAI1 demonstrate tumor invasiveness and prognosis in both node negative and node positive cases [82]. Oncotype DX is a multigene signature test used to predict recurrence and benefit of adjuvant chemotherapy. MammaPrint test is also used to predict recurrence [81]. MammaPrint, Oncotype Dx, Prosigna, EndoPredict, and Breast Cancer Index are molecular signature tests for ER-positive breast cancer cases used in decision making of adjuvant chemotherapy especially in challenging cases including B-like/HER2-negative and node-negative/node 1-3 positive breast cancer [83].

FOLLOW-UP AND LONG-TERM IMPLICATIONS:

Follow-up of breast cancer patients is required to evaluate local recurrence, contralateral breast cancer and therapy related complications. Furthermore, it is required for patient motivation and psychological support. Node positive cases have higher annual recurrence than node negative cancers. In addition, estrogen negative cases have higher recurrence in first year than estrogen positive cases. However, its recurrence after 5-8 years becomes lesser than estrogen positive cases [84]. Risk of recurrence peaks in second year but in 5-20 years remains 2%-5%. In estrogen and progesterone receptor positive cases relapse can occur after 20 years [85].

Follow-up should constitute detailed history, physical examination, routine mammography, breast ultrasound and MRI in young patients with dense breast tissue or familial cases. There is no indication for laboratory tests, imaging tests or tumor marker evaluation in asymptomatic patients. However, in cases of endocrine therapy routine blood tests are indicated to rule out therapy related cardiovascular complications. Gynaecological examination in required in patients taking tamoxifen [86].

Lifestyle modification has a positive impact on prognosis. Regular exercise and nutritional counselling play a significant role in providing functional and psychological benefits [87]. Rehabilitation services play a vital role in decreasing negative impact of physical, psychological and social factors of breast cancer treatment. Physiotherapy should be directed towards prevention and treatment of lymphoedema and postural defect correction. Upon completion of chemotherapy, radiotherapy and antiHER2 therapy pregnancy maybe considered. There is no indication to avoid blood pressure monitoring or venesection following axillary clearance [78].

Psychological support is required following the end of adjuvant chemotherapy and radiotherapy due to increased incidence of depression and fatigue. In long-term survivorship social factors including work, family and sexuality are required to be addressed in follow-up.

Recommendations:

• Recommended follow-up visits include:
1. 3-4 months in first 2 years
2. 6-8 months from 3-5 years
3. Annual visit afterwards

• Annual imaging tests including bilateral and contralateral mammography, ultrasound and breast MRI.
• Laboratory tests, imaging tests and tumor markers are not indicated in asymptomatic patients.
• Lifestyle modification has a positive impact on prognosis
• Access to rehabilitation services
• Psychological support to address social factors associated with long term survivorship.

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Archives of Surgical Research | Review Article

Comparison Of NCCN And ESMO Guidelines In Locally Advanced Breast Cancer And Implications In A Resource-Constrained Healthcare Setting

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IMPORTANCE Locally advanced breast cancer has been associated with poor outcomes in developing countries because of the interplay of multiple factors. The management protocols of this disease are ever evolving. This article aims to compare NCCN and ESMO guidelines regarding the management of locally advanced breast cancer. The articles for comparative review have been taken from PubMed. The article reviews both protocols in domains of diagnosis, primary systemic therapy, surgery, radiotherapy, adjuvant therapy, and surveillance. Moreover, recommendations in special situations of pregnancy, male population, recurrence, and Covid 19 are mentioned. In addition, the applicability of these guidelines in a healthcare setting with limited tools has been analyzed.

KEYWORDS Locally advanced breast cancer. Primary systemic therapy, Neoadjuvant therapy, survival, Management, Epidemiology,

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Review Article

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Locally advanced breast cancer is an entity with evolving knowledge and management protocols. Breast cancer is the most common cancer diagnosed in females and accounts for the second-highest rate of cancer-related mortality in females[1]. Locally advanced breast cancer (LABC) contributes to 20% of cases of breast malignancy. In developing countries, the figures can be as alarming as 75%[2]. It has a five-year survival rate of less than 50%[3]. The rationale of this article was to compare current American and European algorithms for the management of locally advanced breast cancer. As Locally advanced breast cancer cases are on the rise in our region, this analysis would help us in devising management protocols for such patients in our region within the spectrum of available resources.

Locally advanced breast cancer encompasses the malignant tumors located within the breast tissue with locoregional spread. The sub-categories involve non-inflammatory and inflammatory breast cancer. According to AJCC-TNM (American Joint Committee on Cancer Tumor Node Metastasis), locally advanced breast cancer includes stage IIB(T3N0M0), and III. Thus, the spectrum includes:

- Tumors more than 5 cm in size with or without regional lymphadenopathy (N1–3)
- Tumors of any size with direct extension to the chest wall or skin, or both (including ulcer or satellite nodules), regardless of regional lymphadenopathy
- Presence of regional lymphadenopathy (clinically fixed or matted axillary lymph nodes, or any of infraclavicular, supraclavicular, or internal mammary lymphadenopathy) regardless of tumor stage
- Inflammatory breast cancer[4]

AJCC IIB and IIIA are considered operable and IIIB, IIIC are considered inoperable because of decreased chances of achieving Ro resection[5]. The clinical treatment of locally advanced breast cancer is complex and should be individualized[6]. The locally advanced breast cancer remains potentially curable with surgery, radiotherapy, and systemic therapy[7]. There has been an increasing trend towards utilizing primary systemic therapy in non-metastatic breast cancer to achieve control over occult systemic disease, obtain pathological complete response locally and decrease the extent of surgical tumor resection[8].

In the present article, we are reviewing recommendations in the NCCN and ESMO guidelines regarding operable and inoperable locally advanced breast cancer. In addition, we have rationalized the application of these protocols in our setup.

METHODOLOGY

After obtaining prior consent from the Institutional review board, we searched the updated NCCN guidelines version 4.2021 on breast cancer and ABC 5(Advanced Breast Cancer) guidelines from the 5th ESO-ESMO International consensus. In addition, we searched ESMO Clinical practice guidelines for Early breast cancer, locally recurrent and metastatic cancer, cancer, pregnancy and fertility, and 2nd ESO-ESMO International consensus guidelines to look for management options for operable locally advanced breast cancer . We

checked articles relating to the management of locally advanced breast cancer globally and in our region on PubMed to apply recommendations in constrained working situations like ours.

DISCUSSION

NCCN guidelines use categories 1, 2A,2B, and 3. Whereas, ESMO utilizes 5 levels of evidence and I to V and 5 grades of recommendation A to E.

The diagnostic algorithms in both guidelines revolve around the classic triple assessment regime. Genetic counseling is emphasized because 5% of breast cancers have BRCA mutations[9]. The lifetime risk of developing breast cancer in BRCA 1 mutation is 65 to 90%[10]. Both guidelines recommend the AJCC TNM system for clinical and pathological staging. ESMO guidelines include IIB and IIIA inoperable locally advanced breast cancer. NCCN guidelines, despite incorporating the dynamics of IIB, emphasize stage III to be referred to as locally advanced variety with IIIB and IIIC being inoperable ones.

Category	NCCN	ESMO
	History and Physical Exam, Diagnostic Bilateral mammogram, breast, and axillary ultrasound if necessary, with Core biopsy of tumor or lymph node. Pathology review of biopsy tissue with ER, PR, and HER 2 neu status and proliferation/grade. CT Chest, Abdomen +/-pelvis, and Bone scan CBC and a comprehensive metabolic panel including LFTS because of the need for neoadjuvant systemic therapy PET-CT is utilized if there is doubt in the findings of other imaging regimes. Cardiac imaging if chemotherapy is planned	Same recommendations. Emphasis on the categorization of Ki 67 status for luminal type cancers.
Genetic Risk assessment	Recommended in high risk, high probabilities, and family history categories	Endorses NCCN guidelines
Fertility and Sexual Health	Fertility and sexual health counseling mandatory	Same recommendation
Distress management	Required	Special emphasis on psychosocial support
Pregnancy Testing	Mandatory workup in premenopausal women	No clear statement

Table 1: Diagnostic and pretreatment workup

Regarding the pregnant population, both guidelines emphasize going for mammograms with shielding and ultrasound of the breast and axilla. FNA of the lesion is an acceptable option to the standard core biopsy. Ultrasound of abdomen, X-ray chest and CBC with differential and Liver function is undertaken. MRI thoracolumbar spine can be considered in cases of symptoms or equivocal imaging.

Category	NCCN	ESMO
Inoperable locally advanced breast cancer	T4 tumors	III B and IIIC
	N3 nodal disease	
	Bulky or matted N2 Axillary nodes	
	IBC	
Operable Locally Advanced Ca Breast	Large primary tumor relative to breast size in a patient wishing breast conservation	IIB and IIIA
	HER 2 +ve tumors and TNBC, if T>2 or N >1	
	Patients in whom definitive surgery may be delayed	
Monitoring of patient during therapy	Clinical and imaging if indicated	Same recommendation
Progression of disease during therapy	Alternate drug regime or Surgery	Same recommendation
Therapy not recommended in	i) Patients with ill-defined extent invasive carcinoma	No clear statement
	ii) Patients with the poorly delineated extent of tumor	
	iii) Non-palpable or clinically assessable tumors.	

Table 2: Indications of Primary systemic Therapy in LABC

Treatment protocols

Both guidelines endorse primary systemic therapy where possible in locally advanced breast cancer because it has been able to achieve a pathological complete response. This has been associated with extremely favorable disease-free and overall survival in locally advanced breast cancer patients11. In addition, it provides time for genetic testing and planning breast reconstruction. The primary systemic therapy also opens new avenues of research and development of refined management strategies for cancer breast. The chemotherapeutic regimes are similar with anthracyclines and taxanes being the recommended first-

line drugs. The neoadjuvant systemic therapy is the cornerstone in the management of inoperable variety. For the operable variety in which upfront surgery has the highest chances of achieving negative resection margins, decisions to give neoadjuvant systemic therapy should be balanced in terms of achieving breast conservation therapy versus ending up in mastectomy and tumor biology.

Primary Systemic therapy protocols for locally advanced breast cancer: Both guidelines endorse a multi-disciplinary approach for treatment decisions with stringent reviews regarding benefits and risks of a treatment option, patient preference, menopausal and performance status, and assessment of comorbidities. In addition, previous therapies with toxicity profile, disease-free interval, tumor burden, biologic age, socio-economic, psychosocial factors, and available therapies in the patient's country all must be taken into consideration for individualizing treatment protocols. There has been increased stress in both guidelines to deploy aggressive treatment, if permissible, involving radiotherapy and chemotherapy, in high-risk individuals including the young, age < 50, increased tumor burden, T>5 cm and >1 to 3 positive lymph node. lymphovascular invasion, atypical and high-grade histology and with a history of hereditary breast cancer.

These guidelines recommend the placement of detectable clips or markers on the tumor bed and suspicious axillary nodes before starting systemic therapy for cancer. This facilitates localization for future surgery, radiotherapy, and pathology review. Both guidelines endorse sequential chemotherapy with anthracyclines and taxanes and recommend combination therapies for patients with rapid clinical progression, life-threatening visceral metastasis, or the need for rapid symptom/disease control. Luminal B-like with triple-negative HER 2 +ve warrant chemotherapy. Luminal A-type ER+ve has a good overall prognosis and hormonal therapy alone can be given in such cases in absence of high-risk features in selected populations considering co-morbidities. For instance, a 70 to 80-year-old woman with Luminal A variety of locally advanced breast cancer can be given hormonal therapy alone if she cannot tolerate chemotherapy. As most patients are in the advanced stage or high-risk category in both guidelines, chemotherapy is administered to almost all of ER+ve locally advanced breast cancers. Ovarian ablation/ suppression strategies include surgical oophorectomy, ovarian irradiation, and LHRH agonists in both guidelines.

Categories	NCCN	ESMO
HR Positive LABC	Chemotherapy +/- Endocrine therapy. Endocrine therapy may be considered for strong ER-positive disease (at least >10% +ve on IHC) based on comorbidities or low-risk luminal biology based on clinical characteristics and genomic signatures. Endocrine therapy for premenopausal women includes an Aromatase inhibitor with ovarian suppression or Tamoxifen. Aromatase Inhibitor is a preferred option for post-menopausal women.	Chemotherapy with anthracycline- and taxane or endocrine therapy. The choice of Chemotherapy versus endocrine therapy depends on the tumor (grade, biomarker expression) and patient (menopausal status, performance status, com morbidities, preference) considerations. Emphasis is on illustration of Luminal A and B types including Ki 67 status. One of the options is to give endocrine therapy with CDK4/6 inhibitors
Triple-negative LABC	Taxanes (paclitaxel), anthracyclines (doxorubicin and liposomal doxorubicin), anti-metabolites (capecitabine and gemcitabine), microtubule inhibitors (eribulin and vinorelbine), platinum agents are preferred single agents for systemic chemotherapy. Combination chemotherapy regimens containing a platinum agent or a taxane are efficacious in patients with metastatic triple-negative breast cancer but remain controversial. Albumin-bound paclitaxel/carboplatin regimen is the preferred combination.	Chemotherapy with anthracycline- and a taxane. Platinum can be added with taxanes.
HER 2 Positive LABC	Patients with HER2-positive LABC should receive an initial chemotherapy program that incorporates preoperative trastuzumab and pertuzumab	Same recommendation In case of progression on anti-HER2 therapy, a combination of lapatinib with trastuzumab or the addition of TDM-1 is preferred.
Inflammatory LABC	Preoperative systemic chemotherapy with anthracycline and taxane is preferred. HER2-positive tumors can be treated by HER2-targeted therapy. The addition of trastuzumab for up to 1-year duration in systemic chemotherapy may improve the prognosis of HER-2 positive IBC cases. HER-2 positive IBC is more common than HR-positive IBC.	Systemic therapy with anthracycline and taxane with anti-HER2 therapy

Table 3: Primary systemic therapy regimens:

Category	NCCN	ESMO
Surgical options following systemic therapy	Mastectomy + Axillary staging+/- reconstruction Lumpectomy +/-surgical staging axillary staging in case of an initially operable tumor with positive lymph node	Same recommendation
Surgical margins	1mm and no tumor at the inked margin. For DCIS near resection margin, ideally, a 2mm margin is warranted, but the decision should be individualized.	same
After no response to pre-operative therapy	Individualize treatment	Palliative mastectomy not to be done unless surgery will result in an overall improvement in the quality of life of the patient
Axillary dissection	Axillary dissection to level II is recommended, up to level III is only carried out in case of grossly positive level II lymph nodes.	No clear statement

Table 4: Surgical Treatment in Locally Advanced Breast Cancer

Response to therapy is checked after every 2-4 cycles of chemotherapy and 2-4 months of endocrine therapy. This is done by detailed history, examination, and targeted imaging keeping in view the before therapy conducted test.

Recommendations for Surgery: Patients who respond to primary systemic therapy preferably complete therapy and then are planned for breast conservation versus mastectomy with axillary staging + /- reconstruction for non-inflammatory variety. NCCN recommends harvesting at least 10 lymph nodes for accurately staging axilla. Post-mastectomy radiotherapy is recommended in high-risk cases including the ones with involved lymph nodes, >4 positive axillary nodes, T3, T4 tumors. In an inoperable variety, all patients receive whole-breast/chest wall radiotherapy +/- the boost to tumor bed and radiotherapy to supraclavicular, infraclavicular, internal mammary, and axillary nodes at risk. Whereas in operable variety, the ones with positive lymph nodes on pathological TNM necessitate complete radiation protocol. In case of no response to therapy, additional systemic therapy can be considered before individualizing treatment. In the case of Inflammatory breast cancer, mastectomy with level II axillary dissection is a must if a patient responds to neoadjuvant therapy, as is radiotherapy. If the patient does not respond, additional systemic therapy or preoperative radiotherapy is considered. SLNB and breast reconstruction are generally not recommended in IBC patients.

ADJUVANT THERAPY PROTOCOLS

In both guidelines, if a preoperative chemotherapy course is given and not complete, it is administered first. Chemotherapy regimens are given generally before radiotherapy. NCCN recommends 21 gene RT -PCR assay to assess prognosis if a patient is a candidate for chemotherapy by tumor >0.5 cm and 1-3 positive nodes, to assess for prognosis.

Even the patients with favorable histologies end up receiving chemotherapy. Endocrine and chemotherapy are always given sequentially with endocrine therapy following chemotherapy. Endocrine and anti-HER2 medication can be given concurrently with radiation. The decisions are balanced in terms of progress-free survival and overall survival data. The addition of anti-HER2 therapy takes the pathologic complete response rate to 65 %12.

Category	NCCN	ESMO
HR +ve/HER2 -ve	Endocrine therapy. For Premenopausal: Tamoxifen for 5 y+/-ovarian suppression/ablation or an Aromatase inhibitor for 5 year+ ovarian suppression or ablation. If a patient becomes post-menopausal, an additional 5 years of Aromatase inhibitor or Tamoxifen can be given For Post-menopausal: Can be administered Aromatase inhibitor and Tamoxifen for 2-6 years with different regimes and then again to complete 5 or 10 years of endocrine therapy	Endocrine therapy with and without CDK4/6 inhibitors. Everolimus is an option as well in combination Could be AI, Tamoxifen with and without ovarian suppression/ablation, and fulvestrant.
HR-ve/HER2 +ve	Ado-trastuzumab alone for 14 cycles. Administer trastuzumab+/-pertuzumab for one year if toxicity develops to ado.	Continue anti-HER 2 for one year
HR+ve/HER2+ve	Endocrine therapy+ complete one year of trastuzumab+/-pertuzumab	Endocrine therapy + anti-HER2 therapy as maintenance or first-line therapy
HR-ve/HER2-ve	Consider 6-8 cycles of capecitabine	Carboplatin can be added to the regime.

Table 5: Adjuvant Therapy Recommendations

NCCN guidelines give a detailed elaboration of surveillance protocols whereas ESMO guidelines emphasize the important points.

Category	NCCN	ESMO
	History and physical exam 1-4 times per year as clinically appropriate for 5 years, then annually	Medical visits every 3 to 4 months for 2 years, every 6-8 months for the next 3-5 years, then annually
	Periodic screening for family history changes and genetic testing indications	
	Educate, monitor, and refer for lymphedema	
	Mammography every 12 months	Mammography recommended annually
	Routine imaging of reconstructed breast not required	Same recommendation
	Serial echocardiography for patients on anthracyclines-and Anti HER2 neu therapy	
	Screening for metastasis in presence of signs and symptoms	same
	Assess and encourage adherence to adjuvant endocrine therapy	same
	Annual gynecologic assessment of patients on Tamoxifen	
	Patients on an Aromatase inhibitor or who experience ovarian failure secondary to treatment need monitoring of bone health with bone mineral density determination periodically	Bone health monitoring recommended
	Active Lifestyle, healthy diet, limited alcohol intake, and maintaining ideal body weight 20-25 BMI recommended	Same
	Survivorship programs	
	Engagement of patients	
		HRT should not be used

Table 6: Surveillance Recommendations

LABC in Males: Male breast cancer constitute 1% of the disease burden[13]. The recommendations for men with breast cancer have mostly been derived from clinical trials from women. The management protocols are overall similar to the ones for women with breast cancer in both guidelines. Anthracyclines are recommended chemotherapeutic guidelines. Special emphasis has been put forth on adjuvant endocrine therapy as most of these cancers are ER +ve, especially in a recurrent setting where primary systemic therapy is of paramount importance. Surveillance patterns are similar whereby annual ipsilateral mammograms for lumpectomy and contralateral mammograms for mastectomy may be deployed. Fertility counseling, sexual and psychosocial health are dealt with in the same way as women.

	NCCN	ESMO
	The increased emphasis now on breast conservation as compared to traditional mastectomy. Ongoing Research domain	
	Indications for SLNB, ALND, radiotherapy, chemotherapy remain the same	
	21 gene assay score for prognostic information	
	Tamoxifen for 5 -10 years. If it is contraindicated, Aromatase inhibitor with a GnRH analog. Single-agent Aromatase inhibitor not recommended	Tamoxifen preferred option. For AI administration, GnRH analog or orchidectomy is preferred. Single-agent Aromatase inhibitor may be considered with close monitoring of response
	Bone density assessment at baseline and every 2 years for men on GnRH analogs	
	Fulvestrant alone can be used	
	CDK4/6 inhibitors, in combination with AI or Fulvestrant, mTOR inhibitors, and PIK3CA inhibitors may be used as an option as can be PARP inhibitors and immunotherapy	

Table 7: Management of LABC Male Breast Cancer

LABC in pregnancy: Most breast tumors during pregnancy are diagnosed at a locally advanced stage and are ER, PR-ve and around 30% are HER2 +ve14. The decision of terminating or continuing pregnancy should be made after detailed discussions with the patient. SLNB is individualized, should be done without blue dye, and according to NCCN, not recommended for the population under 30 weeks gestation.

Category	NCCN	ESMO
Primary systemic therapy	Chemotherapy not in the first trimester, after 35 weeks gestation, and within 3 weeks of planned delivery. Anthracycline and alkylating agent therapy.	Same recommendation except stopping chemotherapy after 33 weeks of gestation
	Endocrine therapy and radiotherapy contraindicated	same
	Anti-HER2 therapy in the postpartum period	same
Surgery	Recommended in all trimesters	Recommended in all trimesters, slightly increased fetal risk in the first trimester

Table 8: LABC during Pregnancy

Recurrent LABC: Workup for recurrent disease is the same as of locally advanced disease itself with a specification of biopsy of first recurrence and evaluation of ER/PR and HER2 status to differentiate recurrence from new primary. Both guidelines endorse comprehensive germline and somatic profiling, including BRCA, PIK3CA in HR-positive, and PDL-1 in TNBC to identify candidates for additional targeted therapies including PARP inhibitors and Tyrosine kinase inhibitors.

Local regional recurrence after a disease-free interval of 24 months and a complete excision predicts long-term survival. Systemic therapy including chemotherapy and Tamoxifen is recommended after complete excision. Approximately 30% of node-negative and 70% of node-positive breast cancers relapse[15].

Category	NCCN	ESMO
After Lumpectomy	Same recommendation	Mastectomy
After Mastectomy without radiotherapy	Same recommendation	Complete excision+ locoregional radiotherapy
After Mastectomy+ radiotherapy	Surgical resection. The decision of radiotherapy to be balanced between any prior radiation to the area and risk of late normal toxicity from radiation	Complete excision+ re-irradiation to limited areas
Inoperable tumor	Same recommendation	Primary systemic therapy first and the rest follow.

Table 8: Recurrent LABC

NCCN guidelines recommend surgical resection and radiotherapy for axillary recurrence and radiotherapy for supraclavicular and internal mammary recurrence. ESMO guidelines further recommend carefully decided pseudo adjuvant/secondary endocrine, chemo, and anti-HER2 therapy after surgery in selected patients due to the availability of low-quality data. Primary systemic therapy in such patients, with alternate regimes being ineffective or disease progression, will be with endocrine therapy (up to 3 cycles), anti HER 2 therapy as required with chemotherapy preferably for extensive visceral involvement. NCCN recommends similar protocols to previous treatment with emphasis on taxane-based regimes if not used previously, biosimilars for anti-HER2 therapy. Both guidelines encourage the use of other modalities including capecitabine, vinorelbine, and margetuximab

Sequential therapy is recommended but combination regimes can be used in case of high tumor burden, rapidly progressing disease, and visceral crisis. Patients with BRCA mutations are recommended for PARP inhibitors in triple-negative variety in both guidelines. In the case of previously treated disease, platinum-based therapy is recommended in BRCA. Both guidelines advise Alpelisib and fulvestrant in previously treated HR+ve/HER2 -ve lesions. PD L1 entities are treated with Atezolizumab. ESMO recommends against the use of NTRK fusion and MSI-H/d MMR treatment whereas NCCN endorses them when no alternate satisfactory treatment is available. The addition of targeted therapy to chemotherapy increases rates of pathologic complete response which is a predictor of disease-free and overall survival[16].

LABC AND COVID 19

ESMO guidelines endorse locally advanced breast cancer on a high priority list and emphasis is on neoadjuvant therapy with special emphasis on planned lesser hospital visits and oral therapy whenever possible. NCCN has the statement that Cancer won't wait and neither should you, resume screening and treatment of cancer.

Locally Advanced Breast cancer in a resource-limited set up: There are three important aspects to be taken into account regarding managing locally advanced breast cancer in a resource-limited setting

- Therapeutic modalities available
- Financial costs implicated
- Patient preferences

As regards to diagnostic challenges, there must be a fine balance between imaging modalities to pick the lesions and spread of cancer. In addition, PET-CT is not a realistic option in our setup in most situations in the public sector.

The modality of breast conservation therapy and SLNB, although a wonderful tool for many years now, remains a

challenge in our setup, based on the costs involved and detailed follow-up required in a high-volume overwhelmed healthcare setup. In our private sector, it is an excellent option. On the contrary, in the public sector, combined decision-making by patients and doctors to opt for mastectomy rather than breast conservation therapy is a sensible option. This is strengthened by the fact that poor survival outcomes have been reported in locally advanced breast cancer in our region[17].

Systemic chemotherapy, both before and after surgery, has not been able to show significant differences in long-term outcomes[18]. It has improved surgical outcomes when given preoperatively[19]. So in a limited setting like ours, clinical decision making with the experts in locally advanced breast cancers, in achieving upfront negative surgical margins, followed by adjuvant therapy can have a huge impact on the dynamics of the burdened healthcare system. In addition, patients with inflammatory breast cancer; contributing 7-10% of breast cancer-related mortality, can deservingly get primary systemic therapy[20]. This again emphasizes the dire need of making national guidelines for managing these patients within the resource framework.

Advanced breast cancer has reported median overall survival of 2-3 years. What to speak of survival rates in a population with a prevalence of around over 60 %[21]. The probable reason for more cases presenting in a locally advanced stage is multiple including ignorance of disease and screening pathways, the social stigma of being caught by cancer, and hesitancy of getting a checkup from a male-driven health care system. In addition, the use of unconventional therapies is quite common[22]. The situation has worsened because of Covid 19. It is the need of the hour to run empowered national-level education programs involving social, electronic, and print media aimed at developing preventing protocols and diagnosing breast cancer earlier to decrease morbidity and mortality in this patient group.

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Archives of Surgical Research | Invited Commentary

Need For Genetic Testing And Counseling For Hereditary Breast Cancer

Tooba Mahmud Gauhar[1]

IMPORTANCE Breast cancer is the commonest cancer among women and in many instances, it has a hereditary predisposition also. The commonest known genes associated with a familial predisposition of breast cancer are mutated BRCA1 and BRCA 2 which are located on chromosomes 17 & 13 respectively and are inherited in autosomal dominant fashion. All individuals suspected of having a familial predisposition for breast cancer should be subjected to genetic counseling, screening, and testing for BRCA 1&2 genes and if they come out to be positive then their relatives should be counseled and tested too so that safe surveillance and management options can be offered to them.

KEYWORDS Breast cancer, BRCA1 & BRCA2, genetic testing, genetic counseling, screening

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Invited Commentary

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Breast cancer is the commonest cancer among women and the second commonest cause of cancer-related deaths in women[1]. It is present in 1 in 8 women, thus 11% of families will have more than one patient with breast cancer. So it is a challenge to identify females from families having a genetic predisposition for breast cancer from women having sporadic disease due to clustering by chance without any familial predisposition. Although in the majority of cases, breast cancer is sporadic, genetic mutations are associated with 10-15% of the cases2. Nearly 25% of hereditary cases are due to mutation in BRCA1 and BRCA 2 genes which are inherited through autosomal dominant fashion on chromosomes 17 &13 respectively. BRCA mutations exhibit as hereditary breast/ovarian cancer syndrome. These BRCA carriers have an 82% lifetime risk of developing breast cancer and 10-40% risk of ovarian cancer for BRCA 1and 10-20% risk for BRCA 2. They also have a risk of developing fallopian tube, prostate, and pancreatic cancers[3].

DETECTION

BRCA 1 and BRCA 2 associated breast and ovarian cancer should be suspected in people with a personal or family history of the following:

- Breast cancer diagnosed at or before 50 years of age
- Ovarian carcinoma
- Multifocal uni/bilateral primary breast cancer
- Male breast cancer
- Triple-negative breast cancer (ER-ve, PR-ve, HER 2 neu-ve) especially when age is less than 60 years
- Combination of pancreatic and /or prostate with breast cancer
- Ashkenazi jew ancestry
- 2 or more relatives with breast cancer, one < 50years of age
- 3 or more relatives with breast cancer at any age
- Previous family history of BRCA1/BRCA2 [4,5]

SCREENING:

NCCN has issued recommendations for BRCA mutated breast cancer. Surveillance includes monthly self-breast examination, clinical breast examination, annual mammograms, and annual MRI of the breast. These yearly mammograms will start at 25 years of age. MRI is more sensitive than a mammogram in the detection of early-onset breast cancer in young female[7].

RISK ASSESSMENT:

Mutations in BRCA 1&2 genes are familial. Several risk assessment tools have been devised that include patient age at disease onset, gender, age at death, family history of affected members, type of cancer present in patients or relatives. The tools evaluated by USPSTF include Ontario family history assessment tool, Manchester scoring system, Referral screening tool, Pedigree assessment tool,7 Question family history screening tool, International breast carcinoma intervention study instrument, and BRCAPRO. Each of them accurately estimates the risk of carrying BRCA 1&2 mutation [6,8]. These tools help us to assess and refer the patient for genetic counseling for a better risk assessment[8]. The above recommendations clearly define the population to consider for testing[6].

Table 1: The recommendations by US preventive services task force are:

Assessment of risk, Genetic Counseling, and Genetic Testing for BRCA-Related hereditary Cancer: Clinical Summary of the USPSTF Recommendation		
Population	Women population with a personal or family history of breast, ovarian, peritoneal, or tubal cancer or having an ancestry associated with BRCA1/2 gene mutations	Women whose personal or family history or ancestry is not associated with harmful BRCA1/2 gene mutations
Recommendation	Assess with a brief familial risk assessment tool.	Routine risk assessment not needed
Risk assessment	Risk assessment of patients with family or personal history of breast, ovarian, tubal, or peritoneal cancer or ancestry associated with harmful BRCA1/2 mutations should be done using a familial risk assessment tool. The USPSTF found that these tools are accurate .Tools evaluated by the USPSTF include the Ontario Family History Assessment Tool System, Referral Screening Tool, Pedigree Assessment Tool, , Manchester Scoring , International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), 7-Question Family History Screening Tool, and BRCAPRO. Referrals to genetic counseling should be made based on these tools.	
Genetic counseling	Genetic counseling about BRCA1/2 mutation testing to be done by trained health professionals. The process of genetic counseling consists of family analysis and risk assessment for BRCA1/2 mutations and identification of candidates for testing, patient education, discussion of the benefits and harms of genetic testing, interpretation of results, and discussion of management options.	
Genetic testing	A person should be tested for BRCA1/2 mutations when she/he has personal or family history that suggesting an inherited cancer susceptibility, when an individual is willing to see a trained genetic counselor and when test results will help in decision making.	
Treatment and interventions	Women with harmful BRCA1/2 mutations are managed with different interventions to lower future risk of cancer. This includes screening, medications, and mastectomy and salpingo-oophorectomy.	
Other relevant USPSTF recommendations	The USPSTF recommends use of medications such as tamoxifen, raloxifene, or aromatase inhibitors to women at increased risk for breast cancer. The USPSTF does not recommend for screening for ovarian cancer. This recommendation does not apply to women with known BRCA1/2 mutations.	
Note: For a full recommendation statement, and supporting documents, go to https://www.uspreventiveservicestaskforce.org/. USPSTF = U.S. Preventive Services Task Force		

GENETIC COUNSELING:

It can provide the patient the lifesaving info. Pretest counseling is performed by a genetic counselor, medical or surgical oncologist, or health professional with sufficient knowledge of cancer genetics 9. The patient should be informed about the implications of a positive, negative, or inconclusive (VUS) result. It decreases stress and improves risk perception[10]. Genetic counseling for VUS is complex because we have no guidelines about how to disclose variants of unknown significance (VUS). National society of genetic counseling NSGC indicates that counselors should discuss VUS with patients during pretest counseling and during post-test counseling if VUS is found[11].

GENETIC TESTING:

Genetic testing for BRCA 12 is performed only if

• the individual has a personal/family history suggestive of hereditary breast cancer

• the patient is willing to talk to a genetic counselor

• Results will help in decision making and future surveillance and management plans6

This testing can impact multiple family members beyond the one being tested. If the test result is positive, unaffected family members also need to be tested for the presence of the mutant gene for screening and surveillance. But there can be a lack of willingness by family members for this testing [12, 13].

TREATMENT AND PREVENTION:

Three main options are:

• Prophylactic mastectomy:

It is the most effective way to prevent BRCA associated breast cancer. It eliminates the risk for metastatic spread and death. Offers 80% risk reduction. Total mastectomy is preferred over subcutaneous or nipple-sparing mastectomy [14,15]

• Prophylactic oophorectomy

As BRCA 1 is associated with hormones, oophorectomy blocks the effect of ovarian estrogen thus reducing the risk of BRCA 1 associated cancer [16]

• Chemoprevention

By selective estrogen receptor modulators like Tamoxifen/Raloxifene [15,16]

Routine screening (secondary prevention) to detect early cancer [16].

FUTURE GOALS

Till now screening is being offered to those who are thought to have susceptibility to develop BRCA associated

cancer. This may miss a large chunk of the asymptomatic population. Since the cost of genetic panel testing has markedly fallen now so screening for BRCA 1& 2 should be offered to all patients with breast cancer.

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Archives of Surgical Research | Commentary

Role Of Molecular Testing In Breast Cancer Management Plans

Eisha Qanita[1], Muhammad Asif Maqbool[1]

IMPORTANCE The role of genomic testing in hormone positive breast cancer has been recently debated in scientific literature and the guidelines for breast cancer are improving with addition of genomic testing in terms of categorization of the tumors according to their malignant potential and their response to chemotherapy. The objective of this review is to highlight the role of molecular testing specifically in breast cancer. The most commonly used gene panel is Oncotype Dx, which has been compared with other available gene panels. The incorporation of molecular testing in international guidelines will likely save patients from unnecessary chemotherapies and under or overtreatment in several scenarios.

KEYWORDS Oncotype Dx, Molecular Testing, Breast Cancer

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Commentary

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The management plans are shifting from prognostic indexing to a more personalized approach in form of molecular testing to judge the malignant potential of malignancies and then devising personalized treatment plans. Multiple prognostic systems have been previously developed which include Manchester score for small cell lung cancer, MACIS score for papillary carcinoma thyroid, and Nottingham scoring system for carcinoma breast. The dilemma of the conventional scoring system was that they were all dependent on factors like age, tumor size, and grade of tumor, however, none individualized personal risk and reflected a person's response to disease in terms of his or her genetic makeup. The paradigm of prediction and recurrence scoring system has now been shifted towards molecular testing that is individual-based and provides us with genetic assay which makes us wise regarding an individual's response to a disease progression and patient's survival regardless of the treatment regime given.

The Oncotype dx is a genomic testing tool that predicts the beneficial effects of chemotherapy along with hormonal therapy, it involves 21 genes and two types of tests one is for early ER-positive, HER 2neu negative carcinoma breast while another one for already diagnosed DCIS. The risk stratification involves (0-25) as low and (>31) as high. The presence of Oncotype Dx has produced a remarkable change in utilization of chemotherapy for early-stage ER-positive HER2neu negative, node-negative carcinoma breast, ensuring prescription of systemic treatment to high-risk patients while low-risk ones are treated with hormonal therapy solely.

The role of Oncotype dx has been studied in terms of its effects on hormonal therapy, adjuvant therapy, and recently neoadjuvant therapy as well. The NSABP-20 study proves that Recurrence Score (RS) can be used for prediction of patients with node negative, ER positive carcinoma in whom adjuvant chemotherapy will be beneficial for survival and disease-free period compared to hormonal therapy alone[1]. A study published in EJSO, has studies impact of Oncotype Dx RS scores on adjuvant chemotherapy using a group of 201 patients recently diagnosed as ER +, PR – Her 2-neu negative. In all of them chemotherapy was advised by a multidisciplinary team, but Oncotype Dx scoring reduced the figure to 127/201 allowing only 63.2% to get chemotherapy. In node-positive patients, 69.2% were spared of chemotherapy[2]. TAILORx trial concluded that in patients with high RS score, utilization of adjuvant chemotherapy significantly reduces recurrence of cancer and mortality, while patients with low RS score do not gain any additional benefits from chemotherapeutic agents[3].

To fully understand the role of Oncotype Dx in the setting of neoadjuvant chemotherapy we should be fully aware of terms e.g. pathological complete response (pCR), Partial remission, and Disease progression. pCR refers to the complete clinical absence of tumor after neoadjuvant chemo or radiotherapy while Partial remission refers to a mere decrease in the size of the tumor and disease progression means an increase in disease burden after the first line of therapy. Previously neoadjuvant chemotherapy has aided us in opting for breast conservation surgery and sparing patients of unnecessary axillary clearance. Multiple studies have been done on the effects of Oncotype Dx regarding neoadjuvant chemotherapy. One study concludes that opting NAC (neoadjuvant chemotherapy) upon results from Oncotype Dx permits the application of treatment correctly and prevents chemotherapy in approximately half of the patients previously selected for

NAC based on clinical parameters. In this study the researchers have found that 35% of the patients had a high RS (>25) that would advocate long-term chemotherapy[4]. National cancer database executed a large-scale study to analyze the role of Oncotype Dx for predicting the response of neoadjuvant chemotherapy. The researchers found that ER-positive, HER2-neu negative patients with high RS were more likely to have a complete pathological response[5].

Role of Oncotype dx was also studied for prediction of axillary response to neoadjuvant chemotherapy[6]. This study included patients with T1-T2 and N1-N2, ER-positive, HER2-neu negative disease. RS was established as low (<18), intermediate (18-30), high (>30). A total of 158 patients were studied out of which 35.4% were categorized as low RS, 39.2% as intermediate RS, 25.3% as high RS, pathological complete response was observed in totally in 14.6% of patients, out of which 47.8% belonged to high RS score category, 26.1% had an intermediate score and 26.1% had low RS score hence proving that most patients who achieved pathological complete response belonged to high recurrence score category[6].

Multiple other molecular tests used for hormone positive carcinoma of the breast include Mammaprint, Endopredict, Prosigna risk of recurrence, Breast Cancer Index, and Oncotype Dx. Oncotype Dx is the only score that is endorsed in most international guidelines, tells us about the prognosis of disease, its recurrence, and predicts beneficial effects of adjuvant chemotherapy along with hormonal therapy.

Comparison of Oncotype Dx with other molecular tests

There is a growing consensus now about the role of molecular testing of hormone positive cancer for prescribing neoadjuvant chemotherapy. Increased incorporation of Oncotype dx is being observed in trials as well as in clinical implementations of treatments. NICE endorses usage of Oncotype Dx in decision-making for chemotherapy[8]. Moreover, Oncotype DX has been incorporated in other international guidelines like (NCCN)[9], European Society of Medical Oncology (ESMO)[10].

In the coming years, we can expect Oncotype Dx and molecular testing as a promising tool in decision making which is accurate and cost-effective and has advantage of sparing unnecessary chemotherapies and surgeries.

Table 1. Comparative analysis of molecular analysis systems in breast cancer management. (Adapted from Gruz O et al. Breast Care 2013)

	Oncotype Dx / Recurrence Score	**PAM50/ Prosigna Risk of Recurrent**	**Mammaprint**	**EndoPredict**	**IHC_4**	**Breast Cancer Index**
Classification	Continuous score 0-100(RS): L/IM/H risk (<18/18-30/231)	Continuous score 0-100 (RoR ± turn our size): L/M/H risk (<40/41-60/>60 in NO and <15/16-40/>40 in N1)	Two groups: L/H risk	Continuous score reported asL/H risk	Three groups L/M/H risk	Continuous score is 0-10: L/M/H risk
Prognosis	YES	YES	YES	YES	YES	YES
Prediction of endocrine therapy benefit	YES	NO	NO	NO	NO	YES
Prediction of chemotherapy benefit	YES	NO	NO	NO	NO	NO
Guidelines recommendation	St Gallen [2], NCCN [3], NICE [4], ASCO [5], ESMO [8]	St Gallen [2](prognostic)	St Gallen [2](prognostic)	St Gallen [2] (prognostic)	NO	NO
Level of evidence	Prognosis: IB Prediction: IB	Prognosis: IIB	Prognosis: BC	Prognosis: IB	Prognosis: IIB	

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Archives of Surgical Research | Review Article

The Grey Zone: A Review Of The Management Of B3 Lesions Of The Breast

Bushra Rehman[1], Huma Majeed Khan[1]

IMPORTANCE With the advent of widespread breast cancer screening programs along with rising public awareness, the number of patients presenting with B3 lesions on core biopsy has also increased. This grey zone consists of heterogeneous pathological entities with variable malignant potential, necessitating excision biopsy for full histological examination. This puts an additional burden on cost, theater time and requiring invasive procedure on the patient. The term 'malignant potential' confers either an increased probability of finding concomitant cancer on excision biopsy, or evolution towards in situ or invasive cancer over a period of time. The risk is not restricted to the breast where the biopsy or excision of the B3 lesion occurred, but anywhere in the same or contralateral breast. Because of management controversies, a multidisciplinary approach is the need of the hour to decrease the over or under diagnosis, and over or under treatment. This review is aimed at giving an overview of morphology and biological significance of B3 entities and current agreement on its management. It also focuses on the ways these internationally agreed protocols can be adopted in our resource constrained country.

KEY WORDS Core needle biopsy, uncertain malignant potential, upgrade to malignancy, identification rate, Vacuum assisted procedures.

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Review Article

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With the advent of widespread breast cancer screening programs along with rising public awareness, the number of patients presenting with B3 lesions on core biopsy has also increased. This grey zone consists of heterogeneous pathological entities with variable malignant potential, necessitating excision biopsy for full histological examination. This puts an additional burden on cost, theater time and requiring invasive procedure on the patient. The term 'malignant potential' confers either an increased probability of finding concomitant cancer on excision biopsy, or evolution towards in situ or invasive cancer over a period of time. The risk is not restricted to the breast where the biopsy or excision of the B3 lesion occurred, but anywhere in the same or contralateral breast. Because of management controversies, a multidisciplinary approach is the need of the hour to decrease the over or under diagnosis, and over or under treatment. This review is aimed at giving an overview of morphology and biological significance of B3 entities and current agreement on its management. It also focuses on the ways these internationally agreed protocols can be adopted in our resource constrained country.

Patients presenting with radiologically or clinically detected breast lesions are subjected to core needle biopsy (CNB). There is a specific B-coding system for CNB result interpretation, which was first established in the European breast-screening programs[1]. Histology results on conventional needle core biopsy or vacuum assisted biopsy are classified as follows:.

B0: Non- diagnostic.
B1: Normal breast tissue.
B2: Benign breast lesion.
B3: Uncertain malignant potential (heterogeneous)
B4: Suspicious for malignancy.
B5: Malignant.

What are B3 Lesions?

These are a heterogeneous category encompassing a number of lesions that includes the following: [2]

- Atypical intraductal epithelial proliferation (AIDEP)
- Flat epithelial atypia (FEA)
- Lobular lesions (ALH, LCIS)
- Papillary lesions (with or without atypia)
- Cellular fibroepithelial lesions (where phyllodes tumour is considered)
- Radial scars (with or without atypia

A combination of the B3 lesions is known to occur particularly in the spectrum of low nuclear grade neoplasia family (FEA, lobular neoplasia, AIDEP).[3] Other less common lesions within this category include apocrine atypia, myofibroblastoma, vascular lesions and bland spindle cell lesions.

How common is it (Identification rate)?

This mainly refers to the CNB results of the mass screening programs in Europe and North America. The B3 identification rate on CNB varies across different studies. In

the UK, the reported rate was 5%[4], 4.5% in Germany[5], 11.9% in Italy[6] and 17% in Switzerland[7]. While study of 5750 needle core biopsies in the USA showed an incidence of 8%.[8] Swiss Minimally Invasive Breast Biopsy group (MIBB) Database presented histology from 31,574 vacuum assisted biopsies (VAB), from 2007 until 2017. Total 6020 cases i.e. 19.1% showed B3 lesions.

The commonest entity among all B3 lesions in two studies (excluding Phyllodes) was found to be ADH or AIDEP.[5, 8]

What is the significance of B3 diagnosis?

These lesions have a low but significant risk, either to harbor a coexisting malignancy or a potential for malignant change in the future, and thus merit excision to establish a diagnosis after complete specimen histology. Diagnosis of in situ or invasive carcinoma on excision of a B3 lesion is called 'upgrading'. Many studies assessed the upgradation rate to in situ or invasive carcinoma (positive predictive value) following the diagnosis of B3. Each study has shown a different overall upgrade rate and of individual B3 entities.

Upgrading to malignancy (Invasive or In-situ):

Although different studies have shown different rates, overall, the association with malignancy is seen in 20–30% of cases.[4, 5], and[10]. Table 1 shows identification and upgrade rate in different studies.

Name of Author	Type of study	Duration	Total number of core biopsies	Identification rate (of B3)	Upgrade rate
Elsayed et al. 2008.[4]	UK East Midlands region	1999–2006	13,452	5%	20%
Ehrenstein et al.[5]	Germany single Institution	2009-2015	8,388	4.5%	26%
Bianchi et al. 2011.[6]	Multiinstitutional Italian series	1998–2009	26,165	11.9%	21.2%
Saladin et al. [7]	Multi institutional in Switzerland	2009 and 2011,	9,153	17.0%	21.5%
Mooney et al. 2016. 8	US single institution	2003–2014	5750	8%	18%
Rakha et al. 2011.9	UK single Institution	2007–2008	3347	4.5%	10%
Nguyen et al. 2011.10	US single institution (MD Anderson Centre)	1997–2009	5383	9.9%	13.2%
Renshaw and Gould 2016.12	US single institution	2000–2004	Not stated	244	34.6%
Mayer et al. 201724	German single institution	2009–2013	Not stated	219	10%

Table 1: Overall upgrade and identification rate of B3 lesions in different studies.

Name of Author	Total no. of core biopsies	Identification Rate (IR of B3)	Upgrade rate of individual B3 entities:
Elsayed et al. 2008.[4] UK East Midlands region (1999–2006)	13,452	5%	AIDEP 32%, LN 30%, RS/CSL with AIDEP or LN 24% RS/CSL without atypia 9%, Papillary lesion with AIDEP or LN 36% Papillary lesion without atypia 4%
Ehrenstein et al.5 Germany single Institution (2009-2015)	8,388	4.5%	ADH 40%, FEA 20.5%, Papillary lesion 13.5%, Radial scar 16.6% LN 0%.
Bianchi et al. 2011.[6] Multi institutional Italian series (1998–2009)	26,165	11.9%	AIDEP 27.3%, FEA 12.7%, LIN 22%, RS 10.6%, PL 13.3%
Saladin et al. [7] Multi institutional in Switzerland 2009-2011	9,153	17.0%	ADH 25.9%, PL 3.1%, FEA 18.3%, LN 26.4%, RS 11.1%
Mooney et al. 2016. [8] US single institution 2003–2014	5750	8%	ADH 18%, FEA 11% Atypical lobular hyperplasia 9% , LCIS 28% , RS16%
Mayer et al. 2017[24] German single institution 2009–2013	Not stated	n=219 (B3)	PL (with atypia) 28.6%, PL(without atypia) 4.7%, B3 (rest of B3 lesions with atypia) 24.0% , B3 (rest of B3 lesions with atypia) 4.8%
Huang et al[25] Single institution Australian 2012–2019	Not stated)	n=299 (B3)	PL (with atypia) 50%, FEA 37.50%, ADH 24.71% LCIS/atypical lobular hyperplasia with calcification 17.65%, PL (without atypia) 4.72%, RS/ classical LCIS (without calcification) 0%

Table 2: Upgrade potential of different lesions in different studies.

Usually upgrading is to low grade malignancy:

The rate of progression to malignancy is slow and occurs over a long period of time. Cancers that develop in a small proportion of B3 lesions are often of the low-grade hormone receptor–positive type or in-situ cancer.[11, 12, 13]

Upgrade potential of different lesions:

Different B3 categories have different malignant potential that mainly depends on presence of atypia. Following table (table: 2) shows that malignant potential greatly varies among studies, however on average, the greatest malignant potential is for ADH, FEA and PL with atypia.
Forester et al conducted a meta-analysis (129 studies from 1980 and 2015) that included 11,423 lesions with upgrade rate of 17%. The presence of atypia was associated with significant upgrade potential compared to the same lesion without atypia. For Papillary lesions (PL), upgrade rate to malignancy was 7% without atypia compared to 32% with atypia ($p < 0.01$), similarly for radial scars, upgrade rate to malignancy was 6% without atypia compared to 18% with atypia ($p < 0.034$)[14].

Acceptable rates for the risk of underestimation:

Overall, underestimation rates should not exceed 5% for Invasive cancer and 10% for DCIS[15] acc. to the Second International Consensus Conference on B3 lesions.

CURRENT GUIDELINES FOR THE MANAGEMENT OF B3 LESIONS

Traditionally, B3 lesions were managed by surgical excision. However, current recommendations are in favor of the use of VAE (Vacuum assisted excision) for the management of B3 lesions with no atypia[15]. The B3 lesions with atypia and Fibro-epithelial lesions are, however, still managed with diagnostic surgical excision. The second International Consensus Conference on lesions of uncertain malignant potential in the breast recommended VAE as the gold standard for managing the majority of these lesions.[15, 16.]

Follow-up Following a B3 Diagnosis: The International Consensus recommends surveillance following a B3 diagnosis.[15] The current UK guidelines recommend annual mammographic follow-up for 5 years followed by return to the 3 yearly routine breast cancer screening.

IMPORTANT ASPECTS:

The correlations of Histology with the type of mammographic lesion: Concordance between radiological and histological findings is very important. For discordant lesions (e.g. histological findings do not explain a mass lesion or calcification not identified), a repeat VAB (vacuum assisted biopsy) and or a diagnostic excision may be required. Discussion In the multidisciplinary meeting with careful planning and documentation are therefore important.[15, 17]

However, in one study, the morphological type of mammographic lesion does not appear to be correlated with cancer risk.[18]

Diagnostic Vacuum–Assisted Biopsy (VAB): Vacuum-assisted biopsy (VAB) is done with a vacuum biopsy needle (usually 12-9G) for diagnostic purposes only (larger amount of tissue compared with conventional needle core biopsy (CNB) which is 14G. VAB gives a larger sample for the pathologist to assess and and reduces chances of missing concomitant cancer. This helps in avoiding unnecessary surgeries.[11]

Vacuum-Assisted Excision (VAE): Vacuum-assisted excision (**VAE**) is used in place of a surgical excisional biopsy by a larger needle (7G or 8G). VAE is recommended for further sampling of all B3 lesions diagnosed on conventional CNB or VAB in all categories except: Papillary lesions (PL) with atypia, cellular fibroepithelial lesions (PT), B3 spindle cell lesions, vascular lesions and other rare lesions such as myofibroblastoma and apocrine adenosis.

Open surgical excision is regarded as overtreatment within the breast-screening program because the majority of B3 patients show a final benign diagnosis. Small lesions, typically less than 15 mm, may be completely excised by VAE.19 Patients can therefore avoid the complications of surgery such as anesthetic complications, scarring and difficult follow-up mammographic surveillance due to post-surgical changes. It can help in reducing theater time and overall cost of the procedure.

The NHS Breast Screening Program is keen to minimize overtreatment in the context of B3 lesions and have created a new KPI (key performance indicator) where all appropriate B3 lesions should be managed with VAE and < 25% of B3 lesions should be managed with surgery.

Marker Clips: It is important to insert marker clip when sampling calcification or very small lesions. If more than one area is sampled, then a different clip type per area should be used.

Reporting of Atypia: The diagnosis of B3 lesions should always include a comment on the presence/absence of atypia. Atypia is associated with a higher risk of upgrade to in situ/invasive carcinoma among all B3 lesions, [25] thus altering the management plans. For example, benign papillary lesions without atypia are managed by VAE whereas those with atypia require diagnostic surgical excisions

Adequacy of Excision: Due to the piecemeal nature of the vacuum biopsies, it is not possible for pathologists to comment on the adequacy of excision. Decisions on adequate excision in these instances will depend on the radiological impression. Biopsies of microcalcifications should be x-rayed to make sure that the sampling is adequate.

Columnar cell hyperplasia: With increasing identification of microcalcifications on screening mammograms and subsequent biopsies, this histology is more frequently reported in association with micro-calcifications. Columnar cell change or columnar cell hyperplasia is regarded as a benign lesion (B2). Therefore, if there is no discordance with the radiological/clinical features, diagnostic surgical excision or further VAE is not required.

However, when cytological atypia is present, the lesion is reported as FEA (B3), which is believed to be the earliest morphologically identifiable precursor of low grade breast carcinomas. Similarly, if there is architectural atypia then cores should be categorized according to the extent and degree of this and ADH may be reported.[20]

B3 ENTITIES: Characteristics and recommendation (according to the second international consensus)

1. Atypical intraductal epithelial proliferation (AIDEP/ADH): Histologically, the term 'AIDEP' (Atypical intraductal epithelial proliferation or Atypical epithelial proliferation of ductal type) is recommended for describing atypical ductal hyperplasia (ADH) diagnosed on core biopsy and/or diagnostic VAB. The 'ADH' is quantitative term and can only be used after thorough sampling of excision specimen and the extent of the lesion confirmed to be less than 2 mm on final excision.[15, 21] Lesions larger than 2 mm are labelled as ductal carcinoma in situ (DCIS).

Surgical excision is recommended even if the lesion seems to be completely excised by VAB, followed by surveillance.

2. Flat epithelial atypia (FEA): FEA consists of a few layers of neoplastic columnar type cells with low-grade (monomorphic) atypia without any secondary architecture (flat architecture). The immune-phenotype of a FEA lesion is identical to that of a low-grade DCIS. These are often associated with micro-calcifications. It is believed that columnar cell change actually progresses to FEA. FEA should undergo **VAE** along with yearly surveillance for 5 years.

3. Classical lobular neoplasia: Lobular neoplasia (LN) includes a large spectrum of atypical intra-lobular proliferations, consisting of non-cohesive proliferating cells. Under the term "Classical Lobular Neoplasia," two lesions are defined by the WHO classification as classical lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH). In case of LCIS, these cells expand more than 50% of the acini in a terminal duct-lobular unit (TDLU), while in ALH this affects less than 50%.[22]

ALH/LCIS has to be considered as both a risk factor and a non-obligate precursor of invasive breast carcinoma conferring an 8 to 10 times relative risk compared to the general population. The risk is bilateral with ipsilateral predominance.[21, 23]

A lesion containing classical LN, which 'is visible on imaging', should undergo excision with VAB. Thereafter surveillance is justified if there is no pathological–radiological discordance and no residual lesion. In contrast, morphologic variants of LN (LIN 3, pleomorphic LCIS, and florid LCIS), which are reported as B5a lesions should undergo Open excision.

4. Papillary lesions (PL): Histology demonstrates a papillary proliferation as the basis with a central fibro-vascular core arranged in an inner myoepithelial and outer epithelial layer.

In the current WHO classification of breast tumors, papillary lesions are divided into

(a) Papillomas

(b) Papillomas with atypia (ADH or classical LN), both belonging to the B3 category

(c) Papillomas with DCIS or papillomas completely involved by more extended DCIS (encapsulated papillary carcinoma)

(d) Solid papillary carcinoma belonging to B4 or B5a category.

A PL lesion, which 'is visible on imaging', should undergo excision with VAB. If lesions are large and cannot be completely removed by VAB then open excision should be done. Later, surveillance with mammogram should continue.is important to insert marker clip when sampling calcification or very small lesions. If more than one area is sampled, then a different clip type per area should be used.

5. Phyllodes Tumor (PT): Benign and borderline phyllodes tumors are B3 lesions; a malignant PT is a B5b lesion. Only up to 20% of all PT tumors are borderline or malignant.

Surgical excision is required, with free margins in borderline and wider margins in malignant PTs

6. Radial scar/ complex sclerosing lesion (CSL): RS is characterized by a central area mimicking a scar, with a pseudo infiltrative growth pattern. It consists of a central fibro-elastic zone from which radiate out tubular structures They are seen radiologically as stellate lesions, classically with a more lucent centre but may be indistinguishable from carcinomas. There is general agreement that RS alone is a benign lesion, but RS can be occasionally associated with carcinoma[25].Presence or absence of atypia should be

particularly recorded on CNB or VAB[2] [8].RS/CSL should undergo vacuum assisted excision (VAE). Thereafter, follow-up with mammogram is carried out.

B3 LESIONS IN PAKISTAN

In our part of the world, screening programs are non-existent, so mostly symptomatic patients present to the clinicians. Commonest symptoms are feelings of a lump or mastalgia. In addition, biopsies are taken only by conventional CNBs (not VAB) meaning lesser tissue available to the pathologists and relatively higher probability of reporting a B3 lesion only and missing out on coexisting upgraded pathologies. Another issue is the lack of a national database to know the exact B3 lesion identification rate in all core biopsies performed (symptomatic patients usually).

At Ittefaq Hospital (Trust) breast surgery department, about 5% of all breast biopsies (including palpable and impalpable lesions) were found to be B3 lesions. Pathology facilities are relatively better across the country, so that is not a point of concern. However, the awareness of B3 management according to recent guidelines is still very poor among clinicians that may result in, either, avoidable over-treatment or an under-treatment and subsequent risk of missing a malignancy. Also, because of unavailability of vacuum assisted excision, all B3 lesions may mandate open excision. Breast surgery units are recommended to include vacuum assisted biopsy and vacuum assisted excision facilities. In future, screening programs on either a national or a local level, for at least high risk population, will help in reducing mortality, improving survival, conserving breast and cutting treatment costs.

Declaration of conflict of interest: none'. Also, this article has not been published previously.

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Archives of Surgical Research | Systematic Literature Review

Factors Influencing Delayed Presentation of Breast Cancer: A Systematic Literature Review

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IMPORTANCE Breast cancer is the most common cancer in women worldwide. It is amongst the leading cause of cancer-related death in women. Its incidence is higher in developed countries owing to early detection and diagnosis through screening. However, an alarming rise in its incidence and mortality rates are seen in developing countries. Early detection and treatment initiation is crucial for its management. Delayed presentation of the patients is seen to be associated with advanced-stage diagnosis, more aggressive treatment, poorer outcomes, poorer quality of life, and higher mortality rate. Delay in effective oncological treatment could be due to patient presentation delay or provider delay. Identification of these delaying factors is crucial for the removal of the barriers to early detection and treatment of breast cancer patients.

OBJECTIVE The objective of this literature review is to identify the factors that delay the presentation of breast cancer patients in developed and developing countries.

METHODS This systematic literature review is written according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. A comprehensive literature search of PubMed/MEDLINE and ERIC was performed using search terms "delayed presentation" OR "late presentation" AND "breast cancer" OR "breast carcinoma". 143 papers were identified through a literature search. Following the removal of 4 duplicates, titles and abstracts of 139 papers were reviewed. After thorough analysis, 12 papers were included in this literature review.

RESULTS Factors that are seen to delay presentation are overlapping and can be broadly characterized as personal, socio-cultural, and economic. The role of these factors in delaying presentation is seen to vary in developed and developing countries. Hence, the role of these barriers cannot be extrapolated from one region to another as different studies have demonstrated contradicting results. Cancer control programs in developed countries have significantly reduced the influence of sociocultural barriers in delaying patient presentation. However, economic factors play a crucial role in the delay. While in developing countries fear-related barriers, lack of awareness, and poverty are the most prevalent factors.

CONCLUSION The incidence of breast cancer is rising worldwide. Early presentation in breast cancer is crucial for its management. Several personal, socio-cultural, and economic factors influence the presentation of patients. The role and distribution of these barriers are diverse. Social, cultural, and economic differences make it difficult to extrapolate the influence of these barriers from one region to another.

KEYWORDS Breast Cancer, Awareness, Delaying Factors, Ethnicity, Poverty, Developed and Developing Countries.

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Systematic Literature Review

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Cancer is one of the leading causes of death worldwide[1]. It is estimated that 9.6 million people die from different types of cancer each year and 70% of deaths occur in developing and underdeveloped countries[2]. The number of reported deaths occurring due to cancer is increasing continuously especially in moderate-income and low-income countries[3]. Early presentation, diagnosis and timely treatment are seen to be associated with better outcome in patients. While delayed presentation of symptomatic cases is associated with poorer outcomes due to advanced stage presentation and these cases are usually managed with palliative intent[1]. Patients with advanced stage disease have higher fatality rate in developing and underdeveloped countries compared with developed countries [4]. In 2017 WHO provided guideline for early diagnosis of cancer. It outlined three sequential steps: access to care, evaluation of disease, and access to subsequent treatment [5]. In order to diagnose and treat cancers early it is

important to understand the barriers that prevent early intervention in different types of cancers. These barriers have been studied predominantly in high income countries [5].

Breast cancer is the most common type of cancer occurring in women worldwide. In 2018 2.08 million new cases of breast cancer were reported [6]. Incidence of breast carcinoma is higher in developed countries [7]. However, breast carcinoma is the leading cause of cancer related death in less developed countries and second most common cause of cancer related death in women of United States [8]. Higher incidence rates of breast cancer in developed countries can be attributed to early diagnosis, regular screening tests and registry of patients [9]. However, recent studies have shown alarming rise in incidence and mortality due to breast cancer in moderate-income and low-income countries [10]. This can be attributed to several factors such as level of education, awareness about the disease, reproductive factors, family history, alcohol consumption, obesity and income [11]. Racial minorities in developed countries are seen to present at an advanced stage, receive more aggressive treatment, and have overall poorer prognosis and quality of life [12].

Patients who present after three months of initial symptom appearance have 12% higher 5-year mortality rate than patients who present earlier [13]. The 5-year survival for stage 0 and stage I cases is 100%, stage II cases is 93% and stage III cases is 72% [14]. Owing to significance of early presentation WHO proposed increasing awareness about clinical presentations, risk factors, evidence-based diagnosis and management [15]. These strategies have been adopted by developed countries, but due to scarcity of resources these strategies are not employed by developing countries [16].

Africa has the lowest incidence rate of breast cancer worldwide [17]. However, its mortality rate is higher than developed countries [18]. The poorer outcome in African women is associated with delay in initial presentation, diagnosis and effective management. Incidence of breast carcinoma is increasing in Africa due to adoption of western lifestyle [19]. Younger population is affected more commonly in Africa than in high income countries. Presentation in African patients is seen to be delayed by 8-12 months [20].

In Asia incidence and mortality rates of breast cancer are highest in Pakistan. In Pakistan incidence and mortality rates are 5.2 and 2.8 times higher, respectively, than rest of the Asian countries [6]. Breast cancer is the 10th major cause of mortality in women of Pakistan [15,21]. In Pakistan younger population is affected by breast cancer more commonly when compared with affected population of West [6]. More than 50% patients present at an advanced stage (stage III and stage IV) [22]. Its incidence and mortality rates are rapidly rising in Pakistan and probability is that 1 in 9 women are diagnosed with breast cancer during their lifetime [23]. Lack of awareness about risk factors and symptoms, lack of evidence-based approach towards diagnosis and towards effective management is responsible for high incidence, morbidity and mortality rates in developing countries like Pakistan [11,24].

Delay in effective oncological treatment could be due to patient presentation delay and provider delay. Patient presentation delay refers to the time interval between development of symptoms and patient's presentation to health care provider. Patient presentation delay of greater than 3 months is associated with poorer outcomes [25]. While provider delay refers to the interval between first visit to a health care provider and initiation of effective oncological treatment [26]. Delay in presentation is significant in developing and developed countries as it is associated with advanced stage presentation and higher mortality rates [27].

Several studies have reported multiple factors responsible for advanced stage presentation. There is lack of awareness about symptoms and importance of self-breast examination. Patients are often unable to recall their initial symptoms unless these symptoms affect their daily routine[1]. Low socioeconomic status is seen to be responsible for advanced stage presentation and worse outcome [28]. Educational status, awareness about disease and access to health care resources are regarded significant factors [29]. All these factors can broadly be classified as personal, sociocultural and economic barriers [26]. Personal and economic factors are not modifiable such as age, marital status, ethnicity, previous history, family history, monthly income, cost of treatment and educational status of the patient. However, sociocultural factors such as stigmatization, awareness about disease, fear of treatment and social support are modifiable. Steps can be taken to overcome these barriers and decrease the presentation delays. The role of these factors is variable in developed and developing countries. In this article the effect of these factors in delaying patient presentation in developed and developing countries is reviewed.

METHODS

This literature review is written according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines with objective of analyzing data available for determining factors that are responsible for delayed presentation of breast cancer patients.

Search strategy A comprehensive computer literature search of PubMed/MEDLINE and ERIC was performed. The search algorithm was based on combination of terms: "delayed presentation" OR "late presentation" AND "breast cancer" OR "breast carcinoma". All the search papers were reviewed according to the selected search strategy. In addition, reference research papers were also included in this review to expand the search.

Inclusion of articles 143 papers were identified using the computer literature search. Titles and abstracts of all the papers were reviewed using the inclusion and exclusion criteria. 4 papers were excluded for duplication, remaining 139 papers were reviewed and 12 papers related to the topic were included in this literature review. Full text versions of the articles related to the topic were reviewed. No language,

age or gender restriction was applied. All papers from the year 2010 to 2020 were included in the literature search. Exclusion criteria included duplicate papers, poster presentations, papers not related to the topic, papers on other types of cancers, papers only addressing treatment options for breast cancer and papers on psychological effect of cancer on patients. The article selection process is given in Figure 1.

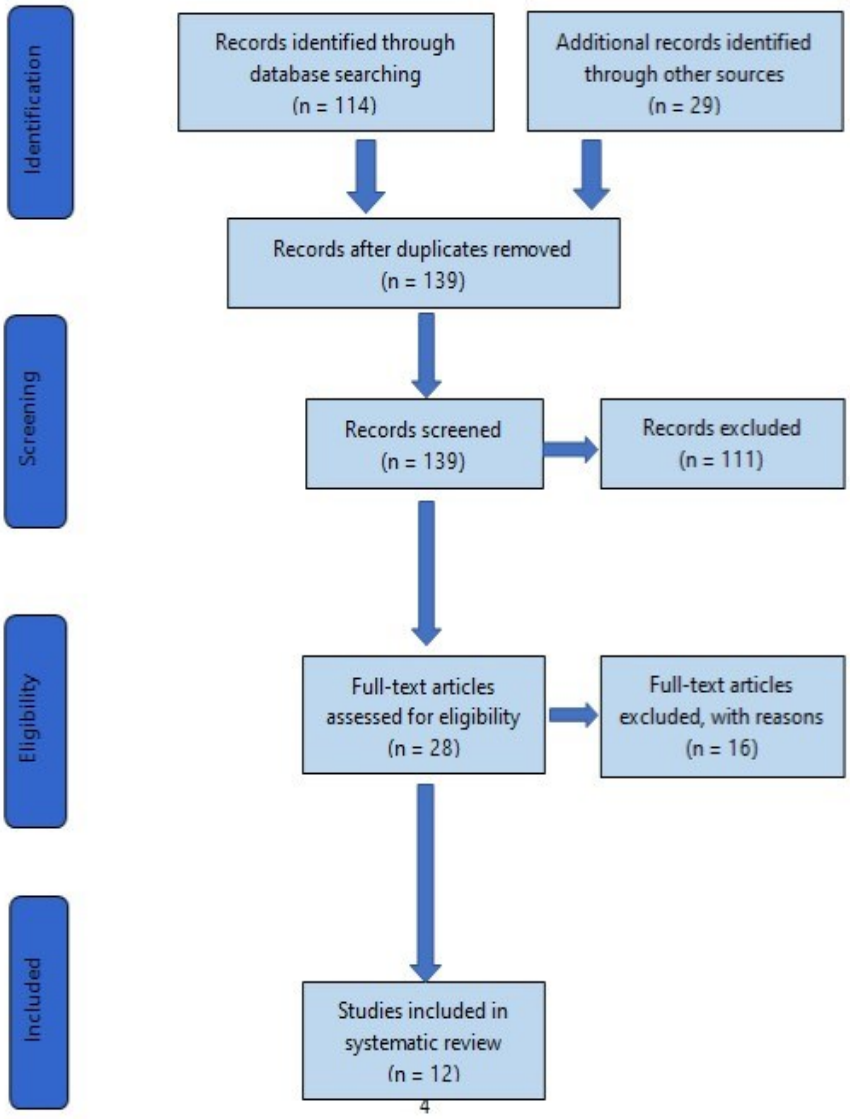

Figure 1: Article selection process through computer literature search

Data extraction and analysis: Thematic analysis of each eligible paper was done. Information about year of origin, author name, country of origin, method of study and theme identified was collected and coded. Barriers that delay presentation and diagnosis of breast cancer patients were identified and coded. The themes identified through analysis of the data are given in Table 1.

RESULTS

143 papers were identified through comprehensive computer literature search. Titles and abstracts of 139 papers were reviewed following removal of 4 duplicate articles. 28 papers related to the topic were thoroughly analyzed and 12 papers were included in this review. Themes identified in the included papers are coded in Table 1.

Year	Author	Country	Research Method	Themes Identified
2012	Sharma (Sharma et al, 2012)	USA	Systematic literature review	Increased access to health care facility and breast cancer awareness can enhance early diagnosis of cancer.
2013	Martins (Martins et al, 2013)	UK	Systematic literature review	Ethnic minorities are diagnosed later especially patients with breast cancer.
2014	Jones (Jones et al, 2014)	UK	Systematic literature review	In UK black women present with advanced stage more frequently than white women. They are also less likely to self-examine breasts and access screening for early detection. Fear of partner abandonment is a concern raised by women before surgical intervention.
2015	Donker (Donker et al, 2015)	Ghana	Systematic literature review	A complex matrix of factors delay presentation in Africa. Lack of awareness, alternate treatment and lack of healthcare facilities primarily delay presentation.
2017	Carolina (Carolina et al, 2017)	France	Systematic literature review	Delayed presentation and diagnosis are associated with poorer outcomes. Creating awareness can increase tendency of early diagnosis and referral and admission to health care facility for timely care.
2018	Baig (Baig et al, 2018)	Pakistan	Cross-sectional study of 89 patients Aged 25-64 years	Lack of awareness and health care facilities major barriers identified.
2019	Dong (Dong et al, 2019)	USA	Retrospective cohort study of 377 patients of stage I to stage IV breast cancer	Clinical and non-clinical factors which are associated with delaying the timely treatment benchmarks.
2019	Gulzar (Gulzar et al, 2019)	Pakistan	Retrospective study of 200 patients	Lack of awareness, illiteracy and poor social status are major presentation delaying factors.
2019	Brand (Brand et al, 2019)	USA	Systematic literature review	Studies on breast cancer and standardization of reporting delaying factors are required in developing countries.
2020	Naomi (Naomi et al, 2020)	USA	Retrospective cross-sectional study of 177,075 women	Racial minorities present at advanced stage receive aggressive treatment and poorer outcomes. Lack of health insurance is seen to have strong association with delayed presentation in developed countries.
2020	Sharma (Sharma et al, 2020)	India	Prospective study of 360 patients	Low educational status, fear of treatment, misinterpretation of symptoms and lack of awareness about disease are major reasons of delayed presentation.
2020	Agodirin (Agodirin et al, 2020)	Nigeria	Meta-analysis review of 236 articles	Misinterpretation of symptoms and fear related factors are most prevalent delaying factors in Africa.

Table 1 Thematic analysis of the 12 included studies summarized in the table

Several different factors are seen to be responsible for delayed presentation of breast cancer patients. These overlapping factors can broadly be classified as personal, sociocultural and economic [26]. The role of these factors in delaying the initiation of effective treatment is seen to be variable in developed and developing countries. The role of these factors is also seen to vary over time, geographic regions and appropriate interventions [30]. Understanding of these factors and their influence is crucial to effectively deal with modifiable factors and reduce the number of delayed and advanced stage presentations.

PERSONAL FACTORS:

Role of personal factors like age, marital status, ethnicity, personal history and family history is variable in developed and developing countries. Personal factors are not modifiable. Ramirez et al concluded that in developed countries there is strong association with older age, moderate association with educational status, non-white ethnicity, clinical presentation and non-disclosure of carcinoma symptoms and no association of marital status with the patient delay [25]. Younger age, lower income, positive family history and co-morbidities are all seen to be associated with missing the surgery or hormone therapy benchmark [31].

However, in developing countries strong association of positive family history, lower educational status and marital status (being unmarried/widowed/divorced) is seen in patient delay. There is evidence of moderate association of older age and clinical presentation to cause patient delay [26].

Age: Younger population is much more commonly affected in developing countries than in developed countries [18]. Breast cancer is generally not suspected in younger population and delay in diagnosis is observed by clinicians [32,33]. Younger population has aggressive presentation of breast cancer. They present with rapidly growing, high grade and negative hormone receptor types of breast cancer [34]. It makes chemotherapy more likely in younger population. In addition, breast cancer diagnosis in younger population

increases the risk of loss of fertility and normal ovarian function [35].

Ethnicity: In United States (US) racial or ethnic minorities present at a later stage and are reported to have higher morbidity and mortality rates [36]. Minorities in US have overall poor prognosis and poor quality of life [37,38]. In a study it is seen in US that 58% of the patients presenting at late stage were unmarried and 31% had less than high school education. It is also seen in the same study that 17% of Non-Hispanic Black women, 16% Hispanic and 15% American Indian and Alaskan natives were diagnosed at an advanced stage (stage III) compared with only 12% Non-Hispanic White and Asian women [14]. In UK black women are more likely to present at an advanced stage with metastatic disease and have poorer outcomes despite lower incidence than white women [39]. This disparity is seen in US and UK due to lower access and uptake of screening in black women than white women of both nations [40].

Knowledge of risk factors and ignorance of symptoms: Lack of knowledge of risk factors and ignorance of initial symptoms is associated with presentation delay and lack of motivation for self-examination of breast [41]. Ethnic minorities in US have less knowledge about risk factors and their potential to develop the disease. In UK only few women without breast cancer have the knowledge about increased risk of breast cancer in women above 70 years of age [42]. African-American and black women have lesser knowledge about increased risk of developing breast cancer if there is positive history in their mothers [41]. Many women in UK are seen to ignore the significance of their symptoms such as pain [41]. African- American women are seen to tolerate their symptoms and present for examination upon worsening of symptoms [43].

Gulzar et al, concluded that in Pakistan most patients presented with more than one symptom such as painless breast lump (81.1%), axillary node (4.25%), nipple discharge (3.2%) or signs of inflammation (2.1%) but due to ignorance of these symptoms' patients presented late. It was also concluded that marital status has strong association (99.2%) with delay as married women have responsibilities at home and they show lack of interest in their own health issues [6]. Baig et al, concluded that majority women delayed presentation as they believed initial symptoms were not significant [21].

SOCIOCULTURAL FACTORS:

Patient delay is influenced primarily by lack of awareness about symptoms and significance of breast self-examination, fear of the treatment especially mastectomy, preference of alternate treatments and lack of social support. Fear of mastectomy is the most common fear related factor. Herbal medicine and spiritual methods are used as alternate treatment options and both are preferred over orthodox medical treatment. In addition, use of herbal medicine is preferred over spiritual methods of care. Advice from family regarding treatment is a common social barrier [30]. However, sociocultural barriers are modifiable.

Sociocultural factors play a significant role in patient delay in developing countries. 34% women in Nigeria and 66% in Zimbabwe linked their delay to lack of awareness [44,45]. In Ghana 11% patients delayed presentation due to fear of diagnosis and 20% due to use of herbal medicine [46]. A study shows that symptom misinterpretation accounts for 50%, fear of diagnosis and treatment accounts for 16% and alternative treatment accounts for 10 % patient delay [30]. It also concluded that advice from family was the most significant social barrier [30].

Awareness and patient education: Lack of awareness about significance of breast self-examination, risk factors, symptoms, early detection though screening and treatment options are consistent findings among majority women. Women unaware of the symptoms lacked confidence for breast self-examination in US [47]. In UK white women are reported to self-examine more frequently than black women [42]. Lack of awareness about symptoms leads to ignorance of initial symptoms. Ignorance of pain due to lack of knowledge is seen to delay presentation in African-American women till the symptoms become intolerable [41]. Breast carcinoma is the second leading cancer related cause of death in US [31,48]. However, its incidence and mortality are reducing in US due to increase in awareness and patient education, early detection through screening and evidence-based treatment [49,50].

Agodirin et al, concluded that symptom misinterpretation is the dominant continent-wide delaying factor in Africa [30]. Before 2010 lack of awareness causing symptom misinterpretation (80%) was the most prevalent delaying factor in Africa, however, after 2010 characterizing symptoms as benign lesions (79%) has become dominant [30]. It indicates that awareness about occurrence of breast cancer has increased in Africa [51]. Gulzar et al, reported that in Pakistan 96% patients delayed presentation due to lack of awareness about symptoms, 73% due to shyness of examination by male doctor, 71% due to use of alternate herbal treatment, 65% due to stigmatization of the disease and 61% due to treatment by spiritual healers [6]. In Pakistan a number of studies have reported that lack of awareness about breast cancer, breast self-examination, and misinterpretation of symptoms contribute in delayed presentation [52,53]. Baig et al, concluded that lack of awareness is the most prevalent factor of delayed presentation in Pakistan [21].

Stigma, fear of examination and treatment: Stigma of breast cancer has appeared as a salient feature in US and UK. In US shorter delay is reported in women who disclose to others [54]. Fear of mastectomy is the most common fear related factor. Dong et al, concluded that patients who were recommended mastectomy did not meet the 45-day time to surgery benchmark. Similarly, patients presenting at advanced stage did not meet the chemotherapy benchmark

[31]. Patients recommended mastectomy had 3-fold greater delay than those recommended lumpectomies [31]. Fear of treatment is a dominant delaying factor in Africa and is seen to be responsible for delayed presentation of black women in developed countries as well [55]. Delay due to fear of treatment usually results in presentation at an advanced stage and more aggressive multidisciplinary treatment [30]. Nearly half of the patient delays were due to non-clinical issues such as seeking second opinion, indecision and family issues [31].

Donker et al, reported that late presentation of breast cancer in Africa is attributed to fear related factors and concluded that symptom misinterpretation is a regional problem [56]. However, Agodirin et al, concluded that symptom misinterpretation is a continent-wide problem and is much more dominant factor than fear related reasons of delayed presentation [30]. In West Africa pursuing alternate treatment options is a common practice probably due to fear related factors.

Social factors: Fear of partner abandonment is a common social barrier seen to delay presentation and seek help in African-American and white women [57]. Lack of support and fear of partner abandonment were significant factors raised during discussion of physical effects of surgery 41. In US family obligations are not seen to hinder presentation of patients [43].

In developing countries advice from family is the most significant social barrier [30]. Women is Pakistan have a key role in the family system [53]. They show lack of interest in their own health problems, in addition other factors such as fear of examination by male doctors, advice from family and shyness are also observed [58]. However, these factors are seen to become secondary once the diagnosed patients become aware about their health status and the disease [21].

ECONOMIC FACTORS:

Role of economic factors like high cost of treatment, high cost of travel to health care facility, access to health care facility, monthly income, and educational status is variable in developed and developing countries.

Health insurance: In developed countries health insurance plays a significant role in patient delay and treatment outcomes [59]. Patients without insurance lack prevention, screening access for early diagnosis and appropriate care, thus presenting at an advanced stage and having worse outcomes in terms of morbidity and mortality [60]. Naomi et al concluded that racial/ethnic minorities in US present at an advanced stage due to lack of health insurance. It was also demonstrated that 31% patients had less than high school education and 27% patients had low median income [14]. Diagnosis at a late stage is linked with high cost of treatment. Mittmann et al, concluded that cost of treatment of breast cancer is increased by stage [61]. Treatment of stage III patients is 58% more costly than stage I or stage II patients [62]. Gorey concluded that bias in health insurance in US is responsible for worse breast cancer outcomes, whereas in Canada due to universal health coverage this disparity is absent [63]. Jemal et al, demonstrated early-stage presentation in low-income patients when provided with health insurance [64]. Dong et al, demonstrated that patients with low income, lack of health insurance, advanced stage cancer and mastectomy surgery type did not meet the 45-day time line to surgery or 1-year hormone therapy benchmark [31].

Personal	Sociocultural	Economic
Age of the patient	Awareness about symptoms and importance of breast self-examination	High cost of treatment
Marital status	Alternate treatment options	High cost of travel to health care facility
Ethnicity / Race	Stigma	Access to health care facility
Clinical presentation of the patient/ Risk factors	Fear of examination by the doctor and fear of treatment	Income
Personal history of the patient	Denial	Educational status
Family history of the patient	Social support	Patient obligations at home

Table 2: A brief overview of personal, sociocultural and economic factors

Poverty and cost of treatment/travel: Infrastructure of developing countries for cancer prevention is non-existent or inadequate in quality, quantity and accessibility [26]. Sharma et al, concluded that poverty is the most common delaying factor in developing countries. Patient delay is commonly associated with low income, low education status, rural residency and lack of access to health care provider in developing countries [26]. In West Africa due to false belief of cheaper treatment, alternate care is pursued [30]. Gulzar et al, reported that in Pakistan 81% patients delayed presentation due to fear of high cost of treatment and 37% due to lack of access to health care facility [6]. Baig et al, demonstrated in a study that patients (63%) belonging to the rural areas had concerns regarding cost of treatment and cost of travel to health care facility [21].

Access to health care facility and education of health care providers: In UK access to health care facility is not seen to hinder presentation in black or white women [41]. However, booking appointment is seen as a more significant barrier than transport problems [42].

In developing countries health care providers should be educated about the significance of triple assessment: clinical examination, radiological evaluation and pathological examination. It can significantly increase the rate of accurate diagnosis, help in quick referral to oncologist and timely

initiation of effective treatment [30]. Education about the symptoms of breast cancer in young and old population is crucial for timely diagnosis. In North Africa misdiagnosis and lack of referral are second most common delaying factors 30. In West Africa and East and Central Africa access to health care is major delaying factor [51]. Baig et al, concluded that lack of access to health care systems is second major contributor of delayed presentations in Pakistan. [21]

DISCUSSION:

Breast cancer is a major health problem worldwide[1]. Alarming rise in its incidence necessitates adoption of steps that can be taken to reduce mortality rate. Variation in its incidence and mortality rates in developed and developing countries may be explained by difference in lifestyle and factors that delay patient presentation. Delayed presentation of breast cancer patients is associated with advanced stage diagnosis and poorer outcomes [14].
This review was aimed to identify major factors that delay presentation in developed and developing countries. On analysis it was found that advance stage presentation can be due to patient delay or provider delay. Patient delay refers to time interval between appearance of initial symptoms and presentation to a health care provider and it is defined as a span greater than 3 months [13]. While, provider delay is the interval between patient presentation to health care provider and start of oncological treatment [26]. Delay in presentation is a significant concern as it is associated with advanced stage diagnosis.

Factors which are seen to delay presentation are overlapping and can be broadly characterized as personal, sociocultural and economic [26]. The role of these factors in delaying presentation is seen to vary in developed and developing countries. These barriers also vary over time, geographic regions and on appropriate interventions [30]. Hence, the role of these barriers cannot be extrapolated from one region to another as different studies have demonstrated contradicting results.

In developed countries like US and UK racial/ ethnic minorities are seen to present at an advanced stage [14]. Advance stage diagnosis, aggressive multidisciplinary treatment, poorer quality of life and high mortality rates are more common in racial minorities of developed countries. Age, marital status, personal history and family history have association with delayed presentation for treatment [31]. Modifiable sociocultural factors are major barriers to presentation. Following the adoption of cancer control programs in developed countries delay due to sociocultural barriers is significantly reduced. Patient education, awareness about cancer and early detection through screening have reduced symptom misinterpretation, fear of diagnosis, fear of treatment and stigmatization of the disease. However, fear of treatment especially mastectomy or diagnosis at advanced stage are still reported to delay presentation [31]. Fear of treatment in developed countries is more prevalent in racial minorities especially black women. Economic factors play a significant role in patient and treatment delay in developed countries. Majority patients with delayed presentation and advanced stage diagnosis in developed countries have low educational status, low income and lack of health insurance. Patients delay presentation due to lack of health insurance and are diagnosed at advanced stage. Treatment cost increases with stage of the breast cancer at time of diagnosis. Treatment of stage III breast cancer is 58% more costly than stage I or stage II treatment [62]. Racial/ethnic minorities in US lack health insurance, hence present at an advanced stage.

In developing countries, a strong association of certain personal factors is seen to be responsible for delayed presentation in some regions. Age, marital status, misinterpretation of clinical symptoms and family history are seen to have strong association in delayed presentation. In developing countries younger population is more commonly affected than in developed countries [1,21]. Lack of awareness and less suspicion of breast cancer in young people is responsible for misdiagnosis and advanced stage presentation. Sociocultural factors play key role in delaying presentation in several developing countries. Due to lack of resources cancer control programs are not fully adopted in developing countries. Lack of awareness and fear related barriers are seen to be most prevalent sociocultural factors in developing countries [30]. These two barriers have been seen to influence presentation of racial/ethnic minorities settled in high-income countries. Lack of awareness, use of alternate treatment, anxiety, fear related problems and lack of social support are key factors to delay presentations in different developing countries. Infrastructure of developing countries is inadequate to reduce economic barriers. High cost of treatment is significant barrier to presentation. Low income, low educational status, lack of access to health care and high cost of treatment are major barriers in moderate-income and low-income countries 6.

Early stage diagnosis is significant for patients, their family and also the society. Diagnosis at an advanced stage negatively impacts patients and their families. Lack of health insurance in developed countries is associated with lack of prevention, screening and care [14]. Patients diagnosed at an advanced stage receive more aggressive treatment with overall poorer quality of life. Patient and provider related barriers are modifiable to varying extent. Fear of mastectomy or advanced stage diagnosis are seen to delay the treatment benchmark [31]. Gulshan et al proposed that mastectomy and concomitant reconstructive surgery could reduce delay in treatment [65]. Multidisciplinary approach is also proposed to reduce treatment delay [66].

Delay of 3-6 months is associated with large tumor size, advanced stage at presentation and poorer outcomes. Jassem et al, concluded that delay is seen to be lesser in women living in urban areas, with intermediate level of education or in those who work [67]. Factors linked to delayed presentation have a diverse distribution in Africa [30]. A study conducted in sub-Saharan Africa concluded that 90% patients present at stage III or stage IV, with large tumors and palpable nodal masses. Diagnosis at this stage has minimal survival rate even with optimal Western treatment [26].

The barriers responsible for presentation delay in developing countries have a very diverse distribution. Several studies have reported contradicting results due to which the findings cannot be generalized. However, taking essential steps to reduce the influence of modifiable factors is developing countries is crucial, owing to alarming raise in incidence rate and mortality rate in developing countries.

LIMITATIONS:

This review is subject to quality and limitations of previously published data. Most of the research is done in developed countries. Several studies propose contradicting results. The findings of developed countries cannot be generalized in developing countries. Limited studies are done on this topic in developing countries. Due to social, cultural and economic differences, findings of developing countries cannot be generalized from one area to another. Variation in role of personal, sociocultural and economic barriers is seen amongst developing countries. In addition, certain studies are done on a specific age group which may not be reflective of general population.

RECOMMENDATIONS:

Analysis of the literature has identified several factors responsible for delayed presentation of breast cancer patients. Certain steps can be adopted to reduce this delay in future:

- Awareness about risk of genetic inheritance can reduce delayed presentation in patients with positive family history.
- Awareness about symptoms, risk factors, importance of breast self-examination and disease can significantly reduce delayed presentation.
- Stigmatization that breast cancer is incurable or is not treatable can be reduced by creating awareness about available treatment options and their effectiveness.
- Increase the number of female doctors especially in rural areas to reduce fear related to examination by male doctor.
- Easy access to affordable health care facilities should be provided especially in rural areas, towns or small cities.
- Breast cancer awareness and control programs should be initiated in developing countries to reduce the effect of modifiable barriers.
- Screening tests for early detection of breast cancer should be made available in all health care facilities.
- Education of clinicians about significance of triple examination, common signs and symptoms and quick referral to oncologist can significantly reduce provider related delay.
- Concomitant breast reconstructive surgery can reduce the delay in treatment due to fear of mastectomy.
- Multidisciplinary approach can reduce delay in chemotherapy or surgical intervention due to fear of treatment.
- Availability of health insurance can reduce the disparity seen in racial minorities of developed countries.

CONCLUSION:

Breast cancer incidence is significantly rising in women worldwide. Early presentation in breast cancer is crucial for its management. Delay in presentation of over 3 months from the time of appearance of initial symptoms is associated with poorer outcomes and higher mortality rate. Several personal, sociocultural and economic factors are observed to play a role in delaying presentation. The distribution of these barriers is diverse over geographic regions. Social, cultural and economic differences make it complex to generalize the role of these barriers to early presentation. However, in developed countries cancer control programs have significantly reduced delays due to sociocultural factors. While economic factors are seen to play a crucial role in delaying presentation. In developing countries, a variation is seen in role of sociocultural and economic factors. Nonetheless, fear related problems, lack of awareness and poverty are seen to be most prevalent.

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Archives of Surgical Research | Invited Review

How to Investigate Bilateral Breast Nipple Discharge: An Account of Extra-mammary Causes and their Management

Asif Hussain

IMPORTANCE Nipple discharge is a common presentation with multiple causes including physiological, systemic and breast related causes. Investigations and management depend on the underlying cause. Detailed history & examination is often very helpful and investigations can confirm the clinical suspicion. This review is mainly focused on extra-mammary or systemic causes of breast discharge. Systemic causes are mainly investigated by medical team but many cases will need surgical input to fix the cause such as prolactinoma.

KEYWORDS Nipple Discharge, Mammary Causes, Extra-mammary Causes

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Invited Review

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Nipple discharge is a common complaint in females. It can be expected if it's within two years of delivery or during pregnancy or after abortion or intentional termination of pregnancy in the second trimester, in the absence of any sinister symptoms or signs. When it's abnormal, the cause can be local within the breast or systemic. Local causes in the breast can be benign (duct ectasia, Fibrocystic disease, ductal papilloma, mastitis, etc.) or malignant. Approximately 5-7% of cases of nipple discharge are due to Breast cancer[1], [Table 1].

Nature of the discharge	Etiologies	Unilateral/ Bilateral	Ducts involved.
Milky	Hyperprolactinemia Post-partum, Medications Chiari-Frommel syndrome.	Bilateral	Multiple
Serous/ Serosanguinous	Intraductal papilloma/ Papillomatosis Intraductal carcinoma.	Unilateral	One or two
Blood	Papilloma / papillomatosis Cancer, Trauma, Infection	Unilateral	One or two
Green	Fibrocystic disease	Bilateral	Multiple

Table 1: Nature of the discharge and possible etiologies

Physiological Vs. Pathological Nipple Discharge:

Clues for pathological discharge include non-lactational, persistent, spontaneous, coming from one duct, unilateral, serosanguinous, no cyclical variations, lump in the breast, lymphadenopathy, breast skin, or nipple changes. Chances of being malignant increase when blood-stained, unilateral, with a lump, past or family history of breast cancer, and the patient is 50 years or above. Multiple duct discharges are rarely malignant [2]. Work up for the local causes will include history, examination, mammogram, ultrasound breast, cytological examination, ductography, ductoscopy, biopsy, and resection [Table 2].

Types of discharge	Investigations	Treatment
Physiological	None	Reassurance
Systemic etiology	Prolactin, Growth hormone, FSH, LH, Oestradiol, Testosterone Thyroid functions, renal & Hepatic functions. Pelvic USS for PCOS MRI Pituitary-Hypothalamic area	Treat the cause Dopamine agonists Somatostatin analogues Pituitary surgery / radiotherapy
Local cause within breast	Mammography, USS Breast, Cytology, Ductography, Ductoscopy, Biopsy.	Treat the cause Surgical &/or XRT &/or Chemotherapy depending on the cause.

Abbreviations: FSH (Follicle Stimulating Hormone), LH (Luteinizing Hormone), PCOS (poly Cystic Ovarian Syndrome), USS (Ultrasound), XRT (Radiotherapy).
Table 2: Summary of the investigations and management.

Investigations to exclude any local cause:

1. Mammography: It's the first line and may show microcalcifications, change in breast tissue density. It has a 10% false-negative and 1-2% false-positive rate for detection of breast cancer in patients with nipple discharge. Mammography can findings should correspond to the area of the release.[3]
2. Ultrasound is complementary to mammography and may also help to take a biopsy. It can see 0.5 mm-sized

intraductal lesions. It may show hyperechoic (papilloma), calcified irregular, and margins with hypoechoic non-uniform lesions are usually carcinoma. Duct ectasia will show multiple dilated ecstatic subareolar tubules.

3. Cytology of the discharge or the sample obtained by ductoscopy or duct lavage is very useful. However, false-negative results are a drawback.
4. Ductography and dye localization of the ductal lesions. However, it can only be done if the nipple discharge is reproducible and if cannulation is possible. It can detect duct irregularities, filling defects, cut-off signs & helps localization of the lesion, which can assist biopsy/resection, hence increasing the yield of the surgical approach from 67% to 99%. It doesn't differentiate benign from malignant and doesn't specify underlying pathology [4, 5]
5. Duct endoscopy can help visualize the ducts and obtain samples and possible therapeutic options such as resection of the lesions[6].
6. Surgical biopsy by terminal duct excision is performed for pathological nipple discharge, especially when it is blood-stained [Table 2].

SYSTEMIC CAUSES FOR NIPPLE DISCHARGE:

Pathophysiological basis of the systemic causes: Any stimulation of thoracic nerves in the chest wall can cause a release of prolactin. Breast simulation, thoracic trauma, and herpes zoster are a few examples. Increased release of prolactin from the hypothalamic-pituitary axis due to hypothalamic damage, pituitary tumors, or the drugs affecting dopaminergic inhibition of prolactin can cause galactorrhea. High prolactin levels due to systemic causes such as hypothyroidism, Cushing, and other endocrine causes also cause nipple discharge. Cyclical causes of nipple discharge are based on hormonal fluctuations, and it changes depending on the days of the menstrual cycle. Usually, it's bilateral, copious, milky, and from multiple ducts.

Prolactin belongs to GH and the placental lactogen family as it shares common structural, functional, binding properties and common genetic ancestry[7]. Prolactin secretion is inhibited by dopamine, Gamma Amino Butyric Acid (GABA) & somatostatin, whereas it's promoted by Thyrotropin Releasing Hormone (TRH), opioids, oxytocin, serotonin, vasopressin, Vasoactive Intestinal Polypeptide (VIP), neurotensin, and galanin[8]. Prolactin has a role in stress as well, along with Adrenocorticotrophic Hormone (ACTH) and cortisol. It's also released from non-pituitary sites such as ovaries, endometrium, breast, lymphocytes, etc. It's metabolized in the liver and excreted through the kidneys [9, 10].

Etiologies of systemic diseases:

1. Pituitary-Hypothalamic causes: Microadenoma (<1cm) or macroadenomas (>1cm) of the pituitary is the commonest cause of pathologically high prolactin. They could be in isolation or part of syndromes such as Multiple Endocrinal Neoplasia (MEN-1) or Carney complex. Hypothalamic damage interrupts dopamine inhibition due to tumors, metastatic disease, stroke, infiltrative diseases, sarcoidosis, or Langerhans cell disease [11, 12].
2. Hypothyroidism also causes high prolactin due to high TRH. Polycystic Ovarian Syndrome (PCOS) can also cause high prolactin and galactorrhea. Renal failure, liver cirrhosis, causes high prolactin, but as the patients are usually sick and the reproductive system is suppressed, nipple discharge is not common [13, 14].
3. Pregnancy, Polycystic Ovarian Syndrome (PCOS), or other gynaecological causes are essential to exclude. Prolactin shares some structural and functional resemblance with placental lactogen.
4. Medications causing increased nipple discharge include antipsychotics (Phenothiazine), anti-emetic (metoclopramide), anti-depressants such as Tri cyclic anti-depressants (TCAs) or selective serotonin reuptake inhibitors (SSRI), a few anti-hypertensive drugs (methyldopa, atenolol), hormones including estrogen and progesterone. Drugs are reducing testosterone level or activity, such as danazol, cimetidine & opioids. Other drugs can affect the hypothalamic axis, including valproate, and drugs of abuse such as cannabis and Amphetamine. Medication-related nipple discharge is evident by history and the improvement when the culprit drug is stopped. First-generation Antipsychotics cause high prolactin more than second-generation drugs due to high Dopamine 2 Receptors (D2R) affinity. Aripiprazole, Olanzapine, and Quetiapine are second-generation with only a mild rise in prolactin and lesser galactorrhea[15] [Table 1].

Investigations for systemic causes: Prolactin level along with other pituitary hormones including Growth Hormone (GH), Thyroid function tests (TFTs), cortisol, and the blood tests for liver and kidney functions. Checking for other pituitary hormones is essential to exclude any co-secreting adenoma as many adenomas secrete prolactin and GH. Also, if there is macroadenoma, it can cause mass effect and hence deficiency of other pituitary hormones. Polycystic ovarian syndrome (PCOS) needs to be excluded, by pelvic scan and reproductive hormonal assessment, as it can also be one cause of nipple discharge. A pregnancy test is essential to make sure it's not due to placental lactogen. Macroprolactin should be excluded as macroprolactin is often not the cause of the discharge, even though the blood levels of prolactin are high. Macroprolactin is biologically not active unless it changes to a monomeric form. The drug list should be screened [16].

MRI Brain with Gadolinium is done to exclude adenoma. MRI Brain becomes especially important if there is no other reason for high prolactin or if there are focal symptoms and signs of pituitary-hypothalamic axis such as headache, visual

loss, raised intracranial pressure, or endocrinal changes suggestive of pituitary-hypothalamic disease. MRI Brain also is very helpful in patients who are on medications that can't be stopped, and we are not sure what was the baseline prolactin level before starting those medications. This is especially true for those on antipsychotics [17], [Table 2].

Management of systemic causes:

1. Pharmacotherapy: Microprolactinoma with no symptoms in a post-menopausal female doesn't require treatment. Dopamine agonists such as bromocriptine, cabergoline, quinagolide are first-line treatments for pathologically high prolactin. They also help reduce tumor size by apoptosis of lactotrophs. Bromocriptine is short-acting, needs a daily dose. Starting dose is 0.625mg to 1.25 mg / day. and the maximum dose is 15 mg/day. Cabergoline can be given once or twice a week, and the dose is 0.5-3.0 mg weekly. Quinagolide is a non-ergot D2R agonist with a once-a-day dose of 25 mcg OD, but the maximum can be 150 mcg/day. Cabergoline is the first choice due to its superior efficacy, convenience of dosing, and better side effect profile. Common side effects include nausea, vomiting, postural hypotension, Raynaud's, mood changes, psychosis, and extrapyramidal side effects. Currently, a screening echocardiogram should be done before stating Dopamine Agonists (DA) and then every 3-5 years to exclude any rare possibility of valvulopathy [18, 19]. Somatostatin analogues can also help control prolactin [20], [Table 2].
2. Surgery is an option for those who don't respond to drug therapy, macroadenoma with pressure effects, pituitary apoplexy, or young people who are not good candidates for lifelong treatment [21, 22].
3. Radiotherapy is the third option after medical and surgical causes[23].
4. Treat the underlying disease: Hypothyroid or chronic kidney disease (CKD) related high prolactin will settle when the underlying cause is treated. Drug-related high prolactin is best managed by stopping the drug when possible. Antipsychotics are not always easy to prevent or reduce the dose due to the risk of worsening of psychosis. Aripiprazole is a safer choice due to its partial agonist at D2R. Sex Hormone replacement is another option [24].

SUMMARY

Nipple discharge is a common presentation and is often due to local causes in the breast. Most important is to exclude any sinister reason, especially breast cancer. Through history, examination and testing are needed. Once local causes have been excluded, and the discharge is bilateral, milky, and coming from multiple ducts and is not serosanguinous, then a systemic search is needed. Drug history, assessment of pituitary-hypothalamic axis, thyroid functions, renal and hepatic functions are the main cornerstones of systemic assessment. Treatment depends on the cause. It can be managed by medications (dopamine agonists, somatostatin analogues, etc.) or surgery if it's prolactinoma. Treating hypothyroidism should normalize the prolactin. Pregnancy and lactation-related discharged or cyclical discharge often needs reassurance[25].

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Archives of Surgical Research | Invited Commentary

Coronavirus Vaccine Landscape in Pakistan: Where Do We Stand?

Maryam Riaz Tarar[1], Shehnoor Azhar[2]

IMPORTANCE Developing countries like Pakistan have had an opportunity to make the ongoing pandemic count. The country has already been on forefront of several natural disaster and conflicts in the past decades. In less than one year, recruitment of over 25000 volunteers nationwide shows the potential and local expertise available to undertake phase III trials for experimental vaccines. It augurs well for the local population to now be able to partake in high quality multi-country research given the health emergency created by SARS-CoV-2 since March 2020. Academic institutions have paved the way for biopharmaceutical sector to capitalize on.

KEY WORDS Clinical Trial, Covid-19 Vaccination, Corona virus Vaccine, CanSino, BIO ZF2001 Vaccine

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Invited commentary

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The year 2020 has seen a novel virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) spreading unchecked at global level resulting in unanticipated increase in morbidity and mortality caused by the new infection termed Covid-19. The transmission of this new virus among populations has been reduced to an extent by non-pharmaceutical interventions (NPIs) like mask usage, hand hygiene and maintaining social distancing. However, it is apparent now that vaccination may be the only way to effectively control this new affliction.

In Pakistan, the handling of the Coronavirus pandemic and strategic decision making from the capital has been under the domain of National Command & Operation Centre (NCOC) and Ministry of National Health Service (NHS). Initial pandemic control rested mostly on NPIs and lockdown of hot-spot areas of Coronavirus transmission in different parts of the country. However, vaccine procurement was not pursued by the government with the urgency it deserved. In Pakistan, the second unanticipated wave of infections in fall of 2020 was a stark reminder that Coronavirus situation was unpredictable and needed more than only promoting NPIs.

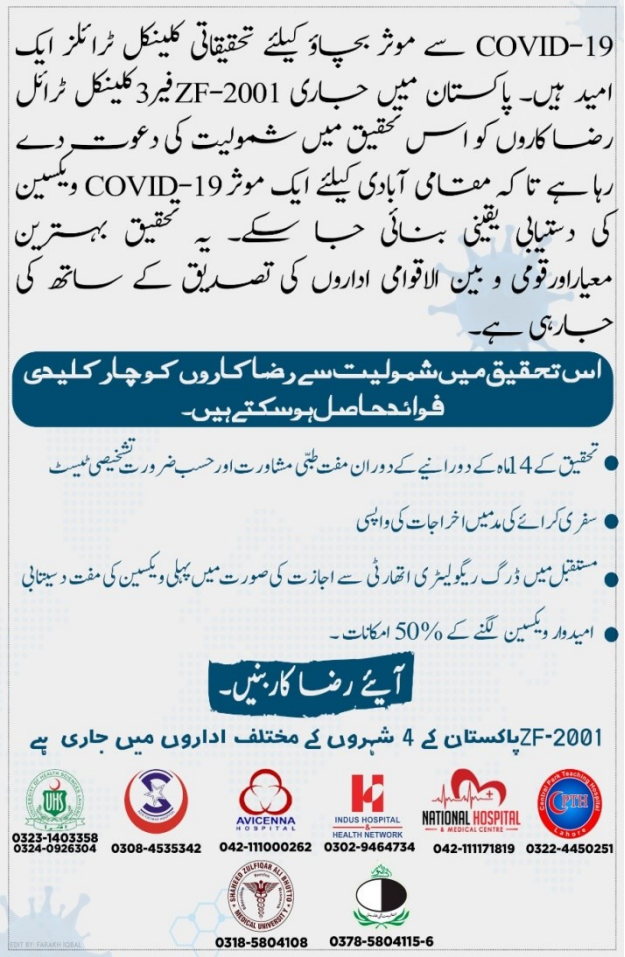
COUNTRY PARTICIPATION IN VACCINE TRIALS

CanSino BIO

The participant recruitment for multi-country study of candidate vaccine "CanSino BIO" started in Pakistan sometimes during late September 2020[1]. This was a product of a Chinese company CanSino Biologics, co-developed by the Chinese military. It was to be administered to above 18-year-old adults as a single shot intramuscular injection. Prior to enrolment at five centres nationwide during August 2020, the National Institute of Health (NIH) Islamabad, acting as the principal investigator on behalf of Government of Pakistan entered into an agreement with the parent company. This was to facilitate inclusion of private and public sector healthcare organizations into a multicentre phase 3 clinical trial, for recruiting volunteers for this vaccine candidate. The trial was approved by the Drug Regulatory Authority of Pakistan (DRAP) and National Bioethics Committee (NBC). In Lahore, University of Health Sciences (UHS) as a public sector organization took an initiative to develop a specially designed vaccine centre for this purpose to facilitate the recruitment process (Fig 1-3). It started enrolling volunteers on October 01, 2020, coincidentally the national day of Peoples Republic of China. A public health expert, directly reporting to the Vice Chancellor UHS, was nominated as a coordinator (Dr S.A) for overseeing the project from start to finish. At this facility, a total of 5000 volunteers were recruited in the trial during next couple of months, out of a total of 17,800 participants recruited on behalf of the NIH at Shifa International Islamabad, Shaukat Khanum & Hospital Research Centre, Indus Hospital and Agha Khan University[2]. The active ingredient was administered to half of the participants whereas the other half received a placebo. Besides Pakistan, participants were also recruited from Russia, Mexico and Chile. The product was based on traditional recombinant protein technology using Adenovirus 5 vector.

Figure 1-3: UHS Vaccination Centre (Picture credits: Mr Kamran Faiq – Autumn Pictures).

After CanSino BIO study, our public and private sector healthcare organizations also took part in another trial for Coronavirus vaccine "ZF2001" (Fig 4). This vaccine is co-developed by Institute of Microbiology in Chinese Academy of Sciences (IMCAS) and Anhui Zhifei Longcom Biopharmaceutical company[2]. Like the CanSino BIO trial, this was also approved by DRAP and NBC. The recruitment of adults above 18 years of age started in April 2021. The vaccine is different from CanSino BIO and belongs to a class called the protein subunit vaccines, based on Chinese Hamster Ovarian (CHO) cell[3]. It requires three doses to be administered by intramuscular injection over a period of two month and is without a placebo arm. The partnership with sponsors of ZF2001 and UHS Lahore has resulted in a project that will lead to development of a "Silk Road Clinical Research Centre" in the coming months, which will be a dedicated trial centre for future collaborative work.



MOVING BEYOND CLINICAL TRIALS

The contribution of our institutions, researchers and general population who acted as participants in Coronavirus vaccine clinical trials, with international companies at the forefront of vaccine production, has put our country's name on the map of vaccine related clinical research. It is of interest to note that one out of four different type of Coronavirus vaccines named on the front page of Dawn Lahore (2 June 2021, p. 1) bore the name PakVac; others being Pfizer BioNTech, Sinovac and Sinopharm. However, PakVac is not a pure Pakistani product as the name suggests. The vaccine concentrate that has been used to make locally packed doses of this vaccine has been procured from China and is a precursor of CanSino BIO vaccine as mentioned above. The PakVac vaccine was launched in the country on the first day of June 2021 at NIH Islamabad. It is hoped that three million doses will be packed every month and will be used to

immunize our population at a fast pace in year 2021 and beyond.

Currently, we are at a slow pace in vaccinating our population, keeping in view that the drive that should have started last year began on 2nd February 2021 with a limited quantity of gifted doses of Sinopharm from our Chinese neighbours. Initially "targeted approach" concentrated on vaccinating individuals in hight risk category like front line health care workers (HCWs) and those above 60 years of age. Now, with getting additional doses of different vaccines like Sinovac, Astra Zaneca and lately Pfizer BioNTech being added to the growing list (latter two vaccines through global COVAX initiative), the idea is to move towards "vaccinate all" approach. The government has now set aside one billion dollars for this purpose which is the way forward.

The procurement of Coronavirus vaccine has been difficult from international market as demand for vaccines surged with pandemic picking up momentum last year with devastating consequences for healthcare services, education sector and global economy. Who would have thought that by the end of year 2020, there would be hundreds of projects, all with one focus of producing the same vaccine? But this was all a part of pandemic control strategy which is dependent on vaccine production at fast pace. World Health Organization (WHO) has developed a landscape and tracker tool for Covid-19 that provides visual analysis of different candidate vaccine categories (Inactivated, Vector-based, m-RNA, Subunit, VLP [Viral like particles] & DNA).[3] It also provides overview about progress on different phases of trials being carried out in different parts of the world. Currently, there are 287 candidate vaccines with 102 in the clinical phase and 185 in the development phase[3]. The amount of interest in rapid development of the Covid-19 vaccines is an understatement as the amount of information being shared on daily basis as publications is difficult to keep a track of. We have seen new vaccine production technologies take the centre stage like messenger RNA vaccines without any stumbling blocks. We have also become familiar with terms like "Emergency Use Authorization" which in the past was only reserved for select situations as far as the vaccines were concerned.

This is certainly not the last pandemic to hit the humanity. It is of utmost importance that we are prepared as a nation to combat any assault of a similar kind in future and clearly define our pandemic control strategies. The wait and see policy in pandemics may work but is a very risky approach. We should not blur our focus from becoming a vaccine producing nation due to reliance on COVAX alliance donated doses. Pakistani public and private sector institutions with their proactive approach should provide a platform to involve biopharmaceutical industry to invest in research and local vaccine production.

As vaccine roll-out gathers momentum, the immediate task should be to allay fears in the mind of public at large so that there are minimum vaccination refusals. About 300,000 people who had received the first dose have failed to turn up for their second doses (Dawn Lahore 13 June 2021, p.6). There should be a fresh awareness campaign with citizen engagement to address this reluctance issue. Coercive measures like blocking salaries or phone SIMs will be counterproductive at this crucial stage (Dawn Lahore 6 June 2021, p. 6). There will be difficult times ahead when vaccination will move into urban areas. The key is to be provide up to date information to the public about success stories in other countries who have opened their borders for renewed business and economic activities. Don't we all wish to be included in "Green list of safe countries" instead of "Red list of unsafe countries" and avoid global travel restrictions?

In the future, there may be more vaccine defying variants than the ones we have at our hands now and more "waves" of infection to tackle. The emphasis must be on timely and smart decisions to fight this pandemic.

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Archives of Surgical Research | Case Report

Emergency Management Of Difficult Airway In Covid-19 Patient With Carcinoma Larynx

Aamir Bashir[1], Muhammad Naveed Azhar[2]

IMPORTANCE COVID-19 patients with airway tumors and requiring emergency airway management pose a significant challenge to anesthetists. This requires the use of advanced airway skills and instruments keeping in view the risk of cross-infection and aerosolization in covid-19 patients. We are presenting a case of 64 years old male patient with significant medical co-morbid conditions and carcinoma Larynx who presented in the emergency department of a tertiary care cancer hospital with worsening respiratory symptoms and came out to be COVID-19 positive. He was planned for mechanical ventilation and considering the anticipated difficult airway, was moved to the operating room for airway management. All the protective measures in the form of personal protective equipment (PPE) were adopted for all the dealing staff members in a designated operating room. He was successfully intubated with McGrath Video Laryngoscope and tracheotomy was avoided. This case highlights the importance of collaborative decision making, careful planning, and teamwork for the management of "Difficult Airway" in laryngeal tumor patients during the COVID-19 pandemic.

KEY WORDS Difficult Airway, Carcinoma Larynx, Covid-19

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Case Report

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COVID-19 pandemic has significant impact in clinical settings especially in patients with airway tumors requiring emergency airway management and it poses significant challenge to anesthetist. This requires use of advanced airway skills and instruments keeping in view the risk of cross infection and aerosolization to the staff members dealing these covid-19 patients. This case highlights the importance of collaborative decision making, careful planning and team work for the management of "Difficult Airway" in laryngeal tumor patients during COVID-19 pandemic.

CASE REPORT

64 years old male presented to COVID camp with history of fever and worsening of respiratory distress from last seven days. His history was notable for diabetes mellitus, ischemic heart disease and post coronary artery bypass grafting and squamous cell carcinoma of larynx for which he got radiation therapy and Cisplatin one years ago. His PCR for COVID-19 was positive. He was admitted to ICU with type-1 respiratory failure. He was put on Non-invasive ventilation for worsening of respiratory failure but he did not respond well. After discussion in multidisciplinary team, it was decided to start invasive mechanical ventilation should respiratory function deteriorate further.

Due to failure of non-invasive ventilation, the ICU team called the anesthesia team for emergency intubation. Consultant Anesthetist on-call responded in due time as per hospital policy that all intubation in COVID-19 patients to be done by consultant anesthetist.

Detailed history, physical examination and investigations were reviewed. CT scan of neck showed marked narrowing of supra-glottic airway due to squamous cell carcinoma of larynx. This was an anticipated difficult intubation. Therefore, we formulated the plan to move the patient from ICU to operating room for endotracheal intubation and had maxillofacial surgery team standby for emergency tracheostomy in case of intubation failure.

Considering the risk of cross infection during airway instrumentation, the whole anesthetic team did proper donning with full PPE (N95 mask, surgical mask, face shield, surgical cap, water impermeable gown, shoe covers, and hazmat suit with double gloves). All emergency drugs and airway equipment were ready during transfer.

Having all standard monitors attached and BiPAP was replaced with non-rebreather face mask and FiO2 kept at 100% in slightly head up position. Inhalation induction was started with Sevoflurane and 100% FiO2 on spontaneously breathing patient. Sevoflurane concentration was increased gradually till we achieved MAC of 1.3. Laryngoscopy was performed with McGrath Video Laryngoscope. Supra-glottic anatomy was all distorted; epiglottis, arytenoid folds and even the vocal cords were not visible. Gum elastic bougie was introduced through the glottic opening and 6mm Micro Laryngeal Tube was railroaded over the bougie. Anesthetic

circuit was attached and ETT position confirmed on capnography. Sedation and muscle relaxation were started and patient remained hemodynamically stable throughout procedure. He was shifted back to ICU with same monitoring, intravenous propofol infusion and put on mechanical ventilator. Further, ETT position was confirmed on chest X-ray in ICU.

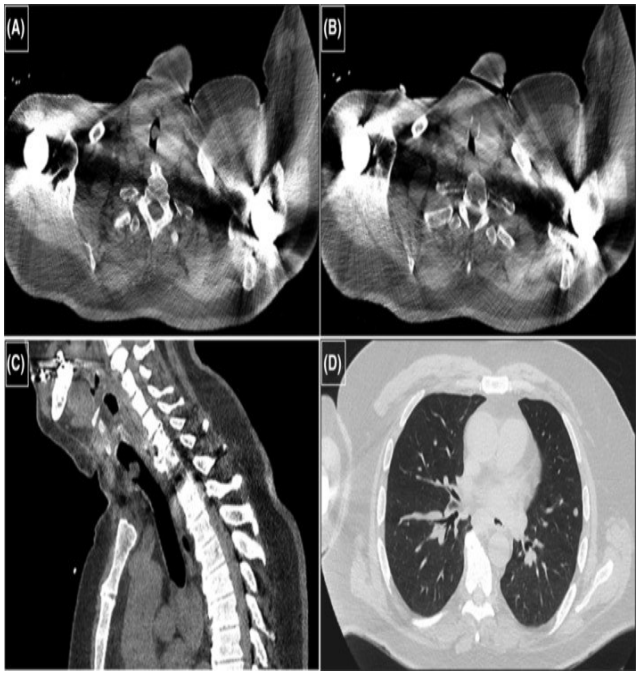

Figure 1: CT scan images of neck

DISCUSSION

In this case report, a patient with potentially difficult airway and confirmed COIVD infection had to undergo emergency endotracheal intubation. This patient was already treated with radiation therapy and chemotherapy one year ago. Guidelines have been developed by the Association of Anesthetist, UK for managing the airway in patients with difficult airway [1].

This was a complex scenario due to laryngeal tumor treated with radiation, COVID infection, multiple co-morbidities and emergency intubation. This complex case put health care workers at greater risk of exposure to COVID infection. Tracheal intubation is a potentially high-risk procedure for the airway manager, particularly as it risks exposure to a high viral load and if transmission occurs to health care workers, this may be associated with more severe illness [2]. For this reason, airway managers should take appropriate precautions. A systematic review of infection risk to health care workers, based on limited literature, ranked airwayprocedures in descending order of risk as: (1), tracheal intubation; (2), tracheostomy (and presumed for emergency front-of-neck airway (FONA)); (3), non-invasive ventilation (NIV); and (4), mask ventilation [3]. Tracheal intubation in critically ill patients is a high-risk procedure with physiological difficulty: around 10% of patients in this setting develop severe hypoxaemia (SpO2< 80%) and approximately 2% experience cardiac arrest. These figures are likely to be higher for patients with severe COVID-19 and drive some of the principles below. The first-pass success rate of tracheal intubation in the critically ill is often < 80% with up to 20% of tracheal intubations taking > two attempts [4]. Patients with head and neck malignancies are commonly treated by a combination of surgery and adjuvant chemotherapy and/or radiotherapy. The degree of airway changes due to the radiation varies from patient to patient. Radiotherapy induces edema with subsequent fibrosis or necrosis in the exposed tissues. These changes may affect the buccal mucosa, bone dentition, and larynx [5].

Video laryngoscopy may be of help to give an indication of the severity of the airway problems if mouth opening is sufficient which was not there in our case. A video laryngoscopic assisted fibreoptic intubation would probably have warned us for the impeding airway disaster[6].

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Author Guidelines

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As a journal covering all surgical specialties, ASR aims to facilitate the transfer of important ideas and thought systems between and across specialties. Hence, ASR will help prevent the trend of increasing sub-specialization which leads to 'tunnel-vision' and the unfortunate concealment of important surgical advances within specific specialties.

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- ASR-Ethical Compliance Undertaking (WORD FORMAT) (PDF FORMAT)
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- ASR-Consent Form of Case Reports (WORD FORMAT) (PDF FORMAT)
- ASR-Peer Reviewer Proforma (WORD FORMAT) (PDF FORMAT)
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- Cover Letter
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- All tables (including titles, description, references)
- Ensure all figure and table citations in the text match the files provided
- Supplemental files, if applicable
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2. SUBMISSION CHECKLIST

(HIGH LEVEL OF COMPLIANCE IS REQUIRED; THE ARTICLES NOT IN COMPLIANCE WOULD BE RETURNED)

The authors must comply with these important checklist items prior to submitting their manuscript for publication as the non-compliant manuscripts would be returned without review: -

1. Manuscripts should be prepared following Uniform requirements for manuscripts submitted to Biomedical Journals as approved by the International Committee of Medical Journal Editors (www.icmje.org). The manuscript handling is done through Committee on Publication Ethics (COPE) guidelines.
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3. All original manuscripts should have Abstract in structured format up to 350 words. It should mention Objective, Methodology, Results, Conclusions and appropriate Key Words.
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11. Disclosure regarding source of funding and conflict of interest if any besides approval of the study from respective Ethics Committee/Institution Review Board.
12. Manuscript must be submitted along with IRB/Ethics Committee Approval letter.
13. Case Reports should be submitted along with Consent Form wherever applicable.

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Further Considerations:

- Manuscript has been checked for correct spelling and grammar
- All Reporting Guidelines have been met
- All references mentioned in the Reference List are cited in the text, and vice versa
- All figures and tables are cited in text
- Permission for use of copyrighted material from other sources has been obtained
- A conflict of interest statement is provided, even if the authors have no conflicting interests to declare
- All research and clinical trials are registered in a public registry
- Journal policies detailed in this guide have been reviewed
- Referees and reviewers suggested by author(s) comply with journal policies as well.

3. BEFORE INITIATING SUBMISSION PROCEDURE

Ethical Confines

The work detailed in the manuscript must be approved by the appropriate ethical committees related to the institution(s) in which it was performed, including verification that all subjects involved gave informed consent. Records of written consent must be kept by the author. Studies involving experiments with animals must follow institution guidelines for the care of animal subjects. Any identification markers of patients and volunteers – including names, initials, and hospital numbers – must NOT be used.

Declaration of Interest

All authors must disclose financial and personal relationships with individuals or organizations that could potentially introduce bias to their article. Examples of possible conflicting interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications or registrations, and grants or other funding. If there are no interests to declare, then please: 'Declaration of interest: none'. This summary statement will be published if the article is accepted.

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Verify that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis), that it is not being considered for publication anywhere else, that its publication is approved by all authors, and by the responsible authorities/institutions where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form without the written consent of the copyright-holder. Verify that the work is original – all manuscripts are checked for plagiarism, and if found to be plagiarized above a certain degree, the author is liable to be blacklisted.

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- Agreement to be responsible for all aspects of the work, and ensuring that the accuracy or integrity of any part of the work is maintained.

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Role of Funding Source

The funding source must be disclosed along with their degree of involvement with the research matter, if any, in the design, collection, analysis or interpretation of data; in the writing of the article, or in the decision to submit the article for publication. If the funding source had no involvement, then this should be stated. Any authors found guilty of scientific misconduct will be blacklisted from future publications.

4. PREPARATION

Reviewing Process

This journal is reviewed using a *double blind* method through OJS. The following categories the journal will accept, out of guest editorials, original articles, review articles, case reports, clinical updates, short communications, book reviews, case studies, clinical notes, Continuation of Medical Education (CME), obituaries , letters, Knowledge-Attitude-Practice (KAP) studies, routine surveys and cross sectional studies. The authors are required to suggest potential refrees for the review process. The journal however would have to discretion to get the article reviewed by the suggested faculty or not.

Reporting Guidelines

Compliance with the relevant reporting guideline is mandatory for submission of the following guidelines:

1. Submit a completed checklist, indicating the page numbers where compliance to the guidelines was ensured.
2. Mention in the 'Methods' section that the research is being reported in line with the relevant guideline, which should be named and cited.

Randomized Controlled Trials

All randomized controlled trials submitted for publication in Archives of Surgical Research must include a completed

Consolidated Standards of Reporting Trials (CONSORT) flow-chart and ensure that all features of the CONSORT checklist are present. A copy of the CONSORT checklist must be uploaded in supplemental material. Refer to the CONSORT statement website here.

Systematic Reviews

Systematic reviews are to be reported in accordance to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines and must include the flow-chart as a figure and the checklist as a supplemental material. Please download a PRISMA Flowchart and a PRISMA Checklist here. To aid and improve the methodological quality of your article, include an AMSTAR 2 checklist as well, which is available here.

Cohort, Case-control and Cross-sectional studies

Cohort, Case-control and Cross-sectional studies must be compliant with the STROCSS criteria (Strengthening the reporting of cohort studies in surgery), which is available here. Cite the following paper: Agha RA, Abdall-Razak A, Crossley E, Dowlut N, Iosifidis C, Mathew G, for the STROCSS Group. STROCSS 2019 Guideline: Strengthening The Reporting Of Cohort Studies in Surgery. Each study type has its own checklist which must be uploaded as supplemental material.

Diagnostic, Quality Improvement and Qualitative studies

Diagnostic studies should be reported according to the STARD statement criteria (Standards for the Reporting of Diagnostic Accuracy studies). The flow-chart should be a figure and checklist should be uploaded as supplementary material. Quality Improvement studies must comply with the Standards for Quality Improvement Reporting Excellence (SQUIRE) criteria, which is available here. Qualitative studies require the Consolidated criteria for Reporting Qualitative Research (COREQ) checklist, available here.

Health Economic Evaluation

Health Economic Evaluation studies should conform to the CHEERS statement, available here.

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Tumor Marker Prognostic studies should be reported according to the REMARK criteria.

Before and After Studies

Before and After studies measure specific characteristics of a population or group of individuals after an event or intervention, compare them with those characteristics before the event or intervention, then measure the effects of the event or intervention. These studies should conform to the STROCSS statement.

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Animal studies must be reported according to the ARRIVE guidelines (Animals in Research: Reporting In Vivo Experiments) and must include the checklist as supplemental material. An example of a completed checklist can be found here. The institutional protocol number must be included at the end of the abstract.

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Qualitative Surveys should be reported according to the criteria detailed in the SRQR Guidelines. Guidelines for synthesis of qualitative research can be found here. Guidelines for interviews and focus groups are available here.

Case Series

Ensure that the case series is compliant with the PROCESS Guidelines and submit a completed PROCESS checklist. State that the work has been reported in line with the PROCESS criteria and cite the following paper: Riaz A. Agha, Mimi R.Borrelli, Reem Farwana, Kiron Koshy, Alex Fowler, Dennis P. Orgill, for the PROCESS Group. The PROCESS 2018 Statement: Updating Consensus Preferred Reporting Of CasE Series in Surgery (PROCESS) Guidelines.

Article Structure

Title Page

The title page should give the title in capital letters and a shorter running title. Avoid abbreviations and formulae if possible. In addition, the title page should also include:

- Correctly spelled names of all authors, and their affiliation addresses where the actual work was done. Include the e-mail address of each author.
- Signpost clearly the correspondence author who will maintain contact at all steps of reviewing and publication, and post-publication, and answer any questions about the research. All information must be updated in case of any changes.
- Present/permanent address of every author.
- The source of funding of the research.
- The number of figures and tables, the total word count and the total number of pages of the manuscript.
- A sample Title Page has been uploaded on this page above.

Abstract

All original articles must accompany a structured abstract of up *to 250-350* words. It should state aims of the study, methodology and materials used, results obtained, and conclusions reached. Specify how the sample selection of study subjects or experimental animals was carried out, specify the observational and analytical methods, and give specific data and its statistical significance, where possible. Highlight novel and significant aspects of the study. Avoid references, but if necessary, cite the author(s) and year(s). Avoid non-standard or uncommon abbreviations, but if necessary they must be defined at their first mention in the abstract. This page should constitute of the abstract and keywords only.

Keywords

Right after the abstract, provide a maximum of *6* keywords, using British spelling. Avoid general and plural terms and

multiple concepts (avoid, for example, 'and', 'of'). Only abbreviations firmly established in the field may be appropriate. These keywords will be used to aid the indexing process of the journal.

Introduction

Outline the aims of the work and provide sufficient background information, avoiding a lengthy literature review or a summary of the results.

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Results

Results should be clear and succinct. They must be presented in the form of text, tables and illustrations. The content of the tables should not be repeated in the text; the tables should be numbered and identified and referenced to as their number. A conclusion that either supports or negates the hypothesis should be included. If the data is inconclusive, that should also be noted.

Discussions

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References from books should include author, title, publisher, and year of publication. Example:

Das JC. *Power System Harmonics and Passive Filter Designs*. John Wiley & Sons, Inc; 2015.

For articles in journals, the authors, title of article, name of journal, year of publication, and an article identifier and page range (where available) must be included. See the following example:

Zhu Z, Hoffman JE. Condensed-matter physics: Catching relativistic electrons. *Nature.* 2014;513(7518):319-320.

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For government reports, technical reports, and scientific reports, if the report number is unavailable, then cite the report as a book. For reports it is usually not individual people that are credited as authors, but a governmental department or agency. Include the name of the agency, the title of the report, the publisher, and the year of publication. An example is as follows:

Government Accountability Office. *The Manager, the Government, and the Accounting Profession*. U.S. Government Printing Office; 1968.

References to Ph.D. dissertations, Master's theses or Bachelor theses follow the format outlined below, and must include author, title, publication detail if applicable, and year of publication.

Campbell AJ. History transformed: Sengoku Daimyo in Japanese popular media. Published online 2012.

For newspaper articles, citation must include the author, title, name of newspaper, full date and page number. The example is as follows:

Kinsley M. Paid Leave Counts as Progress. *New York Times*. May 27, 2017:SR3

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Acknowledgements

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5. FURTHER CONSIDERATIONS

World Limits

Maximum length of the original manuscript should not exceed *4000* words including title page, table and references. For review articles, the maximum word count is *3500,* however considering the demand of the subject it can be up to 8000 words. Maximum number of tables & illustrations should not exceed 5. Short reports of cases, clinical experience, drug trials and their adverse effects can be submitted. Maximum length of these case reports should not exceed *800* words, *5* maximum number of references, and *2* table or illustrations. For letters, maximum words are *600* with *5* references. Extra charges will be applicable for lengthy manuscripts.

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Système Internationale (SI) units should be used, with the traditional equivalent in parentheses where appropriate. Avoid non-standard or uncommon abbreviations, but if necessary they must be defined at their first mention. Submit math equations as editable text. Add simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. Variables are to be written in italics. Powers of e should be denoted by exp. Any equations that have been presented separately from the text (if referred to explicitly) must be numbered consecutively.

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Make sure to use uniform lettering and sizing of original artwork. For original illustrations, use Arial, Courier, Times New Roman, Symbol, or a font that looks similar. Number the illustrations according to their order in the text with a logical naming convention for the artwork files. Provide captions to illustrations separately. Size the illustrations close to the desired dimensions of the published version, avoiding any files that are disproportionately large. Submit each illustration as a separate file. If the electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply in the native document format without alterations or conversions. If the application used is not part of Microsoft Office, convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

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Submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or separately at the end in an appendix. Number tables consecutively according to their sequence in the text and present any table notes below the table body. Keep the use of tables to a minimum and ensure that the data included in them is not repeated in results described elsewhere in the article. Avoid using vertical rules and shading in table cells.

Supplementary Material, Research Data, and Video

Supplementary material such as applications, images, and sound clips, can be published with the article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Submit this material with the manuscript and supply a concise, descriptive caption for each file. If you want share data that supports your research publication, where appropriate, interlink the data with the article. Research data refers to the results of experimentation that validate research results. To enable reproducibility and data reuse, share the software, code, models, algorithms, protocols, methods and other useful materials related to the project. If you have made your research data available in a public data repository, link the dataset directly into your article. To enable transparency, we require you to state the availability of data in your submission if your data is unavailable to access or unsuitable to post. Authors who wish to submit video files with their article are encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed, or separately at the end. Keep the file in one of the recommended file formats with a preferred maximum size of 150 MB per file, 1 GB in total.

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This is in accordance with COPE guidelines.

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6. When a large multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, general supervision of the research group does not qualify any one to be an author. All contributors who do not meet the criteria for authorship should be listed in the acknowledgment section. Those who provide technical support, writing assistance, or department chair who provided just general support should also be mentioned in acknowledgment. It is also important that all those whose names appear in acknowledgement must have given permission to be acknowledged.

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Authorship disputes should be brought to light via email to relevant editors. They are handled through COPE Guidelines.

Complaints and Appeals

Archives of Surgical Research (ASR) follows COPE guidelines in case of appeals to the journal's editor's decisions and complaints about ASR's journal management of the peer review process.

If authors wish to file a complaint or appeal against an editorial decision, they are encouraged to email: editorial@archivessr.com, with the subject heading mentioning "COMPLAINT" or "APPEAL". We have dedicated Ombudsperson for handling such appeals.

Furthermore, Archives of Surgical Research (ASR) consults COPE guidelines if a reviewer is suspected of appropriating or mismanaging author material and may refer such cases to COPE if required.

Data and reproducibility

Archives of Surgical Research (ASR) follows ICMJE data sharing guidelines.

In case of suspected data falsification/fabrication, respective authors will be asked to clarify and explain their methods.

To Improve transparency, we encourage use of and link to international standard reporting guidelines such as those listed in the EQUATOR Network. We encourage pre-registration of clinical trials (and other study designs) in an online clinical study database before data are collected (eg, ClinicalTrials.gov). We encourage journal pre-registration and peer review of study protocols before data are collected (eg, as promoted by the Center for Open Science).

We have system of scruitiny to find such data manipulations, if found may result in:

1. Rejection of their submitted manuscript
2. Communication of the authors' misconduct will be made to relevant institutions and regulatory bodies
3. Black-listing of the authors from ASR for all future submissions

This is in accordance with COPE guidelines.

In case of suspicion of image manipulation in a manuscript, COPE flowchart will be followed.

Ethical Oversight

Archives of Surgical Research (ASR) follows COPE guidelines for ethical oversight, wherever applicable. ASR has it's own consent form for case reports, which is mandatory along with the submission of the manuscript. The consent form is adapted from BMJ Case Reports and is in line with COPE guidelines. To determine whether a study requires ethical approval or not, ASR looks to COPE guidelines.

Furthermore, ASR requires a transparency declaration from the lead author of an original study guaranteeing honesty and accuracy (as published & implemented by the BMJ and endorsed by the EQUATOR network).

Post-publication Review and Audit

If authors whose work has been accepted and/or published wish to retract/correct/revise their articles, please email: editorial@archivessr.com, with the subject heading mentioning "RETRACTION" or "CORRECTION" or "REVISION".

Conflict of Interest Policy

Adopted from Conflict of Interest in Peer-Reviewed Medical Journals which is prepared by WAME Editorial Policy and Publication Ethics Committees.

Articles would be published with statements or supporting documents declaring:

Authors' conflicts of interest

Sources of support for the work, including sponsor names along with explanations of the role of those sources if any in study design; collection, analysis, and interpretation of data; writing of the report; the decision to submit the report for publication; or a statement declaring that the supporting source had no such involvement; and Whether the authors had access to the study data, with an explanation of the nature and extent of access, including whether access is on-going.

To support the above statements, editors may request that authors of a study sponsored by a funder with a proprietary or financial interest in the outcome sign a statement, such as "I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis."

Disclosure form is available from the website, which has been adapted from ICMJE Disclosure Form and should be filled at the time of acceptance of manuscript. Disclosures are also obtained whenever deemed necessary at the time of review and editorial tasks.

9. EDITORIAL POLICIES

Principles of Transparency and Best Practice in Scholarly Publishing are followed as per ICMJE guidelines. This Journal strives to adhere to the ***Principles of Transparency and Best Practice in Scholarly Publishing*** which could be found in the **DOAJ** Web site completely,

This Journal has established a guideline for editorial independence as delineated below. The guideline generally follows that created by the World Association of Medical Editors.

1. This Journal is operated by Pakistan Endocrine & Thyroid Surgeons Association (PETSA), which is publishing organization.
2. The Chief Editor is responsible for independent leadership of This Journal editorial operations. The General Publishing Editor reports to the Editor-in-Chief for all editorial matters.
3. The Editor-in-Chief has full authority over the content of this Journal and its related offerings. This includes summaries and comments on recent medical advances, opinions, blogs and news.
4. Content-related decisions are based on quality, importance, and value to the users of this Journal. Contributing authors, editors, This Journal staff are free to express responsible positions -even if these views are not in agreement with interests, policies or published research, editorial or commentary of PETSA.
5. This Journal actively seeks input regarding editorial matters from the physician Editors-in-Chief in an advisory capacity, as well as from the other editorial board members, internal editorial staff, and readers.
6. Editors-in-Chief of this Journal is empowered to create content and commentary free of commercial and organizational influence. All authors and editors operate without conflict of interest and all potential conflicts are disclosed (please also see Conflict of Interest Policy).

10. PEER REVIEW POLICY

We follow ICMJE recommendations on the manuscript handling. The practice of peer review is to ensure that only good science is published. It is an objective process at the heart of good scholarly publishing and is carried out by all reputable scientific journals. Our referees play a vital role in maintaining the high standards Review Policy and all manuscripts are peer reviewed following the procedure outlined below:

Initial manuscript evaluation

The Editor first evaluates all manuscripts. It is rare, but it is possible for an exceptional manuscript to be accepted at this stage. Manuscripts rejected at this stage are insufficiently original, have serious scientific flaws, have poor grammar or English language, or are outside the aims and scope of the journal. Those that meet the minimum criteria are normally passed on to at least 2 experts for review. Most of the submitted manuscripts are reviewed except few invited or editorial content.

Type of Peer Review

Policy employs double blind reviewing, where both the referee and author remain anonymous throughout the process.

How the Referee is selected

Whenever possible, referees are matched to the paper according to their expertise and our database is constantly being updated. The referee is selected both from the editorial team and outside and depending on the author suggestions.

Referee Reports

Referees are asked to evaluate whether the manuscript: - Is original - Is methodologically sound - Follows appropriate ethical guidelines - Has results which are clearly presented and support the conclusions - Correctly references previous relevant work. This is a systematic process and works on the well-designed Peer Review Proforma. The confidentiality of the peer review is ensured. Reviewers are encouraged to report conflict of interest, ethical misconduct etc.

Language correction is not part of the peer review process, but referees may, if so wish, suggest corrections to the manuscript.

How long does the review process take?

The time required for the review process is dependent on the response of the referees. Should the referee's reports contradict one another or a report is unnecessarily delayed, a further expert opinion will be sought. The Editor's decision will be sent to the author with recommendations made by the referees, which usually includes verbatim comments by the referees. Revised manuscripts might be returned to the initial referees who may then request another revision of a manuscript.

Final Report

A final decision to accept or reject the manuscript will be sent to the author along with any recommendations made by the referees, and may include verbatim comments by the referees.

Editor's Decision is Final

Referees advise the editor, who is responsible for the final decision to accept or reject the article.

Conflict of Interest

All reviewers and editors have to declare any potential conflicts of interest if any. We follow COPE and ICMJE guidelines in this regard.

Editorial and Peer Review Processes Generally Follow these Steps:

We follow and request from authors, reviewers and editors the "ICJME Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals". Editorial reviewer policy is independent of any financial, academic or any other interest.

- When an article is submitted to Archives of Surgical Research, Editor makes the first check of submitted articles (structure, plagiarism, scientific quality).
- Article may be rejected, sent back for structural revision, or sent to at least two reviewers for peer review.
- After peer review process, articles may be rejected, sent back for revision requested by reviewers or accepted for publication.
- Revised articles by authors may be accepted, resent to reviewers, resent to authors for additional corrections/revision or rejected.
- Authors could not see reviewers' information. Editor may make authors' information available to reviewers or not.
- Accepted articles are forwarded to publishing process.
- Editor(s) may require additional materials or changes from authors during copy editing, composing, grammatical editing and/or proof reading steps.
- A fast track review system is in place upon deposition of additional processing fee (Rs. 20,000), however we do not encourage such route and should be employed only in significant circumstances. Moreover, this does not ensure that manuscript if accepted would be published on priority.
- Post-publication review and peer review is encouraged and is managed through letter to the editors.

11. STATEMENT OF INFORMED CONSENT

We follow ICMJE and COPE Guidelines for appropriate consenting. Patient's privacy should not be breached without taking consent. In written descriptions there should not be any specifications regarding patients including names, hospital numbers, photographs or pedigrees unless the information is needed for scientific purposes and the patient allows for publication with written informed consent. It should be disclosed by authors to the patients that any identifiable material could be available on the Internet or in printed form after publication. Patient consent ought to be written and archived with the journal, the authors, or both, as settled by local rules and regulations. Applicable laws vary from territory to territory, and journals should make their own policies with legal guidance. Since a journal that archives the consent will be aware of patient identity, some journals may decide that patient confidentiality is better guarded by having the author archive the consent and instead providing the journal with a written statement that attests that they have received and archived written patient consent.

Nonessential identifying details should be omitted. Informed consent should be obtained if there is any doubt that anonymity can be maintained. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are de-identified, authors should provide assurance, and editors should so note, that such changes do not distort scientific meaning.

The requirement for informed consent should be included in the journal's instructions for authors. When informed consent has been obtained, it should be indicated in the published article.

- International Committee of Medical Journal Editors ("Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals")

12. GUIDELINE FOR REVIEWERS

Peer review in all its forms plays an important role in ensuring the integrity of the scholarly record. The process depends to a large extent on trust, and requires that everyone involved behaves responsibly and ethically. Peer reviewers play a central and critical part in the peer-review process, but too often come to the role without any guidance and unaware of their ethical obligations.

Archives of Surgical Research follows COPE Guidelines for educating the reviewers for the review process.

13. ETHICAL EDITING FOR EDITORS

Becoming an editor of Archives of Surgical Research is an exciting but daunting task, especially if you are working alone without day to day contact with editorial colleagues. This short guide aims to summarize key issues and to provide links to relevant pages of the COPE website as well as those of other organizations. We encourage the editorial team to consult COPE and ICMJE resources frequently for their training and handling of the manuscript and various editorial issues.

14. GUIDELINES FOR JOURNAL MANAGEMENT

We believe that Archives of Surgical Research serves as an important part of the scientific literature. Hence, its management should be of the highest quality and ethically sound. We follow COPE Guidelines to manage the top hierarchy in terms of conflicts of interest and ethical considerations. We also following COPE Guidelines for maintaining relationship of journal management to the Pakistan Endocrine & Thyroid Surgeons Association to ensure editorial independence. The journal editorial teams meets periodically at least biannually. The editorial team is independent of the society and is managed by a transparent process two yearly as per the ethical confines suggested by COPE, ICMJE and local guidelines.

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"publisher-created version" - the definitive final record of published research that appears in the journal and embodies all value-adding publisher activities including copy-editing, formatting and pagination.

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Archives of Surgical Research
A Peer Reviewed Surgical Journal

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