Breast Cancer

Comprehensive Management

Editor-in-Chief
Shashanka Mohan Bose

Editors
Suresh Chander Sharma
Alok Mazumdar
Robin Kaushik

Springer

Breast Cancer

Comprehensive Management

Shashanka Mohan Bose
Editor-in-Chief

Suresh Chander Sharma
Alok Mazumdar • Robin Kaushik
Editors

Breast Cancer

Comprehensive Management

Springer

Editor-in-Chief
Shashanka Mohan Bose
Former Senior Professor and Head
Department of Surgery, PGIMER
Chandigarh, India

Former Professor of Surgery, AIIMS
New Delhi, India

Editors
Suresh Chander Sharma
Former Senior Professor and Head
Department of Radiotherapy
PGIMER, Chandigarh and MM Institute of Medical Sciences, Mullana
Ambala, Haryana, India

Alok Mazumdar
Senior Consultant and Head
Department of General Surgery
Seven Hills Hospital
Visakhapatnam, Andhra Pradesh, India

Robin Kaushik
Professor
Department of General Surgery
Government Medical College and Hospital, Sector 32
Chandigarh, India

ISBN 978-981-16-4545-7 ISBN 978-981-16-4546-4 (eBook)
https://doi.org/10.1007/978-981-16-4546-4

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Foreword

Cancer, once a "whispered-about" illness, has metamorphosed into a lethal entity with not only medical but also scientific and socio-economic implications. In the 1930s, infections used to be the major cause of death, however, over the years, with the control of such diseases, increase in the life expectancy, and changing lifestyle and habits, noncommunicable diseases like cancer are going to be the deadliest epidemic of the twenty-first century. In higher and middle-income countries, cancer has already overtaken cardiac disease as the major cause of death.

Breast cancer is the most common cancer among women in India and worldwide. As per the latest NCRP report, 205,424 women and 5377 men would be inflicted with breast cancer in 2020. Out of these, 75% would be in advanced stages. Notably, all the population-based cancer registries in India have shown an increase in the incidence of breast cancer.

The history of breast cancer dates back to 3000–2500 BC in the surgical papyrus of Edwin Smith. Advances in the understanding of this disease have evolved from the Halstedian concept of supra-radical surgeries to Fisherian concept of systemic disease. In the present era, with tremendous advancements, breast cancer is a classic example of the application of personalized medicine. The surgeries have become less morbid and more cosmetic. Medical management is more targeted and tolerable, and radiation therapy is more precise, focused, as well as shortened in duration. All these developments have led to the management becoming more acceptable to

patients leading to breast conservation and presentation at earlier stages than before. Molecular markers have helped us not only in tailoring the treatment but also have been used from diagnosis till surveillance.

Owing to its common occurrence, breast cancer is being managed at several centers which include rural and remote centers as well. The current book encompasses all possible aspects of breast cancer from anatomy, pathology, imaging, management, and follow-up to the organization of cancer support group. This is bound to be helpful to all those involved in cancer care.

I have known the editors and most of the authors for more than four decades. I wish to congratulate them for the excellent compilation of "breast cancer topics" in this book. The authors are seasoned masters and "teacher to teachers" in this field for several decades. The information contained in the book would serve as a ready reference to those even in the remotest area with limited access to updated scientific information and will certainly help them in at least referring the patients to a comprehensive cancer center as well as early diagnosis. To me this is one of the important contributions this book will make.

I am confident that this book will be highly appreciated, amply rewarded, and accepted by all in need for the basic as well as advanced understanding of breast cancer and would serve its purpose of reaching to all involved in the concern and care of breast cancer.

21 August, 2020

G. K. Rath, MD, FAMS
Professor of Radiation Oncology & Chief;
National Cancer Institute
Jhajjar, India

Dr. B. R. Ambedkar Institute, Rotary Cancer Hospital, AIIMS
New Delhi, India

Preface

From the Desk of Editor-in-Chief — Shashanka Mohan Bose

Breast cancer was presumed to be a common problem of affluent and developed countries, but it is no more true. Its incidence is rapidly increasing, and presently, it is the second most common cancer affecting Indian females; and very soon it will be the leading cancer problem in Indian females.

Indian data are not reliable, but it is estimated that one in 18—20 Indian females is likely to develop breast cancer during their lifetime. 80,000 to 90,000 new patients are seen every year and add to the existing patients; the total breast cancer burden at any given time becomes about 10 lakhs. The complexity of multimodality treatment, the existing healthcare delivery system, and the financial condition of the country make it very difficult to look after this enormous number of patients.

Breast cancer is full of controversies, in all aspects, and this makes it a very poorly understood disease that often defies rational management in all parts of the country. Add to this the unique importance of breasts as an object of beauty and grace. The Editor-in-Chief of this book and the authors of the various chapters have been interested in the problems of breast cancer for a very long time, devoting their careers in the fight against breast cancer, not only for its management but also in teaching and training postgraduate students and upcoming surgeons.

We are not aware of any Indian book which comprehensively deals with all the aspects of breast cancer. I was closely involved with a very interesting and lively seminar on Breast Cancer on August 1–2, 1998, conducted in PGI, Chandigarh, and this was followed by a book on "Consensus on Breast Cancer." 22 years later the situation has not altered much, and there is still no Indian book on the subject that can fill the gap.

Medical science progresses rapidly, and it is said that in 20 years time the entire subject requires complete overhauling. We accepted the challenge and were lucky that the superspecialists of different aspects of breast cancer, most of them being close friends, accepted my requests for their contributions in this book. Unfortunately

(but fortunate for our book), this was the time of coronavirus pandemic, when most of us were without major professional responsibilities, and we could complete our manuscripts in a short time.

Breast cancer has a few peculiar problems in India: the disease is seen in younger females (about 10 years earlier), more than half the patients are in LABC stage on the first consultation, and most of the patients are very poor. They neither can afford sophisticated and costly investigations nor the multimodality treatment. Regular follow-up is also very erratic because of illiteracy and poverty.

In addition to the nonavailability or poor availability of multimodality treatment across the length and breadth of our country, there is an acute shortage of dedicated specialists in all the desired fields—surgeons, medical oncologists, cytologists and pathologists, radiologists and imaging experts, nuclear medicine experts, radiotherapists, counselors, palliative care and rehabilitation experts, and so on. This results in only a fraction of patients with breast cancer receiving comprehensive, multimodality, and standardized treatment under a single roof and under the guidance of an expert team. It is also felt that the knowledge of an average medical doctor is far from satisfactory and hence neither the patient is diagnosed properly nor referred to a specialist.

The first chapter "Current Scenario of breast cancer in India" has been included to draw the attention of all readers to the above-mentioned factors, and the first chapter should be taken as a continuation of Preface.

We thought of coming out with a book on all current aspects of breast cancer, authored by well-known academicians, which would help formulate and guide evidence-based treatment, which can be provided in the majority of centers in our country.

The authors have tried not to get lost in the ocean of breast cancer research, but follow the well-trodden path of evidence-based medicine, and we hope this will be helpful to all the readers of the book. Considering the large number of chapters written by different authors, there is a possibility of repetition of some aspects; we have not gone in great details to avoid the repetition as we feel that it is better to have repetition, of course in different angles, rather than to miss the facts.

We are thankful to all our contributors, reviewers, and supporters who have given their time and mind for the book; the quality of the book entirely depends upon the contributors and reviewers.

I think I shall be echoing the sentiments of all the contributors for conveying our sincere thanks to our colleagues, our support staff, our students and patients, and last but not the least, our families for their constant support and encouragement which allowed us to carry on with our professional activities.

The book is offered to all those who are interested in any aspect of breast cancer, and we sincerely hope that they will find the book interesting, instructive, and educative.

Contents

About the Editors

About the Editor-in-Chief

Shashanka Mohan Bose, MS, FRCS(E), FRCS(G), FAMS, FACS, FICS, FACG did his medical graduation from G R Medical College, Gwalior, India, in 1963, and postgraduation in surgery from Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, in 1966. He joined PGIMER as Registrar in surgery in 1967, continued his ascent, and superannuated as Senior Professor and Head of Surgery Department in 2002. He had also worked as Professor in Surgery at AIIMS, New Delhi. In addition, he was trained in some of the best surgical units of the world—Royal Postgraduate Medical School and Hammersmith Hospital, London; Kings College, London; Memorial Sloan Kettering Cancer Centre, New York, etc. Following his superannuation, he continues to practice as senior consultant oncosurgeon.

Dr. Bose has been interested in surgical oncology and GIT surgery. He is known for his surgical skills and is credited with a number of innovations and initiation of procedures and techniques. He is specially known for his vast experience and expertise in the field of breast cancer surgery, and has probably been one of the first in the country to pioneer breast conservation surgery.

Dr. Bose has always taken active part in professional organizations, held a number of positions in various societies, such as National President of Association of Surgeons of India; Indian Association of Surgical Gastroenterology and President of Chandigarh Surgical Society.

Dr. Bose is a recipient of three National awards: Dr. B.C. Roy National Award as eminent medical teacher, MCI National Award for outstanding research, and

Department of Science & Technology Award for outstanding communication skills. He is a recipient of multiple International and National fellowships including that of WHO, UICC, etc. He is also a recipient of more than 25 prestigious oration awards.

His autobiographical book *Memoirs of a Surgeon beyond Incisions, Blood, & Sweat* has been recently published. He is very much interested in health education of people and has written a number of books, and a large number of articles in lay press.

About the Editors

Suresh Chander Sharma, MD Former Professor and Head, Department of Radiotherapy, Postgraduate Institute of Medical Education and Research, Chandigarh. He was also former Professor & Head, and is presently Professor Emeritus, Department of Radiotherapy, Institute of Medical Sciences and Research, Mullana, Ambala.

Dr. Suresh Chander Sharma did his MD in Radiotherapy from PGIMER, Chandigarh, in 1976. He joined the department as Lecturer in 1980 and rose to become Professor in 1998. He headed the department from April 1994 till his retirement in August 2014. He upgraded the Department of Radiotherapy to become a most modern department with facilities for providing all latest techniques of radiotherapy—3D CRT, IMRT, VMAT, IGRT with motion control facilities, and SRS and SBRT. Apart from iridium brachytherapy, he also introduced HDR cobalt brachytherapy.

Dr. Sharma has special interest in the management of breast cancer, lymphomas, and brachytherapy. He has published nearly 240 scientific papers in National and International journals of repute. He has contributed 6 chapters in different books.

Dr. Sharma is a recipient of prestigious P.K. Halder Memorial Oration of the Association of Radiation Oncologists of India (AROI) in 2005. He was Chairman of Indian College of Radiation Oncology from 1998 to 2002 and President of AROI from 2002 to 2004.

After retirement from PGIMER Chandigarh, He joined MM Institute of Medical Sciences and Research, Mullana, in September 2014 where he established the department of radiotherapy and also started MD Radiotherapy course in 2018.

Alok Mazumdar, MS, DNB, FICS graduated from Christian Medical College, Ludhiana, and did MS in General Surgery from PGIMER, Chandigarh. He worked in the Department of General Surgery, PGIMER, Chandigarh, as Senior Resident for 3 years. He received DNB in General Surgery and also FICS. Presently, he is working as Head of the Department of Surgery, Seven Hills Hospital, Visakhapatnam. He is interested in teaching and training postgraduate students as a part of DNB (Diplomate of National Board, New Delhi). He is a member of a number of professional associations—ASI, AMASI, NASA, IASO, IMA, and others.

Robin Kaushik, MS, DNB graduated from Armed Forces Medical College, Pune, and later qualified for M.S. in General Surgery from Dayanand Medical College and Hospital, Ludhiana. He joined GMCH, Chandigarh soon after, where, among other things, he developed a keen interest in the management of breast cancer. He is an avid reader and writer, and has authored books on surgery and even ventured into fiction. He served as Associate Editor for the *Indian Journal of Surgery* for nearly 14 years, and is currently working on multiple book projects.

Contributors

Anshika Arora, MS
Assistant Professor, Department of Surgical Oncology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, Uttarakhand, India

Jyoti Arora, CCST, FRCR, MD, DMRE, Fellowship in Breast Imaging, Bristol, UK
Associate Director, Imaging and Nuclear Medicine, Medanta the Medicity Hospital, Gurugram, Haryana, India

General Secretary, Breast Imaging Society of India, New Delhi, India

Amanjit Bal, MD, DNB
Professor, Department of Histopathology, PGIMER, Chandigarh, India

Anita Dhar Bhan, DNB, FCLS, PhD
Professor, Department of Surgical Disciplines, AIIMS, New Delhi, India

Anish Bhattacharya, DRM, DNB, PhD
Professor and Head, Department of Nuclear Medicine, PGIMER, Chandigarh, India

Shashanka Mohan Bose, MS, FRCS(E), FRCS(G), FAMS, FACS, FICS, FACG
Former Senior Professor and Head, Department of Surgery, PGIMER, Chandigarh, India

Former Professor of Surgery, AIIMS, New Delhi, India

Aditi Chaturvedi, MS, MCh (Surgical Oncology)
Consultant, Department of Surgical Oncology, Max Institute of Cancer Care, New Delhi, India

Chintamani, MS, FRCS, FACS, FICS
Professor and former Head, Department of Surgery, VMMC, Safdarjang Hospital, New Delhi, India

President, Asian Society of Mastology, Kolkata, West Bengal, India

Ekta Dhamija, MD
Associate Professor, Department of Radiodiagnosis, IRCH, AIIMS, New Delhi, India

Jaya Ghosh, MD, DM
Professor, Department of Medical Oncology, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

K. S. Gopinath, MS (Bom), FRCS (Ed.), FAMS, FAIS
Director, HCG Hospital and Bangalore Institute of Oncology, Bengaluru, Karnataka, India

Professor of Surgery and Oncology, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India

Neeru Goyal, PhD
Associate Professor, Department of Anatomy, Christian Medical College, Ludhiana, Punjab, India

Ishu Gupta, MBBS, MD
Senior Resident, Department of Medical Oncology, VMMC, Safdarjung Hospital, New Delhi, India

Madhur Gupta, MD
Former Professor and Head, Department of Anatomy, PGIMER, Chandigarh, India

Sudeep Gupta, MD DM
Director, Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Mumbai, Maharashtra, India

Professor of Medical Oncology, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

Smriti Hari, MD
Professor, Department of Radiodiagnosis, AIIMS, New Delhi, India

Satish Jain, MS, FAIS, FICS, FACS
Director, Department of Surgical Oncology, Ludhiana Mediways Hospital, Ludhiana, Punjab, India

Sumeet Jain, MS, MCh
Associate Professor, Department of Surgical Oncology, Dayanand Medical College and Hospital, Ludhiana, Punjab, India

Dushyant Jaiswal, MS, MCh
Professor, Department of Plastic and Reconstructive Surgery, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

Jnaneshwari Jayaram, MS
Senior Resident, Department of Surgical Disciplines, AIIMS, New Delhi, India

Kusum Joshi, MD, PhD, FAMS
Former Professor and Head, Department of Histopathology, PGIMER, Chandigarh, India

Pramod Kumar Julka, MD, FAMS
Former Professor and Head, Department of Oncology, AIIMS, New Delhi, India

Senior Director, Max Institute of Cancer Care, New Delhi, India

Rakesh Kapoor, MD, FICRO
Former Professor, Department of Radiotherapy, PGIMER, Chandigarh, India

Director, Homi Bhabha Cancer Hospital and Research Center, Mullanpur and Sangrur, Punjab, India

Abhay K. Kattepur, MS, MCh, DNB, MRCS-Ed
Assistant Professor, Division of Surgical Oncology, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India

Robin Kaushik, MS, DNB
Professor, Department of General Surgery, Government Medical College and Hospital, Sector 32, Chandigarh, India

Niranjan Khandelwal, MD
Former Professor and Head, Department of Radiodiagnosis, PGIMER, Chandigarh, India

Farheen Khan, MS
Senior Resident, Department of Endocrine and Breast Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Krishan Kumar, PhD
Assistant Professor (Clinical Psychology), Department of Psychiatry, PGIMER, Chandigarh, India

Sandeep Kumar, MS FRCS, PhD, MMSc
Former Professor, Department of Surgery, King George's Medical University, Lucknow, Uttar Pradesh, India

Founder Director, AIIMS, Bhopal, Madhya Pradesh, India

Dhritiman Maitra, MS MCh, DNB, FIAGES, FACS
Assistant Professor and In-Charge, Breast and Endocrine Surgery Services, Department of Surgery, Medical College, Kolkata, India

Jeevanjot Matharoo, MD
Fellow in Breast Imaging, Medanta the Medicity Hospital, Gurugram, Haryana, India

Saumya Mathews, MS, MCh
Assistant Professor, Department of Plastic and Reconstructive Surgery, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

S. K. Mattoo, MD
Professor and Head, Department of Psychiatry, PGIMER, Chandigarh, India

Ajeet Pratap Maurya, MS
Associate Professor, Department of Surgery, AIIMS, Bhopal, Madhya Pradesh, India

Alok Mazumdar, MS, DNB, FICS
Senior Consultant and Head, Department of General Surgery, Seven Hills Hospital, Visakhapatnam, Andhra Pradesh, India

Anjali Mishra, MS, PDCC
Professor, Department of Endocrine and Breast Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Mahesh C. Mishra, MS, FRCS, FAMS, DSc (Hon. Causa)
Emeritus Professor, JPN Trauma Centre, AIIMS, New Delhi, India

Former Director, AIIMS, New Delhi, India

Saroj Kanta Mishra, MS, DNB
Professor and Head, Department of Endocrine and Breast Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

R. Muralidharan, MD, DM (Endo)
Director, Department of Endocrinology, Fortis Hospital, Mohali, Punjab, India

Shashank Nigam, MS, MRCS, DNB, MNAMS
Consultant in Surgical Oncology, Lucknow, Uttar Pradesh, India

Ashwin Singh Parihar, MD
Postdoctoral Research Associate, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri, USA

Vani Parmar, MS, DNB
Professor, Department of Surgical Oncology, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

Firuza Patel, MD
Former Professor, Department of Radiotherapy, PGIMER, Chandigarh, India

Mentor and In-charge, Chandigarh Hospice and Palliative Care Service, Chandigarh, India

Manisa Pattanayak, MS
Associate Professor, Department of Surgical Oncology, Himalayan Institute of Medical Sciences, Dehradun, Uttarakhand, India

Manish Rohilla, MD
Associate Professor, Department of Cytology and Gynecological Pathology, PGIMER, Chandigarh, India

S. Raja Sabapathy, MS, MCh, DNB, FRCS
Director and Chairman, Division of Plastic, Hand, Reconstructive Microsurgery and Burns, Ganga Hospital, Coimbatore, Tamil Nadu, India

Sunil Saini, MS
Professor and Head, Department of Surgical Oncology, Himalayan Institute of Medical Sciences, Dehradun, Uttarakhand, India

R. Raja Shanmugakrishnan, MS, MRCS, DNB (Plastic)
Consultant, Division of Plastic, Hand, Reconstructive Microsurgery and Burns, Ganga Hospital, Coimbatore, Tamil Nadu, India

Suresh Chander Sharma, MD
Former Senior Professor and Head, Department of Radiotherapy, PGIMER, Chandigarh and MM Institute of Medical Sciences, Mullana, Ambala, Haryana, India

N. K. Shukla, MS
Professor and Head, Department of Surgical Oncology, Sriram Cancer Centre, Mahatma Gandhi Medical College & Hospital, Mahatma Gandhi University of Medical Sciences & Technology, Jaipur, Rajasthan, India

Rajender Singh, PhD
Principal Scientist, Male Reproductive Biology Laboratory, Endocrinology Division, Central Drug Research Institute, Lucknow, Uttar Pradesh, India

Bhawna Sirohi, FRCP
Consultant Breast and GI Medical Oncologist, Apollo Proton Cancer Centre, Chennai, India

Member, UK TNM committee, London, UK

Radhika Srinivasan, MD, PhD (Mol Oncol), MIAC
Professor and Head, Department of Cytology and Gynecological Pathology, PGIMER, Chandigarh, India

Anurag Srivastava, MS, FRCS, PhD, MPH
Former Professor and Head, Department of Surgical Disciplines, AIIMS, New Delhi, India

Megha Tandon, MS, MRCS (Ed.), DNB
Associate Professor, Department of Surgery, VMMC, Safdarjang Hospital, New Delhi, India

Romila Tiwari, MBBS
Specialist Medical Officer, Max Institute of Cancer Care, New Delhi, India

Hari Venkatramani, MS, MCh (Plastic), DNB (Plastic)
Senior Consultant, Division of Plastic, Hand, Reconstructive Microsurgery and Burns, Ganga Hospital, Coimbatore, Tamil Nadu, India

Dinesh Yadav, MS, MCh
Associate Professor, Department of Surgical Oncology, Sriram Cancer Centre, Mahatma Gandhi Medical College & Hospital, Mahatma Gandhi University of Medical Sciences & Technology, Jaipur, Rajasthan, India

Prabha Yadav, MS
Director and Professor, Department of Plastic and Reconstructive Surgery, Sir H N Reliance Foundation Hospital, Mumbai, India

Former Professor and Head, Department of Plastic and Reconstructive Surgery, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

The Editors would like to thank Dr. Ashim Das, Professor, Department of Histopathology, PGIMER, Chandigarh and Dr. (Professor) Arvind Rajwanshi, presently Director, AIIMS, Rishikesh, Uttarakhand for their help in reviewing a few chapters and Dr. Naveendeep Kaur, Senior Resident, GMCH, Sector 32, Chandigarh for her art work in Chapter 22.

Breast Cancer Scenario in India

1

Shashanka Mohan Bose and Robin Kaushik

1.1 Introduction

Breast Cancer, was not seen commonly in India earlier, but presently has become the most common cancer affecting Indian females. The incidence is rapidly increasing and it has overtaken cancer of cervix in metropolitan cities. Data available from the Indian Council of Medical Research (ICMR) as well as the Global Cancer Observatory (GLOBOCAN) rank breast cancer as number One in incidence, mortality and prevalence by site [1, 2].

Indian data, often a bane in the past, is now reporting more and more cases of breast cancer −1.62 million new cases were diagnosed and 87,090 deaths were reported in 2018 [1, 3]. It is estimated that one out of every 20 Indian females is likely to develop breast cancer during their lifetime. If you add the number of new patients to the existing, the total breast cancer burden at any given time becomes enormous. In addition, the complexity of multi-modality treatment makes it very difficult to look after this enormous number of patients.

Shashanka Mohan Bose, MS, FRCS(E), FRCS(G), FAMS, FACS, FICS, FACG (✉)
Former Senior Professor and Head, Department of Surgery, PGIMER, Chandigarh, India

Former Professor of Surgery, AIIMS, New Delhi, India
e-mail: drsmbose@gmail.com

Robin Kaushik, MS, DNB
Professor, Department of General Surgery, Government Medical College and Hospital, Sector 32, Chandigarh, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_1

1.2 Aetiological Factors Influencing Breast Cancer in India

The incidence of Breast cancer increases with age and this is true in India also. There is a higher incidence of breast cancer in younger women in India and most hospital based series report the median age of breast cancer patients to be a decade younger than western figures; the average age of presentation in India is around 50 years; prognosis is poorer in younger patients [1, 4].

With the exception of 5–10% breast cancer cases, where the main risk factor is genetic, the remaining 90% of sporadic breast cancers, have identified risk factors as either reproductive, life style or environmental, acting primarily through their influence on the hormonal milieu.

Unfortunately, the younger age of Indian patients is associated with larger tumors, higher number of metastatic lymph nodes, poor tumor grade, low rates of hormone receptor-positivity, poor disease free survival and a poorer overall survival [4].

Reproductive factors such as early menarche, late menopause, nulliparity, late age at first child birth and lack of breast feeding are well known to increase the incidence of breast cancer, and the same have been documented from India as well [1, 4].

The increasing incidence of breast cancer in India is usually attributed to rapid modernization; westernization of life style, intake of unhealthy foods, alcohol and tobacco usage that is increasing amongst Indian ladies all may be contributory factors. No breast cancer risk factor that is unique to Indian population, has been yet reported.

Breast cancer can also affect males, but the incidence is very low; for every 99 females, we see one male patient. Males have poorer prognosis as cancer rapidly involves the underlying muscles.

1.3 Genetic Aspects

Breast cancer has a genetic linkage, and is more common amongst females whose first degree relatives had this problem—these ladies are bracketed amongst "high risk patients".

Mutations in the Breast Cancer genes BRCA 1 and 2 are the major causes of breast cancer in up to 36.9% of patients in the United States, but data from India is sparse since genetic screening is not done routinely. Given the younger age of presentation of Indian patients, one would expect a higher incidence of mutation, but surprisingly, only about 4–25% of patients analyzed have shown mutation of the BRCA 1 and BRCA 2 genes [1, 4]; these are passed on in an autosomal dominant manner and are associated with a more aggressive form of disease. A multicentre study published in 2018 [5] estimated the incidence of genetic mutations to be approximately 30% in 1010 patients screened for mutation using a multigene panel—although BRCA 1 and BRCA 2 mutations were predominant, they also documented mutations of non-BRCA genes; however, the high incidence of mutations detected in this study was probably due to a selection bias wherein only indicated patients were screened and the overall incidence in the general population is probably much lower.

As of now, there are no fixed guidelines about performing genetic screening in Indian breast cancer patients. An expert panel meeting in 2017 [6] recommended guidelines for BRCA testing in the Indian context—they concluded that BRCA

testing was not recommended for all breast cancers under the age of 40 years, but it should be done for all breast cancer patients above 60 years, those with maternal family history of ovarian cancer, and in selected cases who have paternal family history of prostate or pancreatic cancer. It was also felt that extended germ line mutation testing (beyond BRCA) should be done for triple negative young breast cancer patients. However, in the vast majority of Indian patients, genetic screening for breast cancer is still not performed routinely outside of a study protocol, possibly due to lack of funds, facilities and availability of adequately trained personnel.

The identification of the abnormal chromosome and its repair by genetic engineering is being made available in developed countries but it may take a longer time for India. The management of Hereditary Breast Cancer has been dealt in Chapter 18.

1.4 Hormone Receptors

Estrogen (ER) and Progesterone (PR)—and Human Epidermal Growth Factor Receptor 2 (HER2neu) are now done in larger number of patients as they are considered to be of prognostic value and also act as a guide for further therapy.

Western studies have reported 70–80% ER + and almost 70% PR + expression, but this is not true for Indian patients, where there is a much lower positivity for these receptors (20–50%) [1, 4, 7]. It is well documented that the vast majority of the Indian breast cancer patients are still ER and PR negative. The percentage of HER2neu positivity is similar (26–50%), [4, 7] and there are a large number of patients who are negative for all three—the so called 'triple negative' breast cancers (TNBC). TNBC are seen in upto 40% of breast cancers in India, and usually present as locally advanced disease with nodal involvement as compared to their western counterparts where presentation of TNBC as early breast cancer is more common. TNBC have a much poorer prognosis and have also been shown to be associated with mutations of the p53 tumour suppressor gene [4, 8, 9].

1.5 Late Presentation and Outcome

Breast cancer can clinically present as (1) Early Breast Cancer (EBC), (2) Locally Advanced (LABC) or (3) Metastatic (MBC); these are discussed in detail in the individual chapters on management of breast cancer by surgery, radiotherapy, chemotherapy and hormonal therapy. In contrast to developed countries, where majority of patients tend to present early with small tumours (often detected on mammography) and limited nodal disease, presentation as EBC is low in India [4]. The vast majority of Indian breast cancer patients present late, as LABC or MBC, where the management is challenging and needs involvement of multiple specialties in order to improve resectability and achieve adequate locoregional control; the overall survival and recurrence free intervals are also poor [4].

Multi-Institutional data published recently reported a high percentage (almost 40%) of Indian patients presenting with tumours larger than 3 cms and with nodal metastasis (upto 50%) [10] (Figs. 1.1–1.5). It is well known that almost 60% of Indian breast cancers present as LABC [1, 4, 11]; these patients have advanced local

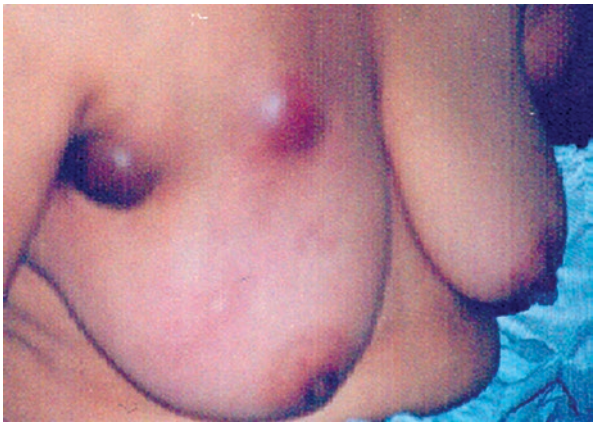


Fig. 1.1 An educated lady, wife of an engineer, living in Chandigarh, carried on with these swellings for 18 months

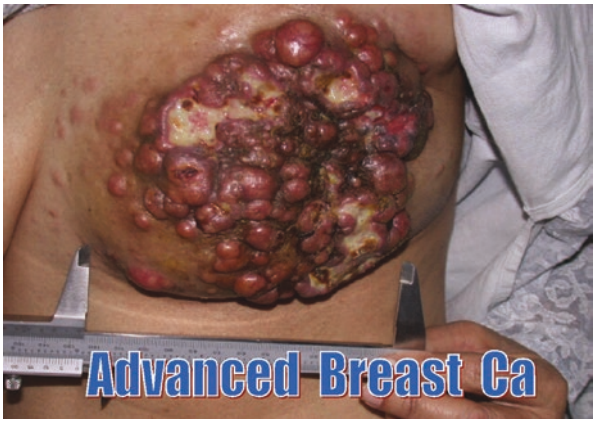


Fig. 1.2 This patient, an educated lady, had LABC. Since she had agenesis of one lung, she was not operated for many years. Ultimately she was operated upon, skin grafting done, followed by adjuvant treatment. She lived after surgery for almost 18 years (disease free for 14 years)

cancer but an absence of distant metastasis; this includes patients with (a) tumours more than 5 cms size with regional lymphadenopathy, (b) tumours of any size with skin or chest wall involvement, (c) significant regional lymphadenopathy irrespective of primary tumour size, and (d) inflammatory breast cancers. LABC can be operable straight off, but by and large, they usually need neoadjuvant chemotherapy (NACT) followed by surgery and then post-operative radiotherapy; it is advisable to get receptor status before initiating NACT in this subset of patients since it is well known that the hormonal status can change after NACT [12]. The management of LABC has been discussed in detail in Chapter 16.

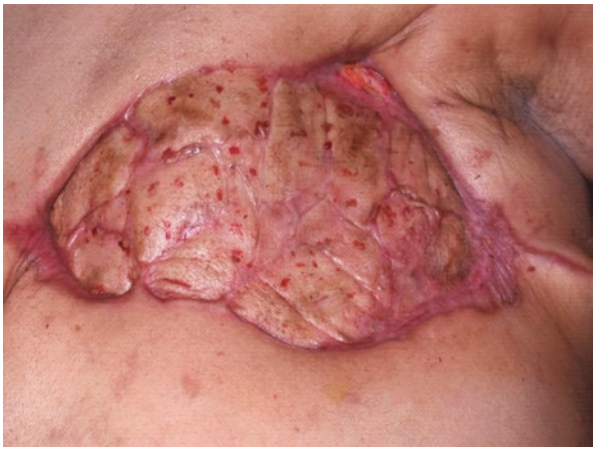


Fig. 1.3 Six years after surgery in previous patient

The next most common group of patients is that of MBC. Almost 6–25% of Indian patients present with metastasis with a higher incidence of skeletal disease [4]. In India, these two groups (LABC and MBC) account for the vast majority of patients seeking medical attention for the first time. A variety of reasons such as illiteracy, unawareness, financial constraints, lack of breast screening programs have been postulated as reasons for delay in presentation [1, 4, 11]. It is easy to understand that in such a situation, not only is the prognosis poorer but patients also require mutilating operations and prolonged management.

Long term survival is directly related to the stage of disease at which treatment is started. A 15 years survival was found to be almost 80% even in patients with axillary node positivity when the tumour diameter was less than 1 cm as compared to 47% when the tumour was larger than 2 cms [13]. This clearly shows the importance of early detection and also explains the poor outcome in India. Quality of treatment and histological type of cancer do have effect on ultimate outcome but these are only minor factors vis-a-vis stage of the disease.

The onus of late presentation lies on (a) patients, who because of lack of awareness / false modesty do not tell about their breast problem even to their spouses (b) relations of patients who do not either have time or are reluctant to care for their female folks, and (c) doctors who do not suspect cancer and hence do not refer the patient to a specialist in time.

It is well known that alternative systems of medicine, namely Homeopathy, Ayurveda, Unani are very commonly used by our folks; in our experience, these systems are not successful in treating cancer patients, and only end up wasting precious time, energy and money.

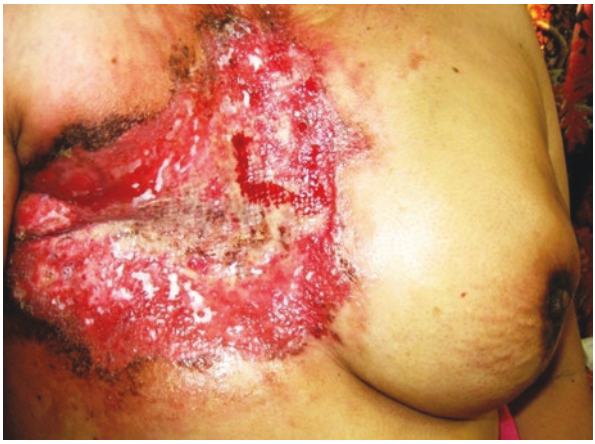


Fig. 1.4 We were really surprised to see this patient; could not believe that she was living in this condition for almost one year

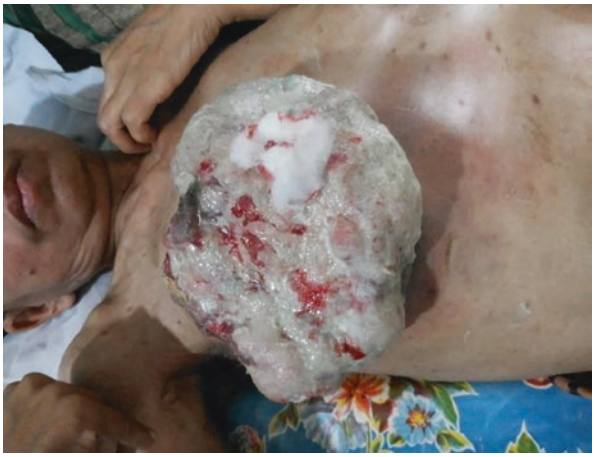


Fig. 1.5 A lady of middle age, living with her family with this problem for the last two years. She had a fungating tumour with bleeding and maggots. We used turpentine oil for eradicating the maggots. She responded to neo adjuvant therapy, was operated upon with adjuvant therapy and survived for almost five years

Presence of a progressively increasing new swelling in the breast or armpit is the commonest presenting feature of breast cancer but our patients tend to ignore this since it is always painless to start with (Figs. 1.6 and 1.7). Similarly the other warning signals of breast cancer (Figs. 1.8–1.10) are often completely ignored by the patient and their close relations. What is surprising and pathetic is that this is not only with illiterate and poor patients only, but by well to do socialites also.

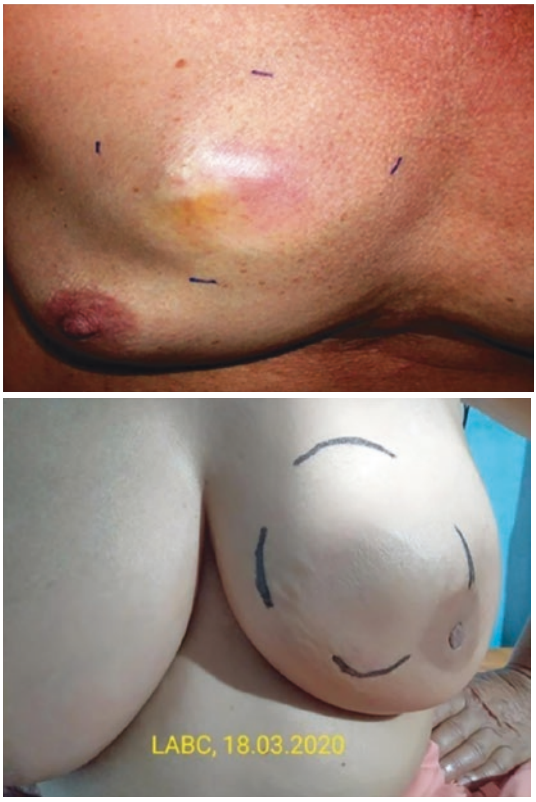


Fig. 1.6 and 1.7 Large swellings occupying almost the whole of the breasts; The patients carried on as there was no pain

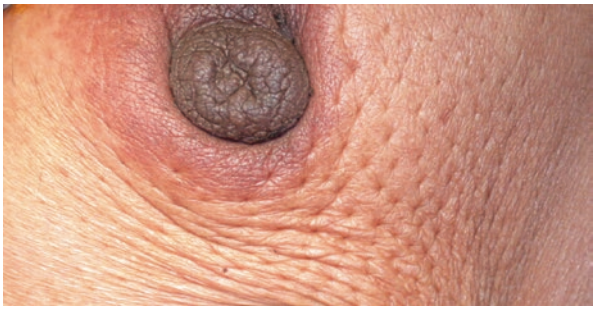


Fig. 1.8 Peau-d'orange is another common sign of Breast Cancer, but is usually neglected

It is surprising that this is also the case in a city like Chandigarh, a city with highest literacy, per capita income and perhaps the best medical centre of the country.

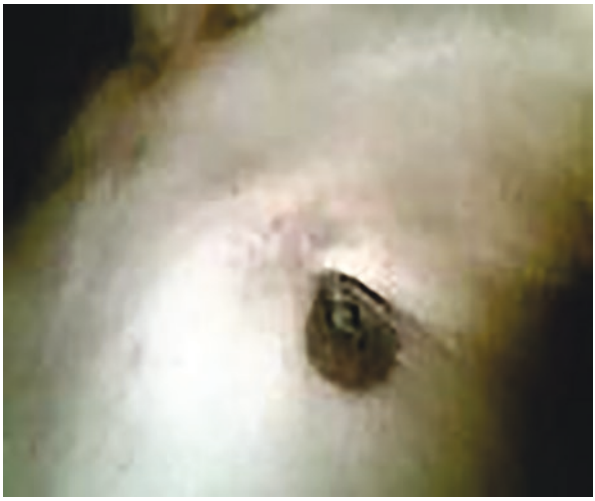


Fig. 1.9 Recent retraction of nipple is a warning sign of breast cancer but again is commonly neglected

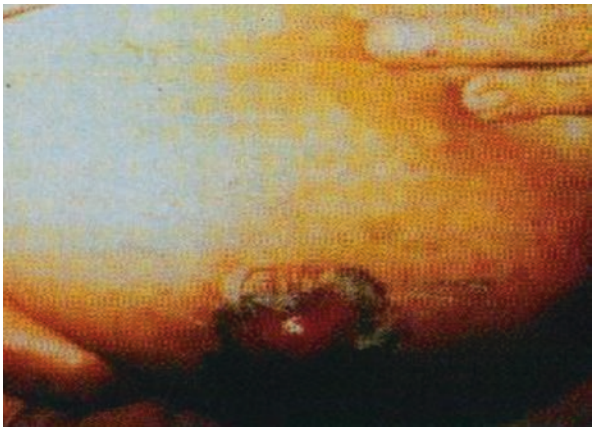


Fig. 1.10 Bleeding from nipple can be a warning sign of Breast Cancer

1.6 Effect of Modernisation

Why is breast cancer commoner in developed countries? Global research has been trying to find an answer to this million dollar question; but present knowledge is limited to hypothesis only. Breast cancer is supposed to be more common among affluent ladies who are exposed to modern environment, drinking alcohol, using

tobacco, taking contraceptive pills, have none or few children, and do not breast feed their children. Modernisation is coming in a very big way in India, and the above mentioned characteristics are often seen in metropolitan cities of India—ICMR and local Cancer Registries tell us that the incidence of breast cancer is increasing every day in these areas [1, 4].

1.7 Radiological Screening and Diagnosis

Breast Cancer can be detected in the asymptomatic stage and this is only possible by following regular screening protocols consisting of mammography, clinical examination by a specialist surgeon and self-examination of breasts.

Screening is supposed to decrease deaths from breast cancer by almost 20% [14]. Breast screening is commonly practiced in developed countries; but in India because of financial constraints and ignorance, it has not yet become a common practice. No guidelines exist in India; although the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) was launched in 2010 to strengthen infrastructure, develop human resources, promote health and aid in early diagnosis, management and referral, but there is still no existing National Screening Program. Most of the effort to screen and raise awareness regarding breast cancer is being done at a local level by hospitals or as part of research studies, and the vast majority of our patients are diagnosed only when they walk in to a hospital.

Mammography costs only Rs.900 and it is a worthwhile investment for all those ladies who can afford it. Self-examination of breasts is also an important method that can help in early detection, and is dealt with in Chapter 29.

Mammography can detect a swelling as small as 0.5 cm in the depth of the breast which may not be felt from the surface. A biopsy of this lump requires to be taken for confirmation of the diagnosis and this can be undertaken by stereotaxis technique or by mammotome—the former technique is available in a few centers but the latter is still to become a standard practice.

PET-CT Scan and dedicated MRI mammography are newer techniques that give more reliable results than mammography, but are costly and not widely available. Radiological and imaging techniques are available in many centres in the country but still many of these sophisticated and costly investigations are not widely available and the other problem is the affordability of these investigations. In private laboratories PET-CT Scan can cost as much as Rs. 25,000, much beyond the reach of a common Indian. In Government institutions it costs around Rs. 10,000 but the waiting period is about six to twelve weeks—can a breast cancer patient wait for that long?

These have been dealt with in detail in Chapters 9, 10 and 12.

1.8 Confirmative Diagnosis

Histopathology is the gold standard for reaching a diagnosis of breast cancer—it should always be done after radiological assessment since it has the potential to distort breast architecture leading to unreliability of imaging findings.

Fine Needle Aspiration Cytology (FNAC) is the commonly used technique for histopathological diagnosis. In this a fine needle is inserted inside the tumour, fluid is aspirated, smeared over a slide, stained and then examined by a cytologist. Reliability is 95% but may give false positive or false negative results also; and hence a surgeon has to use his clinical judgment for proper correlation. Experts in cytology are available only in major institutes. FNAC can be also done under imaging to give correct localization. This has been described in Chapter 7.

FNAC is most commonly used, but more and more experts are recommending core (trucut) biopsy as the method of choice but it has still not become mandatory. A study from the All India Institute of Medical Sciences, New Delhi, reported a sensitivity of 99.7% for FNAC in 1310 patients of breast cancer with a positive predictive value of 100% [15], underscoring the utility of FNAC based diagnosis that can still be relied upon, given its ready availability, ease of performance, low cost and early availability of the report.

However, FNAC does not yield tissue for assessment of hormone receptor status—if this is desired, then core needle biopsy is indicated in which tissue for biopsy examination is obtained by inserting a wide bore needle—this is far more reliable than FNAC as the number of expert histopathologists far exceeds the number of cytologists, but this takes four to five days for reporting, in contrast to FNAC where the report is available in 24 hours.

Another problem associated with Core Biopsy is the implantation of malignant cells in the track—the senior author (SMB) has seen four such patients (Figs. 1.11–1.13).

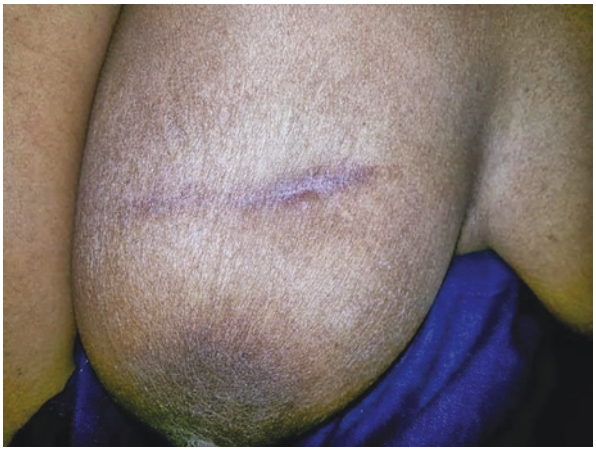


Fig. 1.11 Deposit of malignant cells at the site of insertion of core needle; the patient had core biopsy done in Australia

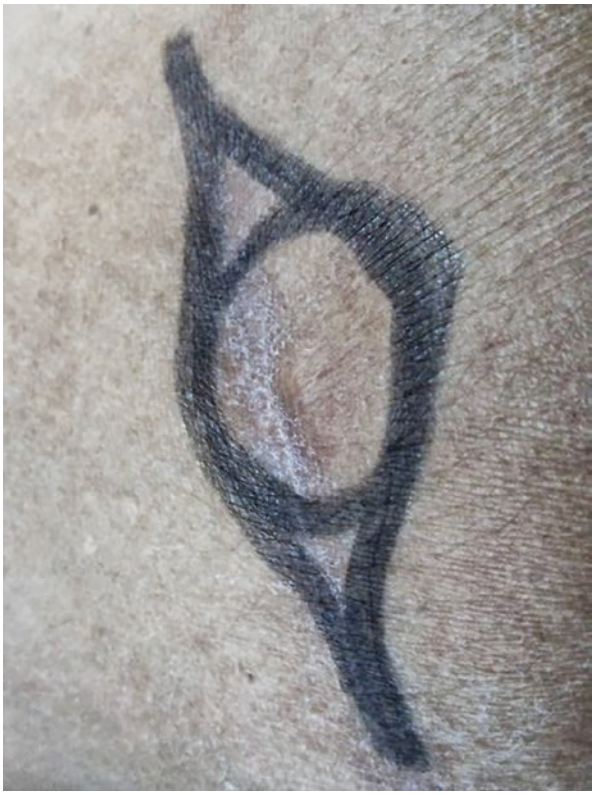


Fig. 1.12 Wide excision was performed for the implantation of malignant cells. Investigations did not reveal the presence of malignancy anywhere else

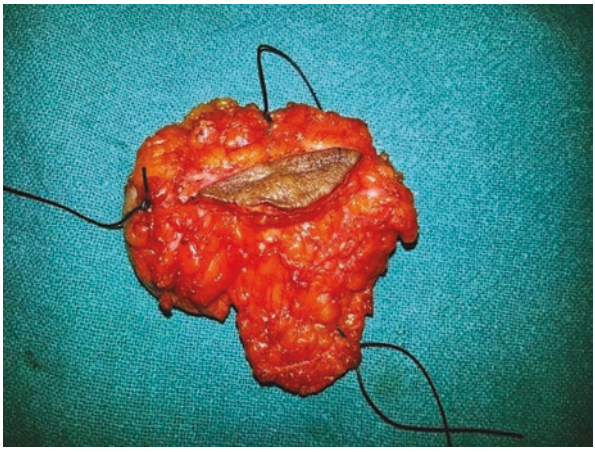


Fig. 1.13 Previous patient, five years post-operatively; the patient remained disease free

1.9 Investigations

A breast cancer patient has to be investigated for staging, to know the prognosis and also for judicious selection of treatment protocol. The patient requires to be assessed for operation, chemotherapy and radiotherapy. In private institutions, it is possible to complete all investigations within 24 hours whereas it takes a bit longer in the government sector.

1.10 Management

It has been conclusively proved that a breast cancer patient has to be treated with multimodality treatment—surgery, chemotherapy, radiotherapy, hormone therapy, target therapy, immunotherapy and others. A right combination with proper planning and sequencing is essential. This treatment protocol depends upon general condition and menstrual status of the patient, stage of the disease, histopathological findings and markers of the excised tumour; and most importantly, the expertise and experience of the treating surgeon.

In good cancer centres, a dedicated group of specialists of various specialties periodically discuss each and every patient of breast cancer and a consensus line of treatment protocol is offered to the patient but unfortunately in India this group treatment is found hardly in a few centres. This has been discussed in Chapter 30.

A clinician when confronted with the planning of treatment for a breast cancer patient aims for the long term survival of the patient, followed by good quality of life and the last consideration is for good cosmetic looks (Fig. 1.14). In our country, majority of ladies are not very much conscious of their physical attributes, they also do not indulge in revealing dresses or in top less sunbathing; so good cosmesis is usually the last consideration. Similarly, since the vast majority of our patients present in advanced stages of the disease, long term survival remains the primary aim for the treating team. This has been discussed in the approach to be followed for a suspected patient of Breast Cancer in Chapter 6.

For over a hundred years, radical surgery (Halsted's Radical Mastectomy—RM) for breast cancer was being practiced all over the world, and so also in India. This mutilating operation had been giving lot of psychological problems to the patients. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B04 and B06 clearly established the oncological safety of less mutilating surgery and paved the way towards breast conservation. It is now well established that RM (total removal of whole breast along with underlying muscles and clearance of axilla) can be easily changed to modified radical mastectomy (MRM) or breast conservation that gives better cosmetic results, lesser hospitalization period and fewer complications. RM, a mutilating procedure, is rarely indicated in the present day in cases with cancer involving the pectoralis major muscle, chest wall, and/or with marked axillary lymph node metastasis and Rotter's node metastasis [16].

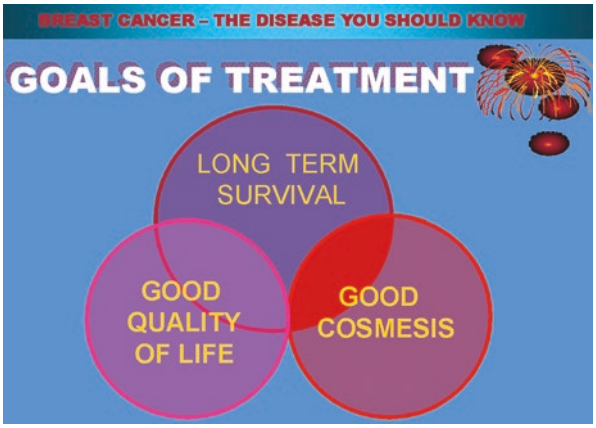


Fig. 1.14 Goals of treatment

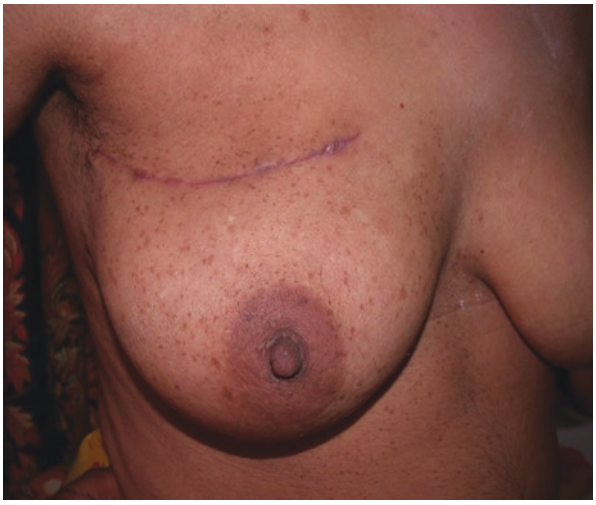


Fig. 1.15 BCS in a middle aged lady with good cosmetic result

MRM is the commonest operation done in our country, in approximately 90 to 95% of patients of Breast Cancer. Advances in surgery have further proved that total removal of breast is not always required—the tumour can be excised along with a minimal rim of normal breast tissue (and axillary nodes) and the breast can be preserved thus giving an excellent cosmetic look to the patient (Figs. 1.15 and 1.16). This is known as Breast Conservation Surgery (BCS) and administration of

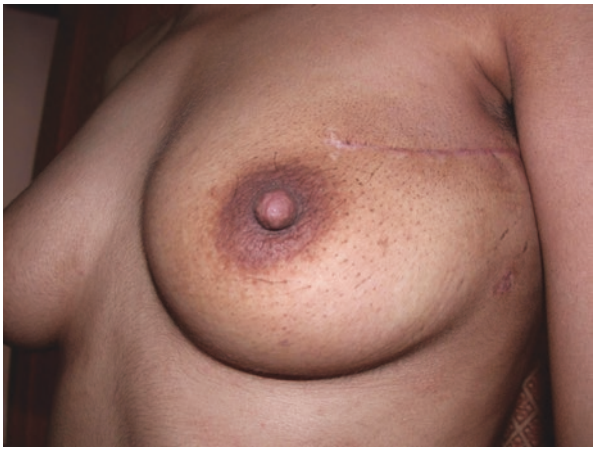


Fig. 1.16 A young unmarried doctor, with LABC, was given neo adjuvant therapy and had a very good response. She later underwent BCS, with excellent cosmetic result

radiotherapy and other treatment modalities in the post-surgical period give better results - survival and recurrence free interval of BCS remains comparable with MRM.

Despite long term results clearly showing that the ultimate results following proper performance of BCS remains equally good if not better than total removal of breast, BCS is still not commonly performed; the main reason for this is the non-availability of expertise or experience of the surgeon. Although specialized breast centres from India have reported an increase in BCS rates from as low as 12% a few decades ago to almost 60%, a large proportion of patients still undergo MRM [1, 4, 17]. It has been reported that even in USA, 50% of patients who are suitable for BCS are subjected to total removal of the diseased breast.

SMB has been performing BCS for more than 35 years (see Chapter 14) and so also a few surgeons in the country. But, at the same time, there are patients who are insistent for breast preservation ignoring the advice of the surgeon. SMB had to face this situation on multiple occasions; five or six times in cases of multicentric tumours (Fig. 1.17), and once when the tumour was in the nipple areola complex and the patient wanted the central part to be excised only (Fig. 1.18). This was done according to the patient's wish, and she was given adjuvant therapy; the patient was followed up for six years and remained disease free.

Skin sparing mastectomy and Nipple sparing mastectomy are done in only a few centres, the main reasons being late presentation of patients and also lack of expertise amongst treating surgeons.

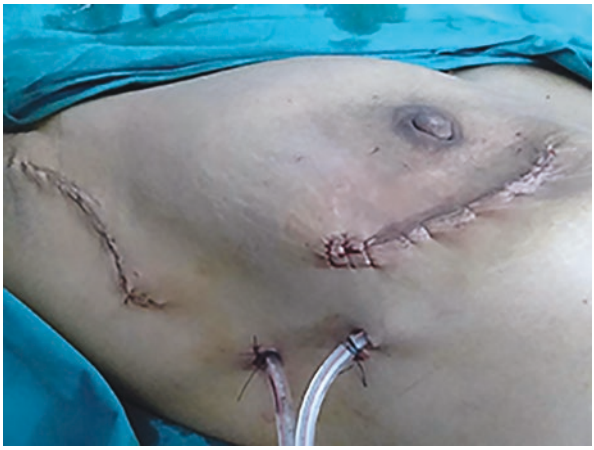


Fig. 1.17 This young patient had multi centric tumour and was advised MRM but she only wanted BCS. She was given 6 cycles of chemotherapy to which she responded very satisfactorily and then underwent BCS. Detailed histopathological examination did not reveal any residual malignant tissue. She has been given post-operative RT and is on Tamoxifen and is planned for breast augmentation

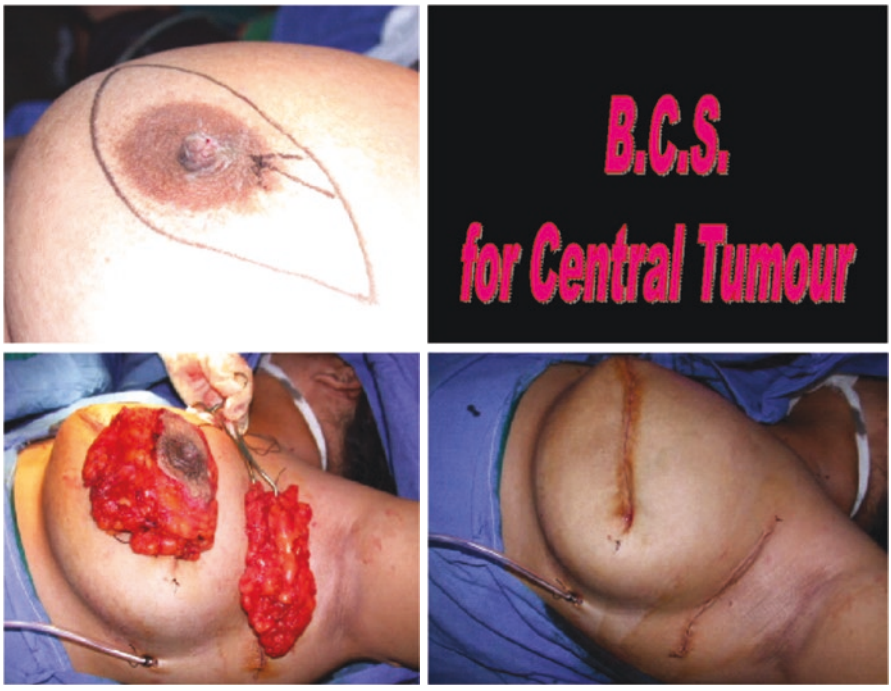


Fig. 1.18 Breast Conservation Surgery for central tumour, not advised but the young patient insisted for it, was done as a test case—patient was followed up for six years and had remained disease free

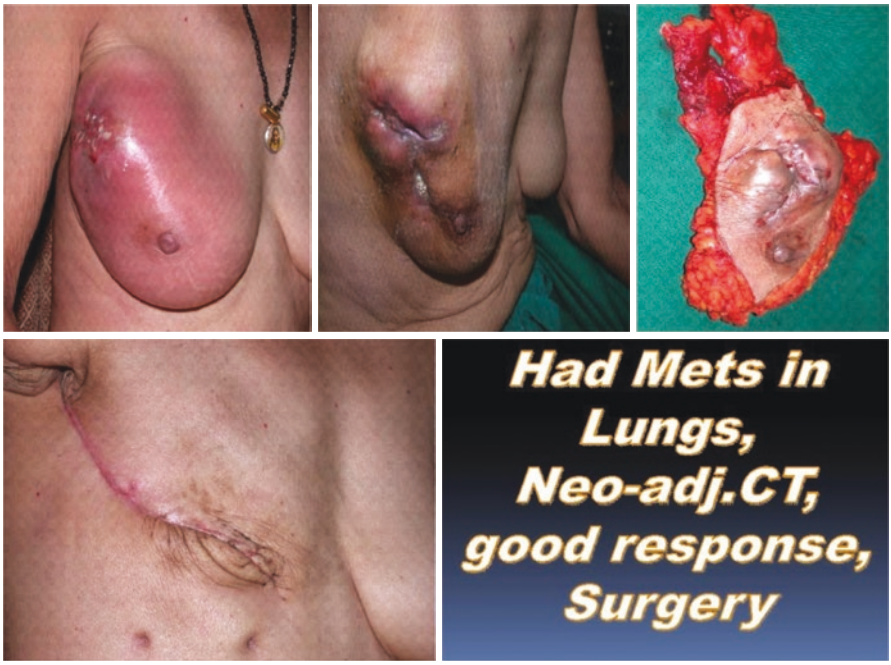


Fig. 1.19 Lady of 85 years, had poor response to two cycles of CMF chemotherapy; underwent MRM purely for palliation; remained well for 3 years

Despite enough evidence about oncological safety, shorter recovery time and better psychological outcomes of BCS, it has still not found a solid footing in our country.

Metastatic Breast Cancer is treated with adjuvant therapy comprising of chemo/ radio/ hormone therapy. Surgery is usually reserved for local complications such as fungating tumours, bleeding, etc (Fig. 1.19). Although a review of the USA SEER database did report survival benefit [18], a recent Cochrane review could not reach a definite conclusion as to the benefits of primary breast cancer resection in metastatic disease [19]. Data on this aspect is limited from India and in most cases, mastectomy in this setting remains palliative rather than definitive. It is felt that in our country where the MBC is very commonly seen, resection of the tumour mass gives excellent palliation, taking away tumour load, taking care of bleeding/pain/ fungation as illustrated by the following photos.

1.11 Management of Axilla

Another important aspect of breast cancer surgery is management of the axilla—a formal axillary dissection still remains the norm in the majority of Indian hospitals, and sentinel lymph node biopsy (SLNB) has still not become the standard, although more and more breast surgeons are now performing SLNB. A major review of 3453 non-metastatic breast cancer patients undergoing upfront surgery reported only 9% of patients having undergone SLNB, highlighting the poor acceptance of this procedure in the past and the need to change attitude [10]. SLNB using blue dye has found greater acceptance than that using radio-isotope technique which requires a set up that is not commonly available [4, 10]. This has been discussed in detail in Chapter 14.

1.12 Breast Reconstruction

Breast reconstruction has also not found wide favour—a wide variety of flaps and procedures are available that can be used to reconstruct the breast (both for MRM and BCS) immediately or at a later stage. Traditionally this was performed by plastic surgeons only, but now, this has given rise to a relatively newer specialty of oncoplastic breast surgery that as of now, remains limited to specialized centres. As of now, it is estimated that only about 2% of our patients undergo breast reconstruction after mastectomy for a variety of reasons such as costs, prolonged and traumatic procedure, possibility of delaying systemic therapy, and the need for post-operative radiotherapy [4, 20]. The various surgical procedures undertaken for reconstruction have been discussed in Chapter 22.

For recurrent disease, a decision to operate or to give adjuvant chemotherapy, what procedure to perform (revision wide excision, redo MRM, axillary management) are also challenging for a large proportion of patients (40–75%) who are referred to specialist centres after inadequate, inappropriate or unintended surgical procedures, often with incomplete or improper pathology reporting. From Tata Mumbai, it was reported that upto 40% of patients who underwent modified radical mastectomy outside, needed completion of surgery—each situation needs a different approach and there are no fixed guidelines for them [4].

Apart from surgery, treatment of breast cancer also heavily relies upon radiotherapy, chemotherapy, hormonal therapy and immunotherapy for disease control and favourable outcomes—these are discussed in the relevant chapters.

A decade ago, the number of hospitals (even Institutes) did not have trained Medical Oncologists to look after these patients. So in such centres either Oncosurgeons or Radiotherapists were giving chemotherapy—the situation has improved now, with a large number of trained medical oncologists available to provide best possible treatment to cancer patients.

A wide variety of chemotherapeutic regimes are in use, but it is well documented that anthracycline based regimens have greater survival benefit than cyclophosphamide, methotrexate and 5-flourouracil (CMF) combinations. Not only do these have

limited availability, but the prohibitive costs of these treatments along with prolonged duration of therapy and side effects, can be felt as a 'burden'—it is estimated that compliance with these adjuvant therapies is poor outside of major centres in our country.

1.13 Rehabilitation, Support and Quality of Life Issues

Breast cancer per se and the body image following surgery may leave behind a psychologically disturbed patient, who does not enjoy social life and her sexual activity takes a big beating. These patients require psychological support from near and dear ones. The body image can be improved tremendously by cosmetic surgery or even with the use of special brassieres.

In the past, there was little research into Quality of Life (QOL) issues of breast cancer patients in India, but over the last few years a lot of research has focused on this particular aspect of breast cancer. It has been reported that cancer patients have poor QOL across physical and psychological domains, and a study from Kerala reported 21.5% incidence of depression in breast cancer patients with an overall poor QOL domain score in them [21].In another study from Delhi, it was reported that the QOL issues improve over long term follow up, but the overall QOL of survivors was less than that of healthy women. The predominant survivor issues were fatigue, restriction of movement at shoulder, body and joint pains, lymphedema, chemotherapy induced cessation of menstruation and loss of sexual desire [22]. Not only the patient, but the family also experiences financial and emotional strain during this time—a study from Bengaluru estimated that almost 43% of families had to resort to desperate measures like selling their property or taking high-interest loans to meet the costs of treatment [23]. This still remains a 'grey' area where there is not enough awareness, and there is a need for providing financial, emotional and psychological succor to breast cancer patients and their families.

Bose et al. had conducted a study way back in 1980 and it was revealed that a large percentage of mastectomy patients even had suicidal tendency [24, 25].

1.14 Outcomes and Follow Up

The high incidence of newly diagnosed cases, advanced disease on presentation, existing cancer burden as well as the complexity of treatment contribute to overall mortality, estimated at 12.7 per 100,000 women [1].

Various studies have reported an overall 5 year survival rate hovering around 60% from India, which is much lower when compared to other countries—EBC has higher disease free survival and overall 5 years survival (upto 90%) but this drops for patients with LABC; node positivity, number of nodes, hormone receptor negative status and HER2neu positivity adversely affect survival.

The follow-up system in our country is not sound; even in the best of centres a 100% follow up has not been reported. It is well known that continued follow-up of

the patient is very important not only for rehabilitation, but also for detecting and managing recurrence or distant metastasis. Unfortunately, the patient may choose to get treated at different institutions or try alternative treatments, thus losing touch with the primary treatment provider.

Another important fact that worldwide research has clearly brought out is the relationship of the treating doctor to the ultimate result of the cancer disease. It has been clearly shown that results are significantly better if the treating surgeon has special experience or expertise in this subject and treatment has been undertaken in specialized breast units but unfortunately, there are few surgeons or units which are solely dedicated to management of breast cancer.

Costs are also an important issue—The cost of multimodality therapy is quite high and beyond the reach of an average Indian—40% of our population is classed below the poverty line; they can't afford the treatment and in the absence of this, outcome is obvious. Money should not be a consideration when health and life are at stake, but Indian health care costs are steeply rising, taking it out of the reach of many citizens.

Although an effort is being made by the government agencies to provide free treatment to financially poor patients in government hospitals but the number of such patients is enormous and at times, complete treatment is either not provided or is delayed.

Governments, both the central and state agencies, are taking active interest in opening cancer care centres but an efficient and patient friendly centre for poor patients is still a distant dream.

1.15 Future Guidance for our Country

1. Government agencies, NGOs, Voluntary organizations, audio and visual media, political, religious, films, celebrities all need to come together to increase the awareness about breast cancer among all sections of the general public.
2. The need is to make all ladies, irrespective of age, social and financial status start with regular breast cancer screening. It is equally important that all ladies should be aware of warning signals of breast cancer and to visit the doctor at the earliest; it is better to get negative verdict rather than to delay the diagnosis.
3. Awareness about breast feeding and its protective effects also need to be imparted to decrease the risk of breast cancer.
4. Regular visits by health workers, mobile mammography units to spread awareness and target women in the interiors of the country, villages, hilly areas etc. will be helpful.
5. Primary and secondary health centres should be roped in for spreading breast cancer awareness and screening can actually be done at grass root levels. Public health workers can be trained in Clinical Breast Examination to reach out and teach Self Breast examination
6. Programmes should be devised for all sections of medical specialists (cytologists, histopathologists, radiologist and imaging specialists, oncologists and

oncosurgeons) for improving their skills, continuously updating their knowledge and expertise in the management of patients of breast cancer. Continued Medical Education can help in training these specialists.
7. Guidelines for systematic management need to be formulated and developed in the country.
8. Cost of chemotherapy and other forms of treatment should be regulated by agencies so as to benefit large number of patients.

In the end, one is reminded of the immortal words of Robert Frost

- *The woods are lovely, dark and deep,*
- *But I have promises to keep,*
- *And miles to go before I sleep,*
- *And miles to go before I sleep.*

References

1. Malvia S, Bagadi SA, Dubey US, Saxena S. Epidemiology of breast cancer in Indian women. Asia Pac J Clin Oncol. 2017;13:289–95. https://doi.org/10.1111/ajco.12661.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424. https://doi.org/10.3322/caac.21492.
3. India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: the global burden of disease study 1990-2016. Lancet Oncol. 2018;19:1289–306. https://doi.org/10.1016/S1470-2045(18)30447-9.
4. Agarwal G, Ramakant P. Breast cancer Care in India: the current scenario and the challenges for the future. Breast Care (Basel). 2008;3:21–7.
5. Singh J, Thota N, Singh S, Padhi S, Mohan P, Deshwal S, et al. Screening of over 1000 Indian patients with breast and/or ovarian cancer with a multi-gene panel: prevalence of BRCA1/2 and non-BRCA mutations. Breast Cancer Res Treat. 2018;170:189–96. https://doi.org/10.1007/s10549-018-4726-x.
6. Parikh PM, Wadhwa J, Minhas S, Gupta A, Mittal S, Ranjan S, et al. Practical consensus recommendation on when to do BRCA testing. South Asian J Cancer. 2018;7:106–9.
7. Kumar RV, Panwar D, Amirtham U, Premalata CS, Gopal C, Narayana SM, et al. Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 status in breast cancer: a retrospective study of 5436 women from a regional cancer center in South India. South Asian J Cancer. 2018;7:7–10. https://doi.org/10.4103/sajc.sajc_211_17.
8. Sultana R, Kataki AC, Barthakur BB, Sarma A, Bose S. Clinicopathological and immunohistochemical characteristics of breast cancer patients from Northeast India with special reference to triple negative breast cancer: a prospective study. Curr Prob Can. 2020;44(5):1. https://doi.org/10.1016/j.currproblcancer.2020.100556.
9. Sarin R, Khandrika L, Hanitha R, Avula A, Batra M, Kaul S, et al. Epidemiological and survival analysis of triple-negative breast cancer cases in a retrospective multicenter study. Indian J Cancer. 2016;53:353–9. https://doi.org/10.4103/0019-509X.200682.
10. Doval DC, Radhakrishna S, Tripathi R, Kashinath RI, Talwar V, Batra U, et al. A multi-institutional real world data study from India of 3453 non-metastatic breast cancer patients undergoing upfront surgery. Sci Rep. 2020;10:5886. https://doi.org/10.1038/s41598-020-62618-3.
11. Rustogi A, Budrukkar A, Dinshaw K, Jalali R. Management of locally advanced breast cancer: evolution and current practice. J Can Res Ther. 2005;1:21–30.

12. Hirata T, Shimizu C, Yonemori K, Hirakawa A, Kouno T, Tamura K, et al. Change in the hormone receptor status following administration of neoadjuvant chemotherapy and its impact on the long-term outcome in patients with primary breast cancer. Br J Cancer. 2009;101:1529–36. https://doi.org/10.1038/sj.bjc.6605360.
13. Narod SA. Tumour size predicts long-term survival among women with lymph node-positive breast cancer. Curr Oncol. 2012;19:249–53. https://doi.org/10.3747/co.19.1043.
14. https://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/ - Last accessed on 09 May 2020.
15. Kazi M, Suhani PR, Seenu V, Mathur S, Haresh KP. Fine-needle aspiration cytology (FNAC) in breast cancer: a reappraisal based on retrospective review of 698 cases. World J Surg. 2017;41:1528–33. https://doi.org/10.1007/s00268-017-3906-x.
16. Nakanishi C, Toi M, Saji S, Bando H. Current indications for mastectomy in patients with breast cancer. Nihon Geka Gakkai Zasshi. 2002;103:821–4.
17. Bothra S, Sabaretnam M, Chand G, Mishra A, Agarwal G, Agarwal A. Indian surgeons' perspective regarding breast-conserving surgery: a cohort study. Int J Mol Immuno Oncol. 2019;4:72–81.
18. Lin Y, Huang K, Zeng Q, Zhang J, Song C. Impact of breast surgery on survival of patients with stage IV breast cancer: a SEER population-based propensity score matching analysis. PeerJ. 2020 Mar 18;8:e8694. https://doi.org/10.7717/peerj.8694.
19. Tosello G, Torloni MR, Mota BS, Neeman T, Riera R. Breast surgery for metastatic breast cancer. Cochrane Database Syst Rev. 2018;3:CD011276. https://doi.org/10.1002/14651858.CD011276.pub2.
20. Mathapati SN, Goel A, Mehta S, Aggarwal J, Aravindan R, Nayak V, et al. Oncoplastic breast reconstruction in breast conservation surgery: improving the oncological and aesthetic outcomes. Indian J Surg Oncol. 2019;10:303–8. https://doi.org/10.1007/s13193-019-00900-1.
21. Purkayastha D, Venkateswaran C, Nayar K, Unnikrishnan UG. Prevalence of depression in breast cancer patients and its association with their quality of life: a cross-sectional observational study. Indian J Palliat Care. 2017;23:268–73. https://doi.org/10.4103/IJPC.IJPC_6_17.
22. Kaur N, Gupta A, Sharma AK, Jain A. Survivorship issues as determinants of quality of life after breast cancer treatment: report from a limited resource setting. Breast. 2018;41:120–6. https://doi.org/10.1016/j.breast.2018.07.003.
23. Alexander A, Kaluve R, Prabhu JS, Korlimarla A, Srinath BS, Manjunath S, et al. The impact of breast cancer on the patient and the family in Indian perspective. Indian J Palliat Care. 2019;25:66–72. https://doi.org/10.4103/IJPC.IJPC_158_18.
24. Mattoo SK, Verma VK, Bose SM. Psycho-social adjustment to breast cancer pre-operative assessment-preliminary report. Bulletin PGI. 1983;17:121–5.
25. Mattoo SK, Verma VK, Bose SM. Psycho-social adjustment to breast cancer post-operative assessment. Bulletin PGI. 1985;19:19–24.

Applied Anatomy of Breast Cancer

2

Madhur Gupta and Neeru Goyal

2.1 Introduction

Breasts are highly specialized accessory glands of the skin. Breasts exist in both sexes but remain rudimentary in males throughout life; in females, the size and shape of the breast depends not only on age and parity but also on genetic, ethnic and dietary factors.

For descriptive purposes, the breast is divided into four quadrants: Superomedial, Superolateral, Inferomedial and Inferolateral.

2.2 Location and Relations

The breast extends vertically from the second to sixth rib and horizontally from the lateral margin of the sternum medially to the midaxillary line laterally. It is mainly present in the superficial fascia of the anterior thoracic wall except for the axillary tail of Spence [1] which is an extension of the superolateral quadrant along the inferolateral border of the pectoralis major muscle that passes through the deep fascia (foramen of Langer) to reach the apex of the axilla. This extension of the breast comes in direct contact with the anterior group of axillary lymph nodes. The axillary tail may be enlarged during the luteal phase of the menstrual cycle and may sometimes be mistaken as a tumor, lipoma or enlarged lymph nodes.

Madhur Gupta, MD (✉)
Former Professor and Head, Department of Anatomy, PGIMER, Chandigarh, India
e-mail: madhurg1@rediffmail.com

Neeru Goyal, PhD
Associate Professor, Department of Anatomy, Christian Medical College, Ludhiana, Punjab, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_2

The deep surface of the breast is related to the pectoral fascia (deep fascia covering the pectoralis major muscle), the fascia covering the serratus anterior muscle and the external oblique aponeurosis. The latter separates the deep surface of the breast from the rectus abdominis muscle. Between the breast and the deep fascia is present a loose connective tissue plane known as the submammary or retromammary space. This loose connective tissue allows some degree of movement of breast on the underlying fascia. In mammary carcinoma, if the cancerous tissue invades the deep fascia, the breast looses mobility and becomes fixed. At times, even in normal subjects small projections of breast tissue may pass through the deep fascia into the underlying muscle.

2.3 Nipple and Areola

The nipple is present at the centre of the breast anteriorly. Its shape varies depending on nervous, hormonal and developmental factors. In adult males and young nulliparous females, the nipple is present in the fourth intercostal space in the midclavicular line. With increasing age and parity, the breasts become larger and pendulous, resulting in dropping of the nipples.

The nipple is surrounded by a circular pigmented area of skin known as areola which has circularly and radially arranged smooth muscle fibres. These smooth muscles compress the lactiferous ducts during lactation and also help in erecting the nipples in response to suckling. The skin covering the nipples and areola is convoluted, containing numerous sweat and sebaceous glands that are usually seen as Montgomery's tubercles at the margins.

2.4 Structure of Breast

The breast is composed of lobes of glandular tissue parenchyma which consist of repeatedly branching ducts and secretary lobules. This glandular tissue is surrounded by connective tissue stroma. Each breast is divided into 15–20 lobes by fibrous septa extending from the dermis of the skin to the pectoral fascia, known as the suspensory ligaments of Astley Cooper. These ligaments are well developed in the superior part of the gland and help support the lobes and lobules of the gland.

The lobes of the breast are arranged in a radial manner like the spokes of a wheel converging towards the nipple. Each lobe consists of compound tubulo-acinar gland drained by a lactiferous duct (Fig. 2.1). Around 15–20 lactiferous ducts open at the tip of the nipple. Near the opening, each duct shows a slight dilatation known as the lactiferous sinus. The lactiferous ducts branch repeatedly to form large number of terminal ducts, each of which leads to a lobule which further consists of many acini. The terminal duct and the associated lobule are termed together as a terminal ductlobular unit. Although the lobes are separated by connective tissue septa, they cannot be distinguished during surgery.

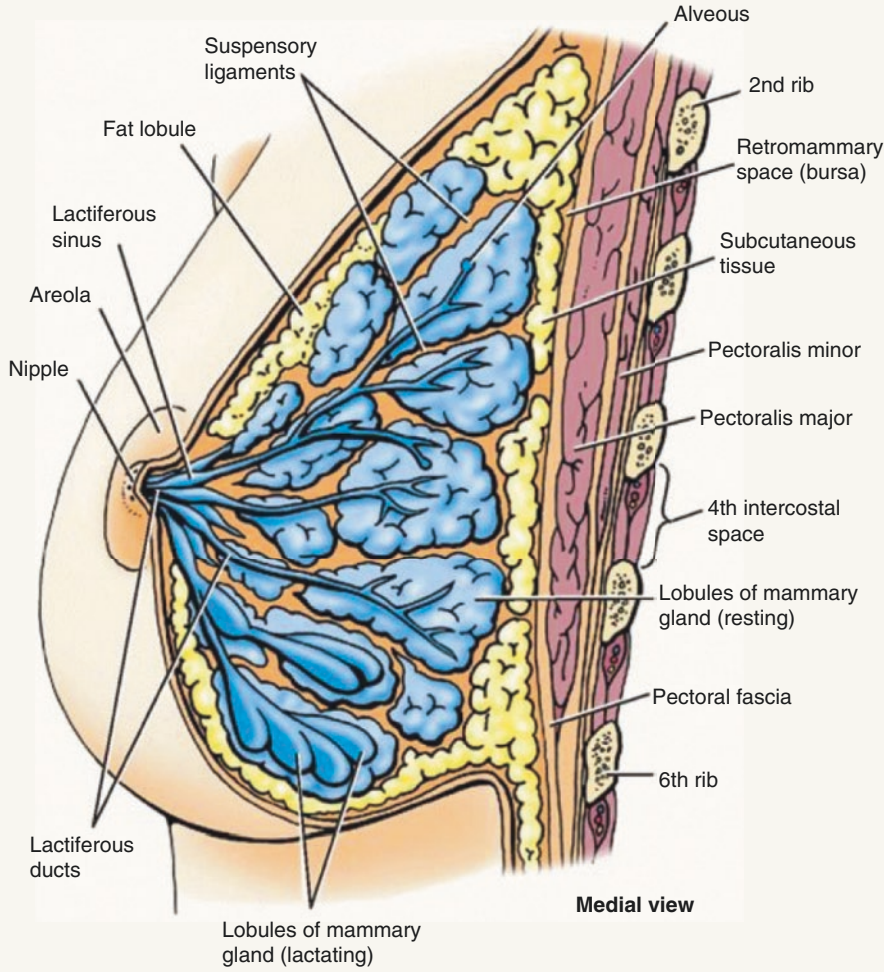


Fig. 2.1 Structure and relations of the breast (From: Moore KL, Dalley AF, Agur AMR Editors, Clinically Oriented Anatomy, 6th edition, Lippincott Williams & Wilkins, 2010)

The larger ducts are the sites of duct papilloma and the duct ectasia whereas the smaller ducts are the sites for fibro-adenomas, cyst formation and sclerosing adenosis. The majority of the cancers of the breast arise from the intralobular portions of the terminal ducts. Spread of cancer along the lactiferous ducts with consequent fibrosis may lead to the retraction of the nipple, which is a clinical sign of breast cancer. At times, the cancer may invade the ligament of Cooper, and, along with lymphatic blockage, lymphatic stagnation and oedema of the skin of the breast lead to contraction and dimpling of the overlying skin giving it an orange peel appearance that is clinically known as Peau-de-orange. If the cancer cells grow along the ligaments to involve the pectoral fascia, the breast becomes fixed and loses its mobility. Sometimes, the growth may also directly involve the skin and hence the skin cannot be pinched up from the growth.

2.5 Dense Breast

Density of breast tissue depends on the amount of fibrous and glandular tissue present in comparison to fatty tissue. The breast with abundant fibrous and glandular tissue and relatively less fat is called dense breast. The breast usually becomes less dense with advancing age. Although dense breast is very common and is not abnormal, women with dense breasts have higher risk of developing breast cancer. Dense breasts can make it difficult to identify tumors in a mammogram; therefore, in women with dense breasts and a strong family history of breast cancer or with BRCA1 or BRCA2 mutations, mammograms along with ultrasound, magnetic resonance imaging (MRI) or digital breast tomosynthesis (3D mammography) can be helpful in early detection of cancer. These have been described in detail in the chapter of Radiology and Imaging.

2.6 Development

Intrauterine development of the mammary gland is similar in both males and females. In the fourth week of intrauterine life, bilateral mammary lines or mammary ridges appear as ectodermal thickenings on the ventral aspect of the embryo in response to the inductive influence of the underlying mesenchyme. Initially, the mammary ridges extend from the axilla to the inguinal region, but by day 49, the thickenings in the thoracic region persist while rest involute. The thoracic ectodermal thickenings invaginate into the underlying mesenchyme and branch into 15 to 20 solid ectodermal buds; proliferation of cells leads to elongation and further branching of the buds. The surrounding mesenchyme gives rise to the connective tissue, fat and blood vessels. Nipple formation begins at day 56.

Under the influence of the placental sex hormones, canalization of the solid buds occurs by the end of the prenatal life and the lactiferous ducts are formed. A small mammary pit appears in the epidermis at the site of breast development into which the lactiferous ducts open. With proliferation of the underlying mesenchyme, this pit is transformed into nipple after birth.

Under the influence of fetal prolactin and maternal estrogen, the breast may undergo temporary hyperplasia and secretion of witch's milk at the time of birth. This is a normal physiological event and usually resolves within two weeks without any treatment.

2.7 Breast and Nipple Abnormality

(a) Accessory breast (Polymastia) or accessory nipples (Polythelia) may develop anywhere along the mammary ridges both in male and females. In males, accessory nipples are usually mistaken as moles. An accessory breast is usually found 7–10 cm below and medial to the normal nipple. Rarely, accessory breast

may occur at a location other than along the mammary ridge, maybe due to displaced tissue. Cancer of an accessory breast is a very rare condition and usually occurs as axillary tumor. Sometimes, the ducts of the accessory breast do not open onto the skin and the breast tissue is not able to discharge its contents, leading to a diagnosis of lipoma since the nipple is not visible.

(b) Amastia or Amazia: Occasionally, breast tissue may fail to develop completely (amastia) or the nipples may be formed without any breast tissue (amazia); when the breast is absent unilaterally, the pectoral muscles are also usually missing on the same side.

(c) Lack of development of the breast (micromastia) usually occurs on one side whereas diffuse hypertrophy (macromastia) may be unilateral or bilateral, with onset during puberty.

(d) Congenital inversion of nipples (retracted nipples) is a condition in which epithelial pit fails to evert, and must be distinguished from inversion of recent onset which may be an indication of underlying breast cancer.

2.8 Age Changes

During most part of life, breasts mainly consist of adipose tissue except during lactation, when the glandular tissue undergoes development. At birth in both sexes, the lactiferous ducts have no alveoli, and till puberty, little branching of ducts occur. In males, the gland does not develop further, but in females, at puberty, under the influence of estrogen and progesterone, the breast enlarges mainly by the accumulation of fat and the ducts branch to form solid masses of polyhedral cells which later on form alveoli.

In non-pregnant women of reproductive age, a well developed ductal system is present but their terminal ends lack alveoli. At this stage, the large ducts are lined with tall columnar epithelium while the smaller ducts are lined with cuboidal epithelium. Near the nipple, the lactiferous ducts are lined with stratified squamous keratinized epithelium, the squames of which may plug the opening of the lactiferous ducts and prevent bacteria from entering the duct. The mammary glands undergo some cyclic changes under the influence of the ovarian hormones—during the follicular phase, the stroma becomes less dense and the lumen of the ducts expands but no secretions are seen; in the luteal phase, the epithelial cells become flat and more prominent and the lumen of the ducts may contain eosinophilic secretions. After 26 days of the ovarian cycle, the duct system undergoes reduction and the epithelial cells undergo apoptosis.

During pregnancy, the gland becomes more vascular, and the number and length of the ducts increases. Secretory alveoli develop at the terminal ends of the ducts. With time, the number of these alveoli increases greatly at the expense of the intralobular and interlobar connective tissue. The amount of adipose tissue in the stroma is reduced while the number of lymphocytes increases greatly. The lining epithelium of the ducts and alveoli changes from cuboidal to low columnar with cytoplasmic vacuoles.

During later stages of pregnancy and for a few days after parturition, the alveoli begin to secrete protein rich colostrum. The lactating gland is composed entirely of alveoli that are lined with squamous epithelium that synthesizes and secretes various constituents of milk. During lactation, the number of lymphocytes and eosinophils reduce in the stroma, but plasma cells keep on synthesizing IgA which are taken up by the alveolar lining cells and released into the milk by exocytosis. After weaning, the breast involute and return to their inactive stage and the alveoli shrink and most of them disappear. Up to the age of 50 years, elastic tissue is laid down around the vessels and ducts (Elastosis) and in the stroma; however, elastosis does not continue in later life [2]. After menopause, the breasts atrophy, the alveoli disappear and only a few ducts are left behind. The size of the breast becomes smaller due to decrease in fat and atrophy of the glandular tissue.

2.9 Nerve Supply

Sensory and sympathetic nerves reach the breast via anterior and lateral branches of the fourth to sixth intercostal nerves. These nerves pass through the pectoral fascia to reach the skin of the breast. The anterior branch of the lateral cutaneous branch of the fourth intercostal nerve forms a plexus in the nipple and supplies it while fewer nerves innervate the skin of the areola. The sensory nerves are responsible for the suckling reflex and the sympathetic nerve fibres supply the smooth muscle. Secretions of the gland are under hormonal control.

Apart from these nerves which innervate the breast, other nerves which don't supply the breast but are vulnerable to injury during surgery of the region include intercostobrachial nerve, long thoracic nerve and thoracodorsal nerve (Fig. 2.2).

Intercostobrachial nerve is the lateral cutaneous branch of the second intercostal nerve. It runs on the medial wall of the axilla, crosses the axilla to its lateral wall and communicates with the medial cutaneous nerve of arm. It may receive fibres from the lateral cutaneous branch of the third intercostal nerve and may communicate with the posterior cutaneous nerve of arm (a branch of radial nerve). It supplies the skin of the floor of the axilla and upper part of the medial aspect of the arm. It's size is quite variable and it's injury leads to sensory loss at the area of skin it supplies.

Long thoracic nerve is formed in the neck above the clavicle by the union of nerve fibres arising from the ventral rami of spinal nerves C5–C7. It traverses the cervico-axillary canal to enter the axilla and descends on its medial wall on the superficial surface of the serratus anterior muscle. It runs posterolaterally towards the midaxillary line accompanied by a branch of the thoracodorsal artery (continuation of the subscapular artery). Injury of the nerve leads to winging of the scapula in which scapula is pulled upwards and medially due to unopposed action of the trapezius.

Thoracodorsal nerve (C6, 7, 8) is a branch of the posterior cord of the brachial plexus. It runs on the posterior wall of the axilla, accompanied by the subscapular artery and supplies the deep surface of the latisimmus dorsi muscle.

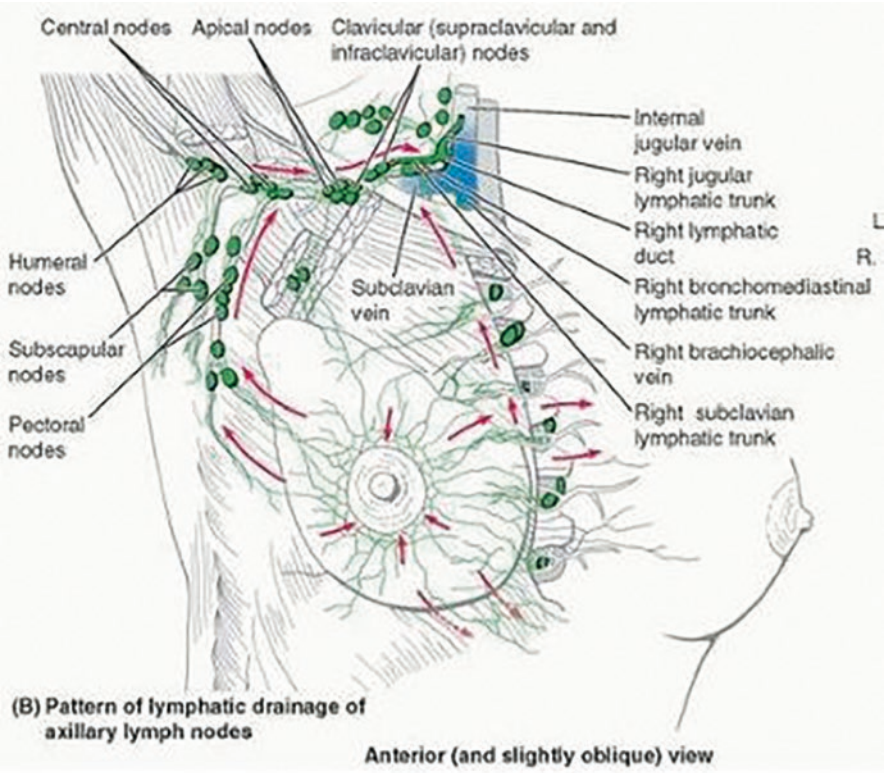


Fig. 2.2 Direction of the lymph flow from the breast (From: Moore KL, Dalley AF, Agur AMR Editors, Clinically Oriented Anatomy, 7th edition, Lippincott Williams & Wilkins, 2014)

2.10 Arterial Supply

The arterial supply of the breasts is derived from the branches of axillary artery, internal thoracic artery and intercostal arteries of the second to fourth intercostal spaces.

(a) Internal thoracic artery (Internal mammary artery): It is a branch of the subclavian artery, provides approximately 60% of total breast flow, mainly to the medial portion, by anterior and posterior perforating branches. They course inferiorly and laterally to anastomose with branches of the lateral thoracic artery at the nipple. Anastomoses with the intercostal arteries occur less frequently.
(b) The branches of the axillary artery which supply the breast are: (1) superior thoracic artery, (2) pectoral branches of the thoracoacromial artery, (3) branches of the lateral thoracic artery which curve around the inferolateral border of the

pectoralis major to reach the lateral part of the breast, and (4) subscapular artery. This artery supplies up to 30% of breast blood flow to the lateral and upper outer portions of the breast.

(c) The third, fourth, and fifth posterior intercostal arteries are the least important of the arteries supplying the breast. Originating from the aorta, they course in the intercostal spaces and mainly supply the inferoexternal quadrant of the breast

2.11 Venous Drainage

The veins draining the breast correspond to the arteries. A circular venous plexus is formed around the areola and this along with blood from the glandular tissue drains into the axillary, internal thoracic and intercostal veins.

The venous drainage of the breast is divided into a superficial system and a deep system.

1. The superficial system lies below the superficial fascia and has been classified into two- transverse and longitudinal veins. Majority are transverse veins and run medially in the subcutaneous tissues and join perforating vessels that empty into the internal mammary vein. Longitudinal veins are less and they empty into the superficial veins of the lower neck.
2. Deep drainage system of the breast includes: (a) Perforating branches of the internal mammary vein, which are the largest vessels of the deep system and empty into the innominate veins. (b) Tributaries of the axillary vein. (c) Perforating branches of posterior intercostal veins.

These veins freely communicate with the vertebral veins and the azygos vein, which leads to the superior vena cava. All three of these venous pathways lead to the pulmonary capillary network and provide a route for metastatic carcinoma emboli to the lungs. The vertebral system of veins provides an entirely different metastatic route. These veins form a vertebral venous plexus and provide a direct venous pathway for metastases to bones of the spine, pelvis, femur, shoulder girdle, humerus, and skull.

Superficial veins that radiate from the breast in close proximity to the skin are accompanied by lymphatics. Phlebitis of these superficial veins feels like a tense cord just below the skin that is known as Mondor's disease which is a benign and self-limiting condition but may be a cause of much apprehension.

2.12 Lymphatic Drainage

Lymphatic drainage of the breast is of great clinical importance owing to the role of lymphatics in the metastasis of the breast cancer. Some characteristic features of the lymphatics draining the breast are: (1) normally, the direction of lymph flow in the lymphatics is parallel to the direction of the venous blood in the veins; (2) lymph enters the regional lymph nodes via the extensive periductal and

perilobular network of lymphatic channels; (3) breast lymphatics branch repeatedly and do not contain valves—blockage by tumor cells leads to a reversal of the lymph flow; (4) lymphatics from both sides communicate with each other and hence a unilateral disease may become bilateral.

The various lymph nodes draining the breast include: 1. Axillary lymph nodes, 2. Deltopectoral nodes, 3. Parasternal/internal thoracic nodes, 4. Intercostal nodes, 5. Supraclavicular nodes.

2.13 Axillary Lymph Nodes

There are approximately 20–30 axillary lymph nodes that are arranged into five groups: Anterior (Pectoral), Posterior (Subscapular), Lateral (Humeral), Central and Apical.

The anterior nodes are 4–5 in number and are present along the inferior border of the pectoralis minor muscle near the lateral thoracic vessels. They lie mainly on the third rib and the axillary tail of breast comes in direct contact with these nodes. Their efferents pass to the central and apical group of axillary nodes.

The lateral nodes are 4–6 in number and are present posteromedial to the axillary vein along the upper part of the humerus. Their efferents pass to the central and apical nodes and to the inferior deep cervical nodes.

The posterior group consists of 6–7 nodes which are present along the subscapular vessels in front of the subscapularis muscle on the inferior margin of the posterior axillary wall. Their efferents also pass to the central and apical nodes.

The central group has 3–4 nodes which are embedded in the axillary fat. Their efferents pass to the apical nodes.

The apical group consists of 6–12 nodes which are present along the superior border of the pectoralis minor muscle, medial to the axillary vein at the apex of the axilla. Their efferents drain into the subclavian trunk and the inferior deep cervical nodes.

2.14 Infraclavicular/Deltopectoral Lymph Nodes

Infraclavicular/deltopectoral nodes are one to two in number, lie outside the axilla, hence are not included in the axillary group of nodes. They lie in the groove between the deltoid and the pectoralis major muscles besides the cephalic vein and play an important role in the lymphatic drainage from the superior part of the breast.

2.15 Parasternal/Internal Thoracic Lymph Nodes

Parasternal nodes are around 4–5 in number on each side and are present in the anterior part of the intercostal spaces, on the sides of the internal thoracic artery. Apart from breast, they receive afferents from thoracic and abdominal wall (above the umbilicus) and liver.

The efferents from the internal thoracic nodes join with those from the tracheobronchial and brachiocephalic nodes to form right and left bronchomediastinal lymph trunks. The right bronchomediastinal trunk may join the right lymphatic duct and the left trunk may join the thoracic duct, but usually they open independently in or near the ipsilateral internal jugular-subclavian junction. The internal thoracic nodes may sometimes drain inferiorly along the superior and inferior epigastric lymphatics towards the groin. Rarely, lymph from the breast may also drain into the liver and subdiaphragmatic lymphatic plexus and this route is known as Gerota's paramammary route [3].

2.16 Intercostal Lymph Nodes

Intercostal nodes are present in the posterior part of the intercostal spaces, near the heads of the ribs. They receive afferents from the posterolateral part of thorax and breast. The afferents may join the lateral intercostal nodes before reaching these nodes. The efferents from these nodes join the thoracic duct on left side and right lymphatic duct on right side.

2.17 Supraclavicular Lymph Nodes

The supraclavicular nodes belong to the posterior triangle group of inferior deep cervical lymph nodes. The left supraclavicular nodes are also known as Virchow's nodes and they receive afferents from distant abdominal organs like stomach, kidney, testis etc. The right supraclavicular nodes drain the breast, lungs and oesophagus. Their efferents from right side join the right lymphatic duct and those on left side join the thoracic duct.

2.18 Lymph Vessels/Lymphatics

Four inter-communicating lymphatic plexus are present in the breast: two superficial and two deep. The superficial plexus are located in the dermis (cutaneous plexus) and in the superficial subcutaneous region (subcutaneous plexus). The deep plexus are located in the fascia covering the pectoralis major muscle (fascial plexus) and in the mammary gland, including lobes and ducts (glandular plexus). The subcutaneous plexus located immediately below the areola is known as the subareolar plexus of Sappey. Anatomical studies have shown that the density of the lymphatic vessels in the superficial plexi is higher than the density in the deep plexi [3, 4]. Plexus of lymphatics situated on anterior sheath (deep fascia) of pectoralis major is called Lake of Stiles, It receives lymphatic communications from subareolar plexus of Sappy.

Lymphatics from the skin of the breast except the skin of the areola and nipple run radially and drain into the neighbouring lymph nodes. The lymphatics from the lateral part of the skin drain into the axillary nodes while those from the superior part drain into the supraclavicular or deltopectoral nodes. The medial area of skin is drained into the internal thoracic lymph nodes.

Lymphatics from the breast lobules pass through the intramammary nodes and most of them pass through the axillary tail to join the axillary lymph nodes. Some of these lymph vessels draining the parenchyma of the breast accompany the lactiferous ducts and communicate with the subareolar plexus. The lymph vessels of the fascial plexus pass through the pectoralis major and minor muscles to join the apical group of axillary lymph nodes. This route of lymphatic drainage is known as Groszman's route. The fascial plexus also communicates with the subcutaneous plexus through the lymphatic vessels running along the fibrous fasciculi of the stroma. Most of these lymphatics drain into the axillary nodes either directly or via the subareolar plexus. The fascial plexus does not have much role in the lymphatic drainage of the breast but this route acts as an alternative channel when the main lymph vessels are obstructed.

The classical teaching is that most (75–90%) of the lymphatic drainage of the breast is to the ipsilateral axillary lymph nodes while some from the medial part drains into the internal thoracic nodes. However, since the lymph vessels form a complex intermingling network, it is believed that both axillary and internal thoracic nodes receive lymph from all the quadrants of the breast with about three-fourth of the lymph draining into the axillary nodes (Fig. 2.2). Connecting lymphatics across the midline may provide access of lymphatic flow to the opposite axilla [2]. Internal thoracic nodes of the two sides communicate with each other via the lymphatics present behind the manubrium sterni. In the early stages of breast cancer, the tumor of the lateral part of breast may metastasize to the internal thoracic nodes without involving the axillary nodes.

Most of the lymph vessels from the breast pass round the anterior axillary border through the axillary fascia and drain into the pectoral or anterior group of axillary lymph nodes. Some lymphatics also join the subscapular or posterior group of axillary lymph nodes while others accompany the lateral cutaneous branches of the posterior intercostal blood vessels to reach the intercostal lymph nodes. These intercostal nodes ultimately drain into the thoracic duct. Lymph from the cranial part of the breast may directly drain into the apical group of axillary nodes (sometimes interrupted by the infraclavicular nodes or interpectoral nodes or directly into the supraclavicular nodes [4]. The lymphatics draining into the internal thoracic nodes accompany the perforating branches of the internal thoracic artery in second to fourth intercostal spaces.

Lymphatics from the left breast ultimately terminate in the thoracic duct and then into the left subclavian vein. On the right side, the lymphatics ultimately drain into the right subclavian vein near its junction with the internal jugular vein [2].

2.19 Levels of Axillary Nodes

Surgically, the axillary lymph nodes are classified into three levels according to their relation to the pectoralis minor muscle. The axillary lymph nodes lying below and lateral to the lateral border of the pectoralis minor are the low nodes (level I). These include the anterior, posterior and lateral group of axillary nodes. The nodes present deep or posterior to the pectoralis minor muscle are the middle group (level II). These include central and some apical nodes. The nodes between the medial border of the pectoralis minor and the lower border of the clavicle are the upper or apical nodes (level III). There may be one to four other nodes present along the thoraco-acromial artery, in between the pectoralis minor and major; this interpectoral group of nodes is also known as Rotter's nodes [5].

2.20 Sentinel Lymph Node

A sentinel is a guard or a watchman—based on the orderly progression of tumour cells within lymphatics, the concept of 'sentinel lymph node' has been hypothesized—this is the first lymph node/group of nodes that receives metastasis from a primary tumor, from which further spread of disease occurs. This concept has gained strength over time, and more and more authors have reported the reliability of assessing the sentinel lymph node in breast cancers; absence of metastasis in the sentinel lymph nodes can avoid a full axillary dissection with its associated morbidity. This has been described in detail in Axillary Dissection in the chapter on Surgical Management of Early Breast Cancer.

2.21 Breast Cancer and Quadrants

Breast cancer is the commonest cancer in women today. Commonly, it arises from the epithelium of the ducts and then infiltrates the surrounding tissue; Different quadrants of breast have been described to have different frequency of the malignant tumors (Fig. 2.3). Majority of breast cancers develop in the superolateral quadrant as this quadrant has been described to have greater amount of the breast tissue [6].

Various strategies such as awareness, regular breast self-examination and mammography have been advocated for early detection of breast cancer, but despite this, patients often present with locally advanced or metastatic disease. Since breast lymphatics do not contain valves, the disease can spread to the opposite breast, neighboring structures as well as the abdomen. Metastatic cancer cells may reach the lymphatics of rectus sheath and then proceed to the porta hepatis and liver through lymphatics in the falciform ligament or to the umbilicus (Sister Mary Joseph nodules), with subsequent transcoelomic spread.

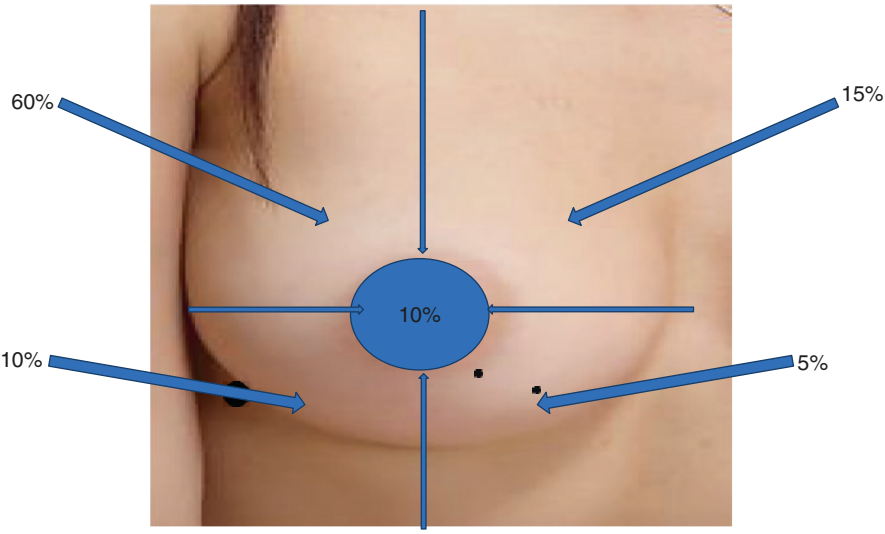


Fig. 2.3 Percentage distribution of malignant tumors in different quadrants of the breast

References

1. Hamdi M, Würinger E, Schlenz I, Kuzbari R. Anatomy of the breast: a clinical application. In: Hamdi M, Hammond DC, Nahai F, editors. Vertical scar Mammaplasty. Berlin: Springer; 2005.
2. Collin T, Cox J. Chest wall and breast. In: Standring S, editor. Gray's Anatomy. 41st ed. London: Elsevier; 2016. p. 945–52.
3. Macéa JR, Fregnani JHTG. Anatomy of the thoracic wall, axilla and breast. Int J Morphol. 2006;24(4):691–704.
4. Tanis PJ, Nieweg OE, Valdes Olmos RA, Kroon BB. Anatomy and physiology of lymphatic drainage of the breast from the perspective of sentinel node biopsy. J Am Coll Surg. 2001;192:399–409.
5. Schuenke M, Schulte E, Schumacher U. Thieme atlas of anatomy. 2nd ed. New York: Thieme Medical Publishers; 2014. p. 208–9.
6. Lee AH. Why is carcinoma of the breast more frequent in the upper outer quadrant? A case series based on needle core biopsy diagnoses. Breast. 2005;14(2):151–2.

Applied Physiology of Breast Cancer

3

R. Muralidharan

3.1 Introduction

The breast is a unique organ with fascinating physiology. Though it subserves its physiologic function of lactation only for a few months in a woman's life, the complex structural and functional perturbations it goes through at different stages of life are immense. Firstly it is the only gland that completes most of its development postnatally that too around puberty. During the reproductive years of a woman it undergoes cyclical changes during each menstrual cycle. It prepares for its intended lactogenic function during pregnancy to reach the most differentiated state postpartum. Involution occurs after weaning and the same cycle is repeated for subsequent pregnancies if any, with accrual of permanent changes of differentiation even after a single pregnancy. After cessation of ovarian function with menopause it involutes again, this time permanently. A host of physiologic changes that occur during these processes are mediated by several hormones and growth factors. These interact among one another not only through traditional endocrine mechanisms but also through paracrine and autocrine pathways of cell-cell communication locally within the breast itself.

Much of the knowledge regarding these processes is derived from animal studies (chiefly rodents) and in vitro cell-culture human studies, due to obvious difficulties with in vivo studies in humans [1]. Extrapolation of animal data to humans has its limitations. Problems also arise because of pulsatile and cyclical changes in hormone levels and discordance between circulating levels and local tissue levels of many of these hormones and growth factors. Still a thorough understanding of physiology of breast helps the clinician to understand the pathogenesis of breast cancer

R. Muralidharan, MD, DM (Endo) (✉)
Director, Department of Endocrinology, Fortis Hospital, Mohali, Punjab, India
e-mail: muraliendo@gmail.com

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_3

through disruption of these processes. This also paves the way for research into targeted pharmacotherapy of this important hormone responsive cancer.

3.2 Role of Hormones and Growth Factors in Breast Physiology

Orchestration of different hormones and growth factors in a complex interplay is a key feature of breast physiology. In addition to traditional endocrine mechanisms where hormones produced by a gland are transported in circulation and act on organs/tissues in distant locations, paracrine and autocrine controls also play a major role. In the former hormones/growth factors produced by a cell act on nearby cells by traversing through interstitial fluid whereas in the latter a cell communicates within itself by the humoral factors secreted by it (Fig. 3.1).

The traditional endocrine factors in breast physiology are summarized in Fig. 3.2.

3.2.1 Estrogen

Estrogen (17 β Estradiol) is the key hormone in breast physiology and pathophysiology [2]. Ovaries are the main source of estrogen secretion due to a concerted action of Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) on the theca cells and granulosa cells of the ovarian follicle respectively. Androstenedione and Testosterone secreted by theca cells under the influence of LH are converted by the granulosa cells to Estrone and estradiol through the FSH dependent enzyme aromatase. The same enzyme abundantly expressed in adipose tissue especially within the breast itself converts adrenal androgens to estrogen providing a key extra- ovarian source. This source assumes importance in obesity and in postmenopausal state after cessation of ovarian function.

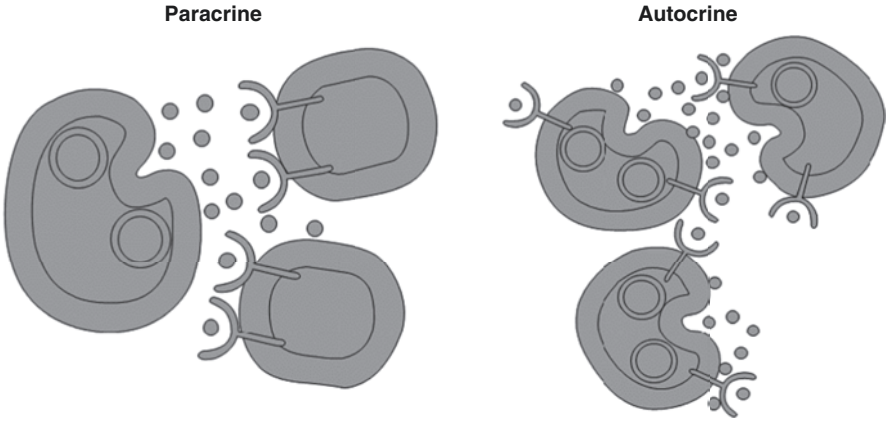


Fig. 3.1 Cell-Cell interactions through Paracrine and Autocrine mechanisms

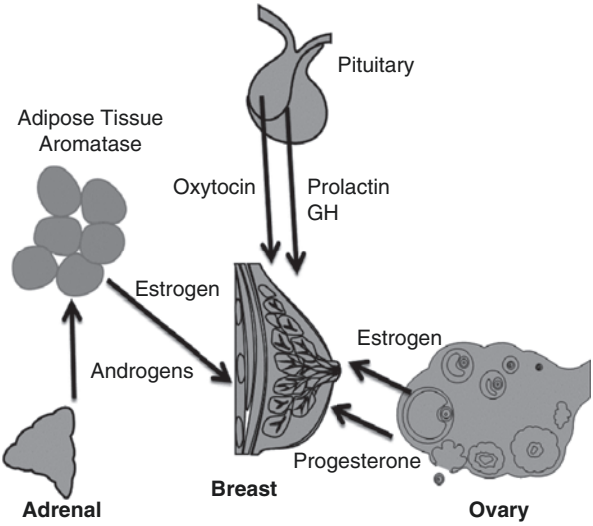


Fig. 3.2 Endocrine control of Breast- A broad overview

The key effects of estrogen on the breast are (1) growth and development of breast ductwork (2) stromal tissue development and (3) deposition of adipose tissue [1, 2]. In addition estrogen primes the breast for subsequent action by progesterone by inducing expression of progesterone receptors.

Estrogen being a steroid hormone predominantly acts through an intracellular nuclear receptor that functions as a DNA binding transcription factor [2]. There are two forms of Estrogen receptor (ER)—ER α and ER β coded on different genes. ER α is predominantly expressed on luminal epithelial cells whereas ER β on stromal and myoepithelial cells [1]. Most clinically significant growth promoting effects are mediated by ER α.

Estrogen after binding to nuclear ER leads to enhancement or repression of transcriptional activity of target genes such as Cyclin D1, Carbonic anhydrase 12 and B Cell Lymphoma 2 (BCL2) [3]. It has also been shown to bind to mitochondrial DNA altering transcriptional activity [2] (Fig. 3.3). In addition estrogen can also mediate some of its actions through non genomic pathways mediated through ERα, ERβ and G Protein coupled ER (GPER) located within caveolae of cell membrane, through which it can activate cellular processes through second messengers such as cyclic AMP and various protein kinases such as mitogen activated protein kinases (MAP kinases) [3]. Due to this there is a crosstalk between membrane estrogen signaling process and other signal transduction pathways like Epidermal growth factor receptor (EGF-R) and Insulin like growth factor 1 receptor (IGF 1-R) signaling pathways [4] (Fig. 3.3). ERα activates gene transcription whereas ERβ usually is inhibitory. ERα activation leads to mammary cell proliferation though paradoxically there is dissociation between cell proliferation and ERα positivity in tissues. This underscores the role of paracrine factors in the mitogenic role of estrogen.

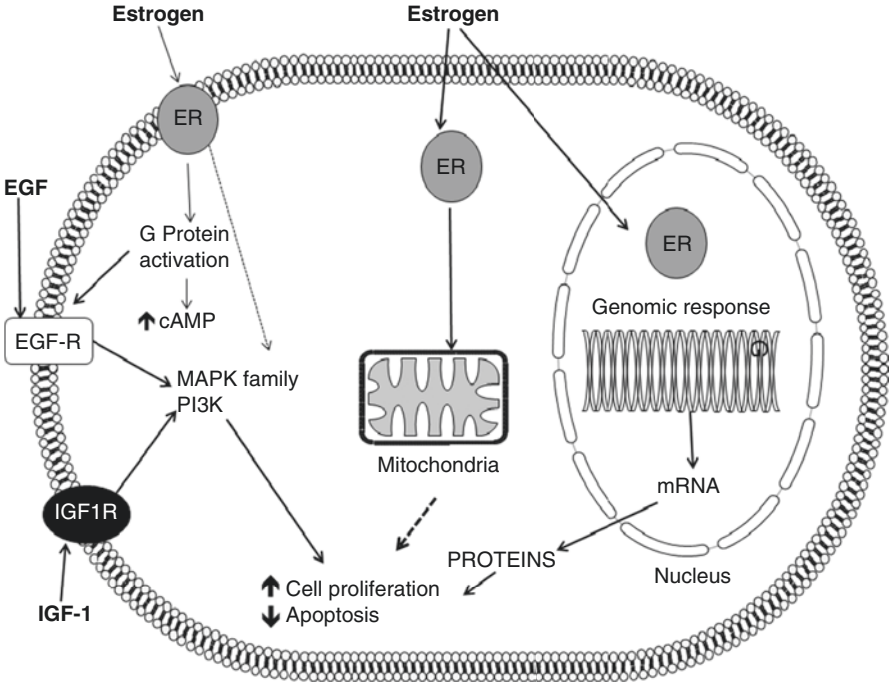


Fig. 3.3 Estrogen receptor Signaling mechanisms and cross talk with growth factor receptor signaling (adapted and redrawn from Information in Ref. [2]. EGF-Epidermal Growth Factor; IGF1-Insulin like growth factor; cAMP- Cyclic AMP; MAPK- Mitogen activated Protein kinase; PI3K- Phosphatidylinositol 3 kinase

3.2.2 Progesterone

Progesterone is produced by the corpus luteum of the ovary in the luteal phase of regular menstrual cycles and early pregnancy and by the placenta from 8–10 weeks of gestation. The key role of progesterone is in promoting mammary duct side branching and lobuloalveolar differentiation preparing the breast for its physiologic function of lactation [1].

Being a steroid like estrogen, progesterone too exerts its action through nuclear Progesterone receptors (PR). Two isoforms PRA and PRB exist. Estrogen induces the expression of PRs. 96–100% of cells expressing steroid receptors in the breast express both ER and PR [1]. The progesterone-PR complex binds to DNA causing transcriptional activation. PRA is associated with lateral duct branching whereas PRB is responsible for lobuloalveolar differentiation. Interestingly it has been found that not all cells that respond to progesterone by proliferation and differentiation have PRs. This underlines the role of paracrine factors. Cells expressing PRs seem to function as steroid sensors and act on adjacent cells that are PR negative through paracrine mediators like RANKL, Wnt and Neuregulin to promote stem cell proliferation and alveologenesis essential for lactation [1, 5].

RANKL (Receptor Activator of Nuclear factor kappa B Ligand) is the mediator through which progesterone induces lobuloalveolar differentiation in pregnancy as demonstrated in mouse gene knockout models [5]. Wnt 4 pathway seems to be downstream of PR activation in the process of tertiary side branching of ducts [6]. Neuregulin that belongs to the EGF family of proteins and is involved in neural development seems to be the paracrine factor through which progesterone promotes lobulo alveolar development [1].

3.2.3 Estrogen-Progesterone Action on the Breast- Role of Paracrine Factors

Estrogen the prime driver of duct elongation and growth during puberty and acts on ERα + cells that secrete a paracrine factor Amphiregulin [5]. This in turn stimulates ER- stromal cells through EGF receptors expressed on them to secrete another paracrine factor most likely Keratinocyte Growth Factor that stimulates mammary stem cells and commits them towards ductal growth [5] (Fig. 3.4).

Similarly Progesterone action on ER + PR+ mammary cells leads to secretion of RANKL that binds to its receptor RANK on ER-PR- stem cells stimulating them to develop into alveolar progenitor and secretory cells thereby promoting duct side branching and alveologenesis [5] (Fig. 3.4).

This explains how estrogen and progesterone in addition to their direct action on receptor positive cells can indirectly stimulate proliferation of receptor negative cells.

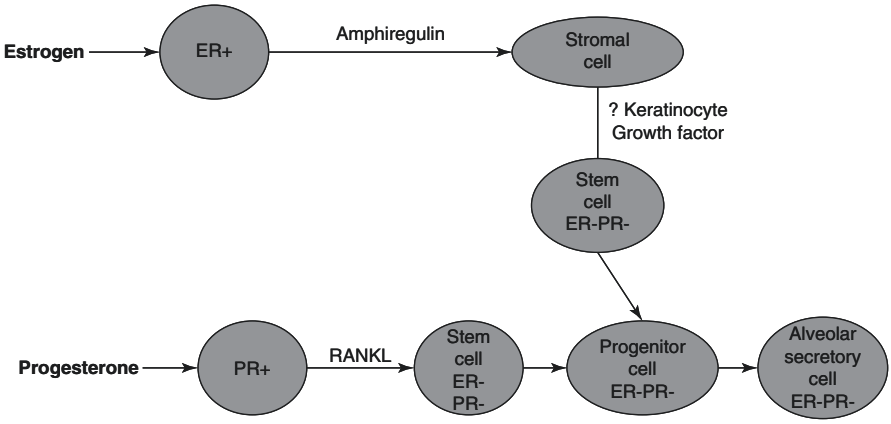


Fig. 3.4 Estrogen and progesterone indirect action on receptor negative cells through paracrine mediators (Adapted and redrawn from information in Ref. [5]

3.2.4 Prolactin

True to its name prolactin is the key lactogenic hormone mediating the physiologic function of the breast i.e. lactation. It is a polypeptide hormone secreted by the lactotrophs of the anterior pituitary and is under inhibitory control by Dopamine from the hypothalamus [7]. The main stimulus to prolactin secretion is the neural reflex arc initiated by nipple stimulation of suckling.

Prolactin plays an important role in mammary growth and development as well as synthesis and secretion of milk from breasts already primed by estrogen and progesterone. During late pregnancy prolactin acts synergistically with progesterone in promoting lobular development [6, 7].

Prolactin acts through its receptor PRL-R which is a member of cytokine receptor superfamily. After prolactin binds to its receptor, dimerization of the receptor occurs leading to protein tyrosine phosphorylation of intracellular JAK/STAT molecules (Signal Transducing Activators of Transcription Proteins STATs 1 through 5) [7]. STAT5a and 5b are essential mediators of lobulo alveolar development. Specifically STAT5 phosphorylation mediates transcriptional activation of the β casein gene important for lactogenesis and galactopoiesis [7].

3.2.5 Growth Hormone (GH)

GH is a 191 amino acid polypeptide secreted by the somatotrophs of anterior pituitary. As the name implies GH in addition to its key role in linear growth has growth promoting effects on most tissues. Rodent studies using ovarian and pituitary ablation and gene knockout experiments have clearly shown GH has a stimulatory effect on mammary development either alone or in combination with estrogen [8]. The growth promoting effects of GH are direct through GH receptor signaling and indirect through generation of Insulin like growth factor 1 (IGF 1 or somatomedin C) from the liver, which is transported to different organs through the blood stream. In addition local generation of IGF1 within the breast itself is important. GH-IGF 1 axis plays a major role in pubertal breast development in humans [8].

3.2.6 Oxytocin

Oxytocin is a neuropeptide synthesized by neurons in the supraoptic and paraventricular nuclei of hypothalamus and transported axonally to the posterior pituitary where it is stored. In addition to its prime role on stimulating uterine contractions during parturition it helps in the process of milk letdown reflex through myoepithelial cell contraction to eject milk from the alveoli into lactiferous ducts [7]. In recent years our understanding of the role of oxytocin has expanded to involve several neuropsychologic processes including love, bonding, trust, mating and maternal behavior [9].

3.3 Role of Growth Factors

3.3.1 Epidermal Growth Factor (EGF)

EGF is a potent mitogen that is expressed on human breast stromal fibroblasts and EGF receptors (EGFRs) are found on epithelial cells. The EGFRs belong to the ErbB family of receptors that are interdependent in binding to different ligands and activation of downstream pathways like Mitogen Activated Protein Kinases (MAPK) and Phosphatidyl Inositol 3 kinase (PI3K/Akt) pathways [1]. The ligands include EGF, Transforming growth factor alpha (TGFα), Amphiregulin and several Neuregulins [1]. EGFR family includes 4 members– HER 1–4 (Human Epidermal Growth factor Receptor) all of which are transmembrane receptor tyrosine kinases [10]. Ligand binding induces dimerization and autophosphorylation. HER2 has the strongest kinase and signaling activity [3, 10].

EGF is a key regulator of mammary ductal growth and branching and in concert with other growth factors like HGF and TGFα plays a major role in lobulo alveolar development [1, 6].

3.3.2 Insulin like Growth Factors

IGF 1 is a major regulator of pubertal ductal morphogenesis mediating the actions of Estrogen and GH during this important physiologic event. IGF1 and IGF2 can bind to several receptors including IGF1R, insulin receptor and EGFR. There is cooperation and cross talk between IGF1 and EGF receptor actions [1, 2]. IGFs bind to specific binding proteins IGFBPs that act as a local depot making them available for cellular processes. Depending on the context these act as endocrine, paracrine or autocrine regulators [1].

3.4 Breast Physiology at Different Stages of Life

3.4.1 Prenatal Breast Development

The development of primordial breast at the mammary ridge/line starts at 5–7 weeks of gestation and involves a coordinated epithelial- mesenchymal interaction. The epithelial component develops into the luminal and myoepithelial cells and the mesenchyme into fat and connective tissue stroma [1]. Branching morphogenesis is the process by which canalization occurs forming the ducts with differentiation into secretory cells [6]. This development is gender neutral in humans and is believed to be hormone-independent based on knockout animal experiments. Yet there is a definite endocrine role as exemplified by secretion of witch's milk from breasts of newborn of both genders in response to prolactin. Estrogen receptor expression is found around 30th week of gestation and both ER and PR are upregulated just before birth [11]. Near term, the fetal breast responds to placental estrogen, progesterone and prolactin.

Several growth factors play a role in prenatal breast development. BCL-2 an inhibitor of apoptosis expressed from week 18 is responsible for cell population expansion. BRCA1 the tumour suppressor gene expressed between 21–26 weeks of gestation is a differentiation agent. TGF α and TGFβ have opposing effects the former stimulating proliferation and differentiation. As in later life EGF receptor mediates estrogen effects. Parathyroid hormone related peptide (PTHrP) modulates ductal branching morphogenesis [1, 6].

3.4.2 From Birth to Puberty

During fetal life the effect of prolactin on the breasts is restrained by the high estrogen-progesterone milieu. After birth release from this inhibitory effect leads to milk secretion (witch's milk) in 80–90% of newborns [7]. In both genders the hypothalamopituitary gonadal (HPG) axis is active in the first 3–6 months of life (Minipuberty). This leads to increase in estrogen and progesterone and consequent breast enlargement in infants. The amount of breast tissue is directly proportional to the estrogen levels that are higher in female infants at 3 months of life. Both ER and PR are expressed in sizable numbers and TGF α levels are high till around 25 days post natal in females. The HPG axis goes into quiescence from 3–6 months of age till puberty leading to regression of breasts to a dormant inactive state [1].

3.4.3 Puberty

Onset of puberty is heralded by the activation of HPG axis. The resultant increase in ovarian steroids estrogen and progesterone is responsible for the physiologic pubertal breast enlargement (called thelarche) [12]. During initial anovulatory cycles unopposed estrogen action primes the breast. Estrogen promotes ductal epithelial thickening, elongation and branching and expansion of stroma and adipose tissue. Progesterone is responsible for lobular development. GH and IGF 1 generated by its action at cellular level are also important mediators. Many local growth factors e.g. TGFs and enzymes (Matrix metallo proteinases) also play a role [1].

3.4.4 Premenopausal Adult

Regular menstrual cycles with varying levels of the key hormones Estrogen and Progesterone during the follicular and luteal phases of the cycle lead to cyclical changes in the breast. Estrogen levels gradually rise during the follicular phase and induce PR expression. Both ER and PR expression in the breast is maximal in days 8–14 of the cycle [1]. As outlined earlier estrogen and progesterone cause cellular proliferation and differentiation through direct as well as paracrine mechanisms. High levels of progesterone and locally increased levels of estrogen in luteal phase along with maximal expression of EGFR during this

phase lead to a high proliferative activity accounting for the premenstrual enlargement and mastalgia experienced by many women.

3.4.5 Pregnancy

Pregnancy is a high estrogen and progesterone milieu because of secretion of both initially by corpus luteum (under influence of Human chorionic gonadotropin, HCG) and subsequently by the placenta. Estrogen levels increase 30 fold and progesterone levels 10 fold from preconception levels [1]. Estrogen promotes duct system elongation and branching whereas progesterone causes terminal side branching and lobuloalveolar expansion [5, 6]. Prolactin levels also increase 10–20 fold in pregnancy and in concert with Human placental Lactogen (HPL) it prepares the breast for lactation. Yet the actual process of milk secretion is inhibited by the high ambient estrogen and progesterone levels [7]. Estrogen, progesterone, prolactin, GH and thyroid hormones act in a well orchestrated manner to bring about the breast changes during pregnancy. Even a single pregnancy carried to term causes permanent alterations in differentiation of mammary lobules [1, 13] This has been proposed to be protective against development of breast cancer.

3.4.6 Lactation

Release of prolactin from the inhibitory influence of estrogens and progesterone after parturition heralds lactation. Prolactin secretion is stimulated by β endorphins during labour. With each nursing episode the suckling stimulus causes a surge in prolactin. Oxytocin released from the posterior pituitary in response to maternal psychological instinct as well as physical suckling stimulus causes milk letdown. The high prolactin inhibits GnRH pulse generator and decreases LH and FSH levels to cause a physiological state of lactational amenorrhea that can last for a variable duration [7].

3.4.7 Postlactational Involution

This is a process that starts with cessation of milk secretion on weaning, initially reversible with suckling. It is followed by alveolar cell apoptosis, autophagy and regrowth of stromal adipose tissue. It is associated with activation of involution associated genes and inactivation of lactation associated genes (e.g. β Casein) [1]. Degradation of cells is mediated by matrix metalloproteinases (MMPs) and apoptosis is favoured by alteration of growth factors. IGFBP initiates apoptosis by sequestering IGF1. TGFβ3 is an apoptosis initiator for alveolar cells upregulated by milk stasis. This process occurs even if another pregnancy ensues in the intervening period suggesting that tissue remodeling is a prerequisite for subsequent lactation [1].

3.4.8 Postmenopausal Involution

Following the cessation of ovarian activity with consequent decrease in estrogen and progesterone the breasts regress with increase in number of less differentiated lobules. The proportion of differentiated lobules remaining is higher with multiparity [13]. In contrast to post lactational involution both lobules and ducts decrease in number. Increased collagenisation of stroma and replacement of glandular epithelium by fat occur. Eventually a few acini and ducts remain in a fatty stroma almost retracing the steps to a prepubertal state.

3.5 Applied Physiology- Implications for Breast Cancer

3.5.1 Estrogen

It is clearly established that among hormones, estrogen is the key driver of breast cancer. There is a strong association between breast cancer risk and elevated blood/urine levels of estrogen and its metabolites [2]. Hyperestrogenic states like obesity and polycystic ovary syndrome are recognized risk entities. Clinical clues to prolonged estrogen exposure like early age at menarche, late age at menopause and late age at first conception with longer time gap (> 14 years) between menarche and first pregnancy are additional risk factors [2, 3]. Metaanalysis of observational epidemiologic studies and randomized controlled trials looking at hormone replacement therapy (HRT) with estrogen with or without additional progesterone have concluded longer duration of estrogen use (>5 years) confers increased risk of breast cancer [14]. Similar data are available for prolonged use of oral contraceptive pills especially the higher estrogen dose formulations.

Estrogen exerts its carcinogenic effect on breast through several mechanisms [2]. Oxidative metabolism of estrogens yields catechol estrogens (16 hydroxy estrone, 2 hydroxy estradiol and estrone and 4 hydroxy estradiol and estrone) that have genotoxic and mutagenic effects on DNA [2]. Estrogen per se through its genomic action on nucleus and mitochondria alters transcription of different proteins responsible for increased cell proliferation and decreased apoptosis. In addition estrogen exerts non-genomic action through membrane receptors activating several second messengers like PI3k, Akt and mammalian target of Rapamycin mTOR, producing mitogenic and angiogenic effects [2, 3]. Activation of Ras-Raf- MAPK pathway increases release of matrix metalloproteinases via Src leading to higher invasive and metastatic potential [3].

Historically targeting estrogen to treat breast cancer was pioneered by Bateson in 1896, through bilateral oophorectomy for advanced disease. Currently targeting estrogen pharmacologically is the cornerstone of endocrine therapy of breast cancer. Three approaches are mainly used. 1) Selective Estrogen receptor modulators (SERMs) e.g. Tamoxifen that block the estrogen receptor 2) Estrogen synthesis inhibitors e.g. Aromatase inhibitors like Letrozole, Anastrozole and Exemestane and 3) Selective Estrogen Receptor Downregulators (SERD) e.g. Fulvestrant that induce destabilization and degradation of estrogen receptors [3].

Aromatase inhibitors are preferred over SERMs in postmenopausal women since the chief source of estrogen in these patients is from aromatization of adrenal androgens [3]. In premenopausal women these are less effective due to escape from drug action by compensatory LH induced increased estrogen synthesis from ovaries.

De novo or acquired resistance to antiestrogen therapy can be explained by several mechanisms- e.g. loss or modification of ER expression, changes in post receptor mechanisms, cross talk between different pathways that can override the block and alterations in drug metabolism [4].

3.5.2 Progesterone

Mechanistic in vitro data and preclinical models show the effect of progesterone on mammary cell proliferation. Synthetic progestins have been found to increase breast cancer risk [15]. In the Women's Health Initiative (WHI) study the increased risk was noted only in the estrogen plus progesterone arm and not in the estrogen only arm, clearly implicating progestogen (medroxyprogesterone). On the contrary epidemiologic data investigating the link between endogenous progesterone levels and cancer risk have been mostly negative. There are several hurdles in investigating the role of progesterone that include pulsatile/cyclical nature of secretion, complex interactions with other hormones and dependence on estrogen for progesterone receptor expression leading to difficulty in dissecting out individual contributions. Moreover many of the actions are mediated through paracrine mediators as discussed earlier causing disparity between circulating levels and tissue actions of hormones [15]. There is an interesting hypothesis that progesterone induced neoplasia ensues when there is a switch from the physiologic paracrine mode of signaling to a pathologic autocrine mode of signaling [16].

Targeting progesterone receptor as a mode of treatment of breast cancer is still experimental. The RANK-RANKL pathway, through which progesterone exerts its proliferative effect, is an attractive target of treatment in early breast carcinoma. Denosumab the humanized monoclonal antibody against RANKL, an approved antiresorptive drug for osteoporosis, has been shown to reduce circulating tumour cell number by inhibiting intravasation of breast cancer cells [17].

3.5.3 Epidermal Growth Factor

Among the 4 receptor tyrosine kinases (HER 1–4) that transduce EGF action HER 2 has the strongest kinase and signaling activity which activates downstream pathways chiefly MAPK and PI3K, culminating in cell proliferation, inhibition of apoptosis, angiogenesis and metastasis [3, 10] (Fig. 3.5).

HER 2 can also be activated by IGF 1 receptor. In addition HER 2 and IGF 1 signaling in turn can lead to ligand independent activation of ER via MAPK, PI3K/Akt or P38 signaling [3].

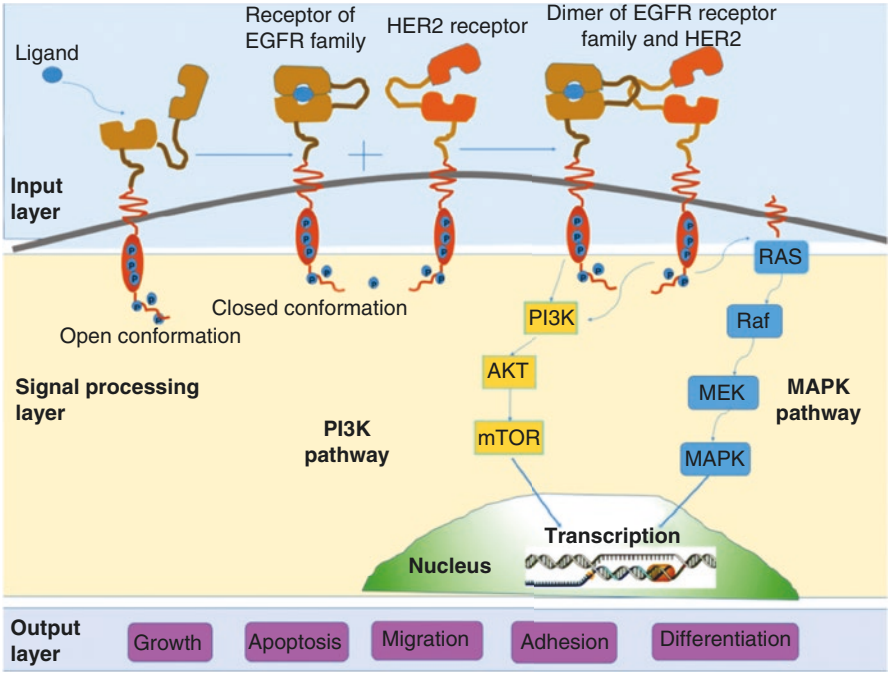


Fig. 3.5 A schema of HER 2 Signaling pathways responsible for mitogenic effects. MAPK-Mitogen activated Protein kinase; PI3K- Phosphatidylinositol 3 kinase (Reproduced from Quanxia et al. Ref. [10] under the terms and conditions of the Creative Commons Attribution (CC-BY) license) (http://creativecommons.org/licenses/by/4.0/)

Targeted breast cancer treatment against HER2 includes monoclonal antibodies and tyrosine kinase inhibitors [10] (Fig. 3.6).

Trastuzumab a monoclonal antibody against HER2 induces internalization and degradation of HER 2 disrupting signaling and promoting apoptosis. Escape mechanism that leads to treatment resistance for this modality is addressed by Everolimus an mTOR inhibitor [3, 10].Tyrosine kinase inhibitors prevent phosphorylation of the cytoplasmic Tyrosine kinase domain of all HER kinases and prevent subsequent intracellular signaling. Lapatinib is the prototype from this class targeting HER1 and 2. Several investigational agents are in pipeline targeting different downstream pathways in the crosstalk between Estrogen, IGF 1 and EGF actions [10] (Fig. 3.6).

3.5.4 Prolactin

Data from murine models have suggested mitogenic effect of prolactin on breast via the JAK2/STAT5 signaling pathways [18]. Prolactin may have a role in decreasing apoptosis, increasing cell motility, metastatic potential and chemoresistance. Even high normal circulating prolactin is shown to be linked to increase in breast cancer risk but there are problems in interpreting isolated values due to many confounders.

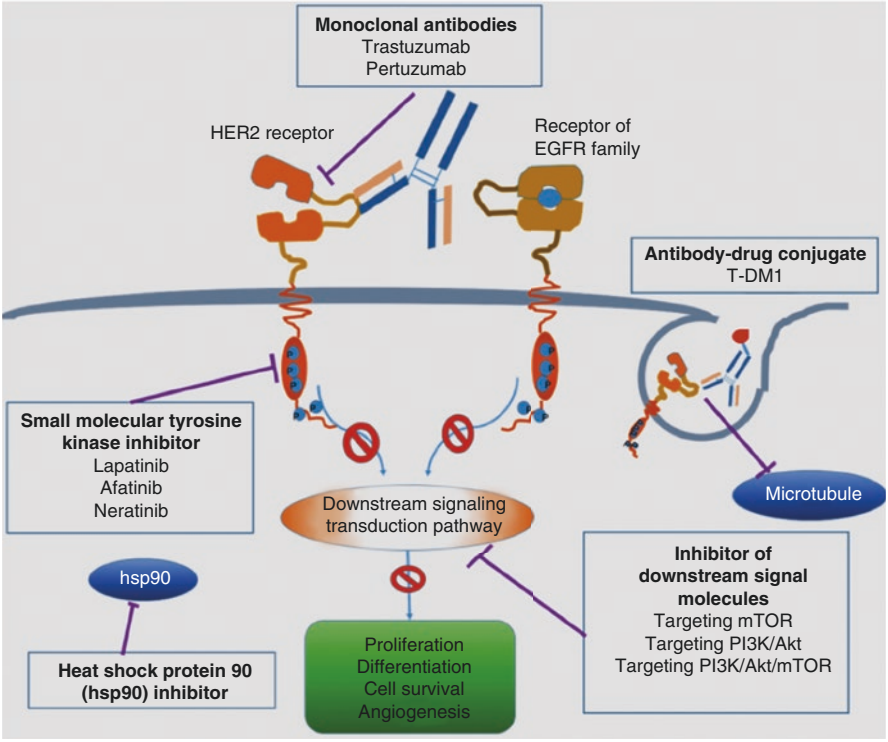


Fig. 3.6 Drugs targeting HER2 and other downstream signaling molecules for breast cancer. mTOR- Mammalian Target of Rapamycin, PI3K- Phosphatidylinositol 3 kinase (Reproduced from Quanxia et al. Ref. [10] under the terms and conditions of the Creative Commons Attribution (CC-BY) license) (http://creativecommons.org/licenses/by/4.0/)

It is also found that extrapituitary prolactin locally produced within the breast itself may play a major role. This explains the lack of success with conventional prolactin lowering dopamine agonist drugs.

Breast tumours express higher levels of prolactin receptors. In vitro studies have shown the beneficial effects of certain prolactin receptor antagonists (G129R-hPRL and Δ1–9) causing apoptosis of both ER positive and negative cell lines and augmenting cytotoxic effects of doxorubicin and paclitaxel [18]. There are significant interactions between prolactin and estrogen. Estrogen upregulates prolactin receptor gene expression. Prolactin can exert its effects through ER. Antiestrogens may have additional action of blocking prolactin receptors [18].

3.5.5 Growth Hormone

Epidemiologic data have shown the link between increased GH-IGF 1 and breast cancer risk [8]. Tall women have higher risk of breast cancer. Conversely in Laron syndrome with GH resistance there is almost zero risk of breast cancer. Animal

studies using GH, GH antagonists and transgenic models have clearly suggested mitogenic effect of GH. Using GH inhibitor Somatostatin or the GH receptor antagonist Pegvisomant blocks this effect. GH has been proposed to act on multiple targets to increase cell proliferation and survival, angiogenesis, invasive and metastatic potential, chemoresistance and stemness [8]. GH-IGF 1 axis is an exciting potential target for breast cancer treatment in combination with established treatment regimens.

3.5.6 Role of Obesity

Obesity is associated with a higher risk of malignancies of different organs in both genders. In women breast and endometrial cancer risks are increased by obesity. Multiple pathogenetic mechanisms include hyperinsulinemia and consequent increase in IGF pathway activation, hyperestrogenism due to increased adipose tissue estrogen synthesis by aromatase and the chronic inflammatory state conferred by obesity [19]. Enhanced secretion of adipocytokines like TNF α, IL-1, IL-6, IL-8 and IL-10 is linked to neoplasia. Metformin an insulin sensitizer that decreases hyperinsulinemia is currently being investigated as an anticancer agent. Evidence from observational clinical studies as well as in vitro cell culture studies show metformin has beneficial effects against breast cancer [20].

3.5.7 Protective Effect of Pregnancy: A Physiologic Approach to Breast Cancer Prevention

Rodent studies have revealed the exciting finding that full term pregnancy prior to exposure to a carcinogenic agent protects the mammary gland from malignant transformation [13]. This is attributed to permanent differentiation changes in the lobules, not dependent on gestational or lactational hyperplasia. The same protective effect can be mimicked by injecting hCG into young virgin rats [13]. It has been seen that nulliparous women have breast lobules type 1 and type 2—the less differentiated types. During pregnancy and lactation the morphology changes to the more differentiated lobule 3 and lobule 4 [13]. In nulliparous women type 1 lobules predominate whereas in parous women there is a preponderance of type 3 lobules. Lobule 1 and lobule 2 are prone to carcinomas while lobule 3 is protected. This lends further credence to the observation that parity, especially pregnancy at a younger age confers protection against breast cancer whereas nulliparity increases the risk. These data provide solid basis for physiologic means of breast cancer prevention and control.

3.6 Summary

Our improved understanding of the physiology of breast has led to refinements in deciphering the pathogenesis of breast cancer. The knowledge gained regarding interplay of different hormones and growth factors, key role of paracrine factors and the cross talk between subcellular signaling pathways has revolutionized our treatment approaches. The quest continues for more effective drugs with less adverse effects and the least propensity for failure. Targeted therapies with several exciting prospective agents are in the pipeline.

References

1. Johnson MC, Cutler ML. Anatomy and physiology of the breast. In: Jatoi I, Rody A, editors. Management of Breast Diseases. Cham: Springer; 2016. p. 1–39.
2. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med. 2006;354:270–82.
3. Fehm T, Ruckhäberle E. Breast cancer. In: Lammert E, Zeeb M, editors. Metabolism of human diseases. Wien: Springer; 2014. p. 379–84.
4. Schiff R, Massarweh SA, Shou J, Bharwani L, Mohsin SK, Osborne CK. Cross-talk between estrogen receptor and growth factor pathways as a molecular target for overcoming endocrine resistance. Clin Cancer Res. 2004;10:S331–6.
5. Stingl J. Estrogen and progesterone in normal mammary gland development and in cancer. Horm Canc. 2011;2:85–90.
6. Sternlicht MD. Key stages in mammary gland development- the cues that regulate ductal branching morphogenesis. Breast Cancer Res. 2006;8:201–11.
7. Melmed S, Kleinberg D, Ho K. Pituitary physiology and diagnostic evaluation. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Williams textbook of endocrinology. 12th ed. Philadelphia, PA: Elsevier Saunders; 2011. p. 175–228.
8. Subramani R, Nandy SB, Pedroza DA, Lakshmanaswamy R. Role of growth hormone in breast cancer. Endocrinology. 2017;158:1543–55.
9. Lee HJ, Macbeth AH, Pagani J, Young WS. Oxytocin: the great facilitator of life. Prog Neurobiol. 2009;88:127–51.
10. Quanxia LV, Meng Z, Yu Y, Jiang F, Guan D, Liang C, Zho J, Lu A, Zhang G. Molecular mechanisms and translational therapies for human epidermal receptor 2 positive breast cancer. Int J Mol Sci. 2016;17:2095. https://doi.org/10.3390/ijms17122095.
11. Dattani MT, Hindmarsh PC, Fisher DA. Endocrinology of fetal development. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Williams textbook of endocrinology. 12th ed. Philadelphia, PA: Elsevier Saunders; 2011. p. 833–67.
12. Styne DM, Grumbach MM. Puberty: ontogeny, neuroendocrinology, physiology and disorders. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Williams textbook of endocrinology. 12th ed. Philadelphia, PA: Elsevier Saunders; 2011. p. 1054–201.
13. Russo J, Russo IH. Toward a physiological approach to breast cancer prevention. Cancer Epidemiol Biomark Prev. 1994;3:353–64.
14. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019;394:1159–68.

15. Trabert B, Sherman ME, Kannan N, Stanczyk FZ. Progesterone and breast cancer. Endocr Rev. 2019;41:1–25.
16. Hilton HN, Graham JD, Clarke CL. Minireview: progesterone regulation of proliferation in the normal human breast and in breast cancer: a tale of two scenarios? Mol Endocrinol. 2015;29:1230–42.
17. D'Oronzo S, Silvestris E, Paradiso A, Cives M, Tucci M. Role of bone targeting agents in the prevention of bone metastases from breast cancer. Int J Mol Sci. 2020;21:3022. https://doi.org/10.3390/ijms21083022.
18. Sethi BK, Chanukya GV, Sri Nagesh V. Prolactin and cancer: has the orphan finally found a home? Indian J Endocrinol Metab. 2012;16(Suppl 2):S195–8.
19. Perks CM, Holly CMP. Hormonal mechanisms underlying the relationship between obesity and breast cancer. Endocrinol Metab Clin N Am. 2011;40:485–507.
20. Alimova IN, Liu B, Fan Z, Edgerton SM, Dillon T, Lind SE, Thor AD. Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest in vitro. Cell Cycle. 2009;8:909–15.

Etiopathogenesis of Breast Cancer and Prevention

4

Farheen Khan, Anjali Mishra, and Saroj Kanta Mishra

4.1 Introduction

Breast cancer is the most common malignant tumour among women worldwide. There is an exponential rise seen in the global burden of breast cancer. According to Globocan 2018, there would be approximately 2.1 million newly diagnosed breast cancer cases, accounting for 1 in 4 cancer cases among women. Breast cancer incidence rates are highest in Australia/New Zealand, Europe and North America. The developed countries with a small proportion of the world population account for nearly 50% breast cancers diagnosed worldwide. In India incidence is on a rising trend. Breast cancer is the second most common cancer among women in the developing countries which contribute to more than half of the global population, hence contributing to the burden of the disease to great extent. According to National Cancer Registry Programme report, in India breast carcinoma is the leading cancer in urban India and second leading cause of death in rural India after uterine cancer [1, 2]. A troubling concern about the scenario of breast cancer in India and developing nations is younger age at diagnosis [3].Presently, almost 48% of patients with breast cancer in India are below 50 years of age [4].

Farheen Khan, MS
Senior Resident, Department of Endocrine and Breast Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Anjali Mishra, MS, PDCC
Professor, Department of Endocrine and Breast Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Saroj Kanta Mishra, MS, DNB (✉)
Professor and Head, Department of Endocrine and Breast Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
e-mail: skmishra_1956@yahoo.com

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_4

Table 4.1 Risk factors influencing breast cancer

	Factor	Effect on risk
General	Increasing age	↑
	Female gender	↑
	Area of residence	↑↓
	Ionizing radiation	↑
Genetic	BRCA and other genetic mutations Family history—early onset/bilateral disease/first degree relative	↑
Hormonal factors	Early menarche	↑
	Late menopause	↑
	Late first term pregnancy/nulliparity	↑
	Breast feeding	↓
	Irregular/anovulatory cycles	↓
	Increasing parity	↓
	Hormone replacement therapy—post menopausal	↑
	Early bilateral oophorectomy	↓
	Oral contraceptive use—past/current	↑
Breast conditions	Increased mammographic breast density	↑
	Proliferative benign breast disease	↑
Obesity and life style related	Physical activity Premenopausal obesity	↓
	Postmenopausal obesity	↑
	Smoking, alcohol	↑
	Endocrine disrupting compounds	↑

Breast cancer genesis is multifactorial and can't be explained by one etiological factor [5, 6]. Like in other organs, damages that occur within the breast tissue at cellular level transform normal tissue to a tumour. This can be explained by the "Genetic model" of breast carcinoma development and is predicated on the speculation of alteration and accumulation of cellular level damages of genes found within the normal breast tissue. The two broad mechanisms that specify the molecular trauma which results in breast carcinogenesis is mutation of DNA and initiation of cell proliferation. However, the question that is still unclear is what causes the induction of cellular proliferation and mutation of the genes.

Epidemiologic research has identified reproductive, and life style risk factors for breast carcinoma. Additionally, a considerable body of scientific evidence indicates that certain pre-existing breast pathologies and exposure to common chemicals and radiation, singly and together also contributes to increasingly high incidence of breast carcinoma observed over past decades. Table 4.1 summarizes the factors that influence breast carcinoma development.

4.2 Geographical and Racial

The consistent pattern of higher rates in certain regions despite temporal and cultural variations reflects differences in underlying breast cancer risks across various nations and cities within nations [7]. The geographical location seems to play an

important role in risk of development of breast cancer. One in 8 or 9 women in USA and UK are expected to develop breast cancer in their lifetime but the incidence in developing nations including India is very low. In India the incidence ranges between 5–40 per 100,000 women; and the urban areas witness higher incidence than rural. In USA white women are more likely to get affected by breast cancer whereas the incidence is low among Indian- Americans and African- Americans. The relationship of geographical location and development of breast cancer seems complex and includes interplay of genetic predisposition, life style choices or simply life expectancy.

4.3 Age and Gender

Breast cancer risk increases with increasing age [5, 7, 8]. Women have 100 times more risk of getting breast cancer than men. About 80% of women diagnosed with breast cancer each year are aged 45 or older, and about 43% are aged 65 or above.

- In women between age 40 to 50, there is one in 68 risk of developing breast cancer.
- Between 50 to 60, that risk increases to one in 42.
- In the 60 to 70 age group, the risk is one in 28.
- In women aged 70 and older, one in 26 is at risk.

Although breast cancer risk increases with advancing age, one of the hormonal factors implicated in the development of breast cancer suddenly decreases with cessation of ovarian function at menopause. The cyclical production of relatively large amounts of oestrogen and progesterone increases the risk of breast cancer genesis as compared in post-menopausal and elderly women who have exposure to constantly low levels of hormones. Ovarian and endometrial cancer have the same complex relationship between age and incidence [8].This decline indicates the crucial role played by hormones in genesis of breast cancer.

4.4 Hormonal Factors

Hormonal factors are also called reproductive risk factors which play a major role in the causation of breast cancer. Ovulatory cycles between menarche and first childbirth results in estrogen exposure and is considered the primary factor contributing to risk of breast cancer. The duration of this estrogen exposure increases the susceptibility of proliferating breast cells to random genetic errors and carcinogenic environmental insults [9]. Duration of exposure to both endogenous and exogenous oestrogens in breast cancer development is undisputed. Studies in mice models suggest role of progesterone in modulating breast cancer biology [10]. Definite role of progesterone in breast cancer genesis is still unclear. However, some studies reported higher risk of breast cancer in women taking progesterone combined contraceptive pills as compared to oestrogen only pills. Direct role of progesterone requires further research [11].

4.4.1 Age at Menarche

Age at menarche has a well-established relationship with development of breast cancer. Each earlier year of menarche has been demonstrated to add 4–5% to the risk of breast cancer. Early menarche <= 9 years and rapid establishment of regular cycles have a four-fold increase in risk of breast cancer than women with late menarche >15 years and long duration of irregular cycles [12]. It is worth remembering that onset of menarche is earlier in developed countries as compared to developing countries, and this may be one of the causes of increased incidence of breast cancer in developed countries.

4.4.2 Age at Menopause

The later a woman experiences menopause the more is the oestrogen exposure in her lifetime which consequently increases lifetime risk of breast cancer. Each additional year until menopause adds a risk of about 4%. Women who experience natural menopause before the age of 45 years have only half the breast cancer risk as compared to those in whom menopause occurs after the age of 55 years. The influence of age at menarche and menopause may partly explain the geographical and temporal variations of breast cancer incidence around the world [13].

4.4.3 Age at First Term Pregnancy

Parity and age at first birth are endogenous hormonal factors that influence breast cancer risk. Age at first childbirth is extremely important for subsequent development of breast cancer. Age less than 20 years for first childbirth can reduce breast cancer risk by 50% compared to first childbirth beyond 30 years of age [14]. Nulliparous women have a relative risk of 1.4 by the age 40–45 years to develop breast cancer as compared to parous women [15]. The longer the interval from menarche to first pregnancy, greater the adverse effect of the first pregnancy. This in part is contributed by the rapid changes and proliferation that happens during first pregnancy. First pregnancy is associated with permanent changes in the glandular epithelium and changes in the biological properties of the mammary cells. After the differentiation of pregnancy, epithelial cells have a longer cell cycle and spend more time in G1, the phase that allows DNA repair. The later the age at full term pregnancy the more likely that defect in DNA repair would have occurred resulting in unregulated proliferation of mammary cells during pregnancy. The susceptibility of mammary tissues to carcinogens decreases after the first pregnancy. Additional live births after the first provide additional long-term protection of approximately 7% per birth. On the other

hand abortion whether spontaneous or induced before full term pregnancy has no protective effect and has been shown to increase breast cancer risk [16].

4.4.4 Lactation

Epidemiologic studies relating breast cancer risk to breast feeding give variable results due to different practices of breast feeding across the world. The most extensive pooled analysis from 47 studies in 30 countries has shown an overall 4.3% reduction in risk per 12 months of breast feeding for all parous women [17].

4.4.5 Oral Contraceptives

Oral contraceptives inhibit gonadotropin secretion thus reducing the ovarian steroidogenesis, but the ovarian steroid loss is compensated for by the synthetic oestrogen and progesterone in the oral contraceptive. Available data shows that the level of sex steroids in combined oral contraceptive pills necessary to provide acceptable contraception appears to produce breast cell proliferation to the same extent as normal ovulatory cycle. The effect of oral contraceptives on breast cancer risk has been a subject of a large number of epidemiologic studies with some reporting modest risk in women using oral contraceptives whereas others did not find an increased risk in current or prior users, including women with a family history of breast cancer [18].

4.4.6 Hormone Replacement Therapy

Hormone replacement therapy has been prescribed for control of postmenopausal symptoms and for long term use for control of osteoporosis and cardiovascular disease. In women with prior hysterectomy, oestrogen replacement therapy is prescribed; and women with intact uterus, oestrogen combined with various regimens of progestins designed to protect the endometrium is used. Although some aspects of relationship between postmenopausal hormones and breast cancer risk remain unresolved, several areas of clear agreement have emerged [8, 9]. Combination of oestrogen and progesterone therapy is carcinogenic in women and causes breast cancer [19]. Increased risk appears to be in users of long duration and current users. Oestrogen appears to act as a promoter at a late stage. For a stipulated period of use of hormone replacement therapy in post menopausal women risk of breast cancer is greater for oestrogen receptor positive than oestrogen receptor negative disease. The risk is greater with oestrogen—progestin combined use than oestrogen only preparations. There is positive causal relationship with daily progesterone use as compared with intermittent use [20].

4.5 Obesity, Life Style and Diet

4.5.1 Obesity

There is some evidence to suggest that premenopausal obesity reduces risk of breast cancer [21]. Although premenopausal obesity is related to decreased sex hormone binding globulin and minimally increases the risk of exposure to estrogen, it causes anovulatory cycles and decreases exposure of breast tissue to progesterone. However, postmenopausal obesity specifically is a risk factor for genesis of breast cancer [5]. The main reason seems to be that in postmenopausal women adipocytes which are one of the major sources of aromatase contributes to estrogen production. Increasing BMI has a linear association with breast cancer with relative risk increasing with BMI more than 25.

4.5.2 Diet, Smoking, Alcohol Intake

Diet deficient in phytoestrogen, and rich in fat and meat has been linked to breast cancer whereas diet rich in fibre is considered to provide protection against breast cancer.

Alcohol consumption is also related to breast cancer development and it seems to be dose dependent [5, 7, 22]. Active and passive exposure to tobacco smoke exposes an individual to polycyclic aromatic hydrocarbons as well as other known chemicals which have been found carcinogenic in mammary tissues in animal models. Several studies in women have found a positive association of smoking with a high risk of development of breast cancer, depending on the pack years smoked, smoke exposure between menarche and first full term pregnancy, ethnicity and concomitant alcohol consumption [23]. There is no evidence of link between smoking and increased risk of breast cancer development in men.

Physical activity has been found to decrease the risk of breast cancer. Exercises decreases estrogen and progesterone levels in the body. There is evidence that exercise before menarche and in pre and postmenopausal women has protective effect on development of breast cancer.

4.6 Breast Pathology/Condition

4.6.1 Mammographic Density

Increased mammographic breast density is associated with increase in risk of breast cancer independent of other risk factors [5, 24]. In a meta-analysis the relative risk associated with dense breasts was 2.92 for breasts that were 50%–74% dense and 4.64 for breasts that were 75% or more dense [25]. Increased breast density is due to increased epithelial and stromal component in relation to fatty component. Increased breast density is multifactorial and is influenced by age, hormonal factor,

reproductive history and genetic predisposition [5]. Therefore it is very difficult to quantify the absolute risk attached with this feature.

4.6.2 Non-proliferative and Proliferative Benign Breast Pathologies

Non proliferative breast lesions like cysts and fibroadenoma have rarely been associated with risk of developing breast cancer. Women with history of proliferative breast disease have increased risk for breast cancer. Biopsy proven atypical hyperplasia is associated with five-fold increase in breast cancer risk and that without atypia is associated with two-fold increase in risk [5, 26].Lobular carcinoma in situ (LCIS) previously considered as pre-invasive cancer is now considered as risk factor and is consistently associated with increased risk of developing invasive cancer and also pre-disposes to developmental of bilateral breast cancer.

4.7 Radiation Exposure

Exposure to ionizing radiation early in life during childhood through adolescence is an important factor in development of breast cancer. Ionizing radiation in any form has enough energy to break the chemical bonds in molecules thereby altering the chemical signals and DNA structure [23]. Women with genetic predisposition to breast cancer are particularly susceptible to environmental factors like radiation exposure in cancer genesis.

4.8 Others

4.8.1 Endocrine Disrupting Compounds (EDCs)

Some chemicals found in plastics, pesticides and cosmetics disrupt the sensitive endocrine system. By interfering with the actions of the natural hormones, exposures to EDCs have been linked to development of a large variety of cancers. There are several important EDCs found to increase risk of breast cancer in studies from non-human models [23].

4.8.2 Late at Night Shift Work

Extensive experience with night shift work and therefore higher exposure to light at night has been shown to increase risk of breast cancer by enhancing the production or secretion of oestradiol and other ovarian hormones. It also may be mediated through levels of melatonin, a light sensitive hormone. There may be ethnic differences in this response [23].

4.9 Genetic/Familial Factors

Epidemiologic studies prove familial clustering of breast cancer. In USA up to 15% women have one of the family members affected by breast cancer [5]. Women at risk are the ones with first degree relative (mother, sister, daughter) with an early onset of bilateral breast cancer and early onset of breast cancer affecting two first degree relatives. But only 5–10% breast cancers are hereditary. The common genetic mutations in hereditary breast cancer are BRCA 1 and BRCA 2. Other known genetic mutations include *Tp53 (*Li-Fraumeni syndrome)*, PTEN (*Cowden syndrome)*, CHEK2, CDH1 (*hereditary diffuse gastric cancer)*, STK11 (*Peutz-Jeghers syndrome) *ATM (*ataxia-telangiectasia*),* and *PALB2* genes. BRCA mutations are more prevalent in Ashkenazi Jews. About 7 out of 10 women with BRCA mutations are likely to develop breast cancer (life time risk of developing breast cancer is 56–84%). These women are more likely to be diagnosed with breast cancer at young age and have bilateral breast cancer and triple negative type of breast cancers.

4.10 Pathogenesis, Molecular Portraits in Breast Cancer and their Significance

Breast cancer is a heterogeneous cancer which presents in different histology subtypes, varied virulence and response to therapy [5, 6, 27]. As is true for any malignancy complex genetic, epigenetic and molecular processes are involved in development and progression of breast cancer [5–7]. While many such processes are still to be understood, great advancements have been made in the field of genetics and molecular biology. What still is controversial is whether breast cancer develops from stem cells or cancer cells themselves have acquired property of stem cell. The major signalling pathways involved in the development of breast cancer include oestrogen receptor, HER2-neu receptors, Canonical Wnt/ß- catenin, cyclin dependent kinase, Notch signalling, Sonic- Hedgehog, breast tumour kinase and PI3K/AKT/mTOR pathways. It is certain that the two major stem cells involved in the pathogenesis of breast cancer cells are luminal and basal cells. The mutated DNA encodes for a protein through mRNA. In a tumour mass there are a large group of heterogeneous DNA and their resultant proteins. These bear the genetic signature of a particular cancer. The genetic signature determines the biological behaviour of the cancer and can predict the possibility of response to various forms of treatment. Based on genetic studies breast cancer can be divided into four broad clusters Luminal type, HER2 enriched, Basal types and normal-like [27]. For therapeutic considerations St. Gallen consensus report has divided breast cancer into four major types: Luminal A, Luminal B, HER2-overexpression and Triple Negative Breast Cancers (TNBC).

Luminal Type*:* these cancers originate from the inner lining luminal cells and express the luminal patterns of genes. These include cytokeratin 8 and 18ER, ESR1, GATA, GATA3, FOXA1, XPB1 and MYB. Based on expressions of ER related genes, proliferation related genes and HER2 neugene. These are further divided into: Luminal Type A and B. Both luminal A and B cancer respond to hormonal therapy [27, 28]. CDK4/6 inhibitors palbociclib/ribociclib) are effective against those which do not express HER2.

Luminal A: high expression of ER related genes, low expression of proliferation related genes and HER2 neu clusters. As per St Gallen consensus 2013 Luminal type A is recognized by positive expression of both ER and PR, negative expression of HER2 and Ki-67 index of less than 14% [28].

Luminal B: relatively lower expression of ER related genes, higher expression of proliferation related genes and HER2 neu clusters. This category is further subdivided into two subcategories. HER2-positive luminal B type breast cancers are ER and HER2 positive; and could have any PR and Ki-67 expression. On the other hand HER2-negative luminal B type are ER positive and HER2 negative; and exhibit low levels of PR (<20%) and high levels of Ki-67 (>14%).

HER2- neu enriched cancers: Breast cancer which has high expression of HER2 neu and proliferation related gene expression, is known as HER2 neu enriched cancer. These cancers have low or no expression of ER and or PR. Though this can make it difficult to differentiate between Luminal B and HER2 neu variety, a true HER2 variant will not express ER and PR. These are prognostically a bad biological variant but show extremely good response to trastuzumab, pertuzumab and ado-trastuzumab emtansine.

Normal variant: close to Luminal cancers but are more virulent.

Basal/Triple negative breast cancer (TNBC): Though all basal types are not TNBC and all TNBC are not basal cancers, TNBC are one of the major subtypes of basal breast cancer. The incidence of TNBC is proportionately high in India [4]. TNBC are defined by absence of expression for estrogen receptor (ER), progesterone receptor (PR) and, absence of overexpression for human epidermal growth factor receptor HER2/neu (HER2). TNBC are generally considered target-less BC because as opposed to hormone receptor and HER2/neu receptor expressing BC, no specific therapeutic agent is available against TNBC. Molecular analyses have revealed that TNBC is a heterogeneous disease [29–31]. According to Lehmann et al., TNBC can be further classified into four molecular subtypes: basal-like1, basal-like2, mesenchymal, and luminal androgen receptor (LAR), each characterized by different clinicopathologic features and different driver signalling pharmacologically targetable pathways [30]. In another study, Jezequel et al. demonstrated three molecular subtypes, basal with low immune response, basal with high immune response, and LAR [31]. LAR subtype of TNBC is basically luminal type characterized by high androgen receptor expression and enrichment of hormonally regulated pathways [30, 31].

4.11 Prognostic and Therapeutic Significance of Breast Cancer Molecular Signatures

It is evident that the amplicons, proliferating genes, anti-apoptotic genes and angiogenic genes play a major role in shaping the outcome of breast cancer. There is strong evidence in favour of using these molecular models in establishing the risk categories of a cancer, genetic testing for hereditary breast cancer and genomic profiling of tumor are being incorporated in various guidelines for management of breast cancer. With fast development in this field and technology becoming inexpensive, these are on verge of becoming standard of care across globe [32–35].

4.12 Testing for Hereditary Breast Cancer

Though guidelines vary and initial ones were limited to detect patients affected with BRCA1 and BRCA2 mutations, the current guidelines have expanded to include other genetic syndromes. However, as the economic, psychological and social impact is huge certain caution is warranted [33]. The general guidelines for genetic testing include- a known family history of BRCA 1, 2 or other high risk mutations or history of multiple breast cancers in first degree relatives, diagnosis of breast cancer before 50 years, bilateral breast cancer, concurrent diagnosis or history of ovarian cancer in patient, multifocal and triple negative breast cancer; and high risk ethnicity i.e. like Ashkenazi Jewish ancestry. These tests should not be prescribed without availability of genetic counsellor who would guide and help patient during pre and post-testing period. The results of genetic testing have far reaching impact and involve screening of family members, management decision of patients, and surveillance for other components of genetic syndrome; prognosis and prediction of therapeutic response. For genes associated with high risk for cancers, such as BRCA1, BRCA2, p53, PTEN, CDH1, and PALB2, high-risk screening and other prophylactic surgeries may be recommended as discussed in prevention of breast cancer section. These women and family members should also be provided guidance regarding surveillance and risk reduction measures for other associated malignancies [34]. Hence a multidisciplinary team should be involved in tackling these patients. Needless to state that surgeons not dealing with genetic disorders shouldn't interpret these tests on their own as on one hand mutation may remain undetected in a patient with hereditary disease, on the other hand not all detectable mutation would have clinical relevance. Currently testing is not available at most of the public hospitals in India. Many commercial labs in India do offer these tests at expense of 20,000 to 25,000 INR (270–340 USD) but testing is mostly limited to BRCA1 and BRCA2. The results need to be interpreted with caution as reliability depends on the technique and expertise. Sanger sequencing remains gold standard but this technique is labor intense. Currently many laboratories are switching over to next generation sequencing (NGS) wherein more than one gene could be tested at a time, but various NGS platforms need to be validated against gold standard [33, 34].

4.13 Prognostic, Predictive and Therapeutic Implications

The pathologic prognostic staging stage groups described in the latest version of AJCC staging system is a major step towards this direction [36]. It wouldn't be too far when results of multigene panels would be incorporated into staging system [35]. Currently these tests e.g. Oncotype DX, MammaPrint, EndoPredict, PAM50, and Breast Cancer Index are commercially available and have a significant role to play in predicting benefit of chemotherapy in node negative, ER positive early breast cancers [35–38].These could help preventing use of chemotherapy in the subset of patients unlikely to be benefitted from such treatment and thus sparing these of its side effects. A potential futuristic utility of multigene assays would be to help identifying hormonal positive cancers with high risk genetic signatures which could benefit for extended endocrine therapy [35]. On the other hand certain genes and/or somatic mutations can effectively predict drug resistance of a particular tumour eg. presence of RB1 and FAT1 mutations might identify ER+ breast cancers that do not respond to CDK4/6 inhibitors [35, 37–39]. Hence a tailored therapy can be initiated without delay. Patients with metastatic breast cancer and a germline BRCA mutation could benefit with use of platinum compounds and PARP inhibitors i.e. olaparib and talazoparib. Similarly in patients with metastatic estrogen receptor positive breast cancers presence of ESR1 and PIK3CA mutations signifies resistance to aromatase inhibitors and fulvestrant respectively. Tumors with PIK3CA mutations could benefit from PI3 kinase inhibitor alpelisib in combination with fulvestrant. Tumors with microsatellite instability could benefit from anti–PD-1 antibody pembrolizumab. Among TNBC PIK3CA, AKT1, PTEN mutations may identify sensitivity to the AKT inhibitors ipatasertib and andcapivasertib. TNBC exhibiting androgen receptors may benefit with use of androgen inhibitors. Molecular signatures, therefore, are essential not only for understanding the biological behaviour of cancer but also to implement precision therapy.Similarly in HER2 positive breast cancers molecular testing could identify the cases likely to benefit with dual blockade [29, 30, 35].

4.14 Prevention of Breast Cancer

Breast carcinoma as a disease results in significant physical and psychological morbidity in terms of treatment and follow up. With rising incidence of breast cancer worldwide, it is reasonable to consider breast cancer preventive measures. Although there are many risk factors, almost half of the patients have no identifiable risk factor. The potential benefits of breast cancer prevention strategy are reflected in the population with high incidence.

A sound preventive strategy for any disease should include characteristics like a substantial risk reduction, feasibility of implementation with least deleterious effects and cost effectiveness. Education, employment and other societal factors

Table 4.2 Suggested Preventive Strategies for Breast Cancer Risk Reduction

Group	Lifetime risk of breast cancer (%)	Risk factors	Preventive measures
Average risk	11–12	No family history or reproductive risk factors	Life style modification, breast self-examination (BSE), clinical breast examination (CBE), screening mammography?
Increased risk	10–20	No family history but at least two reproductive factors	Life style modification, BSE, CBE, screening mammography?
High risk	>20	Atypical hyperplasia with a family history of lobular carcinoma in-situ (LCIS), strong family history: Any first- degree/ second- degree relative with onset <40 years, or ≥ 3 family members with breast cancer	Life style modification, BSE, CBE + start screening mammography one decade prior to history of breast cancer in family member
Very high risk	Upto 85	Breast cancer susceptibility gene (BRCA 1, BRCA 2 or other cancer susceptibility syndromes)	Life style modification, BSE, CBE + start screening mammography one decade prior to history of breast cancer in family member+ chemoprevention/risk reducing surgery

may make certain preventive strategies impractical for the targeted high-risk population [7, 22, 23, 34]. A preventive strategy which matches and targets the daily routine activities would be acceptable in a population especially with wide temporal variance across the globe. Table 4.2 summarizes the suggested risk reduction strategies according to risk stratification of breast cancer.

4.15 Preventive Measures to Reduce Breast Carcinoma Risk

4.15.1 General Preventive Measures

4.15.1.1 Modification of Reproductive Risk Factors

As mentioned earlier, women who have pregnancy at young age, multiple pregnancies and lactation at young age can all have protective effect against breast cancer. It is but obvious that many of these factors could not be modified in existing world but whatever could be should be practised i.e. e.g. using low oestrogen dose contraceptives than high dose preparation, hence effectively reducing the exogenous oestrogen exposure [5, 6]. Similarly avoidance of hormone replacement therapy and encouraging breast feeding would contribute to risk reduction. Similarly early age marriage followed with early pregnancy can be practised in high risk women.

4.15.1.2 Lifestyle Modifications

Continued physical activity performed on a regular basis results in reduction in the length of luteal phase and luteal phase progesterone levels. Early onset strenuous exercise seems to effect total duration of exposure to estrogens by inducing early menopause and late menarche. The etiologic window in a women's life for a protective effect of physical activity is yet to be determined, however, given the protective benefits of regular exercise on fat metabolism, it is justified to advise regular exercise early in life to reduce breast cancer risk. Ingestion of low-fat diet reduces endogenous oestradiol and estrone levels without affecting ovulation. Studies have also shown that reduced consumption of dietary fat during childhood and adolescence may be protective against breast cancer development. Inclusion of fruits, vegetables and fibre in diet has an inverse relationship with development of breast cancer. Soyabeans and soy-based products contain phytoestrogens that interfere with effects of physiologic concentrations of oestrogens. These soya-based foods also contain protease inhibitors which have been shown to have a negative effect on carcinogenesis.

Alcohol consumption and smoking are modifiable risk factors for breast cancer and abstinence/reduced consumption of these substances can be considered as a method of prevention [7, 22, 34].

4.15.2 Preventive Measure for Hereditary/Familial Breast Cancer

4.15.2.1 Chemoprevention

Tamoxifen and other selective estrogen receptor modulators raloxifene and aromatase inhibitor have been used/tried as primary prevention modality in BRCA1 and BRCA 2 carrier, but there is limited data [34, 40, 41]. There is evidence that use of adjuvant tamoxifen significantly reduces the risk of contra-lateral breast cancer in patients with breast cancer including those with BRCA1 and 2 mutations. There is strong evidence that use of tamoxifen results in reduced breast cancer related mortality in high risk groups and risk reducing effect could persists beyond 10 years after cessation of therapy [40, 41]. However, before considering Tamoxifen as chemoprevention, benefits should be carefully weighed against the risks of side effects of the drug. Chemoprevention is not a substitute for screening and screening should be continued in women who have risk factors despite chemoprevention.

4.15.2.2 Risk Reducing Surgery

Risk Reducing Salpingo-oophorectomy (RRSO)

RRSO may be reasonable option in women with BRCA 1 or 2 mutations and reduces the risk of developing breast cancer by approximately 50%, but the effect seems differential with BRAC2 mutation women benefiting more than those with BRCA1 mutaion [33, 34, 42]. It is usually considered after child-bearing or between

ages of 35–40, the main intent of this surgery though is to reduce the risk of ovarian and fallopian tube cancer. It can also be considered in other hereditary syndromes i.e. Lynch Syndrome where it is combined with risk reducing hysterectomy.

Risk Reducing Mastectomy (RRM)

Bilateral RRM is one of the most extreme measures of prevention of breast cancer and it reduces the risk of developing breast cancer by 90% and if combined with RRSO by more than 95% in BRCA carriers [33, 34, 42]. There are no absolute indications for prophylactic bilateral mastectomy and despite undergoing this ablative procedure the risk of developing breast cancer does not always become zero. Skin sparing mastectomy (SSM) and nipple sparing mastectomy (NSM) seem acceptable alternative to total mastectomy but patients need to be followed up with annual breast imaging. In patients with diagnosed early breast cancer on one side, contralateral risk reducing mastectomy (CRRM) results in significant decrease in contralateral breast cancer and breast cancer related mortality. The risk is reduced by 91–95% [43, 44]. RRSO, and risk RRM could also be considered in other hereditary syndromes [34].

4.15.3 Secondary Prevention/Breast Cancer Screening for High Risk Women

The significance of early detection of breast cancer can't be overemphasized as potential goals include improved breast cancer specific survival, reduced breast cancer specific mortality, and opportunity for less extensive intervention in form of surgery and adjuvant therapy. But the best modality for this purpose and their efficacy in achieving the aforementioned goals remain controversial [7, 45–47]. The key features of existing screening methods, breast self-examination, clinical breast examination and mammographic screening are discussed elsewhere in this book.

References

1. NCRP annual reports [Internet]. [cited 2020 Jan 12]. Available from http://ncdirindia.org/NCRP/Annual_Reports.aspx
2. Mathur P, Sathishkumar K, Chaturvedi M, et al. Cancer statistics, 2020: Report from National Cancer Registry Programme, India. JCO Global Oncol. 2020;6:1063–75.
3. Kumar RV, Bhasker S. A peek into epidemiology, screening, management of breast cancer in developing countries: experience from two regional cancer centers in India. Breast J. 2018;24(3):422–3.
4. Thakur KK, Bordoloi D, Kunnumakkara AB. Alarming burden of triple-negative breast cancer in India. Clin Breast Cancer. 2018;18(3):e393–9.
5. Feng Y, Spezia M, Huang S, et al. Breast cancer development and progression: risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis. 2018;5:77e106.

6. Shah R, Rosso K, Nathanson SD. Pathogenesis, prevention, diagnosis and treatment of breast cancer. World J Clin Oncol. 2014 August 10;5(3):283–98.
7. International Agency for Research on Cancer. IARC handbooks of cancer prevention, Vol. 15. Breast cancer screening. Lyon: IARC Press; 2016.
8. Pike MC. Age-related factors in cancers of the breast, ovary, and endometrium. J Chronic Dis. 1987 Jan 1;40:59S–69S.
9. Pike MC, Spicer DV, Dahmoush L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev. 1993;15(1):17–35.
10. Lange CA, Yee D. Progesterone and breast cancer. Womens Health Lond Engl. 2008 Mar;4(2):151–62.
11. van Leeuwen FE. Epidemiologic aspects of exogenous progestagens in relation to their role in pathogenesis of human breast cancer. Acta Endocrinol. 1991;125(Suppl 1):13–26.
12. Lacroix AE, Gondal H, Langaker MD. Physiology, Menarche. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2020 Nov 10]. Available from http://www.ncbi.nlm.nih.gov/books/NBK470216/.
13. Kvåle G, Heuch I, Eide GE. A prospective study of reproductive factors and breast cancer. I. Parity. Am J Epidemiol. 1987 Nov;126(5):831–41.
14. Albrektsen G, Heuch I, Hansen S, Kvåle G. Breast cancer risk by age at birth, time since birth and time intervals between births: exploring interaction effects. Br J Cancer. 2005 Jan 17;92(1):167–75.
15. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev. 1993;15(1):36–47.
16. Hadjimichael OC, Boyle CA, Meigs JW. Abortion before first livebirth and risk of breast cancer. Br J Cancer. 1986 Feb;53(2):281–4.
17. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet Lond Engl. 2002 Jul 20;360(9328):187–95.
18. Soroush A, Farshchian N, Komasi S, et al. The role of oral contraceptive pills on increased risk of breast cancer in Iranian populations: a meta-analysis. J Cancer Prev. 2016 Dec;21(4):294–301.
19. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998 Aug 19;280(7):605–13.
20. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019 Sep 28;394(10204):1159–68.
21. Hunter DJ, Willett WC. Diet, body size, and breast cancer. Epidemiol Rev. 1993;15(1):110–32.
22. Aguas F, Martins A, Gomes TP, de Sousa M, Silva DP, Portuguese Menopause Society, Portuguese Gynaecology Society. Prophylaxis approach to a-symptomatic post-menopausal women: breast cancer. Maturitas. 2005 Nov 15;52(Suppl 1):S23–31.
23. Gray JM, Rasanayagam S, Engel C, Rizzo J. State of the evidence 2017: an update on the connection between breast cancer and the environment. Environ Health. 2017 Sep 2;16(1):94.
24. Free PE. Mammographic breast density: impact on breast cancer risk and implications for screening. Radiographics. 2015;35:302–15. https://doi.org/10.1148/rg.352140106.
25. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomark Prev. 2006;15(6):1159–69.
26. Fitzgibbons PL, Henson DE, Hutter RV, Cancer Committee of the College of American Pathologists. Benign breast changes and the risk for subsequent breast cancer: an update of the 1985 consensus statement. Arch Pathol Lab Med. 1998 Dec;122(12):1053–5.

27. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000 Aug;406(6797):747–52.
28. Harbeck N, Thomssen C, Gnant M. St. Gallen 2013: brief preliminary summary of the consensus discussion. Breast Care. 2013 May;8(2):102–9.
29. Yue Y, Astvatsaturyan K, Cui X, Zhang X, Fraass B, Bose S. Stratification of prognosis of triple-negative breast cancer patients using combinatorial biomarkers. PLoS One. 2016 Mar 1;11(3):e0149661.
30. Lehmann BD, Jovanović B, Chen X, Estrada MV, Johnson KN, Shyr Y, et al. Refinement of triple-negative breast cancer molecular subtypes: implications for neoadjuvant chemotherapy selection. PLoS One. 2016 Jun 16;11(6):e0157368.
31. Jézéquel P, Loussouarn D, Guérin-Charbonnel C, Campion L, Vanier A, Gouraud W, et al. Gene-expression molecular subtyping of triple-negative breast cancer tumours: importance of immune response. Breast Cancer Res. 2015 Mar 20;17:43.
32. Litton JK, Burstein HJ, Turner NC. Molecular testing in breast cancer. 2019. ASCO educational book. asco.org/edbook. https://doi.org/10.1200/EDBK_237715
33. Manahan ER, Kuerer HM, Sebastian M, et al. Consensus guidelines on genetic testing for hereditary breast cancer from the American Society of Breast Surgeons. Ann Surg Oncol. 2019;26:3025–31.
34. Paluch-Shimon S, Cardoso F, Sessa C, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO clinical practice guidelines for cancer prevention and screening. Ann Oncol. 2016;27(Supplement 5):v103–10. https://doi.org/10.1093/annonc/mdw327.
35. Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2016;34:1134–50. https://doi.org/10.1200/JCO.2015.65.2289.
36. Amin MB, Edge S, Greene F, et al., editors. AJCC cancer staging manual. 8th ed. Chicago, IL: Springer; 2017.
37. Lal S, McCart Reed AE, de Luca XM, Simpson PT. Molecular signatures in breast cancer. Methods. 2017 Dec 1;131:135–46.
38. Prat A, Fan C, Fernández A, Hoadley KA, Martinello R, Vidal M, et al. Response and survival of breast cancer intrinsic subtypes following multi-agent neoadjuvant chemotherapy. BMC Med [Internet]. 2015 Dec 18 [cited 2020 Nov 29];13. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4683815/
39. Yu K-D, Zhu R, Zhan M, Rodriguez AA, Yang W, Wong S, et al. Identification of prognosis-relevant subgroups in patients with chemoresistant triple-negative breast cancer. Clin Cancer Res Off J Am Assoc Cancer Res. 2013 May 15;19(10):2723–33.
40. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast CancerRisk Reduction, Version 1. 2020.
41. Pruthi S, Heisey RE, Bevers TB. Chemoprevention for breast cancer. Ann Surg Oncol. 2015;22:3230–5.
42. Domchek SM, Friebel TM, Singer CF, et al. Association of Risk-Reducing Surgery in *BRCA1* or *BRCA2* mutation carriers with cancer risk and mortality. JAMA. 2010 September 1;304(9):967–75. https://doi.org/10.1001/jama.2010.1237.
43. Kiely BE, Jenkins MA, McKinley JM, Friedlander ML, Weideman P, Milne RL, et al. Contralateral risk-reducing mastectomy in BRCA1 and BRCA2 mutation carriers and other high-risk women in the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab). Breast Cancer Res Treat. 2010;120(3):715–23. https://doi.org/10.1007/s10549-009-0497-8. Epub 2009 Aug 11

44. van Sprundel TC, Schmidt MK, Rookus MA, Brohet R, van Asperen CJ, Rutgers EJT, et al. Risk reduction of contralateral breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers. Br J Cancer. 2005;93:287–92.
45. Hackshaw AK, Paul EA. Breast self-examination and death from breast cancer: a metaanalysis. British J Cancer. 2003;88:1047–53.
46. Ngan TT, Nguyen NTQ, Minh HV, et al. Effectiveness of clinical breast examination as a 'standalone' screening modality: an overview of systematic reviews. BMC Cancer. 2020;20:1070. https://doi.org/10.1186/s12885-020-07521-w.
47. World Health Organization. WHO position paper on mammography screening. Geneva: WHO Library Cataloguing-in-Publication Data; 2014.

Classification of Breast Cancer

5

Aditi Chaturvedi and Bhawna Sirohi

5.1 Introduction

Breast cancer (BC) is a broad term used to encompass a diverse group of malignant conditions of the breast. Any malignant tumour arising from the breast epithelial tissue is often termed as 'breast cancer' and historically, all these cases were dealt with as one disease [1]. However, with the evolution of modern oncology and better understanding of tumour biology, BC has been classified into various subtypes. It is well established that different types of BC behave differently in terms of etiopathogenesis, clinical presentation, response to treatment and outcomes [2].

The use of various classification methods aids in better planning of treatment, improved prognostication and comparison of outcomes across centres. A variety of clinical, pathological and molecular methods are currently being used to stratify BC and we will have a brief overview of these commonly used schemes in this chapter.

For the purpose of better understanding, we have subdivided the various classification systems into the following groups:

1. Staging classification
   (a) AJCC (American Joint Committee on Cancer) TNM staging
   (b) Other staging systems
   (c) Clinical grouping: Early, locally advanced, metastatic
2. Pathological classification
   (a) WHO classification

Aditi Chaturvedi, MS, MCh (Surgical Oncology)
Consultant, Department of Surgical Oncology, Max Institute of Cancer Care, New Delhi, India

Bhawna Sirohi, FRCP (✉)
Consultant Breast and GI Medical Oncologist, Apollo Proton Cancer Centre, Chennai, India

Member, UK TNM committee, London, UK
e-mail: Bhawna.sirohi13@gmail.com

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_5

(b) Grading of breast cancers
(c) Classification using biomarkers: Hormone receptors and Her2
3. Molecular/Genetic classification
(a) Molecular/Intrinsic subtype classification
(b) Gene prognostic panel based classification

5.2 Staging Classification

The usage of staging systems has been vital to oncology practice and has continuously evolved since 1904, when Steinthal [3] first classified breast cancer into three stages: Stage I: disease localized to the breast, Stage II: tumors involving the axillary lymph nodes and Stage III: tumors involving surrounding tissues.

The Columbia Clinical Classification System, proposed by Haagensen and Stout [4], expanded from three Stages A to C which were similar to Steinthal's stages to Stage D which included very advanced disease that had metastasized.

It was Peirre Denoix [5] who first started developing the tumor-node-metastasis (TNM) system stressing on the three main factors determining the outcome of cancer patients: T referring to the size of the primary tumor, N to the involvement of regional lymph nodes involvement and M to the presence of distant metastases.

The first TNM system was proposed by the International Union Against Cancer (UICC) [6] in 1958 and the American Joint Committee on Cancer (AJCC) published it in 1977 [7].

5.3 AJCC TNM Staging

Since the 1st edition by AJCC was published, it has been regularly revised to incorporate major updates in the understanding of oncology and survival data. In 2017, the 8th edition of the staging system was announced [8].

TNM staging is based on clinical, radiological and pathological data.

The cTNM clinical staging of BC patients is based on all data collected before surgery for the primary. The pTNM or pathological staging is based on data collected after surgery for the primary tumour and histopathological examination of the excised specimen. yTNM is used to restage patients after neoadjuvant therapy and it can be either clinical or pathological.

Pathologic staging is known to be more precise than clinical staging and is preferred whenever available.

5.4 Staging for Primary Tumour

The T stage is the same whether assessed clinically or pathologically. The largest dimension of a contiguous lesion is used to denote the T stage. If there are multiple tumours, the suffix (m) is to be used and the dimension of the largest invasive

component is to be used for staging. Lobular Cancer In Situ is not included in this staging system.

5.5 Staging for Regional Nodes (N)

The regional nodes included are axillary, internal mammary and supraclavicular nodes on ipsilateral side.

There is separate clinical and pathological criteria for N staging. The suffixes (sn) and (f) should be added to the cN descriptor to note confirmation by sentinel lymph node biopsy or fine needle aspiration/core needle biopsy, respectively. The largest contiguous tumor deposit should define pN.

5.6 Staging for Distant Metastasis (M)

Presence of disease in any non-regional lymph node or other body sites is characterized as metastases. Use of imaging is not essential for M staging. Early breast cancer patients do not need any staging investigations unless symptomatic whereas some form of imaging is recommended for locally advanced disease.

The details about TNM staging can be accessed in the AJCC staging manual 8th edition [8].

5.7 Stage Grouping

The most significant change in BC staging in the 8th edition is the inclusion of histological grade, hormone receptor status such as estrogen receptor (ER) and progesterone receptor (PR), Human epidermal growth factor receptor 2 (Her2) status, proliferation indices like Ki67 or mitotic count and the results of multigene panels to calculate prognostic stages. This has been based on data that proved that integration of biologic markers would improve prognostic acumen over anatomic staging alone [9].

There are two stage groups available-

1. Anatomical stage grouping

The anatomical stage grouping is based on T, N, M characteristics only and it is to be used when information about grade, ER, PR, Her2 neu is unavailable.

2. Prognostic stage grouping

There are clinical and pathological prognostic stage grouping available separately. This utilizes the following information in addition to the TNM staging

1. Grade: The histological grade is calculated using the system of Scarff, Bloom, and Richardson (which was standardized by the Nottingham group and recom-

mended by the College of American Pathologists). For DCIS, the nuclear grade is used.
2. Hormone receptor status (ER and PR): Immunohistochemistry is used for ER/PR status
3. Her2 status: Immunohistochemistry and Fluorescent In Situ Hybridisation (FISH) techniques are used to determine Her2status
4. Multigene panel: The result of genomic testing, in particular Oncotype Dx which is a 21 gene RT PCR based test for T1 to T2 N0, ER-positive, HER2-negative disease is included in prognostic stage grouping if the score is less than 11.

The information regarding ki67 and other prognostic panels like Mammaprint, EndoPredict, PAM50, Breast Cancer Index are also to be recorded as per AJCC but not used for determining stage grouping.

5.8 Other Staging Systems

The usage of other staging systems has considerably declined in order to standardize treatment protocols and comparison of outcomes across centres worldwide.

The Manchester staging system [10] which was frequently used earlier classified BC into:

Stage I: Confined to breast; no palpable lymph nodes.
Stage II: Stage I with palpable mobile nodes in axilla
Stage III:
(a) Skin ulcerated, or fixed, peau d'orange
(b) Fixation to underlying muscle; mobile palpable nodes
Stage IV: Extension of growth beyond breast area by
(a) fixation of axillary nodes
(b) fixation of tumour to chest wall
(c) secondary nodes in supraclavicular region
(d) secondarv skin deposits wide of tumour
(e) secondary deposits in opposite breast
(f) distant metastases, e.g. bone, liver etc.

5.9 Stage Grouping for Clinical Practice

Although TNM staging is widely used, in order to plan treatment, breast cancer is often classified into the following subgroups in various clinics worldwide [11]:

1. Early breast Cancer—This term is used for patient with clinically T1,T2 BC with no or mobile axillary nodes i.e. N0,N1 or patients with T3N0 disease. These patients were conventionally thought to be suitable for upfront surgery. However, now with expanding indications of neoadjuvant systemic therapy [12], a case

based decision is taken depending on breast tumour ratio, nodal disease, hormone receptor and Her2neu status and in certain cases, chemotherapy is preferred to upfront surgery even in this subgroup.

2. Locally advanced breast cancer—This term is used for patients with clinically T3N1 disease, T4 disease or those with any T, but heavier nodal burden (N2, N3). Metastatic work up is a must in this subgroup because of higher possibility of picking up distant disease [13]. Neoadjuvant therapy is often the initial treatment of choice in these patients. Inflammatory breast cancer is a subgroup of locally advanced BC which is classified as T4d disease in TNM staging. It is characterized by the presence of characteristic skin changes such as edema and erythema involving more than one third of the breast skin [14]. Often, no discrete tumour is appreciable clinically or on imaging. Pathologically, it is characterized by the presence of lymphatic dermal emboli. However, it is not essential to demonstrate this in the presence of clinical findings to label a case of inflammatory BC.
3. Metastatic Breast Cancer—As per the self-explanatory term, any patient with clinical, radiological or pathological evidence of disease in non-regional nodes or any distant site is termed to have M1 disease or metastatic BC.

A subgroup of these patients may be termed as having oligometastatic disease. Various definitions have been used to label oligometastatic disease. In principle, any patient with limited tumour burden which may benefit from radical curative intent treatment is classified in this subgroup. Patients with metastatic site size less than 5 cm, with less than 3–5 metastatic deposits in up to 2 organs in a favorable biology patient e.g. Hormone receptor positive disease are stratified to this subgroup [15].

4. Other entities:

(a) Pregnancy associated breast cancer (PABC)—This term is used to classify patients who develop BC during pregnancy or within first post-partum year [16]. (Various definitions have used different criteria ranging from six months to two years post partum). The incidence varies from report an incidence of BC ranging from 2.3 to 40 per 100,000 deliveries [17].

They are classified separately because of the special challenges associated in this situation such as delay in diagnosis due to the associated breast changes during pregnancy and lactation, restriction in the use of diagnostic tools in pregnancy, safety of chemotherapy and surgery during different trimesters etc. Patients with PABC often have advanced disease in presentation, triple negative and higher grade tumours [17]. Their prognosis has been studied to be the same as non pregnancy associated breast cancers when matched stage to stage.

(b) Paget's disease—This term is used to classify in situ carcinoma of the nipple. The pathognomonic feature is the presence of Paget cells (large cells with clear cytoplasm and atypical nuclei) in the nipple epidermis [18]. Clinically, patients may have erosion, redness, ulceration or discharge from the nipple. It is not always associated with an underlying invasive or in situ malignancy of the breast in certain cases [18].

5.10 Pathological Classification

5.10.1 WHO Classification

The commonly used histological classification of breast tumours is the WHO classification which published its 5th edition in 2019 [19].

This provides a detailed description of all pathology of the breast ranging from benign epithelial proliferations and precursors, to papillary neoplasms, to in situ and invasive breast cancer. The list is extensive but the categories which fall under the purview of this chapter are summarized in the Table 5.1:

5.10.1.1 Noninvasive Lesions

Ductal Carcinoma In Situ (DCIS)

This is a neoplastic proliferation of mammary epithelial cells with no invasion in surrounding stroma [20]. There has been a well documented increase in the diagnosis of DCIS due to the use of screening mammography in some parts of the world [21]. Most cases are identified as suspicious calcifications, with a linear, segmental or clustered distribution on mammography whereas some may be picked up as a palpable mass.

Table 5.1 WHO Classification (5th edition) of epithelial tumours of the breast

Benign epithelial proliferations and precursors Adenosis and benign sclerosing lesions Adenomas Epithelial-myoepithelial tumours	Invasive breast carcinoma Infiltrating duct carcinoma NOS Microinvasive carcinoma Invasive lobular carcinoma Tubular carcinoma Cribriform carcinoma Mucinous adenocarcinoma Mucinous cystadenocarcinoma Oncocytic carcinoma Lipid rich carcinoma Invasive micropapillary carcinoma Carcinoma with apocrine differentiation Metaplastic carcinoma
Papillary neoplasms Intraductal Papilloma Papillary ductal carcinoma in situ Encapsulated papillary carcinoma Encapsulated papillary carcinoma with invasion Solid papillary carcinoma Invasive papillary carcinoma	
Non invasive lobular neoplasia Atypical lobular hyperplasia Lobular carcinoma in situ NOS Classical lobular carcinoma in situ Florid lobular carcinoma in situ Pleomorphiclobular carcinoma in situ	Rare and salivary gland type tumours Acinarcell carcinoma Adenoidcystic carcinoma Secretory carcinoma Mucoepidermoid carcinoma Polymorphous adenocarcinoma Tall cell carcinoma
Ductal carcinoma in situ(DCIS) DCIS of low nuclear grade DCIS intermediate nuclear grade DCIS high nuclear grade	Neuroendocrine neoplasms Neuroendocrine tumours grade1,2 Neuroendocrine carcinoma, NOS Neuroendocrine carcinoma, small cell Neuroendocrine carcinoma, large cell

DCIS is categorized as low, intermediate or high grade based on nuclear characteristics. Van Nuys Prognostic Index based on size, pathological classification and width of margins has been developed as an indicator of the aggressiveness of DCIS [22].

Paget's disease is basically a presentation of high-grade DCIS of the subareolar ducts extending to the basal layers of nipple epidermis.

Lobular Carcinoma in Situ

It is characterized by non-invasive neoplastic proliferation of cells in the terminal ductal lobular unit (TDLU) and loss of E-Cadherin [23]. It is no longer considered as a malignant lesion. It is classified as a risk factor along with atypical lobular hyperplasia [8].

5.10.1.2 Invasive Breast Carcinoma

Infiltrating Duct Carcinoma, Not Otherwise Specified (NOS)/No Special Type (NST)

Any invasive BC is designated as a pure special tumour if it contains more than 90% features of a subtype such as lobular, mucinous etc. [19]. All the others, which forms the majority (70–80%), including those with mixed patterns are designated as NST. They are characterized microscopically by nests of tumor cells with varying amounts of gland formation, and cytologic features that range from bland to highly malignant. The malignant cells induce a fibrous response as they infiltrate the breast parenchyma.

Invasive Lobular Carcinoma

It is the second most common type of invasive BC and is characterized microscopically by small cells that insidiously infiltrate the mammary stroma in a single file pattern. They have a higher frequency of bilaterality and multicentricity and are commonly hormone receptor positive [24]. They are also known to metastasize to the gastrointestinal tract and ovary [24].

Mucinous Carcinoma

They are relatively uncommon accounting for 1–2% of invasive BC. This variant is more common in older patients. Microscopically, there are nests of tumor cells amidst pools of extracellular mucin. Mucinous carcinoma represent a prognostically favorable variant of invasive BC [25].

Metaplastic Breast Cancer (MBC)

This is a rare subgroup which is described on histology as a combination of poorly differentiated ductal carcinoma, sarcomatous component and other epithelial components such as squamous cell carcinoma etc. Patients are known to have hormone receptor negative advanced disease and are at risk of a worse prognosis [26].

Other subtypes of invasive BC have also been described. Apart from mucinous, tubular, papillary, medullary, and adenoid cystic carcinoma are associated with a good prognosis whereas apart from metaplastic, micropapillary carcinomas appear to confer a worse prognosis [19].

5.11 Grading of Breast Cancers

Apart from the morphological classification detailed above, histological grading is an essential tool for the subclassification of BC. It is determined based on nuclear features (nuclear grading) alone or using a combination of nuclear and architectural features (histologic grading).

The Nottingham grading system by Elston and Ellis [27], a modification of the grading system proposed by Bloom and Richardson in 1957, is recommended for AJCC staging.

This entails evaluation of (1) tubule formation, (2) nuclear pleomorphism, and (3) mitotic activity. Each of these features is rated on a scale of 1 to 3. The total of these scores forms the overall histologic grade. Tumors with a sum of the scores of 3 to 5 are designated grade 1 (well differentiated), those with sums of 6 and 7 are designated grade 2 (moderately differentiated), and those with sums of 8 and 9 are designated grade 3 (poorly differentiated).

5.12 Classification Using Biomarkers

5.12.1 Hormone Receptors

Estrogen receptor (ER) and progesterone receptor (PR) are members of the nuclear hormone receptor family and have been well established for their role as prognostic and predictive agents in all stages of BC [28].

Conventionally, immunohistochemistry (IHC) application of hormone receptor-specific antibodies is used to determine ER and PR positivity. Tumours expressing more than 1% of cancer cell staining for ER or PR are labeled as positive for the respective hormone receptor as per the College of American Physician (CAP) guidelines [29]. Various scores such as Allred and H score have been established to quantify hormone receptor positivity. As per the 2020 guidelines, tumours with 1–10% of cells staining for ER or PR should be labeled as ‘low positives’ [29].

Any tumour expressing both or either ER and PR positivity by IHC is classified as hormone receptor positive and has been shown to benefit from endocrine therapy and have a favourable prognosis. Within the subgroup of ER positive patients, PR has an independent prognostic value [30]. These tumours constitute the majority of BC (60–70%) especially in the elderly subgroup of patients. Despite their favourable prognosis, they are known to have delayed recurrences after 5 years of disease

free intervals especially in high risk disease [31]. The sites of distant spread in hormone receptor disease are commonly bone, soft tissue and reproductive tract [31].

5.12.2 Human Epidermal Growth Factor 2 (Her2)

Her2 belongs to a group of growth factor receptors and has been shown to be overexpressed in 15–20% of BC [32]. It has both prognostic and predictive potential as there are a multitude of anti Her2 directed therapies such as trastuzumab, pertuzumab, ado-trastuzumab emtansine, lapatinib, neratinib, tucatinib etc. which has shown to give a significant survival benefit in Her2 positive patients [33]. The determination of Her2 status is done by IHC and Fluorescent In Situ Hybridisation techniques [34]. As for hormone receptor testing, CAP has laid down guidelines for Her2 testing. Any tumour with a 3+ score on IHC or a 2 + score on IHC but a positive dual or single probe FISH test is determined to have Her2 positive disease [34]. This subgroup of breast cancer patients may be either hormone receptor positive or negative and may be subclassified accordingly.

5.12.3 Triple Negative Breast Cancer

Breast cancer is classified as 'Triple negative breast cancer' (TNBC) if the tumour does not express ER, PR and Her2. The diagnostic criteria used commonly is less than 1% IHC staining for both ER and PR and are also negative for Her2 by IHC (0 or 1+) or 2+ on IHC but negative on FISH [29, 34]. TNBC constitutes about 13–17% of all breast cancers [26, 35]. It is a more aggressive variant which is more common in younger women, is associated with higher grade tumours, increased response rates to chemotherapy and portends worse prognosis [36, 37]. It is also known to be associated with breast cancer susceptibility gene 1 (*BRCA1*) mutations in upto 20% cases [38].

5.12.4 Ki67

Ki67 is a nuclear protein which acts as a biomarker for the cellular proliferation [39]. Its use as a prognostic or predictive agent is still controversial in view of its potential lack of reproducibility and lack of a standard cutoff [39]. However, it is often used as a surrogate marker along with other biomarkers listed above due to the fact that it is a relatively inexpensive tools and many meta-analyses have suggested its independent prognostic value [40].

IHC4 is a prognostic tool which combines all the ER, PR, Her2neu and Ki 67. It gives a single prognostic score based on semiquantitative IHC assessment of all 4 biomarkers [41].

5.13 Molecular/Genetic Classification

5.13.1 Molecular/Intrinsic Subtype Based Classification

Perou and colleagues published the seminal article that led to the identification of intrinsic subtypes in 2000 [42]. They undertook complementary DNA microarray gene expression analysis followed by hierarchical clustering of differentially expressed genes and identified the 5 main subtypes. Since, then various studies have explored the clinic-pathological correlation of the main intrinsic subtypes and their impact on determining treatment and outcomes [2, 43].

Luminal Subtypes The luminal subtypes are subdivided into luminal A and luminal B. They typically express cytokeratins 8 and 18 and are the most common subtypes of breast cancer. The name "luminal" is originated from their resemblance to the genetic make up of the luminal epithelium of the breast. Most of the hormone receptor positive cancers feature in this subtype and the main difference between A and B is that B are more likely to have a high Ki67 > 14%, have a higher grade, be PR negative or Her2 positive and have a higher expression of proliferation genes [44].

HER2-Enriched This subtype is depicted by high expression of HER2 and proliferation gene clusters and low expression of the luminal and basal gene clusters [45]. These tumors are often negative for ER and progesterone (PR). Not all tumours which are positive for Her2 on IHC/FISH fall in this subgroup or vice versa, as some Her2 positive tumours may fall in the luminal subtype also [45].

Basal Subtypes Most of these tumors fall under the category of TNBC because they are ER, PR, and HER2 negative. The basal-like BC are typically high grade cancers that are characterized by upregulation of genes expressed by basal/myoepithelial cells, including high-molecular-weight cytokeratins (CK5 and 14), P-cadherin and epidermal growth factor receptor [46]. The clinico-pathological correlation of the intrinsic subtypes is summarized in the Table 5.2.

TNBC have been widely studied and subclassified into a variety of subtypes initially by Lehmann et al. in 2011 [47] and subsequently revised [48]. This in depth

Table 5.2 Intrinsic subtypes of BC with their clinico-pathological correlation

	Luminal A	Luminal B	Her2enriched	Basal like
ER/PR expression	Strongly positive	Variable positivity	Positive or negative	Negative
Her2 amplification	Commonly absent	Present in a small subgroup	Common	Absent
Grade	1,2	2,3	2,3	3
Ki67	Low	Intermediate-high	High	High

Table 5.3 Classification of TNBC and its therepeutic implications

TNBC Subtype (Lehman et al)	Therepeutic implication as per subtypes
Basal Like1	Platinums and PARP inhibitors
Basal Like 2	mTOR,growth factor inhibitors
Mesenchymal	mTOR,growth factor inhibitors
Mesenchymal stem like	mTOR,PI3K,MEK inhibitors
Luminal androgen receptor	Androgen antagonists eg enzulatamide,PI3K inhibitors
Immune modulatory	Platinum,PARP inhibitors

analysis on the basic of genetic expression which may have therapeutic implications as well as shown in Table 5.3 [49].

Newer subtypes such as claudin-low and molecular apocrine have also been described [50]. A big fraction of claudin low tumoursare TNBC, metaplastic and medullary breast carcinomas. Although claudin-low and basal-like subtypes share low luminal and HER2 gene expression, claudin-low tumors do not have a high expression of proliferation genes.

5.13.2 Gene Expression Profiles-Prognostic Panels

A large number of multigene expression panels based on various techniques like RTPCR, microarray etc. are now available which can be used for detailed genetic profiling of the tumours. These tests such as all provide a prognostic score which has also shown to have predictive value in certain well selected cases with clinically low risk disease.

They help in classifying breast cancers into low, intermediate or high risk (depending on the test used) and thus predicting the need of chemotherapy (Table 5.4).

Table 5.4 Gene Expression based Prognostic Panels

Type of test	Technique	Indication	Results
Oncotype Dx [51, 52]	21 gene RT PCR	ER+/HER2- Early breast cancer (EBC) LN(lymph node)-or LN+ (1–3+)	High, intermediate or low risk
Mammaprint [53]	70 gene DNA microarray	ER+/HER2- EBC LN-or LN+ (1–3+)	High or low risk+ subtype
Endopredict [54]	11 gene RTPCR	ER+/HER2- EBC LN-or LN+ (1–3+)	High or low risk
PAM50 [55] Prosigna	50 gene nanostring	ER+/HER2- EBC LN-or LN+ (1–3+)	High, intermediate, or low risk + subtype

Table 5.5 Other prognostic classification models

Tools	Information needed	Output
Nottingham Prognostic Index [57]	Size, grade, nodal involvement	Score which is subgrouped into 3 prognostic groups
CTS5 [58]	Node, size, grade, age	Late distant metastasis in women with ER-positive breast cancer who are recurrence-free 5 years after endocrine therapy
Cancer Math [59]	Age, size, histological type, grade, ndoal status, ER,PR,Her2neu status	15 year cancer death rate
Predict [60]	Age, size, presentation, nodal status, grade, ki 67, ER, Her2	5,10,15 year survival, role of chemotherapy, hormone therapy

5.13.2.1 Integrative Clusters

This divides breast cancer into 10 integrative cluster subgroups (lntclusters) based on the integration of genomic and transcriptomic data such as copy-number aberrations [56].

5.13.2.2 Other Classifications

Various models based on clinicopathological features have been proposed which help as prognostic and predictive tools summarized in the Table 5.5.

5.14 Conclusion

The main aim of all the classification systems mentioned in this chapter is to improve the ability to diagnose, treat and prognosticate various cases of BC depending on their anatomical, pathological and molecular subtype. Recent studies based on genomic and transcriptomic data has led to the detailed profiling of tumours, identification of various driver mutations and re-classification of BC. This is an ever-evolving dynamic field and further sub classification seems the way ahead as we tread into the era of precision and personalized medicine.

References

1. Halsted WS. I. The results of radical operations for the cure of carcinoma of the breast. Ann Surg. 1907;46(1):1.
2. Prat A, Pineda E, Adamo B, Galván P, Fernández A, Gaba L, Díez M, Viladot M, Arance A, Muñoz M. Clinical implications of the intrinsic molecular subtypes of breast cancer. Breast. 2015 Nov 1;24:S26–35.
3. Steinthal CF. Zur dauerheilung des brustkrebses. Beitr Klin Chir. 1905;47:226–39.
4. Haagensen CD, Cooley E, Kennedy CS, Miller E, Handley RS, Thackray AC, Butcher HR Jr, Dahl-Iversen E, Tobiassen T, Williams IG, Curwen MP. Treatment of early mammary carcinoma: a cooperative international study. Ann Surg. 1963 Feb;157(2):157.

5. Denoix PF. Nomenclature and classification of cancers based on an atlas. Acta-Unio Internationalis Contra Cancrum. 1953;9(4):769–71.
6. Sobin LH, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. Hoboken, NJ: Wiley; 2011 Aug 31.
7. Beahrs OH, Henson DE, Hutter RV, Myers MH. Manual for staging of cancer. Am J Clin Oncol. 1988 Dec 1;11(6):686.
8. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017 Mar;67(2):93–9.
9. Yi M, Mittendorf EA, Cormier JN, Buchholz TA, Bilimoria K, Sahin AA, Hortobagyi GN, Gonzalez-Angulo AM, Luo S, Buzdar AU, Crow JR. Novel staging system for predicting disease-specific survival in patients with breast cancer treated with surgery as the first intervention: time to modify the current American Joint Committee on Cancer staging system. J Clin Oncol. 2011 Dec 10;29(35):4654.
10. Nachlas MM. Irrationality in the management of breast cancer. I. The staging system. Cancer. 1991 Aug 15;68(4):681–90.
11. DeVita VT, Lawrence TS. DeVita, Hellman, and Rosenberg's cancer: principles & practice of oncology, vol. 22. Philadelphia: Wolters Kluwer; 2008 Apr. p. 1897–8.
12. Asselain B, Barlow W, Bartlett J, Bergh J, Bergsten-Nordström E, Bliss J, Boccardo F, Boddington C, Bogaerts J, Bonadonna G, Bradley R. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018 Jan 1;19(1):27–39.
13. Puglisi F, Follador A, Minisini AM, Cardellino GG, Russo S, Andreetta C, Di Terlizzi S, Piga A. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. Ann Oncol. 2005;16(2):263–6.
14. Dawood S, Cristofanilli M. What progress have we made in managing inflammatory breast cancer? Oncology (Williston Park). 2007 May 1;21(6):673–9.
15. Kwapisz D. Oligometastatic breast cancer. Breast Cancer. 2019 Mar;26(2):138–46.
16. Shah NM, Scott DM, Kandagatla P, Moravek MB, Cobain EF, Burness ML, Jeruss JS. Young women with breast cancer: fertility preservation options and management of pregnancy-associated breast cancer. Ann Surg Oncol. 2019 May;26(5):1214–24.
17. Ruiz R, Herrero C, Strasser-Weippl K, Touya D, Louis JS, Bukowski A, Goss PE. Epidemiology and pathophysiology of pregnancy-associated breast cancer: a review. Breast. 2017 Oct 1;35:136–41.
18. Karakas C. Paget's disease of the breast. J Carcinog. 2011;10:31.
19. Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, Lazar AJ, Morris EA, Sahin A, Salgado R, Sapino A. The 2019 World Health Organization classification of tumours of the breast. Histopathology. 2020 Aug;77(2):181–5.
20. Burstein HJ, Polyak K, Wong JS, Lester SC, Kaelin CM. Ductal carcinoma in situ of the breast. N Engl J Med. 2004 Apr 1;350(14):1430–41.
21. Van Steenbergen LN, Voogd AC, Roukema JA, Louwman WJ, Duijm LE, Coebergh JW, van de Poll-Franse LV. Screening caused rising incidence rates of ductal carcinoma in situ of the breast. Breast Cancer Res Treat. 2009 May;115(1):181–3.
22. Silverstein MJ, Craig PH, Lagios MD, Waisman JR, Lewinsky BS, Colburn WJ, Poller DN. Developing a prognostic index for ductal carcinoma in situ of the breast: are we there yet? Cancer. 1996 Sep 1;78(5):1138–40.
23. Foote FW Jr, Stewart FW. Lobular carcinoma in situ: a rare form of mammary cancer. Am J Pathol. 1941 Jul;17(4):491.
24. Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res. 2004 Jun;6(3):1–8.
25. Bae SY, Choi MY, Cho DH, Lee JE, Nam SJ, Yang JH. Mucinous carcinoma of the breast in comparison with invasive ductal carcinoma: clinicopathologic characteristics and prognosis. J Breast Cancer. 2011 Dec;14(4):308.

26. Beatty JD, Atwood M, Tickman R, Reiner M. Metaplastic breast cancer: clinical significance. Am J Surg. 2006 May 1;191(5):657–64.
27. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 1991;19(5):403–10.
28. Mason BH, Holdaway IM, Mullins PR, Yee LH, Kay RG. Progesterone and estrogen receptors as prognostic variables in breast cancer. Cancer Res. 1983 Jun 1;43(6):2985–90.
29. Allison KH, Hammond ME, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, Hayes DF, Lakhani SR, Chavez-Mac Gregor M, Perlmutter J, Perou CM. Estrogen and progesterone receptor testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists guideline update. Arch Pathol Lab Med. 2020 May;144(5):545–63.
30. Prat A, Cheang MC, Martín M, Parker JS, Carrasco E, Caballero R, Tyldesley S, Gelmon K, Bernard PS, Nielsen TO, Perou CM. Prognostic significance of progesterone receptor–positive tumor cells within immunohistochemically defined luminal a breast cancer. J Clin Oncol. 2013 Jan 10;31(2):203.
31. Hess KR, Pusztai L, Buzdar AU, Hortobagyi GN. Estrogen receptors and distinct patterns of breast cancer relapse. Breast Cancer Res Treat. 2003 Mar;78(1):105–18.
32. Burstein HJ. The distinctive nature of HER2-positive breast cancers. N Engl J Med. 2005 Oct 20;353(16):1652.
33. Figueroa-Magalhães MC, Jelovac D, Connolly RM, Wolff AC. Treatment of HER2-positive breast cancer. Breast. 2014 Apr 1;23(2):128–36.
34. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, Dowsett M, Fitzgibbons PL, Hanna WM, Langer A, McShane LM. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med. 2007 Jan;131(1):18–43.
35. Irvin WJ Jr, Carey LA. What is triple-negative breast cancer? Eur J Cancer. 2008 Dec 1;44(18):2799–805.
36. Ismail-Khan R, Bui MM. A review of triple-negative breast cancer. Cancer Control. 2010 Jul;17(3):173–6.
37. Anders CK, Carey LA. Biology, metastatic patterns, and treatment of patients with triple-negative breast cancer. Clin Breast Cancer. 2009 Jun 1;9:S73–81.
38. Young SR, Pilarski RT, Donenberg T, Shapiro C, Hammond LS, Miller J, Brooks KA, Cohen S, Tenenholz B, DeSai D, Zandvakili I. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer. 2009 Dec;9(1):1–5.
39. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, Ellis M, Henry NL, Hugh JC, Lively T, McShane L. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst. 2011 Nov 16;103(22):1656–64.
40. Petrelli F, Viale G, Cabiddu M, Barni S. Prognostic value of different cut-off levels of Ki-67 in breast cancer: a systematic review and meta-analysis of 64, 196 patients. Breast Cancer Res Treat. 2015 Oct;153(3):477–91.
41. Dowsett M, Sestak I, Lopez-Knowles E, Sidhu K, Dunbier AK, Cowens JW, Ferree S, Storhoff J, Schaper C, Cuzick J. Comparison of PAM50 risk of recurrence score with onco type DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. J Clin Oncol. 2013 Aug 1;31(22):2783–90.
42. Perou CM, Sørlie T, Eisen MB, Van De Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge Ø. Molecular portraits of human breast tumours. Nature. 2000 Aug;406(6797):747–52.
43. Vuong D, Simpson PT, Green B, Cummings MC, Lakhani SR. Molecular classification of breast cancer. Virchows Arch. 2014 Jul;465(1):1–4.
44. Ades F, Zardavas D, Bozovic-Spasojevic I, Pugliano L, Fumagalli D, De Azambuja E, Viale G, Sotiriou C, Piccart M. Luminal B breast cancer: molecular characterization, clinical management, and future perspectives. J Clin Oncol. 2014 Sep 1;32(25):2794–803.

45. Prat A, Carey LA, Adamo B, Vidal M, Tabernero J, Cortés J, Parker JS, Perou CM, Baselga J. Molecular features and survival outcomes of the intrinsic subtypes within HER2-positive breast cancer. J Natl Cancer Inst. 2014 Aug 1;106(8):dju152.
46. Badve S, Dabbs DJ, Schnitt SJ, Baehner FL, Decker T, Eusebi V, Fox SB, Ichihara S, Jacquemier J, Lakhani SR, Palacios J. Basal-like and triple-negative breast cancers: a critical review with an emphasis on the implications for pathologists and oncologists. Mod Pathol. 2011 Feb;24(2):157–67.
47. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, Pietenpol JA. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011 Jul 1;121(7):2750–67.
48. Lehmann BD, Pietenpol JA. Identification and use of biomarkers in treatment strategies for triple-negative breast cancer subtypes. J Pathol. 2014 Jan;232(2):142–50.
49. Abramson VG, Lehmann BD, Ballinger TJ, Pietenpol JA. Subtyping of triple-negative breast cancer: implications for therapy. Cancer. 2015 Jan 1;121(1):8–16.
50. Choi J, Jung WH, Koo JS. Clinicopathologic features of molecular subtypes of triple negative breast cancer based on immunohistochemical markers. Histol Histopathol. 2012;27(11):1481–93.
51. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004 Dec 30;351(27):2817–26.
52. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, Geyer CE Jr, Dees EC, Goetz MP, Olson JA Jr, Lively T. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med. 2018 Jul 12;379(2):111–21.
53. Buyse M, Loi S, Van't Veer L, Viale G, Delorenzi M, Glas AM, Saghatchian d'Assignies M, Bergh J, Lidereau R, Ellis P, Harris A. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J Natl Cancer Inst. 2006 Sep 6;98(17):1183–92.
54. Fitzal F, Filipits M, Rudas M, Greil R, Dietze O, Samonigg H, Lax S, Herz W, Dubsky P, Bartsch R, Kronenwett R. The genomic expression test EndoPredict is a prognostic tool for identifying risk of local recurrence in postmenopausal endocrine receptor-positive, her 2neu-negative breast cancer patients randomised within the prospective ABCSG 8 trial. Br J Cancer. 2015 Apr;112(8):1405–10.
55. Wallden B, Storhoff J, Nielsen T, Dowidar N, Schaper C, Ferree S, Liu S, Leung S, Geiss G, Snider J, Vickery T. Development and verification of the PAM50-based Prosigna breast cancer gene signature assay. BMC Med Genet. 2015 Dec;8(1):1–4.
56. Curtis C, Shah SP, Chin SF, Turashvili G, Rueda OM, Dunning MJ, Speed D, Lynch AG, Samarajiwa S, Yuan Y, Gräf S. The genomic and transcriptomic architecture of 2, 000 breast tumours reveals novel subgroups. Nature. 2012 Jun;486(7403):346–52.
57. Galea MH, Blamey RW, Elston CE, Ellis IO. The Nottingham prognostic index in primary breast cancer. Breast Cancer Res Treat. 1992 Oct;22(3):207–19.
58. Dowsett M, Sestak I, Regan MM, Dodson A, Viale G, Thürlimann B, Colleoni M, Cuzick J. Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor–positive breast cancer treated with 5 years of endocrine therapy: CTS5. J Clin Oncol. 2018 Jul 1;36(19):1941.
59. Miao H, Hartman M, Verkooijen HM, Taib NA, Wong HS, Subramaniam S, Yip CH, Tan EY, Chan P, Lee SC, Bhoo-Pathy N. Validation of the CancerMath prognostic tool for breast cancer in Southeast Asia. BMC Cancer. 2016 Dec;16(1):1–2.
60. Wishart GC, Bajdik CD, Dicks E, Provenzano E, Schmidt MK, Sherman M, Greenberg DC, Green AR, Gelmon KA, Kosma VM, Olson JE. PREDICT plus: development and validation of a prognostic model for early breast cancer that includes HER2. Br J Cancer. 2012 Aug;107(5):800–7.

Approach to a Suspected Case of Breast Cancer

6

Chintamani

6.1 Introduction

Breast cancer is the second most common cancer of mankind and certainly the most common malignancy amongst women. The lifetime risk of developing breast cancer for women in USA is approximately 12% while the incidence is lower in India and the mortality is higher. In India approximately one woman dies of breast cancer every 19 minutes. This could be on account of various factors like delayed presentation and possibly more aggressive biology. Indian breast cancer is different in presentation from the western counterpart especially in terms of age wise distribution. There are two distinct peaks of breast cancer observed in India and also in the subcontinent. The author and his team observed this difference in a cross-sectional study conducted amongst the north Indian population. There were two peaks of incidence observed, one in 30s and 40s and the other one in 60s unlike in the west where incidence would rise as the age advances. Younger women were also found to have strong family history and genetic features like *CYP-17 gene polymorphism and BRCA-1& II mutations* and were also associated with a higher incidence of triple negative breast cancer which is a more aggressive form that is usually advanced at presentation [1–7].

Breast cancers are commonly adenocarcinomas and the two most common types include invasive ductal carcinoma and invasive lobular carcinoma. Both have non-invasive pre-cursors i.e. ductal carcinoma in situ and lobular carcinoma in situ (*not considered a cancer now according to the AJCC-8th edition*). Patients detected at screening may be early with minimal or no clinical signs or symptoms of disease.

Chintamani, MS, FRCS, FACS, FICS (✉)
Professor and former Head, Department of Surgery, VMMC, Safdarjang Hospital, New Delhi, India

President, Asian Society of Mastology, Kolkata, West Bengal, India
e-mail: drchintamani7@gmail.com

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_6

Screening mammography has been responsible for reduction in mortality on account of early detection in the west (“*while in the west they are treating images, most developing countries and India are still treating lumps”*). For this reason and for many other reasons including younger age at presentation, clinical breast examination has been recommended for screening in countries like India. In fact, screening mammography has not been recommended in the developing world as the average lump size is still large and emphasis is being made on increasing awareness as the only way to bring down the T-size [8–11].

The bottom line and the “*gold standard”* approach in the assessment of patients with any suspected breast lesion is “*Triple assessment or Triple test*”. The concept is borne out of the fact that no single modality i.e. clinical examination, imaging and/or histopathology is sensitive enough to provide a reliable diagnosis. The aim is therefore to pick up the median best of these three tests and triple test has shown a positive predictive value of close to 99.9% [12–17].

6.2 Essential Points to Consider

1. Who is a suspected case of breast cancer?
2. Approaching the suspected case—“triple assessment”
3. How accurate is the triple assessment or triple test?
4. How much work up is optimum in a suspected case?

6.3 Who Is a Suspected Case?

6.3.1 Based on History

- Women with increased *oestrogen* exposure like women with higher number of total menstrual cycles [*early menarche, late menopause, and nulliparity*]
- Exogenous *oestrogen* intake: *hormone replacement therapy* after *menopause*
- First full-term *pregnancy* after the age of 35 years
- History of *Breast* cancer in the contralateral *breast*.
- History of ovarian, *endometrial*, or *colorectal cancer*
- BRCA1 or BRCA2 *gene mutations* [*autosomal-dominant inherited gene mutation that is associated with an increased risk for breast cancer (70%) and ovarian cancer. BRCA-positive women develop breast cancer approximately 15–20 years earlier than women without the mutation. It is also important to note that BRCA mutations are found in only 5–10% of all women with breast cancer.*]
- Positive family history (*e.g. first-degree relative affected at a young age*)
- History of Benign breast conditions like (*e.g., fibrocystic change, fibroadenoma), present for a long time and with cellular atypia etc*.)
- Radiational exposure in childhood especially low dose radiations which would rarely be for any malignant disease. Therefore, this is mostly a risk if one lives close to some nuclear plant or has been exposed to disasters like Chernobyl accident or has received Mantle radiations or for some benign condition like adenoids etc.
- Risk factors related to life style like high fat and low fibre diet, alcohol, smoking, obesity especially in *postmenopausal* women (*which is also a high oestrogen state*).

6.3.2 Based on Physical Examination

- There are some glaring features of breast cancer that are detected on routine examination of breast. In the era of screening, which is essentially for asymptomatic women, cancer may be detected long before these features appear.
- Lump breast (not all lumps are cancerous and in fact majority are not)
- If no lump is noticed by the woman, indirect signs and symptoms indicating the possible presence of breast cancer may include the following:
  1. Changes in breast size or shape
  2. Dimpling or skin changes (e.g., thickening, swelling, or redness)
  3. Recent inversion of nipple or skin change or other nipple abnormalities (e.g., ulceration, retraction, or spontaneous bloody discharge)
  4. Axillary nodes

6.3.3 Based on Risk Assessment and Hereditary Reasons [18–20]

The guidelines for risk assessment and genetic counselling [*by United States Services Task Force (USPSTF)*] keep getting updated but by and large the recommendations are [20]:

1. Women that have family members with breast, ovarian, tubal, peritoneal cancer, should be screened to identify groups with increased risk for BRCA1 or BRCA2 gene mutations.
2. Those without such family history of increased risk for mutations should not receive routine genetic counselling or BRCA testing

6.4 Hereditary Basis of Breast Cancer [18–20]

- According to most reports only 7–10% of all the breast cancers are caused by mutation in specific genes. Therefore a good family history is mandatory.
- If multiple tumours are found in the same patient hereditary cancer may be suspected. The search is on as more and more abnormal genes and hereditary cancers are being detected.
- Syndromes like Li-Fraumeni syndrome(LFS) which is also called as Sarcoma, Breast, Leukemia, Adrenal Gland cancer syndrome (SBLA) is a familial genetic syndrome that can cause multiple cancers and is transmitted by autosomal dominant inheritance [*LFS was initially described in 1969 by Frederick Li and Joseph Fraumeni in four families.*]. There is an association of other germ line mutations along with LFS like TP53 tumor suppressor gene
- There are other syndromic scenarios like HBOC (*hereditary breast and ovarian cancer*) syndrome and these patients may have mutation in one or both BRCA1 and BRCA2 genes that principally are DNA repair genes and can be associated with breast or ovarian cancer.

- Those with mutation in either BRCA1 or BRCA2, cumulative risk of developing breast cancer is approximately 70% by the age of 80 years. If there is mutation in BRCA1, risk of developing ovarian cancer is 44% while if the mutation is in BRCA2 it may be around 17%. Those with HBOC are also prone to developing prostate and pancreatic cancers.

6.5 What Is Triple Assessment?

Triple test or assessment is the gold standard approach to any breast disorder and includes three major components:

- Thorough and detailed **history and clinical examination** (remains the cornerstone)
- **Imaging** including mammography, ultrasound and/or magnetic resonance imaging (MRI) of the breast (*MRI is conventionally not a part of triple test*).
- **Pathological tests** range from *Fine needle aspiration cytology (FNAC) to Core needle biopsy (CNB) and open biopsies (which serve as the gold standard).*
- It is vital to understand that the gold standard is not the best available test but the one against which other tests are to be compared. Open biopsy is very rarely needed and would amount to performing two surgeries especially if the first one is performed sub-optimally.
- Therefore, CNB is the most preferred pathological approach and is superior to FNAC for multiple reasons. It is more reliable in terms of lower false negative rates and possibility of providing the tissue diagnosis including invasiveness, grade and status of bio-markers (ER, PR, HER-2neu). These markers are mandatory in planning the optimum management both in neo-adjuvant and adjuvant settings.
- It is important that the three components of triple test must follow the sequence from non-invasive to invasive tests. Invasive test performed before imaging may alter and confuse the findings due to artefacts like hematomas etc.

6.6 Individual Components of Triple Assessment

6.6.1 History Taking and Clinical Examination

Thorough history and clinical examination form the basis of any good approach to rule out malignancy in a suspected case. Most complaints in these women are non-specific but there can be some very specific features that should arouse suspicion. These are:

- Appearance of a lump or changes in a pre-existing lump like rapid increase or change in consistency from firm to hard etc.

- Nipple discharge (clear, bloody, cyclical etc.). **S**pontaneous, **S**erous, **S**ingle duct and **S**ingle side discharge quite suspicious and should be investigated thoroughly to exclude malignancy.
- Changes in the texture of the breast or appearance of nodularity (cyclical versus non-cyclical)
- Pain in the breast is usually not a presenting feature of malignancy, but may be a significant finding if it appears in an otherwise painless lump
- Changes in the skin like erythema, induration, sinuses or fistulae can be a relatively late feature.
- Appearance of nodes in the axilla (ipsilateral or contralateral).
- Any non-specific pain in the bones especially spine along with a lump in the breast might indicate metastases to the bone and should raise suspicion.

History taking in a suspected cases, the art and science of it

- The importance of a good history including detailed family history cannot be over emphasized but this is most often the weakest link in the story. The patient should be put at complete ease and allowed to narrate the history in a relaxed environment.
- Large number of early breast carcinomas are asymptomatic especially when detected during screening. As is often said for the lesions in developing countries like India "*while they are treating images, we are treating lumps*"
- Most lumps or larger tumours are painless (95%). Rarely therefore pain may be associated.
- The onset and progression of the disease must be carefully recorded as it may often clinch the diagnosis. Most develop clinical symptoms rather late in the disease and majority patients especially in the developing world present as locally advanced (30–50%). Various features may include ***asymmetric breasts, firm, hard and poorly defined mass usually in the upper outer quadrant***.
- There may be skin changes: Retractions or dimpling or *Peau d'orange* (skin resembling an orange peel (due to obstruction of lymphatic channels).
- Redness, edema and pitting of hair follicles.
- Nipple changes like inversion, discharge (blood tinged, spontaneous, single duct or multiple ducts etc.).
- Axillary lymphadenopathy, firm enlarged lymph nodes (>1 cm in diameter) may be fixed or mobile.
- History pertaining to radiational exposure, risk factors related to breast cancer must be elicited as these increase the risk of developing a more aggressive form of breast cancer.
- A detailed menstrual and obstetric history is mandatory and facilitates the diagnosis. This should include history of miscarriages and abortions (responsible for un-opposed action of estrogens and thus an increased risk)
- The use of oral contraceptive pills (OCPs) or hormone replacement therapy (HRT). There is no consensus at present regarding the risk caused by OCPs as the dose of estrogen is lower in the present day OCPs and also the fact that age when these are taken, the risk of breast cancer is minimal. HRTs however are a definite risk since they are taken around the menopause with an increased risk of breast cancer.
- The clinician should be alert to symptoms of metastatic spread like bone pains, breathlessness, or jaundice, symptoms of hypercalcemia, localizing neurologic signs, altered cognitive functions, headache etc. in order to rule out any distant metastases (to *lungs, liver, bones and brain*)
- Any history of a lump in the breast should not alarm the patient and one must be conveyed that not all breast lumps are malignant and in fact most are not. History of any lump excision or some invasive procedure must be carefully recorded. Lumps that need to be excised repeatedly may point towards a suspicious lesion and the histopathology of excised lumps in the past must be obtained.

6.6.2 Clinical Breast Examination (CBE) (Figs. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, and 6.8)

- This refers to the traditional technique of physical examination of the breast by a health care provider. CBE has also been a recommended screening modality for developing countries but has not been very well studied when compared with other modalities for breast cancer screening.
- There is however considerable indirect evidence from various studies that CBE can be recommended as a method for screening and detecting breast cancer for public health benefit.
- The examination comprises both systematic inspection and palpation of the nipple, breast, and lymph-draining regions in the axillae and supraclavicular and infraclavicular fossae.
- All cases must be examined in at least **three standard positions:** ***sitting*** *(ideal for inspection)****,*** ***supine*** *(ideal for palpation and lymph node assessment) and* ***reclining*** *(has advantages of both sitting and supine positions)*. Sitting position is ideal for inspection and assessment of the levels of nipple areola complex,

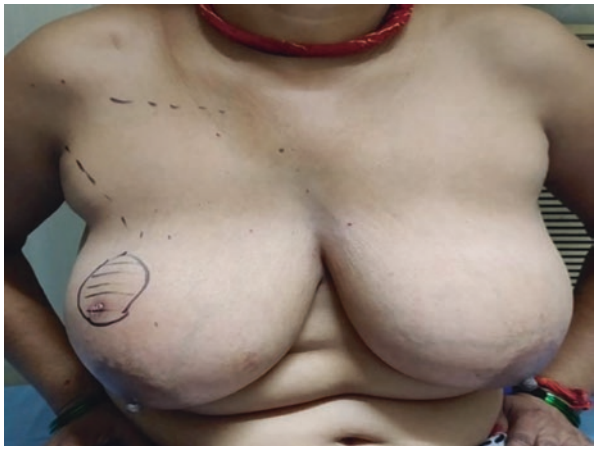


Fig. 6.1 The breasts are best inspected in sitting position with arms by the side, on the waist, lifted above the head. Breasts are examined for the levels of nipple areola complex, any dilated veins, ulcers, sinuses, swellings etc.

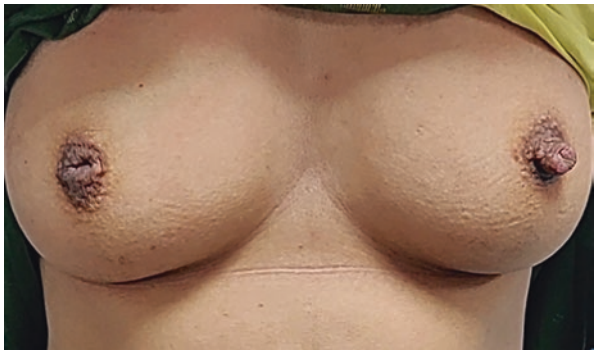


Fig. 6.2 With arms raised above the head, the traction on ligaments of Cooper can make the features like dimpling, retraction of nipple more exaggerated

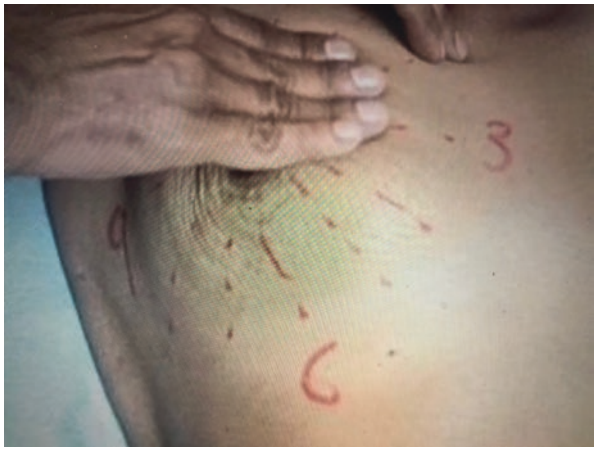


Fig. 6.3 "Dial a clock" method is an easy and reproducible way of palpating the breast. The examination may start or end with examination of lactiferous ducts. The usual method is to go outwards following the clockwise coverage of the entire breast

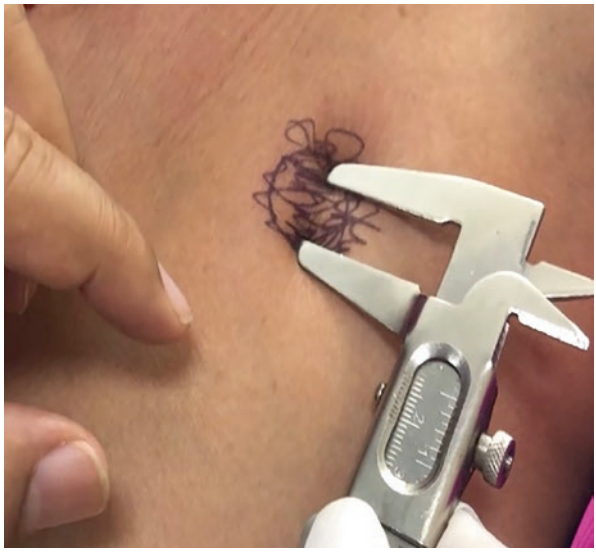


Fig. 6.4 The measurements (T-size) of the lump must always be done using a Vernier caliper for accuracy

change in size of breasts etc. Palpation is best done in supine position as the breast fall apart laterally and the lump can be easily palpated against the chest wall.

- The findings that should raise suspicion include hardness, irregularity, focal nodularity or asymmetry of breast. Fixation of the lump to chest wall or underlying muscles, ulceration, edema or *peau d'orange*, satellite nodules and/or skin are usually features of an advanced disease.
- A complete examination includes assessment of the axillae, supraclavicular fossae, examination of the chest, sites of skeletal pain, abdominal and neurologic examinations.

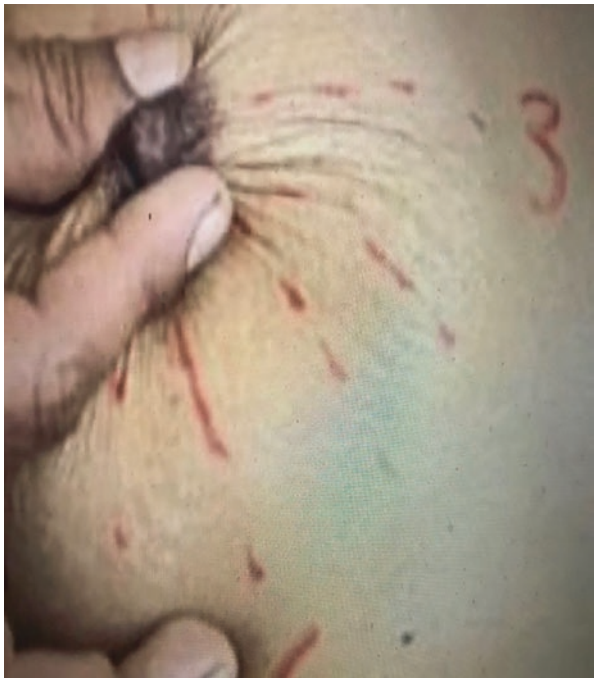


Fig. 6.5 Palpating for the lactiferous ducts is usually done by rolling in between the finger and the thumb in both axis

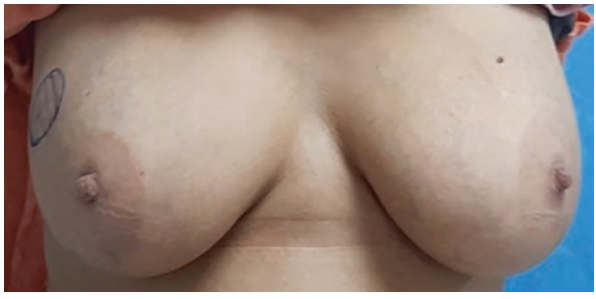


Fig. 6.6 With the arms raised above the head the affected breast can be seen moving upwards

- Whereas recommendations for mammography and breast self-examination (BSE) can be based on the findings of randomized screening trials, there have been no randomized trials of CBE alone on which to base recommendations.
- The examination by itself is inexpensive, as no special equipment is required. It is easy to perform, it can be readily taught to health care providers, and it can be offered ubiquitously.
- CBE should be part of any program for early detection of breast cancer worldwide, provided that follow-up medical and oncology care is available.
- Physicians and women should be informed about the advantages and disadvantages of this modality, especially as there are no data from randomized trials about the contribution of CBE in detecting breast cancer at an early stage and the

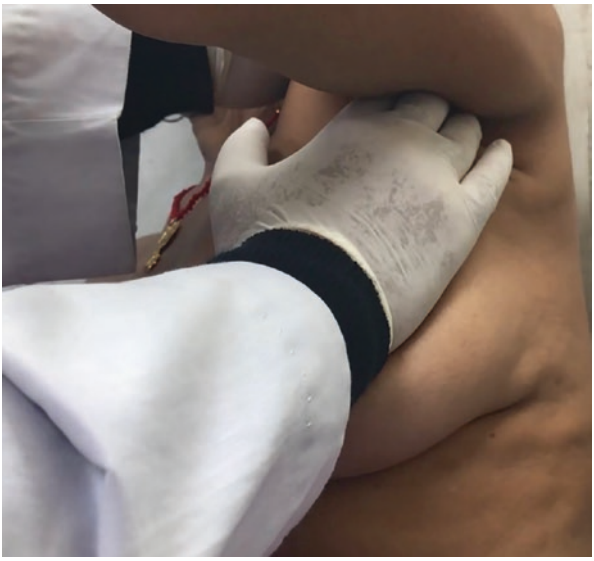


Fig. 6.7 While examining the left axilla, it is useful to put left hand on the left shoulder to stabilize the patient and also with the left hand/forearm of the patient on the left forearm of the examining clinician relaxes the axillary fascia. This allows the right hand of the clinician free to be used effectively to examine all groups of lymph nodes

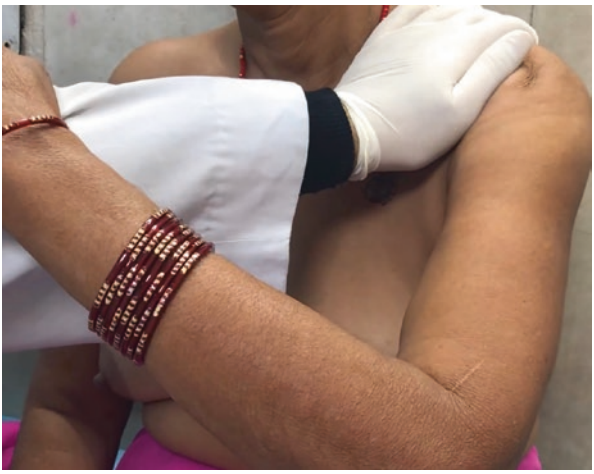


Fig. 6.8 While examining the left axilla, it is useful to put left hand on the left shoulder to stabilize the patient and also with the left hand/forearm of the patient on the left forearm of the examining clinician relaxes the axillary fascia. This allows the right hand of the clinician free to be used effectively to examine all groups of lymph nodes

absolute benefit of this modality in reducing breast cancer mortality and improving quality of life.

- Further research on CBE should be promoted, especially in countries with limited resources, to evaluate its efficacy and effectiveness in relation to age, ethnicity, and race.
- There are studies to suggest that while CBE can detect most breast cancers found on mammogram it can also pick those that are missed by mammogram. The reported sensitivity of CBE is 54% and the specificity of around 94%. The true impact of CBE on breast cancer related mortality is not very well known as there are no trials comparing CBE alone to no screening . Considering the cost and

also the pattern of breast cancer in countries like India (*younger age at presentation etc.*) CBE is being recommended for screening programs rather than screening mammography [9, 12–14].

Summary of clinical breast examination!!! [21, 22]

- General Examination like in any routine case
- Examine for "T", "N" & "M" [tumor, node and metastases]
- Examination of breast(T-size) (all positions [sitting, supine, reclining]). Using caliper to measure the tumor size is a more accurate method to measure. (Figs. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, and 6.8)
- Arms by the side, arms up etc.
- Palpation of breast can be done using "*dial a clock"* method which is reproducible and very easy to learn and teach [22].
- Node(N) examination: examining the axillae and supraclavicular fossae on both sides
- Examination of metastases: Examining abdomen for hepatomegaly, free fluid, spine for any tenderness etc.

Suspicious features in a Breast lump

Non suspicious	Suspicious
• Age < 35 • No family history • Soft movable mass • Size changes with menstrual cycles	• Age > 35 years • Positive family history • Firm, rigid mass with irregular borders • Skin changes • Axillary lymphadenopathy • Asymmetry when compared with the contralateral breast • Fixity (to skin or chest wall)

6.6.3 Imaging

Imaging as a part of triple assessment mostly refers to mammography and ultrasound. Magnetic resonance imaging (MRI) is conventionally not a part of this assessment and is used in special scenarios like when the results of mammography and ultrasound are equivocal. MRI also has a role in high risk and hereditary cancers both for screening and for diagnosis. In order to perform mammography, compression views of the breast are taken across two views, cranio-caudal (CC) and medio-lateral oblique (MLO) making detection of mass lesions or micro-calcifications possible. Generally speaking, the imaging modality of choice is mammography for women aged older than 35 years and ultrasound is more suitable for younger women with denser breasts. Mammography in younger patients with denser breasts and less fat is not very sensitive as the lesion(usually white) will not show up clearly as it would amount to *white against white background.* Breasts in older women have more fat that would provide a much darker background for the white lesions to show up more clearly. 3D Mammography or tomosynthesis is an advanced form of mammography that is more sensitive.

6.7 Mammography

6.7.1 Types and Views!!!

Screening Mammography and diagnostic mammography differ in the views. For a diagnostic mammogram both CC and MLO are the standard views. Some rare views of mammography like Eklund view (that work by displacement) are deployed in women with implants etc.

Breast imaging radiation and data system (BIRADS) is a grading system used to standardize the reporting of mammography. Chapter 9 covers this in detail.

6.7.2 Ultrasound

Ultrasonography (USG): Ultrasound is more sensitive in women that are younger (<35 years) or those with denser breasts or where radiation exposure is to be avoided (pregnancy). According to the AJCC 8th edition, ultrasound is also necessary for assessment and staging of axilla. It is also recommended that most core biopsies should be image (USG) guided for improving the sensitivity and specificity.

6.7.2.1 Important Features of Ultrasound

- Picks up solid versus cystic lesions.
- Is an extension of clinical examination and compliments the mammography, in the assessment of primary and also axillae.
- Is mandatory for axillary lymph node staging [*AJCC 8th edition*]
- There are no radiations so is safe in pregnancy.
- The limitation is however that this modality is operator dependent.

6.8 Magnetic Resonance Imaging (MRI)

- Not used in the mainstay of triple assessment however can be useful in the assessment of lobular breast cancers (and in assessing response to neoadjuvant therapy); whilst it has high sensitivity, it has a low specificity.
- Problem solving tool [*sensitive but is not specific*]
- Is useful in equivocal scenario and also for screening for high risk women.
- Is also indicated in multifocal and multi-centric tumors, also assesses the extent of ductal carcinoma *in situ* (DCIS).
- Scar recurrence or chest wall recurrence.
- Assessment of breasts in the presence of Implants.
- Since the modality is very sensitive but not specific, can reduce the rates of breast conservation by picking up artefacts.

Algorithmic approach in imaging

Clinical scenario	First step
• Women <30 years with a self-palpated lump • Women >30 years with self-palpated breast lump or mammographically detected abnormalities during screening including opportunistic screening	Clinical assessment and Ultrasound/mammography in women with a high probability of malignancy. In women with low probability of malignancy - if there are no obvious signs of malignancy, re-examine within 3–10 days after onset of their menstrual period

6.9 Pathological Assessment

6.9.1 Modalities that Are Employed for this Assessment

1. **Fine needle aspiration cytology (FNAC)**
   - Only cytology hence cannot differentiate between invasive and *in situ* cancers
   - High false negative rates, likely to miss many cancers
   - The procedure and the final assessment is operator dependent
   - Does not provide Tumor details like biology, grade, estrogen receptor (ER), progesterone receptor (PR), HER-2Neu and Ki67 (proliferation marker) status. These details are mandatory in planning the therapy
2. **Core needle biopsy**
   - Must always be performed under image(ultrasound) guidance
   - The ideal needle for performing the procedure optimally is 16 G and preferably six passes in order to improve accuracy further. In order to assess the accuracy of the core biopsy attempt, the tissue removed should not float and the one that sinks is probably right (*what sinks is right in this scenario)*
3. **Excisional biopsy** is considered the gold standard but is rarely done as this may lead to two operations in the event of the first being a sub-optimal job.

6.10 How Accurate Is the Triple Test?

In most studies the sensitivity or true positive rate of triple test is reported to be around 99.6%. In simple terms this would mean that this test would detect cancer in 99.6% of positive cases. The specificity of this test has been found to be around 62%, simply meaning that women who do not have cancer will get normal result in 62% of all cases. In many studies the positive predictive value and also the negative predictive value of triple test has been found to be nearly 100% [12–16].

6.11 Scoring the Triple Test (Creating an Overall Risk Index) [21]

The triple test can be assessed and graded at each stage for its accuracy in detecting breast cancer. The test however needs to be tailored to a case and would vary from case to case. Overall risk index can be calculated as shown in the table. The cases with high suspicion must be discussed in an multidisciplinary team meeting (MDT).

Scoring the Triple test [21]

Examination score	Imaging score (Mammography (M), Ultrasound (U))	Histology Score
P1-Normal	M1/U1-Normal	B1-Normal
P2-Benign	M2/U2-Benign	B2-Benign
P3-Uncertain/likely benign	M3/U3-Uncertain/likely benign	B3-Uncertain/probably benign
P4-Suspicious of malignancy	M4/U4-Suspicious of malignancy	B4-Suspicious of malignancy
P5-Malignant	M5/U5-Malignant	B5-Malignant

6.12 Summary and Conclusions

- Approach to a suspected case of breast cancer must be tailored to the woman, center and the region; Must find "*local solutions to local problems*".
- Mammographic breast screening has impacted the outcomes in the west by reducing mortality by nearly 20% (*Swedish Two County Trial*). This certainly has to do with early detection and management. But these studies are not replicable in developing countries due to different biology of disease and the cost involved. Thus, the approach needs to be individualized and tailored.
- Clinical breast examination rather than mammography has been recommended for screening in developing countries like India although more trials are needed.
- The gold standard approach to any breast related disorder is triple assessment. Classically the approach progresses from non-invasive modalities to invasive modalities in order not to distort the images.
- Mammography for older women (>35 years) and those with less dense breasts (*more fat in the breast*) is the imaging of modality of choice. Ultrasound can be used for younger patients with denser breasts (*less fat in the breast*). Magnetic resonance imaging (MRI) is conventionally not a part of triple assessment but may have a very significant role in selected scenarios (*high risk cases*) and in cases with equivocal results.
- As per the new AJCC-8th edition guidelines, axilla must be assessed using both clinical examination and ultrasound.

- Core needle biopsy (CNB) rather than FNAC is the standard of care and must be utilized for pathological assessment of any lesion. Open biopsy is rarely performed and may be reserved for equivocal CNB results.
- Routine assessment for hereditary cancers or genetic counselling is not a part of triple test but may be indicated in selected cases based on a high-risk family history.

References

1. Chintamani. Paradigm shifts in the management of breast cancer have we arrived? Indian J Surg. 2013 Dec;75(6):419–23.
2. Chintamani. Is Indian cancer unique? Indian J Surg. 2015 Aug;77(4):255–7.
3. Saxena S, Rekhi B, Bansal A, Bagga A, Chintamani MNS. Clinico-morphological patterns of breast cancer including family history in a New Delhi hospital, India--a cross-sectional study. World J Surg Oncol. 2005 Oct 13;3:67.
4. Chakraborty A, Murthy NS, Chintamani, Bhatnagar D, Mohil RS, Sharma PC, Saxena S. CYP17 gene polymorphism and its association with high-risk north Indian breast cancer patients. J Hum Genet. 2007;52(2):159–65.
5. Saxena S, Chakraborty A, Kaushal M, Kotwal S, Bhatanager D, Mohil RS, Chintamani C, Aggarwal AK, Sharma VK, Sharma PC, Lenoir G, Goldgar DE, Szabo CI. Contribution of germline BRCA1 and BRCA2 sequence alterations to breast cancer in northern India. BMC Med Genet. 2006 Oct 4;7:75.
6. Pandrangi SL, Raju Bagadi SA, Sinha NK, Kumar M, Dada R, Lakhanpal M, Soni A, Malvia S, Simon S, Chintamani C, Mohil RS, Bhatnagar D, Saxena S. Establishment and characterization of two primary breast cancer cell lines from young Indian breast cancer patients: mutation analysis. Cancer Cell Int. 2014 Feb 5;14(1):14.
7. Somashekhar SP, Agarwal G, Deo SVS, Chintamani, Raghu Ram P, Sarkar D, Parmar V. Indian solutions for Indian problems-Association of Breast Surgeons of India (ABSI) practical consensus statement, recommendations, and guidelines for the treatment of breast cancer in India. Indian J Surg. 2017 Aug;79(4):275–85.
8. Cancer Research UK. Cancer statistics for the UK (2017). Accessed November 2019 https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk#heading-One.
9. Jatoi I. Screening clinical breast examination. Surg Clin North Am. 2003 Aug;83(4):789–801.
10. Bancej C, Decker K, Chiarelli A, Harrison M, Turner D. Brisson contribution of clinical breast examination to mammography screening in the early detection of breast cancer. J Med Screen. 2003;10(1):16–21.
11. Kardinah D, Anderson BO, Duggan C, Ali IA, Thomas DB. Short report: limited effectiveness of screening mammography in addition to clinical breast examination by trained nurse midwives in rural Jakarta, Indonesia. Int J Cancer. 2014 Mar 1;134(5):1250–5.
12. Nigham M, Nigham B. Triple assessment of breast – gold standard in mass screening for breast cancer diagnosis. IOSR-JDMS. 2013;7:1–7.
13. Barton MB, Harris R. The rational clinical examination. Does this patient have breast cancer. The screening clinical examination: should it be done? How? JAMA. 1999;282:1270–80.
14. Kharkwal S, Sameer AM. Triple test in carcinoma breast. J Clin Diag Res. 2014 Oct;8(10):NC09.
15. Vetto J, Pommier R, Schmidt W, Wachtel M, DuBois P, Jones M, Thurmond A. Use of the "triple test" for palpable breast lesions yields high diagnostic accuracy and cost savings. Am J Surg. 1995 May 1;169(5):519–22.
16. Wai CJ, Al-Mubarak G, Homer MJ, Goldkamp A, Samenfeld-Specht M, Lee Y, et al. A modified triple test for palpable breast masses: the value of ultrasound and core needle biopsy. Ann Surg Oncol. 2013;20:850–5.

17. Khoda L, Kapa B, Singh KG, Gojendra T, Singh LR, Sharma KL. Evaluation of modified triple test (clinical breast examination, ultrasonography, and fine-needle aspiration cytology) in the diagnosis of palpable breast lumps. J Med Soc. 2015;29:26–30.
18. Malkin D, Li FP, Strong LC, et al. Germ line p-53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science (New York, NY). 1990;250:1233–8.
19. Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med. 1969;71:747–52.
20. U.S. Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer: clinical summary of the USPSTF recommendation. Am Fam Physician. 2020;101(4):233–8. As published by the USPSTF
21. https://teachmesurgery.com/breast/presentations/triple-assessment/. Accessed on 01 Jun 2020.
22. Sultania M, Kataria K, Srivastava A, Misra MC, Parshad R, Dhar A, Hari S, Thulkar S. Validation of different techniques in physical examination of breast. Indian J Surg. June 2017;79(3):219–25.

Cytopathology of Breast Cancer

7

Manish Rohilla and Radhika Srinivasan

7.1 Introduction

The presence of a 'lump' in the breast is a very common clinical symptom. These mass forming lesions may have a varied etiology from inflammatory lesions to non-neoplastic to neoplasms, which may be benign or malignant. Obtaining a cellular or tissue diagnosis is critical to their management. Fine needle aspiration cytology or FNAC is a time-tested, simple, rapid, and accurate modality that provides a diagnosis in minutes to a few hours. It is an indispensable tool in the clinical practice of a breast surgeon.

Breast cancer continues to top the list of cancers affecting our women with an increasing incidence. The majority of our patients present in an advanced stage with a large palpable mass in the breast unlike smaller sono-mammography screen-detected breast cancers in the West. A quick and accurate diagnosis of breast cancer can be rendered easily by performing fine-needle aspiration from palpable breast mass lesions. On the basis of the FNA report, patients may be managed by surgery, or FNA may be followed by a core biopsy for molecular testing. On the other hand, cell blocks from FNA provide microbiopsies ideally suited for molecular studies, including immunocytochemistry and FISH studies, as currently mandated. Thus, in many centers across the world, especially in Japan and Europe and in India too, FNA is the first line of investigation and is one of the three components of Triple assessment, consisting of clinical examination, mammography, and cytological/histopathology diagnosis (Fig. 7.1).

Manish Rohilla, MD
Associate Professor, Department of Cytology and Gynecological Pathology, PGIMER, Chandigarh, India

Radhika Srinivasan, MD, PhD (Mol Oncol), MIAC (✉)
Professor and Head, Department of Cytology and Gynecological Pathology, PGIMER, Chandigarh, India
e-mail: drsradhika@gmail.com

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_7

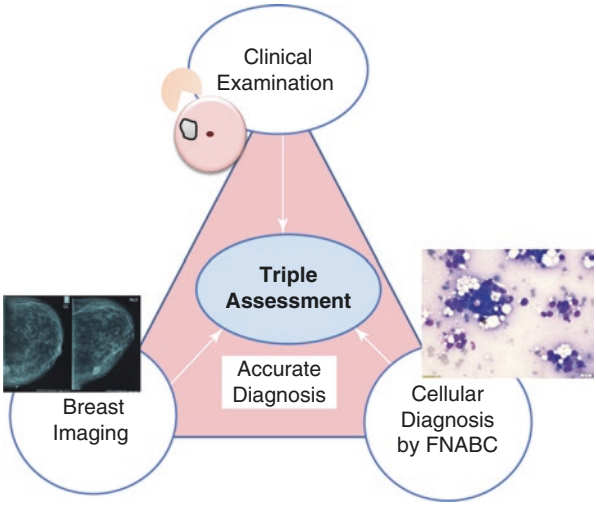


Fig. 7.1 Triple Assessment. The triad includes clinical examination, breast imaging and obtaining a cellular diagnosis by Fine needle aspiration biopsy cytology

7.2 Core Needle Biopsy (CNB) vs. Fine Needle Aspiration Biopsy (FNAB)

FNA continues to be used as a first-line modality in the investigation of a breast lump across many centers worldwide, including Japan, Portugal, France, USA, and India. Core needle biopsy, which is popular in the developed countries and some centers in India has advantages over FNA in its better diagnostic accuracy in mammographic screen-detected non-palpable lesions and small lesions which are <2cms, in lobular carcinoma, in sclerotic lesions, and in the 'gray-zone proliferative breast lesion.' The most important advantage of core biopsy is its ability to demonstrate invasion, which is not possible on FNAC. Further, molecular marker testing is believed to be more reliable on a core biopsy. This is particularly relevant if neoadjuvant chemotherapy needs to be instituted. Hence, core biopsy has gained in popularity over the last decade in some centers. Most core biopsies are performed by the radiologist under ultrasound guidance. The limiting factors for widespread use of core biopsy in India are the high cost of the procedure, which includes the cost of the biopsy gun, time, and expertise required to obtain material as well as its interpretation, which requires an experienced breast histopathologist.

Further, there are reports that CNB may be complicated by tumour seeding [1] and is associated with an increased frequency of distant metastases later in the course of the disease as compared to FNA [2]. On the other hand, it is very pertinent to mention here that cell blocks are being increasingly prepared from FNA, which act as microbiopsies. Thus FNAC is today more appropriately a fine needle aspiration biopsy or FNAB with cyto-histology and material available for any kind of ancillary techniques. Overall, we may conclude that FNA continues to have its own place and is probably superior to CNB for larger palpable breast lesions.

7.3 Fine Needle Aspiration Biopsy Cytology: Technical Considerations

Clinical considerations: The referring clinician and the cytopathologists who perform the FNA must take proper relevant history and conduct a thorough clinical examination before performing FNA. Clinical history includes the duration of symptoms, which include awareness of mass or lump in the breast, nipple discharge, nipple retraction, pain, and discomfort. History of the rapidity of growth must be documented. If nipple discharge is present, the duration and amount must be recorded.

7.4 Breast Examination by Cytopathologist

Both breasts and both axillae must be examined after fully exposing them and with the patient in the sitting position. The breasts and respective axilla must be sequentially palpated. The following information must be recorded after physical examination:

1. Size, location, feel, and margins of the mass
   - Size in cms in two axis.
   - The location should be recorded with respect to the quadrant of the breast.
   - Margins—regular/irregular and ill-defined
   - Consistency—firm, hard, with or without cystic component
   - Mobility—freely moving or fixed to underlying structures
2. Condition of the overlying skin- normal/dimpling/ulceration/peau d' orange should all be recorded.
3. Nipples—retracted/not retracted.
4. Nipple discharge—watery/serous/greenish/brownish/hemorrhagic should be recorded along with whether the discharge is from a single or multiple ducts.
5. Axillary examination: the presence of lump or lymph nodes must be recorded along with the number and size.

7.5 Technique of FNA

1. ***Nipple Discharge:*** The patient may be asked to express the same gently. One glass slide is taken, and discharge is touched gently, and a smear is made with another slide. A minimum of 2 smears—one air-dried and one alcohol-fixed are prepared. If the quantity permits, up to 4 smears can be made.
2. ***FNA of Axillary Lymph nodes:*** The axillary lymph nodes are always aspirated before the breast lump. The patient should be preferably in a sitting position,. Ask the patient to place her hand on your shoulders. Fix the axillary node with two fingers of one hand and perform the FNA. If more than one node is present, each one must be sampled separately.

3. ***FNA breast lump:*** The patient should be preferably in the supine position. She must be made comfortable and should be reassured that the technique is quick, and she will have minimum pain and discomfort. The lump is fixed with two fingers of one hand, and FNA is performed. A minimum of 2 passes is taken, and if required, more passes may be taken from multiple sites of the mass. While the needle is in the lesion, the direction is changed along with to and fro movement so as to sample the lesion adequately.
   (a) ***Nature of aspirated material:*** Particulate mixed with blood/fluidy with particles/microfragments/fluid—serous/yellow/greenish/hemorrhagic/pus/whitish necrotic
      (i). All fluid aspirated must be collected in a screw-capped tube, centrifuged, and sediment smear prepared. Hemorrhagic fluid may be subjected to liquid-based cytology for better results. If the sediment is very cellular, after making smears, it can be processed as a cell block
      (ii). For non-fluidy particulate material, 4–6 direct smears are prepared, and some should be air-dried and others wet-fixed in 95% alcohol.
      (iii). Cell block: A portion of the aspirate must be put for cell block in cases of suspected malignant lesions. In my practice, the 1st pass is dedicated to smears, and the 2nd pass is dedicated to CB.

A picture of the tools required for routine FNA is shown in Fig. 7.2. It is always good practice to perform FNA with a 10 or 20 mL syringe fitted to a handle (Cameco, AB, Taby, Sweden). Non-aspiration techniques (Fine needle sampling) and not using a handle can limit the amount of material aspirated required for a comprehensive report.

Following FNA, the patient should be asked to press on the swab at the puncture site for 5 min. Check for any ooze. If there is persistent oozing, then a small gauze is put and secured with micropore for a few hours. Generally, the oozing subsides on its own within 5 min.

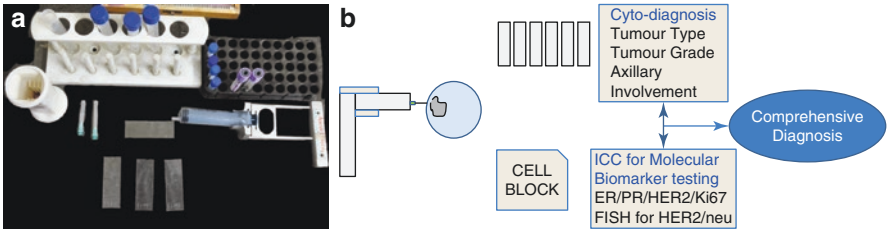


Fig. 7.2 (**a**) FNABC table set-up showing syringe fitted to a handle, numbered slides, coplin jar containing 95% ethanol for fixation, 15 mL screw-capped tubes for collection of aspirated fluid and material for cell block (10% formaline fixation), 2 mL tubes or collecting material for microbiological/molecular studies and purple capped tubes for collecting samples for Flow-Cytometry. (**b**) Flow chart for comprehensive breast cancer diagnosis

Checking Adequacy: The material must be evaluated for its adequacy by the operator soon after FNA. This is achieved by macroscopic evaluation of the aspirated material, and with experience, assessment of adequacy is highly accurate. However, rapid on-site evaluation (ROSE) may be performed if deemed necessary. In our experience, insufficient aspirates are usually obtained from less experienced operators. In general, the rate of insufficient/inadequate FNA should not exceed 5%.

Stains Used: Giemsa or May-Grünwald Giemsa for air-dried smears, and Hematoxyline-Eosin or Papanicolaou stain is used for alcohol-fixed smears.

If possible, rapid on-site evaluation or ROSE must be performed to ensure that the material aspirated is representative and adequate for all ancillary techniques.

Pictorial representation of the FNABC technique and how the material should be allocated for a comprehensive diagnosis is shown in Fig. 7.2b. The broad diagnostic categories are shown in the table below (Table 7.1).

Table 7.1 Broad Diagnostic Categories of FNA of Breast Lesions

Diagnostic categories
Inflammatory
• Acute abscess
• Granulomatous mastitis
• Chronic mastitis
Non-neoplastic
• Fibroadenoma
• Lactational changes/adenoma
• Duct ectasia
• Galactocele
• Cyst, NOS
• Fibrocystic disease
• Fibroadenosis
• Ductal hyperplasia
• Ductal hyperplasia with atypia
• Gynecomastia
• Fat necrosis
Neoplastic
• Primary
– Invasive ductal carcinoma
Not otherwise specified (NOS)
Mucinous
Apocrine
Papillary
– Invasive lobular carcinoma
– Metaplastic carcinoma
– Mixed epithelial-mesenchymal neoplasms
Phyllodes tumour
• Benign
• Malignant
– Non-epithelial neoplasms
– Malignant lymphoma
– Sarcoma
– Others
• Metastatic tumours

7.6 Benign vs. Malignant Lesions

There are some general cytological features seen in benign lesions in comparison to malignant lesions, which are tabulated below and are highlighted in Fig. 7.3 (Table 7.2).

7.7 Invasive Carcinoma

7.7.1 Invasive Ductal Carcinoma, No Special Type (NST) (Synonym-Infiltrating Ductal Carcinoma)

This is the most common type of breast cancer. Patients present with a lump in the breast of a few weeks duration, this is usually painless. The mass is of variable size, shape and often feels firm or hard with poorly defined margins. There may be fixation to the underlying structures, and the overlying skin may show involvement. Nipple retraction may be present.

Cytopathology Smears show variable cellularity ranging from low to high, but are moderately cellular in most cases. The cells are arranged in loose clusters and are also seen as individual dispersed cells (Fig. 7.4). The cell clusters have a syncytial

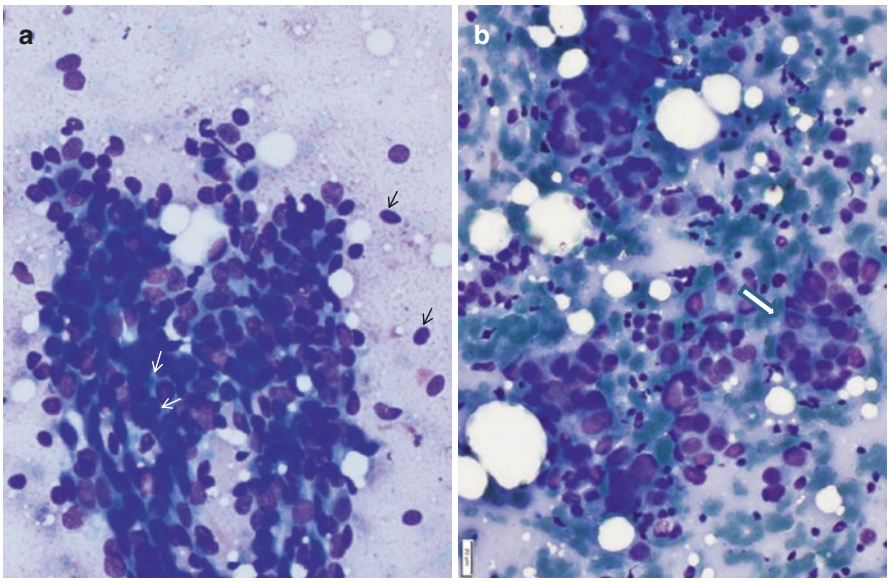


Fig. 7.3 Comparison of benign (**a**) and malignant (**b**) breast aspirates. Cohesive and tight clusters vs loosely cohesive clusters, presence vs loss of polarity, presence vs absence of myoepithelial cells (white thin arrow), stromal bare nuclei vs naked tumour nuclei are noted. In addition, the tumour in (**b**) shows tubule formation (white thick arrow). (**a**-May-Grünwald Giemsa stain; **b**-Hematoxyline-Eosin stain; Original magnifications-**a, b**, ×200)

Table 7.2 Salient Cytomorphological Features of Benign vs. Malignant Breast Lesions

Feature	Benign	Malignant
Prototype lesion	Fibroadenoma	Carcinoma
Cellularity	Good	Variable-low to high
Cell aggregates	Cohesive	Loosely cohesive
Dispersed cells	Few	Many
Cell arrangement	Flat, monolayered, honeycombed clusters, maintained polarity	Multilayered, chaotic with loss of polarity
Cytoplasm	Scanty to minimal	Variable-scanty, moderate or abundant
Mucin	NO	Yes/no
Nuclear size	Small, uniform	Variable, Pleomorphism
Nuclear shape	Round, regular	Round to oval, variable
Nuclear chromatin	Uniform spread	Irregular, coarse, or vesicular
Nucleolus	Not distinct usually	Prominent usually, may have multiple irregular nucleoli
Mitoses	No	Yes, variable numbers
Necrosis	No	Yes/no
Myoepithelial cells	Present	Absent

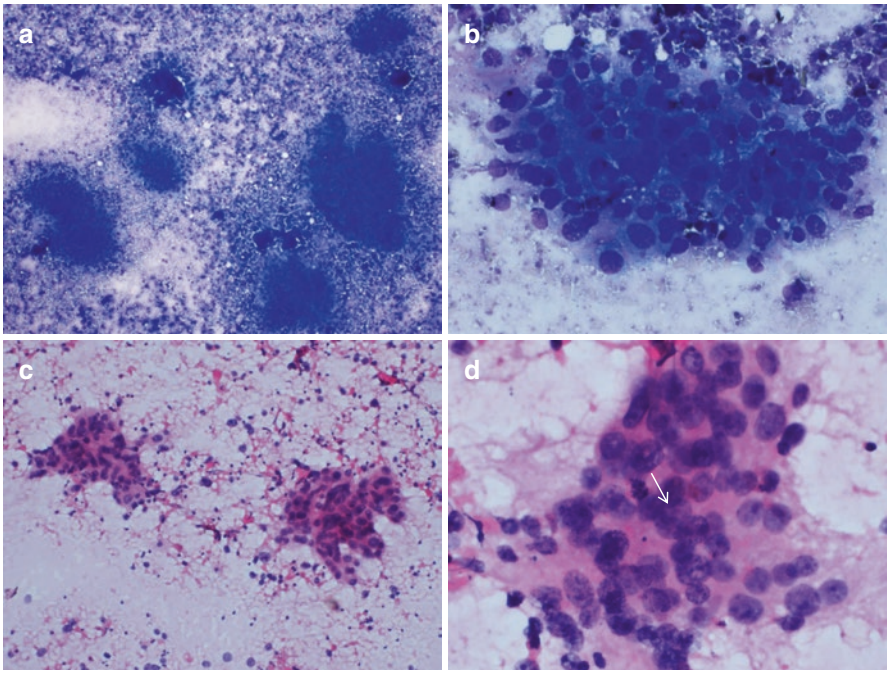


Fig. 7.4 Invasive duct carcinoma breast, no special type, cytopathological features. (**a** and **c**), high cellularity with loosely cohesive clusters and dispersed tumour cells; (**b** and **d**), moderate nuclear pleomorphism and coarse chromatin; arrow shows mitoses in (**d**) (**a, b**-May-Grünwald Giemsa stain; **c, d**- Hematoxyline-Eosin stain; Original magnifications-**a, c** ×100; **b, d** ×400)

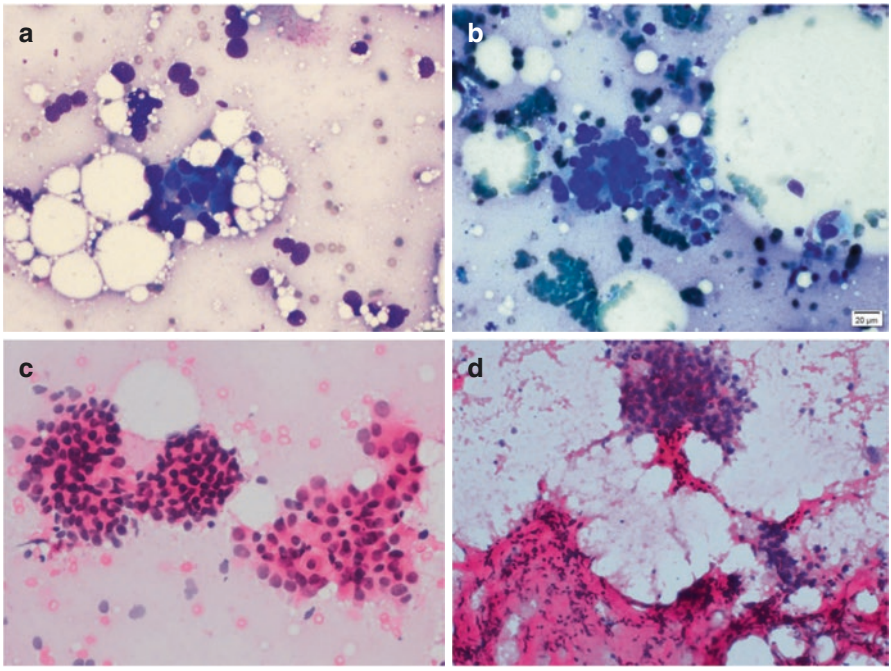


Fig. 7.5 Invasive duct carcinoma breast, no special type, cytopathological features. (**a**) tumour cells with invasion of fat; (**b** and **c**), moderate pleomorphism and tubule formation; (**d**) associated desmoplastic/sclerotic fragment. (**a, b**- May-Grünwald Giemsa stain; **c, d**- Hematoxyline-Eosin stain; Original magnifications- **a, b, c** ×200; ×100)

arrangement and show a lack of polarity and lack of myoepithelial or bipolar cells (Fig. 7.4). This is an important clue to a correct diagnosis of malignancy, especially in low-grade carcinomas. The cells are variably sized, but are generally intermediate or large, round to polygonal, and have moderate to abundant cytoplasm. The nuclei show features of malignancy in the form of nuclear hyperchromasia or coarse, irregular chromatin, irregular nuclear membranes (Fig. 7.4). Nucleoli may be inconspicuous or prominent, with one to multiple nucleoli present. Tubule formation may be seen (Fig. 7.5). The aspirate shows admixture with fat (Fig. 7.5). In some cases, sclerotic fragments may be seen in close association with tumour cells. Tumour necrosis and diathesis may be noted in many cases. Elastoid bright pink stained stromal fragments indicating desmoplasia (Fig. 7.5) are also a feature of breast carcinoma.

7.8 Variants of Ductal Carcinoma

Mucinous Carcinoma: Smears show abundant pools of extracellular mucin in which are embedded the tumour cells. These cells are in small loose aggregates and show mild nuclear pleomorphism and small nucleoli.

Carcinoma with Apocrine Differentiation: Tumour cells show apocrine differentiation in the form of abundant gray-blue or eosinophilic cytoplasm, eccentric nucleus, and prominent nucleolus.

Carcinoma with Medullary Features: Smears show syncytial aggregates of tumour cells with moderate nuclear pleomorphism, prominent nucleolus, and a moderate amount of cytoplasm. There is a prominent infiltration by lymphocytes and plasma cells.

Tubular Carcinoma: This is an uncommon variant with only a handful of reports in FNA literature. Smears are usually of low cellularity and show scattered tumour cells with low-grade nuclear features of malignancy. Tubule formation may be appreciated in smears. As there is only minimal pleomorphism, the diagnosis can be missed on FNA, and a false-negative report of benign neoplasm may be offered.

Papillary Neoplasm of the Breast: A definitive diagnosis of papillary lesions of the breast can be made only after histopathological evaluation of the surgically resected specimen. FNA has a limited role in their diagnosis as invasion cannot be demonstrated in cytology specimens.

Clinical Features Intraductal papillary lesions frequently present with nipple discharge, usually from a single duct, which may be blood-tinged or frankly hemorrhagic.

Cytopathology Nipple discharge cytology or fine needle aspirations from a palpable mass lesion, if present, are the samples evaluated on cytology. Benign nipple discharge is paucicellular and shows only a few macrophages. However, in the presence of a papillary neoplasm, smears show papillary clusters with numerous RBCs and macrophages in the background (Fig. 7.6). The papillary clusters may show mild cytological atypia. Such cases should be signed out as consistent with papillary

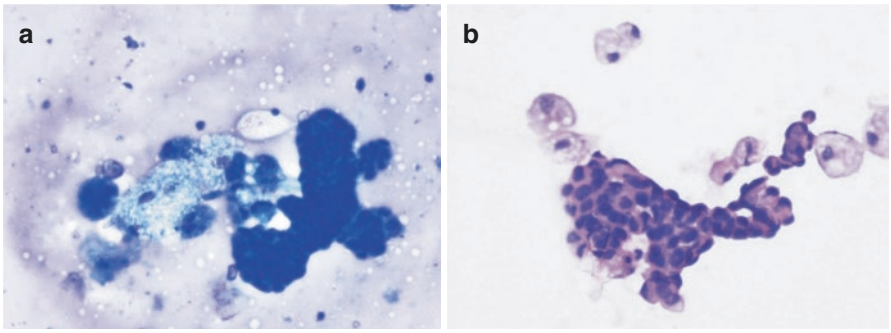


Fig. 7.6 Nipple discharge of papillary neoplasm showing papillary clusters of cells show mild pleomorphism admixed with macrophages. Papillae have rounded contours. (**a**, May-Grünwald Giemsa stain; **b**-Hematoxyline-Eosin stain; Original magnifications- **a, b**, ×200)

neoplasm with the rider that cytology cannot distinguish benign from malignant papillary lesions. Correlation to ductography/mammography is essential.

Papillary Carcinoma Invasive papillary carcinoma presents as a cystic mass lesion. FNA of such lesions yields hemorrhagic fluid with some particles. An effort must be made to completely aspirate the lesion, followed by palpation and re-aspiration of the residual mass. Ultrasound guidance to target the solid part of the lesion is useful.

Smears show numerous papillary aggregates of tumour cells in a hemorrhagic background with mild to moderate cytological atypia. Again, the sign-out is of a papillary neoplasm, and the final diagnosis is deferred to histopathological examination.

Metaplastic Carcinoma This is an uncommon variant of breast cancer which has a more aggressive behaviour and therefore needs to be recognized. It is also referred to as carcinosarcoma. The word 'metaplastic' refers to the transformation of the glandular to non-epithelial components.

Smears show sarcomatous features with spindle cells in fascicles and dispersed singly, having nuclear pleomorphism and atypia. They may show areas resembling fibrosarcoma, chondrosarcoma, leiomyosarcoma, and rhabdomyosarcoma. The carcinomatous component is poorly differentiated. Squamous differentiation of tumour cells and osteoclastic tumour giant cells may be seen.

7.9 Invasive Lobular Carcinoma

Invasive Lobular carcinoma has a higher frequency of bilaterality and multicentricity. It may be a well-defined palpable lump or maybe poorly defined and non-palpable. It may sometimes present with distant metastases in the bones, in other viscera, effusions, and with the meningeal spread.

Cytopathology FNA of lobular carcinoma show variable cellularity. In about one third of cases, there is poor cellular yield, and consequently, such cases may be missed and require a core biopsy for diagnosis. In other cases, the aspirate is moderately cellular and shows a predominantly dispersed population of uniform small-sized cells showing an eccentric nucleus and having minimal or mild nuclear pleomorphism (Fig. 7.7). The nuclear chromatin is evenly dispersed, and nucleoli are not seen. The cytoplasm is moderate in amount and can show intracytoplasmic lumina or vacuoles (Fig. 7.7). Targetoid inclusions containing magenta bodies are specific to lobular carcinoma. At times, the cells display an Indian-file arrangement, better appreciated when fragments are aspirated. However, low cellularity due to associated sclerosis leads to false-negative reports, and some cases may have overlapping morphology with ductal carcinoma.

Due to the small nuclear size and lack of nuclear pleomorphism, some cases may be misinterpreted as benign. A clue to malignancy is the lack of bipolar naked nuclei or the myoepithelial cells.

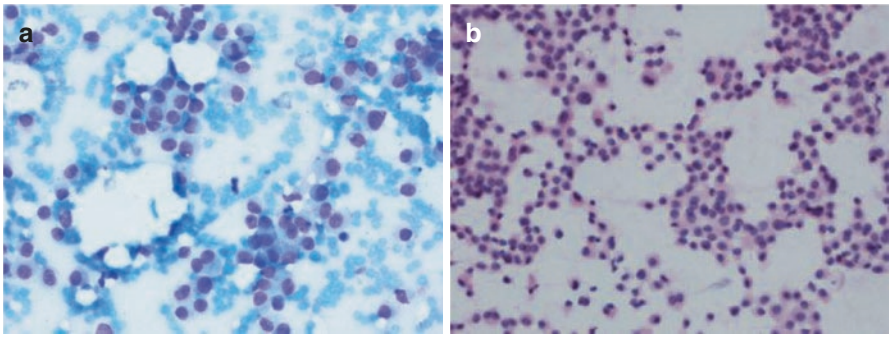


Fig. 7.7 Lobular carcinoma breast, cytopathological features. (**a**) Predominantly dispersed population of cells with eccentric nucleus having bland chromatin (**a**, May-Grünwald Giemsa stain; **b**-Hematoxyline-Eosin stain; Original magnifications- **a, b**, ×200)

7.10 Mixed Epithelial-Mesenchymal Neoplasms

7.10.1 Phyllodes Tumour

Clinical Features These tumours present as large mass lesions and can mimic giant fibroadenomas. FNAC must be performed from multiple sites (at least three sites).

Cytopathology Smears show an admixture of epithelial elements represented by benign ductal epithelial clusters and mesenchymal elements represented by cellular stromal fragments and scattered spindled stromal cells. Metachromatic stromal material may be seen associated with the fragments. The relative proportion of the two elements is to be noted as in phyllodes tumour, the mesenchymal elements generally predominate.

Benign phyllodes tumours do not show any nuclear atypia, pleomorphism, or mitoses (Fig. 7.8). Malignant phyllodes tumours are characterized by overgrowth of the mesenchymal fragments with very occasional benign ductal epithelial clusters. Further, they show discohesiveness in the spindled stromal cells with significant nuclear pleomorphism, atypia, and even focal mitoses. (Fig. 7.9).

Differential Diagnosis *Fibroadenoma vs. benign phyllodes tumour:* Cellularity of the stromal fragments is the only distinguishing feature, with phyllodes tumours displaying more cellular stromal fragments. In difficult cases, the sign-out diagnosis can be fibroepithelial neoplasm, benign, and both diagnostic possibilities are mentioned. The treatment for both neoplasms essentially remains the same.

Malignant phyllodes tumour vs. sarcoma and carcinosarcoma: The distinguishing feature of the former lesion is the benign epithelial component. However, this may not be represented adequately in smears with overgrowth of the mesenchymal

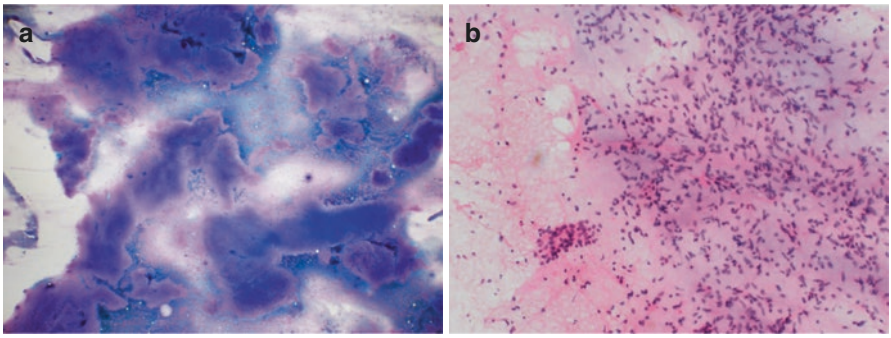


Fig. 7.8 Benign Phyllodes tumour. (**a**) Smear shows numerous cellular stromal fragments. (**b**) higher magnification showing high cellularity but showing mild nuclear pleomorphism in the stromal fragemnts and cells. Arrow shows an occasional breast epithelial cell cluster. (**a**, May-Grünwald Giemsa stain; **b**-Hematoxyline-Eosin stain; Original magnifications- **a** ×100, **b** ×200)

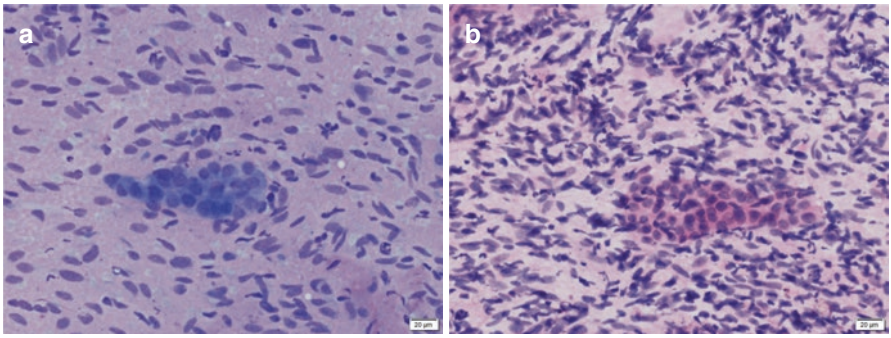


Fig. 7.9 Malignant Phyllodes tumour. (**a** and **b**), Smears shows numerous dispersed stromal cells with moderate nuclear pleomorphism admixed with an occasional breast epithelial cell cluster. (**a**, May-Grünwald Giemsa stain; **b**-Hematoxyline-Eosin stain; Original magnifications- **a** and **b** ×200)

elements and so may be mistaken for a sarcoma. Reactive atypia in the epithelial elements can be mistaken for carcinosarcoma.

Sarcoma breast: Pure sarcomas of the breast are rare neoplasms and will not be discussed further here.

7.11 Breast Lymphoma

The breast may be involved secondarily by nodal lymphoma or maybe the primary site when it is referred to as primary breast lymphoma. These lesions present as nodular mass lesions. Smears show atypical lymphoid cells with numerous lymphoglandular bodies in the background. These lymphoid cells show similar features to their nodal counterparts. Immunocytochemistry on the cell block aids in their further categorization. Lymphomas show positivity for CD45 and are negative for cytokeratins. Primary lymphomas of the breast are commonly of the B-cell type

Table 7.3 Grading of breast carcinoma in Cytopathology

	Robinson's cytological criteria		
Parameter	Score1	Score 2	Score 3
Cell dissociation	Mostly in clusters	A mixture of single-cell and cluster	Mostly single cell
Cell size	1–2 times of RBC	3–4 times of RBC	>5 times of RBC
Cell uniformity	Monomorphic	Mildly pleomorphic	Pleomorphism
Nucleoli	Indistinct	Noticeable	Prominent
Nuclear margin	Smooth	Folds	Clefts
Chromatin	Vesicular	Granular	Clumped
Grade	Grade 1	Grade 2	Grade 3
Score	6–11	12–14	15–18
Modified Scarff–Bloom–Richardson cytological grading method			
Parameter	Score1	Score 2	Score3
Tubule formation	>75%	10–75%	<10%
Nuclear pleomorphism	Minimal	Moderate	Marked
Mitotic count	0–5	6–11	11+
	Add the scores		
Grade	Grade 1	Grade 2	Grade 3
Score	3–5	6–7	8–9

(CD20+) with diffuse large B-cell lymphoma followed by extranodal MALT-type lymphoma being reported and are uncommonly of the T-cell type (CD3+).

7.12 Grading of Breast Carcinoma on Cytology Smears

Grading of breast carcinoma is an important feature that has prognostic implications. Histopathological grading is the definitive gold standard. However, it is possible to grade infiltrating or invasive duct carcinoma, no specific type on cytology using many types of grading systems reviewed by Bansal et al. [3]. The Robinson cytologic and modified Scarf-Bloom-Richardson scoring systems have been commonly used, respectively [4, 5]. Grading is preferably performed on a Papanicolaou or a Hematoxyline-Eosin stained smear, and the worst areas with adequate cellularity must be selected (Table 7.3).

7.13 Role of Ultrasound-Guided FNA of Axillary Lymph Nodes

Ultrasound examination of the axilla is more sensitive than physical examination for the detection and documentation of lymph nodal metastases for the preliminary staging of breast carcinoma. The type of surgery to be performed with respect to total axillary lymphadenectomy or sentinel lymph node biopsy is determined by

documentation of the presence or absence of axillary nodal involvement. In an original study from the MD Anderson Hospital by Krishnamurthy et al. [6], US-guided FNA of axillary lymph nodes was found to be useful in documenting metastases in non-palpable indeterminate and suspicious axillary lymph nodes with a 86% sensitivity of 100% specificity. This has been confirmed by many other studies [7]. US-FNA in cases of lymph nodes suspicious for malignancy was shown to prevent more than 50% of sentinel lymphadenectomies, significantly shortening the time interval to definitive therapy [8] False-negative was attributed to the small nodal size of <5 mm and the presence of micrometastases. However, recent studies [9] and meta-analysis [10] have shown that the overall sensitivity of FNA is around 74% compared to 88% for a core needle biopsy.

7.14 Reporting Breast Fine Needle Aspiration Biopsy Cytopathology: Standardized Format [11]

The International Academy of Cytology (IAC) has recently published a standardized reporting format, also referred to as the Yokohama system, for reporting breast FNAC. Five categories were recognized that could be stratified by their risk of malignancy (ROM) (Table 7.4).

7.15 Diagnostic Accuracy and Limitations of FNA

Breast FNA has a high diagnostic accuracy for the diagnosis of both benign and malignant neoplasms. In one recent study Dong, et al. showed a 100% negative predictive value of a benign diagnosis, and 91% sensitivity, and 95% specificity, implying a very high diagnostic accuracy [12]. The application of the International system allows for the assessment of the risk of malignancy in a given category and has been successfully applied recently in many countries [13–15]. It is seen that

Table 7.4 International Academy of Cytologists Standardized Reporting Categories for Breast FNA (Yokohama System)

Category	ROM	Management recommendation
Insufficient	2.6–4.8	Review clinical and imaging findings. If imaging is benign, consider repeat FNAB
Benign	1.4–2.3%	Review with clinical findings: If benign, no further action; if suspicious, repeat FNA
Atypical	13–15.7%	Review clinical and imaging findings; repeat FNA if atypia likely due to a technical issue; if good material is available and atypical, preferably proceed to core needle biopsy
Suspicious	84.6–97.1%	Review clinical and imaging findings; CNB is mandatory
Malignant	99–100%	Review clinical and imaging findings; CNB if discrepant findings; if the triple test is concordant and malignant, proceed to definitive surgery

although there is a high diagnostic accuracy, there will be a small proportion of false-negative cases, and the reasons could be broadly divided as sampling issues or interpretational issues.

Sampling issues leading to false negatives can occur in i) very small tumours with a dominant large benign lesion ii) carcinomas arising focally in a proliferative breast disease or in a papillary lesion, iii) lesions which show cystic degeneration such as some papillary cancers, iv) lesions which show dense sclerosis due to associated desmoplasia and v) lesions which are predominantly necrotic.

Interpretational issues leading to false-negative reporting can occur in low-grade carcinomas such as tubular carcinoma and lobular carcinoma, which show low nuclear atypia and so misinterpreted as benign lesions.

All these can be avoided to a large extent by an experienced person performing and interpreting smears. Correlation to the clinical findings and the imaging findings on sono-mammography is of utmost importance to minimize errors in reporting.

7.16 Molecular Typing of Breast Carcinoma by Molecular Biomarker Testing

Details of molecular typing of breast carcinoma are dealt with in the chapter on histopathology. Suffice it to say that all the molecular phenotypes can be demonstrated on FNA cell blocks provided they are sufficiently cellular and show at least 100 tumour cells. Although there are reports demonstrating the ability to perform immunocytochemistry on smears, these are not to be preferred as they are unreliable, have a poor signal to noise ratio and the admixture with blood and necrosis can make interpretation difficult. Further, all staining protocols that are standardized on histopathology sections can be directly applied to cell blocks, which act as microbiopsies of the tumour. Smears may be used only in cases without sufficient material on cell blocks. ICC is reliably performed on cell blocks [12, 16–19]. Hence, in our institution, it is now mandatory to prepare cell blocks from either primary or metastatic lesions for molecular typing. Providing accurate molecular typing is even more important in the context of neoadjuvant chemotherapy for locally advanced diseases. The molecular types are shown in Table 7.5 below. A case of ductal carcinoma, no special type which showed ER-/PR-/HER2+ and low Ki-67 conforming to HER2 overexpressing molecular type, is illustrated in Fig. 7.10. Another case of invasive lobular carcinoma confirmed by loss of E-cadherin and showing ER+/PR+/HER2+ with moderate Ki-67 index conforming to luminal B molecular type is illustrated in Fig. 7.11.

Table 7.5 Molecular classification of breast cancer

Molecular Type	Estrogen receptor (ER)	Progesterone receptor (PR)	HER2
Luminal A	+	+/–	–
Luminal B	+	+/–	+
HER2 overexpressing	–	–	+
Triple-negative	–	–	–

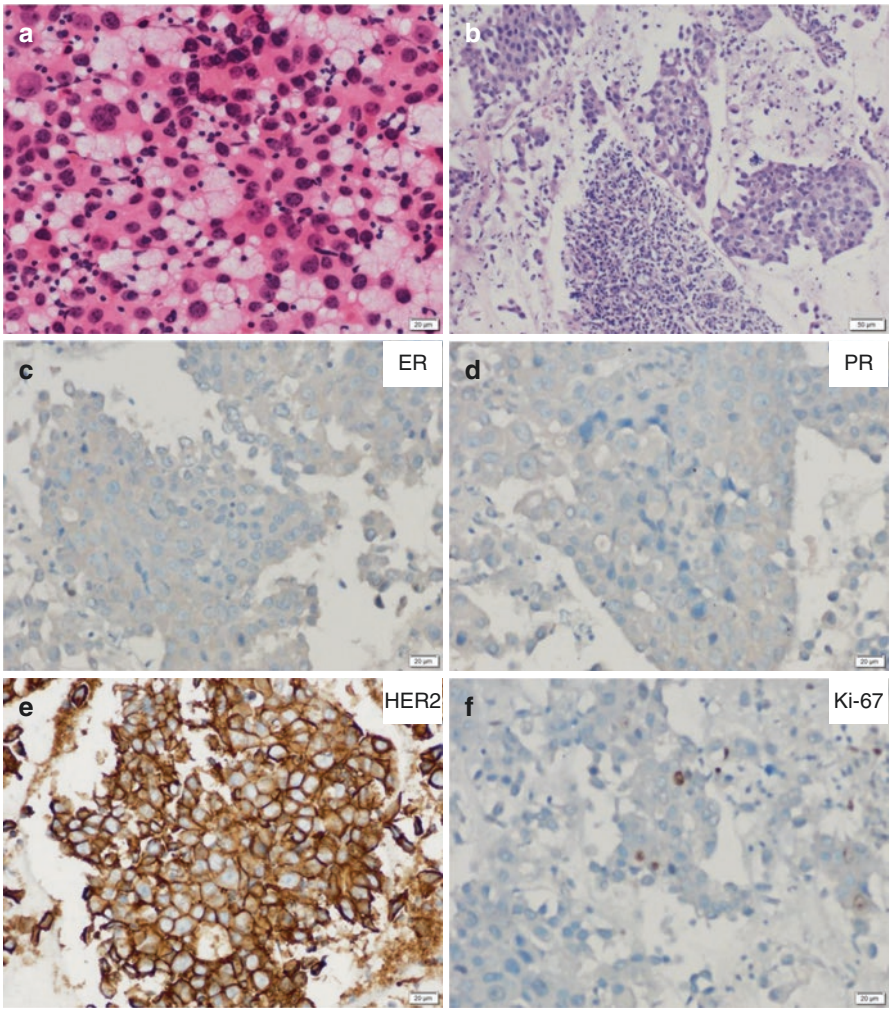


Fig. 7.10 Molecular typing of invasive ductal carcinoma, NST. (**a**) smear; (**b**) cell block; (**c**) ER negative; (**d**) PR negative; (**e**) HER2/neu 3+ positive (complete membranous) and (**f**) Ki-67 (<5%). Features are of HER2 overexpressing type. (**a** and **b**, Hematoxyline-eosin stain; **c–f**, immunoperoxidase stain; magnification **a–f** ×200)

Studies evaluating the concordance of immunocytochemistry on cell blocks from FNA versus tumor tissue have shown high concordance rates ranging from 90% [17] to 96% and 98% [12]. Suffice to say here that FNA-cell blocks are equivalent to tumour tissue specimens for molecular typing. Indeed this is equivalent or better than core biopsies for performing molecular typing.

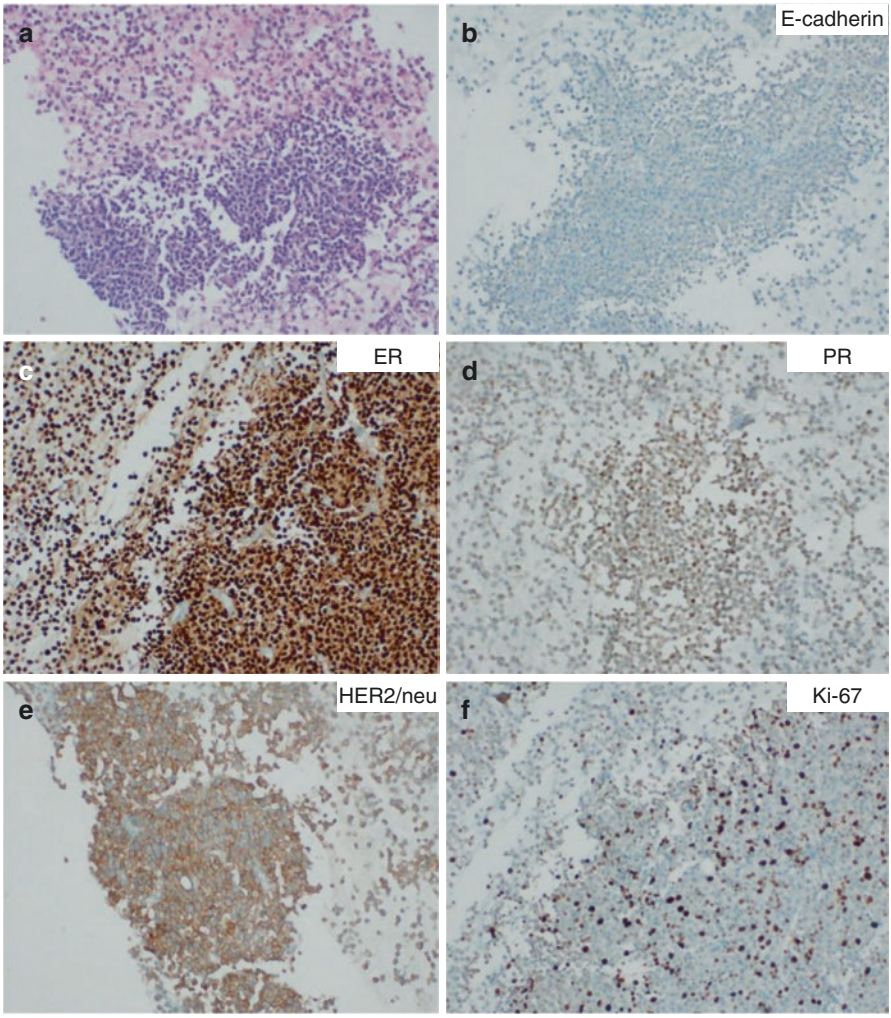


Fig. 7.11 Molecular typing of invasive lobular carcinoma, NST. (**a**) cell block; (**b, e**)-cadherin loss; (**c**) ER +; (**d**) PR +; E, HER2/neu 2+ positive and F, Ki-67 (25%). Features are of luminal B type. (**a**, Hematoxyline-eosin stain; **b–f**, immunoperoxidase stain; magnification **a–f** ×200)

7.17 HER2 Fluorescence In Situ Hybridization (FISH) on FNA Material

In cases where expression of HER2 is equivocal as in 2+ scoring, FISH for determining HER2 gene amplification is currently recommended. FISH may be performed on FNA smears [20, 21] or on cell blocks [12] with an excellent concordance with the resected tumour. A case is illustrated in Fig. 7.12.

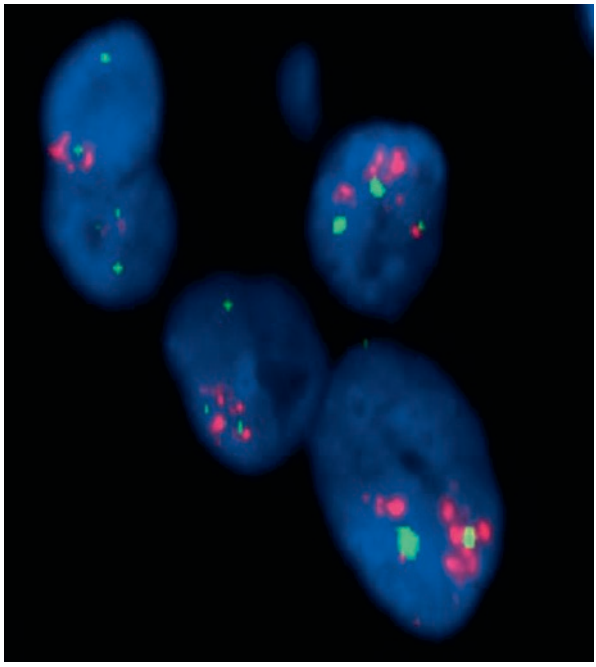


Fig. 7.12 Fluorescence in situ hybridization (FISH) for HER2/neu amplification. The LSI-HER2/neu probe shows orange signal and the CEP chr 17 probe is green. Note that for 2 green signals there are 4–12 orange signals indicating positivity for gene amplification

7.18 Metastatic Breast Carcinoma

Cytopathology plays a pivotal role in the diagnosis of breast carcinoma metastasis.

The various metastatic sites are—i) Lymph nodes—axillary, cervical; ii) Effusions: Pleural effusion is most frequent, followed uncommonly by pericardial effusion and ascites; iii) CSF- in cases with brain metastases with meningeal involvement; iv) Liver; v) Bone.

Lymph nodes, liver, and bone lesions are subjected to fine-needle aspiration. The cytomorphology is similar to the primary tumour.

In effusion cytology and CSF, breast carcinoma cells can show aggregates forming a 3-D ball-like cluster or may be seen as dispersed tumour cells admixed with mesothelial cells and inflammatory cells.

Immunocytochemistry: ICC is required to document that the malignant cells are indeed of breast origin as patients with breast cancer may have developed a second malignancy elsewhere. The markers employed for proving the breast primary include GATA3 (nuclear positivity) and GCDFP-15, the former being more specific. Note that GATA3 is also positive in tumours of urothelial origin. It is also important to perform molecular typing of breast carcinoma in metastatic sites as there may be a change in its molecular subtype, as shown in several studies [22, 23]. Discordance in ER, PR, and Her2 was seen to occur in 18%, 36%, and 8% in one study. In another study, 63% of metastatic tumours in pleural fluid became HER2 positive. A representative case is illustrated in Fig. 7.13. The molecular typing revealed low levels of ER and was negative for PR and HER2.

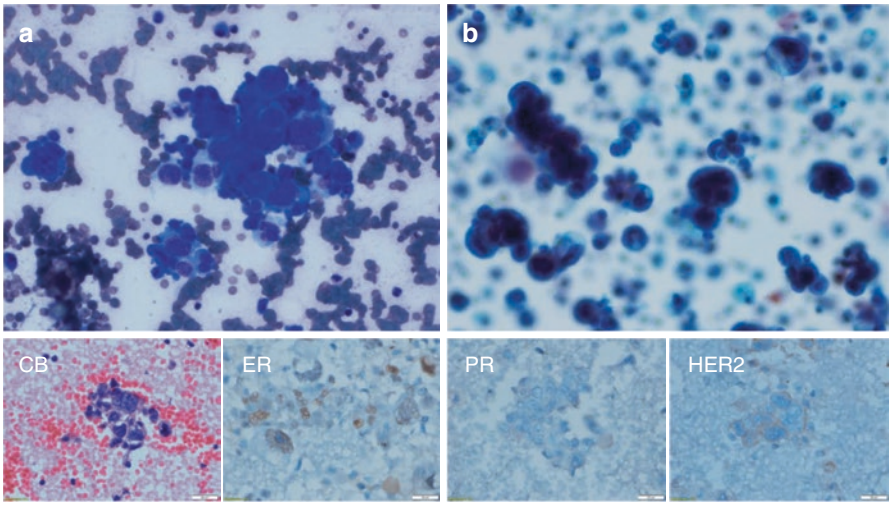


Fig. 7.13 Breast cancer metastases in pleural effusion. (**a** and **b**), 3-D ball like clusters and dispersed cells showing moderate nuclear pleomorphism. The bottom panels shows molecular typing on cell block with weak focal ER+ but PR- and HER2 1 + (weak and incomplete membranous). Molecular typing is consistent with luminal A type. (**a**, May-Grünwald Giemsa stain; **b** Papanicoloau stain of liquid based cytology preparation; Original magnifications- **a** and **b** ×200)

7.19 Limitations of FNA

The major limitation of FNABC is its inability to distinguish in-situ from invasive carcinoma, and it is for this very reason that core needle biopsy gained popularity. However, in-situ carcinomas are usually screen-detected and generally non-palpable lesions, and here CNB has a definite advantage and must be the technique of choice. However, the vast majority of invasive cancers are palpable breast mass lesions wherein FNABC delivers well on par with CNB with added cost-effectivity.

Key Messages

- FNABC of palpable breast mass lesions can provide an accurate diagnosis of breast carcinoma with great accuracy, with no complications and with minimal discomfort to the patient, and with the added advantages of being highly economical and having a quick turnaround time.
- The cytopathology report must mention the tumour type and tumour grade in cases of invasive ductal carcinoma, NST, to be as close to a histopathology report.
- FNABC must be combined with cell block for molecular biomarker testing by immunocytochemistry for ER, PR, HER-2, and, when required, HER-2 FISH.
- The cytopathology report based on morphology combined with the molecular report on cell block immunocytochemistry can provide a comprehensive breast carcinoma report which aids in appropriate management.
- The FNABC report MUST be correlated with the clinical findings and the imaging findings, which are the key components of the TRIPLE assessment of any breast lesion.

References

1. Uematsu T, Kasami M. Risk of needle tract seeding of breast cancer: cytological results derived from core wash material. Breast Cancer Res Treat. 2008;110(1):51–5.
2. Sennerstam RB, Franzen BSH, Wiksell HOT, Auer GU. Core-needle biopsy of breast cancer is associated with a higher rate of distant metastases 5 to 15 years after diagnosis than FNA biopsy. Cancer Cytopathol. 2017;125(10):748–56.
3. Bansal C, Pujani M, Sharma KL, Srivastava AN, Singh US. Grading systems in the cytological diagnosis of breast cancer: a review. J Cancer Res Ther. 2014;10(4):839–45.
4. Robinson IA, McKee G, Nicholson A, D'Arcy J, Jackson PA, Cook MG, et al. Prognostic value of cytological grading of fine-needle aspirates from breast carcinomas. Lancet. 1994;343(8903):947–9.
5. Howell LP, Gandour-Edwards R, O'Sullivan D. Application of the Scarff-Bloom-Richardson tumor grading system to fine-needle aspirates of the breast. Am J Clin Pathol. 1994;101(3):262–5.
6. Krishnamurthy S, Sneige N, Bedi DG, Edieken BS, Fornage BD, Kuerer HM, et al. Role of ultrasound-guided fine-needle aspiration of indeterminate and suspicious axillary lymph nodes in the initial staging of breast carcinoma. Cancer. 2002;95(5):982–8.
7. Fung AD, Collins JA, Campassi C, Ioffe OB, Staats PN. Performance characteristics of ultrasound-guided fine-needle aspiration of axillary lymph nodes for metastatic breast cancer employing rapid on-site evaluation of adequacy: analysis of 136 cases and review of the literature. Cancer Cytopathol. 2014;122(4):282–91.
8. Rocha RD, Girardi AR, Pinto RR, de Freitas VA. Axillary ultrasound and fine-needle aspiration in preoperative staging of axillary lymph nodes in patients with invasive breast cancer. Radiol Bras. 2015;48(6):345–52.
9. Bhandari A, Xia E, Wang Y, Sindan N, Kc R, Guan Y, et al. Impact of sentinel lymph node biopsy in newly diagnosed invasive breast cancer patients with suspicious node: a comparative accuracy survey of fine-needle aspiration biopsy versus core-needle biopsy. Am J Transl Res. 2018;10(6):1860–73.
10. Balasubramanian I, Fleming CA, Corrigan MA, Redmond HP, Kerin MJ, Lowery AJ. Meta-analysis of the diagnostic accuracy of ultrasound-guided fine-needle aspiration and core needle biopsy in diagnosing axillary lymph node metastasis. Br J Surg. 2018;105(10):1244–53.
11. Field AS, Raymond WA, Rickard M, Arnold L, Brachtel EF, Chaiwun B, et al. The international academy of cytology Yokohama system for reporting breast fine-needle aspiration biopsy cytopathology. Acta Cytol. 2019;63(4):257–73.
12. Dong J, Ly A, Arpin R, Ahmed Q, Brachtel E. Breast fine needle aspiration continues to be relevant in a large academic medical center: experience from Massachusetts General Hospital. Breast Cancer Res Treat. 2016;158(2):297–305.
13. Montezuma D, Malheiros D, Schmitt FC. Breast fine needle aspiration biopsy cytology using the newly proposed IAC Yokohama system for reporting breast cytopathology: the experience of a single institution. Acta Cytol. 2019;63(4):1–6.
14. Wong S, Rickard M, Earls P, Arnold L, Bako B, Field AS. The international academy of cytology Yokohama system for reporting breast fine needle aspiration biopsy cytopathology: a single institutional retrospective study of the application of the system categories and the impact of rapid onsite evaluation. Acta Cytol. 2019;63(4):280–91.
15. Hoda RS, Brachtel EF. International academy of cytology Yokohama system for reporting breast fine-needle aspiration biopsy cytopathology: a review of predictive values and risks of malignancy. Acta Cytol. 2019;63(4):292–301.
16. Bueno Angela SP, Viero RM, Soares CT. Fine needle aspirate cell blocks are reliable for detection of hormone receptors and HER-2 by immunohistochemistry in breast carcinoma. Cytopathology. 2013;24(1):26–32.

17. Kumar SK, Gupta N, Rajwanshi A, Joshi K, Singh G. Immunochemistry for oestrogen receptor, progesterone receptor and HER2 on cell blocks in primary breast carcinoma. Cytopathology. 2012;23(3):181–6.
18. Vohra P, Buelow B, Chen YY, Serrano M, Vohra MS, Berry A, et al. Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression in breast cancer FNA cell blocks and paired histologic specimens: a large retrospective study. Cancer Cytopathol. 2016;124(11):828–35.
19. Shield PW, Crouch SJ, Papadimos DJ, Walsh MD. Gata3 Immunohistochemical staining is a useful marker for metastatic breast carcinoma in fine needle aspiration specimens. J Cytol. 2018;35(2):90–3.
20. Kapila K, Al-Awadhi S, Francis I. Her-2 neu (Cerb-B2) expression in fine needle aspiration samples of breast carcinoma: a pilot study comparing FISH, CISH and immunocytochemistry. J Cytol. 2011;28(2):54–6.
21. Durgapal P, Mathur SR, Kalamuddin M, Datta Gupta S, Parshad R, Julka PK, et al. Assessment of Her-2/neu status using immunocytochemistry and fluorescence in situ hybridization on fine-needle aspiration cytology smears: experience from a tertiary care Centre in India. Diagn Cytopathol. 2014;42(8):726–31.
22. Matsui A, Murata Y, Masuda N, Mori K, Takahashi M, Yamashiro K, et al. Clinical significance of evaluating hormone receptor and HER2 protein using cell block against metastatic breast cancer: a multi-institutional study. Oncotarget. 2019;10(55):5680–9.
23. Francis IM, Alath P, George SS, Jaragh M, Al Jassar A, Kapila K. Metastatic breast carcinoma in pleural fluid: correlation of receptor and HER2 status with the primary carcinoma-a pilot study. Diagn Cytopathol. 2016;44(12):980–6.

Pathology of Breast Cancer

8

Amanjit Bal and Kusum Joshi

8.1 Introduction

Breast carcinoma is the most common malignancy in females world-wide and the second most common malignancy in females in India. Breast carcinoma is a heterogeneous disease having specific histopathological types with different prognostic and clinical characteristics. The histological subtype, tumor size, lymph node metastasis are the conventional histo-morphologic prognostic factors of breast cancer; whilst the expression of oestrogen receptor (ER) and progesterone receptor (PR), proliferative rate (Ki-67 index), and Her-2 neu are the more recently recognized (molecular) oncogenic-prognostic determinants of breast carcinoma. In recent years, molecular pathology of invasive breast cancer has received a great attention and attempts have been made to provide molecular classification of the breast cancer, which also has a bearing on pathogenesis and newer therapies.

8.2 Pathologic Classification and Microscopic Sub-types of Breast Cancer

Breast carcinoma is usually classified primarily by its histological appearance. There are two main types/stages of breast cancer:

Amanjit Bal, MD, DNB
Professor, Department of Histopathology, PGIMER, Chandigarh, India

Kusum Joshi, MD, PhD, FAMS (✉)
Former Professor and Head, Department of Histopathology, PGIMER, Chandigarh, India
e-mail: joshi.kusum@gmail.com

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_8

1. The tumor is limited by the basement membrane of terminal duct-lobular unit (TDLU) (in situ carcinoma) and or
2. The tumor has invaded the stroma and reached beyond the basement membrane of TDLU to become invasive carcinoma.

Also, there are two main morphological patterns of the tumor:

A. Ductal carcinoma and
B. Lobular carcinoma.

Although the nomenclature implies that these two tumor types arise from the ducts or the lobules of the breast, it is well known that both tumor types arise from the same segment of the mammary gland, i.e. terminal duct lobular unit (TDLU), and only the cytoarchitectural features are used to determine the tumor to be ductal or lobular.

8.2.1 Ductal Carcinoma In Situ (DCIS)

Ductal carcinoma in situ (DCIS) is a malignant, clonal proliferation of cells growing within limited by the basement membrane-bound structures of the breast and with no evidence of invasion into the surrounding stroma. Increased use of screening mammography has resulted in an increased detection of DCIS as suspicious calcifications having a linear or clustered distribution. DCIS is considered as a heterogeneous group of lesions that differ in their growth pattern, histological features and biological potential.

DCIS has been classified based on the following features:

1. *Nuclear grade: High nuclear grade* is characterized by size of nuclei ≥2.5 times the size of normal ductal epithelial cell nuclei, marked pleomorphism, irregular nuclear contour, coarse or vesicular chromatin, multiple prominent nucleoli and frequent mitoses. *Low nuclear grade* is characterized by the size of nuclei 1.5–2 times the size of normal ductal epithelial cell nuclei. The nuclei are monomorphic, have regular nuclear contour, fine chromatin, inconspicuous nucleoli and absent to few mitoses. The *intermediate nuclear grade* includes cases with nuclei that lies in-between high grade and low grade.
2. *Necrosis:* Necrosis is defined as the presence of ghost cells and karyorrhectic debris. It can be of two types; comedo necrosis or central zone necrosis within ducts if sectioned longitudinally and; punctate necrosis or non-zonal type of necrosis in which foci of necrosis do not exhibit a linear pattern if sectioned longitudinally.
3. *Cell polarization/architectural differentiation:* Cell polarization reflects the radial orientation of apical portion of tumor cells towards lumen like spaces or minute microacinar spaces.

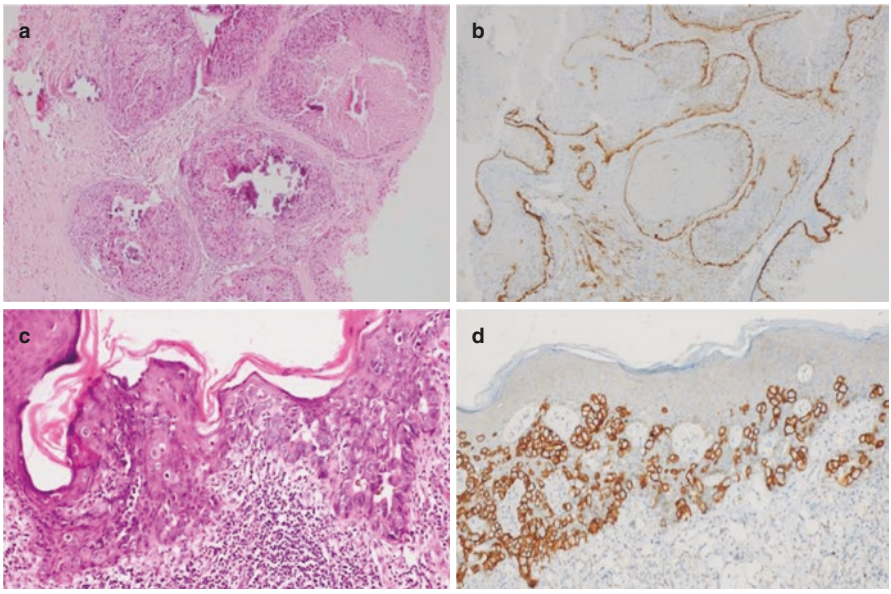


Fig. 8.1 Photomicrographs showing (**a**) High grade comedo DCIS, (**b**) calponin immunostain showing intact myoepithelial layer, (**c**) Paget's disease of nipple, and (**d**) Her-2 membranous positivity in Paget's cells

Various architectural growth patterns have been described for ductal carcinoma in situ and include:

- *Comedo pattern:* Characterized by prominent necrosis in the centre of the involved ducts and the necrotic material frequently becomes calcified (Fig. 8.1a,b).
- *Solid pattern:* Tumor cells fill and distend the involved ducts and lack significant necrosis, fenestrations, or papillae.
- *Cribriform Pattern:* Characterized by the formation of back-to-back glands giving punched out appearance without intervening stroma.
- *Papillary Pattern:* Shows intraluminal projections of tumor cells with fibrovascular cores and thereby constitute true papilla.
- *Micropapillary pattern:* Shows small tufts of cells without fibrovascular core oriented perpendicular to the basement membrane of the involved spaces projecting into the lumina.

Based upon the above features DCIS is classified as:

1. High-Grade DCIS,
2. Low-Grade DCIS and
3. Intermediate-Grade DCIS.

Table 8.1 The Van Nuys Prognostic Index (VNPI) Scoring System

Score	1	2	3
Size	≤<15 mm	16–40 mm	>401 mm
Margins	>10 mm	1–9 10 mm	<1 mm
Pathologic classification	Non-high grade without necrosis (nuclear grade 1 and 2)	Non-high grade with necrosis (nuclear grade 1 and 2)	High grade with or without necrosis (nuclear grade 3)
Age (Years)	>60	40–60	<40

This classification system of DCIS reflects the biological potential of these lesions for local recurrence and/or progression to invasive carcinoma.

The Van Nuys Prognostic Index (Table 8.1) attempts to objectively determine the aggressiveness of DCIS and the probability that local recurrence will occur after breast-conserving therapy. Scores for tumor size, surgical margin, pathologic classification and age of the patient are added to produce a total VNPI score of 4–12, with increasing scores representing a progressively worse prognosis.

Scores for tumor size, surgical margin, pathologic classification and age of the patient are added to produce a total VNPI score of 4–12, with increasing scores representing a progressively worse prognosis.

8.2.1.1 Evolution of DCIS

The natural history of DCIS is different and it depends on its grade and type. The risk of developing invasive carcinoma is directly proportional to and depends on the grade and the type of the DCIS. It has been observed that if these lesions are not treated, they will invariably progress to an invasive carcinoma.

The transformation of pure DCIS to an invasive carcinoma may take many years or decades. DCIS is a possible but not an obligate precursor of invasive breast cancer, which suggesting that pure DCIS and DCIS associated with infiltrating duct carcinoma (IDC) may be genetically distinct. The evolution from DCIS to IDC is complex and many different definite pathways are suggested and it is not a linear model.

8.2.1.2 Lobular Carcinoma In Situ (LCIS)

LCIS is an intralobular proliferation of small, uniform and loosely cohesive cells, originating in the TDLU with or without involvement of terminal ducts, leaving the underlying lobular architecture intact. Atypia, pleomorphism, mitoses and necrosis in comparison to DCIS are rarely seen. Intracellular mucin or signet ring cell appearance may be evident. There are no distinct gross features, and can be multicentric or bilateral in a majority of cases. The cells of LCIS lack E-cadherin and beta-catenin expression and show positivity for high molecular weight keratin (CK18). DCIS is positive for E-cadherin and beta catenin with reduced or no expression of CK18.

8.2.2 Paget's Disease

Paget's disease of the breast is clinically characterized as a scaly, fissured or erythematous lesion on the nipple-areola complex. Morphologically it shows tumor cells localized within the epidermis of the nipple-areola complex and are limited by the basement membrane. Paget's cells are large, pale epithelial cells with hyperchromatic, atypical nuclei, dispersed between the keratinocytes singly or as a cluster of cells (Fig. 8.1c). Paget's cells are negative for ER/PR and show strong membranous positivity for Her-2 neu (Fig. 8.1d). The underlying breast parenchyma may show associated high-grade DCIS or invasive carcinoma.

8.3 Invasive Breast Carcinoma

8.3.1 Invasive Duct Carcinoma

Invasive breast carcinoma is the most commonly diagnosed breast cancer and is categorized into morphological subtypes. About 75% of breast cancers, have no specific histologic characteristics other than invasion through the basement membrane of a breast duct and are termed as Invasive duct carcinoma, no special type (IDC-NST). It has wide histological variations with implications on clinical behaviour, such as size of tumour, grade of tumour, relative proportion of tumor cell and stroma, and types of margins. The tumor shows a heterogenous type of growth pattern, including in form of diffuse sheets, nests, cords, or single cell distribution with variable amount of duct formation ranging from complete absence to upto 70% of tumor tissue. Tumor cells are pleomorphic, usually with prominent nucleoli, numerous mitoses, necrosis and calcification can be detected in 60% of cases. Metaplastic changes can occur.

Invasive breast carcinoma that shows special histological pattern in >90% of the tumor is labelled as special subtype. The morphological subtypes of breast carcinoma are as follows:

• Tubular Carcinoma

Is an uncommon histologic type constituting 1–2% of all breast cancers. It is characterized by the presence of well-formed angulated tubular or elongated glandular structures with open lumina that are elongated and lined by single layer of epithelial cells with low-grade nuclei and apical cytoplasmic snouts (Fig. 8.2a). They have relatively good prognosis and are more frequent in elderly patients. The tubular component should constitute more than 90% in pure tubular carcinomas and the presence of 10–90% tubular carcinomas; atleast 75% are known as mixed tubular carcinomas. About 10–20% of the patients have been found to have multifocal (or multicentric) tubular carcinomas. When the tumor has areas with different proportions of both invasive lobular and tubular carcinoma, it is referred to as tubulolobular carcinoma. Multifocality is more frequent in tubulo-lobular carcinoma than in pure tubular carcinoma.

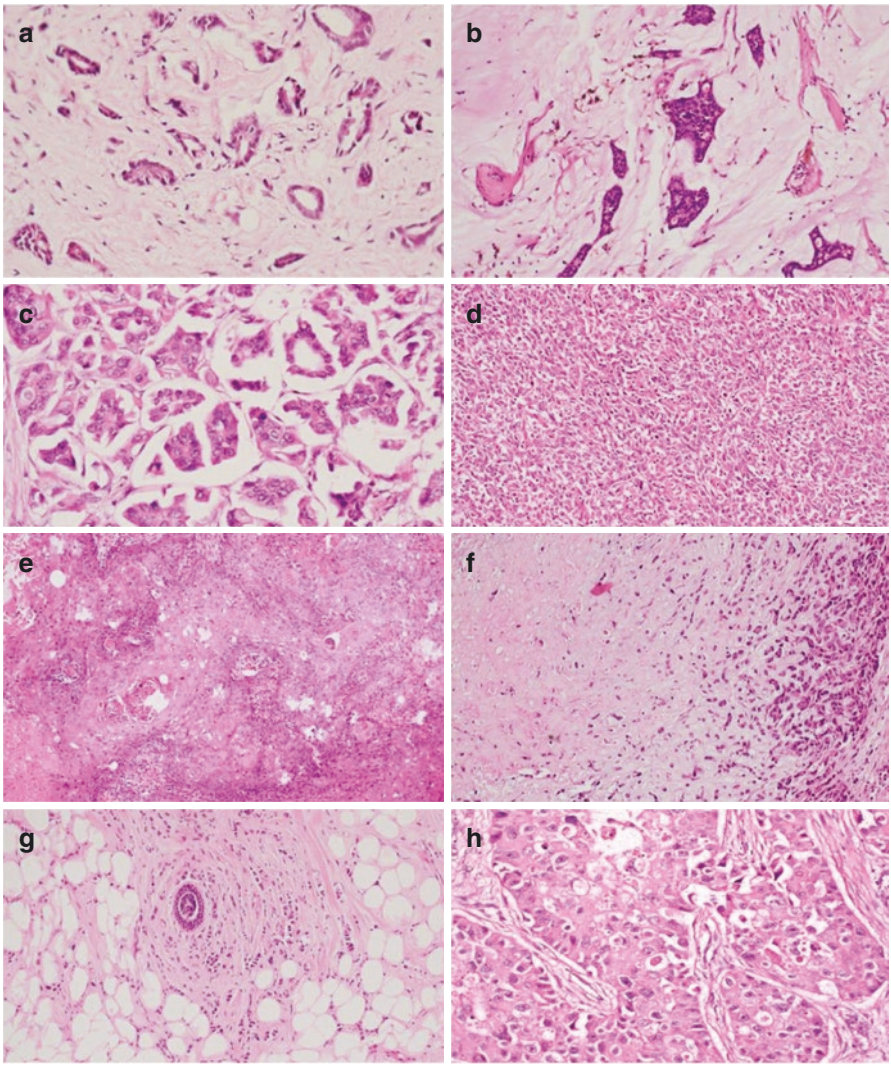


Fig. 8.2 Photomicrographs showing different histological variants of infiltrating breast carcinoma. (**a**) Tubular carcinoma, (**b**) Mucinous carcinoma, (**c**) Micropapillary carcinoma, (**d**) Metaplastic carcinoma-spindle cell type, (**e**) Metaplastic squamous cell carcinoma, (**f**) Metaplastic matrix producing carcinoma, (**g**) invasive lobular carcinoma, Apocrine carcinoma, (**h**) Apocrine carcinoma invasive lobular carcinoma

• Mucinous Carcinoma

This tumor is also more common in elderly post-menopausal women. Mucinous (colloid) carcinoma is a rare histologic type for which mucin production is the histologic hallmark (Fig. 8.2b). Type A mucinous carcinoma is the classic hypocellular variant with large quantities of extracellular mucin whereas type B mucinous

carcinoma is hypercellular consisting of large epithelial clusters with neuroendocrine differentiation. For diagnosing pure mucinous carcinoma, the mucinous component should be >90%. This tumour is also known as; gelatinous carcinoma, colloid carcinoma, mucous carcinoma, and mucoid carcinoma.

• Cribriform Carcinoma
Is a rare type of breast carcinoma associated with favorable prognosis. It is characterized by islands of tumor cells with low-grade atypia that have a cribriform appearance similar to that seen in cribriform DCIS. However, there is evidence of stromal invasion.

• Papillary Carcinoma
Encompasses a spectrum of histologic subtypes; however, most papillary carcinomas of the breast are predominantly intra-ductal lesions. There are two common types: non-invasive form and invasive form.

(A) *Non-invasive papillary carcinomas:* are centrally located and present as bloody nipple discharge. The malignant intraductal papillary lesions include three entities; intraductal papillary carcinoma, encapsulated papillary carcinoma, and solid papillary carcinoma. These are characterized by papillae formed by malignant cells having mild nuclear atypia with delicate fibrovascular core devoid of myoepithelial cells. The encapsulated papillary carcinoma consists of a tumor with fibrovascular cores within a cystic lesion having a thick fibrous capsule. Solid papillary carcinoma has a solid expansile growth pattern with very thin fibrovascular cores and often show neuroendocrine features and extracellular mucin production without any floating malignant cells. Non-invasive papillary carcinomas have an indolent course and a good prognosis. Invasive papillary carcinomas are rare and should be diagnosed when more than 90% of the invasive component is papillary. They bear a better prognosis than IDC-NST.
(B) *Invasive micropapillary carcinomas:* are characterized by the growth of small clusters of tumor cells arranged in micropapillary structures floating in the clear empty spaces resembling lymphovascular spaces (Fig. 8.2c). The tumor cells display a characteristic reverse polarity (apical surface is towards outer side rather than the inner lumen ductal space). Invasive micropapillary carcinoma has high incidence of lymph node metastasis seen in around 70% of cases.

• Metaplastic Carcinoma
Invasive breast carcinomas with differentiation of neoplastic cells into squamous and/or mesenchymal elements. Accounts for less than 1% of breast cancer cases and encompasses the histologic variants characterized by the dominant component of metaplastic differentiation. These include;

- Spindle-cell carcinoma (Fig. 8.2d)

- Squamous cell carcinoma (Fig. 8.2e)
- Matrix-producing carcinoma (Fig. 8.2f)

Metaplastic carcinomas are typically ER negative, PR negative, and *HER2* negative tumors.

• Inflammatory Breast Carcinoma
Inflammatory breast carcinoma (IBC) is a highly aggressive locally advanced breast cancer characterized by diffuse erythema and edema (peau d' orange) involving skin of the breast. The characteristic histologic finding is the presence of tumor restricted only to dermal lymphatics in the form tumor emboli which is responsible for its gross appearance.

• Rare morphological variants
- *Apocrine carcinoma* with large tumor cells having abundant acidophilic, granular cytoplasm, positive for Periodic Acid Schiff staining (PAS) (Fig. 8.2g). These tumors express androgen receptor.
- *Neuroendocrine carcinomas* exhibit morphological and immunohistochemical features similar to those of neuroendocrine tumors of other sites. These tumors have solid aggregates of tumor cells arranged in organoid, nests, trabecular, and rosette patterns. The tumor cells express neuroendocrine markers like chromogranin and synaptophysin, which are mandatory for the final diagnosis of neuroendocrine tumor.
- *Secretory carcinoma and Adenoid cystic carcinoma :* Both are rare tumors in the breast, which are identical to their salivary gland counterparts. Despite being triple negative, both tumors are indolent with excellent prognosis and fall under the new category of low grade triple negative breast cancers, a biologically distinct invasive carcinoma of the breast.

8.3.2 Invasive Lobular Carcinoma

The classical invasive lobular carcinoma is composed of discohesive cells that are arranged in the "Indian file" arrangement in the fibrous connective tissue (Fig. 8.2h). The tumor cells are small, uniform in appearance, have eccentric nuclei and cytoplasmic vacuoles. The surrounding TDLUs show tumor cells in a concentric (targetoid) pattern. The pleomorphic/histiocytoid variant of lobular carcinoma is characterized by large cells having hyperchromatic nuclei with prominent nucleoli and relatively abundant, eosinophilic cytoplasm. Invasive lobular carcinomas lack expression of E-Cadherin on immunohistochemistry due to mutations in cadherin (CDH1) gene.

8.3.2.1 Histo-morphological Prognostic Factors in Breast Cancer
(Elston/Nottingham modification of Bloom-Richardson system)

This classification has been recommended by the National Comprehensive Cancer Network (NCCN) in grading of invasive breast carcinoma. This is based on the separate scores given for tubule formation, nuclear pleomorphism, and mitotic counts.

The tubule formation:

- Score 1: >75% tubule formation
- Score 2: 10–75% tubule formation
- Score 3: <10% tubule formation

Nuclear pleomorphism:

- Score 1: Nuclei only slightly larger than benign breast epithelium (<1.5 times the normal)
- Score 2: Nuclei distinctly enlarged than benign breast epithelium (1.5–2 times the normal)
- Score 3: Markedly enlarged vesicular nuclei than benign breast epithelium (>2 times the normal)

Mitotic counts: Counting cells in hotspots with definite mitosis in 10 consecutive fields. Mitotic count varies with the microscope used.

The Final grading is based on the above scoring and the total score ranges between 3 and 9 (Fig. 8.3).

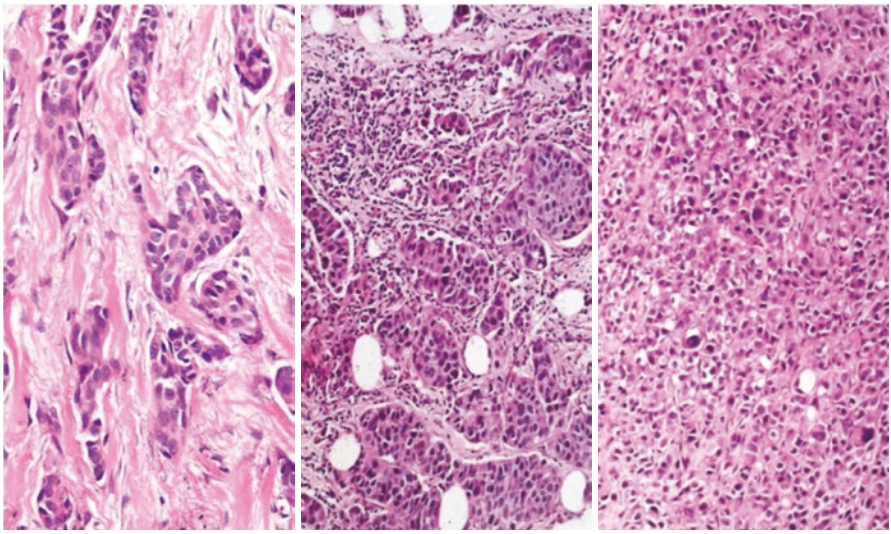


Fig. 8.3 Photomicrographs of different histological grades of infiltrating breast carcinoma as classified by Elston/Nottingham modification of Bloom-Richardson system

- Grade I: score 3, 4 or 5
- Grade II: score 6 or 7
- Grade III: score 8 or 9

• Lymph Node Metastasis
Axillary lymph node (LN) metastasis is one of the most important prognostic determinants in breast carcinoma. Based on the number of positive LNs, patients are divided into three N stages: N1 (1–3 positive LNs), N2 (4–9 positive LNs), and N3 (>9 positive LNs). The metastatic tumor deposits are categorized as isolated tumor cells (<0.2 mm or <200 tumor cells), micrometastasis (>0.2 mm and/or >200 tumor cells and <2 mm) and macrometastases (>2 mm tumor deposit).The positive LN ratio, defined as the ratio of the LNs with metastatic deposits to the total number of LNs examined or the percentage of positive axillary LN is a strong predictor of breast cancer survival. Extranodal spread is also a predictor of poorer outcome.

• Others
The other histological features which have a bearing on the outcome are involvement of skin, nipple and areola, presence or absence and the extent of DCIS or atypical hyperplasia in the breast, deep margins, stroma type, extra tumoral lymphovascular emboli, and peri-neural invasion. It is important that all these histologic features find a mention in the pathology report. The guidelines issued by the College of American pathologists can form a basis of formulating the complete pathology report.

8.3.3 Recent (Molecular) Prognostic and Predictive Factors

8.3.3.1 Oestrogen and Progesterone Receptors
Hormone receptor status is determined by the expression of nuclear receptors for oestrogen (ER) and progesterone (PR) in the tumor cells using immune histochemistry (Fig. 8.4). For assessment of ER/PR immune staining, the Allred scoring system is used. A proportion score (PS) is assigned representing the proportion of tumor cells with positive nuclear staining. An intensity score (IS) is assigned representing the average staining intensity of all positive tumor cells. A total score(TS) is calculated as the sum of PS plus IS (ranging from 0 to 8). Both ER and PR are considered positive if TS $\geq$ 3.

8.3.3.2 Human Epidermal Growth Factor Receptor 2 (HER2/neu)
Her2/neu immune staining is graded as per ASCO–CAP HER2 Test Guideline Recommendations 2018 (Fig. 8.4). These are:

- *Negative (IHC 0 or 1+):* no staining observed or membranous staining that is incomplete, faint/barely perceptible in >10% tumor cells

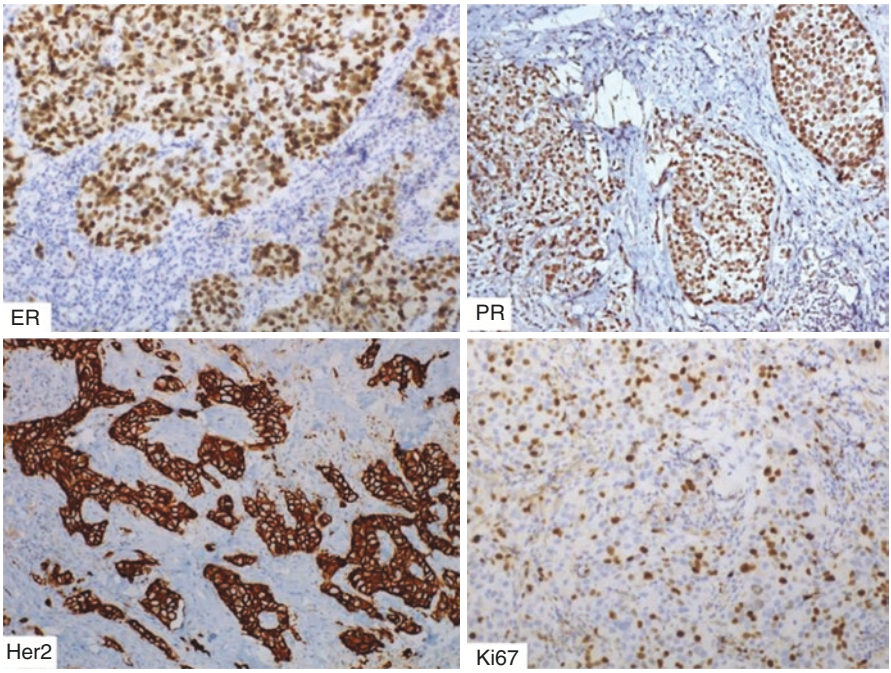


Fig. 8.4 Photomicrographs showing different predictive markers used for guiding therapy in breast cancer (estrogen receptor: ER, Progesterone receptor: PR, Her-2 neu, and Ki67)

- *Equivocal (IHC 2+):* weak to moderate complete membrane membranous staining observed in >10% of tumor cells
- *Positive (IHC 3+):* circumferential intense complete membranous staining in >10% tumor cells

• Her-2 Neu FISH

In equivocal cases Her-2 neu FISH using probes directed at the HER2 gene and the chromosome 17 centromeric probes is done and reported as a ratio(HER2:CEP17 ratio). A ratio of 2.0 or greater more regardless of HER2 copy number, or a ratio of less than 2.0 with 6.0 or more HER2 signals copy numbers per cell, indicates amplification. A ratio less than 2.0 with average HER2 copy number of fewer than 4.0 signals per cell indicates no HER2 amplification.

• Ki67 Index

The Ki-67 antigen is expressed in the nuclei of cells that are not in G0 phase of the cell cycle, and therefore reflects cell proliferation. Ki-67 can be assessed by immunohistochemistry and nuclear positivity is interpreted as positive. The current cut off for low and high Ki67 proliferation index is <14% and >14% respectively (Fig. 8.4).

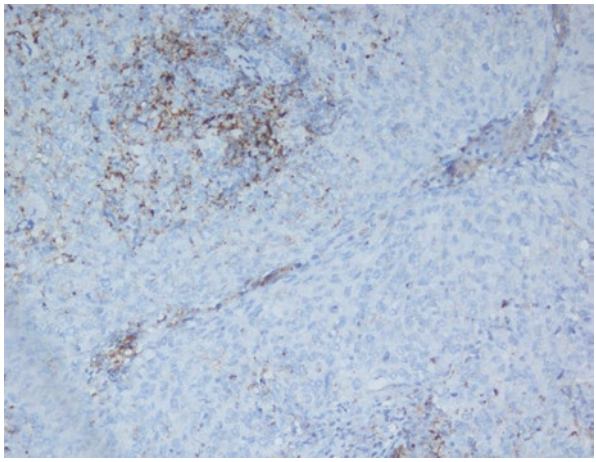


Fig. 8.5 Photomicrograph of PD-L1 immunostaining showing >1% immune cell score

PD-L1 Testing

Immune checkpoint inhibitor atezolizumab, in combination with nab-paclitaxel, has now been approved for locally advanced and metastatic triple negative breast cancer. The companion diagnostic test for patient selection is the Ventana PD-L1 (SP142) assay developed by Roche. This is a qualitative immunohistochemical assay utilizing an anti-PD-L1 clone SP142 rabbit monoclonal primary antibody to recognize the PD-L1 protein in the tumor infiltrating lymphocytes (TILs). The cut off used is PD-L1–stained TILs of any intensity covering ≥1% of the tumor area (Fig. 8.5).

8.3.4 Molecular Classification of Breast Cancer

Invasive breast cancer is heterogeneous and gene expression profiling and a panel of marker of estrogen receptor (ER), progesterone receptor (PR), Her2, CK5/6, CK14 and CK 8/18 has categorized invasive breast carcinomas into four surrogate molecular subtypes: luminal A, luminal B, HER2 positive, and Triple negative.

Luminal A: This is the most common subtype and the cells are phenotypically similar to the inner (luminal) cells lining the mammary ducts and express CK8/18. Luminal A tumors are positive for oestrogen receptor (ER+) and/or progesterone receptor (PR+) and negative for HER2/neu (HER2−). Of all the subtypes, luminal A tumors tend to have the best prognosis, with fairly high survival rates and fairly low recurrence rates.

Luminal B: Luminal B tumors are classified in two different ways: oestrogen receptor positive (ER+) and/or progesterone receptor-positive (PR+), Her-2 negative and Ki67 >14% or oestrogen receptor positive (ER+) and/or progesterone receptor-positive (PR+), Her-2 positive and any Ki67 index. These tumors also express luminal cytokeratin 8/18. Compared to luminal A tumors, they have high tumor grade, larger tumor size, frequent p53 gene mutations and poorer prognosis.

HER2+ subtype:

Express Her2 on immunohistochemistry and have high levels of genes located in the HER2 amplicon (17q11), including HER2, GRB7, GATA4 and high-levels of NF-kB activation. HER2 tumors have additional features, such as high levels of p53 mutation, aggressive clinical behavior, poor prognosis and do not respond to hormonal therapy.

Triple negative:

Triple negative breast cancers are negative for oestrogen receptor (ER−), progesterone receptor (PR−) and HER2/neu (HER2−). Triple negative phenotype is associated with larger tumor size, grade III histology and high mitotic index.

8.3.5 Multigene Prognostic Biomarkers

Many algorithms have been generated for breast cancer that estimate the rate of cancer recurrence and/or survival. These genetic signatures are obtained by computer-based models, validated in clinical studies and are then translated to commercial prognostic assays. A few of these used in clinical practice includes;

1. ***Oncotype Dx:*** It is a clinically validated assay that is used to predict likelihood of recurrence of early stage breast cancer, and therefore used in decision making with respect to systemic therapy. The Oncotype DX assigns a score to the expression of 16 cancer-related genes relative to the mean expression of five reference genes to generate an overall recurrence score. The Oncotype DX assay is optimized for formalin-fixed paraffin-embedded tumour samples. The Oncotype DX DCIS assay is also now available that is developed by modifying the 21-gene assay by eliminating analysis of genes related to proliferation.
2. ***PAM50:*** PAM50 provides information on intrinsic subtypes and risk of recurrence (ROR) score generated from the expression of the 50 genes (Prosigna by NanoString Technologies). It has been recommended for decisions on adjuvant systemic treatment for node negative, hormone receptor-positive and Her-2 neu2-negative breast cancer.
3. ***EndoPredict:*** EndoPredict combines prognostic information from an 8-gene analysis (EP score) with tumor size and the patient's nodal status. It is developed to guide treatment decisions about adding chemotherapy in addition to antihormone treatment.
4. ***Foundation One CDx:*** The first FDA-approved broad companion diagnostic (CDx) that is clinically and analytically validated for solid tumours. The test is based on the individual genomic profile of each patient's cancer, this test is designed to provide physicians with clinically actionable information e.g. deciding to consider appropriate therapies for patients and understanding results with the evidence mechanisms of resistance based on the individual genomic profile of each patient's cancer. Every The test result includes information on microsatellite instability (MSI) and tumour mutational burden (TMB) to help inform immunotherapy decisions. Tumour mutation burden (TMB) is defined as the

total number of somatic mutations present in the tumor exome. Cancer patients with higher TMB have been shown to have a higher expression of neoantigens. These neoantigens could potentially be recognized by the host immunity as foreign and thereby help in providing immunity against tumor cells. TMB is assessed using whole exome sequencing (WES), or various targeted sequencing panels (that includes all possible cancer related genes). TMB can be evaluated in tumor tissue or blood samples, with the latter being referred to as liquid biopsy.

References

1. WHO Classification of Tumors Editorial Board. Breast tumors, WHO classification of tumors series, vol. 2. 5th ed. Lyon, France: International Agency for Research on Cancer; 2019.
2. Weigelt B, Reis-Filho J. Histological and molecular types of breast cancer: is there a unifying taxonomy? Nat Rev Clin Oncol. 2009;6:718–30.
3. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med. 2018;142(11):1364–82.
4. Vieira AF, Schmitt F. An update on breast cancer multigene prognostic tests-emergent clinical biomarkers. Front Med. 5:248. https://doi.org/10.3389/fmed.2018.00248.

Imaging in Breast Cancer

9

Ekta Dhamija and Niranjan Khandelwal

9.1 Introduction

Breast cancer is the most common cancer in female population worldwide and consensus shows increasing trend in future which is concerning [1]. Diagnosis of breast cancer encompasses clinical palpation, imaging evaluation and histopathological confirmation. Imaging plays significant role in work up of breast cancer patients. It envisages diagnostic evaluation of patient, image guided biopsy of the lesions, surveillance follow up after treatment and tumor localization at the time of biopsy or surgery. The basic imaging modalities include Mammography, ultrasound (USG) and Magnetic Resonance Imaging (MRI). Mammography is the one of the important diagnostic tools which is proven to reduce mortality due to breast cancer by early detection with sensitivity ranging from 83 to 95% [2]. However, its sensitivity and accuracy decreases to 30–48% in dense breasts [3]. Ultrasound and MRI are the modalities used to evaluate such breasts with dense glandular parenchyma and also as screening modalities in younger patients. Many studies have shown increased cancer detection rate with USG as the screening modality especially in younger patients with dense breasts and also when it is used in adjunct to mammography [4, 5]. In a Japanese randomized trial, addition of ultrasound had better sensitivity of cancer detection, that is, 91.1% as compared to 77% with mammography alone; however with reduced specificity (87.7% vs 91.4%) [6]. MRI is superior in detection of additional occult cancer foci and larger index cancers (18% vs 7.2%) as compared to mammogram [7, 8]. However, MRI is expensive technique, needs

Ekta Dhamija, MD (✉)
Associate Professor, Department of Radiodiagnosis, IRCH, AIIMS, New Delhi, India
e-mail: drektadhamija.aiims@gmail.com

Niranjan Khandelwal, MD
Former Professor and Head, Department of Radiodiagnosis, PGIMER, Chandigarh, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_9

contrast injection and is time consuming. Since each modality has its own advantages and disadvantages; there has to comprehensive evaluation using multiple modalities with case base approach.

The last few decades have witnessed immense progress and development in the field of breast imaging which includes evolution of full field digital mammography from screen-film mammograms, advent of computer aided detection, digital breast tomosynthesis and contrast enhanced mammography; addition of elastography to B-mode USG and Diffusion weighted & dynamic contrast enhanced sequences using dedicated breast coils in MRI.

9.2 Imaging Techniques

9.2.1 Mammography

Mammography is considered as the optimal imaging modality in screening for breast cancer. However, its role is limited in cases of dense and glandular breasts [3, 9, 10]. An effective mammogram requires high quality images with optimal contrast resolution at low radiation dose. Hence, the mammography equipment and techniques are different from standard radiographs of other anatomical parts. Conventional screen-film mammogram (SFM) was considered as the standard for breast imaging during screening, diagnosing and follow up. However, it had limitations like inability to perform any post processing, variations while developing the films in dark room and limited dynamic range [11]. Full-field digital mammography (FFDM), though expensive than SFM, has overcome these limitations and has largely replaced the latter. It does not require any dark room film development and images can be viewed directly on the high-resolution consoles which improves efficiency and accuracy also as it enables post processing of the images.

The basic evaluation is performed by obtaining standard two views of breast-craniocaudal (CC) and a mediolateral-oblique (MLO) view. The former view is obtained with vertical X-ray beam while the latter is taken with a 45° tube angulation with horizontal. The breast is pulled and compressed with compression paddle so as to include maximum possible parenchyma in the view. Table 9.1 describes the

Table 9.1 Criteria for well-positioned mediolateral oblique and craniocaudal views

For MLO view
• Nipple should be seen in profile
• Pectoralis muscle should extend inferior to the posterior nipple line, which is an imaginary line drawn from the nipple to pectoralis muscle or film edge and perpendicular to the pectoralis muscle
• An open inframammary fold should be visible
• There should be no skin folds superimposed on the breast
For CC view
• Nipple should be in profile
• The posterior nipple line is drawn from the nipple to the pectorlalis muscle or film edge and the length of this line should be within 1cms of the line on MLO projection

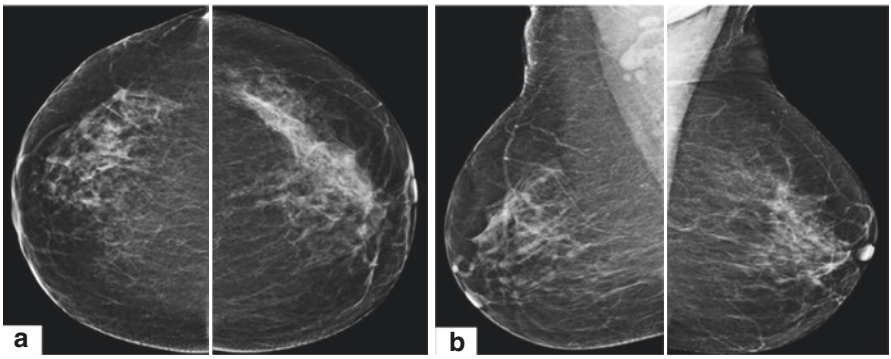


Fig. 9.1 Interpretation of mammogram: The mammograms should be read in optimally lighted room with Craniocaudal (**a**) and Mediolateral oblique (**b**) views of both breasts placed side to side for comparability of tissues

criteria defining well positioned MLO and CC views. Supplementary views are taken in special cases as problem solving tools.

Interpretation of mammogram is done with MLO and CC views of both breasts placed side by side so that symmetry of the breast tissue can be studied. For example, right and left MLO projections should be viewed together and similarly CC projections should be viewed together (Fig. 9.1). The mammograms should be systemically approached with description of the breast density followed by the normal or abnormal findings and then, secondary changes in skin, subcutaneous tissue and nipple-areola complex followed by axillary nodal status.

The abnormal findings on mammogram are categorized into mass, calcification, architectural distortion or asymmetry. A breast mass is defined as three-dimensional space occupying lesion seen on both views which is assessed for its size, shape, margin and density. Benign lesion like intramammary lymph node is seen as round to oval, circumscribed, iso to hyperdense lesion with fatty hilum or lucent center-and is categorized as BI-RADS category 2 while classic malignant mass (BI-RADS 4c or 5) will be denser, irregular, spiculated with or without pleomorphic calcification, architectural distortion, skin and nipple retraction (Fig. 9.2).

Calcifications are evaluated for number, distribution and morphology. Benign calcifications typically are coarse, larger than 0.5 mm and/or have lucent center. These include involuted or involuting fibroadenomas, dermal, dystrophic and vascular calcifications. Calcifications with high probability of malignancy, on the other hand, are irregular, smaller than 0.5 mm and are pleomorphic-variable in size, shape and density.

Architectural distortion refers to focal trabecular distortion and focal speculation & retraction of the parenchyma whereas asymmetry is a soft tissue finding identified on one view with no matching tissue at similar location in contralateral breast parenchyma.

At the end, depending on the descriptors, BI-RADS (Breast Imaging Reporting and Data System) category should be assigned [12] (Table 9.2).

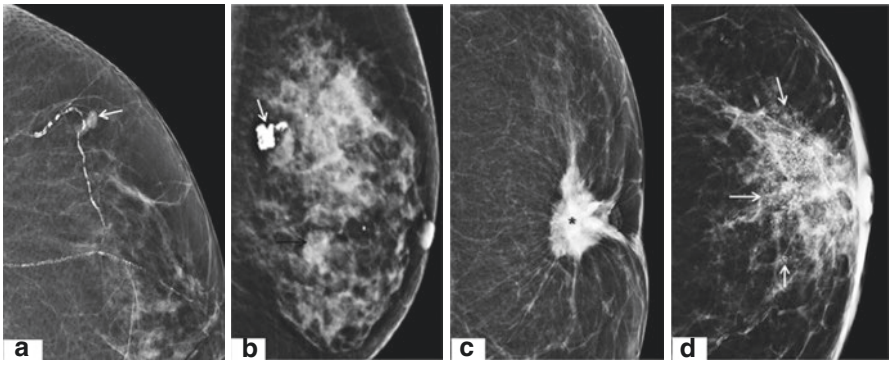


Fig. 9.2 Imaging features on mammograms: Benign lesions are seen as oval to round (arrows in **a** & **b**), circumscribed, low to equal density (white arrow in a, black arrow in **b**) lesions with lucent center (**a**) or with coarse popcorn calcification (white arrow in **b**) within. (**c**) Spiculated high density mass with overlying skin thickening and retraction of nipple is categorized as highly suspicious for malignancy. Tram track vascular calcification (**a**) and popcorn calcification (white arrow in **b**) are classic benign calcifications whereas (**d**) scattered pleomorphic calcifications with architectural distortion, skin thickening suggest underlying malignancy

Table 9.2 ACR BI-RADS mammographic assessment categories

Category	Description	Likelihood of malignancy	Next step in evaluation
0	Incomplete; need additional imaging evaluation or comparison with previous imaging	Unknown	Additional mammographic views; evaluation with USG or MRI; comparison with previous imaging
1	Negative	Essentially 0% likelihood of malignancy	Routine screening
2	Benign finding	Essentially 0% likelihood of malignancy	Routine screening
3	Probably benign finding	>0% but ≤2%	Short interval (6 month) follow up
4	Suspicious abnormality 4a: Low suspicion for malignancy 4b: Moderate suspicion for malignancy 4c: High suspicion for malignancy	>2% but ≤95% >2% but ≤10% >10% but ≤50% >50% but <95%	Biopsy
5	Highly suggestive of malignancy	≥ 95%	Biopsy
6	Known malignancy	N/a	Definitive treatment

9.2.1.1 Computer Aided Detection

Computer-aided detection (CAD) is a software system that is designed to highlight areas of concern like masses and calcification and thus serve as a second reader. It thus reduces the chances of overlooking these abnormalities because the radiologist then evaluates the sites more carefully. It has been shown that it increases the cancer detection rate but is associated with high false positive rates [13, 14].

9.2.1.2 Digital Breast Tomosynthesis and Synthesized View

Dense glandular parenchyma is a known limitation of mammography. It may hide the mass or may simulate a mass on mammogram giving both false negative or false positive information respectively. The technique of Digital breast tomosynthesis (DBT) has gained wide acceptance as it provides consecutive sectional images, of breast which helps to distinguish between the normal glandular breast tissue from a true lesion. (Fig. 9.3) Hence, DBT has become an integral part of FFDM for interpreting mammograms [15–20]. However, addition of DBT to FFDM increases radiation to breast. With this view, recently, there have been further advent of obtaining a 2D image or synthesized view from these tomo images which has been claimed to be as good as the standard FFDM image [21–25]. Multiple studies are going on in this respect as this will have major implications in term of reduction of radiation dose.

9.2.1.3 Contrast Enhanced Mammography

Combining high resolution mammography with functional information obtained with contrast enhancement will offer another potential application for mammography especially to study and assess neovascularity in the breast masses or malignancies.

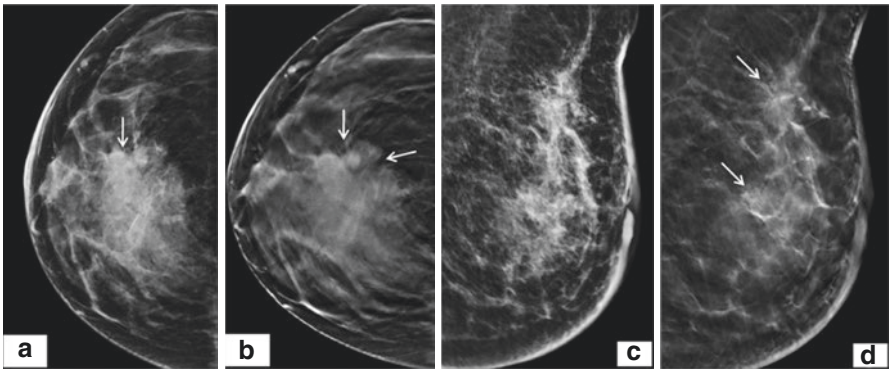


Fig. 9.3 Digital Breast tomosynthesis: (**a**) Craniocaudal view of right breast show presence of an irregular mass of equal density (arrow) with indistinct margins; (**b**) Tomosythesis slice of same could highlight spiculated margins of the mass (arrows). (**c**) MLO view of left breast in a different patient shows diffuse architectural distortion with skin and trabecular thickening; however, tomosynthesis (**d**) revealed two equal density masses in upper and central quadrant with spiculated margins (arrows) suggesting multifocal/ multicentric disease

Many authors have highlighted its potential role as an adjunct modality with high cancer detection rate as compared to conventional mammography, tomosynthesis and ultrasound [26] with comparable accuracy when compared to MRI [27].

9.2.2 Ultrasound

Ultrasound (USG) is the most commonly used modality in assessment of breast diseases- either as an adjunct or independently. It is cost effective, readily available, less time consuming (when compared to MRI) and has no risk of radiation exposure to patient or operator. Breast USG is performed using high frequency (5–15 MHz) linear array transducer with patient lying supine in radial and anti-radial planes followed by axillary evaluation.

The abnormality is detected and morphology is carefully assessed. The mass is evaluated in terms of its size, location, shape, orientation, margins, echogenicity and posterior acoustic features. Oil cysts and simple cysts are categorized into BI-RADS 2-seen as circumscribed hypo to anechoic lesions with posterior acoustic enhancement. A hypoechoic mass which is round to oval, wider than taller, circumscribed with no echogenic halo or posterior acoustic shadowing- is classified under probably benign BI-RADS category. Most commonly fibroadenomas, cluster of microcysts and complicated cysts fall into this category. Stability over one to two years reassigns the lesion into category 2; however during follow up, any change in the lesion upgrades the BI-RADS to 4 and mandates biopsy. On the other hand, malignant mass of category 4c or 5 will be seen as a hypoechoic mass with antiparallel orientation, irregular shape, not circumscribed margins (angular, microlobulated or spiculated) showing posterior acoustic shadowing and thick echogenic halo (Fig. 9.4).

Role of USG is not only limited to differentiate solid and cystic lesions but also to characterize solid lesions. It is the imaging modality of choice in young females, below 30 years of age, who have predominantly glandular parenchyma which limits evaluation with mammography. USG assessment also enables evaluation of patient for image guided biopsy in same setting.

9.2.2.1 Elastography

Ultrasound elastography evaluates tissue stiffness based on explanation that the malignancies tend to be harder due to schirrhous nature while the normal breast and benign lesions tend to be softer [28]. The technique has evolved from assessing the tissue elasticity by applying manual pressure which faced significant interobserver variability to shear wave elastography (SWE) where an acoustic radiation force impulse (ARFI) is induced in the tissues and the wave propagation is captured by the USG probe [29, 30]. It provides qualitative as well as quantitative elasticity parameters of the abnormality with respect to normal breast tissue and these can be compared. (Fig. 9.5) Studies have shown that malignant lesions have significantly higher elasticity values than the benign lesions [31–33]. Hence, SWE is considered as an adjunct technique in evaluation of breast masses especially in BI-RADS 3 & 4 category masses.

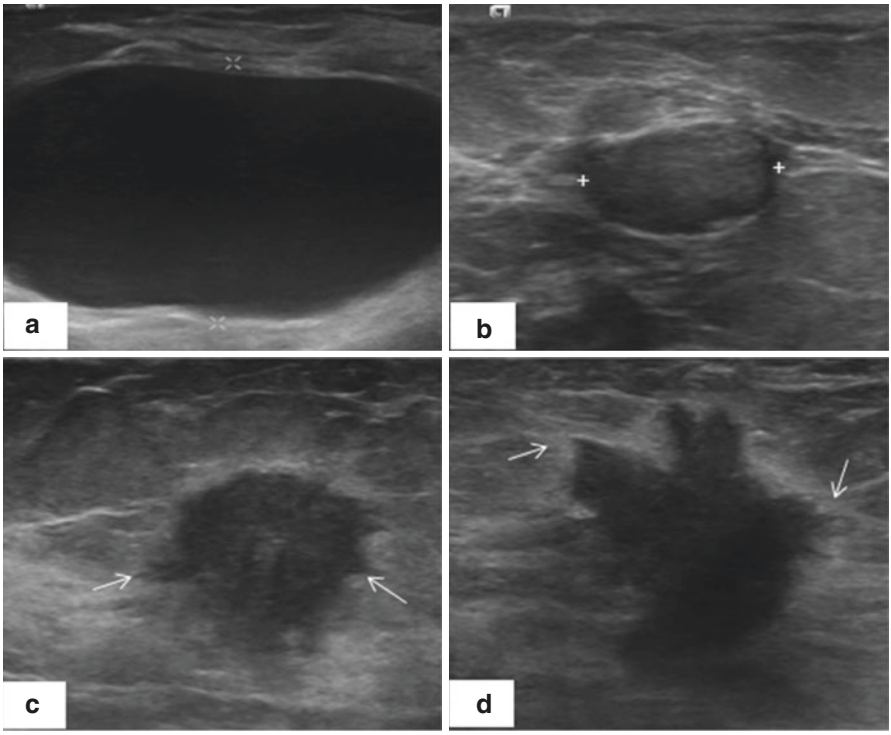


Fig. 9.4 Imaging features on ultrasound: Benign BI-RADS 2 lesions seen as simple anechoic cyst (**a**) and (**b**) circumscribed, oval, wider than taller lesion, stable over 2 years (sequential imaging not shown) with posterior enhancement. (**c**, **d**) Hypoechoic lesions which are taller than wider, have angular or spiculated margins (arrows in **c**), thick echogenic rim (arrows in **d**) and posterior shadowing are highly suspicious for malignancy and are assigned BI-RADS 4c/5

9.2.2.2 Contrast Enhanced Ultrasound

During last few years, contrast enhanced ultrasound (CEUS) has gained popularity especially in liver diseases to characterize various hepatic lesions [34]. Its role has also been evaluated in demonstrating the patterns of vascularity in benign and malignant breast lesions. Several studies have proven the potential of CEUS in differentiating malignant from benign lesions in breast with varying sensitivity (67–95%) and specifity (58–62%) but its role needs to be validated further for clinical application and utility [35].

9.2.3 MRI

MRI has sensitivity of more than 90% in detection of breast carcinomas [36]. Owing to its better soft tissue resolution and demonstration of enhancement kinetics post contrast administration, it offers promising role in evaluation of patients with breast implants and post lumpectomy recurrences. Contrast enhanced MRI is based on

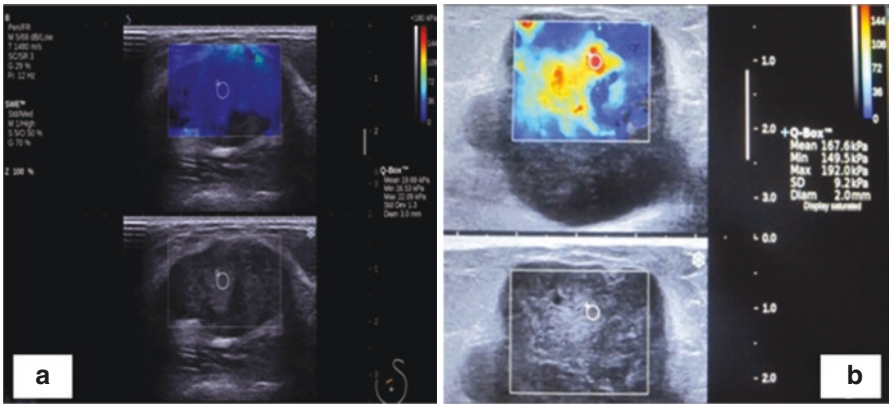


Fig. 9.5 Ultrasound Elastography: (**a**) B-mode ultrasound showing round hypoechoic lesion with circumscribed lobulated margins. The lesion shows low elasticity values (homogeneous blue color with Emean 21.6 kPa) on shear wave elastography suggesting benignity; in contrast to (**b**) high elasticity values (heterogeneous color coding with red color on qualitative assessment and quantitative value of Emean 167.6 kPa) in another mass raising index of suspicion for malignancy

depiction of neoangiogenesis within the malignant lesions: these new vessels have increase capillary permeability causing leakage of contrast which is seen as enhancement on the post contrast sequences. (Fig. 9.6).

Breast MRI is performed using dedicated breast coils at 1.5T or higher strength MR field. Patient lies down prone with breasts placed in the cups provided within the coil. Adequate cushioning is applied to avoid motion artifact as the examination might take more than 30 min. Precontrast T1, T2 and diffusion weighted sequences are obtained in axial planes followed by dynamic contrast enhanced fat suppressed T1 weighted sequences which are acquired sequentially at every 1 min for 5–7 min.

Like mammography, bilateral breasts are studied together while interpretation for proper comparison, in MRI. Description includes background enhancement of glandular tissue, morphological features and enhancement pattern of any mass or focus and characteristics of nonmass like enhancement (NME), if any. Like mammogram, on MRI, mass is seen on all the pre and post contrast sequences. It has to be evaluated morphologically (shape, margin and enhancement) and functionally in terms of kinetics of contrast enhancement. Benign cysts are seen as well-defined lesions with hyper intense signal on T2 WI with no abnormal enhancement. Rim enhancement can be seen in complicated cysts. Fibroadenomas may show homogeneous or heterogeneous enhancement with well-defined margins. Spiculated margins are frequently seen in malignancies and radial scars. Ductal carcinomas show varied imaging features- may show rim or central enhancing areas or present as NME lesions.

MRI is radiation free and is highly sensitive in detecting recurrences post radiation therapy and post-surgery. It is performed to detect implant rupture and pick up lesions in breast parenchyma in these patients. MRI has served as useful tool in

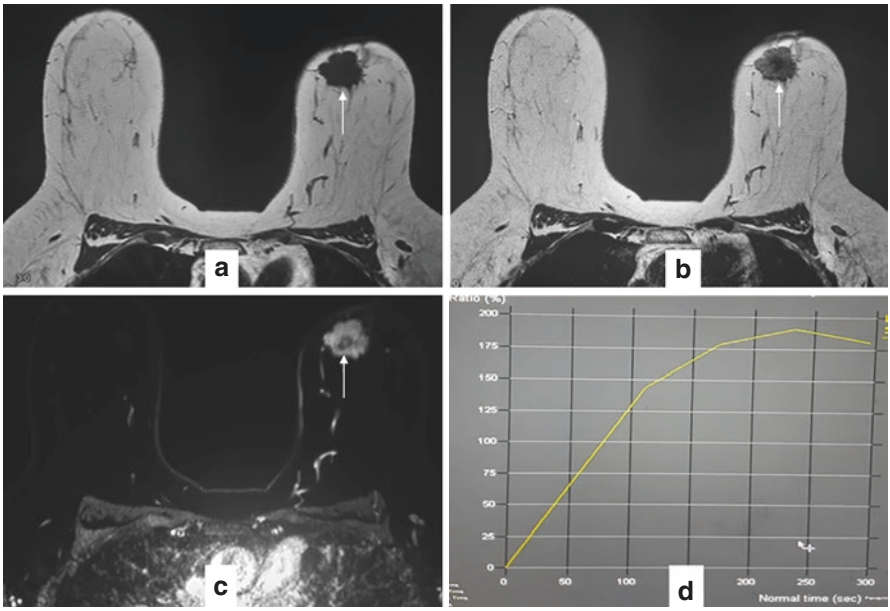


Fig. 9.6 Imaging features of carcinoma on MRI: Spiculated hypointense mass on T1 and T2 weighted images (arrows in **a**, **b**) showing intense enhancement (arrow in **c**) and type III kinetic curve (**d**) raise high suspicion for malignancy

screening high risk patients and patients with dense breasts. However, it is limited by its low specificity as it relies on tissue enhancement which can be seen in many other non-malignant lesions like lymph nodes, papilloma, radial scars resulting in false positive examinations leading to unnecessary biopsies. In addition, MR is costly, time consuming and is unable to image calcifications. Hence, it is used in selected situations (Table 9.3).

9.2.4 Positron Emission Tomography

^{18}FDG PET has emerged as another imaging modality in evaluation of breast cancer patients especially in locally advanced breast cancers. PET incorporated with CT at the same setting has increased sensitivity in detecting distant unsuspected metastases. Garg et al. showed that when compared to conventional imaging for tumor staging, PET/CT upgraded the staging and influenced management in approx. 18% of patients [37]. They emphasized the role of PET/CT in evaluation in patients with locally advanced breast cancer as it helps in accurate staging, appropriate decision making and prognosticating the patients [37]. The modality has been studied and found suitable for staging, monitoring response after neoadjuvant chemotherapy and for loco-regional recurrence [38, 39].

Table 9.3 Indications for dynamic contrast enhanced MRI

Screening • Women at high risk of breast cancer (e.g., BRCA mutation) • Post breast implants
Diagnosis • Indeterminate palpable finding with negative mammogram and ultrasound • Suspicious lesion on mammography which could not be seen on USG • Bloody nipple discharge • Occult primary in metastatic axillary lymph nodes
Staging • Preoperative evaluation before conservative surgery • To detect multifocal or multicentric cancer • To detect recurrence/ residual disease post lumpectomy • To evaluate chest wall invasion • In patients with limited mammographic evaluation like dense breasts, DCIS without microcalcification, invasive lobular cancer
Post treatment study • Early response assessment to neoadjuvant chemotherapy • Residual disease after completion of chemotherapy • To differentiate recurrence from post operative scar

9.3 Image Guided Interventions

Breast interventions majorly encompasses biopsy from suspicious site under USG, stereotactic or MRI guidance as it enables accurate tissue sampling and reduces need of multiple repeat biopsies as compared to blind biopsies. Increase in incidence of breast cancer and its association with genetic mutation predisposing younger age group to higher risk of cancer mandates stringent follow up by screening and surveillance programs. This has led to early pick up of non-palpable suspicious lesions which need guided biopsy or excision after hook wire localization. Institution of neo-adjuvant chemotherapy (NACT) in the treatment regime of breast cancer has improvised the surgical outcome as it reduces the overall tumor burden making breast conservative surgery possible (BCS) [40]. However, many times there is complete clinical and radiological response to NACT and surgery is warranted to establish pathological complete response. In such settings, tumor marker placed pre-chemotherapy serves as the target for site for surgical removal. Thus, these localization techniques have therapeutic as well as diagnostic applications. Various image guided breast interventions have been discussed in detail in the dedicated intervention chapter.

9.4 Future Vision

Mammography has witnessed drastic changes and reformation in last few decades. Screen-film mammograms have largely been replaced by Full Field Digital Mammograms with or without tomosynthesis. Moreover, synthesized two-dimensional view (2D view) from tomosynthesis is being evaluated to replace

standard 2D views in population based screening programmes since it reduces the radiation dose to breasts. Contrast enhanced mammography is in early stage at present and its role though looks promising but still needs validation for incorporation in routine clinical practice. Similarly, USG has its established role in breast evaluation with incorporation of elastography for assessment of BI-RADS 3 and 4 lesions. Contrast enhanced ultrasound can be used in assessment of breast lesions but has not been a part of any guidelines so far. Both elastography and CEUS are being studied for their potential role in predicting responders and non-responders amongst patients on NACT. MRI, on other hand, has been the problem-solving tool in majority of situations owing to its cost and availability. Abbreviated MRI for intermediate risk population consists of shorter MRI breast protocol reducing the image acquisition and interpretation time, has shown comparative results and may become the standard screening modality for such patients in future [41].

To conclude, full field digital 2D mammography remains the standard screening and diagnostic modality for breast diseases with CAD, tomosynthesis and ultrasound as supplement modalities. In young patients, USG and MRI are preferred imaging tools than mammography as the latter has lower sensitivity in this population. MRI is used for screening of high risk patients like BRCA mutation positive patients. Not only in diagnostic setting but also in the setting of interventions, all imaging modalities have become an indispensable part of patient management.

References

1. Statistics of Breast Cancer in India: Trends in India [Internet]. [cited 2018 Mar 23]. Available from: http://www.breastcancerindia.net/statistics/trends.html.
2. Mushlin AI, Kouides RW, Shapiro DE. Estimating the accuracy of screening mammography: a meta-analysis. Am J Prev Med. 1998;14(2):143–53.
3. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007;356(3):227–36.
4. Devolli-Disha E, Manxhuka-Kërliu S, Ymeri H, Kutllovci A. Comparative accuracy of mammography and ultrasound in women with breast symptoms according to age and breast density. Bosn J Basic Med Sci. 2009;9(2):131–6.
5. Tan KP, Mohamad Azlan Z, Rumaisa MP, Siti Aisyah Murni MR, Radhika S, Nurismah MI, et al. The comparative accuracy of ultrasound and mammography in the detection of breast cancer. Med J Malaysia. 2014;69(2):79–85.
6. Ohuchi N, Suzuki A, Sobue T, Kawai M, Yamamoto S, Zheng Y-F, et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan strategic anti-cancer randomized trial (J-START): a randomised controlled trial. Lancet. 2016;387(10016):341–8.
7. Sardanelli F, Giuseppetti GM, Panizza P, Bazzocchi M, Fausto A, Simonetti G, et al. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in fatty and dense breasts using the whole-breast pathologic examination as a gold standard. Am J Roentgenol. 2004;183(4):1149–57.
8. Schnall Mitchell D, Jeffery B, Bluemke David A, DeAngelis Gia A, Nanette DB, Steven H, et al. MRI detection of distinct incidental cancer in women with primary breast cancer studied in IBMC 6883. J Surg Oncol. 2005;92(1):32–8.
9. Mandelson MT, Oestreicher N, Porter PL, White D, Finder CA, Taplin SH, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. J Natl Cancer Inst. 2000;92(13):1081–7.

10. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology. 2002;225(1):165–75.
11. The Role of Imaging Techniques in Diagnosis of Breast Cancer [Internet]. [cited 2018 Mar 3]. Available from: http://www.chsjournal.org/archive/vol37-no2-2011/reviews/the-role-of-imaging-techniques-in-diagnosis-of-breast-cancer.
12. D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA, et al. ACR BI-RADS® Atlas, breast imaging reporting and data system. Reston: American College of Radiology; 2013.
13. Birdwell RL. The preponderance of evidence supports computer-aided detection for screening mammography. Radiology. 2009;253(1):9–16.
14. Fm A. False positive value of computer-aided detection in full field digital mammography in diagnosis of breast malignancy. J Med Diagn Methods. 2015;4(4):1–5.
15. Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. Lancet Oncol. 2013;14(7):583–9.
16. Friedewald SM, Rafferty EA, Rose SL, Durand MA, Plecha DM, Greenberg JS, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. JAMA. 2014;311(24):2499–507.
17. Gennaro G, Toledano A, di Maggio C, Baldan E, Bezzon E, Grassa ML, et al. Digital breast tomosynthesis versus digital mammography: a clinical performance study. Eur Radiol. 2010;20(7):1545–53.
18. Nguyen T, Levy G, Poncelet E, Le Thanh T, Prolongeau JF, Phalippou J, et al. Overview of digital breast tomosynthesis: clinical cases, benefits and disadvantages. Diagn Interv Imaging. 2015;96(9):843–59.
19. Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology. 2013;267(1):47–56.
20. Svahn TM, Chakraborty DP, Ikeda D, Zackrisson S, Do Y, Mattsson S, et al. Breast tomosynthesis and digital mammography: a comparison of diagnostic accuracy. Br J Radiol. 2012;85(1019):e1074–82.
21. Zuckerman SP, Maidment ADA, Weinstein SP, McDonald ES, Conant EF. Imaging with synthesized 2D mammography: differences, advantages, and pitfalls compared with digital mammography. Am J Roentgenol. 2017;209(1):222–9.
22. Zuckerman SP, Conant EF, Keller BM, Maidment ADA, Barufaldi B, Weinstein SP, et al. Implementation of synthesized two-dimensional mammography in a population-based digital breast tomosynthesis screening program. Radiology. 2016;281(3):730–6.
23. Zuley ML, Guo B, Catullo VJ, Chough DM, Kelly AE, Lu AH, et al. Comparison of two-dimensional synthesized mammograms versus original digital mammograms alone and in combination with tomosynthesis images. Radiology. 2014;271(3):664–71.
24. Aujero MP, Gavenonis SC, Benjamin R, Zhang Z, Holt JS. Clinical performance of synthesized two-dimensional mammography combined with tomosynthesis in a large screening population. Radiology. 2017;283(1):70–6.
25. Kang H-J, Chang JM, Lee J, Song SE, Shin SU, Kim WH, et al. Replacing single-view mediolateral oblique (MLO) digital mammography (DM) with synthesized mammography (SM) with digital breast tomosynthesis (DBT) images: comparison of the diagnostic performance and radiation dose with two-view DM with or without MLO-DBT. Eur J Radiol. 2016;85(11):2042–8.
26. Sudhir R, Sannapareddy K, Potlapalli A, Krishnamurthy PB, Buddha S, Koppula V. Diagnostic accuracy of contrast enhanced digital mammography in breast cancer detection in comparison to tomosynthesis, synthetic 2D mammography and tomosynthesis combined with ultrasound in women with dense breast. Br J Radiol. 2021 Feb 1;94(1118):20201046. https://doi.org/10.1259/bjr.20201046. Epub 2020 Dec 2. PMID: 33242249; PMCID: PMC7934319..
27. Xiang W, Rao H, Zhou L. A meta-analysis of contrast-enhanced spectral mammography versus MRI in the diagnosis of breast cancer. Thorac Cancer. 2020 Jun;11(6):1423–32. https://doi.org/10.1111/1759-7714.13400. Epub 2020 Mar 31. PMID: 32233072; PMCID: PMC7262891.

28. Lee SH, Chang JM, Cho N, Koo HR, Yi A, Kim SJ, et al. Practice guideline for the performance of breast ultrasound elastography. Ultrasonography. 2014;33(1):3–10.
29. Sigrist RMS, Liau J, Kaffas AE, Chammas MC, Willmann JK. Ultrasound elastography: review of techniques and clinical applications. Theranostics. 2017;7(5):1303–29.
30. Yoon JH, Kim MH, Kim E-K, Moon HJ, Kwak JY, Kim MJ. Interobserver variability of ultrasound elastography: how it affects the diagnosis of breast lesions. Am J Roentgenol. 2011;196(3):730–6.
31. Olgun DÇ, Korkmazer B, Kılıç F, Dikici AS, Velidedeoğlu M, Aydoğan F, et al. Use of shear wave elastography to differentiate benign and malignant breast lesions. Diagn Interv Radiol. 2014;20(3):239–44.
32. Xue Y, Yao S, Li X, Zhang H. Benign and malignant breast lesions identification through the values derived from shear wave elastography: evidence for the meta-analysis. Oncotarget. 2017;8(51):89173–81.
33. Khamis MEM, Alaa El-deen AM, Azim Ismail AA. The diagnostic value of sonoelastographic strain ratio in discriminating malignant from benign solid breast masses. Egypt J Radiol Nucl Med. 2017;48(4):1149–57.
34. Claudon M, Cosgrove D, Albrecht T, Bolondi L, Bosio M, Calliada F, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS)—update 2008. Ultraschall Med. 2008;29(01):28–44.
35. Kook S-H, Kwag H-J. Value of contrast-enhanced power Doppler sonography using a microbubble echo-enhancing agent in evaluation of small breast lesions. J Clin Ultrasound. 2003;31(5):227–38.
36. Debbie S, Carla B, Wylie B, Steven H, Leach MO, Lehman CD, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2009;57(2):75–89.
37. Garg PK, Deo SVS, Kumar R, Shukla NK, Thulkar S, Gogia A, et al. Staging PET–CT scanning provides superior detection of lymph nodes and distant metastases than traditional imaging in locally advanced breast cancer. World J Surg. 2016;40(8):2036–42.
38. Garg PK, Deo SVS, Kumar R. Role of positron emission tomography-computed tomography in locally advanced breast cancer. Indian J Surg Oncol. 2015;6(4):420–6.
39. Yoon JH, Kim MJ, Kim E-K, Moon HJ. Imaging surveillance of patients with breast cancer after primary treatment: current recommendations. Korean J Radiol. 2015;16(2):219–28.
40. Teshome M, Hunt KK. Neoadjuvant therapy in the treatment of breast cancer. Surg Oncol Clin N Am. 2014;23(3):505–23.
41. Chhor CM, Mercado CL. Abbreviated MRI protocols: wave of the future for breast cancer screening. Am J Roentgenol. 2016;208(2):284–9.

MRI in Breast Cancer

10

Jyoti Arora and Jeevanjot Matharoo

10.1 Introduction

Breast MRI is a very sensitive modality which significantly improves cancer detection in high-risk women. It also has a role in clinical diagnosis, problem solving, and staging, thereby impacting patient management. However, it has reduced specificity therefore, correlation should be done with clinical and other imaging findings from mammography and ultrasound.

Initial results regarding magnetic resonance imaging (MRI) of the breast were published more than three decades ago, but the clinical use started during 1990s after the development of contrast- enhanced protocols [1]. Breast MRI is today one of the important modality for diagnosing breast diseases, together with mammography, ultrasound, and image-guided needle biopsy. It is based on the utilization of a strong magnetic field provided by a high-quality magnet; and low-energy electromagnetic waves (radiofrequency waves, similar to those of radio, television, and portable phones) radiated and received by special coils (antennas) inside the magnet and positioned close to the investigated body part. MRI can well differentiate lesions and abnormalities of the breast from the background breast tissue with the help of contrast material, which also help in differentiating benign from malignant lesion but there is an overlap in imaging findings. Injection of contrast is not required for evaluation of breast implant integrity. MRI does not expose the patient to radiation,

Jyoti Arora, CCST, FRCR, MD, DMRE, Fellowship in Breast Imaging, Bristol, UK (✉)
Associate Director, Imaging and Nuclear Medicine,
Medanta the Medicity Hospital, Gurugram, Haryana, India

General Secretary, Breast Imaging Society of India, New Delhi, India
e-mail: Dr.jyotiarora76@gmail.com

Jeevanjot Matharoo, MD
Fellow in Breast Imaging, Medanta the Medicity Hospital, Gurugram, Haryana, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_10

but other important precautions, contraindications, and potential side effects from contrast agents should be considered

Several studies have confirmed the diagnostic importance of Breast MRI. When it comes to detection of cancer, MRI outperforms (but not entirely substitutes) both mammography and ultrasound. However, MRI also picks up benign lesions that otherwise would have gone undetected, thereby leading to additional otherwise unnecessary work-up. Costs must also be taken into account, as MRI is more expensive than mammography and ultrasound [2].

For at least 20 years Breast MRI has been part of the breast imaging armamentarium. As opposed to just depending on morphologic changes as seen with mammography, contrast-enhanced MRI is effective because it relies on cancer-associated changes at the functional level, most particularly the neovascularity and abnormal capillary permeability that accompany malignancy.

With a sensitivity between 98 and 100%, and a specificity of up to 88%, MRI is a far more accurate modality in diagnosis and characterization of breast malignancy than either mammography or breast ultrasound [3].The negative predictive value (NPV) of MRI is close to 100% and probably its most powerful attribute, as it provides the ability to unequivocally exclude malignancy [4]. Furthermore, its ability to delineate cancer by combining both morphological and functional (contrast enhancement) capabilities means that MRI is the best tool we can have in terms of local cancer staging and identifying residual or recurrent disease.

Mammography is considered the single most effective screening tool and has been credited with reducing breast cancer-related mortality by 20–30%. There is no doubt that mammography is a very cost-effective tool for breast cancer screening; however, the sensitivity (67.8%) and specificity (75%) are less than ideal [5]. In addition, the use of ionizing radiation and lower spatial resolution (compared to MRI) are viewed as disadvantages in younger women and in women with dense breasts.

Coupled with mammography, the use of ultrasound has become the standard when working up a clinically suspicious lesion. However, it is a limited tool when used for screening. The most obvious disadvantages are ultrasound's inability to detect microcalcifications and the modality's heavy dependency on operator's skill. Many of the changes associated with cancer on mammography relate to hypoxia and regression—desmoplastic reaction, spiculation and micro-calcifications. This means that many of the most typical breast cancers found on mammogram are the least biologically active [6]. The higher grade and more aggressive subtypes, for example, triple negative cancers, may be less conspicuous or at least appear similar to benign entities on conventional breast imaging. The high-grade DCIS may not be calcified or reveal few calcific specs while the MRI may actually show a much larger area of NME (Fig. 10.1).

Magnetic resonance imaging, on the other hand, demonstrates best the most biologically active cancers (high grade intra-ductal and invasive) and with addition of kinetic enhancement assessment, the ability to differentiate benign-appearing cancers from true benign lesions is further improved [6]. Kinetic or dynamic

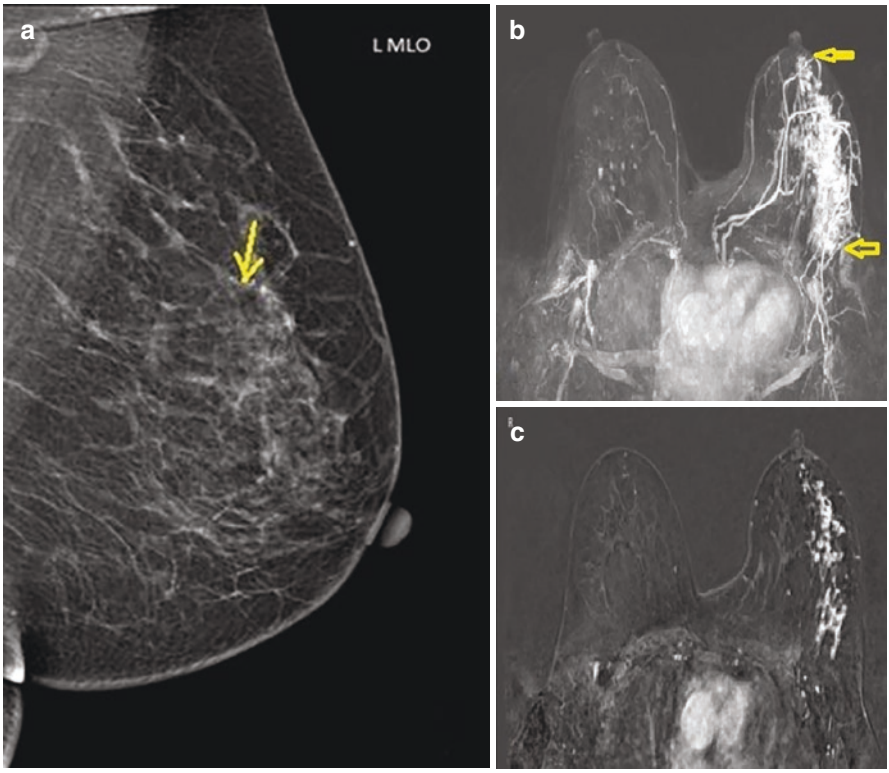


Fig. 10.1 A 53-year-old female presented with clear left nipple discharge. Mammogram (**a**) revealed focal asymmetry with few subtle specks of calcification (thin yellow arrow) in the upper half of left breast. MIP (**b**) and contrast enhanced T1 weighted fat-sat axial (**c**) images shows segmental area of non-mass enhancement in the upper outer half of left breast extending from nipple up till the chest wall (yellow arrows in fig. **b**), much larger than the mammographic abnormality. HPE: High grade DCIS. Patient underwent left modified radical mastectomy

enhancement refers to the progressive enhancement of a mass or non-mass lesion. It is plotted as the time: intensity curve on a graph. Modern software calculates an average for the entire enhancing area. The intensity (percentage) of initial enhancement in the first 2 min and the degree of contrast persistence or washout following the first 2 min are reflected in the curve. The more intense (rapid) the initial enhancement and the more rapid the washout, the higher the likelihood of malignancy. It is very important to realize that kinetic enhancement assessment is not always accurate and there is a considerable overlap between benign and malignant entities. It should not be used to downstage lesions but can be helpful in upstaging them. It is a valuable tool when used in combination with morphology (shape, outline) to determine the likelihood of malignancy.

Recent advances include dedicated multi-channel breast coils, better fat suppression, higher resolution scans and computer-aided detection (CAD) programmes that

allow better interpretation of kinetic assessment. In addition, evidence-based descriptors in the last two editions of the Breast Imaging, Reporting and Data System (BI-RADS) manual have standardized breast MRI assessment and reporting. The American College of Radiology (ACR) has built the BI-RADS atlas which describes various imaging characteristics on each modality that show higher or lower suspicion of a cancer. These developments have meant better specificity and the ability to expand the role of breast MRI.

MRI affords the radiologist unique advantages over mammography and ultrasound. They are: Lack of ionizing radiation, better contrast resolution, multiplanar 3D capabilities, and ability to capture neoangionesis which enhance the role of breast MRI in local staging of cancer due to following reasons.

1. Ability to detect occult, multifocal/multicentric disease
2. Better ability to delineate the actual or true size of a cancer (often underestimated on mammography and US)
3. Ability to image both breasts, axillae and the chest wall and predict chest wall or skin involvement
4. Ability to accurately biopsy lesions and insert localisation wires under MRI guidance has adequately improved the value of pre-treatment staging MRI [6]

Breast MRI aids in thorough evaluation of tumor involvement because it is the best method for determining involvement of pectoralis muscle and chest wall. Involvement of the muscle in the pectoralis muscle is seen as enhancement on MRI which may be surgically removed at the time of mastectomy to attain local control. However, when there is enhancement of underlying serratus anterior muscles or ribs, the patient is considered to have distant metastases (T4a).

Breast MRI is not without disadvantages. The heightened sensitivity of MRI when compared to mammography (99% vs. 67.8%) is balanced by the wider specificity (37–97%). The main reason for this broad specificity range is that both benign and malignant lesions enhance and there is a big overlap in their findings. For areas of non-mass enhancement, MRI has much lower positive predictive value which adds to the diagnostic challenge for the radiologist. Non-mass enhancement is associated with physiologic enhancement, fibrocystic change, benign conditions, DCIS or invasive carcinoma. In addition, MRI is expensive, requires the use of intravenous contrast and is limited in its use in patients who cannot lie prone, are obese (over the weight limit of the scanner being used), have extremely large breasts, and are claustrophobic [7]. Its contraindicated in patients with pacemaker, aneurysmal clip etc.

10.2 Indications of Breast MRI

1. Inconclusive findings in conventional imaging as problem solving tool.
2. Preoperative staging.
3. Unknown primary with metastatic axillary lymphadenopathy.

4. The evaluation of therapy response in the neoadjuvant chemotherapy setting.
5. Imaging of the breast after conservative therapy to exclude recurrence.
6. High risk screening in young patients.
7. In patients with breast implants to access implant integrity.
8. MR-guided biopsy and lesion localization.

10.2.1 Inconclusive Findings in Conventional Imaging/ Problem Solving

When the findings of conventional imaging are inconclusive, MRI can be used as a problem-solving modality due to its high sensitivity. In general, a negative breast MRI excludes malignancy.

Breast MRI is typically used for findings that are not certainly benign but that cannot be sampled for biopsy by using conventional imaging guidance. The most common are mammographic asymmetries that are visible only in one view where a negative MRI effectively rules out the presence of cancer. Equivocal findings from breast tomosynthesis can also be evaluated. In a meta- analysis, a sensitivity of 99% with an NPV of 100% was reported for the evaluation of noncalcified equivocal findings. In mammographically detected calcified lesions, the NPV of breast MRI is not high enough to exclude malignancy. In meta-analysis, the absence of enhancement at the site of calcifications is associated with an NPV of 93%, and the presence of invasive cancer is unlikely in this setting. For nipple discharge, MRI outperforms galactography, with a sensitivity for causative lesions of 92% versus 69%. In these patients, cancers are detected with an equally high sensitivity and a high specificity of 97% [2].

10.2.2 Preoperative Staging

Breast tumors may be solitary, well-circumscribed masses that are well appreciated at mammography and/or sonography. However, tumor size may be underestimated severely by mammography and ultrasound, especially in tumors larger than 2 cm, in case of invasive lobular carcinoma, or in cases of multifocality. Tumor size of invasive carcinomas on MRI correspond in general well to pathologic sizes. Unfortunately, MRI has a tendency to overestimate the size of pure DCIS lesions. Furthermore, in about 25% of the cases, the tumor is multi-focal; in other words, there are more invasive tumors in one quadrant. Approximately about 20% of invasive tumors depict multicentricity (Fig. 10.2a, b), which means one or more invasive foci is more than 4 cm from the primary lesion. Inadequate estimation of size or failure to pick up additional foci of disease may thus result in positive margins after surgery or early recurrent disease [8].

The sensitivity of breast MRI is, in the setting of preoperative assessment, close to 100% [9]. MRI is the most reliable imaging technique to measure the tumor size and it detects additional foci of the tumor in the ipsilateral breast in 10–30% of patients [10]. Also the presence of an intraductal component can be better assessed

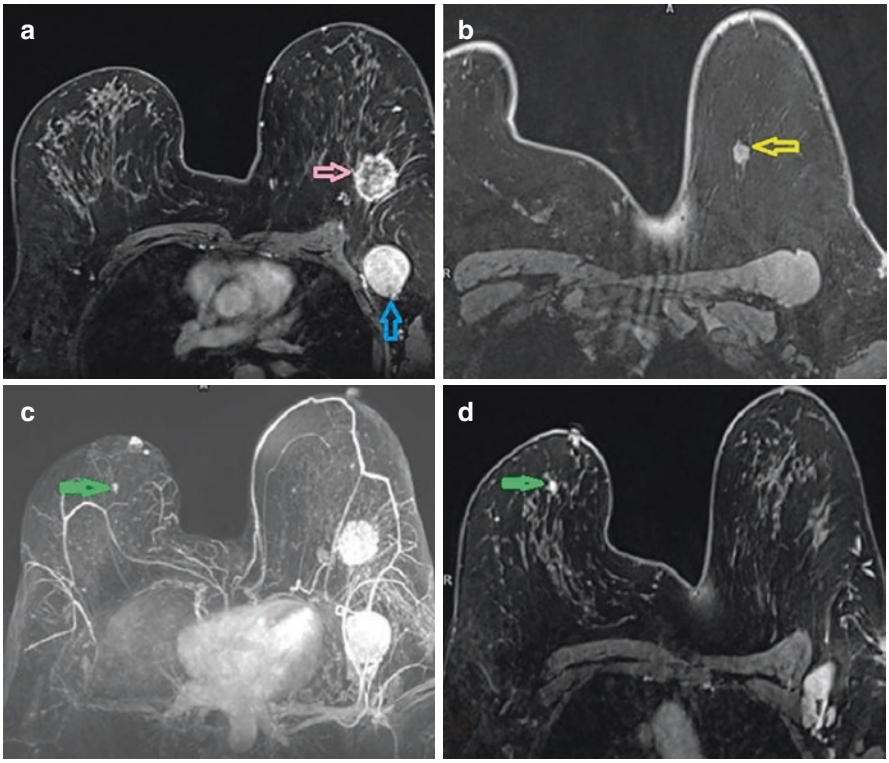


Fig. 10.2 Patient presented with lump in the left breast. Post contrast T1 Weighted axial fat sat images shows (**a**) an irregular heterogeneously enhancing mass (light pink arrow) in the outer half of left breast with a grossly enlarged ipsilateral node (blue arrow) [HPE: IDC]. (**b**) A small irregular enhancing nodule (yellow arrow) was seen in the upper inner quadrant of ipsilateral breast which was more than 4 cm apart from index lesion. It was biopsied on second look ultrasound and HPE showed IDC. MIP (**c**) and axial post contrast T1 weighted fat sat (**d**) images show tiny irregular enhancing focus (green arrow) in the retro areolar region of right (contralateral) breast. Patient underwent MRI guided vacuum assisted breast biopsy for the tiny right breast focus and HPE showed benign breast change

by MRI than with mammography. On MRI this may be seen as an area of non-mass enhancement close to the primary tumor. However, around 20% of the additional foci recognised by MRI are benign [11] (Fig. 10.2b,c). Consequently, before large adjustments to the surgical management are executed, histological analysis of MR-detected additional foci should be done.

Several studies have shown a change in surgical management in about 20–30% of all patients undergoing preoperative MRI. Changes were greatest in patients with tumor size greater than 4 cm, lobular carcinoma or in dense breast.

However, it is so far unclear whether breast MRI contributes to better control of the disease or survival of all patients with diagnosed breast cancer. Only one study has evaluated such outcomes, and although MRI appears to reduce the incidence of local recurrence (1.2% vs. 6.8%), confounding differences in tumor characteristics between patients treated with and without MRI did occur.

Synchronous bilateral breast cancer is reported in about 2–3% of all breast cancer patients, but it is probably more common. Synchronous contra-lateral lesions are occult on mammography in about 75% of cases. MRI detects otherwise occult lesions in 3–5% of patients that undergo preoperative MRI. Some studies reveal even more alarming results and report MRI-only detected contralateral breast cancer in 19%–24%. These lesions would probably have presented as metachronous contralateral carcinomas without MRI. Mann et al showed that the rate of contralateral carcinomas detected at follow-up decreased from 4% without MRI to 1.7% with MRI [8].

Screening of the contralateral breast in patients with proven unilateral breast cancer is thus a valid indication for the performance of preoperative breast MRI. In practice this means that preoperative MRI is recommended in all patients with histologically proven breast cancer, even though the indication for ipsilateral staging of the cancer is still under investigation.

Especially in the case of dense breasts, MRI is recommended preoperatively. Moreover, in patients with histology proven invasive lobular carcinoma, a preoperative MRI is strongly recommended as these tumors show a more permeative growth pattern and, consequently, are more difficult to measure, are more often multifocal or multicentric (additional foci in 32%) and are more frequently complicated by concurrent contralateral carcinomas (occult tumors detected in 7%) [8].

However, guidelines differ widely in their recommendations for the performance of preoperative breast MRI in women with a new diagnosis of breast cancer [12].

10.2.3 Unknown Primary

In the case of a carcinoma of unknown primary, metastases are diagnosed, but a primary tumor site cannot be identified. These metastases may either present in the axillary lymphnodes, the supraclavicular lymphnodes, the bones, the liver, the brain or the lungs.

In case of metastatic axillary lymph nodes, MRI is even able to detect a primary breast tumor in 75–85% of patients [13]. MRI thus can subsequently be used to plan the most appropriate treatment as the size of these lesions on MRI is usually concordant with the size at pathology, thus MRI may prevent unnecessary mastectomies (Fig. 10.3).

If breast MRI is negative, immediate surgery may be avoided. In cases of axillary metastases, patients are usually treated with radiotherapy to the ipsilateral breast. In such cases, follow-up MRI can be proposed [2].

10.2.4 The Evaluation of Therapy Response in the Neoadjuvant Chemotherapy Setting

Neoadjuvant chemotherapy is the administration of chemotherapy before surgical treatment of cancer. Its principal indication is the treatment of unresectable breast cancers, and its goal is to reduce the tumor to a size so as to allow resection. Because there are some theoretical benefits in the neoadjuvant setting, and tumor response

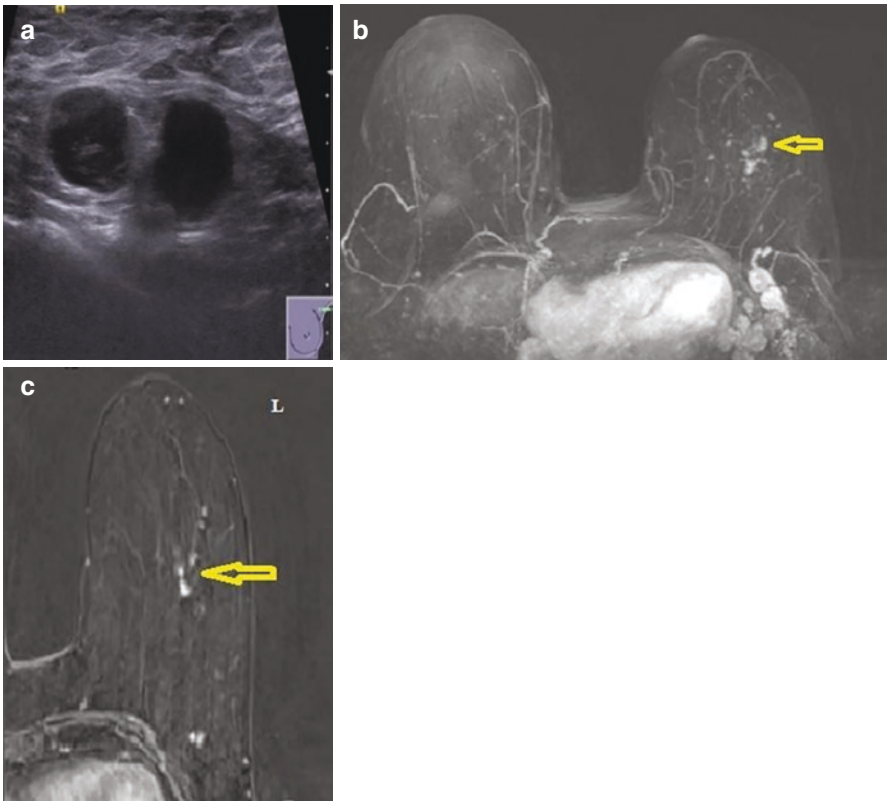


Fig. 10.3 A 50-year-old lady presented with lump in the left axilla. Ultrasound (**a**) revealed rounded nodes with grossly thickened cortex and loss of fatty hilum. Ultrasound guided biopsy was performed for axillary node. HPE: Metastatic Lobular carcinoma with IHC profile favouring a primary from the breast. MIP (**b**) and post contrast T1 weighted fat-sat axial (**c**), images demonstrated few tiny clustered enhancing foci (yellow arrows) in the outer half of left breast which were not evident on ultrasound. HPE: Lobular carcinoma

can be closely evaluated with the tumor in situ, neoadjuvant chemotherapy is also the standard of care in large T2 and T3 tumors. MRI has been shown to be superior to evaluate tumor response to neoadjuvant chemotherapy compared to clinical examination, mammography or ultrasound and is thus the imaging investigation of choice (Fig. 10.4).

If neoadjuvant chemotherapy is given to a patient, the first breast MRI should be performed before the start of chemotherapy. A second MRI, for the evaluation of the effect of chemotherapy on the tumor, should be performed when approximately half of the course of chemotherapy has been administered. A third MRI investigation should be performed after the final course of chemotherapy to evaluate the residual disease. In most hospitals four to six cycles of chemotherapy are given in the neoadjuvant setting.

Response is normally measured using the RECIST criteria [12]. Using these, complete response (CR) is defined as complete vanishing of the tumor, partial

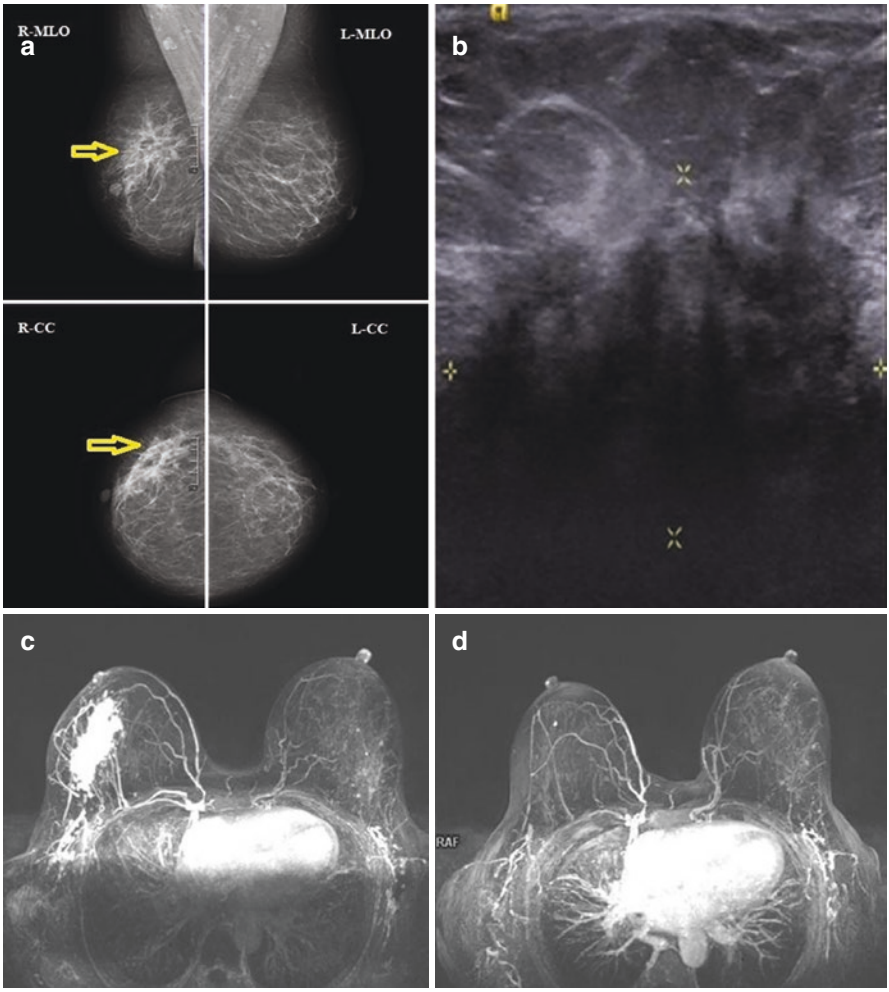


Fig. 10.4 A 49 year old female presented with a right breast lump. Mammogram showed (**a**) large mass with distortion associated with spiculation (yellow arrows) in the upper outer quadrant of the right breast causing nipple retraction. Targeted breast ultrasound (**b**) revealed large abnormal area of shadowing associated with altered echo pattern, distortion and spiculations. MIP image (**c**) demonstrated large mass in the outer half of right breast. MIP image post 4 cycles of NACT (**d**) showed resolution of the abnormal area seen previously suggesting good response. HPE: grade 3 IDC

response (PR) is defined as decrease of the sum of the longest axes of all individual lesions by more than 30%, progressive disease (PD) is defined as an increase of this sum by more than 25% and the remainder is classified as stable disease (SD). Response to chemotherapy is especially well evaluated in the non-responders (SD, PD) and the good-responder group (CR).The effect of the chemotherapy in partial responders is less well established.

Several studies compared the ability of clinical examination, mammography, ultrasound and MRI in the assessment of final response. They showed that MRI

measurement after therapy correlated best with the pathological findings and was the best technique for assessing response.

Nonetheless, MRI is unable to detect small residual tumor foci that may remain after neoadjuvant chemotherapy. Radiological complete response is thus no proof for pathological complete response (PCR); therefore, resection of the initial tumor bed is still essential in the treatment of these patients [8].

Observation of response during treatment is important as this is the only estimate that justifies the applied chemotherapeutic regimen and it is the only response evaluation that allows a change in this regime before its completion. Currently, the performance of MRI halfway during treatment may only change the treatment in clear non-responders and those with progressive disease as there are no other criteria for early response assessment. This is due to the fact that size of the tumor often does not immediately decrease. Therefore, the performance of MRI earlier in the treatment (e.g., after the first cycle) not recommended, although in one study complete responders had a change in diameter by at least 45% after the first dose of chemotherapy. In another study early change in volume was the most predictive of final response [8]. In patients with response to neoadjuvant chemotherapy, it is reported that type 3 pharmacokinetic curves with wash-out either flatten (type 1) or form a plateau (type 2) [14]. In study conducted by Balu-Maestro and colleagues [15] took into account that pathological complete response is seen as disappearance of early and initial contrast enhancement in the tumor after treatment. Rieber et al. [14] had committed that flattening or disappearance of the kinetic curve segment in the pharmacokinetic curve after the first course of chemotherapy or absence of enhancement after four cycles of chemotherapy indicate pathological complete response.

Several other techniques, such as MR spectroscopy, diffusion imaging and FDG-PET show promise in the (early) evaluation of tumor response to therapy. However, none of these techniques have been tested in large-scale prospective studies and thus cannot yet be recommended for routine clinical practice.

10.2.5 Imaging of the Breast After Conservative Therapy

MRI may be considered after breast-conserving therapy (BCT) in the following conditions: first as an evaluation tool in patients with residual disease after positive tumor margins, second as a method of evaluation in suspected recurrence by either clinical examination, mammography or ultrasound and third as a screening tool in follow up patients of BCT (Fig. 10.5). Unfortunately, early postoperative MRI is hampered by strongly enhancing resection margins in response to the surgical intervention. Therefore, MRI is unable to rule out residual tumor at the post operative cavity sufficiently, and hence does not change the surgical approach consisting in a larger resection of the tumor bed in the direction where pathological analysis of the surgical specimen showed positive margins [8].

However, as MRI may reveal more extensive disease throughout the breast remote from the lumpectomy site, it can provide valuable information regarding the decision of wider excision versus mastectomy. Morakkabati et al. have shown that post radiation changes occur during and up to 3 months after radiation therapy, but

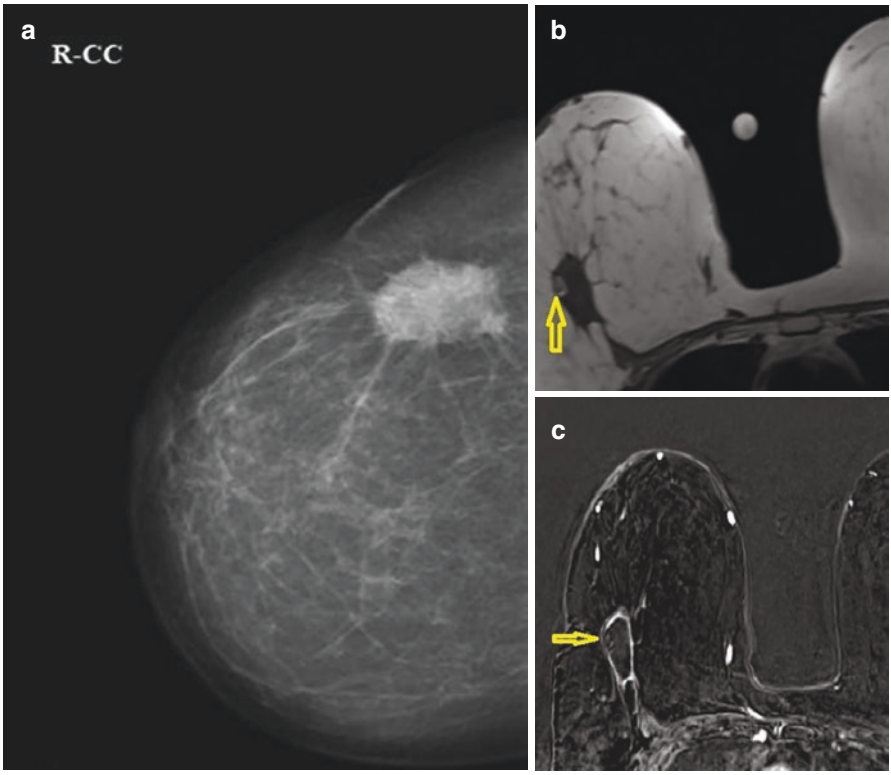


Fig. 10.5 Patient underwent wide local excision of the right breast and came for follow up. Mammogram (**a**) revealed a spiculate lesion in the outer half of right breast at the scar site. Axial non enhanced T1 weighted image (**b**) shows an irregular hypointense area with a small hyperintense nodule (yellow area) along its lateral wall. (**c**) post contrast T1 weighted fat-sat image shows mild peripheral rim enhancement with minimal enhancement of the small nodule (yellow arrow). Findings suggested the possibility of fat necrosis at the operative site. HPE: fat necrosis

do not reduce the accuracy of MRI to identify residual or recurrent tumor compared to patients without radiation therapy [16].

Most local recurrences after BCT and radiotherapy occur within 5 years after the initial surgery, and the annual risk is estimated at 1–2% per year [17]. Early detection and treatment of recurrent disease are important as it may still present without distant metastases. Second primary ipsilateral carcinomas in the treated breast can occur at any site and develop on average 7 years after the first primary tumor [18]. The sensitivity of mammography for recurrent disease in the treated breast is limited, but breast MRI can be a valuable complementary tool as explained earlier.

A local recurrence on MRI has the same appearance as a new primary malignancy with strong early enhancement, while a fibrous scar will show either no enhancement or very slow enhancement. In a treated breast, the specificity of breast MRI is higher than in an untreated breast.

In situations when there is suspicion of a local recurrence on clinical findings or abnormalities on mammography or ultrasound, MRI can be used to exclude local

recurrence with a high negative predictive value and thus avoiding unnecessary biopsies. Analogous to the situation in preoperative staging, MRI is able to detect multi-focality and multicentricity unnoticed by conventional imaging. Needless to say, in these cases, the evaluation of the contralateral breast is also important [8].

The risk of local recurrence is strongly dependent on the age of the patient at the time of diagnosis. Patients over 50 have a risk of approximately 4% after 5 years, but this risk is estimated at 12% after 5 years for patients who were under 45 years of age [19] and at 20% after 5 years for patients under 40 [20]. Although additional boost radiotherapy to the tumor bed can reduce this risk to 10% at 5 years, these patients have a lifetime risk that is probably still greater than 20%, which is equal to the lifetime risk demanded for MRI screening in the general population.

Therefore, annual MRI screening is an option for all patients under 50 at the time of diagnosis of the first primary carcinoma, but this should first be investigated in larger trials.

10.2.6 High Risk MRI Screening

The high sensitivity for cancer makes breast MRI an advisable technique for screening purposes. Therefore, many countries have performed screening studies in high-risk populations. The American Cancer Society (ACS) has issued guidelines for the performance of MR screening based upon the analysis of six studies. As the most important of these studies were all performed in Europe (e.g. the Dutch MRISC study, The UK-based MARIBS study, the German single-center study and the Italian HIBCRIT study), the ACS recommendations apply mostly to the European situation. In case of these high risk populations, the overall sensitivity for breast cancer is between 71 and 100% for MRI compared to 16–40% for mammography. The specificity ranges from 81 to 99% for MRI and 93 to 99% for mammography, which is explanatory for the higher detection rate of MR and the higher recall rate that sadly complicates MR screening [8].

There is evidence for the value of annual MR screening in BRCA gene mutation carriers, their first degree, untested relatives and all women with a lifetime risk of 20–25% according to models that depend largely upon family history (Fig. 10.6). Furthermore, MRI screening is advised in patients who have received radiation to the chest in their second or third decade (mostly patients with a history of lymphoma) and patients with syndromes like LiFraumeni and Cowden syndrome and their first-degree relatives, even though there is no direct evidence for these latter recommendations [7].

Currently there is not sufficient evidence to recommend MRI in women with a life time risk of 15–20%, those with high-risk lesions (LCIS, ALH, ADH) and those with heterogeneously or extremely dense breasts on mammography [7].

Women with a lifetime risk of less than 15% should currently not be taking up MRI screening programs.

In most high- risk patients, annual MRI screening starting at the age of 30 should probably be sufficient. However, in families where the first carcinomas presented at

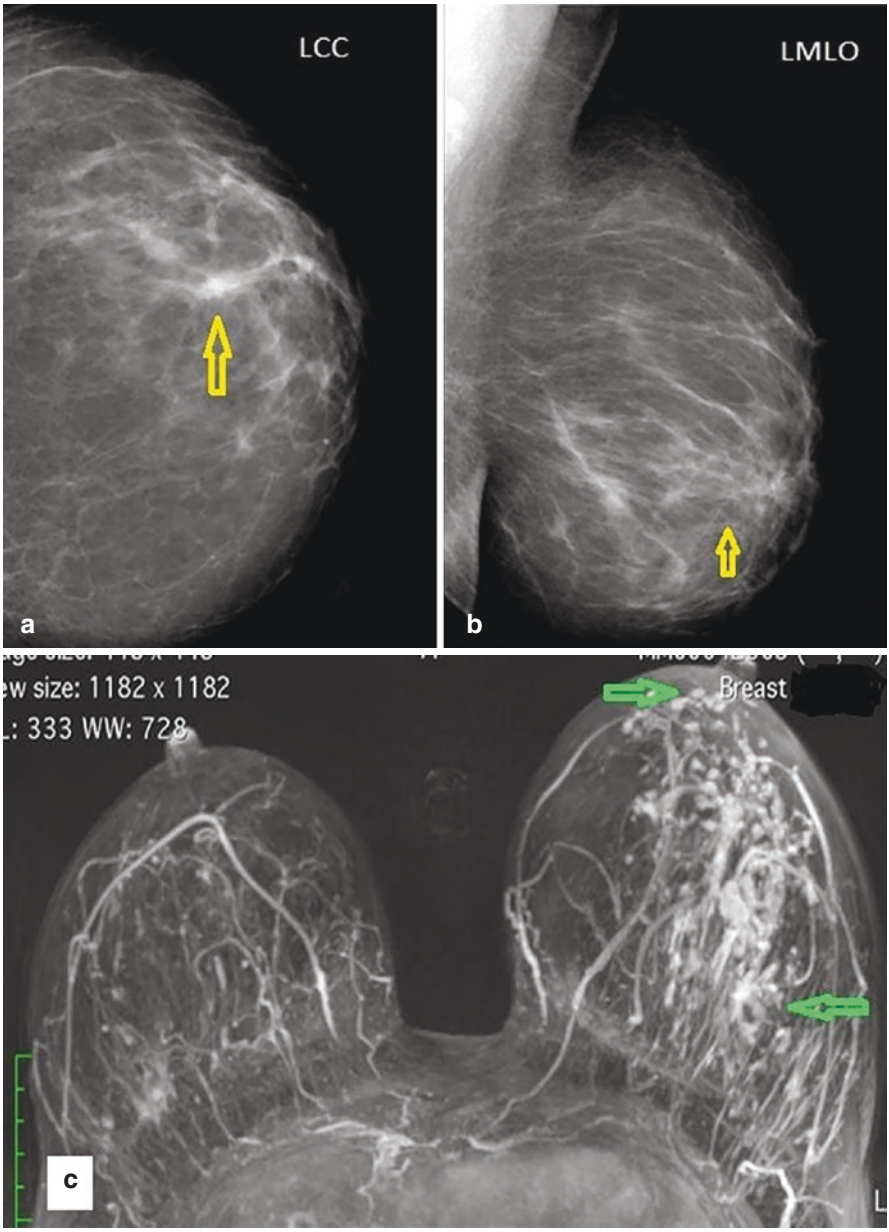


Fig. 10.6 35 Y old lady was a first degree relative of BRCA gene positive patient. Screening mammogram. (**a, b**) revealed subtle asymmetry in the lower outer quadrant of left breast (yellow arrows). MIP image (**c**) shows segmental non mass enhancement in the lower half of left breast with multiple tiny foci within (green arrows). HPE: invasive lobular carcinoma

younger ages, the screening needs to be intensive and should start earlier. In older women the breast density decreases significantly, and the added value of MR might thus decrease. However, at every age, the sensitivity of breast MRI for breast cancer is higher than that of mammography.

10.2.7 In Patients with Breast Implants

The evaluation of breast implants, which are either placed for breast augmentation or for breast reconstruction after surgery for breast cancer, can be done with MRI. This requires specific sequences that are targeted at the visualization of silicone and provide simultaneous suppression of the water signal. By applying these sequences and specific criteria for evaluation , MRI is regarded the most accurate modality in implant integrity evaluation. Its sensitivity for rupture is between 80% and 90%, and its specificity is approximately 90% [21], whereas the sensitivity of mammography is approximately 25% [22] (Fig. 10.7).

Nonetheless, the indication for breast MRI is less clear than might be expected. Ten years after insertion, approximately 50% of all breast implants are ruptured. It seems therefore advisable to use breast MR only when there are specific complaints that might be caused by leaking prostheses (e.g., local inflammation or the formation of silicone granulomas). MRI may then be used to exclude a ruptured prosthesis as the underlying cause of the complaints, and it may also aid explanation of surgery as it documents the presence and extent of silicone leakage better than any other imaging modality.

In patients with implants and prior breast cancer, MRI may be used to evaluate suspected recurrent disease or as a postoperative screening modality contrast enhanced study should be performed. The presence of the implant does not seem to decrease the sensitivity of breast MRI.

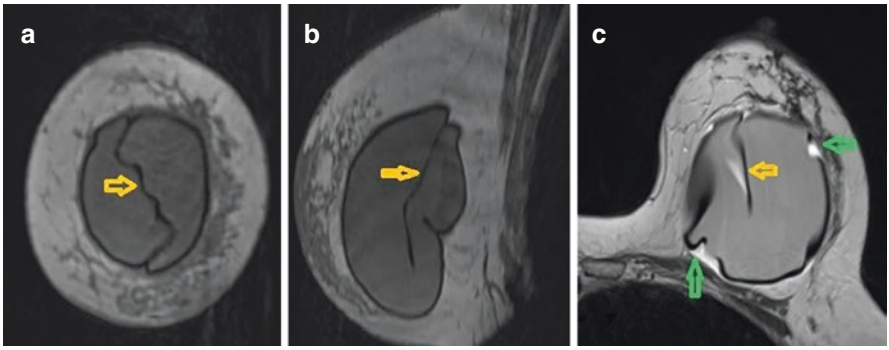


Fig. 10.7 A 53 year old patient with history of breast augmentation 8 years back complained of tense cystic area in the upper half of left breast. T1 weighted non contrast coronal and sagittal (**a, b**) image and T2 weighted axial non contrast (**c**) images shows irregular contour of the implant with floating curvilinear membrane (linguine sign depicted with yellow arrows), suggestive of intracapsular rupture. Minimal peri implant fluid (green arrows) was seen between the implant and fibrous capsule on T2W images. Patient underwent left breast implant removal with capsulotomy

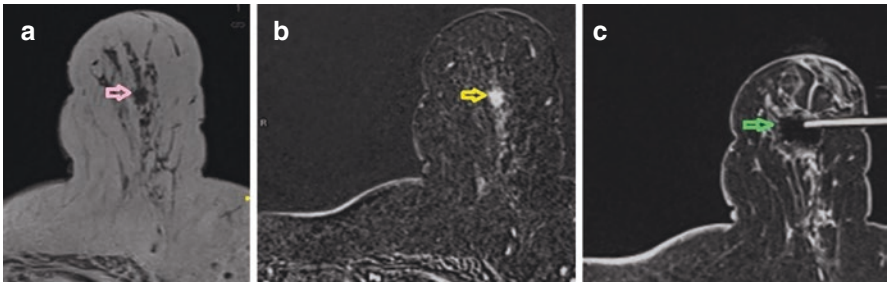


Fig. 10.8 Non-contrast T2w axial image (**a**) shows a sub centimeter sized finely spiculated focal lesion (pink arrow) at the left peri areolar edge at 12 O clock position. Early contrast-enhanced T1-weighted fat sat image (**b**) depicts the corresponding mass in the left breast (yellow arrow). (**c**) Post biopsy cavity as seen on MRI guided vacuum assisted biopsy (green arrow). HPE: IDC

10.2.8 MRI-Guided Breast Biopsy and Lesion Localization

It is clear that the increasing list of indications for the performance of breast MRI leads to the detection of many lesions that are neither palpable nor visible on conventional imaging techniques. Although most MR-detected lesions can be found (and biopsied) at second-look ultrasound, many (57%) may not be visible. This emphasizes the importance of performing MR-guided biopsies and localizations. Any institution that performs breast MR examinations should either be able to perform MR-guided interventions in the breast or should be in close contact with a centre that can perform these investigations for them [8] (Fig. 10.8).

10.3 Scheduling the Scan

In premenopausal women, contrast enhanced MRI is preferred to be performed between days 7 and 14 of the menstrual cycle, when the background enhancement of the normal fibro-glandular breast tissue is low and hence abnormalities are better detected and false positives being less frequent. During the remaining days of the menstrual cycle, lesions may be masked by enhancement of the fibro-glandular tissue significantly reducing the diagnostic value of the examination. If necessary, breast MRI may be performed in the third week of the menstrual cycle, taking into consideration that the results could be suboptimal. The use of oral contraceptives does not contraindicate contrast enhanced MRI, but the above defined rules should be observed. Women with irregular menses (e.g.in peri-menopausal phase) may undergo blood sampling for serum progesterone to determine the optimal time for breast MRI, especially if earlier examinations have been non-diagnostic due to strong glandular enhancement. Premenopausal women who need only implant integrity evaluation can undergone Non-contrast breast MRI at any time. All post-menopausal women can undergo CEMRI at any time. In fact, post-menopausal hormone replacement therapy has been recently reported to have negligible effect on

parenchymal background enhancement [2]. In any case, breast MRI optimal scheduling should not substantially delay therapy planning and in suspected cases MRI can be planned irrespective of the menstrual phase.

10.4 Breast MRI Technicalities and Requirement

Breast MRI studies should be interpreted by radiologists with expertise in breast imaging, including mammographic and ultrasound studies, as these examinations are often complementary to each other.

It is best practice to use a field strength of at least 1.5 T to acquire images at a sufficiently high resolution. Utilization of a dedicated breast coil is mandatory to obtain images of diagnostic quality. Women lie in the prone position with the breasts hanging free in the recesses of the coil. This design allows the breast tissue to spread, which facilitates detection of abnormalities and prevents motion artifacts induced by respiration. A breast coil should have at least four channels, but modern designs have 16 channels or more, and sometimes also dedicated channels for the axillary region. In general, coils with more channels obtain a higher signal-to-noise ratio (SNR). More channels also enable the use of higher parallel imaging factors, which can increase the speed of image acquisition [2].

As Breast MRI aims to depict lesions that are occult with other modalities, it is essential that imaging facilities have tools to biopsy and localize these lesions for surgery. This may require an additional biopsy coil, as the latest generations of breast coils have closed recesses because of the high number of channels that are brought in proximity to the breast, consequently blocking access to the breast for interventional procedures. Also, a device that immobilizes the breast during biopsy is indispensable because introduction of a needle will change the shape of the breast and the position of the lesion [12].

Breast MRI is performed using MRI scanners working at 1.5 or 3 T (1.5 Tesla = 15,000 Gauss). Clear instructions and explanation regarding the procedure are provided by a technician or a nurse. The woman is asked to sign a specific informed consent. The optimal dose of the contrast medium depends on the contrast agent used. In literature, applied doses range roughly from 0.05 to 0.2 mmol/kg. However, a dose of 0.1 mmol/kg of contrast medium is probably sufficient [8].

The woman should keep still during the entire examination as patient movement causes most artifacts, which strongly reduce image quality and make interpretation difficult and sometimes impossible.

Any clothing containing metal, jewelry, and other foreign objects must be removed. Dedicated breast coils are mandatory. Women are asked to lie prone on the MRI table with each breast hanging in the recess of the coil. A technician or a nurse positions the breasts avoiding folding of breast tissue on the edges of the coil. In some centers, slight breast compression is applied to reduce motion artifacts.

When the woman is optimally positioned, table and patient are moved into the magnet, so that her breasts are in the centre of the tube: the magnetic field is most homogeneous at that position allowing for optimal image quality.

The procedure commonly takes 15–30 min, except when additional sequences are done for clinical purposes.

Prior to reading images, image co-registration using special software is sometimes used. In the case of artifacts or strong enhancement of background glandular tissue in women not examined in the right phase of the menstrual cycle or with unexpected other hormonal influences, a repeat breast MRI may be required.

10.5 Breast MRI Report and Bi-Rads Categories

The report should contain the indication for the scan, relevant clinical information, hormonal status of the patient and type and dose of administered contrast agent. In premenopausal women, the day or the week of the menstrual cycle on which MRI was performed should be stated. Techniques used should be very briefly summarized. Therefore, it is best that breast MRI should be evaluated by a dedicated breast radiologist.

Reported image findings include breast density, amount of parenchymal background enhancement (Fig. 10.9), and a usually structured description of relevant abnormalities, including those in the axillae or incidental findings in the imaged part of thorax and abdomen, when visible. Side, size, location and distance from nipple of any breast lesions should be described. Lymphnode status should be mentioned when the examination reveals a possible unsuspected nodal metastasis in the axilla or internal mammary region.

Each report should end with a conclusion, commonly associated with a diagnostic category and recommendations. The most commonly applied system is the Breast Imaging Reporting and Data System (BI-RADS) developed by the American College of Radiology.

Conclusive BI-RADS diagnostic categories are used as follows:

0 = incomplete, additional imaging evaluation is needed;
1 = negative, no abnormalities;
2 = benign findings;
3 = probably benign findings (short-term follow-up within 6 months recommended; needle biopsy may be performed only in special cases, such as on patient request or high-risk patients);
4 = suspected malignancy (needle biopsy recommended);
5 = highly suspected malignancy (needle biopsy recommended);
6 = already histologically proven cancer (typically reserved for MRI scans made for cancer staging or in the case of neo-adjuvant chemotherapy).

Needle biopsy is advised for BI-RADS 4 & 5 lesions which is a general rule for isolated newly diagnosed lesions. It is not to be performed in the case of a lesion adjacent or close to a lesion already known to be cancer where it can be removed along with the index lesion without change in the treatment plan. Around 50–60% of lesions initially detected at MRI are identified with *second-look* targeted

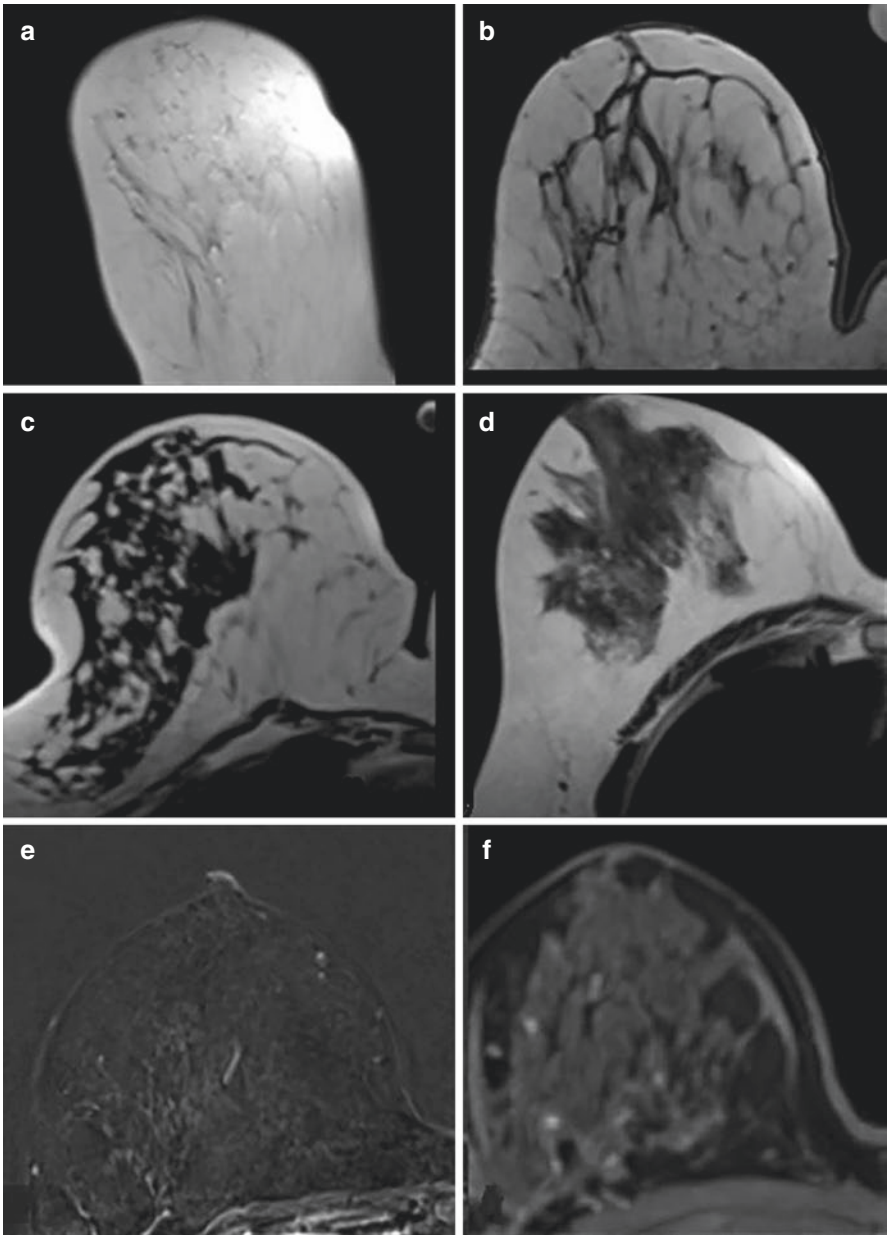


Fig. 10.9 Axial T1 weighted non contrast axial images showing types of fibro-glandular tissue on MRI (**a**) Fatty (**b**) scattered fibro glandular tissue (**c**) heterogeneously dense (**d**) extremely dense. Types of background parenchymal enhancement as seen on post contrast T1 weighted fat sat axial images (**e**) minimal (**f**) mild (**g**) moderate (**h**) marked parenchymal enhancement

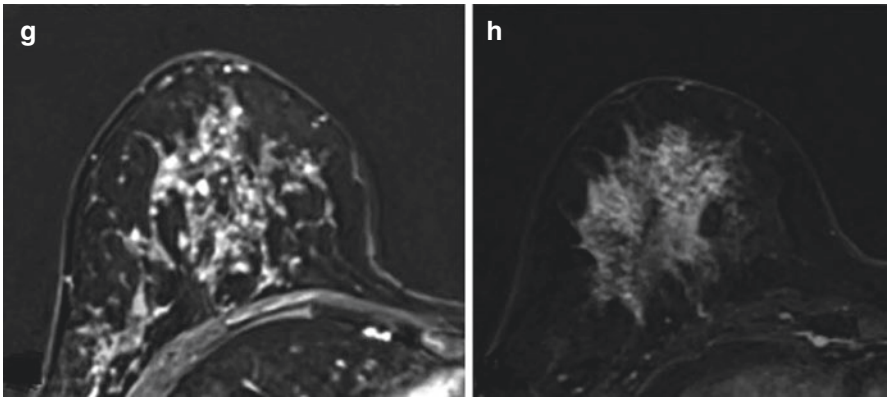


Fig. 10.9 (continued)

ultrasound, even though this rate is variable among studies. In that case, needle biopsy is performed under ultrasound guidance, a quicker, less invasive, and cheaper procedure than MR-guided biopsy. When the lesion is not detected with ultrasound and the indication for biopsy still stands, an MR- guided biopsy is indicated. It takes longer than a diagnostic breast MRI, and it is a special procedure, requiring dedicated targeting and sampling equipment as well as trained radiologist [2].

However, in the case MR-guided biopsy cannot be performed (e.g., dedicated equipment not available; lesion site not accessible, such as those very close to the thoracic wall), MR-guided presurgical localization may be performed.

BI-RADS 3 findings form a special diagnostic category, having a chance of being malignant below 2% [23]. However, the actual chance of an MR-detected BI-RADS 3 lesion being malignant is sometimes higher, especially in high-risk women [24]. For a BI-RADS-3 lesion, short-term follow-up is recommended instead of biopsy due to the low malignancy probability and its expected that treatment efficacy is not reduced for a shortly delayed diagnosis. This implies repeat MRI examinations within 6 months and potential further repeat MRI at 1 year and 2 years after initial detection. When, at MRI follow-up, an MR-detected lesion disappears, shrinks, or remains unchanged in size, and does not show any new sign of malignancy, it can be downgraded to benign (BI-RADS-2) without biopsy. However, in some cases, mostly when the patient prefers an immediate conclusion of the diagnostic pathway to alley her anxiety or when follow up is not feasible, a needle biopsy can be directly performed for a BI-RADS 3 lesion.

10.6 Interpretation

The conventional breast MRI investigation begins with pre-contrast T2 and T1-weighted images. In the T2-weighted images water-containing lesions or edematous lesions have a high signal intensity, and in this sequence small cysts and

myxoid fibroadenomas are well identified. In most cases, cancer does not yield a high signal on T2-weighted images; thus, these sequences can be useful in the differentiation between benign and malignant lesions [8].

Most masses with high signal intensity at T2-weighted imaging are benign (e.g., apocrine metaplasia, cyst, myxoid fibroadenoma (Fig. 10.10), fat necrosis , and lymph nodes. Most cancers do not show high signal intensity relative to parenchyma at T2-weighted imaging because of their high cellularity and low water content. However, mucinous carcinoma, necrotic cancer, and metaplastic carcinoma can have high signal intensity on T2-weighted images. T2-weighted imaging also helps to depict peri-focal or pre-pectoral edema within the breast, which improves lesion classification (lesions with edema are more often malignant) and is a poor prognostic sign in patients with known breast cancer [12].

The most commonly used sequence in breast MRI is a T1-weighted, dynamic contrast enhanced acquisition. The sequence is called 'dynamic' because it is first performed before contrast administration and is repeated multiple times after contrast administration.

A T1-weighted 3D or 2D (multi-slice) spoiled gradient echo pulse sequence is acquired before contrast injection and then repeated as rapidly as possible for 5–7 min after a rapid intravenous bolus of a Gadolinium-containing contrast agent After contrast material administration, the T1-weighted acquisition is repeated to depict enhancing abnormalities. It is essential to obtain an image approximately 60–90 s after contrast material administration, as most breast cancers will show peak enhancement at that time. Lesion detection is primarily performed by using these post contrast images. For images obtained without fat suppression, creating subtraction images from the pre- and post-contrast acquisitions is required. Subtraction images are also helpful because they help differentiate truly enhancing structures from lesions with native high signal intensity at T1 [8, 12].

In case of breast cancer, peak enhancement occurs within the first 2 min after the injection of contrast medium. Therefore, relatively short data acquisition times, in

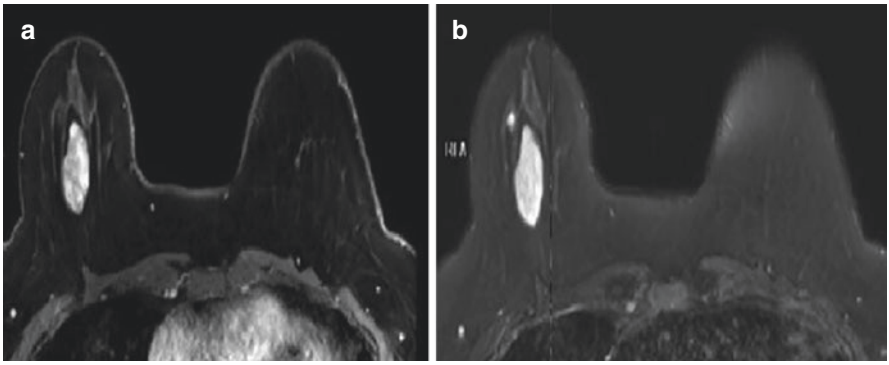


Fig. 10.10 42 year old female presented with right breast lump. Axial T2 weight fat sat (**a**), contrast enhanced T1 weighted axial fat sat (**b**) images showed a well circumscribed hyperintense enhancing lesion in the lower half of right breast. HPE: myxoid fibroadenoma

the order of 60–120 s per volume acquisition, are necessary. This permits sampling of the time course of signal enhancement after contrast injection, which is helpful because the highly vascularized tumor of the breast shows a faster contrast uptake than the surrounding tissue. Importantly, it allows a complete analysis of morphologic details as in the very early postcontrast phase, the contrast between the cancer and the adjacent fibroglandular tissue is ideal. Tumors show wash out as early as 2–3 min after contrast medium injection, whereas the adjacent fibroglandular tissue may still show substantial enhancement, resulting in lower contrast differentiation between the cancer and the fibroglandular tissue. Long acquisition times will be associated with the risk of not resolving fine details of margins and internal architecture; this could have pivotal importance for the differential diagnosis, and may even have the risk of missing small cancers altogether because they are masked by adjacent breast tissue.

A dynamic sequence demands at least three time points to be measured, that is, one before the administration of contrast medium, one approximately 2 min later to capture the peak and one in the late phase to evaluate whether a lesion continues to enhance, shows a plateau or shows early wash-out of the contrast agent (decrease of signal intensity) [20]. In malignant masses which have leaky vessels, the peak contrast material accumulation will have passed, and contrast material is being removed from the lesion in late phase. In benign lesions with less-permeable vessels, the contrast gradient over the vessel wall will still be positive, and therefore the enhancement of the lesion still increases. This is reflected in the shape of the time–signal intensity curves; a persistent increase is most commonly seen in benign lesions (type 1 curve), whereas a decrease in the late phase is common in malignant lesions (type 3 curve) (Fig. 10.11) [25]. Approximately 85% of cancers manifest with a washout curve [25–28]. Persistent curves are rare in malignancies, although they

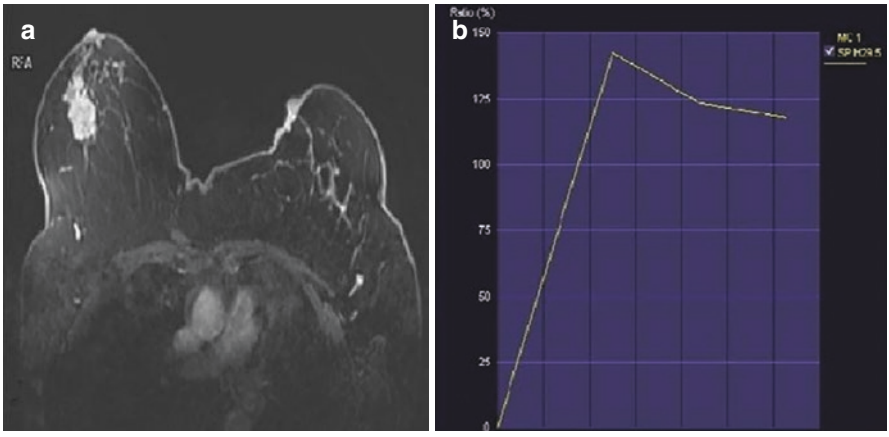


Fig. 10.11 A 54 year patient came with history of right breast lump. Early post contrast T1 weighted axial fat sat (**a**) image show an irregularly heterogeneously enhancing lesion in the outer half of right breast. Time signal intensity curve (**b**) reveals type 3 curve because of rapid uptake and washout of contrast. HPE: IDC

may be present in ductal carcinoma in situ (DCIS) and more diffuse-growing invasive cancers, particularly lobular breast cancers.

DWI quantifies the random movement of water molecules in tissue, which is affected by tissue microstructure and cell density. Cancers show decreased water diffusion because of increased cell density, which leads to higher signal intensity at DWI. DWI is performed in a short acquisition time and does not rely on the administration of a contrast agent. To obtain adequate DWI acquisitions, the selection of appropriate b values, adequate fat suppression, minimization of artifacts, and sufficient SNR are crucial.

The apparent diffusion coefficient (ADC) is a quantitative measure of diffusivity derived from DWI. Values are usually expressed in 10^{-3} mm^2/s. Because of the hindered diffusion in cancers, mean ADCs are generally low (range, 0.8–1.3 $\times 10^{-3}$ mm^2/s) compared with those in benign lesions (range, 1.2–2.0 $\times 10^{-3}$ mm^2/s). Consequently, cancers have a low signal intensity on the derived ADC maps.

The morphologic and kinetic features of findings are described by using the BI-RADS lexicon. Lesions are categorized as foci (5 mm or less of enhancement and by definition too small to characterize any further, but standing out from the surroundings), masses (space-occupying lesions), and non-mass enhancement (NME) (areas of enhancement without a clear space-occupying lesion present). Masses are further characterized on the basis of their shape (oval, round, irregular), margins (circumscribed, irregular and spiculate) and internal enhancement pattern (homogenous, heterogenous, rim enhancement) (Fig. 10.12). Areas of NME are further described according to distribution (focal, linear, segmental, regional) and internal enhancement pattern (homogenous, heterogenous, clumped, clustered ring) (Figs. 10.13 and 10.14). For both lesion types, initial and delayed phase enhancement are described to improve the differential diagnosis. Focus (Fig. 10.15) are

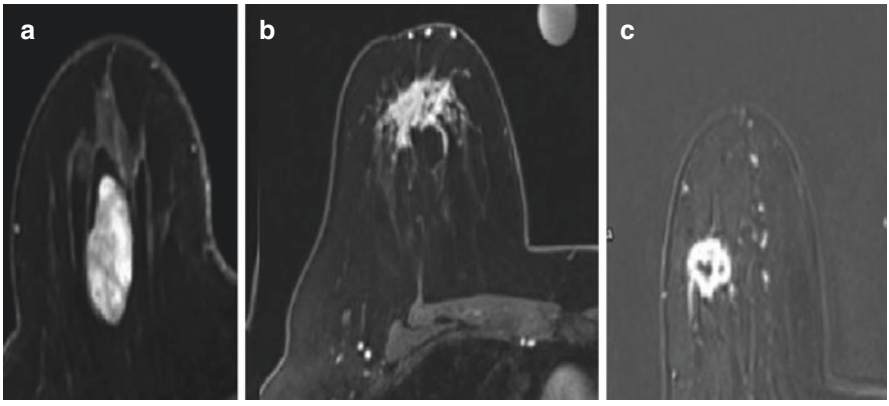


Fig. 10.12 Types of masses and their characteristics based on shape, margins and internal enhancement on axial post contrast T1 weighted fat sat images (**a**) Well circumscribed oval mass showing dark internal septations, HPE Fibroadenoma. (**b**) Irregular lesion showing spiculated margins with heterogenous enhancement, HPE: IDC. (**c**) Round lesion with irregular margins showing rim enhancement

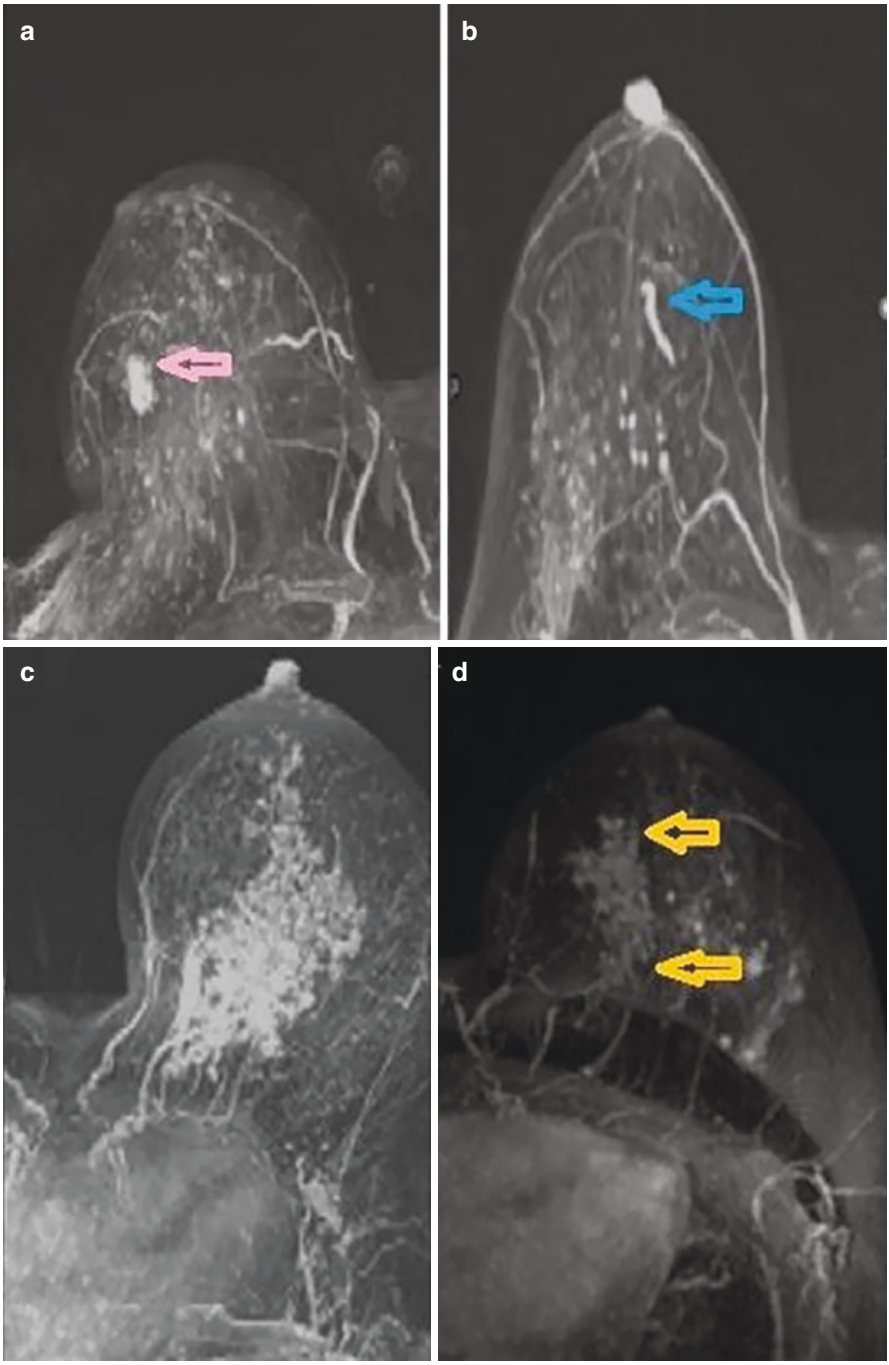


Fig. 10.13 MIP images of non-mass enhancement based on distribution pattern (**a**) focal (light pink arrow) (**b**) linear (blue arrow) (**c**) segmental (**d**) regional (yellow arrows)

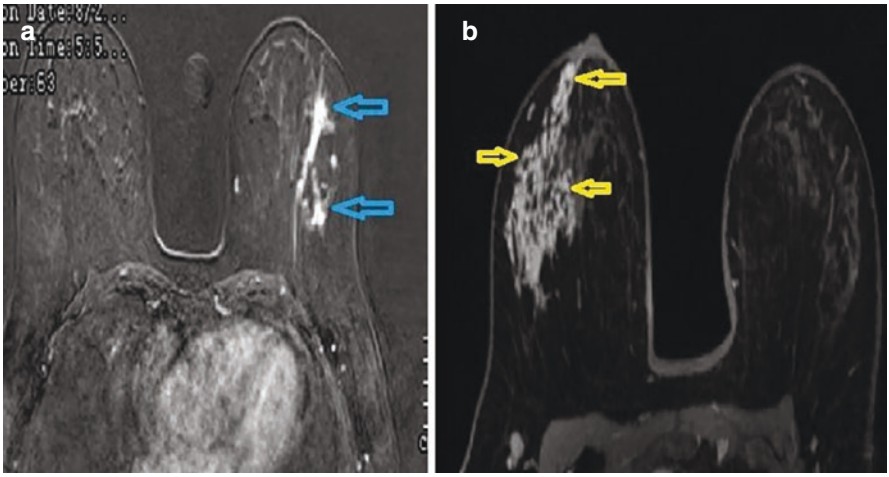


Fig. 10.14 T1 weighted post contrast fat sat axial images showing descriptor of non-mass enhancement based on internal enhancement pattern (**a**) clumped (blue arrows) (**b**) clustered ring (yellow arrows)

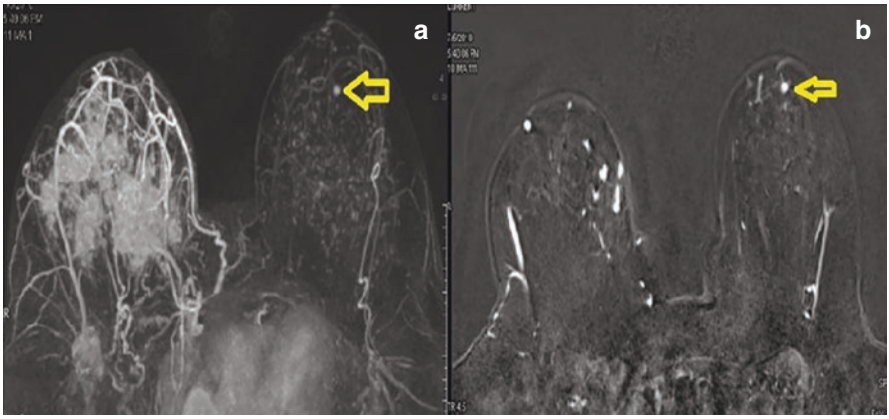


Fig. 10.15 Axial post contrast T1 weighted fat sat MIP (**a**) and single image (**b**) shows a tiny sub centimetric enhancing focus (yellow arrows) in the left breast in a patient with locally advanced right breast cancer which is too small to characterize but standing out from the surrounding. HPE: IDC

usually categorized as BIRADS 3 lesions unless there is relevant clinical history to prompt biopsy.

Approximately two-thirds to three-quarters of cancers manifest as a mass, including most invasive ductal cancers; the remainder are visible as areas of NME, including the majority of cases of DCIS. Typical malignant masses have an irregular shape and margin, heterogeneous or rim enhancement patterns, and show washout

of contrast. While benign lesions like fibroadenomas appear as well circumscribed masses showing homogenous enhancement with thin non enhancing septae within and reveal persistent enhancement. Classic malignant areas of NME have a segmental distribution and a clumped or clustered ring pattern of internal enhancement. While most cancers are easily recognizable by their morphologic features alone, smaller lesions are more difficult to assess [12].

10.7 Conclusion

In the hands of experienced teams, MRI allows for improvement of surgical practice, reducing re-excisions while preventing unnecessary mastectomies. Likewise, MRI enables patient selection to neoadjuvant chemotherapy and is the modality of choice for modification of therapeutic agents, for pre- surgical assessment of residual tumor size to determine candidates for breast- conserving surgery, and for prediction of pathologic complete response to triage patients to clinical trials omitting surgery. Although there is concern about the long-term deposition of gadolinium in patients undergoing an annual screening MRI examination, this examination leads to earlier cancer detection in virtually all evaluated populations at high sensitivity and with very low interval cancer rates. From an economic perspective, and to improve patient comfort, breast MRI can be optimized by adjusting the protocol with regard to the indication. For indications where the exclusion of disease is most important, abbreviated protocols may be used. On the other hand, when lesions need to be characterized in detail, or when the frequency of findings is high, multiparametric protocols are mandatory.

To summarize

1. Breast MRI is an invaluable tool in the diagnosis and management of breast cancer.
2. Breast MRI is a more sensitive examination than both mammography and ultrasound, and when used in the appropriate clinical situations, the modality clinical situations, the modality can alter patient management and improve outcomes apart from other indications
3. Breast MRI is also used as a problem-solving tool in specific clinical situations, particularly as a novel way to evaluate patients with a new cancer diagnosis.
4. Breast MRI can be used to evaluate the morphology of the primary lesion, detect adjacent satellite lesions and other ipsilateral and contralateral lesions thus altering the patient management based on findings.

For adequate performance, some important points should be kept in mind.

- A mandatory dedicated bilateral breast coil.
- The spatial and temporal resolution must be sufficient.
- A T1-weighted sequence should be obtained for at least three time points, one prior to and two after contrast administration.

- Reporting should be performed by a radiologist with experience in breast MRI, using the ACR BI-RADS MRI Lexicon and should correlate with mammography and breast ultrasound findings.
- Availability or tie up with centres performing MRI-guided breast biopsy is must.

References

1. Heywang SH, Hahn D, Schmidt H, et al. MR imaging of the breast using gadolinium-DTPA. J Comput Assist Tomogr. 1986;10:199–204.
2. Mann RM, Balleyguier C, Baltzer PA, et al. Breast MRI: EUSOBI recommendations for women's information. Eur Radiol. 2015;25:3669–78.
3. Kuhl C. The current status of breast MR imaging. Part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice. Radiology. 2007;244(2):356–78.
4. Kuhl C. Current status of breast MR imaging. Part 2. Clinical applications. Radiology. 2007;244(3):672–91.
5. Kolb T, Lichy J, Newhouse J. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology. 2002;225(1):165–75.
6. Kuhl C. The changing world of breast cancer. Invest Radiol. 2015;50(9):615–28. https://doi.org/10.1097/RLI.0000000000000166.
7. Shahid H, Wiedenhoefer JF, Dornbluth C, et al. An overview of breast MRI. Appl Radiol. 2016:7–13.
8. Mann RM, Kuhl CK, Kinkel K, Boetes C. Breast MRI: guidelines from the European Society of Breast Imaging. Eur Radiol. 2008;18(7):1307–18.
9. Berg WA, Gutierrez L, NessAiver MS, Carter WB, Bhargavan M, Lewis RS, Ioffe OB. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology. 2004;233:830–49.
10. Del Frate C, Borghese L, Cedolini C, Bestagno A, Puglisi F, Isola M, Soldano F, Bazzocchi M. Role of pre-surgical breast MRI in the management of invasive breast carcinoma. Breast. 2007;16(5):469–81.
11. Liberman L, Morris EA, Dershaw DD, Abramson AF, Tan LK. MR imaging of the ipsilateral breast in women with percutaneously proven breast cancer. AJR Am J Roentgenol. 2003;180:901–10.
12. Mann RM, Cho N, Moy L. Breast MRI: state of the art. Radiology. 2019;292:520–36.
13. Orel SG, Weinstein SP, Schnall MD, Reynolds CA, Schuchter LM, Fraker DL, Solin LJ. Breast MR imaging in patients with axillary node metastases and unknown primary malignancy. Radiology. 1999;212:543–9.
14. Rieber A, Brambs HJ, Gabelmann A, Heilmann V, Kreienberg R, Kühn T. Breast MRI for monitoring response of primary breast cancer to neo-adjuvant chemotherapy. Eur Radiol. 2002;12:1711–9.
15. Balu-Maestro C, Chapellier C, Bleuse A, Chanalet I, Chauvel C, Largillier R. Imaging in evaluation of response to neoadjuvant breast cancer treatment benefits of MRI. Breast Cancer Res Treat. 2002;72:145–52.
16. Morakkabati N, Leutner CC, Schmiedel A, Schild HH, Kuhl CK. Breast MR imaging during or soon after radiation therapy. Radiology. 2003;229:893–901.
17. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;17(366):2087–106.

18. Trentham-Dietz A, Newcomb PA, Nichols HB, Hampton JM. Breast cancer risk factors and second primary malignancies among women with breast cancer. Breast Cancer Res Treat. 2007;105:195–207.
19. Elkhuizen PH, van de Vijver MJ, Hermans J, Zonderland HM, Leer JW. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. Int J Radiat Oncol Biol Phys. 1998;40:859–67.
20. Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den BW, Barillot I, Fourquet A, Borger J, Jager J, Hoogenraad W, Collette L, Pierart M. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med. 2001;345:1378–87.
21. Holmich LR, Vejborg I, Conrad C, Sletting S, McLaughlin JK. The diagnosis of breast implant rupture: MRI findings compared with findings at explantation. Eur J Radiol. 2005;53:213–25.
22. Ikeda DM, Borofsky HB, Herfkens RJ, Sawyer-Glover AM, Birdwell RL, Glover GH. Silicone breast implant rupture: pitfalls of magnetic resonance imaging and relative efficacies of magnetic resonance, mammography, and ultrasound. Plast Reconstr Surg. 1999;104:2054–62.
23. Spick C, Szolar DH, Baltzer PA, et al. Rate of malignancy in MRI-detected probably benign (BI-RADS 3) lesions. AJR Am J Roentgenol. 2014;202:684–9.
24. Liberman L, Morris EA, Benton CL, Abramson AF, Dershaw DD. Probably benign lesions at breast magnetic resonance imaging: preliminary experience in high-risk women. Cancer. 2003;98:377–88.
25. Dorrius MD, Pijnappel RM, der Jansen-van Weide MC, Oudkerk M. Breast magnetic resonance imaging as a problem-solving modality in mammographic BI-RADS 3 lesions. Cancer Imaging. 2010;10:S54–8.
26. Neubauer H, Li M, Kuehne-Heid R, Schneider A, Kaiser WA. High grade and non-high grade ductal carcinoma in situ on dynamic MR mammography: characteristic findings for signal increase and morphological pattern of enhancement. Br J Radiol. 2003;76:3–12.
27. Partridge SC, Stone KM, Strigel RM, DeMartini WB, Peacock S, Lehman CD. Breast DCE-MRI: influence of postcontrast timing on automated lesion kinetics assessments and discrimination of benign and malignant lesions. Acad Radiol. 2014;21(9):1195–203.
28. Kollias J, Ellis I, Elston C, et al. Prognostic significance of synchronous and metachronous bilateral breast cancer. World J Surg. 2001;25(9):1117–24.

Radiological Interventions for Breast Cancer

11

Ekta Dhamija and Smriti Hari

11.1 Introduction

Breast interventions majorly includes biopsy from suspicious site under USG, stereotactic or MRI guidance as it enables accurate tissue sampling and reduces need of multiple repeat biopsies [1]. Increase in incidence of breast cancer and its association with genetic mutation predisposing younger age group to higher risk of cancer mandates stringent follow up by screening and surveillance programs. This has led to early pick up of non-palpable suspicious lesions which need guided biopsy or excision after hook wire localization. Institution of neo-adjuvant chemotherapy (NACT) in the treatment regime of breast cancer has improvised the surgical outcome by reducing overall tumor burden making breast conservative surgery possible (BCS) [2]. However, many times there is complete clinical and radiological response to NACT and surgery is warranted to establish pathological complete response. In such settings, tumor marker placed pre-chemotherapy serves as the target for site for surgical removal. Thus these localization techniques have therapeutic as well as diagnostic applications.

11.1.1 Biopsy

Any suspicious breast lesion (BIRADS Category 4 and 5) need histopathological analysis for further management. Fine needle aspiration cytology (FNAC) is being replaced by core needle biopsy (CNB) in breast lesions as it is associated with high

Ekta Dhamija, MD (✉)
Associate Professor, Department of Radiodiagnosis, IRCH, AIIMS, New Delhi, India
e-mail: drektadhamija.aiims@gmail.com

Smriti Hari, MD
Professor, Department of Radiodiagnosis, AIIMS, New Delhi, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_11

false negative rates [3] and it cannot differentiate *in situ* from invasive cancer. The latter, however, requires skill and expertise to perform and requires a couple of days to get the results. In certain situations where IHC is not required, for example BIRADS Category 3 lesion in patients with known carcinoma, lymphoma and leukemia; FNAC is preferred as it is less invasive, time and cost-effective.

Image guided biopsies are performed predominantly for non-palpable screen detected lesions and palpable lesions undergo manually/palpation guided percutaneous biopsy. However, it has been observed that false negative diagnosis are more commonly seen with blind/palpation guided breast biopsy as compared to image guided biopsy [4]. Hence, it is recommended that the histopathological result of any core biopsy should be correlated with clinical features and imaging characteristics to reduce false negative diagnosis of carcinoma. Any rad-path discordant result warrants re-evaluation, assessment and repeat biopsy with appropriate guidance and follow up [5].

The techniques and instrumentation have evolved over years with improvement in diagnostic accuracy of these procedures (Fig. 11.1). Basic knowledge of the diagnostic imaging and the intervention equipment is essential to select appropriate lesion and the biopsy technique.

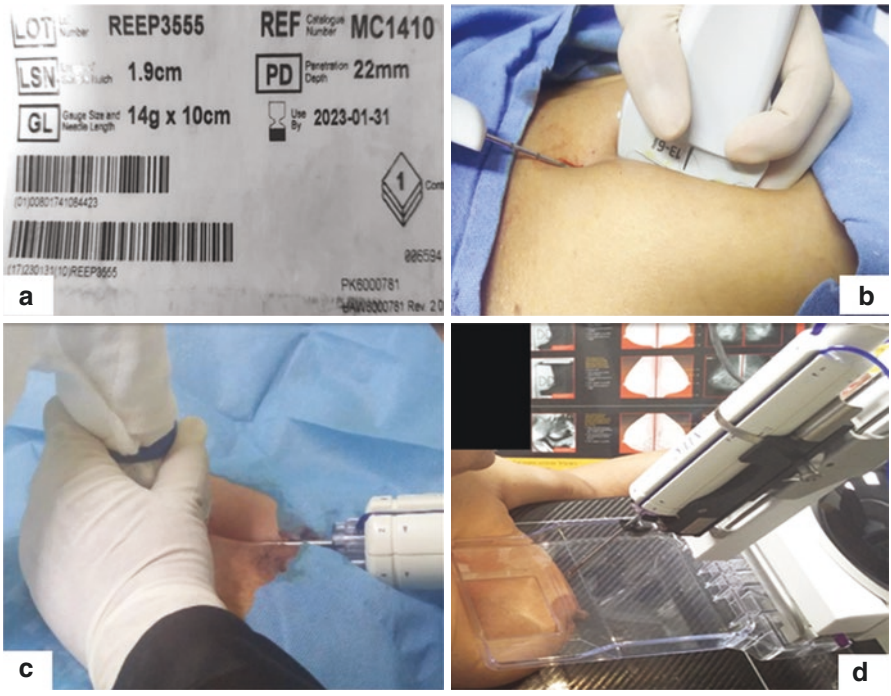


Fig. 11.1 Breast biopsy instruments: (**a**) Core needle biopsy for breast should be performed using 14G biopsy needle with 2 cm throw. (**b**) Linear transducer is used for performing ultrasound guided breast biopsy where the biopsy needle is inserted and kept parallel to the plane of chest wall. (**c**) Vacuum assisted biopsy with 9G biopsy needle can be used for ultrasound guided as well as stereotactic biopsy (**d**)

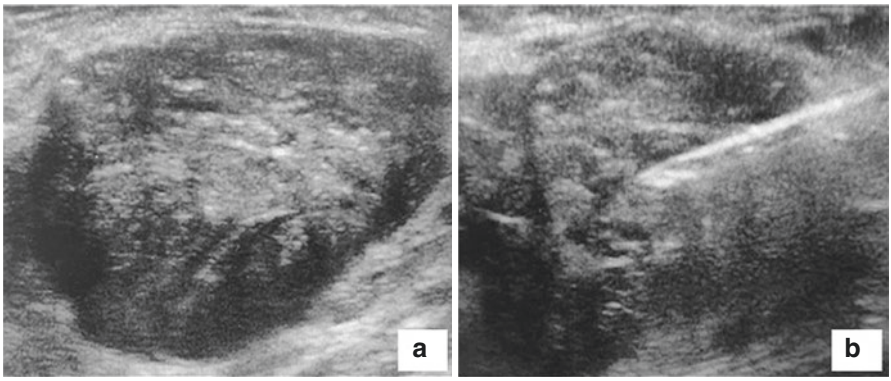


Fig. 11.2 Ultrasound guide breast biopsy of a mass. (**a**) The 14G core biopsy needle is inserted and then fired (**b**) into an irregular heteroechoic mass, to obtain tissue cores

Biopsy from breast pathologies differs from the routine biopsies of other body parts. Unlike CNB of any other body part, breast CNB is done using 14G automatic/semiautomatic biopsy needles with 2 cm throw, to avoid insufficient sampling error and atleast 4–5 cores should be obtained for adequate pathological analysis [6] (Fig. 11.2).

Vacuum assisted breast biopsy (VAB) was introduced in late 1990s [7]. It is an improved technique of CNB which can be used with any imaging modality-USG, mammography or MRI. The basic principle is application of vacuum which sucks and holds the tissue at sample notch of biopsy needle and another vacuum which transports this sample to sample notch outside the breast. The entire procedure is performed after single time insertion of the biopsy needle in contrast to standard CNB in which multiple insertions are required. Other advantage with VAB is the provision of continuous irrigation of the biopsy site with saline or local anesthetic agent which reduces the chances of hematoma formation. Also, the quality of cores obtained are better as it uses 7–11G needles and multiple cores around the needle can be taken by rotating the needle for an angle of 360°. It also enables the operator to place marker clip at the site through the biopsy probe without removing the needle especially in cases of small lesions or calcification where the entire lesion can get removed during the procedure. VAB is considered to be more accurate than CNB with negative predictive value reaching upto 99.9% [8–10]. Despite all this, VAB is not routinely performed because it is very expensive and is performed only in situations where CNB is inconclusive.

Ultrasound is the most common modality used for performing breast intervention procedures as it is readily available, cheaper, radiation free, less time consuming and enables real-time needle visualization. Suspicious screen detected non-palpable calcifications are biopsied using stereotactic unit of mammography equipment which is based on trigonometrically detecting depth of the target. Stereotactic biopsies are often VAB to avoid multiple re-insertions of the needle and a marker clip can be placed in the same setting. Post biopsy specimen radiograph should be obtained to ensure presence of calcification in the sample (Fig. 11.3). MR

guided biopsy is recent development in this field for suspicious lesions only seen on MRI; however, it is time consuming, expensive and the facility is not available everywhere.

11.1.1.1 Pre Biopsy Evaluation

Any suspicious breast lesion categorized as BIRADS 3 (few specific indications, Table 11.1), 4 and 5 should undergo sampling. Hence it is only logical that the lesions should be detected and assigned an appropriate BIRADS category. Before performing biopsy, three important things need due consideration and evaluation-first, the choice of appropriate modality; second is to determine best possible approach to lesion and last but not the least, patient's counselling and written informed consent after explaining the procedure. Breast biopsy can be done on out-patient basis without any prior admission and the coagulation profile workup needed for other biopsies, is not routinely required for breast biopsy. The abnormality is targeted on the imaging modality which demonstrates the lesion best; for example, microcalcifications are sampled with stereotactic biopsy and palpable masses are better seen on USG. Safest approach to the lesion should be assessed and pre-planned like determination of the shortest distance, avoiding the vessels close to the mass to reduce risk of bleeding and hematoma formation, the needle should be parallel to chest wall in order to avoid inadvertent injury to chest wall or lungs.

11.1.1.2 Post Biopsy Care

Firm compression along the biopsy tract should be applied to achieve hemostasis. Cold fomentation with ice pack should be done at biopsy site for atleast 30 min after

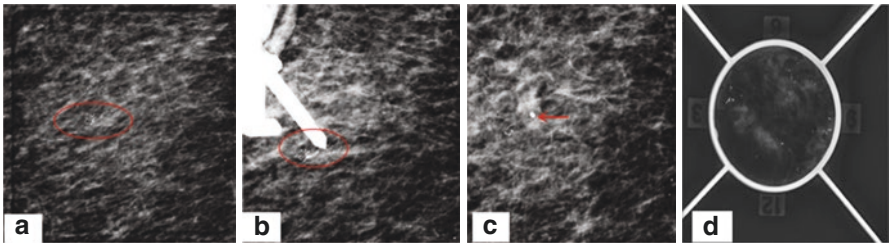


Fig. 11.3 Vacuum assisted Stereotactic breast biopsy: (**a**) Cluster of suspicious microcalcification is identified on mammogram which is then targeted using stereotactic apparatus (highlighted area in **a** & **b**). After adequate tissue removal, marker clip is placed in same sitting through the VAB needle (arrow in **c**). (**d**) Specimen mammogram confirms presence of calcification within the tissue

Table 11.1 Indications of breast biopsy of BIRADS 3 category lesions

Patient with known carcinoma in contralateral breast
Patient with known carcinoma in ipsilateral breast but different quadrant
Strong family history
Anxious patient or anxious surgeon/physician
Known carcinoma of another primary site like ovary, lung- to rule out second primary or metastases
Lymphoma, leukemia patients on treatment or surveillance- to rule out breast involvement/ recurrence

the procedure to reduce the chances of hematoma formation. Patients are instructed not to do strenuous activities using the ipsilateral upper limb like heavy weight lifting and cooking activities. Analgesics are indicated only if necessary. Patient should be informed that mild discoloration and oozing at the biopsy site is expected and resolves on its own.

11.1.1.3 Complications

Percutaneous breast biopsy is minimally invasive but safe procedure. Most common complications are vasovagal reaction and hematoma formation which may rarely get infected. Rate of occurrence of minor complications which can be managed conservatively is approximately 1.4% [11]. Vasovagal reaction can be caused due to anxiety, fear or pain and it can be managed by elevating the feet and monitoring pulse and blood pressure. Significant hematoma formation or development of abscess which may need surgical drainage has been reported in upto 0.1% cases. The small hematomas formed following biopsies are visible on imaging for few days to weeks [12, 13]. Good compression following biopsy and patient compliance prevent formation of large hematomas. Strict aseptic precautions during the procedure reduce the chances of infection. This percutaneous breast biopsy generally does not cause long term changes like scarring or architectural distortion. Complication rates of biopsy with biopsy gun and VAB are similar [14].

11.1.2 Lesion Localization

Surgery remains the treatment of choice for breast cancer patients; however, there have been immense change in the pattern of surgical approach from mastectomy to breast conservation surgery. The basic aim is to achieve loco-regional disease removal on histopathological examination and at the same time, preserving the cosmetic and functional outcome in the patient. Thus, neoadjuvant chemotherapy (NACT) is administered in the patients especially in setting of locally advanced breast cancer so as to reduce the pre-operative tumor bulk. NACT may achieve complete resolution of clinically palpable mass and radiological abnormality in upto 30% cases which demands the need for some mean to localize the tumor at the time of surgery to establish complete pathological response as well [15, 16]. Literature highlights many innovative techniques like skin tattooing, imaging guided radio-opaque tumor marker placement like custom made clips using angiographic wire, commercially available marker clips or radioactive seed (I-125) and magseeds [15, 17–21]. Edieken et al. observed that in 29 of 49 patients (47%), the markers were the only evidence of original tumor site post NACT [22]. Hence, tumor localization with clip placement becomes essential in order to reduce chances of local recurrence [23].

The basic purpose of all these is to serve as marker for tumor site at the end of chemotherapy. Prior to surgery, these markers are identified and sterotactic or USG guided hook wire insertion is performed to guide surgeon about the site and pattern of incision and removal of the tumor bed with the marker. After removal, specimen

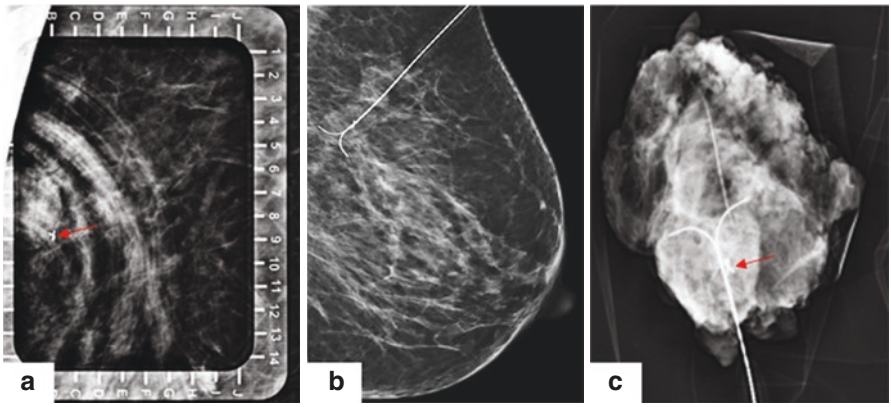


Fig. 11.4 Hook wire localization: (**a**) Clip is seen on craniocaudal mammogram performed using alphanumeric compression paddle (arrow) followed by placement of Y-shaped hookwire (**b**). Specimen radiograph demonstrates and confirms removal of the tumor along the site of clip(arrow) alongwith the hookwire (**c**)

radiograph is obtained to confirm removal of the target site with good margins along with removal of the clip and wire (Fig. 11.4).

Indications for hook wire localization without clip placement include screening detected small suspicious non-palpable lesions for diagnostic surgical excision biopsy especially in settings where facility of stereotactic biopsy is not available. "Hookwire Bracketing" is a technique which involves placement of multiple hookwires in same breast either for localization of multiple lesions or to mark extents of large lesion or cluster of microcalcification.

Radioguided Occult lesion localization (ROLL) is another method of tumor localization which is performed by injecting particles of colloidal human serum albumin labeled with radioactive technetium (^{99m}Tc) which can be intra-operatively detected using handheld gamma probe. Failure to visualize lesion due to dispersal of this isotope by inadvertent intraductal injection is potential complication associated with this procedure in addition to the cost issue [24].

Newer localization techniques include placement of radioactive iodine (I^{125}) seed 5–7 days prior to the day of surgery which can then be localized intra-operatively with a hand held gamma probe. This precludes the risk of migration or displacement of hookwire and is less invasive [25]. Since it is associated with radiation exposure, magseeds composed of iron oxide and paramagnetic steel have been used by many breast surgeons. The latter can be placed 2–30 days before surgery and are not associated with any radiation; however, are more expensive and need a dedicated Sentimag detector for localization [26]. Due to these reasons, marker clip followed by hookwire localization is still the more commonly used tumor localization technique.

Intra-operative ultrasound is an effective but under-utilized technique of lesion localization which enables localization as well as planning of the surgery, obviating need for wire localization. The radiologist can assist by demonstrating the tumor

on-table in the operation theatre, mark the tumor margins and confirm the findings on resected specimen during the surgery itself [27, 28]. It can yield good results in the peripheral centers or hospitals where the other localization techniques are not feasible and radiologist is available on-site. Needless to say, it needs multidisciplinary effort with good communication and understanding between the surgeon and radiologist with active participation of latter in surgical planning.

11.1.3 Miscellaneous Interventions

Majority of the radiological interventions aim at either reaching or excluding the diagnosis of carcinoma but there has been expansion of the role of radiologist beyond biopsy, in curative as well as palliative care field. One of the most common benign breast diseases is simple or complicated cysts which present with palpable lump and breast pain. Patients with mastitis may develop abscess which does not respond to antibiotics alone and need manual drainage. The open incision and drainage was considered as the treatment of choice for abscess or cyst drainage but it is more invasive and is associated with risk of fistula formation, inability to feed from the ipsilateral breast [29]. *USG guided cyst/abscess aspiration* has thus become the most acceptable substitute for this as it is less invasive and does not intervene with routine activities. Furthermore, it can be repeated on out-patient basis, if required and is equally efficacious [30].

The various other interventions with therapeutic intent include radiofrequency ablation of breast lesions; complete removal of benign lesions like fibroadenomas using VAB; targeted removal of USG detected positive axillary lymph nodes during surgery instead of removing the entire axillary nodal chain; accelerated partial breast irradiation (APBI) post BCS.

Radiofrequency ablation administers thermal energy which induces coagulative necrosis of the tumor. Its role has been studied for early stage breast cancer and found to be effective in single masses of less than 2 cm size [31–33]. Due to its limitations in determining the optimum zone, status of tumor margins; it is yet to be validated as an alternate to surgery [33, 34].

Involvement of axillary lymph nodes alters the management and prognosis of breast cancer to a great extent. The nodes are addressed with Sentinel Lymph node biopsy (SLNB) and/or Axillary lymph node dissection (ALND) depending on the various parameters including tumor size, stage, pre-NACT nodal status. Since ALND has increased association with post-op morbidity, it has been postulated to remove only the suspicious lymph nodes instead of radical removal of the nodes. USG is being evaluated to ascertain and detect the abnormal lymph nodes using certain diagnostic criteria followed by removal of only these suspicious nodes rather than the radical surgery, especially in post NACT patients [35–37]. The lymph nodes are considered suspicious if they have asymmetrical cortical thickening/abnormal cortex to hilum ratio/peripheral blood flow/loss of fatty hilum (Fig. 11.5). The nodes can be sampled and clipped prior to NACT which serves as marker at the time of surgery.

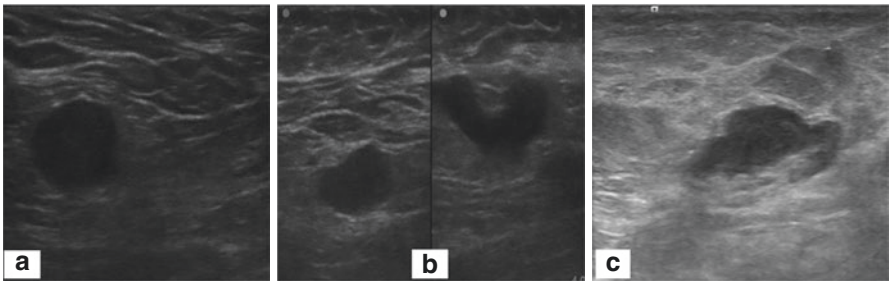


Fig. 11.5 Suspicious axillary lymph nodes: Ultrasound features raising suspicion of metastatic/involved axillary lymph nodes in patients with known breast cancer include- (**a**) loss of fatty hilum, (**b**) asymmetrical cortical thickening and (**c**) Focal cortical thickening

The standard external whole breast irradiation following breast surgery extends over a period of 6–6.5 weeks and involves irradiation to the chest wall, lung and heart in addition to the breast resulting in more complications. APBI has emerged as an alternative to WBI; which delivers radiation to the tumor bed at a higher dose per fraction in shorter time period [38]. APBI should ideally be planned at the time of surgery where catheters can be placed in the operative bed at same setting but it can be planned after surgery where these catheters are placed by identifying the surgical bed on USG seen as seroma or irregular surgical scar or echogenic surgical clips.

Breast cancer patients experience deterioration of quality of life (QOL) especially in metastatic setting. Distant metastases can lead to significant dyspnea (pleural effusion), bone pain (metastases), abdominal distension (ascites), and jaundice or liver dysfunction (liver metastases); where palliative interventions serve in improving the QOL.

Malignant pleural effusion needs drainage with percutaneous catheter placement under USG or CT guidance before pleurodesis is considered [39]. Similarly, ascites should be drained for symptomatic relief. Vertebroplasty can be considered for bone pain whereas perioperative pain can be reduced by giving USG guided nerve block such as pectoralis or serratus anterior block [40, 41].

To conclude, radiology has a crucial role in diagnosing and planning the treatment of breast diseases which has expanded to therapeutic field as well as palliative care. Multidisciplinary approach is necessary for management of any breast disease and the radiologist is a vital part of the disease management team for treatment and follow up of the patients.

References

1. Hari S, Kumari S, Srivastava A, Thulkar S, Mathur S, Veedu PT. Image guided versus palpation guided core needle biopsy of palpable breast masses: a prospective study. Indian J Med Res. 2016;143(5):597–604.
2. Teshome M, Hunt KK. Neoadjuvant therapy in the treatment of breast cancer. Surg Oncol Clin N Am. 2014;23(3):505–23.

3. Mendoza P, Lacambra M, Tan PH, Tse GM. Fine needle aspiration cytology of the breast: the nonmalignant categories. Patholog Res Int. 2011;2011:547580. https://doi.org/10.4061/2011/547580.
4. Shah VI, Raju U, Chitale D, Deshpande V, Gregory N, Strand V. False-negative core needle biopsies of the breast: an analysis of clinical, radiologic, and pathologic findings in 27 concecutive cases of missed breast cancer. Cancer. 2003;97(8):1824–31. https://doi.org/10.1002/cncr.11278.
5. Youk JH, Kim E-K, Kim MJ, Lee JY, Oh KK. Missed breast cancers at US-guided core needle biopsy: how to reduce them. Radiographics. 2007;27(1):79–94.
6. Parker SH, Jobe WE, Dennis MA, Stavros AT, Johnson KK, Yakes WF, et al. US-guided automated large-core breast biopsy. Radiology. 1993;187(2):507–11.
7. Burbank F, Parker SH, Fogarty TJ. Stereotactic breast biopsy: improved tissue harvesting with the mammotome. Am Surg. 1996;62(9):738–44.
8. Jackman RJ, Marzoni FA, Rosenberg J. False-negative diagnoses at stereotactic vacuum-assisted needle breast biopsy: long-term follow-up of 1,280 lesions and review of the literature. Am J Roentgenol. 2009;192(2):341–51.
9. Zhang C, Lewis DR, Nasute P, Hayes M, Warren LJ, Gordon PB. The negative predictive value of ultrasound-guided 14-gauge core needle biopsy of breast masses: a validation study of 339 cases. Cancer Imaging. 2012;12(3):488–96.
10. Lee SH, Kim E-K, Kim MJ, Moon HJ, Yoon JH. Vacuum-assisted breast biopsy under ultrasonographic guidance: analysis of a 10-year experience. Ultrasonography. 2014;33(4):259–66.
11. Kettritz U, Rotter K, Schrer I, et al. Stereotactic vacuum-assisted breast biopsy in 2874 patients: a multicenter study. Cancer. 2004;100:245–51.
12. Huber S, Wagner M, Medl M, Czembirek H. Benign breast lesions minimally invasive vacuum-assisted biopsy with 11-gauge needles: patient acceptance and effect on follow-up imaging. Radiology. 2003;226:783–90.
13. Lamm RL, Jackman RJ. Mammographic abnormalities caused by percutaneous stereotactic biopsy of histologically benign lesions evident on follow-up mammograms. Am J Roentgenol. 2000;174:753–6.
14. Philpotts LE, Hooley RJ, Lee CH. Comparison of automated versus vacuum assisted biopsy methods for sonographically guided core biopsy of the breast. Am J Roentgenol. 2003;180:347–51.
15. Baron LF, Baron PL, Ackerman SJ, Durden DD, Pope TL. Sonographically guided clip placement facilitates localization of breast cancer after neoadjuvant chemotherapy. Am J Roentgenol. 2000;174(2):539–40.
16. Pennisi A, Kieber-Emmons T, Makhoul I, Hutchins L. Relevance of pathological complete response after neoadjuvant therapy for breast cancer. Breast Cancer (Auckl). 2016;10:103–6.
17. Margolin FR, Kaufman L, Denny SR, Jacobs RP, Schrumpf JD. Metallic marker placement after stereotactic core biopsy of breast calcifications: comparison of two clips and deployment techniques. Am J Roentgenol. 2003;181(6):1685–90.
18. Espinosa-Bravo M, Sao Avilés A, Esgueva A, Córdoba O, Rodriguez J, Cortadellas T, et al. Breast conservative surgery after neoadjuvant chemotherapy in breast cancer patients: comparison of two tumor localization methods. Eur J Surg Oncol. 2011;37(12):1038–43.
19. 028418502127347600.pdf [Internet]. [cited 2018 Mar 6]. Available from: https://www.tandfonline.com/doi/pdf/10.1080/028418502127347600
20. Braeuning MP, Burke ET, Pisano ED. Embolization coils as tumor markers for mammography in patients undergoing neoadjuvant chemotherapy for carcinoma. Am J Roentgenol. 2000;174(1):251–2.
21. Zhang Y, Seely J, Cordeiro E, Hefler J, Thavorn K, Mahajan M, et al. Radioactive seed localization versus wire-guided localization for nonpalpable breast cancer: a cost and operating room efficiency analysis. Ann Surg Oncol. 2017;24(12):3567–73.
22. Edeiken BS, Fornage BD, Bedi DG, Singletary SE, Ibrahim NK, Strom EA, et al. US-guided implantation of metallic markers for permanent localization of the tumor bed in patients with breast cancer who undergo preoperative chemotherapy. Radiology. 1999;213(3):895–900.

23. Oh JL, Nguyen G, Whitman GJ, Hunt KK, Yu T-K, Woodward WA, et al. Placement of radiopaque clips for tumor localization in patients undergoing neoadjuvant chemotherapy and breast conservation therapy. Cancer. 2007;110(11):2420–7.
24. Corsi F, Sorrentino L, Bossi D, Sartani A, Foschi D. Preoperative localization and surgical margins in conservative breast surgery [Internet]. Int J Surg Oncol. 2013 [cited 2018 Mar 6]. Available from: https://www.hindawi.com/journals/ijso/2013/793819/
25. Hughes JH, Mason MC, Gray RJ, McLaughlin SA, Degnim AC, Fulmer JT, et al. A multi-site validation trial of radioactive seed localization as an alternative to wire localization. Breast J. 2008;14(2):153–7.
26. Harvey JR, Lim Y, Murphy J, Howe M, Morris J, Goyal A, et al. Safety and feasibility of breast lesion localization using magnetic seeds (Magseed): a multi-centre, open-label cohort study. Breast Cancer Res Treat. 2018;169(3):531–6.
27. Rahusen FD. Ultrasound-guided lumpectomy of nonpalpable breast cancer versus wire-guided resection: a randomized clinical trial. Ann Surg Oncol. 2002;9(10):994–8.
28. Krekel NM, Haloua MH, Lopes Cardozo AM, de Wit RH, Bosch AM, de Widt-Levert LM, et al. Intraoperative ultrasound guidance for palpable breast cancer excision (COBALT trial): a multicentre, randomised controlled trial. Lancet Oncol. 2013;14(1):48–54.
29. Imperiale A, Zandrino F, Calabrese M, Parodi G, Massa T. Abscesses of the breast: US-guided serial percutaneous aspiration and local antibiotic therapy after unsuccessful systemic antibiotic therapy. Acta Radiol. 2001;42(2):161–5.
30. Ulitzsch D, Nyman MKG, Carlson RA. Breast abscess in lactating women: US-guided treatment. Radiology. 2004;232(3):904–9.
31. Burak WE, Agnese DM, Povoski SP, Yanssens TL, Bloom KJ, Wakely PE, et al. Radiofrequency ablation of invasive breast carcinoma followed by delayed surgical excision. Cancer. 2003;98(7):1369–76.
32. Kinoshita T, Iwamoto E, Tsuda H, Seki K. Radiofrequency ablation as local therapy for early breast carcinomas. Breast Cancer. 2011;18(1):10–7.
33. Ito T, Oura S, Nagamine S, Takahashi M, Yamamoto N, Yamamichi N, et al. Radiofrequency ablation of breast cancer: a retrospective study. Clin Breast Cancer. 2018;18(4):e495–500.
34. Sun X, Chen J, Zhang C, Li F, Xu L, Zhu H, et al. A meta-analysis of clinical trials assessing the effect of radiofrequency ablation for breast cancer. OncoTargets Ther. 2016;1759.
35. Giuliano AE. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011;305(6):569.
36. Henke G, Knauer M, Ribi K, Hayoz S, Gérard M-A, Ruhstaller T, et al. Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial. Trials [Internet]. 2018 Dec [cited 2019 Oct 1];19(1). Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-3021-9
37. Verheuvel NC, Voogd AC, Tjan-Heijnen VCG, Roumen RMH. Potential impact of application of Z0011 derived criteria to omit axillary lymph node dissection in node positive breast cancer patients. Eur J Surg Oncol. 2016;42(8):1162–8.
38. Vicini F, Beitsch P, Quiet C, Gittleman M, Zannis V, Fine R, et al. Five-year analysis of treatment efficacy and Cosmesis by the American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial in patients treated with accelerated partial breast irradiation. Int J Radiat Oncol. 2011;79(3):808–17.
39. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ, on behalf of the BTS Pleural Disease Guideline Group. Management of a malignant pleural effusion: British Thoracic Society pleural disease guideline 2010. Thorax. 2010;65(Suppl 2):ii32–40.
40. Bashandy GMN, Abbas DN. Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery: a randomized clinical trial. Reg Anesth Pain Med. 2015;40(1):68–74.
41. Blanco R, Parras T, McDonnell JG, Prats-Galino A. Serratus plane block: a novel ultrasound-guided thoracic wall nerve block. Anaesthesia. 2013;68(11):1107–13.

Role of Nuclear Medicine in Breast Cancer

12

Ashwin Singh Parihar and Anish Bhattacharya

12.1 Introduction

Nuclear Medicine involves the use of radioactive elements (*radionuclides*), tagged with molecules in minute concentrations (*tracers*) to target specific functional pathways in the human body. The applications have a diverse range from multiple diagnostic indications to therapeutic utilities and cover a plethora of oncologic and non-oncologic conditions [1].

Once administered (commonly via the intravenous route), the radiotracers localize according to their specific properties and reveal specific functional aspects of tissues/organ systems. The in-vivo detection of these radiotracers can be done using probe detectors, which provide radioactive counts over various regions, but are unable to provide an image of the radiotracer distribution. For obtaining images of the radiotracer localization, gamma cameras are utilized for single photon emitters (e.g. ^{99m}Tc, ^{131}I) and Positron Emission Tomography (PET) detectors for positron emitters (e.g. ^{18}F, ^{68}Ga). ^{99m}Tc (half-life: 6 h) is the most common radionuclide for gamma camera imaging which is labelled with suitable molecules/pharmaceuticals for oncologic imaging [e.g., ^{99m}Tc-Methylene diphosphonate (MDP) for skeletal

Ashwin Singh Parihar, MD
Postdoctoral Research Associate, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri, USA

Anish Bhattacharya, DRM, DNB, PhD (✉)
Professor and Head, Department of Nuclear Medicine, PGIMER, Chandigarh, India
e-mail: anishpgi@yahoo.co.in

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_12

imaging, ^{99m}Tc-Sestamibi (MIBI) for breast tumour imaging, ^{99m}Tc-Sulfur colloid for sentinel lymph node imaging]. ^{18}F (half-life: 110 min) is the most common radionuclide for PET imaging (e.g. ^{18}F-Fluorodeoxyglucose; FDG for majority of oncologic imaging, ^{18}F-Sodium Fluoride; NaF for skeletal imaging). Addition of Single Photon Emission Computed Tomography (SPECT) and Computed tomography (CT) capabilities to the gamma camera can further enhance detectability by providing 3-dimensional images, in comparison to the planar, 2-dimensional images [2].

Today, most PET scanners are coupled with CT (PET/CT) to provide anatomic correlation to the functional radiotracer distribution. PET detectors have a higher resolution and can detect smaller lesions in comparison to planar gamma cameras and SPECT. However, PET/CT is quite expensive compared to planar gamma camera studies or SPECT/CT. The CT component of PET/CT may be a low dose CT for attenuation correction, or a full dose diagnostic CT, with or without oral/intravenous contrast. Several centres perform PET with diagnostic, contrast enhanced CT, thus obviating the need for a separate diagnostic CT and reducing the overall radiation burden to the patient [3].

The advantage of Nuclear Medicine imaging over conventional imaging, especially in an oncologic setting, is the capability to detect functional changes which usually long precede structural/anatomic changes. This is applicable at initial staging, where small metastatic sites might not have caused significant structural abnormalities and may be missed on conventional imaging. However, the functional disruptions in the local tissues can be detected using Nuclear Medicine imaging. This also applies to response assessment, where the structural features of the tumour might not show an immediate significant change, whereas the functional component may show a significant degree of response, signifying favourable response to therapy [4]. Gamma camera imaging and PET/CT additionally have the advantage of whole-body scanning, which provides an overall picture of global disease burden in a single setting and is useful in detecting otherwise occult sites of metastases [4].

Breast cancer is the most commonly diagnosed malignancy and the leading cause of mortality in women worldwide, despite a decreasing mortality trend [5]. The reduction in mortality rates has been primarily attributed to advances in breast cancer screening and adjuvant therapies [6, 7]. Early detection of disease and accurate staging enables prompt institution of stage-appropriate management, leading to improvement in patient morbidity and mortality.

Applications of nuclear medicine in breast cancer cover virtually every aspect of patient management, from screening, diagnosis, staging and response assessment to therapy in selected cases. Some of these indications have gained widespread clinical use and will be discussed in detail in the following sections. PET/CT is one such modality with significant clinical benefit in select patients, especially for staging and response assessment. Other notable applications that are not widely available or have better alternatives shall be briefly covered.

12.2 Applications of Nuclear Medicine in Breast Cancer

12.2.1 Dedicated Breast Imaging

Mammography and breast ultrasound are the common conventional imaging modalities for breast tumours. Contrast Enhanced Magnetic Resonance Imaging (CEMRI) is helpful as a supplemental screening technique in high-risk patients. Nuclear Medicine based dedicated breast imaging (DBI) employs SPECT or PET radiotracers for lesion localization. Breast Specific Gamma Imaging (BSGI) and Molecular Breast Imaging (MBI) are gamma camera/SPECT based modalities using ^{99m}Tc-MIBI as the radiotracer, whereas Breast PET and Positron Emission Mammography (PEM) are PET based techniques, using primarily ^{18}F-FDG. DBI can complement conventional screening techniques, especially in high-risk patients with equivocal findings on other imaging modalities. It can also help in diagnosis and staging of the primary tumour in selected patients by localizing the lesion and assisting in guided biopsy.

12.2.2 Breast Specific Gamma Imaging, Molecular Breast Imaging

BSGI and MBI are gamma-camera based DBI techniques, using ^{99m}Tc-MIBI as the radiotracer. ^{99m}Tc-MIBI binds intracellularly to the mitochondria and is localized to sites with increased cellularity/metabolic activity resulting in increased mitochondrial density [8]. It is thus not a tumour-specific agent, but represents sites showing higher cellularity/metabolic activity in comparison to the normal tissue forming the background [9]. Another aspect of ^{99m}Tc-MIBI is that it undergoes rapid efflux from cells bearing high levels of the transmembrane protein P-glycoprotein (PGp-170). PGp production is regulated by the Multidrug Resistance Gene (MDR1) which is also responsible for resistance to cytotoxic drugs. Thus, rapid efflux of ^{99m}Tc-MIBI is an in-vivo surrogate marker for MDR1 expression that can help provide prognostic information in patients undergoing chemotherapy [8].

The American College of Radiology (ACR) in their practice parameters described the following potential indications for BSGI/MBI [10]

(a) Assessment of disease extent/Pre-surgical staging in a patient with newly diagnosed breast cancer.
(b) Assessment of response to neo-adjuvant chemotherapy.
(c) Detection of local recurrence in breast cancer.
(d) Detection of primary in women with metastatic breast cancer with unknown primary site.
(e) Screening in high-risk women with dense breasts.
(f) Adjunct imaging to conventional breast imaging in indeterminate cases.

BSGI incorporates a single panel detector (Sodium/Caesium iodide based), while MBI has two detector panels (Semi-conductor; Cadmium-Zinc-Telluride based) [11]. 5–10 min after the intravenous injection of ^{99m}Tc-MIBI (dose ~4–8 mCi

for MBI systems), images of the breast are obtained in cranio-caudal (CC) and medio-lateral oblique (MLO) views, similar to the traditional views in mammography. The resolution of BSGI and MBI systems ranges from 4 to 5.6 mm, reflecting the threshold size for lesion detection, keeping all other parameters aside [12]. The sensitivity of MBI has been reported from 90 to 100% while the specificity ranges between 83–97% [13]. In a study of 1696 asymptomatic women with dense breasts and negative screening mammography, the incremental cancer detection rate with MBI was 7.7% (95% CI, 4.5–13.1%). The effective radiation dose received from screening MBI in this study was 2.3 mSv, higher than an average 0.56 mSv from digital mammography, but lower than the annual radiation exposure from natural sources (~3 mSv) [14]. The performance of BSGI and MBI does not deteriorate with increasing breast density, thus bearing an advantage over mammography in this setting [15]. However, the extra radiation dose, added costs and limited availability are constraints limiting their widespread use.

12.2.3 Dedicated Breast Positron Emission Tomography, Positron Emission Mammography

Dedicated breast imaging using PET detectors differs from traditional PET imaging in that the former has detector placement closer to the breasts and a smaller field of view. This improves resolution (Spatial resolution ~2 mm), and thus lesion detectability [12]. Two primary designs of breast specific PET imaging systems include dedicated breast PET (dbPET) which utilizes a ring shaped detector to image the patient lying prone, with breasts being suspended freely; and Positron emission mammography (PEM) which has two planar detectors, similar to MBI and imaging is performed like traditional mammography examinations with CC, MLO views (additional views being optional). dbPET because of closer approximation to the breasts, yields better resolution and image contrast but is costlier than PEM systems [16].

The common radiotracer used in both dbPET and PEM systems is ^{18}F-FDG, which targets the glycolytic pathway and is preferentially localized in cells with increased glucose demand and metabolism via the Glucose Transporters (GLUT). Around 5–10 mCi of ^{18}F-FDG is injected intravenously and images of the breasts in multiple views are obtained 60–90 min later. Since the uptake of ^{18}F-FDG is dependent on glucose metabolism, the patients should be prepared adequately for the study (e.g., fasting for 4–6 h prior to scan, avoiding strenuous exercise etc.), more of which will be discussed in the subsequent sections. The effective radiation dose from intravenous injection of 10 mCi of ^{18}F-FDG is ~7 mSv, significantly higher than that from conventional mammography.

The use of dbPET/PEM is primarily directed towards the staging, re-staging and response assessment of the primary breast cancer as it offers improved resolution and detectability over conventional whole-body PET/CT. In a multi-centre randomised prospective study of 388 women, with newly diagnosed breast cancer,

PEM and MRI had comparable sensitivity, but PEM had a higher specificity than MRI (79.9% vs 65.6%, respectively). The authors concluded that the PEM is a valuable alternative for women unable to undergo MRI imaging and because of higher specificity, can reduce unnecessary biopsies [17].

12.2.4 ^{18}F-FDG PET/CT in Breast Cancer

12.2.4.1 Principles and Procedure of ^{18}F-FDG PET/CT

^{18}F (half-life: 110 min) is a cyclotron produced radionuclide used for the synthesis of ^{18}F-FDG. The uptake of ^{18}F-FDG is mediated via the GLUT receptors, and once inside the cell, ^{18}F-FDG is phosphorylated and trapped intracellularly. As ^{18}F-FDG is a glucose analogue, high levels of blood sugar cause competitive inhibition of intra-cellular uptake of ^{18}F-FDG. To ensure optimum scan quality, certain preparations are required including instructions to patients which should be communicated and explained while scheduling the scan (Table 12.1).

PET/CT is performed as a sequential study, with the CT acquired first, followed by the PET component. Intravenous and oral contrast agents may be used, especially when performing a diagnostic CT as a part of the PET/CT procedure. The reconstructed PET/CT images are then reviewed with visual and semi-quantitative analyses. Standardized Uptake Value (SUV) is a common and frequently employed dimension-less indicator to determine the relative radiotracer concentration at a given site. It is calculated as:

$$\text{SUV} = \frac{\text{tracer activity in the region of interest}\left(\text{ROI}\right)}{\left(\text{injected activity / patient weight}\right)}$$

SUV has several types, based on its normalization parameters (SUV_{bw}: body weight; SUV_{lbm}: lean body mass; SUV_{bsa}: body surface area) and the analysis of the region of interest (ROI) - (SUV_{max}: maximum value; SUV_{av}: mean value; SUL_{peak}: peak value) [20, 21]. SUV_{max} is a commonly used parameter for determining the radiotracer activity in a lesion, however it should be interpreted carefully along with the visual analysis and review of relevant clinical information, and not as a standalone criterion for differentiating between benign and malignant entities. SUL_{peak} is the peak value of standardized uptake value normalized by lean body mass, taken in a spherical 1 cm^3 volume of interest. It is used in specific situations, such as response assessment by PERCIST criteria.

12.2.4.2 Utility of ^{18}F-FDG PET/CT in Patients with Newly Diagnosed Breast Cancer

Staging of breast cancer is done using the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) Tumour, Nodes and Metastases (TNM) classification system, currently in its 8th Edition [22].

Table 12.1 Guidelines for ^{18}F-FDG PET/CT in patients with Breast Cancer [18, 19]

Category	Recommendations
Patient preparation	Fasting for 4–6 h prior to administration of ^{18}F-FDG, avoiding any solids/liquids other than plain water. Any dextrose containing intravenous fluids are also restricted during this period Blood glucose levels measured prior to radiotracer injection should be <200 mg/dL (*to prevent altered biodistribution of ^{18}F-FDG*) No strenuous physical activity or exercise for at least 24 h (ideally 48 h) preceding the scan (*to prevent muscular uptake*) Diabetics on metformin or regular insulin need to be given special instructions. Metformin may be discontinued for 48 h prior to the study (*to avoid excessive gastrointestinal uptake of ^{18}F-FDG*). Regular insulin may be taken on the night before the scan with the patients being scheduled for early next day (*to prevent altered biodistribution of ^{18}F-FDG*) Ensuring adequate hydration: 1–2 L water, orally, as tolerated, immediately preceding injection and during the uptake period of ^{18}F-FDG (*to expedite urinary excretion of ^{18}F-FDG*) The patient should be well-rested in a warm environment, before the injection and during the uptake period of ^{18}F-FDG. Oral beta-blocker such as propranolol or short-acting benzodiazepines such as lorazepam may be administered prior to radiotracer injection in select cases (*to prevent uptake of ^{18}F-FDG in brown adipose tissue*)
^{18}F-FDG administration and scan period	^{18}F-FDG should be injected (Dose: 0.15 mCi/kg body-weight) via an indwelling intravenous catheter, in the upper extremity contralateral to the site of primary breast malignancy (*to avoid artefactual uptake in the axillary lymph nodes on the affected side in the event of extravasation of the tracer during injection*) The patient should be well-rested during the radiotracer uptake period (~60–90 min), avoiding any physical activities, even minor ones, such as chewing gum, talking etc. (*to prevent muscular uptake of ^{18}F-FDG in specific muscle groups*) Patients should be instructed to void frequently, and especially prior to being positioned for PET/CT scan (*to facilitate excretion of the radioactive urine*, *avoiding artefacts*) PET/CT scan is usually acquired from the vertex to the mid-thigh, with a few variations from centre-to-centre and based on the specific clinical history of the patient Patients should be instructed to avoid any movement during the scan and between the CT and PET components of the PET/CT. Sedation may be required in some patients (*to reduce any motion related artefacts*)

T-Stage

^{18}F-FDG PET/CT has a low sensitivity for staging of the primary breast tumour, in comparison to mammography, ultrasound, MRI and DBI. This is a result of the relatively low spatial resolution of PET/CT, severely degrading its ability to detect subcentimetric lesions. The sensitivity of ^{18}F-FDG PET/CT in pT1 tumours (<2 cm in maximum dimension) was reported as 47.7% in 144 patients with histopathologically proven breast tumours, while the same rose to 80.6% in pT2 tumours (>2 but <5 cm in maximum dimension) [23]. Additionally, some histological subtypes, such as invasive lobular carcinomas (ILC) and mucinous carcinomas have an inherent

low uptake of ^{18}F-FDG, lowering the sensitivity of PET/CT [23]. However, any incidentally detected ^{18}F-FDG avid breast lesion on PET/CT must be further evaluated using mammography, ultrasound or MRI and subjected to fine needle aspiration or core biopsy examination to rule out malignancy [24]. Studies have shown that 37–83% of such lesions turn out to be malignant on histopathology [25–27]. dbPET and PEM systems have a higher sensitivity and specificity in comparison to traditional whole body ^{18}F-FDG PET/CT and should be considered in appropriate clinical settings, as discussed earlier.

Table 12.2 provides a list of causes for false-negative results on ^{18}F-FDG PET/CT in patients with breast cancer.

^{18}F-FDG PET/CT also has a low specificity for staging of the primary breast tumour. This is because ^{18}F-FDG is concentrated at sites of increased glucose metabolism such as sites of inflammation/infection, in addition to neoplastic entities. This may result in false-positive radiotracer uptake in the breast which might be mistaken for cancer. Dual-time point imaging (at ~60 and 110 min) has been shown to improve specificity of ^{18}F-FDG PET/CT. It works on the basis that malignant cells continue to accumulate ^{18}F-FDG over time, whereas the inflammatory cells do not. This can help in differentiating between non-malignant and malignant entities [29]. Table 12.3 provides a list of entities that may mimic breast cancer on ^{18}F-FDG PET/CT

N-Stage

Regional nodal staging includes the ipsilateral axillary and extra-axillary (internal mammary and supraclavicular) lymph nodes. A distinction has to be made between the Berg level I and II axillary lymph nodes (cN1 if movable, cN2a if fixed), which are usually removed in routine axillary clearance, and involvement of Berg level III or infraclavicular lymph nodes (cN3a) which can upstage the disease to AJCC stage IIIC [22].

Sentinel lymph node biopsy (SLNB) and histopathologic examination is considered the gold standard for the evaluation of the axillary lymph nodes [31]. ^{18}F-FDG PET/CT has low sensitivity in evaluation of axillary nodal metastases, primarily resulting from its limited resolution, and inability to detect micro-metastatic sites. Its sensitivity is not superior to ultrasound or MRI for detection of suspicious

Table 12.2 Causes of false-negative findings in patients with breast cancer on ^{18}F-FDG PET/CT [28]

Factors	Causes
Tumour characteristics	Tumour size – Sub-centimetric lesions Tumour grade – Low grade, indolent tumour Tumour differentiation - well-differentiated tumours Tumour histology – Lobular, mucinous carcinomas, carcinoma-in-situ
Patient characteristics	Dense breasts Uncontrolled blood sugar levels Non-compliance to preparatory instructions for ^{18}F-FDG PET/CT Patient movement

Table 12.3 False-positive findings in breast on ^{18}F-FDG PET/CT [28, 30]

Etiology	Examples
Physiologic	Lactational state
Infection/inflammation	Mastitis (bacterial, fungal, tubercular) Breast abscess Intra-mammary lymphadenitis Sarcoidosis
Benign lesions	Fibroadenoma Breast fibromatosis Florid epitheliosis Ductal hyperplasia/adenoma Ductal ectasia Gynaecomastia
Post-intervention	Post-surgery/biopsy Surgical seroma Silicone granuloma following breast augmentation Breast implant rupture Metabolic flare post-chemo/radio-therapy
Post-traumatic	Hematoma Fat necrosis

axillary nodal metastases, and thus cannot replace the SLNB technique [32, 33]. However, the specificity of ^{18}F-FDG PET/CT is much higher for axillary nodal metastases. In the absence of any infectious/inflammatory pathology, axillary nodal avidity on ^{18}F-FDG PET/CT is highly suggestive of metastasis with a positive predictive value of more than 80% [34]. The mean sensitivity and specificity of ^{18}F-FDG PET/CT for axillary nodal staging was reported as 56% (range: 44–67%) and 96% (range: 90–99%) respectively, in a systematic review comprising seven studies with 862 patients of breast cancer [35].

However, ^{18}F-FDG PET/CT is valuable in evaluation of ipsilateral Berg level III or infraclavicular and other regional extra-axillary nodal stations (ipsilateral internal mammary and supraclavicular lymph nodes) [36–38]. As discussed previously, identification of ipsilateral regional adenopathy other than Berg level I-II, up-stages the disease and has important treatment and prognostic implications for the patient (Fig. 12.1).

M-Stage

Metastatic disease is encountered in around 40% of all patients with breast cancer, either at initial staging or in a post-treatment setting of an initially loco-regional disease [39]. ^{18}F-FDG PET/CT has a high sensitivity and specificity (with the CT component used to exclude the benign causes of ^{18}F-FDG avidity) in detection of distant metastases, leading to a highly accurate disease staging [36, 40] (Fig. 12.2).

Inflammatory breast cancer (T4d), which is diagnosed when the cutaneous changes involve one-third or more of the entire skin over the breast, has a high associated risk of distant metastases (Fig. 12.3). In a prospective study of 59 women with unilateral breast cancer, ^{18}F-FDG PET/CT identified distant metastases in 18 patients (30.5%), while only six (10.2%) were detected on conventional workup [40].

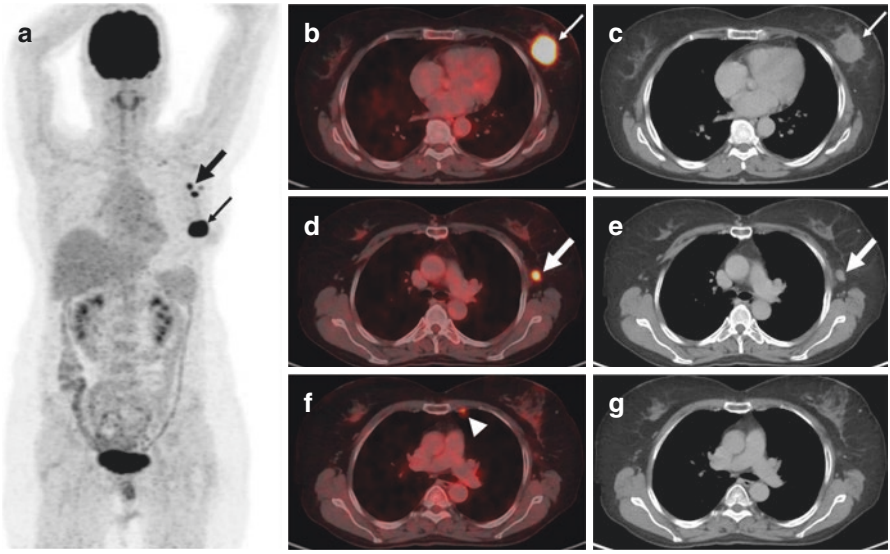


Fig. 12.1 60 year-old-woman with newly diagnosed carcinoma left breast (biopsy – IDC, grade II). A CT chest done for staging showed presence of a left breast mass and involved left axillary lymph nodes. ^{18}F-FDG PET/CT was performed for initial staging. Maximum intensity projection (MIP) image (**a**), trans-axial fused PET/CT (**b**) and CT (**c**) images show intensely tracer avid left breast mass (thin arrow), left axillary nodal disease (**d**, **e**; thick arrow) and additional involvement of a sub-centimetric left internal mammary lymph node (**f** - arrow-head, **g**). ^{18}F-FDG PET/CT upstaged the patient to AJCC stage IIIC. Physiological radiotracer activity is also seen in the brain, liver, kidneys, intestines and urinary bladder in the MIP image

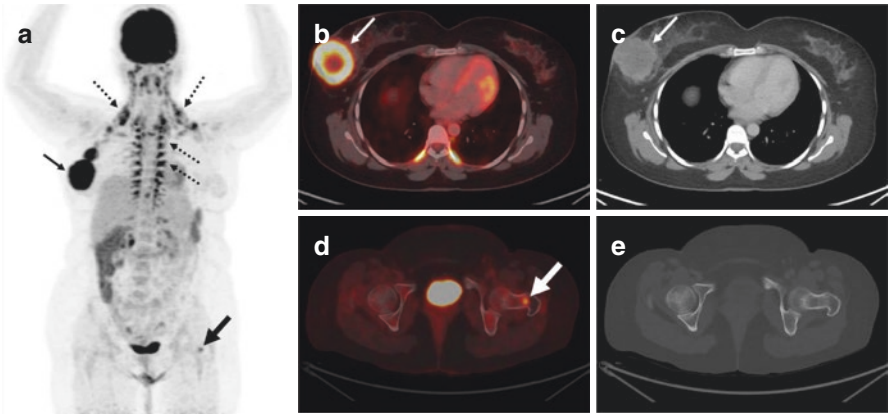


Fig. 12.2 A 38 year-old-woman with newly diagnosed right breast carcinoma (IDC, grade II) – staging done with CT Chest, abdomen and pelvis showed a right breast mass with multiple matted right axillary lymph nodes, no distant metastases; whole body bone scan – normal study. ^{18}F-FDG PET/CT was performed for initial staging. Maximum intensity projection image (**a**) shows physiologic brown fat uptake of ^{18}F-FDG in the bilateral cervical, supraclavicular and para-vertebral regions (dotted arrows). Trans-axial fused PET/CT (**b**) and CT (**c**) images show the tracer avid, necrotic right breast primary mass (thin-arrow) with a tracer avid marrow lesion in the neck of the left femur (**d**; thick-arrow), that was inconspicuous on CT (**e**) and not detected on prior imaging. The patient was up-staged to AJCC stage IV in view of distant metastasis

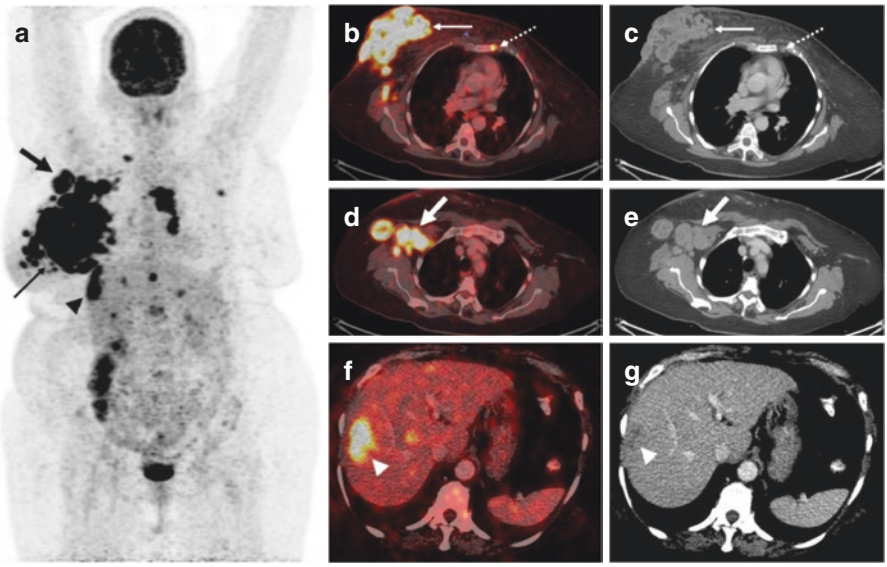


Fig. 12.3 A 57 year-old-woman with newly diagnosed carcinoma right breast (Inflammatory breast carcinoma) underwent ^{18}F-FDG PET/CT for initial staging. Maximum intensity projection image (**a**) and trans-axial fused PET/CT and CT images show intensely tracer avid right breast mass, infiltrating the skin (**b**, **c**; solid thin arrow), multiple enlarged, matted right axillary lymph nodes (**d**, **e**; solid thick arrow) and tracer avid hypodense liver lesions (**f**, **g**; arrow-head) in addition to multiple skeletal lesions (representative sternal lesion shown in **b**, **c**; dotted arrow)

In a prospective study of 254 consecutive women with stage II and III breast cancer, ^{18}F-FDG PET/CT detected distant metastases in 2.3% patients of stage IIA, 10.7% of stage IIB, 17.5% of stage IIIA, 36.5% of stage IIIB and 47.1% of stage IIIC. Additionally, PET/CT results changed the clinical stage in 30.3% of all patients [41].

The risk of distant metastases increases with increasing loco-regional stage, and with the presence of high-risk factors (younger age at diagnosis, triple negative histology) [42, 43]. In a study of 232 women with triple negative breast cancer, ^{18}F-FDG PET/CT detected previously occult distant metastases in 30 patients (13%) up-staging them to stage IV, out of which majority of the patients previously belonged to stage IIIB (57%). 15% of these patients were earlier in stage IIB, which demonstrates the utility of performing staging ^{18}F-FDG PET/CT in early stage breast cancer patients with triple negative histology [44].

The common sites of metastatic breast cancer include bones, non-regional lymph nodes, lungs, brain and liver [45]. ^{18}F-FDG PET/CT has a high detection efficiency for osteolytic, mixed lytic-sclerotic or skeletal marrow lesions, but lower sensitivity for detection of purely sclerotic metastases as these lesions have low-grade ^{18}F-FDG uptake [46]. However, these sclerotic metastases are osteodense and easily identified on the corresponding CT images, thereby negating the requirement of additional skeletal scintigraphy in most cases [36, 47].

The main limitation of ^{18}F-FDG PET/CT in metastatic workup is in the detection of brain lesions, because of the high physiological background ^{18}F-FDG uptake in the brain parenchyma. Additional investigations, such as MRI may be required in patients with high clinical suspicion of brain metastases.

Indication of ^{18}F-FDG PET/CT for Initial Staging

As highlighted in the previous sections, ^{18}F-FDG PET/CT is not indicated in all patients with newly diagnosed breast cancer. As per the latest National Comprehensive Cancer Network (NCCN) guidelines (version 1.2021, January 15, 2021), the use of ^{18}F-FDG PET/CT for initial staging is not recommended as a first-line staging modality in clinical stage I, II or operable stage III breast cancer. The guidelines mention that ^{18}F-FDG PET/CT is optional and helpful where conventional imaging studies are equivocal or suspicious [48].

However, clinical experience and growing evidence suggests that the use of ^{18}F-FDG PET/CT may be appropriate for initial staging of patients with locally advanced breast cancer including clinical stage IIB (T3N0), IIIA-IIIC [36, 41, 49]. A recent meta-analysis evaluating the impact of ^{18}F-FDG PET, PET/CT and PET/MRI, as an initial staging modality on the staging and management of breast cancer showed that the use of PET altered the stage of 34% (95% Confidence Interval: 27–42%) patients that were initially stage III. This change in stage of around one-third of patients, directly leads to a significant change in management [50]. Accurate initial staging by ^{18}F-FDG PET can thus help in avoiding inappropriate therapeutic decisions. As more evidence is gained, primarily through robust, randomized clinical trials, the NCCN guidelines may be re-evaluated to incorporate ^{18}F-FDG PET/CT in patients with newly diagnosed breast cancer who are at a higher risk of extra-regional nodal and metastatic disease and stand to benefit from an accurate PET/CT based staging [51].

12.2.4.3 Utility of ^{18}F-FDG PET/CT in Response Assessment of Patients with Breast Cancer

Response Assessment in Loco-Regional Disease After Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy (NAC) is the first line treatment (to downstage and regain resectability) in inoperable locally advanced and inflammatory (T4d) breast cancer. Additionally, it is used in bulky but operable tumours, to potentially facilitate breast conservation or to avoid axillary lymph nodal dissection (ALND). Early assessment of response to NAC, offers the option to change an ineffective treatment, thereby increasing therapeutic efficacy and minimizing side-effects.

In a study of 20 women with triple-negative loco-regional breast cancer, ^{18}F-FDG PET/CT was performed at baseline and after two cycles of NAC. Using the ^{18}F-FDG uptake values to distinguish between the responders and the non-responders, 45% of the responders (>42% decrease in ^{18}F-FDG uptake) had residual tumour at surgery compared to 100% of the non-responders (<42% decrease in ^{18}F-FDG uptake) [52].

However, areas of controversy in the assessment of response to NAC by ^{18}F-FDG PET/CT include the lack of standard and uniform histopathology criteria to define response, [53, 54] the optimal timing for performing PET/CT [53–55] and the problem in patients with low-grade ^{18}F-FDG avid breast cancer at the baseline scan, which could itself be indicative of resistance to chemotherapy [54].

Response Assessment in Metastatic Disease

Response assessment in patients with metastatic breast cancer has predominantly been performed using conventional imaging, most commonly CT. Anatomic imaging such as CT requires a significant change in the tumour size to demonstrate response, which usually takes multiple cycles of treatment. ^{18}F-FDG PET/CT can detect metabolic changes in the tumour, which occur early in the treatment course and can help in guiding subsequent treatment [49]. In a study of 65 women with metastatic breast cancer, post first or second-line systemic therapy, comparison of response assessment using CT (RECIST 1.1) versus ^{18}F-FDG PET/CT (PERCIST) was performed. PET/CT based response assessment classified 40% additional patients as responders, who were non-responders based on CT. The one-year progression free survival in responders vs. non-responders was 59% vs 27% based on CT and 63% vs 0% based on PET/CT respectively. ^{18}F-FDG PET/CT based response assessment was also a superior predictor for disease specific survival than that based on CT [56].

^{18}F-FDG PET/CT is also superior to CT in response assessment of osseous lesions. Appearance of sclerosis after therapy with a reduction in ^{18}F-FDG uptake mostly represents responding osseous metastases (Fig. 12.4). However, CT alone or conventional skeletal scintigraphy can falsely label these sclerotic sites as new osteoblastic metastases [57]. While assessing response to treatment with PET/CT, one must be aware of a paradoxical increase in ^{18}F-FDG uptake at 1–2 weeks after therapy initiation. This is called as a '*metabolic flare*' and usually denotes favourable response to therapy [58].

In future, with more evidence on PET based response evaluation criteria and their prognostic significance, the role of PET/CT in response assessment of solid tumours will be further strengthened.

12.2.4.4 Utility of ^{18}F-FDG PET/CT in Re-staging of Patients with Breast Cancer

^{18}F-FDG PET/CT has a better diagnostic performance than conventional imaging (Ultrasound, mammography for local recurrence; skeletal scintigraphy, whole-body CT for distant recurrence) in patients of breast cancer with suspected recurrence [59–62]. In a study of 228 asymptomatic women with rising CA 15-3 and/or CEA levels, ^{18}F-FDG PET/CT was positive in 79.5% patients and had a sensitivity and specificity of 93.6% and 85.4%, respectively. The findings on PET/CT led to treatment modification in 54% patients [62].

^{18}F-FDG PET/CT not only helps in early detection of site of recurrence, it is also useful in detecting additional sites of involvement when one such site has been

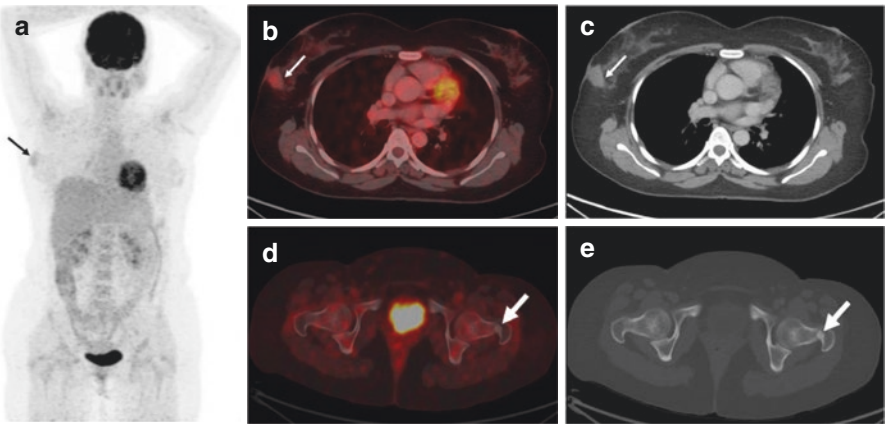


Fig. 12.4 A 38 year-old-woman with right breast carcinoma (IDC, grade II) – initial staging done with ^{18}F-FDG PET/CT – AJCC Stage IV (shown in Fig. 12.2). ^{18}F-FDG PET/CT was performed for response assessment, after the patient had received 8 cycles of chemotherapy. Maximum intensity projection image (**a**) shows absent brown fat uptake of ^{18}F-FDG (compare with Fig. 12.2). Trans-axial fused PET/CT (**b**) and CT (**c**) images show a mildly tracer avid right breast lesion (thin-arrow), with significant reduction in size and ^{18}F-FDG uptake; and a non-tracer avid sclerotic lesion in the neck of the left femur (**d**, **e**; thick-arrow). The appearance of sclerosis and resolution of ^{18}F-FDG avidity denotes healing of the osseous metastasis. Overall findings suggested favourable response to therapy

detected on conventional imaging. In a study of 56 women with diagnosed locoregional recurrence, ^{18}F-FDG PET/CT identified additional lesions in 57% patients. The clinical management was affected in 48% patients due to the detection of more extensive loco-regional disease or distant metastases. The overall sensitivity and specificity of ^{18}F-FDG PET/CT was 97% and 92%, respectively [60].

12.2.5 Skeletal Imaging: Whole-Body Bone Scintigraphy and ^{18}F-NaF PET/CT

Bones are the most common sites of metastatic disease in patients with breast cancer [63]. While ^{18}F-FDG PET/CT has a high sensitivity for detecting osteolytic and mixed lytic-sclerotic skeletal lesions, it is less efficient in detection of purely osteoblastic metastases, as discussed previously. Skeletal imaging is performed either using whole-body gamma camera imaging/SPECT with ^{99m}Tc-Methylene diphosphonate (MDP) or using PET/CT with ^{18}F-Sodium Fluoride (NaF). Both ^{99m}Tc-MDP whole-body bone scintigraphy (WBBS) and ^{18}F-NaF PET/CT have high diagnostic performance in detecting osteoblastic lesions. However, it must be emphasized here that neither of these agents is tumour-specific. Radiotracer localization is based on high blood flow and increased osteoblastic activity, which can be seen in inflammation, infection, trauma and degenerative processes, in

addition to osteoblastic metastases and reparative processes following osteolytic metastases [64, 65].

12.2.5.1 Whole-Body Bone Scintigraphy

^{99m}Tc-MDP is the commonly used radiotracer for WBBS. It is administered intravenously (in the upper extremity contralateral to the site of breast cancer) at a dose of ~13–30 mCi (~300–350 μCi/kg) and the whole-body planar scan acquired in anterior and posterior views, 3–5 h later [66]. Additional SPECT/CT may be performed for suspicious lesions, which increases the sensitivity and specificity of WBBS. The effective whole-body radiation dose from WBBS with ^{99m}Tc-MDP is around 3.6–5.4 mSv in adults [66].

WBBS has higher sensitivity in early detection of osseous metastases compared to conventional radiography [67]. The advantages of WBBS include its superior performance in detection of purely osteoblastic metastases, wider availability, and relatively low cost compared to PET/CT (Fig. 12.5).

The estimated detection rate of osseous metastases by WBBS increases with the clinical stage of the patient (Table 12.4).

Routine WBBS based screening is not recommended in patients with early stage breast cancer. The Society of Nuclear Medicine and Molecular Imaging has described appropriateness criteria for the use of WBBS in patients with breast cancer (Table 12.5).

One of the limitations in using WBBS for response evaluation is the '*flare phenomenon*' in which the lesions have increased intensity on the post-therapy scans, compared to the baseline study. This gives a false impression of disease progression. The flare response typically occurs at 3–5 months after initiation of therapy and is usually predictive of favourable response to treatment [70].

12.2.5.2 ^{18}F-Sodium Fluoride PET/CT

^{18}F-NaF is the counterpart of ^{99m}Tc-MDP for PET/CT. It has better tracer kinetics, better resolution (due to PET/CT) and a higher target to background ratio compared to ^{99m}Tc-MDP (Fig. 12.6). Imaging with ^{18}F-NaF can be started around 30–45 min after intravenous injection, as it has rapid skeletal binding and rapid urinary excretion of the unbound radiotracer [71]. These favourable imaging characteristics lead to a higher accuracy of ^{18}F-NaF PET/CT in detection of osseous metastases compared to WBBS [72].

The limitations with ^{18}F-NaF PET/CT are the higher cost and limited availability of the radiotracer and PET/CT instrumentation, in comparison to WBBS. However, these constraints notwithstanding, ^{18}F-NaF PET/CT should be preferred over traditional WBBS for detection of osseous metastases in patients with breast cancer.

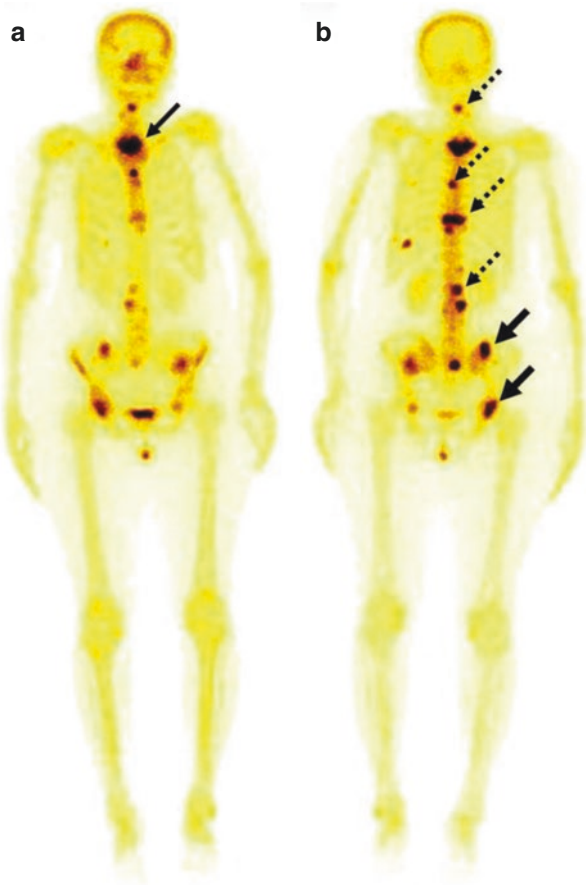


Fig. 12.5 A 42-year-old woman with history of carcinoma right breast – post total mastectomy with axillary clearance. WBBS (**a** – anterior view, **b** – posterior view) performed for complaint of bony pains showed multiple sites of focal tracer avidity in the axial skeleton (solid thin arrow – sternum; solid thick arrows – pelvic bones; dotted arrows – multiple cervico-dorso-lumbar vertebrae), suggestive of skeletal metastases

Table 12.4 Detection rate of osseous metastases by whole-body bone scan in patients with breast cancer [68]

Clinical stage	Detection rate
I	0.82%
II	2.55%
III	16.75%
IV	40.5%

Table 12.5 Appropriate clinical indications for whole-body bone scintigraphy in breast cancer [69]

Clinical setting	Indication
Initial staging	Asymptomatic patient with clinical stage I/II breast cancer and elevated alkaline phosphatase (ALP) levels Symptomatic patient (bony pains, pathologic fracture) with any clinical stage Clinical stage III and above
Re-staging	Asymptomatic patient with change in treatment plan Asymptomatic patient with increase in ALP Patient with new-onset skeletal symptoms (bony pains, pathologic fracture) Patient detected with a non-osseous site of recurrence Evaluation for radionuclide bone-pain palliation therapy Patient with remote history of breast cancer with equivocal, incidentally detected osseous findings on imaging for another indication

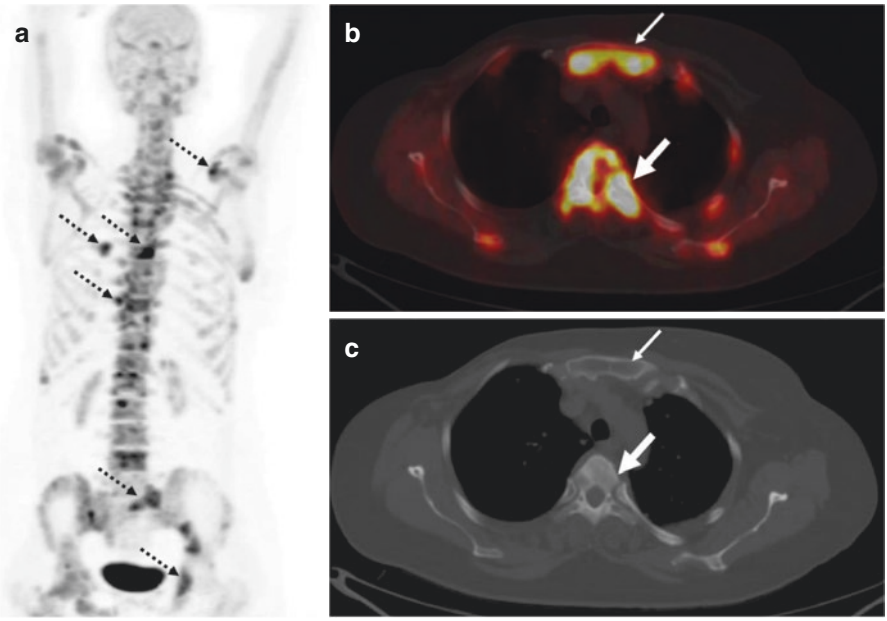


Fig. 12.6 A 53 year-old-woman with carcinoma breast underwent ^{18}F-Sodium Fluoride PET/CT done as a part of initial staging. The scan showed multiple tracer avid skeletal metastases, as shown in the maximum intensity projection image (**a**, dotted-arrows). Representative trans-axial fused PET/CT (**b**) and CT (**c**) images show intensely tracer avid lesions in the dorsal vertebral body (thick-arrow) and sternum (thin-arrow)

12.2.6 Miscellaneous

12.2.6.1 Sentinel Lymph Node Imaging

The sentinel lymph node (SLN) is any lymph node that lies on the direct drainage pathway from the tumour site. Thus, for a given tumour, there may be more than one SLN. The concept of SLN imaging is that tumour metastases spread in an orderly pattern, with first involvement of the SLN. Thus, SLN negative on biopsy would be highly predictive of tumour negative downstream lymphatics. These patients, with negative results on SLN biopsy could potentially be spared from ALND, reducing the post-operative long-term morbidity and complications.

Multiple studies have shown identification of the SLN in about 96% patients with accurate prediction of status of the downstream axillary lymph nodes in >95% patients [73, 74].

Indications and Contraindications of SLN Imaging and Biopsy

SLN biopsy is indicated in patients with early breast cancer (T1 or T2) with no clinically positive lymph nodes or in patients with DCIS where mastectomy is being contemplated [75].

Clinically positive lymph nodes and inflammatory breast cancer (T4d) are absolute contraindications for the SLN procedure, as these patients require ALND [75]. Locally advanced breast cancer is a relative contraindication.

Technique

Several studies have demonstrated the efficacy of lymphoscintigraphy with intra-operative gamma-probe guided surgery of the SLN [76, 77]. Colloid particles labelled with ^{99m}Tc (e.g., Sulfur colloid, Antimony trisulfide, Nanocolloid) are most frequently utilised for SLN imaging. Multiple injection sites have been explored (including intra-tumoural, peri-tumoural, sub-dermal, sub-areolar, peri-areolar) and most of these techniques are complementary [78]. The peri-areolar injection is frequently performed, based on the sub-areolar plexus of Sappey which is a convergence of lymphatics from various lobules [79]. The peri-areolar injection involves four aliquots of ^{99m}Tc-Sulfur colloid, each being injected sub-cutaneously at 12′, 3′, 6′ and 9’o clock positions at the margins of the areola, corresponding to each of the quadrants, followed by planar image acquisition under a gamma camera in multiple views. The addition of SPECT/CT improves the detection of SLN with greater anatomic correlation. The patient is shifted to the operation theatre once the imaging is complete and intra-operative gamma probe-guided surgery of the SLN performed. Some centres use a combination of pre-operative ^{99m}Tc-sulfur colloid and intra-operative blue dye injection for increased accuracy in SLN identification.

Outcomes

An accuracy of 97% in SLN resection was noted in a multi-centre randomized trial in patients of breast cancer with clinical stage I/II and cN0 axilla [80]. Another clinical trial randomized patients with breast tumours of diameter ≤2 cm, post breast-conserving surgery to either ALND group or to SLN biopsy followed by ALND group (only if SLN involved). 36% of the 259 patients in the SLN group had a positive SLN biopsy and underwent ALND. The overall 5-year survival of all patients was 96.4% in the ALND group versus 98.4% in the SLN group. This demonstrated that SLN biopsy procedure could potentially avoid unnecessary ALND in a large patient population [81].

12.2.6.2 Radio-Guided Occult Lesion Localization (ROLL)

The widespread use of screening has led to increased identification of clinically non-palpable, small breast lesions. Excision of these lesions with safe margins requires accurate tumour localization. Wire-guided localization is the standard technique which involves ultrasound guided wire placement in the lesion and keeping it in-situ till surgical excision. However, this technique has several drawbacks, e.g., patient discomfort, difficult placement in dense breasts, wire displacement or transection [82].

Radio-guided occult lesion localization (ROLL) involves the radiotracer injection (^{99m}Tc-labeled colloid) in the non-palpable breast lesion, under ultrasound guidance. A hand-held intra-operative gamma probe is then used to guide the lesional excision [83]. ROLL is associated with lesser subjective discomfort to the patient and does not have any wire-related complications (displacement, transection). The results of ROLL are comparable to wire-guided localization in terms of the localization rate. Moreover, ROLL is associated with shorter localization and excision time and lower risk of positive tumour margins [82]. Additionally, the procedure may be utilized for sentinel lymph node localization in the same sitting, also called as Sentinel Node and Occult lesion localization (SNOLL) [84].

12.2.6.3 Multi-Gated Radionuclide Angiography (MUGA)

Chemotherapeutic drugs, such as Anthracyclines have an increased risk of cardiotoxicity, manifesting as irreversible cardiomyopathy (Type-I) and heart failure. The anthracycline related cardiomyopathy manifests as a decline in left ventricular ejection fraction (LVEF) which terminally leads to cardiac failure [85].

Patients receiving anthracycline drugs thus need to be monitored to detect an early decline in the left ventricular function, which may not be apparent clinically. The chemotherapy regimen can then be altered appropriately to minimize further cardiotoxicity.

Echocardiography is the readily available and commonly used technique to assess LVEF in these patients, but has certain limitations including high inter-observer variability and the need for an optimal acoustic window [86]. Cardiac MRI is the standard for measurement of LVEF but is limited by the long study duration and costs. Multi-gated Radionuclide Angiography (MUGA) involves the labelling of ^{99m}Tc to the erythrocytes. These radio-tagged erythrocytes are then imaged under a

gamma camera as they pass through the left ventricular chamber during multiple cardiac cycles. The advantages of MUGA include its reduced operator dependence, high inter-observer reproducibility and shorter study duration, as compared to MRI [87, 88]. Serial MUGA scans can document the trend of LVEF over several treatment cycles [85]. The disadvantages include limited availability compared to echocardiography and associated radiation exposure, even though minimal (~5–10 mSv).

12.2.6.4 Positron Emission Tomography/Magnetic Resonance Imaging (PET/MRI)

The advent of PET/MRI devices ushered in a new era of hybrid imaging, combined with the functional imaging prowess of PET and superior soft tissue contrast of MRI. Most of the current limitations of ^{18}F-FDG PET/CT for T-staging in breast cancer are addressed by the use of a hybrid PET/MRI system, with the added benefit of significantly reduced radiation exposure (due to the elimination of the CT component).

Initial studies based on fusion of PET images to multi-parametric MRI images of the breast showed an increase in specificity from 53% to 97% and increase in positive predictive value from 77% to 98% [89]. The addition of diffusion weighted imaging and dynamic contrast enhanced MRI with PET has shown increased diagnostic accuracy for liver and osseous metastases compared to PET/CT alone [90, 91]. Recurrence evaluation with whole-body PET/MRI yielded 100% detection rate of metastatic lesions with superior results compared to PET/CT, CT or MRI alone [92]. The current challenges with PET/MRI systems include technical hardware limitations, long scan duration, high costs and limited availability. With advances in technology, increased penetration of this modality and further growth in evidence, the indications of PET/MRI in breast cancer will expand with time.

12.2.6.5 Radionuclide Bone Pain Palliation

Pain from osseous metastases is a significantly debilitating symptom and contributes to increased morbidity in patients with advanced stage breast cancer. Management options such as medical analgesics, local radiation therapy, chemotherapy and local surgical excision of the metastases are used, based on the severity of pain and localized vs diffuse skeletal involvement.

Radionuclide therapy for bone pain palliation is indicated in patients with diffuse painful osseous metastases that are positive on WBBS, indicating increased bone turnover. It utilizes therapeutic radionuclides such as ^{89}Sr, ^{32}P, ^{188}Re, ^{153}Sm and ^{177}Lu. Studies using ^{186}Re for bone pain palliation have shown a high clinical response rate (50–92%) in patients with metastatic breast cancer [93, 94]. In a study of 40 patients of metastatic breast cancer undergoing bone pain palliation with ^{89}Sr, higher overall clinical response rate was observed in patients who received re-treatment (83% response rate) versus those receiving a single treatment [95].

Overall, radionuclide therapy for osseous pain palliation in patients with metastatic breast cancer is a safe and effective option, with good clinical response and limited adverse effects.

12.2.6.6 Novel Diagnostic and Theranostic Radiotracers in Breast Cancer

Traditionally, ^{18}F-FDG, targeting glucose metabolism has been at the forefront of oncologic imaging with PET/CT [4, 18, 96, 97]. Advances in radiochemistry have led to the development of several radiotracers that target different functional aspects of the tissues. Some of these targets are useful for oncologic imaging and have been used to study different aspects of tumour micro-environment and tumour biology.

Hormone Receptor and HER2 Imaging

The 8th edition of AJCC staging in breast cancer has incorporated biological prognostic factors, including the status of hormonal receptors (Estrogen Receptor; ER, Progesterone Receptor; PR) and Human epidermal growth factor receptor 2 (HER2) status, among others [22].

PET radiotracers have been developed targeting these specific hormone receptors for non-invasive, in-vivo assessment of the tumour receptor status. These include ^{18}F-Fluoroestradiol (FES) for ER imaging and ^{18}F-Fluoro-furanyl-norprogesterone (FFNP) for PR imaging. ^{18}F-FES and ^{18}F-FFNP PET/CT have been used to assess the receptor heterogeneity at the primary tumour and metastatic sites. A single whole-body scan can provide the receptor functional status of all the lesions, whereas conventional histopathology based immunohistochemistry only provides the receptor status of the single excised tumour specimen [98]. Further, as these radiotracers not only identify the receptor density, but specifically the receptor functional status, they can predict response to hormone-directed endocrine therapies in patients with breast cancer, thereby guiding patient selection, providing prognostic information and facilitating modification of therapy later on in the course, if needed [99, 100].

HER2 is a receptor tyrosine-kinase protein, the over-expression of which is a hallmark of increased tumour aggressiveness. It is also a target for directed therapies, such as antibodies (Trastuzumab, Pertuzumab) and tyrosine kinase inhibitors (Lapatinib) in patients with the primary tumour bearing HER2 positivity [101, 102]. There is a sub-group of patients where the primary tumour is HER2 negative, but the distant sites are HER2 positive and thus would respond favourably to targeted therapy. PET/CT targeting the HER2 receptors (e.g., ^{89}Zr-Trastuzumab) can identify the metastatic sites with a functional receptor status [103]. Additionally, HER2 can be a potential theranostic target where a beta-emitting radionuclide, such as ^{177}Lu can be tagged to HER2 seeking molecules, providing novel therapeutic options [104].

Others

Targeting amino-acid metabolism (^{18}F-Fluciclovine, ^{11}C-Methionine) using PET/CT has been utilized for assessment of treatment response in breast cancer and in the detection of metastatic sites from low ^{18}F-FDG avid carcinomas, such as ILC [105, 106]. Because of their different mechanism of localization from ^{18}F-FDG, these agents may be utilized in the initial workup of patients with suspected metastatic ILC.

Angiogenesis imaging (using ^{68}Ga-RGD, ^{18}F-Galacto-RGD) has been shown to be useful in several solid tumours, in whole-body disease assessment and recurrence evaluation [107–110]. It is also a potential target for development of novel radionuclide therapies [109]. ^{68}Ga-PSMA is another potential neo-angiogenesis targeting radiotracer. It was initially developed for prostate cancer, but was later found to be capable of targeting neo-angiogenesis, thus helping in detection of other solid tumours [111–114]. Several studies have documented its utility in breast cancer as well (Figs. 12.7 and 12.8) [114, 115].

Table 12.6 provides a list of non- ^{18}F-FDG PET tracers with present and evolving utilities in breast cancer.

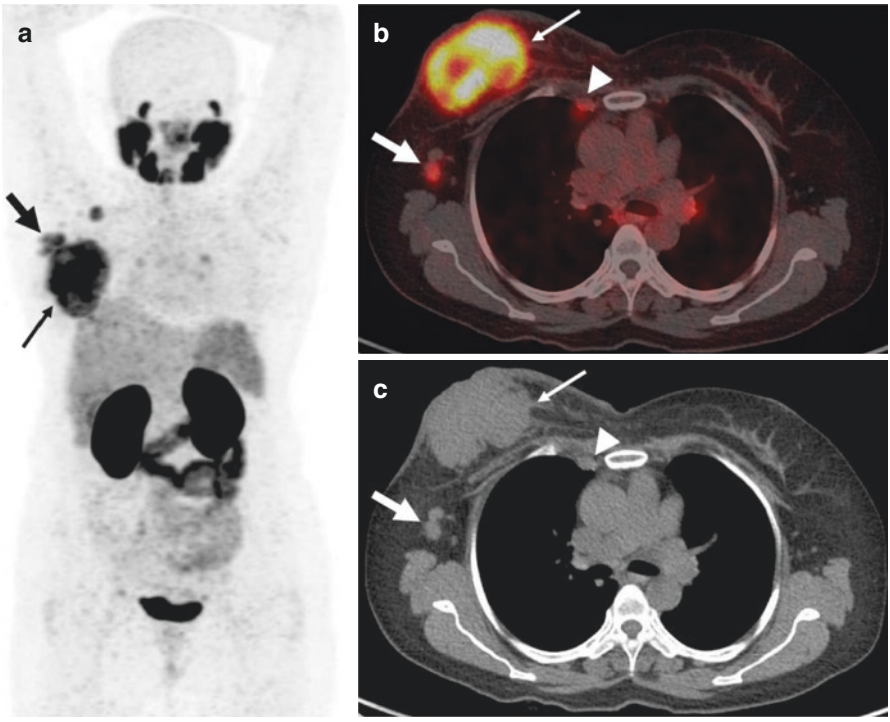


Fig. 12.7 A 46 year-old-woman with newly diagnosed carcinoma right breast (IDC, grade II, triple negative). ^{68}Ga-PSMA PET/CT maximum intensity projection image (**a**), transaxial fused PET/CT (**b**) and CT image (**c**) show intensely tracer avid primary breast mass (thin arrow) and tracer avid sub-centimetric right axillary (thick arrow) and right internal mammary (arrow-head) lymph nodes, representing nodal metastases. Physiological radiotracer activity is also seen in the lacrimal and salivary glands, liver, kidneys, proximal small intestine and urinary bladder in the MIP image

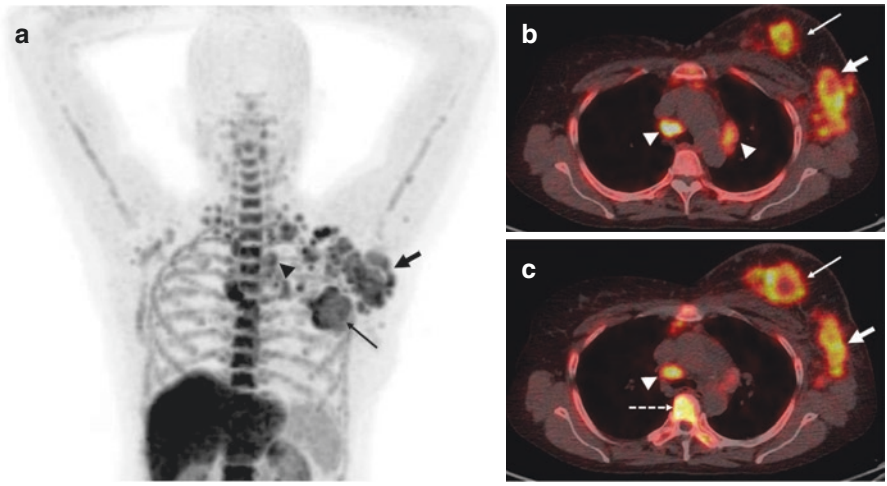


Fig. 12.8 A 50 year-old-woman presented with newly diagnosed carcinoma left breast (Infiltrating ductal carcinoma, grade III; T4bN3Mx). ^{18}F-FLT PET/CT maximum intensity projection (MIP) image (**a**), and transaxial fused PET/CT images (**b**, **c**) show increased tracer uptake, suggestive of high cellular proliferation in the primary breast mass (solid thin arrow), enlarged left axillary lymph nodes (solid thick arrow), mediastinal lymph nodes (arrow-heads) and skeletal lesions (dashed arrow), representing metastatic disease. Physiological radiotracer uptake is also seen in the liver, spleen, kidneys and bone marrow in the MIP image

Table 12.6 PET radiotracers other than ^{18}F-FDG in breast cancer

Radiotracer	Mechanism of localization	Applications
^{18}F-FES, ^{18}F-FFNP, ^{89}Zr-Trastuzumab	Hormone receptor expression	Non-invasive, in-vivo assessment of functional hormone receptor status Guiding hormonal treatment [98]
^{18}F-Fluciclovine, ^{11}C-methionine	Amino-acid metabolism	Treatment response assessment [116] Imaging of tumour histologies with low ^{18}F-FDG avidity, e.g., ILC [106]
^{18}F-Galacto-RGD, ^{68}Ga-RGD, ^{68}Ga-PSMA	Neo-angiogenesis	Tumour aggressiveness assessment Novel theranostics [107, 114, 115]
^{18}F-MISO, ^{18}F-FETA, ^{18}F-FAZA	Hypoxia imaging	Identifying potential future resistance to chemo-radiation [117]
^{18}F-Fluorothymidine (Fig. 12.8)	Tumour proliferation	In-vivo tumour proliferation index [118] Response assessment to chemotherapy [119]

12.2.6.7 Male Breast Cancer

Male Breast Cancer (MBC) is a rare entity, accounting for approximately 0.5–1% of all breast-cancers diagnosed each year [5]. MBC is usually detected at an advanced stage, with higher T and N stages, as compared to women [120, 121]. A retrospective study of 39 patients with MBC who underwent ^{18}F-FDG PET/CT for initial staging showed detection of previously unsuspected distant metastases in 16%

patients with prior stage IIB and 33% patients with stage III, upstaging the disease to stage IV [122]. In another retrospective study of 23 patients with previously treated, histopathology proven MBC, ^{18}F-FDG PET/CT detected recurrence in 82.6% patients. The presence of nodal and distant metastases on PET/CT were the main predictors of survival on disease-specific survival analysis [123]. Because of paucity of available data, there are no present gender-specific guidelines for the use of PET/CT imaging in patients with MBC.

References

1. Graham MM. Clinical molecular imaging with radiotracers: current status. Med Princ Pract. 2012;21:197–208.
2. Hicks RJ, Hofman MS. Is there still a role for SPECT–CT in oncology in the PET–CT era? Nat Rev Clin Oncol. 2012;9:712–20.
3. Wong TZ, Paulson EK, Nelson RC, Patz EF, Coleman RE. Practical approach to diagnostic CT combined with PET. Am J Roentgenol. 2007;188:622–9.
4. Gallamini A, Zwarthoed C, Borra A. Positron emission tomography (PET) in oncology. Cancers (Basel). 2014;6:1821–89.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7–30.
6. Munoz D, Near AM, van Ravesteyn NT, Lee SJ, Schechter CB, Alagoz O, et al. Effects of screening and systemic adjuvant therapy on ER-specific US breast cancer mortality. J Natl Cancer Inst. 2014;106.
7. De Gelder R, Heijnsdijk EAM, Fracheboud J, Draisma G, De Koning HJ. The effects of population-based mammography screening starting between age 40 and 50 in the presence of adjuvant systemic therapy. Int J Cancer. 2015;137:165–72.
8. Taillefer R. The role of 99mTc-sestamibi and other conventional radiopharmaceuticals in breast cancer diagnosis. Semin Nucl Med. 1999;29:16–40.
9. Parihar AS, Bhadada S, Bhattacharya A, Mittal BR. Facial dysmorphism due to multiple brown tumors secondary to large parathyroid adenoma, diagnosed on 99mTc-Sestamibi parathyroid scintigraphy. Indian J Nucl Med. 2018;33:255–6.
10. American College of Radiology. ACR practice parameter for the performance of molecular breast imaging (MBI) using a dedicated gamma camera [Internet]. 2017 [cited 2020 May 7]. Available from: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/MBI.pdf?la=en
11. Narayanan D, Berg WA. Dedicated breast gamma camera imaging and breast PET: current status and future directions. PET Clin. 2018;13:363–81.
12. Hsu DFC, Freese DL, Levin CS. Breast-dedicated radionuclide imaging systems. J Nucl Med. 2016;57:40S–5S.
13. Conners AL, Hruska CB, Tortorelli CL, Maxwell RW, Rhodes DJ, Boughey JC, et al. Lexicon for standardized interpretation of gamma camera molecular breast imaging: observer agreement and diagnostic accuracy. Eur J Nucl Med Mol Imaging. 2012;39:971–82.
14. Shermis RB, Wilson KD, Doyle MT, Martin TS, Merryman D, Kudrolli H, et al. Supplemental breast cancer screening with molecular breast imaging for women with dense breast tissue. Am J Roentgenol. 2016;207:450–7.
15. Rechtman LR, Lenihan MJ, Lieberman JH, Teal CB, Torrente J, Rapelyea JA, et al. Breast-specific gamma imaging for the detection of breast cancer in dense versus nondense breasts. Am J Roentgenol. 2014;202:293–8.
16. Freifelder R, Karp JS. Dedicated PET scanners for breast imaging. Phys Med Biol. 1997;42:2463–80.
17. Berg WA, Madsen KS, Schilling K, Tartar M, Pisano ED, Larsen LH, et al. Breast cancer: comparative effectiveness of positron emission mammography and MR imaging in presurgical planning for the ipsilateral breast. Radiology. 2011;258:59–72.

18. Ulaner GA. PET/CT for patients with breast cancer: where is the clinical impact? Am J Roentgenol. 2019;213:254–65.
19. Surasi DS, Bhambhvani P, Baldwin JA, Almodovar SE, O'Malley JP. 18F-FDG PET and PET/CT patient preparation: a review of the literature. J Nucl Med Technol. 2014;42:5–13.
20. Thie JA. Understanding the standardized uptake value, its methods, and implications for usage. J Nucl Med. 2004;45:1431–4.
21. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50(Suppl_1):122S–50S.
22. American Joint Committee on Cancer. In: Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al., editors. AJCC cancer staging manual. 8th ed. Springer; 2017. 1049 p.
23. Avril N, Rosé CA, Schelling M, Dose J, Kuhn W, Bense S, et al. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations. J Clin Oncol. 2000;18:3495–502.
24. Parihar AS, Mittal BR, Vadi SK, Kumar R, Nambiyar K, Radotra B, et al. 18F-FDG PET/CT detects metastatic renal cell carcinoma masquerading as primary breast malignancy. Nucl Med Mol Imaging. 2018;52:475–8.
25. Korn RL, Yost AM, May CC, Kovalsky ER, Orth KM, Layton TA, et al. Unexpected focal hypermetabolic activity in the breast: significance in patients undergoing ^{18} F-FDG PET/CT. Am J Roentgenol. 2006;187:81–5.
26. Kang BJ, Lee JH, Yoo IR, Kim SH, Choi JJ, Jeong SH, et al. Clinical significance of incidental finding of focal activity in the breast at 18F-FDG PET/CT. Am J Roentgenol. 2011;197:341–7.
27. Litmanovich D, Gourevich K, Israel O, Gallimidi Z. Unexpected foci of 18F-FDG uptake in the breast detected by PET/CT: incidence and clinical significance. Eur J Nucl Med Mol Imaging. 2009;36:1558–64.
28. Kumar R, Rani N, Patel C, Basu S, Alavi A. False-negative and false-positive results in FDG-PET and PET/CT in breast cancer. PET Clin. 2009;4:289–98.
29. Basu S, Chen W, Tchou J, Mavi A, Cermik T, Czerniecki B, et al. Comparison of triple-negative and estrogen receptor-positive/progesterone receptor-positive/HER2-negative breast carcinoma using quantitative fluorine-18 fluorodeoxyglucose/positron emission tomography imaging parameters: a potentially useful method for disease characterization. Cancer. 2008;112:995–1000.
30. Adejolu M, Huo L, Rohren E, Santiago L, Yang WT. False-positive lesions mimicking breast cancer on FDG PET and PET/CT. Am J Roentgenol. 2012;198:304–14.
31. Hindié E, Groheux D, Brenot-Rossi I, Rubello D, Moretti JL, Espié M. The sentinel node procedure in breast cancer: nuclear medicine as the starting point. J Nucl Med. 2011;52:405–14.
32. Cooper K, Meng Y, Harnan S, Ward S, Fitzgerald P, Papaioannou D, et al. Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: systematic review and economic evaluation. Health Technol Assess (Rockv). 2011;15:1–134.
33. Ueda S, Tsuda H, Asakawa H, Omata J, Fukatsu K, Kondo N, et al. Utility of 18F-fluorodeoxyglucose emission tomography/computed tomography fusion imaging (18F-FDG PET/CT) in combination with ultrasonography for axillary staging in primary breast cancer. BMC Cancer. 2008;8:165.
34. Heusner TA, Kuemmel S, Hahn S, Koeninger A, Otterbach F, Hamami ME, et al. Diagnostic value of full-dose FDG PET/CT for axillary lymph node staging in breast cancer patients. Eur J Nucl Med Mol Imaging. 2009;36:1543–50.
35. Cooper KL, Harnan S, Meng Y, Ward SE, Fitzgerald P, Papaioannou D, et al. Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: a systematic review and meta-analysis. Eur J Surg Oncol. 2011;37:187–98.
36. Segaert I, Mottaghy F, Ceyssens S, De Wever W, Stroobants S, Van Ongeval C, et al. Additional value of PET-CT in staging of clinical stage IIB and III breast cancer. Breast J. 2010;16:617–24.

37. Jochelson MS, Lebron L, Jacobs SS, Zheng J, Moskowitz CS, Powell SN, et al. Detection of internal mammary adenopathy in patients with breast cancer by PET/CT and MRI. Am J Roentgenol. 2015;205:899–904.
38. Aukema TS, Straver ME, Peeters MJTFDV, Russell NS, Gilhuijs KGA, Vogel WV, et al. Detection of extra-axillary lymph node involvement with FDG PET/CT in patients with stage II-III breast cancer. Eur J Cancer. 2010;46:3205–10.
39. Abe O, Abe R, Enomoto K, Kikuchi K, Koyama H, Masuda H, et al. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365:1687–717.
40. Alberini J-LL, Lerebours F, Wartski M, Fourme E, Le Stanc E, Gontier E, et al. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging in the staging and prognosis of inflammatory breast cancer. Cancer. 2009;115:5038–47.
41. Groheux D, Hindie E, Delord M, Giacchetti S, Hamy A-S, de Bazelaire C, et al. Prognostic impact of 18FDG-PET-CT findings in clinical stage III and IIB breast cancer. J Natl Cancer Inst. 2012;104:1879–87.
42. Xiao W, Zheng S, Yang A, Zhang X, Zou Y, Tang H, et al. Breast cancer subtypes and the risk of distant metastasis at initial diagnosis: a population-based study. Cancer Manag Res. 2018;10:5329–38.
43. Colzani E, Johansson ALV, Liljegren A, Foukakis T, Clements M, Adolfsson J, et al. Time-dependent risk of developing distant metastasis in breast cancer patients according to treatment, age and tumour characteristics. Br J Cancer. 2014;110:1378–84.
44. Ulaner GA, Castillo R, Goldman DA, Wills J, Riedl CC, Pinker-Domenig K, et al. 18F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging. 2016;43:1937–44.
45. Chen MT, Sun HF, Zhao Y, Fu WY, Yang LP, Gao SP, et al. Comparison of patterns and prognosis among distant metastatic breast cancer patients by age groups: a SEER population-based analysis. Sci Rep. 2017;7:1–8.
46. Nakai T, Okuyama C, Kubota T, Yamada K, Ushijima Y, Taniike K, et al. Pitfalls of FDG-PET for the diagnosis of osteoblastic bone metastases in patients with breast cancer. Eur J Nucl Med Mol Imaging. 2005;32:1253–8.
47. Morris PG, Lynch C, Feeney JN, Patil S, Howard J, Larson SM, et al. Integrated positron emission tomography/computed tomography may render bone scintigraphy unnecessary to investigate suspected metastatic breast cancer. J Clin Oncol. 2010;28:3154–9.
48. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. NCCN guidelines version 1. Breast Cancer. 2021; [cited 2021 Mar 9]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
49. Groheux D, Espié M, Giacchetti S, Hindié E. Performance of FDG PET/CT in the clinical management of breast cancer. Radiology. 2013;266:388–405.
50. Han S, Choi JY. Impact of 18F-FDG PET, PET/CT, and PET/MRI on staging and management as an initial staging modality in breast cancer. Clin Nucl Med. 2021;46(4):271–82.
51. Ulaner GA, Jacene HA, Parihar AS, Groheux D. Evidence based best practices: 18F-FDG PET staging of newly diagnosed breast cancer. Clin Nucl Med. 2021;46(7):569–70.
52. Groheux D, Hindié E, Giacchetti S, Delord M, Hamy AS, De Roquancourt A, et al. Triple-negative breast cancer: early assessment with 18F-FDG PET/CT during neoadjuvant chemotherapy identifies patients who are unlikely to achieve a pathologic complete response and are at a high risk of early relapse. J Nucl Med. 2012;53:249–54.
53. Rousseau C, Devillers A, Sagan C, Ferrer L, Bridji B, Campion L, et al. Monitoring of early response to neoadjuvant chemotherapy in stage II and III breast cancer by [18F]fluorodeoxyglucose positron emission tomography. J Clin Oncol. 2006;24:5366–72.
54. Schwarz-Dose J, Untch M, Tiling R, Sassen S, Mahner S, Kahlert S, et al. Monitoring primary systemic therapy of large and locally advanced breast cancer by using sequential positron emission tomography imaging with [18F]fluorodeoxyglucose. J Clin Oncol. 2009;27:535–41.

55. Schelling M, Avril N, Nährig J, Kuhn W, Römer W, Sattler D, et al. Positron emission tomography using [18F]fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. J Clin Oncol. 2000;18:1689–95.
56. Riedl CC, Pinker K, Ulaner GA, Ong LT, Baltzer P, Jochelson MS, et al. Comparison of FDG-PET/CT and contrast-enhanced CT for monitoring therapy response in patients with metastatic breast cancer. Eur J Nucl Med Mol Imaging. 2017;44:1428–37.
57. Iagaru A, Minamimoto R. Nuclear medicine imaging techniques for detection of skeletal metastases in breast cancer. PET Clin. 2018;13:383–93.
58. Mortimer JE, Dehdashti F, Siegel BA, Trinkaus K, Katzenellenbogen JA, Welch MJ. Metabolic flare: indicator of hormone responsiveness in advanced breast cancer. J Clin Oncol. 2001;19:2797–803.
59. Radan L, Ben-Haim S, Bar-Shalom R, Guralnik L, Israel O. The role of FDG-PET/CT in suspected recurrence of breast cancer. Cancer. 2006;107:2545–51.
60. Aukema TS, Rutgers EJT, Vogel WV, Teertstra HJ, Oldenburg HS, Vrancken Peeters MTFD, et al. The role of FDG PET/CT in patients with locoregional breast cancer recurrence: a comparison to conventional imaging techniques. Eur J Surg Oncol. 2010;36:387–92.
61. Evangelista L, Baretta Z, Vinante L, Cervino AR, Gregianin M, Ghiotto C, et al. Tumour markers and FDG PET/CT for prediction of disease relapse in patients with breast cancer. Eur J Nucl Med Mol Imaging. 2011;38:293–301.
62. Champion L, Brain E, Giraudet A-L, Le Stanc E, Wartski M, Edeline V, et al. Breast cancer recurrence diagnosis suspected on tumor marker rising. Cancer. 2011;117:1621–9.
63. Solomayer EF, Diel IJ, Meyberg GC, Gollan C, Bastert G. Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. Breast Cancer Res Treat. 2000;59:271–8.
64. Love C, Din AS, Tomas MB, Kalapparambath TP, Palestro CJ. Radionuclide bone imaging: an illustrative review. Radiographics. 2003;23:341–58.
65. Parihar AS, Sood A, Lukose TT, Seam RK, Mittal BR. Metabolic bone superscan in carcinoma breast with occult graves' disease: looking beyond skeletal metastases. Indian J Nucl Med. 2018;33:145–7.
66. Bartel TB, Kuruva M, Gnanasegaran G, Beheshti M, Cohen EJ, Weissman AF, et al. SNMMI procedure standard for bone scintigraphy 4.0. J Nucl Med Technol. 2018;46:398–404.
67. Hortobagyi GN, Libshitz HI, Seabold JE. Osseous metastases of breast cancer. Clinical, biochemical, radiographic, and scintigraphic evaluation of response to therapy. Cancer. 1984;53:577–82.
68. Hamaoka T, Madewell JE, Podoloff DA, Hortobagyi GN, Ueno NT. Bone imaging in metastatic breast cancer. J Clin Oncol. 2004;22:2942–53.
69. Donohoe KJ, Cohen EJ, Giammarile F, Grady E, Greenspan BS, Henkin RE, et al. Appropriate use criteria for bone scintigraphy in prostate and breast cancer: summary and excerpts. J Nucl Med. 2017;58(4):14N–7N.
70. Janicek MJ, Hayes DF, Kaplan WD. Healing flare in skeletal metastases from breast cancer. Radiology. 1994;192:201–4.
71. Sabbah N, Jackson T, Mosci C, Jamali M, Minamimoto R, Quon A, et al. 18F-sodium fluoride PET/CT in oncology: an atlas of SUVs. Clin Nucl Med. 2015;40:e228–31.
72. Chakraborty D, Bhattacharya A, Mete UK, Mittal BR. Comparison of 18F fluoride PET/CT and 99mTc-MDP bone scan in the detection of skeletal metastases in urinary bladder carcinoma. Clin Nucl Med. 2013;38:616–21.
73. Albertini JJ. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. JAMA. 1996;276:1818–22.
74. Borgstein PJ, Pijpers R, Comans EF, Van Diest PJ, Boom RP, Meijer S. Sentinel lymph node biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. J Am Coll Surg. 1998;186:275–83.
75. Lyman GH, Temin S, Edge SB, Newman LA, Turner RR, Weaver DL, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2014;32:1365–83.

76. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet. 1996;349:1864–7.
77. Parihar AS, Bhattacharya A, Rathod R, Bakshi J, Vadi S, Mittal B. Imaging of the human lymphatic system: principles and practice of lymphoscintigraphy and sentinel lymph node imaging. J Nucl Med. 2018;59:1217.
78. Alazraki NP, Styblo T, Grant SF, Cohen C, Larsen T, Aarsvold JN. Sentinel node staging of early breast cancer using lymphoscintigraphy and the intraoperative gamma-detecting probe. Semin Nucl Med. 2000;30:56–64.
79. Klimberg VS, Rubio IT, Henry R, Cowan C, Colvert M, Korourian S. Subareolar versus peritumoral injection for location of the sentinel lymph node. Ann Surg. 1999;229:860–5.
80. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol 2007;8:881–8.
81. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. Lancet Oncol. 2006;7:983–90.
82. Sajid MS, Parampalli U, Haider Z, Bonomi R. Comparison of radioguided occult lesion localization (ROLL) and wire localization for non-palpable breast cancers: a meta-analysis. J Surg Oncol. 2012;105:852–8.
83. Nadeem R, Chagla LS, Harris O, Desmond S, Thind R, Titterrell C, et al. Occult breast lesions: A comparison between radioguided occult lesion localisation (ROLL) vs wire-guided lumpectomy (WGL). Breast. 2005;14:283–9.
84. Lavoué V, Nos C, Clough KB, Baghaie F, Zerbib E, Poulet B, et al. Simplified technique of radioguided occult lesion localization (ROLL) plus sentinel lymph node biopsy (SNOLL) in breast carcinoma. Ann Surg Oncol. 2008;15:2556–61.
85. Schwartz RG, McKenzie WB, Alexander J, Sager P, D'Souza A, Manatunga A, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. Am J Med. 1987;82:1109–18.
86. Walker CM, Saldaña DA, Gladish GW, Dicks DL, Kicska G, Mitsumori LM, et al. Cardiac complications of oncologic therapy. Radiographics. 2013;33:1801–15.
87. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJS, Cleland JGF, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance. Are they interchangeable? Eur Heart J. 2000;21:1387–96.
88. Møgelvang J, Stokholm KH, Saunämaki K, Reimer A, Stubgaard M, Thomsen C, et al. Assessment of left ventricular volumes by magnetic resonance in comparison with radionuclide angiography, contrast angiography and echocardiography. Eur Heart J. 1992;13:1677–83.
89. Moy L, Noz ME, Maguire GQ, Melsaether A, Deans AE, Murphy-Walcott AD, et al. Role of fusion of prone FDG-PET and magnetic resonance imaging of the breasts in the evaluation of breast cancer. Breast J. 2010;16:369–76.
90. Reiner CS, Stolzmann P, Husmann L, Burger IA, Hüllner MW, Schaefer NG, et al. Protocol requirements and diagnostic value of PET/MR imaging for liver metastasis detection. Eur J Nucl Med Mol Imaging. 2014;41:649–58.
91. Melsaether AN, Raad RA, Pujara AC, Ponzo FD, Pysarenko KM, Jhaveri K, et al. Comparison of whole-body 18F FDG PET/MR imaging and whole-body 18F FDG PET/CT in terms of lesion detection and radiation dose in patients with breast cancer. Radiology. 2016;281:193–202.
92. Sawicki LM, Grueneisen J, Schaarschmidt BM, Buchbender C, Nagarajah J, Umutlu L, et al. Evaluation of 18F-FDG PET/MRI, 18F-FDG PET/CT, MRI, and CT in whole-body staging of recurrent breast cancer. Eur J Radiol. 2016;85:459–65.
93. Kolesnikov-Gauthier H, Carpentier P, Depreux P, Vennin P, Caty A, Sulman C. Evaluation of toxicity and efficacy of 186Re-hydroxyethylidene diphosphonate in patients with painful bone metastases of prostate or breast cancer. J Nucl Med. 2000;41:1689–94.

94. Serafini AN. Therapy of metastatic bone pain. J Nucl Med. 2001;42:895–906.
95. Fuster D, Herranz R, Vidal-Sicart S, MuÑOZ M, Conill C, Mateos JJ, et al. Usefulness of strontium-89 for bone pain palliation in metastatic breast cancer patients. Nucl Med Commun. 2000;21:623–6.
96. Parihar AS, Ga A, Sood K, Seam RK, Kaushal V, Sood A, et al. Incidental detection of synchronous lung melanoma on 18F-FDG PET/CT in a patient with parotid gland myoepithelial carcinoma. Clin Nucl Med. 2018;43:127–9.
97. Parihar AS, Mittal BR, Vadi SK, Sood A, Kumar R, Goni V. 18F-FDG PET/CT in isolated primary extraskeletal osteosarcoma. Clin Nucl Med. 2018;43:E463–4.
98. Peterson LM, Mankoff DA, Lawton T, Yagle K, Schubert EK, Stekhova S, et al. Quantitative imaging of estrogen receptor expression in breast cancer with PET and 18F-fluoroestradiol. J Nucl Med. 2008;49:367–74.
99. van Kruchten M, Glaudemans AWJM, de Vries EFJ, Schröder CP, de Vries EGE, Hospers GAP. Positron emission tomography of tumour [18F]fluoroestradiol uptake in patients with acquired hormone-resistant metastatic breast cancer prior to oestradiol therapy. Eur J Nucl Med Mol Imaging. 2015;42:1674–81.
100. Kurland BF, Peterson LM, Lee JH, Schubert EK, Currin ER, Link JM, et al. Estrogen receptor binding (18F-FES PET) and glycolytic activity (18F-FDG PET) predict progression-free survival on endocrine therapy in patients with ER+ breast cancer. Clin Cancer Res. 2017;23:407–15.
101. Arteaga CL, Sliwkowski MX, Osborne CK, Perez EA, Puglisi F, Gianni L. Treatment of HER2-positive breast cancer: current status and future perspectives. Nat Rev Clin Oncol. 2012;9:16–32.
102. Henry KE, Ulaner GA, Lewis JS. Human epidermal growth factor receptor 2-targeted PET/single- photon emission computed tomography imaging of breast cancer: noninvasive measurement of a biomarker integral to tumor treatment and prognosis. PET Clin. 2017;12:269–88.
103. Paik S, Kim C, Wolmark N. HER2 status and benefit from adjuvant trastuzumab in breast cancer. N Engl J Med. 2008;358:1409–11.
104. Ray GL, Baidoo KE, Keller LMM, Albert PS, Brechbiel MW, Milenic DE. Pre-clinical assessment of 177Lu-labeled trastuzumab targeting HER2 for treatment and management of cancer patients with disseminated intraperitoneal disease. Pharmaceuticals. 2011;5:1–15.
105. Ulaner GA, Schuster DM. Amino acid metabolism as a target for breast cancer imaging. PET Clin. 2018;13:437–44.
106. Tade FI, Cohen MA, Styblo TM, Odewole OA, Holbrook AI, Newell MS, et al. Anti-3-18F-FACBC (18F-Fluciclovine) PET/CT of breast cancer: an exploratory study. J Nucl Med. 2016;57:1357–63.
107. Nieberler M, Reuning U, Reichart F, Notni J, Wester H-J, Schwaiger M, et al. Exploring the role of RGD-recognizing integrins in cancer. Cancers (Basel). 2017;9:116.
108. Chen H, Niu G, Wu H, Chen X. Clinical application of radiolabeled RGD peptides for PET imaging of integrin αvβ3. Theranostics. 2016;6:78–92.
109. Parihar AS, Sood A, Kumar R, Bhusari P, Shukla J, Mittal BR. Novel use of 177Lu-DOTA-RGD2 in treatment of 68Ga-DOTA-RGD2-avid lesions in papillary thyroid cancer with TENIS. Eur J Nucl Med Mol Imaging. 2018;45:1836–7.
110. Parihar AS, Mittal BR, Kumar R, Shukla J, Bhattacharya A. 68Ga-DOTA-RGD2 positron emission tomography/computed tomography in radioiodine refractory thyroid cancer: prospective comparison of diagnostic accuracy with 18F-FDG positron emission tomography/computed tomography and evaluation toward potential Theranostics. Thyroid. 2020;30:557–67.
111. Parihar AS, Vadi SK, Mittal BR, Kumar R, Bal A, Singh SK. 68Ga-PSMA-HBED-CC-avid synchronous urinary bladder paraganglioma in a patient with metastatic prostate carcinoma. Clin Nucl Med. 2018;43:329–30.

112. Parihar A, Singh H, Kumar R, Shukla J, Bhattacharya A, Mittal B. Pearls and pitfalls in 68Ga-PSMA PET/CT imaging – the 'non-specificity' issue. J Nucl Med. 2019;60(supplement 1):1144.
113. Parihar AS, Sood A, Mittal BR, Kumar R, Singh H, Dhatt SS. 68Ga-PSMA-HBED-CC PET/CT and 18F-FDG PET/CT in Ewing sarcoma. Clin Nucl Med. 2020;45(1):e57–8.
114. Parihar AS, Mittal BR, Sood A, Basher RK, Singh G. 68Ga-prostate-specific membrane antigen PET/CT and 18F-FDG PET/CT of primary signet ring cell breast adenocarcinoma. Clin Nucl Med. 2018;43:414–6.
115. Sathekge M, Lengana T, Modiselle M, Vorster M, Zeevaart JR, Maes A, et al. 68Ga-PSMA-HBED-CC PET imaging in breast carcinoma patients. Eur J Nucl Med Mol Imaging. 2017;44:689–94.
116. Ulaner GA, Goldman DA, Corben A, Lyashchenko SK, Gönen M, Lewis JS, et al. Prospective clinical trial of 18F-fluciclovine PET/CT for determining the response to neoadjuvant therapy in invasive ductal and invasive lobular breast cancers. J Nucl Med. 2017;58:1037–42.
117. Cheng J, Lei L, Xu J, Sun Y, Zhang Y, Wang X, et al. 18F-fluoromisonidazole PET/CT: a potential tool for predicting primary endocrine therapy resistance in breast cancer. J Nucl Med. 2013;54:333–40.
118. Kenny LM, Vigushin DM, Al-Nahhas A, Osman S, Luthra SK, Shousha S, et al. Quantification of cellular proliferation in tumor and normal tissues of patients with breast cancer by [18F]fluorothymidine-positron emission tomography imaging: evaluation of analytical methods. Cancer Res. 2005;65:10104–12.
119. Dittmann H, Jusufoska A, Dohmen BM, Smyczek-Gargya B, Fersis N, Pritzkow M, et al. 3′-Deoxy-3′-[18F]fluorothymidine (FLT) uptake in breast cancer cells as a measure of proliferation after doxorubicin and docetaxel treatment. Nucl Med Biol. 2009;36:163–9.
120. Greif JM, Pezzi CM, Klimberg SV, Bailey L, Zuraek M. Gender differences in breast cancer: analysis of 13,000 breast cancers in men from the national cancer data base. Ann Surg Oncol. 2012;19:3199–204.
121. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men: a population-based study. Cancer. 2004;101:51–7.
122. Ulaner GA, Juarez J, Riedl CC, Goldman DA. 18F-FDG PET/CT for systemic staging of newly diagnosed breast cancer in men. J Nucl Med. 2019;60:472–7.
123. Vadi SK, Mittal BR, Sood A, Singh G, Bal A, Parihar AS, et al. Diagnostic and prognostic value of 18F-FDG PET/CT imaging in suspected recurrence of male breast cancer. Nucl Med Commun. 2019;40:63–72.

Tumour Markers, Prognostic and Predictive Factors in Breast Cancer

13

Dhritiman Maitra and Anurag Srivastava

13.1 Introduction

Tumour markers comprise of proteins or carbohydrate antigens (abnormal ones or normal ones in abnormal quantity), genetic changes in the DNA or RNA, DNA adducts and epigenetic changes, which when detected in the tumour itself or in the blood, bone marrow or other body fluids of a subject, can indicate the presence of cancer in that individual.

Some of them are helpful for diagnosing cancer in clinically occult cases, in differentiating a benign from a malignant tumour, identifying the organ of origin and confirming the nature of the tumour in case several possibilities are indicated by an equivocal histo-pathological examination. These are called diagnostic bio-markers.

Some bio-markers may also point towards an increased propensity of an individual to develop cancer. Such bio-markers are helpful for screening and dispensing risk-reducing measures like chemoprevention to prevent the occurrence of cancer. These are called risk factor and exposure bio-markers. There are some surrogate end-point bio-markers which are biologic alterations that occur between cancer initiation and clinical manifestation. Such markers may be used as end-points to evaluate the efficacy of a chemoprevention strategy.

Bio-markers may correlate with tumour burden, aggressiveness of tumour and aid in subtype classification for staging and planning of suitable treatment.

Dhritiman Maitra, MS MCh, DNB, FIAGES, FACS (✉)
Assistant Professor and In-Charge, Breast and Endocrine Surgery Services, Department of Surgery, Medical College, Kolkata, India
e-mail: drdhritiman@gmail.com

Anurag Srivastava, MS, FRCS, PhD, MPH
Former Professor and Head, Department of Surgical Disciplines, AIIMS, New Delhi, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_13

The prognostic bio-markers provide information regarding cancer outcomes irrespective of treatment and predictive bio-markers provide information regarding response to therapy [1–6]. Some bio-markers have mixed significance. While estrogen receptor positivity is a strong predictive marker for responsiveness to endocrine therapy, it does not have much prognostic significance; however, a HER2 expression indicates both an adverse prognosis and good response to anti-HER 2 therapy.

There are several other prognostic and predictive factors which are dubbed as patient-related and those related to the tumour stage and pathology. Sometimes a combination of bio-markers are studied together using softwares, nomograms and next generation gene sequencing to diagnose, classify, prognosticate, treat and monitor the response to treatment.

13.2 Characteristics of an Ideal Tumour Marker

(a) validated by clinical testing
(b) should provide significant independent predictive value without interaction with other factors
(c) measurable and quantifiable by widely available, feasible and reproducible laboratory tests
(d) easily interpretable
(e) not unnecessary or superfluous and possessing therapeutic implications
(f) should not require too much tissue which may hamper primary histopathological evaluation [7, 8]

13.3 Strength of a Prognostic or Predictive Marker

The tumour marker utility grading system (TMUGS) is used to ascertain the clinical utility of a tumour marker [9]. Hayes et al. proposed that the prognostic factors may be classified on the basis of their associated hazard ratios (HR) as follows:

(a) HR < 1.5-weak factor,
(b) HR 1.5–2-moderate factor and
(c) HR > 2-strong factors [10].

Strength of predictive factors are determined by "Relative Predictive Value (RPV)" which is defined as the ratio of probability of response to treatment in a factor positive patient compared to a factor negative one. On the basis of RPV, the predictive factors are classified as (a) Weak with RPV of 1–2, (b) Moderate with RPV of 2–4 and strong with RPV >6.

13.4 Prognostic Factors-Clinical

13.4.1 Age

Age of presentation below 35–40 years is associated with worse prognosis than older premenopausal as well as post-menopausal ladies. EORTC meta-analysis revealed greater mortality and loco-regional recurrence rates in the young. Chemotherapy was equally effective in estrogen receptor negative patients irrespective of age. However, in hormone positive patients less than 35 years of age, relapse rate following chemotherapy was significantly more than older premenopausal and post-menopausal ladies. SEER database review observed that patients in the younger age-group could have confounding factors like greater incidence of larger, hormone receptor negative cancer of higher grade associated with inherited genetic mutations. However, even after matching for these factors, younger age remained a statistically significant factor for worse prognosis [11–13].

13.4.2 Menopausal Status

It may act as a proxy for age. The time to recurrence has been found to have a correlation with menopausal status in node positive disease and is prolonged in the post-menopausal group than in the premenopausal group [14].

13.4.3 Race/Ethnicity

The prognosis in different races parallels with the average age, tumour types and stage of presentation.

13.4.4 Clinical Tumour Size

Clinical Tumour size recorded on the basis of clinical examination and imaging may be erroneous due to surrounding desmoplastic reaction and presence of DCIS at the margins. Size of the invasive component on histopathological examination post-surgery is more relevant in prognostication.

13.4.5 Clinical Stage

Worse prognosis is associated with clinically evident locally advanced disease comprising of large primary tumours more than 5 cm (T3) with axillary lymph node disease or even smaller tumours with large, fixed or matted axillary nodes or

involvement of the supraclavicular or internal mammary nodal basins or a tumour fixed to the chest wall (T4a), skin involvement (T4b) in the form of fungation, ulcer, peau d' orange, satellite nodules or both skin and chest wall(T4c). The worst prognosis is seen in inflammatory cancer (T4d) which presents with a rapidly progressing (3–6 months) cancer with involvement of the breast by oedema or peau d'orange in over 1/3rd of the area, redness, raised temperature with or without a mass along with bulky fixed lymph node in one or more lymph node basins. Sometimes the entire breast feels like a hard fixed mass. These features predominantly earn neoadjuvant therapy for the patient.

13.5 Prognostic Factors-Pathologic

13.5.1 Primary Tumor Size (pT)

According to the 8th edition AJCC TNM staging system for breast cancer, tumors of size less than and upto 1 mm are called microcracinoma.T1a tumours are >1 mm to 5 mm, T1b tumours are >5 mm upto 1 cm and T1c tumors are >1 cm upto 2 cm in the greatest diameter. At approximately the 20th cell division, the tumours develop their own blood supply and become capable of throwing up tumour seedlings into the systemic circulation. By the 27th cell division, when the tumour size reaches 0.5 cm, successful implantation of metastatic foci may occur predictably. Tumors >2 cm upto 5 cm are grouped as T2 and those which are >5 cm are included in T3. T4 tumours are those with chest wall, skin involvement or inflammatory carcinoma irrespective of size as the presence of any of these worsen the prognosis for even a small tumor. Analysis of various data have shown a gradual worsening of prognosis with advancing size [15]. If there are multiple tumours, the size of the largest tumour is used for ascertaining the T-stage with a "m(multiple)" added as a suffix and not the cumulative size of the tumours.

13.5.2 Regional Lymph Node Status (pN)

Pathological staging of nodes takes into account the number of positive nodes, whether they are found to be positive on sentinel node biopsy or are harvested by axillary dissection and also on the site of involvement as all of these factors affect the prognosis. Presence of 1–3 axillary nodes with at least one of them >2 mm is staged as pN1,4–9 nodes is staged as pN 2 and 10 or more is classified as pN3. NSABP-04 and NSABP-06 [16, 17] showed that the 10-year survival dipped with increase in number of positive nodes. Another systematic review revealed that the number of positive nodes increase with the increase in size of primary tumour [18]. Node positivity and heavy nodal burden(>4 nodes) were found to have a relationship with the molecular sub-types of breast cancer with higher incidence in Luminal B and Her 2 +ve tumours compared to Luminal A or, basal cancers [19]. Low grade tumours and certain histopathological subtypes like tubular, invasive cribriform, mucinous, papillary etc. were associated with a much lower incidence of nodal spread.

13.5.3 Nodal Micrometastasis

In the pathological nodal staging. pN0 (i+) denotes nodes less than 0.2 mm detected by HPE or IHC including ITC(isolated tumour cells), a term used to describe less than 200 cells in a cluster or a cluster of cells less than 0.2 mm. The notation pN0 (mol+) is used to describe nodes which show tumour deposits only on RT-PCR. The symbol pN1(mic) or micrometastasis(MM) stands nodes with a malignant focus of >200 cells or tumour deposits >0.2 upto 2 mm in size. With the progress in Sentinel Lymph node Biopsy(SLNB) technology, specimens started to be subjected to imprint cytology and IHC staining for markers like cytokeratin 19 and mammaglobin. Some early studies showed a poorer disease free survival and overall survival when ITC or micrometastasis were present. The NSABP-32 randomized trial, which established SLNB as a procedure of choice for clinically node negative patients showed that occult metastases had independent prognostic value, albeit the difference was very small at 5 years. However, the ACoSOGZ0010 randomized trial established that there is no role of axillary dissection even if ITC or MM were detected on SLNB. The IBISSG23-01 randomized trial also presented similar results [20–22].

13.5.4 Extracapsular Spread of Nodal Metastasis

Extracapsular spread strongly correlates with the number of positive nodes and lymphatic and vascular invasion within the breast parenchyma [23, 24].

13.5.5 Tumour Grade

Grading is most commonly done by the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system.

Three parameters are assessed namely tubule formation, mitotic counts per high power field and nuclear pleomorphism. Each of these parameters may have a score of 1–3, the total possible score being 3–9.Now, a total score of 3–5 is considered as low grade or grade 1, that of 6–7 is considered intermediate or grade 2 and 8–9 is classified as high grade or grade 3. In multivariate studies, tumour grade was detected as an independent prognostic marker with a highly significant difference in survival and recurrence rates between grade 3 and grade 1. Grade 2 was more of a heterogenous group with patients at both ends of the spectrum. To dispel this dichotomy, a 97 gene study called “Gene Expression Grade Index” has been formulated. It has a perfect correlation with conventional grading system in detecting Grade 1 and 3 tumours. The grade 2 tumours can be further sub-classified according to aggressiveness on the basis of different findings of this genetic analysis [25]. For patients, who undergo neoadjuvant chemotherapy, the tumours are assessed by the Miller Payne grading system after surgery. It classifies a complete pathological response as Grade 5 and poor response with no reduction in overall cellularity as Grade 1 with others in between. Complete pathological response is seen to translate to longer over-all survival and disease free survival.

13.5.6 Tumour Histology

Adenocarcinoma is the predominant cancer of the breast with ductal adenocarcinoma being the commonest variety so much so that this type is dubbed as "Not Otherwise Specified"(NOS). Other varieties are lobular carcinoma which has a tendency to be bilateral, multicentric and relatively chemoresistant. However, they are more often hormone receptor positive and respond to endocrine therapy. The other special variants like tubular carcinoma, mucinous carcinoma, cribriform carcinoma, adenoid cystic carcinoma are all considered to have better prognosis than NOS. According to the NCCN guidelines, in view of low risk of recurrence, patients with these special tumours upto a size of 3 cm size may be treated without chemotherapy in adjuvant setting if they have no nodal metastasis whereas NOS tumours above 1 cm are considered for adjuvant chemotherapy [15].

13.5.7 Over-All TNM Stage

Classically the clinical and pathological TNM staging were used over the years which was done on anatomical grounds. SEER analysis showed a 100% 5 year survival for Stage 0 and Stage 1 breast cancer followed by 86% for stage 2, 57% for stage 3 and 20% for stage 4. However, in the 8th edition AJCC–TNM staging, prognostic staging has been introduced which also takes into account hormone receptor status, HER-2 status and grade of tumour. A patient with classical Stage 3 disease but favourable hormone receptor status, Her-2 status and grade may be downstaged to a prognostic Stage 2 disease with a better survival than Stage 3 patients. The results of a 21-gene assay called Oncotype Dx is also taken into consideration for T1 and T2 node negative, estrogen receptor positive disease and if a low risk score is detected(<11), then the tumour is Staged as Stage 1A irrespective of grade, hormone receptor and Her-2 status. Such patients may do without adjuvant chemotherapy.

13.5.8 Lymphovascular Invasion (LVI)

Retraction artifact, which was previously considered to be the main reason behind a high inter-observer variability in interpreting LVI, is now considered a poor prognostic marker itself related to tumor-stromal interactions. LVI is an adverse prognostic variable; however in some studies it was associated with adverse outcome only in patients already thought to be at high risk of recurrence and not in those who were considered low risk on the basis of other factors. Some studies however established LVI as an independent adverse marker for over-all survival [26–28].

13.5.9 Hormone Receptor Status as a Prognostic Marker

Hormone receptor status is meant by estrogen receptor(ER) and progesterone receptor(PR) expression by tumours. Another receptor of interest in this regard is the androgen receptor expression. These are intranuclear steroid hormone receptors. There are two isoforms of estrogen receptor ER-alpha and ER-beta which are encoded by separate genes. In clinical practice, the term ER refers to ER-alpha. Tumours may express both ER and PR or only ER. Though cases with PR +ve and ER −ve status are also encountered, they are often presumed to be due to sampling error. An immunohistochemical assay is used to quantify ER and PR. It can be performed on paraffin fixed tissue also and with very small amount of tissue in contrast to the erstwhile DCC-LBA (Dextran Charcoal Coated Ligand Binding Assay) which could be performed only on fresh or snap-frozen tissue of considerable amount. The finding on a sample obtained by core biopsy is more reliable than that on the final operative specimen. In core biopsy, the tissue amount is small and is immediately fixed in formalin. However the operative specimen is big and formalin may not penetrate to all parts of the tumour and formalin fixation can only be done after the whole procedure is over which takes some time [18]. However, if there is tumour heterogeneity, then core biopsy specimen may not be fully representative. Allred score is used to report the ER and PR status individually. It is a composite score, which is the sum of the percent score(0–5) and intensity score(0–3). The over-all score is either 0 or 2–8 with score ≥3 being considered as positive and likely to benefit with endocrine therapy. RNA-based assays using RT-PCR or microarray analysis are also used to quantify ER expression which have been found to be more accurate than IHC [29].

Although ER is more commonly used as a predictive factor, it also finds use as a prognostic marker. Recurrence rates are 5–10% less in ER positive tumours not receiving systemic therapy than their ER negative counterparts in the initial years. However over time, the difference in recurrence rates dwindles indicating that ER positive tumours are indolent, slow-growing tumours with limited metastatic potential. ER positive tumours are mostly well-differentiated, with less proliferative activity and absence of mutation or amplification of other breast cancer genes.

Of the ER positive tumours, the PR positive subset has a better prognosis being smaller and less proliferative than ER +ve/PR −ve tumors. All ER positive tumours are of Luminal type by molecular gene expression profiling but of them the PR −ve ones correlate with the aggressive Luminal B type of tumours. The ER +ve/PR +ve tumours behave as the molecular class of Luminal A cancers [30, 31]. When androgen positivity is present in ER/PR +ve patients, prognosis is better. However when PR –ve, androgen receptor helps in tumor proliferation. In TNBC and HER-2 rich groups also androgen receptor positivity acts as a negative influence.

13.5.10 HER-2 Amplification as a Prognostic Marker

There are four types of HER receptors.HER1 is also called EGFR. HER-2 positivity leads to ligand mediated augmentation of cell proliferation, invasiveness and tumor cell survival by altered signal transduction initiation by homo or hetero-dimerization of the receptors. Now-a-days it is considered to be a more important predictive than a prognostic factor owing to the widespread use of anti-HER-2 agents in the treatment of breast cancer. The receptors also have a tyrosine kinase domain which can be targeted by tyrosine kinase inhibitors.

13.5.11 Measures of Tumour Proliferative Activity, Angiogenesis, Apoptotic and Antiapoptotic Factors

Several markers have been identified as indicators of cell proliferation namely thymidine labelling index, flow cytometry and high S-phase DNA, aneuploidy, cyclin D, E and their inhibitors p27 and p21, topoisomerase II alpha and Ki-67 among others.

Mitotic index, which is one component of the breast cancer grading system already described, has been identified as an independent marker of proliferation and a strong prognostic factor in node negative disease. Ki-67 has been found to be an independent prognostic marker as well by Colozza et al., ASCO and has been reported by using the REMARK tool [32]. In the neo-adjuvant setting, Ki 67 correlated with pathological complete response. Ki-67 levels may be used as a surrogate end-point marker for hormone therapy in neoadjuvant setting or metastatic setting as effective hormone therapy reduces Ki-67 and persistently high Ki −67 levels worsen the prognosis by reducing the recurrence free survival [33, 34]. ER,PR,HER-2 and Ki-67 have been combined to form a panel of 4 immunohistochemical markers called IHC4 which acts as a predictor of cancer recurrence and is more widely available and cheaper than commercially available gene based recurrence scores.

Proliferative cell nuclear antigen is a protein associated with DNA polymerase and is normally found in different phases of the cell cycle. It has been identified as an important prognostic marker for breast carcinoma as well [35].

Overexpression of VEGF (vascular endothelial growth factor) is correlated with microvessel density and recurrence in node negative cancers. An angiogenesis index has been developed which combines microvessel density (CD31), thrombospondin and p53. Both VEGF and angiogenesis index act as both prognostic and predictive markers. Bevacizumab (an antiVEGF monoclonal antibody) has been approved by US-FDA for use in the treatment of metastatic breast carcinoma along with paclitaxel [36].

Apoptotic markers like over-expression of bcl2 and a reduced bax:bcl2 ratio have been found to have significant prognostic value in breast cancer and are associated with higher grade, axillary node metastasis and reduced DFS and overall survival [37].

13.6 Predictive Factors

13.6.1 Hormone Receptor Status as Predictive Marker

The use of adjuvant Tamoxifen (SERM or selective estrogen receptor modulator) in pre-menopausal estrogen receptor positive ladies and Anastrozole or Letrozole (Aromatase Inhibitors) in estrogen receptor positive post-menopausal ladies) with or without chemotherapy has become the standard of care. The use of Tamoxifen in hormone positive node negative cancer in patients less than 50 years was first established by NSABP-14 trial which showed a reduced rate of in-breast recurrence and 50% reduction in opposite breast cancers. Later, a meta-analysis of various trials proved it to be equally effective in node positive patients [38].

The EBCTCG overview and another meta-analysis proved that there was no role of tamoxifen in ER −ve/PR −ve tumours. The ER+/PR −ve group had less benefit than those with both ER and PR positive. It was seen that Aromatasie Inhibitors could be more effective in ER +ve/PR −ve group. ER −ve/PR +ve patients, which forms a very small group, may benefit from hormone therapy by tamoxifen. However, some believe that this subset of ER −ve/PR +ve patients may actually be having heterogenous tumours with unsampled ER +ve parts or false negative ER status. ATAC and BIG 1–98 adjuvant trials have ruled out correlation of PR levels with outcomes of endocrine therapy.

Higher ER levels were associated with greater risk reduction [39]. However weakly positive tumors also had significant benefits over negative tumors. Current AJCC and College of American Pathologists define ER-positivity by staining of more than merely 1% cells on IHC.

The benefit of use of Tamoxifen for 5 years versus a prolonged duration of 10 years was studied in aTTom and ATLAS trial. Both showed a benefit of using tamoxifen for a longer duration especially in high risk ladies (like node positive) by reduction in mortality following recurrence. This benefit of longer use became evident only in the long-run due to the carry-over effect of the use of first 5 years during years 5–9 of use. Benefit has been seen even if tamoxifen is started 5 years after primary therapy due to some delay.

Aormatase inhibitors (anastrozole, letrozole) should be used in post-menopausal women as by inhibiting estrogen formation from androgens, they cause withdrawal of inhibitory negative feedback mechanism on hypothalamus and pituitary gland to cause increase in GnRH and FSH secretion, thereby leading to more secretion of androgens and estrogen from ovaries in the premenopausal ladies and upregulation of estrogen receptors and increased aromatase synthesis [40]. If they are intended to be used in premenopausal ladies, then they should be used following ovarian suppression by a GnRH analogue or oophorectomy.

The ATAC trial studied the benefit of Anastrozole, Tamoxifen alone or in combination in adjuvant setting. It showed that combination therapy was equivalent to Tamoxifen but inferior to AI. Hence anastrozole was found to be better than Tamoxifen. The Big-I-98 trial compared monotherapy with Letrozole or Tamoxifen,

sequential administration of tamoxifen for 3 years followed by AI for 2 years and vice versa. AI monotherapy was significantly better than others.

The TEAM trial showed a non-steroidal AI called exemestane to have similar disease free survival as with Tamoxifen when used in adjuvant setting.

The IES and ITA trial showed benefits in disease free survival by switching over to exemestane or anastrozole for 3 years following an initial 2 years of therapy with tamoxifen, provided the patient did not remain premenopausal [41, 42].

NCIC-MA 17 trial proved additional therapy with letrozole following 5 years of Tamoxifen to be beneficial. NSABP-33 embarked on a similar trial using exemestane but was prematurely terminated after positive results of MA17 trial were published.

Hormone therapy has been used in neo-adjuvant setting also in patients with hormone positive tumors who are unfit for chemotherapy. It has been used for 4–12 months with a median of 7.5 months required to achieve best response to treatment. Though pathological complete response was rarely observed, surrogate markers like change in KI-67 activity or rate of breast conservation were studied in the PROACT and IMPACT trials. AIs were significantly better than tamoxifen for neo-adjuvant therapy. The Proluton study of Tata Memorial Hospital also showed that manipulation of the hormonal milieu by injecting medroxy progesterone just within 2 weeks prior to surgery in T2N1 cancers can improve the outcomes of treatment. The POETIC trial is underway in the lines of the former.

In hormone positive metastatic breast cancer, not associated with visceral crisis, Aromatase inhibitors have long been used and seen to alter the progression of disease. In case of hormone receptor positive recurrence in a patient pre-treated with hormone therapy or if there is progression while on hormone therapy, a second line of hormone therapy proves beneficial to overcome endocrine resistance. Fulvestrant, which is an anti-estrogen has been proved to be effective in metastatic breast cancer in hormone receptor positive cancer both as a first line and a second line agent. In hormone receptor positive Her2 negative metastatic cancers CDK 4/6 inhibitors like Palbociclib and Ribociclib have altered the progression free survival but not in hormone negative tumours.

Some primarily hormone positive tumours may throw up hormone negative metastasis. The ER status of the metastatic tumor is a better predictor of survival than the ER status of the primary tumour. Loss of PR expression in metastases is also an independent predictor of poorer survival and response to therapy than patients who retain the PR positivity. Patients who develop endocrine resistance have been found to have developed alterations in other pathways, namely PIKC3AKT/m-TOR/ERBB2 which pronounce a poorer survival [43].

Ovarian ablation with GnRH analogues have also been effective in hormone receptor positive patients.

Fifty to 60% of DCIS express ER. PR is not routinely measured in DCIS. ER +ve DCIS have been shown to get benefitted by adjuvant tamoxifen for 5 years in the NSABP-24 trial leading to reduction of recurrence or occurrence of future invasive carcinoma by 40%. NSABP-35 trial is now underway to assess the efficacy of AI in DCIS.

Now, several subsets of hormone positive patients have been identified by combining various factors with ER and PR status to develop prognostic indices and molecular signatures which can more accurately predict the outcome of endocrine therapy in different individuals. These indices and molecular/genetic signatures include Sensitivity to Endocrine therapy Index (SET), Adjuvant online, Mammaprint, IHC4, Oncotype DX, Endopredict, NHSPredict etc. SET index is a 165 gene assay which identifies ER and PR correlated genes and combines it with IHC to enable us to predict more accurately which patients will benefit to what extent with endocrine therapy. The other indices and genetic assay based prognostic and predictive scores have been discussed later.

13.6.2 HER2 Amplification and Or/Over-Expression as a Predictive Marker

HER-2 positivity is measured by immunohistochemistry and reported as 3+ which indicates positivity and 1+ which is interpreted as negative. The intermediate group reported as 2+ is considered as equivocal. It has been proved that there is absence of 100% concordance between HER-2 gene amplification and receptor expression detected by IHC. Response to treatment correlates better with actual gene amplification (genotype) rather than receptor expression (phenotype). Hence.in such dichotomous situation, Fluorescent in Situ Hybridization (FISH) is performed to confirm the amplification status. Overall, amplification of HER-2 gene occurs in 20% patients [44].

HER-2 positive tumours respond to targeted therapies by trastuzumab (anti HER-2 monoclonal antibody for extracellular domain), pertuzumab (monoclonal antibody against HER2 and HER3), adotrastuzumab or trastuzumab-emtansine immunoconjugate and lapatinib (small molecule tyrosine kinase inhibitor of HER1 and HER2).

The ASCO overview showed that increased response to anthracycline by HER-2 positive tumors was supported by level II evidence only. However, there was significant benefit on addition of a taxane like paclitaxel or docetaxel [45].

Clinical benefits of trastuzumab in HER2 +ve tumours was established first in metastatic breast cancer. This paved the way for other trials to ascertain the efficacy of trastuzumab in adjuvant and neoadjuvant setting. It also gave impetus to the development of the other anti HER-2 agents and trials to prove their efficacy.

The randomized NSABP-31 and HERA trials were the earliest to establish the benefit of using trastuzumab in HER-2 +ve women in the adjuvant setting after completion of their chemotherapy. HERA trial established that 1 year of treatment with trastuzumab is non-inferior to 2 year treatment. This remains the recommended duration of treatment till date though in compliance with later trials(BCIRG 006), treatment with trastuzumab(Herceptin or H) is now started concurrently with docetaxel following four cycles of AC (adriamycin+cyclophosphamide) or along with the first dose docetaxel(T) and carboplatin(C) in the “TCH” regimen.

The application of trastuzumab was expanded to neoadjuvant setting along with chemotherapy in HER-2 positive patients following the results of a randomized trial by MD Anderson Cancer Center and the NOAH trial. The down-side of trastuzumab therapy is its cardiotoxicity especially when used along with anthracyclines which may downplay the gain in overall and disease free survival achieved by it.

In the metastatic setting, trastuzumab monotherapy was only marginally beneficial in heavily pre-treated HER2 +ve ladies. However its efficacy was increased when used in combination with chemotherapy. Efficacy of endocrine therapy decreases in ER +ve patients who are also HER2 +ve. The TAnDEM trial established the advantage of adding trastuzumab to endocrine therapy in ER +ve, HER2 positive tumours in metastatic setting.

Even on progression on trastuzumab therapy, continuation of trastuzumab with second line therapy has shown to increase the median over-all survival [46]. The effect of trastuzumab in brain metastasis improves after treatment with radiation. It is postulated that trastuzumab can cross the blood brain barrier only after it has been damaged by therapeutic radiation.

Lapatinib was also studied for use in neo-adjuvant setting. The first trial called TEACH has no clinical relevance. The German GeparQuinto trial showed that pathological complete response (PCR) achieved with a combination of chemotherapy and trastuzumab was significantly more than that of chemotherapy and lapatinib. The NeoALTTO trial showed no statistically significant difference when paclitaxel was combined with either trastuzumab or lapatinib or both in neoadjuvant setting. NSABP-41 also compared lapatinib with trastuzumab and concluded that Lapatinib is not superior to trastuzumab. In the metastatic setting Lapatinib with letrozole have shown good response in ER +ve, HER2 + VE tumours. Lapatinib and capecitabine have also been approved in metastatic patients previously treated with trastuzumab, taxanes and anthracyclines. Lapatinib finds place in brain metastasis. Newer agents like neratinib and afatinib also show promise in brain metastases.

Pertuzumab was found to augment the effectiveness of trastuzumab by Neosphere trial in the neo-adjuvant setting and the APHINITY trial in adjuvant setting when used in combination with trastuzumab and a chemotherapeutic regimen. The CLEOPATRA trial showed that pertuzumab helps in overcoming resistance to trastuzumab and increased PFS and OS in HER-2 positive cancers in recurrent and metastatic setting.

Adotrastuzumab or, trastuzumab emtansine (T-DM1) is a conjugate of a monoclonal antibody with DM1which is a potent antimicrotubule agent. This ensures delivery of DM1 to HER-2 positive cancer cells and also is less cardiotoxic than trastuzumab.

Adotrastuzumab has also been studied in metastatic and recurrent cancer, especially in ladies heavily pre-treated with trastuzumab and cardiotoxic anthracyclines. The EMILIA trial established that adotrastuzumab more effectively prolongs PFS and OS.

It has been studied that activating mutations in PIK3CA pathway, loss of PTEN (as in Cowden's syndrome) etc. may contribute to resistance to trastuzumab.

13.6.3 Emerging Markers with Predictive Value

Markers of all pathways which are currently being targeted by molecular therapy could act as potential predictors. All of these are currently being used or investigated in metastatic setting with the end-point of progression free survival. PIK3 inhibitors, like Alpelisib (SOLAR-I trial) have been effective especially in PTEN deficient tumors. In ER +ve, HER2 –ve metastatic tumours, CDK 4/6 inhibitors Palbociclib and Ribociclib have been proved to be effective in prolonging PFS by the PALOMA and MONALEESA trials respectively. The m-TOR inhibitors like everolimus have been proved to be effective by the BOLERO-2 trial in the metastatic setting along with tamoxifen therapy in patients who developed resistance to AI therapy. Its role in trastuzumab resistance in HER2 +ve tumours is now being studied in BOLERO-3 trial. PARP inhibitors like olaparib (Olympiad trial) have been found to be effective when used with platinum agents in triple negative BRCA positive breast cancer in the metastatic setting. Other agents under investigation are insulin/insulin-like growth factor-I receptor, histone deacetylase inhibitors(SAHA-suberoyl anilide hydroxamic acid), fibroblast growth factor receptor and heat shock protein(HSP)-90 inhibitors.

13.6.4 Coexpression of Biomarkers

13.6.4.1 Classification into Molecular Subgroups with Similar Prognosis

A 50 gene assay called PAM-50 done by RT-PCR on formalin fixed paraffin embedded specimens formed the basis of classification of breast cancers into intrinsic subtypes [47]. Though IHC does not correlate perfectly with multigene assays, the St. Gallen's consensus conference adopted the IHC based classification of breast tumours into different subtypes corresponding to the intrinsic classes determined by PAM-50 [48]. These classes differ in biology, distinguish good and poor prognosis patients and predict the response to different therapies.

The different classes are:

1. **Luminal A** (30–40%): On IHC, they are ER +ve/PR +ve, HER2-ve with low Ki-67 levels. On multigene assay, genes for ER activation, those of expression of luminal cytokeratins 8 and 18 are raised in both Luminal A and B tumours. In Luminal A, genes for GATA3 and PR have high expression and there is low expression of HER2 gene and proliferation associated genes including Ki-67. PIK3CA mutations were seen in both the Luminal types [25, 49–53].
2. **Luminal B** (10–15%): On IHC, they are ER +ve (may be weakly positive), PR +ve or negative, HER2 +ve or Ki-67 positive with HER2 negativity. These are more aggressive than Luminal A tumours. Genetic assays confirm higher and lower expressions of genes corresponding to the IHC parameters. TP53 mutation, which contributes to endocrine therapy resistance, is present in 29% of Luminal B tumours compared to 12% in Luminal A tumours [52–54].

When Luminal A and B patients are also assessed by Oncotype Dx recurrence score, 70% of Luminal A have low scores and can do without chemotherapy. 90% of the high score patients are of Luminal B subtype [55].

3. **HER2** enriched (5–10%): HER2 +ve tumours are either Luminal HER2 +ve or HER2 enriched. On IHC they are ER –ve/PR –ve and HER +ve. They have high expression of HER2 gene and other genes that reside near HER2, proliferative genes and low expression of luminal and basal cluster genes. Seventy-five percent are high grade with 70% of them expressing TP53 mutation. A considerable proportion have PIK3CA positivity also. Investigations are underway to identify further sub-class of patients to predict who would respond better to trastuzumab therapy [54].
4. **Normal**-like: this rare group is thought to be artifactual due to excessive amounts of normal breast tissue in samples subjected to genetic assay.
5. **Basal**-like: Phenotypically they are ER −ve, PR −ve, HER2 –ve or so called triple negative(TNBC). But all basal like cancers are not triple negative and vice versa. 25% of genetically determined basal like tumours may express ER/PR/HER2 on IHC. 75% of TNBCs are however basal like [56, 57].

   They have high expression of proliferation genes, the genes representing the basal cluster comprising of typical basal cytokeratins 5, 6, 14 and 17 and other markers like EGFR, c-kit, vimentin, P-cadherin etc. They show similarities with tumours arising from the basal layer of epidermis like squamous cell carcinoma of lung and epithelial ovarian tumours. TP53 mutation is present in 85%. In the PIK pathway, there is less occurrence of PIK3CA mutation and more of loss of PTEN. Most basal like cancers are sporadic but most of the BRCA-I related cancers are basal like (80%). Genes regulating DNA repair mechanisms are also deficient in them and DNA repair occurs through abnormal pathways like PARP, leading to propagation of the tumour. So these could become predictors of response to treatment with PARP inhibitors and DNA damaging agents like platinum chemotherapy [54, 58, 59].

   It has a racial preponderance occurring more in races with poorer prognosis [60].
6. **Other subtypes**
   (i) Claudin low: Majority of these tumours are high grade, TNBC or metaplastic cancer with poor prognosis. They have low expression of luminal genes and HER2 cluster genes. They differ from basal like cancers in that they have lower expression of cell-cell adhesion proteins like Claudin 3,4,7 and E-cadherin. These tumours are rich in immune system response genes (CD4, CD79a, IL-6, CXCL2). They also express markers which are indicators of metaplastic cancers and mammary stem cells [22, 61].
   (ii) TNBCs were further classified by Lehmann et al. into basal like group, luminal or androgen receptor positive group, mesenchymal or Claudin low group. TNBCs were also classified into prognostic groups as those with and without immune cell infiltrates and those with and without significant fibroblast invasion. Androgen receptor positive tumours have been targeted with

antiandrogens like bicalutamide which were hitherto used in prostate cancer, adding to its predictive value. Androgen receptor positivity has also been seen in some ER +ve tumours.

13.6.4.2 Risk Scores(Non-genetic and Genetic Assay Based)

The traditional prognosticators are Nottingham Prognostic Index, St. Gallen's Concensus and Adjuvant! Online. Nottingham Prognostic Index is calculated as 0.2X size of tumour in cm + grade + lymph node satus. Scoring for grade is 1 for grade 1, 2 for grade 2 and 3 for grade 3. For lymph node status, the scores are 1 for no node, 2 for 1–2 nodes and 3 for ≥3 nodes. On the basis of the total score patients are classified into 4 different groups(score of 2–2.4, >2.4–3.4, >3.4–5.4 and >5.4) with 5-year survival rates of 93%, 85%, 70% and 50% respectively. The others also use tumor size, grade, lymph node status and hormone receptor status to predict a patient's clinical outcome. There are predictive scores like NHS Predict 2.0 also, which can be calculated online by simple parameters to decide whether to subject a patient to adjuvant chemotherapy or not.

Genomic technology has facilitated the development of biology based prognosticators. These are currently meant to complement and not replace the traditional prognostic markers.

Recurrence Risk Score (Oncotype Dx)

It is a 21 gene assay. It has been incorporated in prognostic staging of breast cancer in the 8th edition AJCC for T1, T2, N0 ER +ve cancers. It was validated on subjects enrolled in the NSABP-14 adjuvant tamoxifen trial and ATAC trial. The results are reported on a scale of 0–100 (RS or recurrence score) categorizing patients into 3 groups namely, low risk <18, intermediate risk >18–31 and high risk >31. The high risk group has higher chances of metastasis in both node negative and node positive tumours. The low risk groups are more often Lumial A tumours as there is considerable overlap in the genes studied in PAM50 and Oncotype Dx. It has both a prognostic and a predictive role. Low-risk groups with node negative ER +ve disease with 1–3 cm tumours may be exempted from chemotherapy. The RxPONDER trial is evaluating its predictive value in whether ER +ve, node positive (1–3) patients with early breast cancer and a low risk score may skip chemotherapy or not. In addition to predicting a poor outcome with hormone therapy, a high score also predicts good response to chemotherapy. In the TailorX study ER +ve, HER2 −ve, node negative patients were accrued and divided into 3 groups with RS < 11, RS > 11–25 and RS >25.The objective was to study if the intermediate group could be treated with only hormone therapy in the adjuvant setting.

Amsterdam 70 Gene Profile (Mammaprint)

Developed in Amsterdam Netherlands, it classifies patients into those having a poor or good 70 gene signature. The mean 5 year survival was 74% in the poor group versus 97% in the good group. It could predict prognosis irrespective of nodal status but finds clinical use in node negative patients. 94% of ER −ve patients turn out to

be in the poor group and hence this profiling is recommended only in ER +ve patients to be of prognostic and predictive value. It has been approved for use by the US-FDA in node negative small to intermediate size tumours. Patients undergoing Mammaprint are also evaluated by Adjuvant! Online simultaneously. It effectively predicts chances of metastasis especially in the first 5 years. The MINDACT trial is evaluating whether node negative or 1–3 node positive patients with a good mammaprint signature may do without chemotherapy [62, 63].

Endopredict (EP)

It is an 8-gene assay developed to predict the risk of recurrence in ER positive, HER-2 negative tumours. EPclin classification incorporates EP, tumor size and number of nodes. It has both prognostic and predictive value [64].

Other indices like Breast Cancer Index (7 gene assay) and several other scores to predict response to different types of therapy have been developed.

13.6.5 Circulating Tumour Cells/Disseminated Tumour Cells/ Minimal Detectable Disease

According to the concept of Fischer, micrometastasis may be present from an early stage even in absence of axillary lymph nodes. When micrometastases are present in blood or bone marrow they are called Minimal Detectable Disease (MDD).When detected in bone marrow they are called disseminated tumour cells (DTC). When detected in blood they are called circulating tumour cells (CTC).

DTC is present in 12–42% of even early breast cancer patients. They are present in metastatic breast cancer patients even without overt bone metastasis. Presence of DTCs is associated with higher risk of recurrence and mortality. However they would be detected in patients who were anyway candidates for adjuvant therapy. Patients with low risk disease as per other parameters would mostly be negative for DTC. Persistence of more than 1 DTC, 12 months after neoadjuvant therapy is associated with reduced recurrence free survival and overall survival. The disappearance of DTCs by zoledronic acid therapy have been documented [65, 66].

CTC positivity by Cell Search is variably defined as more than one cell/7.5–22.5 ml of blood. They may be positive even in early breast cancer where presence of one cell is also considered significant. Presence of CTCs in early breast cancer have been associated with worse prognosis. However, it has no well-defined clinical utility. The persistence of CTCs following NACT may prompt alteration of the chemotherapeutic agent.

In the metastatic setting >5 cells/7.5 ml of blood is considered significant while defining progression free survival. A high level of CTC before and during treatment may predict higher chance of treatment failure. SWOG conducted a trial to demonstrate that ladies who have raised CTC after one cycle of first line chemotherapy have improved outcomes due to early switch over to alternate therapy. CTCs may also identify patients on ineffective hormone therapy. USFDA has approved the use of CTC in monitoring treatment response in metastatic setting [61, 67].

Estimating free DNA called circulating tumour DNA (ct-DNA) may be a more robust test than detection of CTCs [93].

Detection of circulating MUC1 protein (CA15-3 and CA27.29) and CEA have also been described but there is not much clinical significance. Moreover, there are high false positive rates due to over-expression of these markers by normal hematopoietic cell and leukocytes.

13.7 Biomarkers for Ruling Out Other Differential Diagnoses

Low grade DCIS are ER +ve. High grade DCIS have a preponderance of HER2 and Ki67 positivity and TP53 mutations. All DCIS have positivity for adhesion molecule E-cadherin whereas it is absent in LCIS. Several markers are also used to differentiate DCIS from other proliferative and atypical breast lesions. Pleomorphic variety of LCIS (PLCIS) need to be excised in contrast to classical LCIS. PLCIS can be identified by Gross cystic disease fluid protein-15 which is also expressed by invasive lobular carcinoma and apocrine carcinoma [68]. LCIS also show accumulation of p120 catenin and loss of beta-catenin [37]. Gain and loss of several chromosomal domains are also characteristic of different types of cancers. Tubular, invasive cribriform and type A mucinous carcinomas have molecular markers similar to Luminal A tumours. Type B mucinous cancers have neuroendocrine differentiation expressing chromogranin A, synaptophysin and neuron specific enolase like the neuroendocrine tumours [69, 70].

Medullary tumours appear to be a subset of basal type of tumours expressing basal cytokeratins, EGFR, TP53 mutations and lack of ER, PR and HER2 and greater chromosomal instability. Most BRCA 1 associated tumours are medullary in nature [71].

In cases of suspicion of invasive papillary carcinoma or ER −ve, PR −ve, HER2 –ve lymph node metastases with an occult primary in breast, IHC of axillary lymph node tissue has to be performed to rule out metastasis from other organs like lung, thyroid, kidney etc.

Adenoid cystic carcinomas are mostly triple negative expressing kit protein and several translocations and fusion defects in different chromosomes [69].

Metaplastic cancers may be similar to squamous carcinoma, basal like carcinomas and Claudin low carcinomas in their expression of biomarkers as described before and may also express p63.

The differential diagnosis of Paget's disease includes superficial spreading melanoma, Bowen's disease (squamous cell carcinoma in situ) and clear cell changes of epidermal squamous cells (Toker cells). Paget's cells are mostly ER, PR and HER 2 negative/positive. They are negative for HMB 45 and high molecular weight keratins but positive for CK7, CAM-5.2 and AE1/AE3 and occasionally immunoreactive to S100. Melanomas are positive for HMB 45, S100 and only rarely positive for CAM5.2 and CK7. Squamous carcinomas, though positive for AE1/AE3, are also positive for high molecular weight keratins and always negative for mucin, HMB45 and CAM5.2. Both Toker cells and Paget's cells are positive for CK7, epithelial

membrane antigen and are negative for p63. However, Toker cells are positive for ER, PR and negative for CD138 and p53 [72, 73].

Inflammatory breast cancer has a unique set of markers. They are mostly triple negative or HER2 enriched. Loss of p53, activation of NFKB/RAS/MAPK, overexpression of RhoC GTPase and WISP3 loss are common. There is also an overexpression of E-Cadherin, MUC-1 and VEGF. There is higher level of CD133 membrane expression, Notch 3 nuclear expression and high prevalence of the stem cell phenotype of CD44+/CD 24−/low [74].

Breast cancers in pregnancy are mostly ER −ve, PR –vE and Her2+. Male breast cancers are mostly hormone positive and also express androgen receptors (81%). Those who express androgen receptors have a poorer prognosis [75]. Male breast cancers are associated more with BRCA-2 mutations. In males, PR-positive, bcl2 positive tumours have good prognosis. HER2, Ki-67 and p21 +ve tumors have higher grade. P53 accumulation and PR −ve status are independent predictors of decreased survival [76–81].

References

1. Dillon DA. Molecular markers in the diagnosis and staging of breast cancer. Semin Radiat Oncol. 2002;12:305.
2. Esteva FJ, et al. Molecular prognostic factors for breast cancer metastasis and survival. Semin Radiat Oncol. 2002;12:319.
3. Haffty BG. Molecular and genetic markers in the local-regional management of breast cancer. Semin Radiat Oncol. 2002;12:329.
4. Morabito A, et al. Prognostic and predictive indicators in operable breast cancer. Clin Breast Cancer. 2003;3:381.
5. Rogers CE, et al. Molecular prognostic indicators in breast cancer. Eur J Surg Oncol. 2002;28:467.
6. Rampaul R, Ellis IO, Robertson JFR. Prognosticindic ES in breast cancer. World Br Cancer Rep iPRI. 2012:323–32.
7. Cianfrocca M, Goldstein LJ. Prognostic and predictive factors in breast cancer. Oncologist. 2004;9:606–19.
8. Weigel MT, Dowsett M. Current and emerging biomarkers in breast cancer:prognosis and prediction. Endocr Relat Cancer. 2010;17:R545–262.
9. Hayes DF, Bast RC, Desch CE, et al. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst. 1996;88:1456–66.
10. Hayes DF, Trock B, Harris AL. Assessing the clinical impact of prognostic factors: when is "statistically significant" clinically useful? Breast Cancer Res Treat. 1998;52:305–19.
11. Goldhirsch A, Gelber RD, Yothers G, et al. Adjuvant therapy for very young women with breast cancer: need for tailored treatments. J Natl Cancer Inst. 2001;30:44–51.
12. de Bock GH, van der Hage JA, Putter H, et al. Isolated locoregional recurrence of breast cancer is more common in young patients and following breast-conserving therapy: long-term results of the European Organization for Research and Treatment of cancer studies. Eur J Cancer. 2006;42:351–6.
13. Gnerlich JL, Deshpande AD, Jeffe DB, et al. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg. 2009;208:341–7.
14. Demicheli R, Bonadonna G, Hrushesky WJM, et al. Menopausal status dependence of the timing of breast cancer recurrence after surgical removal of the primary tumor. Breast Cancer Res. 2004;6:R689–96. http://breast-cancer-research.com/content/6/6/R689

15. Ries LAG, Eisner MP. Cancer of the female breast. In: Ries LAG, Young JL, Keel GE, et al., editors. SEER survival monograph: cancer survival among adults: U.S. SEER program, 1988–2001, patient and tumor characteristics. NIH Pub. No. 08-6215. Bethesda: National Cancer Institute, SEER Program; 2007. p. 101–10.
16. Fisher ER, Costantino J, Fisher B, et al. Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 4). Discriminants for 15-year survival. Cancer. 1993;71:2141–50.
17. Fisher ER, Anderson S, Redmond C, et al. Pathologic findings from the National Surgical Adjuvant Breast Project Protocol B-06. Cancer. 1993;71:2507–14.
18. Michaelson JS, Silverstein M, Sgroi D, et al. The effect of tumor size and lymph node status in breast carcinoma lethality. Cancer. 2003;98:2133–43.
19. Wiechmann L, Sampson M, Stempel M, et al. Presenting features of breast cancer differ by molecular subtype. Ann Surg Oncol. 2009;16:2705–10.
20. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis. A randomized clinical trial. JAMA. 2011;305:569–75.
21. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection vs no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomized controlled trial. Lancet Oncol. 2013;14:297–305.
22. Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. N Engl J Med. 2011:412–21.
23. Stitzenberg KB, Meyer AA, Stern SL, et al. Extracapsular extension of the sentinel lymph node metastasis: a predictor of nonsentinel node tumor burden. Ann Surg. 2003;237:607–13.
24. Neri A, Marrelli D, Roviello F, et al. Prognostic value of extracapsular extension of axillary lymph node metastases in T1 to T3 breast cancer. Ann Surg Oncol. 2005;12:246–53.
25. Orlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A. 2003;100:8418–23.
26. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international consensus on the primary therapy of early breast cancer 2007. Ann Oncol. 2007;18:1133–44.
27. Lee AHS, Pinder SE, Macmillan RD, et al. Prognostic value of lymphovascular invasion in women with lymph node negative invasive breast carcinoma. Eur J Cancer. 2006;42:357–62.
28. Zaorsky NG, Patil N, Freedman GM, et al. Differentiating lymphovascular invasion from retraction artifact on histological specimens of breast carcinoma and implications on prognosis. J Breast Cancer. 2013; https://doi.org/10.4048/jbc.2012.155.4.478.
29. Badve SS, Baehner FL, Gray RP, et al. Estrogen- and progesterone-receptor status in ECOG 2197: comparison of immunohistochemistry by local and central laboratories and quantitative reverse transcription polymerase chain reaction by central laboratory. J Clin Oncol. 2008;26:2473–81.
30. Schmitt M, Thomssen C, Ulm K, et al. Time-varying prognostic impact of tumour biological factors urokinase (uPA), PAI-1 and steroid hormone receptor status in primary breast cancer. Br J Cancer. 1997;76:306–11.
31. Creighton CJ, Kent Osborne C, van de Vijver MJ, et al. Molecular profiles of progesterone receptor loss in human breast tumors. Breast Cancer Res Treat. 2009;114:287–99.
32. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007;25:5287–312.
33. Colozza M, Azambuja E, Cardoso F, et al. Proliferative markers as prognostic and predictive tools in early breast cancer: where are we now? Ann Oncol. 2005;16:1723–39.
34. McShane LM, Altman DG, Sauerbrei W, et al. Reporting recommendations for tumor marker prognostic studies (REMARK). Nat Clin Pract Oncol. 2005;2:416–22.
35. Van Dierendonck JH, et al. Cell-cycle-related staining patterns of anti-proliferating cell nuclear antigen monoclonal antibodies. Comparison with BrdUrd labeling and Ki-67 staining. Am J Pathol. 1991;138:1165.
36. Gasparini G, et al. Prognostic significance of vascular endothelial growth factor protein in node-negative breast carcinoma. J Natl Cancer Inst. 1997;89:139.

37. Binder C, et al. Expression of Bax in relation to Bcl-2 and other predictive parameters in breast cancer. Ann Oncol. 1996;7:129.
38. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Goodwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011;378(9793):771–84.
39. Harvey JM, Clark GM, Osborne CK, et al. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol. 1999;17(5):1474–81.
40. Miller WR. Biological rationale for endocrine therapy in breast cancer. Best Pract Res Clin Endocrinol Metab. 2004;18(1):1–32.
41. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (intergroup Exemestane study): a randomised controlled trial. Lancet. 2007;369(9561):559–70.
42. Jonat W, Gnant M, Boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol. 2006;7(12):991–6.
43. Kuukasjarvi T, Kononen J, Helin H, et al. Loss of estrogen receptor in recurrent breast cancer is associated with poor response to endocrine therapy. J Clin Oncol. 1996;14:2584–9.
44. Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. Clin Breast Cancer. 2004;5(1):63–9.
45. Hayes DF, Thor AD, Dressler LG, et al. HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med. 2007;357(15):1496–506.
46. Lu C-H, Wyszomierski SL, Tseng LM, et al. Preclinical testing of clinically applicable strategies for overcoming trastuzumab resistance caused by PTEN deficiency. Clin Cancer Res. 2007;13(19):5883–8.
47. Parker JS, Mullins M, Cheang MC, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol. 2009;27:1160–7.
48. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes–dealing with the diversity of breast cancer: highlights of the St. Gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol. 2011;22:1736–47.
49. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000;406:747–52.
50. Oh DS, Troester MA, Usary J, et al. Estrogen-regulated genes predict survival in hormone receptor-positive breast cancers. J Clin Oncol. 2006;24:1656–64.
51. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98:10869–74.
52. Hu Z, Fan C, Oh DS, et al. The molecular portraits of breast tumors are conserved across microarray platforms. BMC Genomics. 2006;7:96.
53. Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. N Engl J Med. 2006;355:560–9.
54. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490:61–70.
55. Kelly CM, Bernard PS, Krishnamurthy S, et al. Agreement in risk prediction between the 21-gene recurrence score assay (Oncotype DX®) and the PAM50 breast cancer intrinsic classifier™ in early-stage estrogen receptor-positive breast cancer. Oncologist. 2012;17:492–8.
56. Cheang MC, Martin M, Nielsen TO, et al. Quantitative hormone receptors, triple-negative breast cancer (TNBC), and molecular subtypes: a collaborative effort of the BIG-NCI NABCG. 2012 ASCO Annual Meeting. J Clin Oncol. 2012;30(15):1008.
57. Bertucci F, Finetti P, Cervera N, et al. How basal are triple-negative breast cancers? Int J Cancer. 2008;123:236–40.
58. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434:917–21.

59. Rouzier R, Perou CM, Symmans WF, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res. 2005;11:5678–85.
60. O'Brien KM, Cole SR, Tse CK, et al. Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina breast cancer study. Clin Cancer Res. 2010;16:6100–10.
61. Lucci A, Hall CS, Lodhi AK, et al. Circulating tumour cells in non-metastatic breast cancer: a prospective study. Lancet Oncol. 2012;13(7):688–95.
62. Mook S, van't Veer LJ, Rutgers EJ, et al. Individualization of therapy using Mammaprint: from development to the MINDACT trial. Cancer Genomics Proteomics. 2007;4:147–55.
63. Van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med. 2002;347:1999–2009.
64. Dubsky P, Filipits M, Jakesz R, et al. EndoPredict improves the prognostic classification derived from common clinical guidelines in ER-positive, HER2-negative early breast cancer. Ann Oncol. 2013;24:640–7.
65. Mathiesen RR, Borgen E, Renolen A, et al. Persistence of disseminated tumor cells after neoadjuvant treatment for locally advanced breast cancer predicts poor survival. Breast Cancer Res. 2012;14(4):R117.
66. Aft R, Naughton M, Trinkaus K, et al. Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: an open label, randomised, phase 2 trial. Lancet Oncol. 2010;11(5):421–8.
67. Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med. 2004;351(8):781–91.
68. Reis-Filho JS, Pinder SE. Non-operative breast pathology: lobular neoplasia. J Clin Pathol. 2007;60(12):1321–7.
69. Weigelt B, Horlings HM, Kreike B, et al. Refinement of breast cancer classification by molecular characterization of histological special types. J Pathol. 2008;216(2):141–50.
70. Weigelt B, Geyer FC, Horlings HM, et al. Mucinous and neuroendocrine breast carcinomas are transcriptionally distinct from invasive ductal carcinomas of no special type. Mod Pathol. 2009;22(11):1401–14.
71. Cheang MC, Voduc D, Bajdik C, et al. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res. 2008;14:1368–76.
72. Di Tommaso L, Franchi G, Destro A, et al. Toker cells of the breast. Morphological and immunohistochemical characterization of 40 cases. Hum Pathol. 2008;39:1295–300.
73. Ramachandra S, Gillett CE, Millis RR. A comparative immunohistochemical study of mammary and extramammary Paget's disease and superficial spreading melanoma, with particular emphasis on melanocytic markers. Virchows Arch. 1996;429:371–6.
74. Overmoyer BA, Almendro V, Shuh S, et al. JAK2/STAT3 activity in inflammatory breast cancer supports the investigation of JAK2 therapeutic targeting. Cancer Res. 2012;72(24 (Suppl 3)) P4-06-01.
75. Kwiatkowska E, Teresiak M, Filas V, et al. BRCA2 mutations and androgen receptor expression as independent predictors of outcome of male breast cancer patients. Clin Cancer Res. 2003;9:4452–9.
76. Brenner B, Siris N, Rakowsky E, et al. Prediction of outcome in locally advanced breast cancer by post-chemotherapy nodal status and baseline tumor markers. Br J Cancer. 2002;87:1404–10.
77. Sotiriou C, Wirapati P, Loi S, et al. Gene expression profiling in breast cancer: understanding the molecular basis of histologic grade to improve prognosis. J Natl Cancer Inst. 2006;98:262–72.
78. Lim E, Vaillant F, Wu D, et al. Aberrant luminal progenitors as the candidate target population for basal tumor development in BRCA1 mutation carriers. Nat Med. 2009;15:907–13.
79. Wiedswang G. Comparison of the clinical significance of occult tumor cells in blood and bone marrow in breast cancer. Int J Cancer. 2006;118:2013–9.
80. Dabbs DJ, Bhargava R, Chivukula M. Lobular versus ductal breast neoplasms: the diagnostic utility of p120 catenin. Am J Surg Pathol. 2007;31(3):427–37.
81. Marchio C, Iravani M, Natrajan R, et al. Genomic and immunophenotypical characterization of pure micropapillary carcinomas of the breast. J Pathol. 2008;215:398–410.

Management of Early Breast Cancer – Surgical Aspects

14

Alok Mazumdar, Sumeet Jain, Satish Jain, and Shashanka Mohan Bose

14.1 Introduction

Breast Cancer is the most feared cancer in women because of its common occurrence and its psychological and social impact. It affects the perception of sexuality and self-image far greater than any other cancer. Physical as well as psychological trauma has lessened in recent years because of better results, thanks to early diagnosis, more treatment options, and greater availability of reconstruction and rehabilitation programs.

Defining early breast cancer (EBC) is a challenge for both practitioners and researchers, and there is no universally accepted definition. However, the most accepted definition of 'early breast cancer' refers to both non-invasive (carcinoma -in - situ) and invasive cancer confined to the breast, with or without regional lymph node involvement, with the absence of distant metastatic disease.

Alok Mazumdar, MS, DNB, FICS (✉)
Senior Consultant and Head, Department of General Surgery, Seven Hills Hospital, Visakhapatnam, Andhra Pradesh, India
e-mail: alok_mazumdar@yahoo.com

Sumeet Jain, MS, MCh
Associate Professor, Department of Surgical Oncology, Dayanand Medical College and Hospital, Ludhiana, Punjab, India

Satish Jain, MS, FAIS, FICS, FACS
Director, Department of Surgical Oncology, Ludhiana Mediways Hospital, Ludhiana, Punjab, India

Shashanka Mohan Bose, MS, FRCS(E), FRCS(G), FAMS, FACS, FICS, FACG
Former Senior Professor and Head, Department of Surgery, PGIMER, Chandigarh, India

Former Professor of Surgery, AIIMS, New Delhi, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_14

Another way of defining breast cancer is as per stage based on the TNM classification (Refer to our Chap. 5). Hence, early breast cancer would include Stages 0, I, and II.

Early breast cancer generally includes in situ cancer i.e., Stage 0 and Stage I and II of TNM staging (AJCC, 2018, 8th Edition).

Stage 0	Tis NO, N1
Stage IA	T1, NO, M0
Stage I B	T0N1miM0; T1N1miM0
Stage IIA	T0, N1, M0; T1, N1, M0
	T2, N0, M0
Stage IIB	T2, N1, M0; T3, N0, M0

14.1.1 Significance of Early Breast Cancer

In the recent past, there have been improvements in screening, imaging, and diagnostic strategies. This has led in the early detection of the disease and overall improvement in survival. Owing to the advent of newer regimes and options available, in recent years a multitude of therapeutic options has been developed and tested. This has lead to major oncologic breakthroughs. Classifications based on molecular biology and personalized treatments have also evolved in the past decade. All these advancements have also led to improvements in overall, disease free, progression-free and relapse-free survival.

Breast cancer is the most frequently diagnosed cancer in American women and the second most frequent cause of cancer death [1]. Over the past several decades, there has been a steady increase in the incidence of the disease, and collected data indicates that lifetime risk of developing breast cancer in the USA is 12.2% or 1 in 8 women. Currently, about half of the patients with breast cancer can be expected to live out the rest of their lives without recurrence, and one-third will die of their disease, but there is no time point at which patients can be reassured [2]. More and more cases are now diagnosed as EBC. In developed countries about 70–75% of newly diagnosed cases are classified as EBC [3].

There is no data available on the incidence of EBC in India. One study showed that 61% of patients presented with EBC i.e., stage I (14%) and stage II (47%) [4].

Early-stage breast cancer is potentially curable whereas patients with distant metastatic disease are not. In developed countries, more than 80% of patients with early-stage breast cancer have long-term survival after surgery.

In developed countries, like Spain, 5-year survival rate estimations are greater than 80% [5]. This progress could be explained by the combination of developments with the enhanced modality of treatments and early diagnosis. In developing countries like India and others, the estimations indicate that 5-year survival is approximately 77% [6], which is quite similar to Latin American countries, such as Porto Rico 71.2%.

14.2 Classification of Early Breast Cancer

EBC would include Stage 0, Stage I, and II, and this would describe both types, noninvasive and invasive breast cancer.

14.2.1 Non-invasive Breast Cancer or In Situ Breast Cancer or Stage 0 Breast Cancer

Carcinoma in situ (CIS) represents non-invasive cancer, and it is defined as confinement or presence of malignant cells within the basement membrane. The widespread use of mammography has lead to an increase in the overall incidence of in-situ lesions [7].

They differ in natural history, pathological appearances, and biological characteristics. The clinical presentation & treatment options are also different.

14.2.1.1 CIS of the Breast (Stage 0) Includes

1. *Ductal carcinoma in situ (DCIS).*
2. *Lobular carcinoma in situ (LCIS)**
3. *Paget's disease of the nipple*

{*In recent classification, Lobular carcinoma in situ has been included in benign breast disease}

Besides this, there are some other groups that are also being considered in stage 0. These are atypical lobular hyperplasia and intraductal papilloma with atypical hyperplasia or intraductal papilloma with ductal carcinoma in situ or lobular carcinoma in situ.

14.2.2 Ductal Carcinoma In Situ (DCIS)

14.2.2.1 Introduction

- DCIS of the breast is a complex pathological entity in which the malignant cells arise and proliferate within the breast ducts, and the basement membrane is not invaded.
- It is noninvasive breast cancer that encompasses a wide spectrum of diseases. It may range from low-grade lesions to high-grade lesions that may harbour foci of invasive breast cancer.
- Prior to the use of screening mammography, DCIS was usually diagnosed by surgical removal of a suspicious breast mass.

14.2.2.2 Incidence

- DCIS consists of approximately 84% of all in situ diseases.

- It is highly uncommon before the age of 35–39 years. After that, the incidence rises steadily to a peak of 96.7 per 100,000 at ages 65–69 and then declines slowly until age 79 and steeply after that [8].
- DCIS was rarely diagnosed before 1980, and the gradual and significant increase in the prevalence of DCIS since the early 1980s was mainly due to the increased use of mammographic screening.
- Approximately 20–25% of breast cancers diagnosed in the United States are DCIS, and over 60,000 women have been diagnosed in the US alone in 2015 [8].
- The figures for India are not available, but the trend would be more or less the same.
- The risk of developing metastases and, or death in a patient diagnosed with pure DCIS is rare (<2%).

14.2.2.3 Pathology

Traditionally, the classification of DCIS has based on its architectural or morphologic appearance. Details of DCIS can be found elsewhere in the book.

14.2.2.4 Risk Factors

1. Age: The incidence of DCIS, like invasive breast cancer, is strongly related to age. Between the ages of 40 and 64, 21 to 22.8% of all breast cancers are DCIS. Several well-designed studies found that women who were older at the time of first birth or had no children had a higher risk of developing DCIS compared to younger women.
2. Breast density: Many studies consistently have found that increased breast density is associated with increased risk of DCIS.
3. BMI: The association between body composition and BMI has not been widely studied. The Iowa Women's Health study did not find a decreased risk of DCIS to be associated with body mass index. In contrast, Kerlikowske found that heavily obese (body mass index $\geq$35.0 kg/m^2) postmenopausal women not taking HRT had increased odds ratio of DCIS [9].
4. Family history of breast cancer or a first-degree relative with breast cancer has increased risk of DCIS.
5. DCIS is higher among carriers of the BRCA1/2 gene mutation and among those with an estimated risk of breast cancer of more than 25% [10].
6. The effect of oral contraceptive use and DCIS were examined in five studies, and none found any association.
7. The relationship between hormone replacement therapy (HRT) and DCIS was examined in both observational and randomized studies. A large prospective cohort study from the United Kingdom found a 56% increased risk of DCIS in current HRT users as compared with never users [11].
8. Other US-based studies found that the increased risk of DCIS with HRT varied with duration of use. However, the Women's Health Initiative found no increased risk of DCIS associated with HRT [12]. The Million Women Study cohort failed to comment on whether they observed any increase in DCIS associated with HRT use.

14.2.2.5 Clinical Examination

(a) The most common presentation is an abnormality found radio graphically, either during screening mammography or done to rule out carcinoma in situ lesions, especially in high-risk individuals. It is found in approximately 20% of all screening mammograms. There is no palpable breast lesion found in majority of these patients.
(b) In the past (pre mammography era), most DCIS had presented as a palpable mass. Now, <10% of the disease presents as a palpable mass.
(c) DCIS may present as pathologic nipple discharge.
(d) Along with discharge, it may present with or without a mass.
(e) It may be identified incidentally in a breast biopsy performed to diagnose or treat another breast abnormality.

14.2.2.6 Other Important Facts

1. Patients with a palpable mass have a significantly higher potential for occult invasion, multicentricity, and local recurrence than those who present with non-palpable lesions.
2. Majority of the tumours were found in the upper outer quadrant (43.9%). 9% were present in the upper inner quadrant, while the central quadrant had 8.5% lesions. 8.1% was present in the lower outer quadrant, while6.9% was present in the lower inner quadrant [13].

It is evident that the anatomic location of DCIS is not significantly different from that of invasive carcinoma.

3. If left untreated, invasive breast cancer may develop in 30–50% of DCIS in the ipsilateral breast, 10–20 years after the initial diagnosis [14]. The cumulative risk of contralateral breast cancer is low (less than 1% per annum) [15].
4. DCIS may progress to invasive disease, and whether any sub types of DCIS are more likely to progress than others is less well understood. An estimate of the risk of progression of DCIS may be obtained from patients previously misdiagnosed with benign breast disease who received no treatment and for whom subsequent evaluation of biopsy specimens revealed DCIS. In the largest series by Eusebi et al., only 14% of such women developed invasive cancer, although the average progression rate from many studies combined was 43% [16].
5. Frequently, DCIS can occur in conjunction with invasive cancer. It can be either in the same lesion or in the same breast but in a different lesion. It can be present in the contralateral breast too.
6. DCIS may involve multiple foci within one or more breast lobules. This phenomenon of multicentricity is seen in 8–33% of cases. The likelihood of multicentricity increases as the tumour size increases. DCIS measuring over 2.5 cm in diameter would be 50% times multicentric in origin. However, many studies have found that DCIS is rarely multicentric. In one study, the radiologic and pathologic correlative comparison of mastectomy specimens found that one multicentric lesion was present out of 82 mastectomy specimens [17].

14.3 Evaluation of DCIS

14.3.1 History

1. An adequate history and physical examination with evaluation of the patient's overall health should be performed.
2. History assessment should include a personal or family history of malignancy, use of oral contraceptives, and hormonal replacement therapy (HRT).
3. Past history, including previous breast biopsies, history of abnormal mammograms, should be enquired.
4. History of age at first childbirth, nulliparous, late menopause, and obesity in postmenopausal women.

14.3.2 Physical Examination

1. In a palpable lesion, it is important to document all about the tumour.
2. Complete examination (CBE) of the opposite breast and both axillae to detect the presence of lymph node. The chances of axillary lymph node metastasis are very low as there is no breach in the basement membrane, and hence there is no metastasis. A palpable lymph node may be suggestive of the presence of invasive cancer along with DCIS.
3. The overall breast size and configuration should be taken into consideration for the assessment of various treatment options.

14.4 Investigations

14.4.1 Laboratory

These include the haematological, renal and hepatic profile.

14.4.2 Radiological Evaluation

14.4.2.1 Bilateral Mammography

Bilateral mammography can detect features suggestive of DCIS in a nonpalpable lesion or in a palpable lesion.

- Mammography alone may underestimate the extent of disease, especially in cases of larger lesions. In a review of mammographically detected DCIS, calcifications were present in 72% while12% presented as calcifications with an associated soft tissue abnormality. Of malignant appearing microcalcifications, 92% were associated with a malignant histopathological diagnosis [18].
- It is essential that all patients should have a mammogram performed before surgical resection, and selected patients should have a mammogram performed after surgical resection (specimen radiography of lumpectomy), in order to ensure the completeness of resection.

Technological advances in mammography like Digital mammography (DM) and Digital Breast Tomosynthesis (DBT), and Contrast-enhanced mammography (CEM) have further enhanced the chances of diagnosis of DCIS.

14.4.2.2 Ultrasound (US)

US is used in majority of patients presenting as an adjunctive tool to analyse a mammographic abnormality, like whether a soft tissue mass is solid or cystic and to differentiate benign from malignant masses.

DCIS can now be diagnosed due to the improved resolution as microcalcification can produce a speckled pattern, but DCIS with no calcification is difficult to detect.

14.4.2.3 Role of MRI

- In the detection of pure DCIS, MRI has a role as it can identify the non-calcified component.
- In cases in which the mammogram is normal, MRI is helpful in detecting high grade DCIS.
- The sensitivity of MRI in detecting DCIS varies widely, from 60 to 100%. This is especially noted when high-resolution sequences are acquired and helps to distinguish calcified from non-calcified carcinoma.
- Identifiable lesion on MRI was associated with the malignancy, was seen in 85.9% of cases. It could pick up lesions up to 98.1% in DCIS with invasive ductal carcinoma [19].
- In another study by Kuhl et al., sensitivity of MRI (92%) was far superior to mammography (56%) for the detection of DCIS. In the same study they found that 87% of the lesions not detected in MRI were low-grade tumors [20].

14.4.2.4 Pathological Evaluation

- Pre-operative histopathological assessment of focal lesions in the breasts is crucial in the planning of further therapeutic management.
- In a palpable lesion, the tissue diagnosis can be obtained by ultrasound-guided FNAC or Tru-cut biopsy. In a nonpalpable lesion image guided biopsy is required to ascertain the nature of the lesion.
- Core Needle Biopsy (CNB) helps to establish a correct preoperative diagnosis much more frequently than Fine Needle Aspiration Biopsy (FNAB) (78% vs. 55%) in DCIS.
- CNB has limitations which include: underestimation of invasion and failure to recognize the components of DCIS in papillary and atypical lesions.
- In a meta-analysis conducted by Brennan et al., 1736 of 7350 lesions diagnosed in CNB as DCIS were verified as invasive cancers after postoperative specimen examination. This accounts for as many as 24% of false negative results (the study investigated both 11G Vacuum Assisted Biopsy (VAB) and 14G CNB [21].
- Vacuum-Assisted Biopsy (VAB) is another newer technique. Large core biopsy is also known as ABBI (Advanced Breast Biopsy Instrumentation), it can remove 5–20 mm of breast tissue and provide a better and accurate histopathological evaluation.

14.4.3 Wire Localization Procedure and Its Role in Early Detection of Breast Cancer

- Wire localization of nonpalpable mammographically detected breast lesion is a well-established technique, especially in DCIS.
- The key is accurate localization, which is essential for achieving complete surgical excision with optimal cosmetics and minimal morbidity.
- Imaging guidance is commonly performed with mammography or sonography. Such procedures are less often performed with MRI or CT.
- A marker in the breast is placed, which could be small calcium deposit, a biopsy marker or clip, on a suspicious lesion seen on a mammogram or ultrasound. This helps to the put the wire in place.
- The wire is placed into the breast lesion using a needle. This acts as the guide to the surgeon for the precise location of the abnormal breast tissue or cancer during surgery (Fig. 14.1). The needle containing a hooked wire is placed into the breast under local anesthesia.
- It is usually placed on the same day prior to localized excision biopsy or lumpectomy.

Once the wire-localized lesion is removed, the whole specimen containing the wire is sent for a radiological examination to confirm complete removal of the lesion [22] (Fig. 14.2).

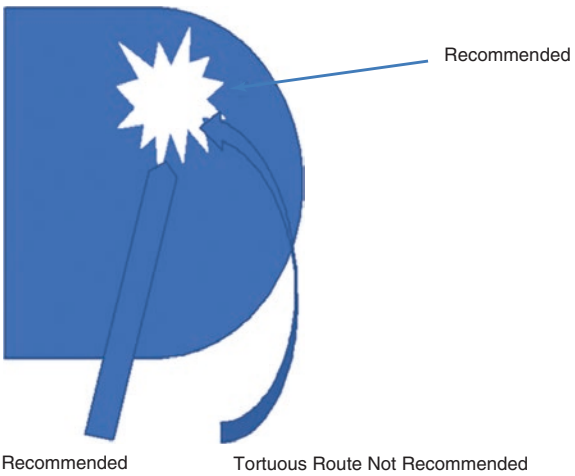
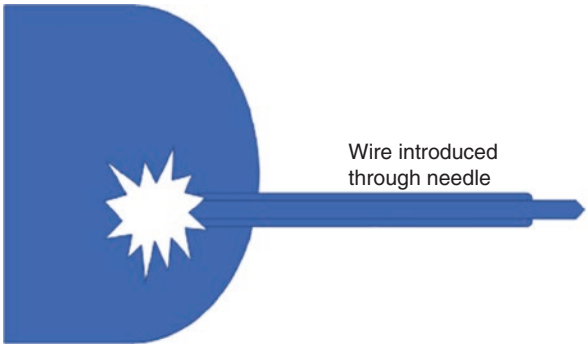
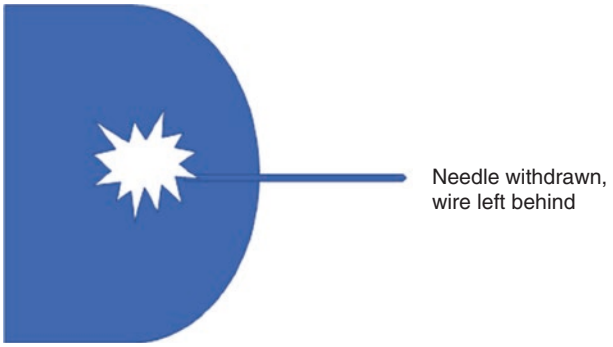


Fig. 14.1 Recommended way for wire placement



Step 2: Tip of the wire left inside the tumour



Step 3: Ready for surgery, wire left behind for location of the tumour in the breast.

Fig. 14.1 (continued)

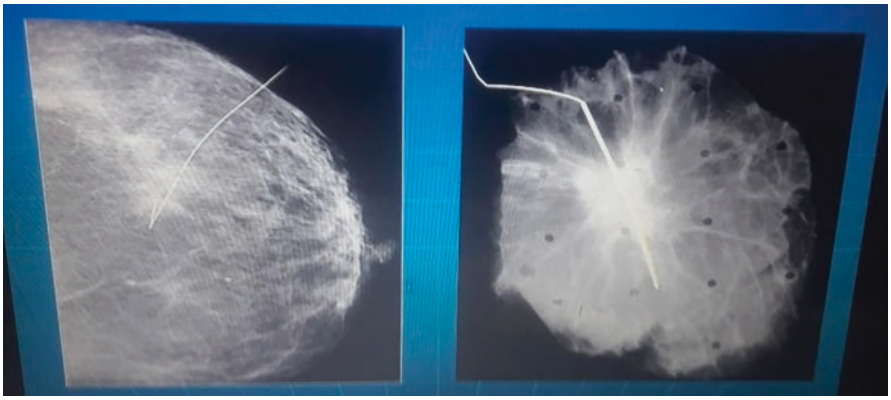


Fig. 14.2 Wire localization and subsequent mammogram showing complete excision of the tumour

14.4.4 Sentinel Lymph Node Biopsy (SLNB): Role in DCIS

- In general, SLNB is not recommended for definitive diagnosis of DCIS because the pre-invasive cells do not metastasize. However, about 15–20% of patients who are initially diagnosed with only DCIS on core needle biopsy were found to have invasive breast cancer when the excised mastectomy specimen was subjected to histopathological examination.
- In axillary lymph node staging after definitive surgical treatment for DCIS, especially if there is invasive component in the final diagnosis. SLNB is still feasible for most patients after excision of the suspicious lesion. It is not feasible after total mastectomy.
- Patients with pure DCIS have less risk of SLN metastasis when compared with DCIS with micro invasion. In pure DCIS, the overall risk of SLN metastases is <1% [23].
- SLNB is not likely to affect important outcomes (survival, recurrence, and quality of life) for most patients with DCIS, especially if excision is planned [24].
- However, the findings of SLNB may lead to overtreatment (axillary lymph node dissection and cytotoxic chemotherapy), which may negatively affect the patient's quality of life.

14.4.5 Miscellaneous Investigations

Chest X-Ray, Abdominal ultrasound and Electrocardiogram (ECG) and ECHO are done as part of a routine examination.

14.5 Treatment of DCIS

- Despite being pre- or non-invasive, DCIS is regarded as an early form of (Stage 0) breast cancer. The lesion is classified as low, medium or high grade, which is mainly based on the level of aggressiveness. Some studies have shown that there is a slight tendency for high-grade DCIS to progress to invasive breast cancer, but others have demonstrated that grade is not significantly associated with the risk of local invasive recurrence [25].
- Therefore, conventional management includes breast conserving surgery or mastectomy. It is supplemented with radiotherapy; in some centers, adjuvant endocrine therapy is added.
- There are reports in the literature that, at times the current therapeutic approaches may result in overtreatment of some women with DCIS [26].

14.5.1 Surgery

Currently, breast-conserving surgery (BCS) is recommended for DCIS.

All aspects of BCS have been explained in detail in the latter part of this chapter.

A total mastectomy is advised if the DCIS is too extensive to allow breast conservation.

14.5.1.1 BCS in DCIS: Surgical Technique and Considerations

1. Margins: Patients with negative margins after BCS for DCIS are at lower risk of local recurrence when compared with patients with positive margins. The optimal margin width has been debated for many decades.
   - The NCCN guidelines state that margins of at least 2 mm are associated with a reduced risk of ipsilateral breast tumour recurrence (IBTR) as compared to narrower negative margin widths in patients receiving whole breast radiotherapy [27].
   - The American Society of Breast Surgeons and many others define a negative margin in patients with DCIS as no ink on the tumor [28].
   - Currently, there is no noted standard technique for intraoperative margins assessment. One of the most commonly used techniques is the intraoperative specimen radiogram, which would verify the removal of suspicious calcification. It will further guide a possible intraoperative re-excision. (Fig. 14.3) [29].
   - Positive margins patients can either be treated by total mastectomy or by re-operative surgery.
2. Skin Excision: There is no need to remove the skin for noninvasive breast cancer. The only exception is if there are extensive malignant appearing micro calcifications just beneath the skin as seen on preoperative imaging.
3. Margins from cavity: Many surgeons do not routinely obtain breast tissue from the cavity (shave margins). The reason is that it might adversely affect the cosmetic outcome as additional normal breast tissue that is uninvolved by DCIS is removed.

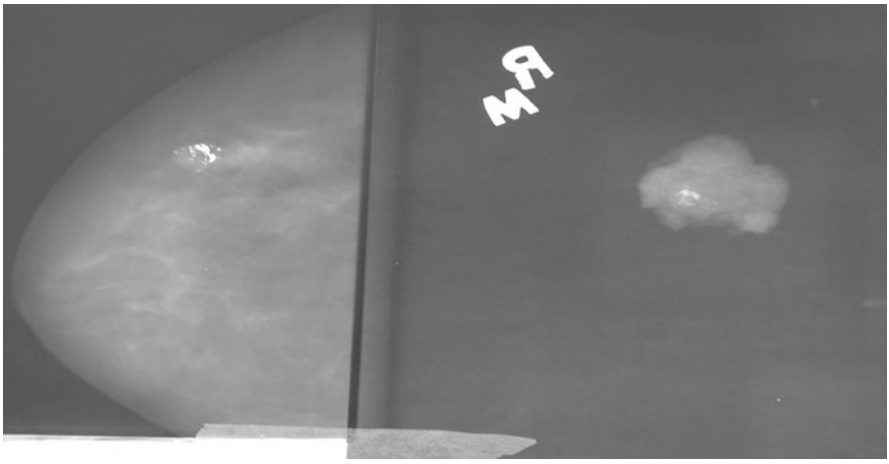


Fig. 14.3 Specimen radiogram showing complete removal of micro calcification in one of our cases

Instead, targeted resection of any suspicious margins based on the intraoperative assessment by imaging and pathology. Selective frozen section analysis of close or suspicious margins identified on the intra-operative images can be done. Approximately 35% of such cases move from positive intra-operative margins to negative final pathologic margins for DCIS [30].

14.5.2 Role of Radiotherapy

- Four randomized clinical trials were performed to investigate the role of radiotherapy in BCS for DCIS after complete local excision of the lesion. In a meta-analysis, these trials have shown a 50% reduction in the risk of local recurrences (LR) for both in situ and invasive lesion after whole-breast radiation therapy (WBRT) [31, 32].
- Radiotherapy helps reducing the risk of local recurrence in all analyzed subgroups according to age, clinical presentation, grade and type of DCIS.
- Radiation Therapy and Oncology Group (RTOG) 9804 clinical trial - in this 7-year IBTR risk was less than 1% among patients treated with WBRT without a boost. This study showed that a tumour bed boost is not needed in the patient population of low-risk DCIS [32].
- Local recurrence risk depends on many factors: palpable mass, larger size, higher grade, close or involved margins, and age <50 years.
- If the individual risk is considered as low, these patients may be treated by wide local excision alone.
- Select patients with low-risk DCIS may be considered suitable for APBI (Accelerated Partial Breast Irradiation) if they meet all aspects of the definition of low-risk DCIS. These are, as considered from the RTOG 9804 trial, includes screen-detected DCIS, low to intermediate nuclear grade, tumour size ≤2.5 cm, and surgical resection with margins negative at >3 mm

14.5.3 Role of Endocrine Therapy

- The role of adjuvant endocrine therapy after surgical excision has been the subject of scientific debate in view of the in situ nature of this neoplasm.
- Two randomized clinical trials have investigated the role of tamoxifen vs. placebo in DCIS. Tamoxifen reduced the risk of developing subsequent invasive ipsilateral breast cancer and similar results were seen in the NSABP trial too [33].
- However, recent data showed that there is no scientific evidence that adjuvant endocrine therapy reduces the incidence of ipsilateral breast invasive recurrence.
- Adjuvant endocrine therapy can be considered after a rigorous multidisciplinary discussion and patient counselling in a carefully selected subgroup of patients with high-risk estrogen receptor-positive DCIS.

14.5.4 Role of Active Surveillance

- Recently, three clinical trials randomized patients with low-risk DCIS between active surveillance and standard treatment.
- The primary outcomes of the trials are based on the occurrence of invasive disease during follow-up. It is important to exclude an invasive component at the time of enrolment of the patients. One might still miss an invasive disease at diagnosis and this is approximately up to 26%.
- However, it was found that, among trial-eligible patients, there was upstaging of 6–10% compared with a general upstaging of 17% at the time of surgery for preoperatively diagnosed DCIS of all types. Final results are yet to come [34].

14.5.4.1 Microinvasive Carcinoma vs. Ductal Carcinoma In Situ

- Microinvasive carcinoma, previously a subcategory of DCIS, is relatively rare and accounts for <1% of all breast cancers. Since Lagios et al. introduced the term "microinvasion" in 1982; several other terms have been used to describe microinvasive carcinoma [35].
- AJCC defines microinvasive carcinoma as "the extension of cancer cells beyond the basement membrane into adjacent tissue with no focus more than 0.1 cm in greatest dimension". It formally includes microinvasive carcinoma in the T staging system, where this disease is categorized as T1mi [36].
- In microinvasive carcinoma although axillary staging is performed, the chance of lymph node metastasis is a rare event.
- Kim M et al., in their study suggested that microinvasive carcinomas can be treated and followed up as pure DCIS, although axillary staging surgery is necessary. The study also indicates that subset of patients with triple-negative DCIS or having evidence of microinvasive carcinoma need close follow-up. Such cancer patients are associated with high chances of tumour recurrence, especially invasive recurrence [37].

14.5.4.2 Consequences of Over Diagnosis in DCIS

- The diagnosis of DCIS labels women as being at risk for invasive cancer later in life. Although it has a good prognosis and normal life expectancy, women diagnosed with DCIS experience substantial psychological distress and are fearful [38].
- This has led to the debate whether to treat or not to treat. A recent study based on the American Cancer Registry of >100,000 women diagnosed with DCIS suggests that any form of aggressive treatment might not be necessary in order to save lives. These findings prompted to explore innovative studies that could circumvent the need for surgical intervention for treating an indolent condition. One such thing is to keep them in active surveillance.

14.5.4.3 Prognostic Factors after Surgery

- The factors that indicate a high risk of local recurrence after breast-conserving therapy for DCIS are young age, high nuclear grade, presence of come do necro-

sis, large tumour size, close to the margin and human epidermal growth factor receptor Type 2 (HER 2) positive [39].
- The presence of vascular or lymphatic invasion, tumour necrosis, and an inflammatory infiltrate has been associated with an increased risk of breast cancer recurrence. This risk is approximately 10–15% at 5 years [40].

14.5.4.4 Van Nuys Prognostic Index

- The Van Nuys Prognostic Index (VNPI) classifies patients with DCIS to guide decisions on the best treatment option [41].
- The index also uses patient age, tumour size, tumor growth patterns (histological grade) and the amount of healthy tissue surrounding the tumour after removal (resection margin width) to predict the risk of cancer recurrence.
- There are 3 variables. Each variable is assigned a score of 1–3, and the sum total defined the Van Nuys Prognostic Index.
- This scheme is made from the retrospective analysis of a patient cohort in which several methodological shortcomings were found and it has not been independently validated.

Van Nuys Prognostic index for DCIS takes into consideration the size, grade, excision margin and age and patients are classified into three categories [42]:

- Low-risk (total VNPI score of 4–6) - breast conserving surgery (BCS) without radiotherapy is recommended for this group
- Intermediate-risk (total VNPI score of 7–9) - BCS with radiotherapy is recommended.
- High-risk (total VNPI score of 10–12) mastectomy is recommended.

VNPI also provides recurrence rate and survival rates.

14.5.5 Lobular Carcinoma In Situ (LCIS)

Foote and Stewart first described LCIS in 1941 as a rare form of mammary cancer originating in lobules and terminal ducts.

- Even though classic LCIS constitutes both a risk factor and a non-obligate precursor of invasive breast cancer, it is currently managed as a benign lesion. It does not require complete removal and/or evaluation of margin status.
- There are still some surgeons who would treat them in a more aggressive way.

14.5.5.1 Incidence

Classic LCIS is usually an incidental finding in a breast needle core biopsy or surgical excision specimen targeting another lesion. It is therefore, difficult to estimate the actual incidence of LCIS.

LCIS is identified in 0.5–1.5% of benign breast biopsies and in 1.8–2.5% of all breast biopsies. The annual incidence of breast carcinoma in women with LCIS is about 2%.

14.5.5.2 Clinical Features

1. LCIS occurs predominantly in premenopausal women.
2. LCIS is multicentric in 60–80% of patients and bilateral in 20–60%.
3. Classic LCIS is clinically and mammographically occult, although recent studies report an association with grouped amorphous or granular mammographic calcifications or heterogeneous non-mass-like enhancement with persistent enhancement kinetics on MRI.

Pathological details have been described in the chapter on Pathology.

14.5.5.3 Natural History and Prognosis

LCIS is a risk factor and a non-obligate morphologic precursor of invasive breast carcinoma.

The cumulative risk of subsequent invasive breast carcinoma is 8% after 5 years, 15% after 10 years, 27% after 15 years, 35% after 20 years, and over 50% after 23 years [43].

14.5.5.4 Treatment

Historically, mastectomy is recommended for women with LCIS, based on the observation that there is an increased risk of subsequent invasive breast cancer.

A number of factors, including personal preferences, come into play for treatment for lobular carcinoma in situ (LCIS). There has been a change in the treatment modalities.

There are three main approaches to treatment:

- Active Surveillance
- Chemoprevention
- Surgery

14.5.5.4.1 Active Surveillance

- Haagensen et al., pioneered the concept that "when LCIS occurs alone without accompanying infiltrating carcinoma, it is a distinctive benign disease and advocated a more conservative approach of close follow-up as an alternative to mastectomy [44].
- In the 8th edition of the AJCC staging system, LCIS has been removed from the staging classification system and is no longer included in the pathologic tumour in situ (pTis) category 3 [45].
- Currently, there is a general agreement that LCIS represents both a risk factor and also a precursor of breast cancer. Hence many would just put these patients on observation alone.

- In case of active surveillance, the NCCN guideline recommends every 6–12 months a complete breast examination (CBE) in conjunction with an annual mammogram.

14.5.5.4.2 Chemoprevention

- Tamoxifen or aromatase inhibitors is recommended in LCIS.
- Randomized controlled clinical trials support the use of tamoxifen or aromatase inhibitors for risk reduction among women at increased risk of breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (P-1) demonstrated that the subsequent risk of invasive breast cancer could be significantly reduced by tamoxifen [46].
- Along with chemoprevention, the NCCN guidelines recommend follow-up of patients with annual diagnostic mammograms.

14.5.5.4.3 Surgery

- The variant Pleomorphic lobular carcinoma in situ (PLCIS) carries a greater risk of breast cancer than the more common classical type. If the biopsy reveals PLCIS, lumpectomy should be done to remove the suspicious area, though there's disagreement among doctors about whether surgery should be recommended in all cases.
- Radiation therapy to the breast after lumpectomy may be considered based on individual circumstances.
- The NCCN guidelines recommend surgical excision for PLCIS and classic LCIS with discordant imaging findings. According to them, PLCIS may have a similar biological behaviour to that of DCIS. However, an attempt for complete excision with negative margins, may lead to a high mastectomy rate without any proven clinical benefit [27].
- Also, according to the 2012 WHO consensus statement, "in the absence of better information on the natural history of PLCIS, caution should be exercised in recommending more aggressive management strategies, such as excision to negative margins or mastectomy".

14.5.5.5 Role of Prophylactic Mastectomy in LCIS

- Another option for treating LCIS is preventive or prophylactic mastectomy. This surgery removes both breasts and not just the breast affected with LCIS.
- This is done to reduce the risk of developing invasive breast cancer as LCIS increases risk of developing breast cancer in either breast [47].
- This is particularly an option if additional risk factors for breast cancer, such as an inherited gene mutation BRCA1/2 mutation, or a very strong family history of the disease, young age and diffuse high-grade lesion are present in the patient.
- King T A et al., in a study found that women opting for bilateral prophylactic mastectomy were young patients and premenopausal, have dense breasts and have stronger first-degree family histories of breast cancer compared with women. Thirty-two women opting for bilateral prophylactic mastectomy are still in active follow-up with a median follow-up time of 68 months (range, 22 to 237 months); all remain cancer free [48].

14.5.6 Paget's Disease

Paget's disease was first described by Sir Paget in 1874 as an eczematous lesion of the nipple associated with an underlying cancer. In fact, Paget's disease of the breast is a malignant disease and mostly it presents itself as eroding and bleeding ulcer of the nipple. It is usually considered an extension of ductal breast adenocarcinoma.

Primary invasive or in situ carcinoma of the breast is associated with Paget's disease.

14.5.6.1 Incidence

Paget's disease is a rare entity. It represents 1–4% of all breast cancer cases & associated with an underlying malignancy in more than 95% of cases. Paget's disease is seen even in males, in whom it has a very poor prognosis [49].

14.5.6.2 Pathology

The histopathological picture is characterized by the presence of Paget's cells located throughout the epidermis. It's described in detail in the Chap. 8 on Pathology.

14.5.6.3 Clinical Presentation [50]

Paget's disease mainly affects postmenopausal women.

- The lesion in the nipple develops insidiously. The nipple is involved first and then it shows a centrifugal growth to reach the areola and then the adjacent skin.
- The colour of the skin changes ranging from pink to red. Many times, retraction, ulceration or frank bleeding of the nipple is seen, especially in advanced disease.
- Patients also complain of pruritus, burning, tingling sensation and pain.
- In about one third of the cases at the time of presentation, a palpable mass is present below the nipple-areola complex.
- Examination of the axilla may reveal enlarged ipsilateral axillary lymph nodes in about 50% of cases.
- At times it is confused with an eczematous lesion as associated oozing is a prominent feature and often, there is a delay in diagnosis as a large number of these patients are treated by physicians with steroidal creams.

14.5.6.4 Differential Diagnosis

In the early stages, Paget's disease is not diagnosed as it looks like one of the common benign diseases. Clinical conditions closely resembling Paget's disease of the nipple include:

1. Eczema,
2. Erosive adenomatosis of the nipple,
3. Bowen's disease
4. Tuberculosis of nipple
5. Pagetoid basal cell carcinoma and
6. Melanoma

14.5.6.5 Investigations

The goal is to confirm that the cutaneous disease is Paget's and whether there is an underlying malignancy or not.

- A proper full thickness tissue biopsy from the edge of the lesion is required for diagnosis. Along with tissue biopsy, a cytological examination of the exudates is also helpful. At the same time, evaluation for hormonal receptors can also be done.
- Bilateral mammography and Ultrasound are the initial imaging workup. In the presence of a palpable mass, the sensitivity of mammography to detect an underlying tumour is approximately 97%, whereas it is only 50% in the absence of a palpable mass [51].
- Breast MRI is done for clinically and mammographically occult malignancies. It can also be used to create additional images to determine whether an underlying cancer is present or not.
- MRI will locate the extent of occult disease, thereby guiding surgical planning [52].

14.5.6.6 Treatment

- Paget's disease being rare, it is not possible to have randomized studies evaluating the optimal treatment strategy for patients affected by it. The various treatment options are derived from several retrospective reviews.
- The treatments may include modified radical mastectomy, simple mastectomy and breast-conserving surgery. It depends on whether Paget's disease of the breast is associated with ductal carcinoma or not, the histological type of ductal carcinoma, multicentricity, multifocal and axillary lymph node metastases.
- Traditionally a grossly invasive tumour of the breast would require a MRM with axillary clearance.
- Recently more conservative approach has been suggested. Conservative surgery comprises of complete resection of nipple-areola complex, ensuring tumour free margins, confirmed intra-operatively by frozen section. This is also known as Central Segmentectomy. Axillary dissection may not be necessary in clinically and radiologically node negative axilla [53].
- In BCS, it is advisable to follow it with whole breast radiotherapy.
- SLNB may be done if an invasive carcinoma component is present or there is a palpable lump. Many studies have shown a high degree of accuracy in the identification of SLN in patients with Paget's disease of the breast.
- Paget's disease can be treated by radiotherapy as an alternative to radical surgery in selected patients when tumour is confined to the nipple, without clinical or radiological detectable breast tumour [54].

14.5.7 Invasive Breast Cancer

1. Invasive (Infiltrating) Ductal Carcinoma (IDC) (Adenocarcinoma of the Breast)

- It accounts for 80% of breast cancers and the axillary lymph node metastasis is present in up to 60% of cases.
- Occurs in the fifth to sixth decades of life as a solitary, firm mass.

2. Invasive lobular carcinoma (ILC)
   - ILC sometimes called infiltrating lobular carcinoma is the second most common type of breast cancer after invasive ductal carcinoma.
   - ILC accounts for about 10% of all invasive breast cancers.
   - ILC may be harder to detect on physical examination. Even on imaging, like mammograms, the detection is less likely than IDC.

14.5.8 Less Common Types of Invasive Breast Cancer

Some special types of breast cancer that are sub-types of invasive carcinomas are also known. They typically make up fewer than 5% of all breast cancers. Some of these may have a better prognosis than the more common IDC. However, all of these sub-types are still treated like IDC.

14.5.8.1 Clinical Presentation

- The most common clinical presentation is the awareness of a lump in the breast. A lump has to be at least 1 cm to be felt by the patient. The lump is usually painless, or at times the patient may complain of dull aching pain.
- Discharge from the nipple is the second most common presentation and usually, it is blood stained. Nipple retraction may or may not be present.
- Irregular changes in the size and shape of the breast along with axillary lymph node enlargement can also be noted by the patient.
- Skin may become hard and thickened and look like orange peel peau-de-orange.

14.5.9 Investigations

14.5.9.1 Mammography

- B/L mammogram is to be performed in all patients with a breast lump. A normal mammogram in the presence of a palpable mass does not exclude malignancy, and further workup with a different imaging modality should be undertaken.

14.5.9.2 Digital Mammography (DM)

It is more sensitive than film mammography in screening women, particularly younger women with dense breasts.

14.5.9.3 Ultrasonography

- It is used to characterize a lesion identified either by physical examination or during mammography.

- Ultrasound evaluation of the axilla should be performed and if morphologically abnormal lymph nodes are identified, then ultrasound-guided needle FNA sampling should be done.
- The benefit of performing a FNA on suspected axillary lymph nodes is the avoidance of unnecessary SLNB if positive findings are found on FNA.

14.5.9.4 Magnetic Resonance Imaging

- Magnetic Resonance Imaging (MRI) is being used with increasing frequency for screening and diagnosis of EBC.
- In patients with indeterminate mammographic or ultrasonographic findings, MRI may be used for clarifying the imaging but should not replace biopsy for clinically suspicious lesions.
- MRI is indicated in the clinical setting of occult primary breast cancer (negative clinical breast examination) with axillary lymphadenopathy [55].
- Additional disease in the contralateral breast and multicentric origin can be detected in about 2–3% of cases. In a meta-analysis of 50 studies that included 10,811 women with breast cancer, MR imaging findings prompted conversion from lumpectomy to mastectomy in 12.8% of cases, whereas this conversion was inappropriate in 6.3% [56].
- In patients with invasive lobular cancer (ILC), MRI can be considered to assess tumour size, if breast conserving surgery is a treatment option.

14.5.9.5 PET Scanning

- The current evidence does not support the use of FDG-PET-CT in the staging of locoregional disease (the low sensitivity for detection of axillary nodal metastases), due to its limited sensitivity when compared with gold standard SLNB.
- PET or PET- CT scan has a high false-negative rate in the detection of lesions that are small (<1 cm) and/or low grade [57].
  Details about imaging modalities can be found in other chapters.

14.5.10 Accurate Way to Measure the Size of Breast Lump

- Tumour size is an independent prognostic factor in breast carcinoma and is a good predictor of lymph node metastasis. The measurement of tumour size should be accurate as the entire treatment depends on it. A small discrepancy can affect not only the stage of the disease but also the treatment.
- Techniques used to assess tumour size includes, clinical examination (CE), mammography (MG), ultrasonography (USG), magnetic resonance imaging (MRI) and pathologic examination (PE). The last is still considered the blueprint for final staging and for formulating an appropriate treatment plan.
- Clinical examination and preoperative MRI significantly overestimate tumour size. Measurements obtained on USG and MG is more accurate irrespective of breast density.
- USG measurements being slightly more accurate than MG measurements [58].

14.6 Tissue Diagnosis

The various techniques of tissue diagnosis are as follows.

- F. N. A. C. has been described in the chapter on cytology.
- Core-needle –biopsy
  Core-needle biopsy (CNB) gives a larger tissue sample than FNA and has 95% accuracy in diagnosing malignancy in palpable lesions. A minimum of four cores is suggested in order to achieve greater accuracy.
- Excision Biopsy
  Historically, surgical excision was the "gold standard" for the diagnosis of palpable breast masses. In contemporary practice, core needle biopsy (guided by mammography, ultrasound, or MRI) has largely, but not completely, replaced surgical excision.

  Current indications for excision biopsy are as follows:

1. Discordance between imaging characteristics (mammographic/sonographic and MRI) and core biopsy histology.
2. Non-diagnostic specimen from core biopsy (i.e., insufficient material, lack of calcifications, haemorrhage).
3. Lesion anatomically unsuitable for core biopsy (lesion too far anterior, too far posterior, too close to breast implant).
4. Suspicious interval changes in a lesion previously diagnosed benign by core biopsy.
5. Atypical hyperplasia (duct or lobular) or LCIS on core biopsy, papillary and/or sclerosing lesion on core biopsy.
6. "Fibroepithelial lesion" (i.e., fibroadenoma vs. benign phylloides tumour) on core biopsy.
7. Suspicious nipple discharge with normal breast imaging.

Excision biopsy and lumpectomy should not be confused with one another. Lumpectomy is performed when the diagnosis of breast cancer is confirmed. The aim is to remove all cancer with a healthy margin of tissue around the tumour. An excision biopsy is not a surgical treatment; it is a diagnostic procedure.

- Incisional biopsy
  It is generally used for tissue diagnosis in large tumours when CNB is nondiagnostic. It can also be done in an ulcerating growth. However, it is seldom done these days.

14.6.1 Significance of Regional Nodal Involvement and Sentinel Lymph Node Biopsy (SLNB)

- The presence of tumour cells in regional nodes is an indication of regional progression. It may also be an indicator of systemic dissemination of disease, although it is yet to be settled.

- Axillary nodal involvement is an established indicator of poor prognosis, with the 5-year survival decreasing by approximately 28 to 40%. Thus, axillary surgery not only helps in staging but also improves locoregional control. This may ultimately result in improved survival [59].
- The role of Axillary lymph node dissection (ALND) in patients with cN0 disease has been debated as most of them (70–80%) will have pathologically free nodes (pN0). Thus, subjecting these patients to ALND exposes them to unnecessary morbid outcomes. These include arm lymphedema, axillary numbness, and shoulder abduction deficits [60].
- The role of axillary surgery in cN0 axilla was first evaluated by the NSABP B-04 trial. It was also validated by the Cancer Research Campaign Working Party (King's/Cambridge) [61].
- These trials have shown that preferred treatment of cN0 axilla with either surgery or radiotherapy (RT) did not have any positive impact on overall survival (OS) as compared to observation alone and treatment at the time of recurrence [61].

14.6.2 Sentinel Lymph Node (SLN) Hypothesis

The tumour cells migrate in an orderly manner from a primary tumour. Therefore, SLN is defined as the first LN that receives lymphatic drainage from the primary tumour. Locoregional spread of EBC occurs via the lymphatic system. SLN status accurately predicts the status of the other distant lymph nodes and is important to establish staging and prognostic outcomes of breast cancer.

14.6.3 Technique

- SLNB, as an ideal nodal staging method for breast cancer, was introduced by Krag *and* Giuliano in 1993 and 1994. Krag described and developed the gamma probe localization of SLN using radioisotope, whereas Giuliano described the SLN using blue dye alone.
- SLNB has since become the new standard of care for axillary staging in clinically and radiologically node-negative breast cancer. Clinical trials have demonstrated a properly performed SLNB is equivalent to axillary lymph node dissection (ALND) for the staging of axilla.
- The traditional SLNB techniques proposed by Krag and Giuliano have been developed both as a single technique and as dual complementary procedures. Giuliano reported a 93% SLN identification rate using blue dye (BD) alone, while Krag reported 82% SLN identification rate using only radio-isotope (RI) and gamma probe [62, 63].
- Three types of blue dye (BD) have been described: isosulfan blue, methylene blue and patent blue. (Fig. 14.4). The injection site can be at the periphery of the tumour (peritumoral), in correspondence of the palpable edge of the tumour, in the peri areolar site or into the subareolar plexus. Subareolar and peri areolar

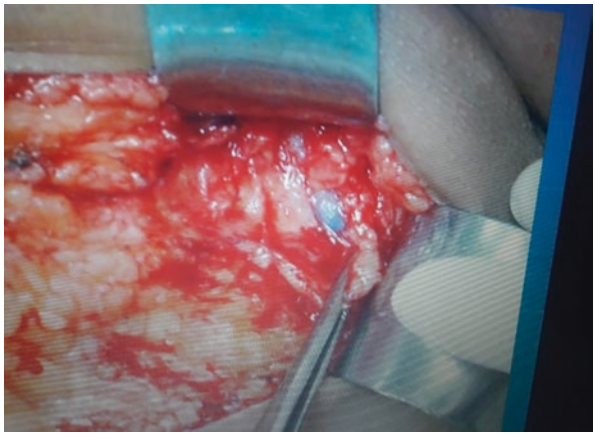


Fig. 14.4 Blue SLN (Methylene blue-stained lymphatic leading to blue LN)

injection have produced higher SLN identification rates than peritumoral injection.

- The commonly used RI tracer is the Technetium 99 m (Tc), Tc-Sulphur colloid in the USA and ^{99m} Tc-nanocolloid human serum albumin in Europe. Recently intra-operative injection of Tc in a large series of patients revealed that it could detect lymph node in 100%. A handheld scintillation counter (a gamma probe) is used to direct the surgeon to the labelled lymph nodes.
- The sensitivity, specificity, and accuracy of SLNB were 97.40%, 100% and 98%, respectively. The false negative rate was 2.60%. Therefore, the gold standard for SLNB identifications is the dual tracer technique which assures higher sentinel lymph node identification rates and lower false negative (FN) rates.

14.7 Newer Techniques [64]

14.7.1 Indocyanine Green (ICG)

ICG is injected directly into the breast; SLN is then localized using a fluorescent imaging system.

The advantage of ICG is that it enables real time visualization of lymph flows from the breast to the axilla. Thereby SLNs is thus identified and this can be resected quickly and easily, especially in cases with multiple lymph drainage pathways. A recent meta-analysis reported that ICG guided SLNB had a 98% sensitivity.

14.7.2 Superparamagnetic Iron Oxide (SPIO)

Superparamagnetic iron oxide is injected subcutaneously. SPIO moves into SLNs within few minutes and the deposition of iron can be seen predominantly within sinuses and in macrophages. In the event of presence of metastatic node, SPIOs are

taken up within the uninvolved areas of the node only. The nodes can then be visualized on MRI and during operation are often seen coloured brown or black.

14.7.3 SPIO Enhanced MRI

14.7.3.1 Contrast Enhanced Ultrasound (CEUS) with Microbubbles

This is a new and an innovative technique where a microbubble contrast agent, based on the sulphur hexafluoride gas dispersion, is injected intradermally around the areola. The breast lymphatics channels are then visualized by the CEUS technique and are followed to identify and biopsy SLNs.

Randomized controlled trials are needed to review their outcomes against the gold standard of dual technique before it is approved as the new standard of care for SLNB.

14.7.4 Metastatic Workup for EBC

The probability of finding metastatic disease in patients with EBC is <1–2%

1. In a review of data from prospective and retrospective studies evaluating the role of staging by imaging in order to detect the presence of occult distant metastasis was rare. The reported median prevalence was 0.2% (range 0–5.1%) in stage I after conventional imaging tests (excluding PET/CT), and 1.2% (range 0–34.3%) in stage II after imaging tests that included PET/CT [65].
2. Evidence does not support the use of routine imaging for metastatic disease in pathological stage I and II disease [66].
3. Those patients who have symptoms suggestive of metastases, appropriate imaging investigations should be performed, regardless of tumour stage.
4. Patients with EBC are not comfortable if they were not referred to systemic staging to rule out distant metastatic diseases, even if the physician's recommendation is against it and in compliance with evidence-based guidelines.
5. Modern methods such as CT and PET/CT have higher costs and are not easily available in every centre.
6. The detection of metastatic diseases, even in a small fraction of the EBC population, could spare futile surgery and, or radiation therapy for the primary tumour and other adjuvant treatment like chemotherapy. This helps in cutting costs and also avoids unnecessary side effects. Therefore, an accurate estimation of the risk of distant occult metastasis in cases of EBC is also critically important.

However, there is lot of variance and debate regarding this topic and it may vary from patient to patient.

7. According to some surgeons, stage I or II patients with unfavorable biology (Triple Negative subgroup or Her2 positive) have higher chances of distant metastasis rate and these patients would need a metastatic work up [67].

14.8 Treatment Modalities for Invasive Early Breast Cancer

The local treatment of breast cancer has been a source of controversy for many years; local treatment was considered to be the domain of the surgeon; however, changes in our understanding of biology of the disease, the detection of smaller tumours, an increasing emphasis on systemic therapy and doctor-patient participation in the decision-making process have radically changed the approach to local treatment of breast cancer over the last 60 years. Today, treatment of breast cancer involves a collaborative effort between surgeons, radiologist, pathologist, radiation oncologist, social and health worker, reconstructive surgeons, medical oncologists and psychologists, all working with the patient. As a matter of fact, in good centers there is a "Breast Cancer Management Group" which is jointly managing the patient right from day one (Chap. 30).

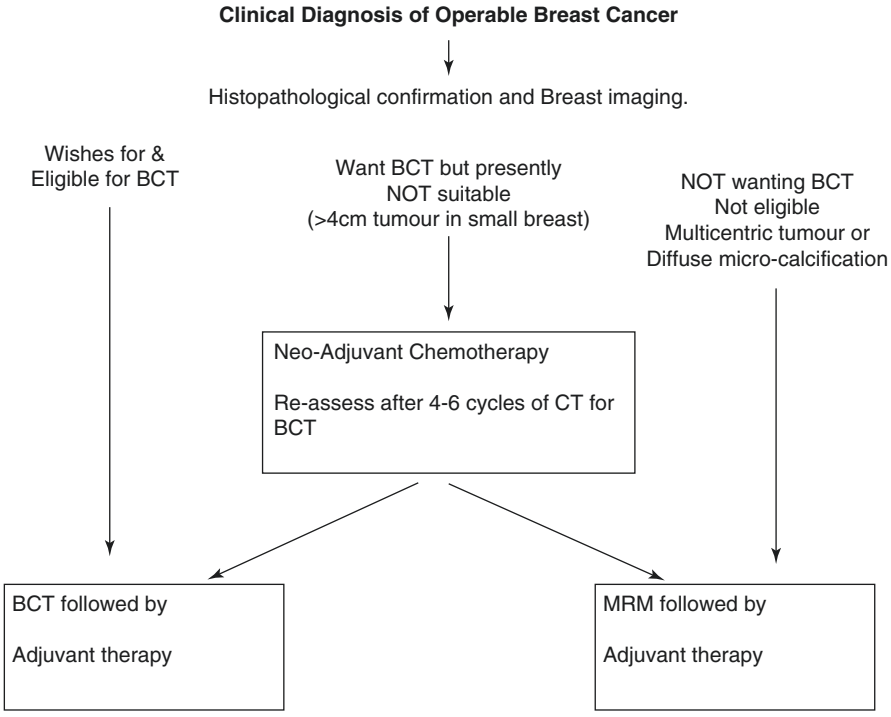
When we talk about surgery for breast cancer, one must remember that patient participation is very crucial. Once breast cancer is diagnosed, it should not be projected as a surgical emergency; the patient should be explained about the disease, the various treatment options and taken into confidence for breast cancer management.

Treatment of early breast cancer is complex. It often involves a combination of local modalities, which includes surgery and radiotherapy (RT), systemic anticancer treatments (Chemotherapy, Endocrine therapy and molecularly targeted therapies). Along with it, other supportive measures are delivered in diverse sequences. The predictive biomarkers such as ER, PgR, HER2 and Ki67 and approved genomic signatures help in determining the treatment of choice. Adjuvant treatment has been discussed in other chapters.

Very young or elderly patients need particular attention. However, age is a continuous variable and its cut-offs in clinical trials are always arbitrarily chosen. 'Younger' patients must not be over-treated because they are 'young', just as 'older' patients should not be undertreated solely based on their calendar age.

In younger premenopausal patients, possible fertility issues should be discussed. Based on this, guidance about fertility preservation techniques should be provided before initiating any form of systemic treatment [68].

14.8.1 Management Scheme in Operable Breast Cancer



14.8.2 Surgical Treatment for Early Breast Cancer

The various options are:

1. Breast conserving surgery (BCS) i.e., wide local excision with axillary clearance.
2. Modified Radical Mastectomy (MRM).
3. MRM with primary breast reconstruction.
4. MRM with interval breast reconstruction, after adjuvant radio and \ or chemotherapy.
5. Partial Mastectomy with reconstruction.

The key change in the surgical treatment of primary breast cancer has shifted towards breast conservation techniques, which started more than 30 years ago. Currently, in Western Europe, 60–80% of newly diagnosed cancers are amenable to breast conservation (wide local excision and RT) either at diagnosis or after Primary Systemic Therapy (PST).

A neoadjuvant approach should be preferred in subtypes of cases highly sensitive to chemotherapy, such as triple-negative and HER2-positive, in tumours >2 cm and/or having a positive axilla.

14.8.3 Breast Conserving Surgery

The first attempt to conserve the breast was probably that of Hirsch from Germany. In fact, the first randomized study on breast conservation was started in the UK by Atkins et al., in 1961 [69].

The principles of the MRM also contributed to the development of breast conservation treatment. In addition, the observation that moderate dose of radiotherapy (RT) was effective in eliminating subclinical foci of breast cancer after mastectomy. This lead to BCS, with the aim to remove the bulk of the tumour surgically (with negative margins) and then use radiotherapy to eradicate any microscopic residual cancer.

BCS is the primary surgical choice for early breast cancer, although in India it has not yet become very popular. It is estimated that even in the USA, less than 50% of eligible patients are undergoing BCS. For patients undergoing BCS, there is greater emphasis placed on achieving acceptable cosmesis. Breast surgeons are trained to undertake oncoplastic approaches to scale back the impact of local tumour excision on cosmesis, often using tissue displacement or replacement techniques. Oncoplastic procedures may result in better cosmetic outcomes. This is especially seen in patients with large breasts, a less favourable tumour/breast size ratio, or a cosmetically challenging location (central or inferior) of the tumour within the breast. Details can be found in the chapter on Breast Reconstruction.

In spite of the overall trend towards breast conservation, a sizable number of patients are opting for mastectomy not only on the affected side but also undergoing prophylactic contralateral mastectomy (risk-reducing surgery) along with bilateral reconstruction of the breasts. This is because of the impression that left over breast tissue has left over cancer cells which can give rise to recurrence. There is a study suggesting that patients undergoing BCS may have even better survival compared with those who undergo MRM [70].

14.8.4 Aim of BCS

The aim of local treatment of breast cancer is to attain long-term local disease control with less or minimum of local morbidity. Women with moderate sized breasts are the candidates that are suitable for BCS. The major advantages of breast-conserving treatment (BCS) are:

- An acceptable cosmetic appearance in the majority of women (Fig. 14.5).
- Improved body image

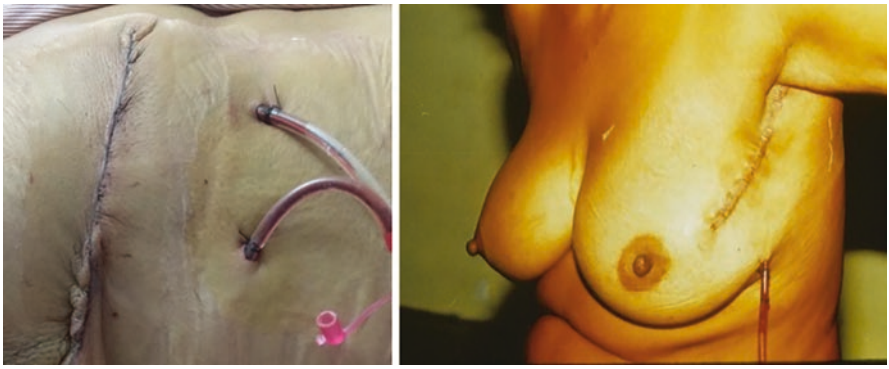


Fig. 14.5 Cosmetic looks of a patient of MRM vs. BCS

- Lower levels of psychological morbidity
- Less anxiety and depression; increased sexuality and self-esteem compared with mastectomy
- There is equivalence in terms of disease outcome for BCS and MRM, this has been shown by systematic reviews.

14.8.5 Indications of BCS

Patients with a single mammographic lesion measuring 4 cm or less without signs of local advancement (T1, T2 < 4 cm) limited to a single quadrant of the breast, no extensive nodal disease (N0, N1) or distant metastasis (M0) anywhere in the body are traditionally considered suitable for BCS (NIH Consensus Conference 1991) [71].

Tumour bigger than 4 cm may be also treated by BCS in a patient with large breasts, however, for practical purposes, it is safer to include up to T2 lesions only. Many surgeons now a day's give more emphasis on the tumour/breast size ratio. Tumours more than 4 cm, multifocal and multicentric in adjacent quadrants are now being offered BCS. This has been made possible because of two main reasons: extensive use of Neoadjuvant Chemotherapy to reduce the tumour size and Oncoplastic breast procedures. These oncoplastic procedures can be in the form of volume displacement and replacement techniques.

Lately, neoadjuvant treatment is being given to cases of LABC to download the tumour size and then the patient may be subjected to BCS followed by adjuvant therapy. This has been discussed in detail in the chapter on LABC (Fig. 14.6).

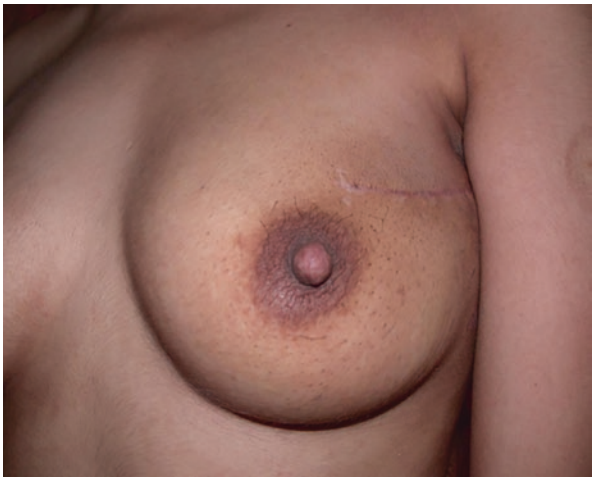


Fig. 14.6 LABC, responded well to neoadjuvant therapy, underwent wide excision along with axillary clearance. The cosmetic result is very satisfactory

14.8.6 Selection of patient's for BCS

The breast conservative approach is considered successful if it produces satisfactory cosmetic outcomes and the probability of tumour control or late sequalae are not inferior to mastectomy. This requires careful evaluation and selection of cases; good quality breast imaging; wide excision of the primary tumour with negative margins and with appropriate axillary surgery by experienced surgeons; meticulous histopathological evaluation and reporting of the resected specimen; quality assured technique of radiotherapy delivery in standard doses; and regular clinical and mammographic follow up to detect and salvage breast recurrences early. This would require infrastructure, equipment (e.g., LINAC, which is required in >75% BCS cases) and expertise. Centres with requisite facilities and expertise should offer BCS to eligible women or if they lack such facility, refer the eligible women who wish to conserve their breasts to such centers.

14.8.7 Absolute Contraindications

1. First & second trimesters of pregnancy*
2. Two or more gross tumours in separate quadrants of breast
3. Diffuse indeterminate or malignant appearing microcalcifications.
4. Previous breast irradiation.
5. Pt not willing for BCS
6. Conservative surgery not possible because of the nature of the disease (multicentric)
7. Persistent positive surgical margin.

Note It may be possible to perform breast-conserving surgery in the third trimester and administer irradiation after delivery.*

14.8.8 Relative Contraindications

1. Large tumour/breast ratio (a large tumour in a small breast operated with adequate margins might result in an unwanted cosmetic appearance).
2. History of Collagen Vascular Problem –Due to Poor Irradiation Tolerance.
3. Tumour Location beneath the Nipple.
4. Large Breast Size.
5. Local positive margin.
6. Young Patients with BRCA I & II Mutations.

14.8.9 Important Points for Consideration

- The final and critical factor in the selection of local therapy is the patient's desire. However, the surgeon should discuss all the options with the patients.
- Patients with bilateral disease can also be treated by bilateral conservation.
- A family history of breast cancer is not considered as a contraindication to BCS [72].
- Age alone should not be the criteria for determining surgical strategy. However, older women may have co- morbid conditions that need to be considered. (Fig. 14.7)
- A woman, who probably is going to have difficulty with general anaesthesia might benefit from a lumpectomy performed under local anaesthesia.
- Woman who has difficulty in complying with 6 weeks of radiation treatments are more suitable candidate for mastectomy.
- The status of the margins of resection after lumpectomy is important in determining the optimal surgical treatment. Patients in whom negative margins can be achieved along with adequate preservation of normal breast tissue are candidates for conservative surgical therapy. If tumour remains at the margin after re-excision, and all the measures undertaken as discussed in subsequent paragraphs then MRM may be the treatment of choice [73].

14.8.10 Techniques of BCS Procedures

Two breast conservation surgical procedures have been extensively studied and described: Quadrantectomy and Wide Local Excision.

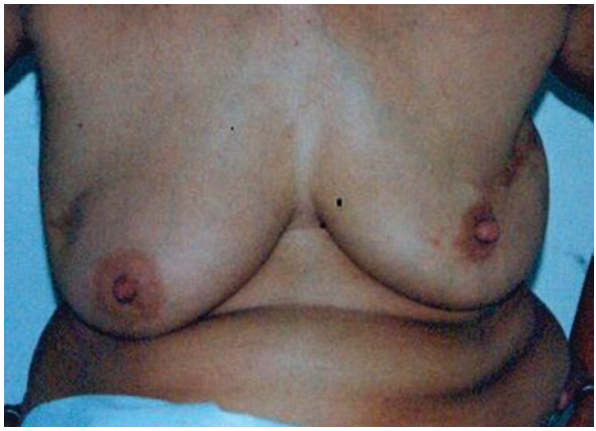


Fig. 14.7 80 years old women who had BCS on left side 24 years back and 16 yrs. back on right side and is disease free till now

14.8.11 Quadrantectomy

This relates to the large amount of breast tissue excised around the tumour instead of removing the cancer and its draining duct. Quadrantectomy isn't any longer advocated because it produces a significantly poorer cosmetic outcome when compared with wide local excision. The consensus view is that most patients having BCS can be adequately treated by wide local excision only. These patients do not require the more extensive excision of a quadrant.

14.8.12 Surgical Technique of Wide Local Excision

Wide local excision (Figs. 14.8, 14.9, and 14.10) is aimed to remove all invasive and any ductal carcinoma in situ with surgical aim of 1-cm macroscopic margin of normal surrounding breast tissue [74]. It is important to place the incision properly in a place that will give the optimal cosmetic result. Curvilinear incisions along the Langer's lines give the best cosmetic results. Radial incisions shouldn't be used. The exceptions are when tumour is present directly medial or lateral to the nipple or if the tumour is present in the lower part of breast.

A radial incision can also be given for a tumour in the upper and outer quadrant of the breast where one also wants to undertake axillary clearance (Single incision BCS). A single incision can serve both the purposes as shown in the picture (Figs. 14.10 and 14.11).

An incision to excise a cancer should be placed directly over the lesion. Circumareolar incision can be placed to excise tumours close to nipple areola complex. (Fig. 14.12 a) Excising skin directly overlying a tumour is only necessary if the carcinoma is very superficial or the skin is tethered. The cosmetic result after

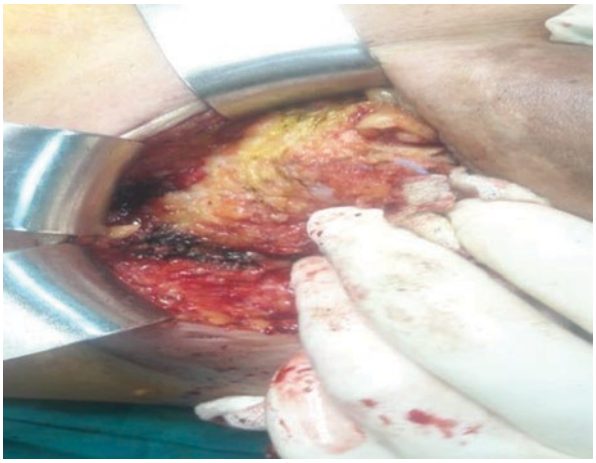


Fig. 14.8 (Incision + Dissection)

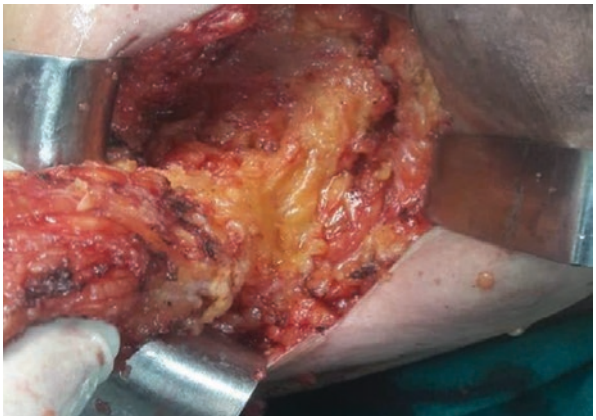


Fig. 14.9 (Dissection near completion)

BCS is influenced by the amount of skin excised with poor results being obtained in those patients in whom large part of skin has been removed.

After making the skin incision, the skin and subcutaneous fat are dissected off from underlying breast tissue. While elevating skin, it is important not to dissect into the subcutaneous fat as thin skin flaps give a poor cosmetic result. The skin flaps should be elevated just beyond the edge of the tumour. The fingers of the non-dominant hand are then placed over the palpable cancer and the breast tissue divided beyond the fingertips. The line of incision should be 1 cm beyond the limit of the palpable mass. Breast tissue is divided beyond the edge of the cancer. The dissection then follows the deep aspect of the tumour, which can be palpated and breast tissue under the tumour gradually divided. It is not necessary to remove full thickness of breast tissue if the lesion is superficial. For the majority of patients, however, to

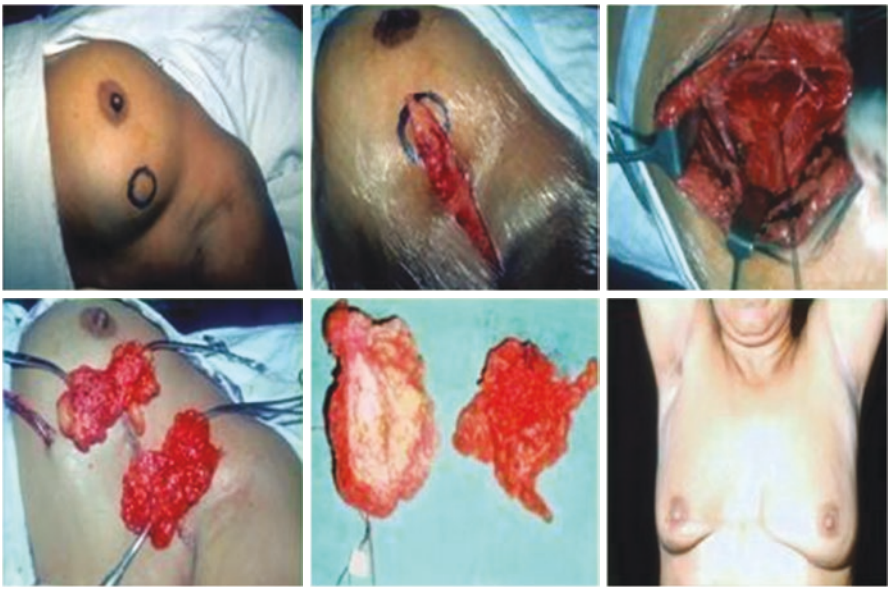


Fig. 14.10 BCS through single radial incision in the upper outer quadrant, through which axillary clearance was also done

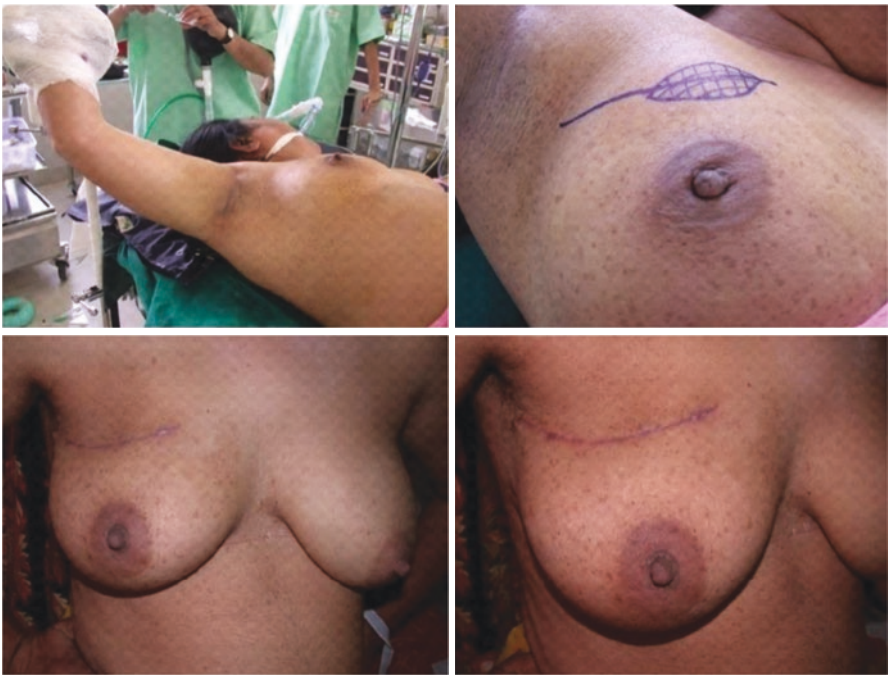


Fig. 14.11 Transverse incision for a tumour in the upper outer quadrant, allows axillary clearance. A good scar adds to satisfactory cosmesis

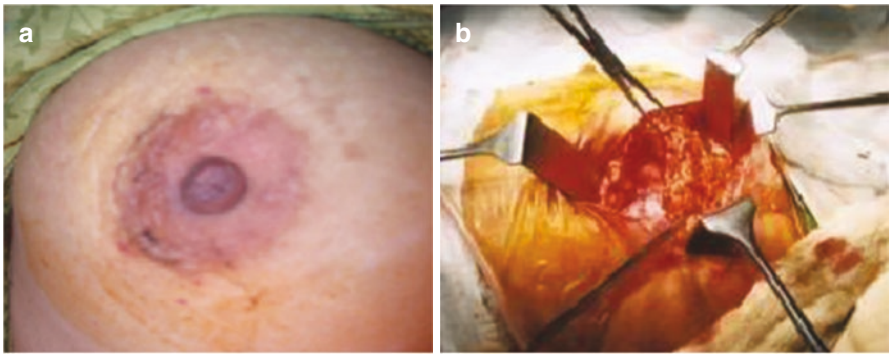


Fig. 14.12 (**a**) BCS through a circumareolar incision. The scar is hardly visible and the fullness of the breast is also good. (**b**) Breast flap being raised to fill up the cavity

ensure that there is an adequate margin deep to the tumour, dissection through the breast tissue is continued down up the pectoral fascia. This helps the breast tissue containing the cancer to be lifted off the fascia. The excision of pectoral fascia is not required unless the tumour is tethered to it. If a tumour is infiltrating the chest wall muscles, then a portion of the affected muscle should be removed beneath the tumour in order to excise tissue beyond the limits of the cancer.

The tumour along with surrounding breast tissue is lifted off the chest wall muscles grasped between the finger and the thumb of the non-dominant hand and excision is completed at the remaining other margins (Fig. 14.9). The glandular tissue is approximated keeping in mind to have an acceptable cosmetic appearance. The specimen is immediately oriented prior to submission to the pathologist with sutures or liga clips. It has become customary to follow this trend for marking sutures – Long thread laterally (L), Short thread superiorly (S) and another thread in the front – anteriorly. This trend avoids confusion and there is no need for keeping a note for this. The specimen is then subjected to radiography. This helps the surgeon to determine that the target lesion has been completely removed or not. It also allows for assessment of the completeness of excision at radial margins. If the radiography of the specimen shows that the cancer or any associated microcalcification is very close to a radial margin, then the surgeon can remove some more tissue from that margin area.

Having excised the cancer tissue from the breast, the next step is suturing the defect. If the adjacent breast tissue is not mobilized then it may result in distortion of the breast contour. Small defects (<5% breast volume) do not require mobilisation and can be left open and produce a good final cosmetic result. Defects which are large should be closed by mobilizing the surrounding breast tissue. This can be done from both the overlying skin and subcutaneous tissue and the underlying chest wall. (Fig. 14.12 b). If large defects (>10% breast volume) are not closed, they are

usually filled with seroma. This later on gets absorbed and as a result scar tissue forms, it then contracts, often producing an ugly, distorted breast. Following large-volume excisions, breast tissue can be mobilized from surrounding areas. It is usually possible to close the defect in the breast plate with a series of interrupted absorbable sutures. Latissimus dorsi muscle miniflap can be used to fill larger defects. Drains preferably should not be used. They do not protect against hematoma formation, may increase infection rates and gives disfigurement. Complete haemostasis and filling of the gap with breast tissue is more important.

Marking the tumour bed with clips in a standardized way facilitates accurate planning of the radiation boost if indicated.

Incision wounds should be closed in layers with absorbable sutures, finishing with a subcuticular suture. Staples and interrupted sutures are not acceptable methods of wound closure in the breast. Some surgeons like to infiltrate the wound with local anesthetic agent, usually a combination of bupivicaine and adrenaline, but it is not always necessary.

If frozen section facilities are available then one must confirm the margins or tissues from the cavity right at the time of surgery so that in case of involvement, further resection may be carried out then and there.

One of us (SMB) has been practicing another method of determining the status of the tumour bed by taking biopsy pieces from the left over cavity (as shown in the picture) from 12, 3, 6, and 9 O'clock positions. These biopsy pieces can be examined by frozen section technique, result obtained in half an hour or in the post-operative period within 5 days, prompting the surgeon to take steps for adequate clearance (Fig. 14.13).

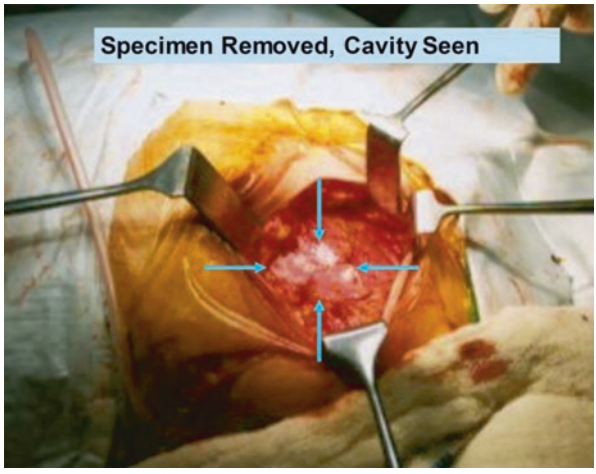


Fig. 14.13 Tumour excised, cavity left behind, biopsy pieces to be taken from all around, 12, 3, 6 and 9 0 clock sites and sent for frozen or HP confirmation for left over malignant tissue

14.8.13 Available Techniques for WLE of Central Tumors (Figs. 14.14, 14.15, 14.16, 14.17)

Central tumours can be removed from under the nipple, provided they are not very superficial. This can be done by a standard wide excision preserving the overlying nipple skin. If the lesion is very superficial and is tethering or inverting the nipple, then it is necessary to remove the nipple areola complex. In women with large breasts, the nipple areola complex can be incorporated into an elliptical incision and the cancer is excised along with the nipple/areola skin. This technique does alter the breast shape and often produces a breast that is very flat centrally.

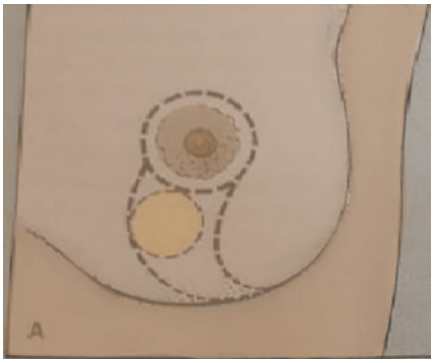


Fig. 14.14 Incision all around the areola with marking of the joining skin to cover the defect after mobilization

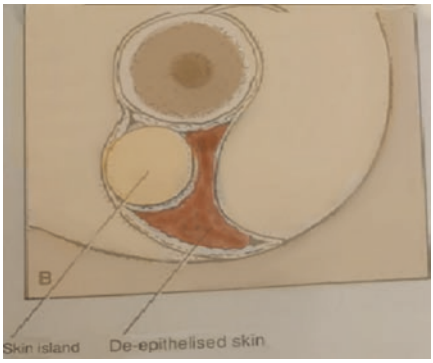


Fig. 14.15 Dissection in progress

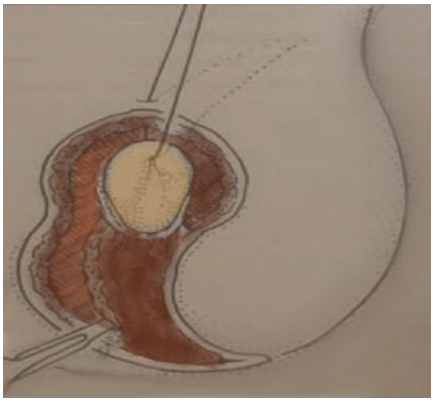


Fig. 14.16 Skin with breast tissue mobilized for coverage of the defect

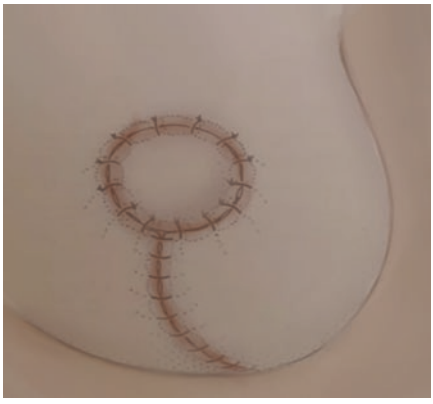


Fig. 14.17 Final closure

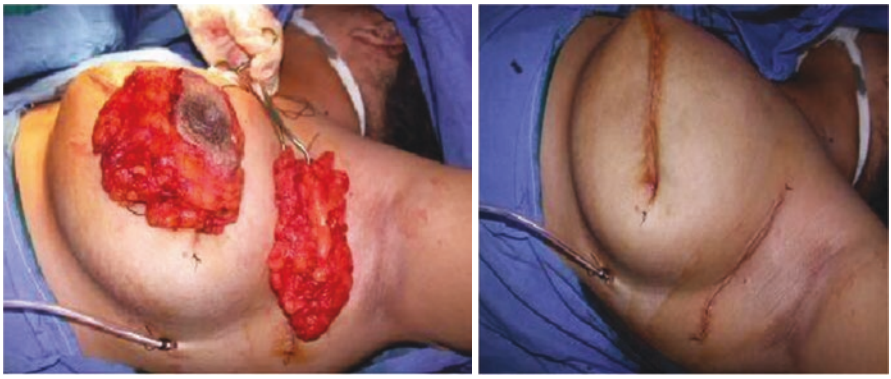


Fig. 14.18 Central tumour excision with axillary dissection

Acceptable results can be obtained in some women with large ptotic breasts. An alternative approach for such central tumours involves removal of the nipple-areola complex along with an underlying cone of breast tissue till the pectoral fascia.

The reconstruction of the breast is done with a skin and breast tissue flap rotated in from the lower outer quadrant of the breast. An island of skin is identified and marked (Figs. 14.16 and 14.17). The flap of tissue to be rotated and to fill the defect is first defined. The circle of skin that will close the central cutaneous defect is left as it is and the rest of the skin is de-epithelialized (Fig. 14.17). The breast tissue is incised and divided in order to rotate the flap and allow the island of skin to lie in the position of the nipple areola complex. The flap is sutured and fixed with absorbable sutures.

Another technique is shown in (Fig. 14.18), when the patient opts for the breast mound and does not mind the absence of nipple areola complex.

14.9 Management of the Axilla in BCS

It has several aims:

- Eradication of metastatic disease within the axillary nodes
- Assessment of nodal status for evaluation of prognosis
- Assessment of nodal status to determine adjuvant therapy.

It can be done by either of these methods

1. Sentinel lymph node biopsy (SLND)
2. Axillary lymph node dissection (ALND)
3. Axillary node sampling

14.9.1 A. Role of Sentinel Lymph Node Biopsy (SLNB) in EBC

For clinically node-negative invasive breast cancer patients.

Sentinel lymph node biopsy (SLNB) has replaced the once performed axillary lymph node dissection (ALND) for the staging of clinically node-negative invasive breast cancer patients. It is based on randomized clinical trial data that have demonstrated equivalent survival between SLNB and ALND with reduced morbidity for SLNB alone [75].

The reason to perform ALND in cN0 patients includes opportunity for complete axillary staging and likelihood of decreasing the loco regional relapse. The possibility of an accurate adjuvant systemic treatment planning and improved survival rates are the other reasons to perform ALND.

For clinically negative axilla or with 1 or 2 positive sentinel nodes.

- The Data from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial have clearly demonstrated that ALND may be omitted in few selected patients with 1 or 2 positive SLNs [76].
- International Breast Cancer Study Group Trial 23-01, which compared ALND vs. SLNB alone for patients with micro metastases (0.2–2.0 mm) in the SLN. No differences in overall or disease-free survival were noted in this trial after 5 years of follow-up [77].

14.9.2 B. Axillary Lymph Node Dissection (ALND)

14.9.2.1 Indications for ALND Include

- ALND should be offered to women with SLN metastases who would be undergoing mastectomy.
- Patients with clinically involved axillary nodes.
- Patients with histologically proven involved axillary lymph nodes after freehand or ultrasound-guided fine-needle aspiration biopsy/core biopsy.
- Patients with larger tumour having a mastectomy and reconstruction for which a second operation in the axilla or axillary radiotherapy is best avoided.

14.9.2.2 Technique

- It is usually performed through a separate incision. However, if the lesion is in the upper outer quadrant one can use a single transverse incision.
- A trans axillary incision along the skin crease about 1–1½ in. below the axillary hair line can be also used. The skin incision is deepened and flaps dissected to expose the pectoralis major and latissimus dorsi muscles. The pectoralis minor muscle is retracted upwards to expose the apex. Axillary vein is identified and contents of axilla below the axillary vein is cleared off, preserving the long thoracic nerve, thoracodorsal nerve and vessels and if possible, the intercostobrachial nerve.

- Routinely the axillary contents above the axillary vein should not be dissected otherwise the incidence of Lymphedema increases.
- Dissection of the lower axillary contents should continue into the axillary tall of the breast. A single Romovac suction drain is placed in the axilla and the wound is closed in two layers similar to the breast incision.
- It is done for accurate staging and also to reduce the risk of recurrence in axilla, level I and II nodes should be removed. If nodes in level II and III are enlarged then level III dissection is done.

14.9.2.3 ALND in Elderly Patients

ALND in patients over age 70 with early breast cancer have shown no significant impact on overall survival. In patients with T1 tumors, ALND had not been demonstrated to influence postoperative treatment, decrease recurrence, or improve survival [78].

Based on this evidence, the NCCN guidelines recommend that in the absence of definitive data demonstrating superior survival, the performance of axillary staging may be considered optional in the elderly or in those with serious co morbid conditions [79].

14.9.3 Axillary Sampling

The aim is to remove at least four nodes, usually from the lower axilla. Sampling may miss nodes and under stage the axilla, and if a lymph node is positive, it must be followed by radiotherapy. It is seldom done these days.

14.9.3.1 Post-operative Management

- If the patient is feeling well and is mobile, she can be discharged on the 1st post-operative day after instructions on drain management.
- The drain is removed on the 5th postoperative day, regardless of volume, as studies have shown that the rate of infection increases thereafter, although a few surgeons want to wait till the daily discharge comes to below 25 ml per day.
- Prior to discharge home, the patient is seen by a physio-therapist and advised to do shoulder exercises which need to be carried out several times a day.
- A follow-up visit is advised 1 to 2 weeks after the operation, when the wounds are assessed and also the histopathological report is available.

14.9.4 Complications of Lumpectomy and Treatment

- Haematoma formation can occur. This can cause pain and swelling, and also the area might feel hard. A tense haematoma needs drainage and possible inspection for the source of bleeding needs to be dealt with.

- Seromas requiring aspiration may be present in the breast if a significant defect was evident after surgery or in the axillary wound. Aspiration using a needle attached to a nonreturnable valve and syringe should be performed aseptically. Repeat aspirations may be necessary until there is no more fluid. Persistent seromas, such as seen in the back wound after latissimus dorsi flap reconstruction, are not a common problem in the axilla.
- Superficial and deep wound infection may occur.
- Decreased shoulder movements have been shown to reduce seroma formation. This however, can lead to a frozen shoulder. Consequently, regular postoperative shoulder exercises are advocated, despite the tendency to increase the incidence of seroma.
- Nerve pain can be there especially in outer quadrant tumours and one may experience numbness, tingling or a shooting pain in armpit, upper arm, and shoulder or chest wall. The reason for this is possible damage to the nerves during surgery.

14.9.5 Complications of Axillary Dissection

Axillary dissection is associated with both short and long term complications:

- These are seroma formation, post-operative infections; numbness over the inner side of the arm due to injury to the intercostobrachial nerve, restriction of shoulder movements, and the most dreaded of all is the development of lymphoedema.
- There is morbidity associated with axillary dissection and it would be beneficial to omit this procedure whenever the possible morbidity clearly outweighed the clinical benefits [80, 81].

14.9.6 Radiotherapy Following BCS

- Women who undergo BCS should be advised for RT. Omission of RT after BCS increases the risk of local recurrence [82]. Boost to breast should be considered in women at high risk for local recurrence.
- Optimal sequencing of chemotherapy and breast RT is not clearly defined. In cases where the resection border is involved, then radiotherapy should be given first for local control; and in cases where resection margin is not involved but the number of involved lymph nodes are more than systemic chemotherapy should be given first. In other cases, when the number of involved lymph nodes is not high and the resection borders are not involved then the priority can be either of the two.
- Conventional fractionated radiotherapy (CFRT) vs. hypo fractionated and accelerated scheme are now studied [83].

  Role of radiotherapy is discussed in detail in the Chap. 19.

14.9.7 Risk Reduction Therapy for Ipsilateral Breast Following BCS

- If patient has undergone BCS followed by RT and is ER positive, one must consider endocrine therapy for 5 years.
- Endocrine therapy includes tamoxifen for premenopausal patients and tamoxifen or aromatase inhibitor for postmenopausal patients. Some study gives some advantage for aromatase inhibitor therapy in patients who are <60 years or with concerns for thromboembolism.

The benefit of endocrine therapy for ER-negative DCIS is uncertain.

14.9.8 Cancer Recurrence After BCT

Most recurrences in the treated breast are at or near the site of the primary tumour and 80% occur within 2 years. The incidence of local recurrence varies from 2 to 21%.

The factors affecting local recurrences depend on:

Patient Related Factors

1. Age: Younger the age, greater is the chance of local recurrence. The credence for this comes from the study by Kurtz et al., who demonstrated that lymphatic stromal reaction and histological grade of tumour are high and there is Extensive intraductal component (EIC) in young females.
2. Breast size: Larger the size, more the chances of local recurrence. The exact cause is not known.

Tumour Related Factors

1. Histology: Histological grade of the tumour has not been associated with an increased risk of loco-regional failure although the presence of lymphatic and vascular invasion is associated with increased incidence of local recurrence.
2. Extensive Intraductal Component (EIC): It is defined as intraductal carcinoma, comprising 25% of the index lesion and is present in non-involved adjacent breast tissue. In the Boston experience, an extensive in situ component was the most important factor determining the risk of local failure.

Treatment Related Factors

1. **Positive resection margin**: Many studies have suggested that positive resection margins may be a factor for increased local recurrence, however, this is more evident if the patient is treated with lower doses of radiation therapy or incomplete therapy.
2. **Absence of adjuvant therapy**: If the patient does not get adjuvant radiation therapy or chemotherapy, the chances of local recurrence are more.

14.9.9 Treatment of Local Recurrence

Local recurrence rates vary widely in the literature but rates of 1% or less per year after BCT are achievable. It has been dealt in the chapter on Management of Late breast cancer.

14.9.9.1 Modified Radical Mastectomy (MRM)

Modified radical mastectomy (MRM) with axillary clearance is still considered by many as an appropriate surgical option for all stages of operable breast cancer and also after neoadjuvant treatment. However, as more and more patients are diagnosed early, BCS option should be discussed and offer to them.

Modified radical mastectomy is the most common operative treatment for patients with invasive carcinoma [84, 85]. More than 50% of the patients in stage I and II are treated with mastectomy in USA [86].

The reasons attributed to this are the presence of medical contraindication to breast conservation therapy, lack of access to such therapy because of low income, geography, patient preference for mastectomy and physician's bias [87].

14.9.9.2 MRM

The evolution of less radical technique resulted in modified radical mastectomy (MRM); This technique was popularized by Patey and Dyson in 1948. It soon became as an acceptable therapeutic option to the age old Halsted radical approach.

This conservative approach was a departure from the previous time-honoured and known proven methods like Radical Mastectomy. The pectoralis major muscle was preserved and pectoralis minor removed.

Auchincloss, and later Madden, preserved both the pectoralis major and minor muscles and advocated low axillary node dissection (levels I and II) with less extensive skin resection.

- A modified radical mastectomy involves removal of the entire involved breast using an elliptical skin incision, including the skin overlying the tumour and the nipple – areola complex along with the underlying pectoralis fascia, sparing both the pectoralis muscles, along with the removal of at least levels I and II axillary lymph nodes.
- Level III axillary lymph nodes should always be excised in large tumours, node positive axilla and locally advanced breast cancers post chemotherapy.
  A full axillary clearance that includes level III lymph nodes be undertaken as a standard procedure in breast cancer surgery in developing countries. There is relative abundance of large, non-screen detected cancers and locally advanced breast cancer in these regions with high possibility of axillary nodal involvement [88]. It needs to be noted that extensive axillary procedures could lead to increased incidence of adverse effects like shoulder stiffness and arm edema [89].

  Now a day it's the Auchincloss MRM that is practiced.

14.9.9.3 Technique

The technique has been described in the chapter on management of LABC (Chap. 16).

14.9.9.4 BCS vs. MRM

- The Milan group (Veronesi et al. [90]) published their 20 years follow-up results and showed a significant difference in local recurrence. In the ipsilateral breast it was 2.3% in the mastectomy group while 8.8% in the BCS group.
- The disease-specific survival was similar between the two groups. The death rate from breast cancer being 24.3% in the mastectomy group and 26.1% in the BCS group.
- An overview of the randomized trials (Table 14.1) has shown that there is no significant difference in survival in between women treated with total mastectomy and those treated with lumpectomy with or without irradiation [91].
- However, if radiotherapy is added after breast conservation surgery, the rate of local recurrence is decreased without any significant overall survival benefit. Radiotherapy following surgery resulted in lower local recurrence which was three times less when compared to surgery alone.

14.9.10 Survival After BCT vs. Mastectomy Alone: Is BCS Better?

- Aggarwal S et al., demonstrated that with a tumor size of 2 cm or smaller or even tumour larger than 2–4 cm, undergoing BCT had a higher survival rate when compared to those undergoing a mastectomy procedure alone [92].
- Hwang et al., showed a lower hazard of death associated with BCT. They found that the presence of unaccounted variables representing tumour aggres-

Table 14.1 Summary of survival and recurrence in prospective trials of mastectomy vs. breast conserving surgery

Local study group	Interventi-ons	No. of patients	Survival %	Disease free survival %	Local Rec. %
Veronesi et al. (Milan), 1990	BCS + RT TM	352 349	68 66	– –	8.8 2.3
Fisher et al. NSABP (1989)	BCS BCS+/– RT TM	636 629 590	83 84 82	64 71 67	39 10 8
Blichert-Toft et al. (Denmark) (1992)	BCS + RT TM	430 429	79 82	70 66	– –
van Dongen et al. (EORTC) 1992	BCS + RT TM	426 456	60 60	– –	11 8
Jacobson et al. (NCI) 1995	BCS + RT TM	121 116	77 75	72 69	5 10
Arriagada et al. (InstitutGustave-Roussy) (1996)	BCS + RT TM	88 91	73 65	55 44	9 14

siveness (e.g., lymphovascular invasion or extra nodal extension) couldn't have contributed to such a significant difference in survival between the BCT and mastectomy groups. More studies would be required to verify this claim [93].

- The improved survival noted among these patients who received BCT may be due to differences related to adjuvant therapy they received postoperatively. The adjuvant therapy could be chemotherapy and radiation therapy.

14.9.11 Survival After BCS vs. Mastectomy with Radiation: Controversy

In an analysis by Aggarwal et al., those patients who underwent mastectomy with radiation have worse survival rates than patients who undergo BCT. It is contrary to other studies.

They noted that patients who underwent a mastectomy with radiation were young and had high-grade tumors (which were larger in size). They were more likely to be node-positive when compared with patients who underwent BCT or a mastectomy alone. To administer postmastectomy radiation was probably related to tumour characteristics such as lymphovascular invasion, size of nodal metastases, extra nodal invasion, all of which are signs of poorer prognosis.

Their study showed that it is highly unlikely that patients who had a mastectomy followed by radiation are at a survival disadvantage compared with patients of BCT according to criteria given by NCCN. The inference is that patients undergoing a mastectomy with radiation are implicitly different from those undergoing BCT [93]. Similar results were seen by Sun G et al. [94]. There were 4209 women with T1-2N1M0 breast cancer treated, and all had received lumpectomy or mastectomy and axillary lymph node dissection without neoadjuvant chemotherapy. 3858 patients underwent modified radical mastectomy (MRM), 832 (21.6%) of them received postoperative RT (MRM + RT). 351 patients received BCS, all of them received postoperative RT (BCS + RT). At a median follow-up of 70 months (range, 6–226 months), the 5-year overall survival (OS) rates of the BCS and MRM group were 96.0% and 92.7% ($p = 0.005$), and the corresponding 5-year disease free survival (DFS) rates were 92.8% vs. 84.0% ($p < 0.001$).

14.9.12 BCS vs. MRM and Role of Systemic Therapy

- The overall survival is improved only when adjuvant chemotherapy is given along with RT in breast conservation therapy or for that matter in MRM.
- There was no significant difference in 10 years survival. Although local therapy alone has little influence on survival, whereas systemic therapy does have benefi-

cial effect. So, some form of systemic therapy should be combined either before or after surgery.

- Adjuvant chemotherapy has reduced the probability of recurrence, morbidity and also mortality in patients with localized breast cancer. However, when the prognosis is good, this benefit is often minimal and the treatment also has definite side effects. Hence, clinical or genetic platform is often used to determine the risk of recurrence and to decide whether adjuvant chemotherapy should be administered or not [95].

14.9.13 BCS vs. MRM in Young Patients of EBC

- Two very large population-based database studies compared the effectiveness of BCT and mastectomy in women 40 years of age or younger diagnosed with EBC. Van der Sangen et al., analysed 1451 patients out of which 889 (61.3%) received BCT and 562 received mastectomy (38.7%). In the mastectomy group, 37% of patients received post mastectomy radiotherapy. At a median of 9.5 years of follow-up in the BCT cohort, the 5-, 10- and 15-year local risk (LR) risks were 8.3%, 18.4%, and 28.2% respectively. No significant associations were found between the risk of LR and age group (<30, 30–35, and 35–40 years). The 10-year overall survival (OS)rates did not differ significantly between patients undergoing BCT and those undergoing mastectomy (74.9% vs. 71.2%, $p = 0.215$) [96].
- Mahmood et al. analysed 6640 patients who received BCT (45.0%), and 8124 received mastectomy (55.0%) and overall survival. In the mastectomy group, 17% received post mastectomy radiotherapy. Median follow-up was 5.7 years. Matched-pair analysis of 4644 patients confirmed no difference in the 5, 0, and15 year rates of cause-specific survival ($p = 0.88$) and OS ($p = 0.99$). Although the Surveillance, Epidemiology and End Results database does not contain information about local recurrence, the multivariable and matched-pair analyses on such a large number of patients provide reassurance about the comparable survival outcomes with BCT and mastectomy [97]. Hence BCS is a good option for young patients.

14.9.14 BCS vs. MRM: Body Image and Quality of Life (QOL)

- In a multicentre randomised clinical trial in 1980 by EORTC-BCCG significant benefit in body image and satisfaction with treatment were observed in the BCS patients [98].
- Bhat V et.al, conducted a cross-sectional study to compare the QOL in women who underwent MRM and BCS for breast cancer in the last 5 years. There were

significant differences in the quality of life of women from both groups in terms of physical function and body image, with the BCS group appearing to have a better QOL [99].

14.9.15 Local Recurrence and Effects on Survival

- The EBCTCG (2005) overview of randomised trials of local treatment has clearly shown that local recurrence may impact on patient survival [100]. For every four additional local recurrences at 5 years, one woman will have died by the 15-year follow-up. This means that women at higher risk for local recurrence may require more radical surgery and/or radiotherapy treatments. Additional excision surgery after BCS may be required if margins are positive or close [101]. Several groups have demonstrated in randomized controlled trials that this approach (BCS plus radiation) is at least equivalent to mastectomy [102].
- Mcintosh A et al., studied the role of radiotherapy in patients who accepted RT after BCS despite having a close or positive resection margin. 200 patients EBC were treated by radiation with a nonnegative margin < or =2 mm from January 1974 to September 2001. Margins were positive in 29% and close (< or =2 mm) in 71%. The median dose of radiation given was 64 to 66 Gy and the median period of follow up was 5.9 years. Reasons for not re-excising were advanced age or presence of co-morbidities in 7% of the patients. The other reasons were the anterior location under skin in 25%, or posterior location to muscle in 15%. Focal involvement was present in 13% and there was no extensive intraductal component in 5%.Surgeonrefusal was the reason in 15%, and patient refusal in another 20%. The risk of local recurrence at 5 and 10 years was 3% and 5%, respectively.

  Although, re-excision or mastectomy would be the ideal, however in a subset of patients alone RT can be tried [103].

14.9.16 Indian Study

Tata Memorial Hospital carried out a retrospective audit of cases managed in 2009 to report the disease-free survival (DFS) in EBC and LABC in patients registered at a tertiary cancer centre in India.

The study included 2192 patients, of these 888 (40.5%) were EBCs Stage I and II, 833 (38%) were LABCs (Stage III) and 471 (21.5%) were de novo metastatic or relapsed cancers at presentation. The 5-year DFS in the women with EBC was 85.5% and in LABC, it was 67.7%, $P < 0.001$.

The factors adversely affecting DFS in EBC were node metastasis, higher metastatic nodes, hormone receptor negativity, and human epidermal growth factor receptor 2 (Her2neu) positivity.

They concluded that the survival rates in this study are equal to the documented global rates; nodal disease burden emerged as the most important prognostic factor. In addition, in EBCs, a lack of hormone receptor expression and in LABC, Her2neu over expression appear to worsen the outcome [104].

14.9.17 Is MRM Still Preferred Choice for EBC

Jeffery Gu et al. did a systematic review to find out why some patients prefer MRM over BCS. The women's choice depends on clinicopathologic factors, physician factors, and individual factors. Larger tumour size and increasing stage was associated with increased rates of mastectomy.

Extremes of age were associated with an increased likelihood of mastectomy. Higher socioeconomic status was associated with higher BCT rates. Rural location and increased distance from radiation treatment facilities were associated with lower rates of BCT.

Individual belief factors influencing women's choice of mastectomy (mastectomy being reassuring, avoiding radiation, an expedient treatment) differed from factors influencing choice of BCT (body image and femininity, physician recommendation, survival equivalence, less surgery). Surgeon factors, includes higher case numbers and individual surgeon practice, were associated with increased BCT rates [105].

In some patients, mastectomy is still carried out due to:

- Tumour multicentricity
- Tumour size to breast size ratio e.g., large sized tumour in a small sized breast
- Inability to achieve negative surgical margins even after multiple resections
- Radiation therapy given earlier to the chest wall or breast
- Contraindications to Radiation
- Not suitable for oncoplastic breast conservation
- Patient choice [106]

14.9.18 Other Options Besides Auchincloss Mastectomy

- Skin-sparing mastectomy (SSM) that preserves the skin envelope and nipple-sparing mastectomy (NSM) has been increasingly used in the last decade.
  Nipple-sparing mastectomy is safe from oncological point of view in selected patients. It also improves cosmetic outcomes for therapeutic and prophylactic surgeries.

Both the procedures have been discussed in the chapter on "Oncoplastic and Reconstructive Surgery for Breast Cancer" (Chap. 22).

14.9.18.1 Mastectomy and Breast Reconstruction

- Immediate reconstruction following mastectomy can be made to accept by patients and this would allay the fear of losing a breast [107]. However, some women may not prefer or defer reconstruction because of personal preferences.
- There is no evidence available in literature that reconstruction makes detection of local recurrence more difficult. There is no basis for the view that patients should wait 1–2 years after mastectomy before being offered breast reconstruction.
- Breast reconstruction following mastectomy is currently a well-accepted procedure and is performed quite commonly by reconstructive surgeons throughout the world.

Mastectomy with breast reconstruction and partial Mastectomy with reconstruction is an option. The details of this aspect have been dealt in the chapter on "Breast cancer reconstruction & oncoplastic surgery".

14.9.19 Occult Breast Cancer Presenting with an Axillary Metastasis

- Axillary metastatic lymphadenopathy when no primary tumour is identified in the ipsilateral or contralateral breast on physical examination, mammography or on ultrasound, is referred to as occult breast cancer [108].
- The most likely source of metastatic lymphadenopathy in the axilla is the ipsilateral breast [109]. In 0.3–1.0% of all women with breast cancer, metastatic lymphadenopathy is the first presenting symptom [110]. Nowadays MRI of the breast is frequently applied when other diagnostic modalities fail to find a primary source in the breast.
- A systematic review by Bresser et al., in which 8 retrospective studies were included, found that breast MRI can detect an otherwise occult breast cancer. It could detect the tumour in more than two thirds of patients with a high sensitivity but lower specificity. Even the size and localization of the lesions found on MRI most often correlated closely with findings at pathology. The possibility of breast conserving surgery increased in one thirds of patients following MRI of the breast [111].
- As for routine investigation work up for all carcinomas of unknown primary, a staging by CT scans of abdomen, thorax and pelvic must be performed. This is done to exclude another primary site or presence of other metastatic sites [112].
- Treatment remains very controversial and must include a multidisciplinary approach. Axillary dissection with breast conservation and ipsilateral breast radiotherapy is a good therapeutic option. This can be recommended to improve local control in addition to good cosmetic results [113].

14.9.20 Role of Neoadjuvant Chemotherapy (NACT) in EBC

- The pivotal meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) provides high quality data on the role of NACT in EBC. The investigators showed that the survival was similar in patients treated with the same chemotherapy before or after surgery. They also found that there was a significantly higher frequency of local recurrence in patients receiving NACT compared with the adjuvant group. This difference in local recurrence was not accompanied by a decrease in survival [114].

NACT provides a means for de-escalation of surgery in patients suitable for resection at initial diagnosis. In this context, NACT could lead to conversion from mastectomy to breast-conserving therapies, reduce volume resection in breast conserving therapies

- It also enables minimally invasive axillary staging by sentinel biopsy with targeted axillary dissection in patients with clinically node-positive disease at baseline who convert to being node negative after NACT [115].

14.9.21 NCCN Guideline Version 2: 2019

These are unconventional cases where neoadjuvant chemotherapy is given to decrease the size of the tumour, for it to be suitable for breast conservation therapy.

1. In triple negative breast cancer and Her2 Neu + (30)
2. T tumor>2 cm,
3. Positive axilla.

14.9.22 Follow up

The patient is advised close follow up for life time. Details of Follow up and Rehabilitation have been described in Chap. 28 and should be referred for further details.

References

1. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1996. CA Cancer J Clin. 1996;46:5–27.
2. Seidman H, Mushinski MH, Gelb SK, Silverberg E. Probabilities of eventually developing or dying of cancer—United States, 1985. CA Cancer J Clin. 1985;35(1):36–56.

3. Tabar L, Vitak B, Chen TH, Yen AM, Cohen A, Tot T, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. Radiology. 2011;260(3):658–63.
4. Sofi NY, Jain M, Kapil U, et al. Epidemiological characteristics of breast cancer patients attending a tertiary health-care institute in the National Capital Territory of India. J Can Res Ther. 2019;15(5):1087–91.
5. Macia F, Porta M, Murta-Nascimento C, et al. Factors affecting 5- and 10-year survival of women with breast cancer: an analysis based on a public general hospital in Barcelona. Cancer Epidemiol. 2012;36(6):554–9.
6. Ganesh B, Talole SD, Dikshit R, et al. Estimation of survival rates of breast cancer patients—a hospital-based study from Mumbai. Asian Pac J Cancer Prev. 2008;9(1):53–7.
7. Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet. 2002;359(9310):909–19.
8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7–30.
9. Kerlikowske K, Walker R, Miglioretti DL, et al. Obesity, mammography use and accuracy, and advanced breast cancer risk. J Natl Cancer Inst. 100(23):1724–33.
10. Brekelmans CT, Seynaeve C, Bartels CC, et al. Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. J Clin Oncol. 2001;19(4):924–30.
11. Reeves GK, Beral V, Green J, et al. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol. 2006;7(11):910–8.
12. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the women's health initiative randomized trial. JAMA. 2003;289(24):3243–53.
13. Ernster VL, Barclay J, Kerlikowske K, et al. Mortality among women with ductal carcinoma in situ of the breast in the population-basedsurveillance, epidemiology and end results program. Arch Intern Med. 2000;160:953–8.
14. Erbas B, Provenzano E, Armes J, Gertig D. The natural history of ductal carcinoma in situ of the breast: a review. Breast Cancer Res Treat. 2006;97(2):135–44.
15. Delaney G, Ung O, Bilous M, Cahill S, Greenberg ML, Boyages J. Ductal carcinoma in situ. Part I: definition and diagnosis. Aust NZ J Surg. 1997;67:81–93.
16. Leonard GD, Swain SM. Ductal carcinoma in situ, complexities and challenges. J Natl Cancer Inst. 2004;96(12):906–20.
17. Holland R, Hendriks JHCL, Verbeek ALM, Mravunac M, Schuurmans Stekhoven JH. Extent, distribution, and mammographic/histological correlations of breast ductal carcinoma in situ. Lancet. 1990;335(8688):519–22.
18. Berg WA, Gutierrez L, NessAiver MS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology. 2004;233(3):830–49.
19. Rosen EL, Smith-Foley SA, DeMartini WB, Eby PR, Peacock S, Lehman CD. BI-RADS MRI enhancement characteristics of ductal carcinoma in situ. Breast J. 2007;13(6):545–50.
20. Kuhl CK, Strobel K, Bieling H, Leutner C, Schild HH, Schrading S. Supplemental breast MR imaging screening of women with average risk of breast cancer. Radiology. 2017;283:361–70.
21. Brennan ME, Turner RM, Ciatto S, et al. Ductal carcinoma in situ at core-needle biopsy: meta-analysis of underestimation and predictors of invasive breast cancer. Radiology. 2011;260(1):119–28.
22. Dimitrovska MJ, Mitreska N, Lazareska M, Jovanovska ES, Dodevski A, Stojkoski A. Hook wire localization procedure and early detection of breast cancer—our experience. Open Access Maced J Med Sci. 2015;3(2):273–7.
23. El H, Chehade H, Headon H, Wazir U, Abtar H, Kasem A, Mokbel K. Is sentinel lymph node biopsy indicated in patients with a diagnosis of ductal carcinoma in situ? A systematic literature review and meta-analysis. Am J Surg. 2017;213(1):171–80.

24. Broekhuizen LN, Wijsman JH, Peterse JL, Rutgers EJ. The incidence and significance of micrometastases in lymph nodes of patients with ductal carcinoma in situ and T1a carcinoma of the breast. Eur J Surg Oncol. 2006;32(5):502–6.
25. Kerlikowske K, Molinaro A, Cha I, Ljung BM, Ernster VL, Stewart K, Chew K, Moore DH 2nd, Waldman F. Characteristics associated with recurrence among women with ductal carcinoma in situ treated by lumpectomy. J Natl Cancer Inst. 2003;95(22):1692–702.
26. Kanbayashi C, Iwata H. Current approach and future perspective for ductal carcinoma in situ of the breast. Jpn J Clin Oncol. 2017;47(8):671–7.
27. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines; Breast Cancer. Version 1. 2017.
28. American Society of Breast Surgeons. The American Society of Breast Surgeons Position Statement on Breast Cancer Lumpectomy Margins; Revised February 22, 2015.
29. Mazouni C, Rouzier R, Balleyguier C, et al. Specimen radiography as predictor of resection margin status in non-palpable breast lesions. Clin Radiol. 2006;61:789–96.
30. Chagpar A, Yen T, Sahin A, Hunt KK, Whitman GJ, Ames FC, et al. Intraoperative margin assessment reduces re-excision rates in patients with ductal carcinoma in situ treated with breast-conserving surgery. Am J Surg. 2003;186:371–7.
31. Delaney G, Ung O, Bilous M, Cahill S, Boyages J. Ductal carcinoma in situ. Part II: treatment. Aust NZ J Surg. 1997;67:157–65.
32. McCormick B, Winter K, Hudis C, Kuerer HM, Rakovitch E, Smith BL, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma insitu comparing radiotherapy with observation. J Clin Oncol. 2015;33:709–15.
33. Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol. 2011;12:21–9.
34. Pilewskie M, Stempel M, Rosenfeld H, Eaton A, Van Zee KJ, Morrow M. Do LORIS trial eligibility criteria identify a ductal carcinoma in situ patient population at low risk of upgrade to invasive carcinoma? Ann Surg Oncol. 2016;23:3487–93.
35. Lagios MD, Westdahl PR, Margolin FR, Rose MR. Duct carcinoma in situ: relationship of extent of noninvasive disease to the frequency of occult invasion, multicentricity, lymph node metastases, and short-term treatment failures. Cancer. 1982;50:1309–14.
36. Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, et al. Breast cancer: major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67:290–303.
37. Kim M, Kim HJ, Chung YR, et al. Microinvasive carcinoma versus ductal carcinoma in situ: a comparison of clinicopathological features and clinical outcomes. J Breast Cancer. 2018;21(2):197–205.
38. Mukhtar RA, Wong JM, Esserman LJ. Preventing overdiagnosis and overtreatment: just the next step in the evolution of breast cancer care. J Natl Compr Canc Netw. 2015;13:737–43.
39. Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853—a study by the EORTC breast cancer cooperative group and EORTC radiotherapy group. J Clin Oncol. 2006;24:3381–7.
40. Fourquet A, Campana F, Zafrani B, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25-year follow-up. Int J Radiat Oncol Biol Phys. 1989;17:719–25.
41. Silverstein MJ. The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast. Am J Surg. 2003;186:337–43.
42. Solin LJ. A quantitative multigene RT-PCR assay for predicting recurrence risk after surgical excision alone without irradiation for ductal carcinoma in situ (DCIS): a prospective validation study of the DCIS score from ECOGE5194. In: 34th annual San Antonio breast cancer symposium. 2011.
43. McDivitt RW, Hutter RV, Foote FW Jr, Stewart FW. In situ lobular carcinoma. A prospective follow up study indicating cumulative patient risks. JAMA. 1967;201:82–6.

44. Haagensen CD, Lane N, Lattes R, Bodian C. Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. Cancer. 1978;42:737–69.
45. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC cancer staging manual: breast cancer. Ann Surg Oncol. 2018;25:1783–5.
46. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and bowel project P-1 study. J Natl Cancer Inst. 1998;90:1371–88.
47. Wen HY, Brogi E. Lobular carcinoma in situ. Surg Pathol Clin. 2018;11(1):123–45.
48. King TA, Pilewskie M, Muhsen S, Patil S, Mautner SK, Park A, et al. Lobular carcinoma in situ: a 29-year longitudinal experience evaluating clinicopathologic features and breast cancer risk. J Clin Oncol. 2015;33:3945–52.
49. Trebska-McGowan K, Terracina KP, Takabe K. Update on the surgical management of Paget's disease. Gland Surg. 2013;2(3):137–42.
50. Tan A, Ralston SH. Clinical presentation of Paget's disease: evaluation of a contemporary cohort and systematic review. Calcif Tissue Int. 2014;95(5):385–92.
51. Kothari AS, Beechey-Newman N, Hamed H, et al. Paget disease of the nipple: a multifocal manifestation of higher risk disease. Cancer. 2002;95:1–7.
52. Morrogh M, Morris EA, Liberman L, et al. MRI identifies otherwise occult disease in select patients with Paget disease of the nipple. J Am Coll Surg. 2008;206:316–21.
53. Bijker N, Rutgers EJ, Duchateau L, Peterse JL, Julien JP, Cataliotti L, et al. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer Study of 61 patients. Cancer. 2001;91:472–7.
54. Fourquet A, Campana F, Vielh P, Schlienger P, Jullien D, Vilcoq JR, et al. Paget's disease of the nipple without detectable breast tumor: conservative management with radiation therapy. Int J Radiat Oncol Biol Phys. 1987;13:1463–5.
55. Sardanelli F, Boetes C, Borisch B, et al. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer. 2010;46(8):1296–316.
56. Plana MN, Carreira C, Muriel A, et al. Magnetic resonance imaging in the preoperative assessment of patients with primary breast cancer: systematic review of diagnostic accuracy and meta-analysis. Eur Radiol. 2012;22(1):26–38.
57. Riegger C, Koeninger A, Hartung V, et al. Comparison of the diagnostic value of FDG-PET/CT and axillary ultrasound for the detection of lymph node metastases in breast cancer patients. Acta Radiol. 2012;53(10):1092–8.
58. Shoma A, Moutamed A, Ameen M, Abdelwahab A. Ultrasound for accurate measurement of invasive breast cancer tumor size. Breast J. 2006;12(3):252–6.
59. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer. 1989;63:181–7.
60. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a meta-analysis. Cancer. 2006;106:4–16.
61. Cancer Research Campaign Working Party. Cancer Research Campaign (King's/Cambridge) trial for early breast cancer: a detailed update at the tenth year. Lancet. 1980;2:55–60.
62. Giuliano AE, Kirgan DM, Guenther JM, et al. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg. 1994;220:391.
63. Krag DN, Weaver DL, Alex JC, et al. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol. 1993;2:335.
64. Ferrucci M, Franceschini G, Douek M. New techniques for sentinel node biopsy in breast cancer. Transl Cancer Res. 2018;7(Suppl 3):S405–17.
65. Lin NU, Thomssen C, Cardoso F, et al. International guidelines for management of metastatic breast cancer (MBC) from the European School of Oncology (ESO)-MBC task force: surveillance, staging, and evaluation of patients with early-stage and metastatic breast cancer. Breast. 2013;22:203–10.
66. Robertson IJ, Hand F, Kell MR. FDG-PET/CT in the staging of local/regional metastases in breast cancer. Breast. 2011;20(6):491–4.
67. Al-Mahmood S, Sapiezynski J, Garbuzenko OB, Minko T. Metastatic and triple-negative breast cancer: challenges and treatment options. Drug Deliv Transl Res. 2018;8(5):1483–507.

68. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(8):1194–220.
69. Atkins H, et al. A treatment of early breast cancer. A report after ten years of clinical trial. Br Med J. 1972;2:423–9.
70. Gentiline OD, et al. Less is more. Breast conservation might even better than mastectomy in early breast cancer patient. Breast. 2017;35:32–3.
71. Vicini FA, Aberlien TJ, Conolly JL, et al. The optional extent of resection of patients with stages I or II breast cancer treated with conservative surgery and radiotherapy. Am J Surg. 1991;214:200–4.
72. Fowble B, Rosser C, Hanlon A, Bland K, Copeland E. Conservative surgery and radiation for stages I and II breast cancer. In: Bland KI, Copeland EM, editors. The breast: comprehensive management of benign and malignant diseases. 2d ed. Philadelphia: W.B. Saunders; 1998. p. 1172–8.
73. Gage I, Schnitt SJ, Nixon AJ, Silver B, Recht A, Troyan SL, et al. Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. Cancer. 1996;78:1921–8.
74. Michael Dixon J, Soon PSM. Mastery of surgery: breast conserving surgery. Chapter 43. 5th ed; 2007. p. 502–17.
75. Krag DN, Anderson SJ, Julian TB, et al. Sentinellymph-node resection compared with conventional axillary-lymph-node dissection in clinically nodenegative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927–33.
76. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The ACOSOG Z0011 (Alliance) randomized clinical trial. JAMA. 2017;318(10):918–26.
77. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micro metastases (IBCSG 23- 01): a phase 3 randomised controlled trial. Lancet Oncol. 2013;14(4):297–305.
78. Feigelson BJ, Acosta JA, Feigelson HS, Findley A, Saunders EL. T1 breast carcinoma in women 70 years of age and older may not require axillary lymph node dissection. Am J Surg. 1999;172:487.
79. National comprehensive cancer network clinical practice guidelines in oncology: Breast Cancer (Version 2.2018).
80. Masel RE, Followfield L, Kissin M, et al. Randomized multi centric trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer the ALMA NAC trial. J Natl Cancer Inst. 2006;98:599–609.
81. Brar P, Jain S, Singh I. Complication of axillary lymph node dissection in treatment of early breast cancer. A comparison of MRM and BCS. Indian J Surg Oncol. 2011;2(2):126–32.
82. Joshi SC, Khan FA, Pant I, Shukla A. Role of radiotherapy in early breast cancer: an overview. Int J Health Sci (Qassim). 2007;1(2):259–64.
83. Pazos M, Schönecker S, Reitz D, Rogowski P, Niyazi M, Alongi F, Matuschek C, Braun M, HarbeckNBelka C, Corradini S. Recent developments in radiation oncology: an overview of individualised treatment strategies in breast cancer. Breast Care. 2018;13:285–91.
84. Lazovich D, White E, Thomas DB, et al. Under utilization of breastconserving surgery and radiation therapy among women stage I and II breast cancer. JAMA. 1991;266:3433–8.
85. Samet J, Hunt W, Farrow D. Determinants of receiving breast conserving surgery and the surveillance, epidemiology and end results programme 1983-1986. Cancer. 1994;73:2344–8.
86. Nattinger A, Gottleib M, VeumJ, et al. Geographic variation in the use of breast conserving treatment for breast cancer. N Engl J Med. 1992;326:1102–7.
87. Tarbox B, Rochwood J, Abernathy C. Are modified radical mastectomies done for T1 breast cancer because of surgeon's advice or patient's choice? Am J Surg. 1992;164:417–22.
88. Sandhu DS, Sandhu S, Karwasra RK, Marwah S. Profile of breast cancer patients at a tertiary care hospital in North India. Indian J Cancer. 2010;47(1):16–22.

89. Ewertz M, Jensen AB. Late effects of breast cancer treatment and potentials for rehabilitation. Acta Oncol. 2011;50(2):187–93.
90. Verunesi U, Cascinallin N, Mariani L. Twenty year follow up ofrandomized study comparing breast conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347:1227.
91. Early Breast Cancer Trialists Collaborative Group, Corke M, Collins R, Godwin J, Gray R, Peto R. Effects of radiotherapy and surgery in early breast cancer. An over view of the randomized trials. N Engl J Med. 1995;333:1444–55.
92. Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. JAMA Surg. 2014;149(3):267–74.
93. Hwang ES, Lichtensztajn DY, Gomez SL, Fowble B, Clarke CA. Survival after lumpectomy and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status. Cancer. 2013;119(7):1402–11.
94. Sun G, et al. Radiotherapy plays an important role in improving the survival outcome in patients with T1-2N1M0 breast cancer—a joint analysis of 4209 real-world cases from two institutions. Int J Radiat Oncol Biol Phys. 105(1):S194.
95. Denduluri N, Chavez-MacGregor M, Telli ML, et al. Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol. 2018;36(23):2433–43.
96. Van der Sangen MJ, van de Wiel FM, Poortmans PM, et al. Are breast conservation and mastectomy equally effective in the treatment of young women with early breast cancer? Longterm results of a population-based cohort of 1,451 patients aged less than or equal to 40 years. Breast Cancer Res Treat. 2011;127:207–15.
97. Mahmood U, Morris C, Neuner G, et al. Similar survival with breast conservation therapy or mastectomy in the management of young women with early-stage breast cancer. Int J Radiat Oncol Biol Phys. 2012;83:1387–93.
98. Curran D, Van Dongen JP, Aaronson NK, et al. Quality of life of early breast cancer patients treated with radical mastectomy or breast conserving procedures: results of EORTC trial 10801. The European Organization for Research and Treatment of Cancer (EORTC), breast cancer co-operative group (BCCG). Eur J Cancer. 1998;34:307–14.
99. Bhat V, Roshini AP, Ramesh R. Does quality of life among modified radical mastectomy and breast conservation surgery patients differ? A 5-year comparative study. Indian J Surg Oncol. 2019;10(4):643–8.
100. Early Breast Cancer Trialists' Collaborative Group, Clarke M, Collins R. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366(9503): 2087–106.
101. Scottish Intercollegiate Guidelines Network (SIGN). Management of breast cancer in women: a national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2005.
102. Arriagada R, Lê MG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave Roussy Breast Cancer Group. J Clin Oncol. 1996;14:1558–64.
103. McIntosh A, Freedman G, Eisenberg D, Anderson P. Recurrence rates and analysis of close or positive margins in patients treated without re-excision before radiation for breast cancer. Am J Clin Oncol. 2007;30(2):146–51.
104. Nair N, Shet T, Parmar V, et al. Breast cancer in a tertiary cancer center in India—an audit, with outcome analysis. Indian J Cancer. 2018;55:16–22.
105. Jeffrey G, Groot G, Boden C, et al. Review of factors influencing women's choice of mastectomy versus breast conserving therapy in earlystage breast cancer: a systematic review. Clin Breast Cancer. 18(4):e539–4.
106. Association of Breast Surgery at Baso 2009. Surgical guidelines for the management of breast cancer. Eur J Surg Oncol. 2009;35(Suppl 1):1–22.

107. Wilson AR, Marotti L, Bianch S, et al. The requirements of a specialized breast cancer centre. Eur J Cancer. 2013;49(17):3579–87.
108. Mazumdar A, Vasishta RK, Bose SM. A small axillary nodule—a therapeutic dilemma? Postgrad Med J. 2001;77(904):126–36.
109. Patel J, Nemoto T, Rosner D, et al. Axillary lymph node metastasis from an occult breast cancer. Cancer. 1981;47(12):2923–7.
110. Knapper WH. Management of occult breast cancer presenting as an axillary metastasis. Semin Surg Oncol. 1991;7(5):311–3.
111. de Bresser J, de Vos B, van der Ent F, Hulsewé K. Breast MRI in clinically and mammographically occult breast cancer presenting with an axillary metastasis: a systematic review. Eur J Surg Oncol. 2010;36(2):114–9.
112. Fizazi K, Greco FA, Pavlidis N, Pentheroudakis G. Cancers of unknown primary site: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011;22(Suppl 6):vi64–8.
113. Ellerbroek N, Holmes F, Singletary E, Evans H, Oswald M, McNeese M. Treatment of patients with isolated axillary nodal metastases from an occult primary carcinoma consistent with breast origin. Cancer. 1990;66(7):1461–7.
114. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19:27–39.
115. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol. 2013;14:609–18.

Breast Cancer Surgery Under Local Anaesthesia

15

Shashanka Mohan Bose

15.1 Introduction

Advent of general anaesthesia has brought in lot of changes in the management of surgical cases. Majority of patients of breast cancer, are very apprehensive, depressed and nervous at the time of surgery. A large percentage of patients get jittery and lose their coolness as soon as they hear about operation and in these patients general anaesthesia is a great boon.

General anaesthesia is considered to be patient friendly as the patient only feels the prick of a single needle and after that she is put to sleep. The premedication itself quietens the patient and then general anaesthesia takes over. The technology has progressed so much that as soon as the last stitch is put in, the patient comes out of anaesthesia. In view of these advantages, in the present era general anaesthesia is used even for small surgical operations, like lumpectomy, excision biopsy or in a few cases even for a fibroadenoma. But then nothing is 100% fool proof, complications do happen once in a while, and general anaesthesia is no exception.

15.2 Minor Procedures Under LA

Excision biopsy of the lump, where diagnosis of malignancy has not been firmly established, is usually done under local anaesthesia although a few patients will opt for general anaesthesia mostly because of fear of pain and few surgeons because of non-cooperation by the patient. In majority of patients of small breast lumps, local

Shashanka Mohan Bose, MS, FRCS(E), FRCS(G), FAMS, FACS, FICS, FACG (✉)
Former Senior Professor and Head, Department of Surgery, PGIMER, Chandigarh, India

Former Professor of Surgery, AIIMS, New Delhi, India
e-mail: drsmbose@gmail.com

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_15

anaesthesia with sedation is satisfactory for excision biopsy. This can be done as a day care procedure, with minimum cost to the patient and with minimum side effects of anaesthesia, particularly in patients of high risk because of co morbid problems. A large number of surgeons in our country undertake this routinely. I have myself done these in a large number of patients and have not yet come across any problem or complication.

15.3 Major Procedures Under LA

I have done MRM under local anaesthesia plus sedation in six patients, all these patients had been rejected by anaesthesia teams of high profile corporate hospitals, mostly because of their cardiac conditions. I shall like to describe my first operation of MRM under local anaesthesia in detail.

This was a patient of 65 years, had been admitted in a corporate hospital under the care of neurologists as a patient of Encephalitis, the aetiology of which could not be ascertained even after undertaking all the relevant investigations. She had remained drowsy for about two weeks. One of the attending residents had detected a small lump in her right breast and I was called for surgical consultation. The tumour, about 3 cm in diameter, hard and mobile, looked suspicious for malignancy. No lymph node was palpable in the axilla. FNAC revealed infiltrating duct carcinoma. Further investigations did not show metastasis anywhere else. Clinically she was classified as a case of Cancer Breast T2N0M0. The relations wanted surgery to be undertaken at the earliest. The anaesthetists of the corporate hospital declared that she was not suitable for general anaesthesia.

We discussed and decided to undertake lumpectomy under local anaesthesia.

15.4 Operative Technique

Patient was taken up for surgery, she was given Inj Diclofenac 50 mgs via NS infusion, and the anaesthetist started Oxygen through face mask. After preparation and draping of the part, 30 ml of 0.25% Inj Lignocaine with Adrenaline with one ampoule of Inj Hyalurinodase was infiltrated around the lump. Spinal needle 20 G was used for this.

The incision was made, for lumpectomy. I usually give a transverse elliptical incision that can be extended in a full-fledged incision required for MRM. Dissection was started and I found that I could carry out a classical MRM (Total mastectomy with axillary clearance). It took around 70 to 80 min. The patient tolerated it very satisfactorily, without much complaint. The usual protocol of MRM was followed, was given IV fluids for six hours, one dose of antibiotics at start, analgesia as and when required. She was made mobile after about 24 hours and started taking normal diet from next day.

Histopathology revealed Infiltrating Duct Carcinoma with no lymph node involvement. Patient recovered from her surgery, and was given adjuvant therapy in the post-operative phase.

She was advised CMF chemotherapy, starting three weeks after surgery. She was given six cycles of chemotherapy followed by Radiotherapy and also hormone therapy–Tab Letrozole 2.5 mg daily for 5 years. Her motor and sensory powers were restored, she could speak, she had loss of memory for a very long time, could not recognise anyone but that also gradually improved. One year later she could recall all her memories except that even today (nine years have passed) she does not remember anything about her illness and hospitalisation. The relations maintain that this is god's gift to her—for forgetting the bad days of her illness. She is back to normal health without any evidence of local or systemic recurrence.

Details of this case can be found in my book—"Winners of breast Cancer".

15.5 More Operations for Breast Cancer Under Local Anaesthesia

Encouraged by the successful management of the previously mentioned case, I performed five more cases of modified radical mastectomy during the last five years. Anaesthetists had refused to administer general anaesthesia because of the extreme high risks. Brief accounts of two more patients are given below:

A sophisticated 83-year-old lady doctor, former Chief Medical Officer of a University Polyclinic, had undergone segmental mastectomy with axillary clearance for right breast cancer in 1992, I was the surgeon. She had been given radiotherapy, followed by Tamoxifen, which she continued to take for almost 7 years. 23 years later, she developed a small nodule on the lateral side of the scar, core needle biopsy was positive for malignancy. She was having Ischemic Heart disease; her cardiac ejection fraction was very poor. PET-CT scan had not shown evidence of malignancy anywhere else. In December 2014 (22 years later), total mastectomy on the right side was undertaken under local anaesthesia and sedation. She was taken up as a day care patient, and she made an uneventful recovery. She received radiotherapy and subsequently was put on Tab Letrozole 2.5 mgs daily. Two years later in 2016, a lymph node was detected in contra lateral axilla (left side), it looked suspicious and FNAC revealed metastatic adenocarcinoma. PET-CT scan again did not reveal presence of any lesion elsewhere. Axillary clearance on the left side was carried out under local anaesthesia and sedation. Presently, six years following MRM under local anaesthesia, she is on Letrozole 2.5 mg daily. She comes regularly for follow-up and is disease free.

A 55-year-old woman from eastern India was brought to me for consultation. Her digital mammography and FNAC had confirmed the presence of breast cancer (T2N1M0) in her right breast.

I was informed that she had severe mitral valve incompetence and anaesthetists in her home town and nearby large hospitals were not willing to give her general anaesthesia.

She was taken to a very large corporate cancer hospital in Delhi, where she was advised to undergo open heart surgery first and then surgery for breast cancer. She

was given an estimate of Rs. 7 lakhs for her heart surgery only and they could not afford it.

Her son-in-law was working in Chandigarh in a multinational IT firm. Look at the coincidence. The director of his organisation, based in USA, was the son of the lady (breast tumour with encephalitis) who had been earlier operated by me under local anaesthesia. One day while discussing his work with his boss on Skype he told him about his mother-in-law's problem and his boss narrated his own mother's illness and advised him to show the patient to Dr. Bose of Chandigarh. That is how the patient was brought to me from the far off place. Repeat investigations confirmed the presence of cancer in the upper and outer quadrant of the breast. She was referred to anaesthesia department of the biggest and the most popular corporate hospital, anaesthetists opined that she was not suitable for general anaesthesia. I then suggested breast cancer surgery under local anaesthesia. It was accepted and on a scheduled date modified radical mastectomy was carried out under local anaesthesia, following the same protocol as described earlier. She withstood the procedure very well. Her ER, PgR were strongly positive. Her histo-pathological analysis was suggestive of early stage disease and she was prescribed Hormone therapy, which she is continuing. I saw her last in the second week of December 2018; she is disease free for the last forty six months.

I have undertaken two more MRM for cancer breast patients of 70 plus age during the last two years and both of them are doing good.

All the five patients of breast cancer operated under local anaesthesia had withstood the operation without excessive pain or stress. All had primary healing of the incision wounds, their requirements for post-operative analgesia duration was much less, and are without any loco regional disease. The expenditure incurred for surgery and hospitalisation is almost fifty percent of the conventional procedures and this is of great importance for a country like India. Total time taken for the full procedure is also the same (Fig. 15.1).

Very few cases are described in literature and none from this part of the world.

Carlson et al. had [1] treated four female patients with stage 4 disease by total mastectomy under local anaesthesia. However, these patients had advanced disease and did not undergo axillary dissection. Similarly, Oakley et al. [2] performed simple mastectomy with local anaesthesia in 36 high-risk patients.

Modified Radical Mastectomy under Local Anaesthesia has also been reported in high-risk male breast cancer [3]. However there are many patients undergoing breast oncological procedures under Thoracic Epidural Analgesia (TEA). In comparison with GA, TEA was associated with lesser incidence of complications of nausea/vomiting [4].

My experience of MRM under local anaesthesia has been very satisfactory and I shall like my surgical colleagues to try this procedure.

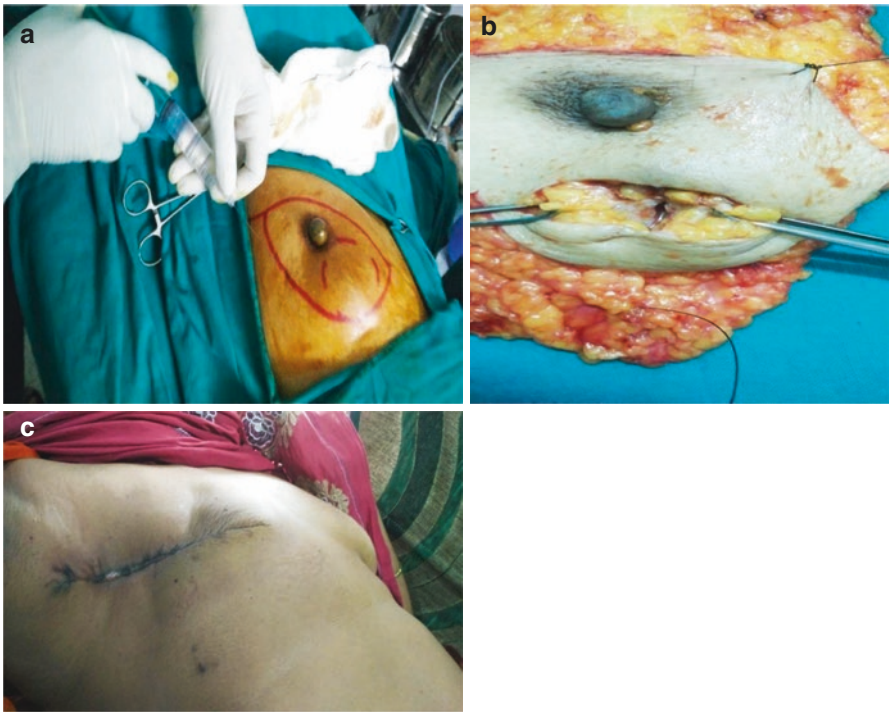


Fig. 15.1 (**a**) Incision marked with local infiltration. (**b**) Excised specimen. (**c**) Post op scar

References

1. Carlson GW. Total mastectomy under local anaesthesia: the tumescent technique. Breast J. 2005;11:100–2.
2. Oakley N, Dennison AR, Shorthause AJ. A prospective audit of simple mastectomy under local anaesthesia. Eur J Surg Oncol. 1996;22:134–6.
3. Çolak E, Alıcı Ö. Modified radical mastectomy under local anaesthesia in high-risk male breast cancer. J Breast Health. 2015 Apr 1;11(2):98–100.
4. Ravi PR, Jaiswal P. Thoracic epidural analgesia for breast oncological procedures: a better alternative to general anesthesia. J Mar Med Soc. 2017;19:91–5.

Management of Locally Advanced Breast Cancer

16

Dinesh Yadav, N. K. Shukla, and Mahesh C. Mishra

16.1 Introduction

In 2018, new cases of breast cancer, numbering 1, 62,468 and 87,090 deaths were reported in India [1].

Locally advanced breast cancer (LABC) (T 3, 4, N 0-3, M 0) is recognized to be a heterogeneous group with wide variability in the disease presentation at diagnosis, large primary tumour with/without involvement of skin, and/or chest wall and metastases to lymph nodes ranging from minimal to extensive regional nodal burden; but with absence of distant metastasis. Within the different groups of LABC, there are also prognostically distinguishable biologic subtypes with varied response to systemic therapy. Finally, LABC is associated with a significant risk for systemic disease. Treatment of LABC, therefore must include 2 major goals: control of loco regional disease and eradication of occult systemic metastases. Management of LABC, from the beginning, requires a multimodality approach and therapy.

Dinesh Yadav, MS, MCh
Associate Professor, Department of Surgical Oncology, Sriram Cancer Centre, Mahatma Gandhi Medical College & Hospital, Mahatma Gandhi University of Medical Sciences & Technology, Jaipur, Rajasthan, India

N. K. Shukla, MS
Professor and Head, Department of Surgical Oncology, Sriram Cancer Centre, Mahatma Gandhi Medical College & Hospital, Mahatma Gandhi University of Medical Sciences & Technology, Jaipur, Rajasthan, India

Mahesh C. Mishra, MS, FRCS, FAMS, DSc (Hon. Causa) (✉)
Emeritus Professor, JPN Trauma Centre, AIIMS, New Delhi, India

Former Director, AIIMS, New Delhi, India
e-mail: mcmishra@gmail.com

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_16

16.1.1 Incidence

According to the Union Health Ministry, India, breast cancer ranks as the number one cancer among Indian women with a rate of 25.8 per 100,000 and mortality of 12.7 per 100,000 women. According to estimates, approximately 17, 97,900 women in India might have breast cancer by 2020 [1]. Breast cancer, previously seen as a malady of the whites, affluent women of the developed world, but breast cancer is now seen everywhere; in most emerging economies breast cancer is a relatively new concern. It is projected that, in near future 70% of all breast cancer cases worldwide will be in developing countries. It is also estimated that half of all Indian women with disease go entirely without treatment.

LABC is a very common clinical scenario, especially in developing countries (30–60%), possibly due to various factors like lack of education and poor socio-economic status [2].

India continues to have a low survival rate for breast cancer, with only 66.1% women diagnosed with the disease between 2010 and 2014 surviving, a Lancet study found [3].

The USA and Australia have survival rates as high as 90%, "for women diagnosed during 2010–2014", five-year survival rates for breast cancer was 89.5% in Australia and 90.2% in the USA. As per Global surveillance of trends in cancer survival 2000–2014 (CONCORD-3) international differences remain very wide, with levels as low as 66.1% in India. CONCORD-3, is a global programme for worldwide surveillance of cancer survival, led by the London School of Hygiene and Tropical Medicine. The study analyzed individual records of 37.5 million patients diagnosed with cancer during the 15-year period from the year 2000 to 2014 [3].

Poor survival rates of breast cancer in India is due to low awareness for cancer and non-availability of suitable treatment. The cases come for treatment at third or fourth stages of the disease, where despite multimodality management, treatment failure remains high. The normal screening of breast cancer in Indian women is very low [4]. In a recent analysis of more than 1000 women with breast cancer in the Indian scenario, it turned out to be disease of younger woman who lack the characteristic reproductive and demographic risk factors [5].

The major reason is lack of awareness for early signs of breast cancer and screening methods, secondly non-availability of diagnostic modalities and expertise centers for comprehensive multimodality management of breast cancer. Affordability issues (unavailability of financial resources) make survival rates worse and this is also true for all cancers in India. Besides, all the factors mentioned above, in rural and semi-urban areas, there are other societal issues (women's health not a priority in society), myths (that breast cancer is contagious), quackery, trial of home remedies, homeopathy, and other non-effective ayurvedic, unani, siddha systems of practice lead to inordinate delays.

A large proportion of Indian patients present with LABC, is a subset of breast cancer characterized by the most advanced breast tumours in the absence of distant

metastasis. With this wide spectrum of presentation, management of LABC is a challenge for the surgeon. Treatment of LABC has evolved from single modality treatment, consisting of radical mutilating surgery or higher doses of radiotherapy in inoperable disease to multimodality management consisting of surgery, radiation therapy (RT), chemotherapy, with or without hormonal therapy. In this article we shall discuss the evolution of the management of LABC and attempt to provide guidelines for current practice.

Patients with stage III b disease are usually not considered upfront for surgical therapy; and combined loco regional therapy of surgery and radiotherapy (RT) leads to high rate of treatment failures (70% in 3 years) sooner than later, therefore, the need to identify LABC as a separate group of breast cancers arose. The treatment failures are linked to poorer 5-year survival (7–8%).

16.1.2 Definition

The definition of LABC is not globally uniform considering the varied spectrum of presentation. In 2002, the sixth edition of the American Joint Committee on Cancer staging manual categorized ipsilateral supraclavicular lymphadenopathy as distant metastasis in breast cancer; however, such spread was reclassified as regional lymphadenopathy (N3) in LABC in the seventh edition of the AJCC manual in 2010.

16.1.3 Clinical Presentation

There is a wide range of clinical presentations in LABC. The presentation can be as follows:

1. Lump in the breast: The size of the lump which is more than 5 cm is responsible for the distortion of the breast configuration when it is compared to the normal side breast. Although it is well known that massive enlargement of the breast may not always be malignant. Examination may reveal the lump fixity to the chest wall (Fig. 16.1).
2. Nipple areola complex may be retracted, lifted, deviated and often asymmetry is noted.
3. Skin changes in the form of extensive edema of skin over the breast, peau d'orange, satellite nodules and at times there is a fungating mass (Fig. 16.3a).
4. Patient may present with a lump in the axilla (Fig. 16.2b) or edema of the arm (Fig. 16.3b).
5. There may be lump present in the neck region suggestive of supraclavicular lymph node involvement. The patient may also have intercostal nodules and infraclavicular lump.

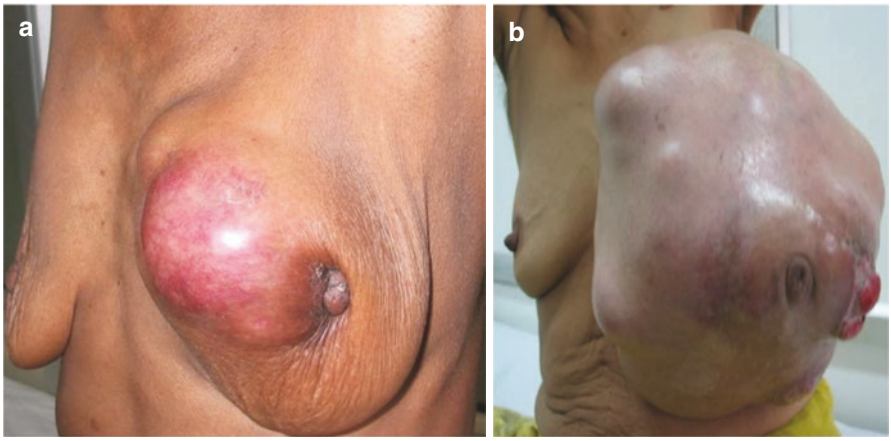


Fig. 16.1 (**a**) Large Primary Tumor (T4b) in Left Breast Involving Medial half of left breast. (**b**) Massive enlargement of left Breast in 40 years women mimicking cancer/CystosarcomaPhylloides but it turned out to be of non-malignant pathology

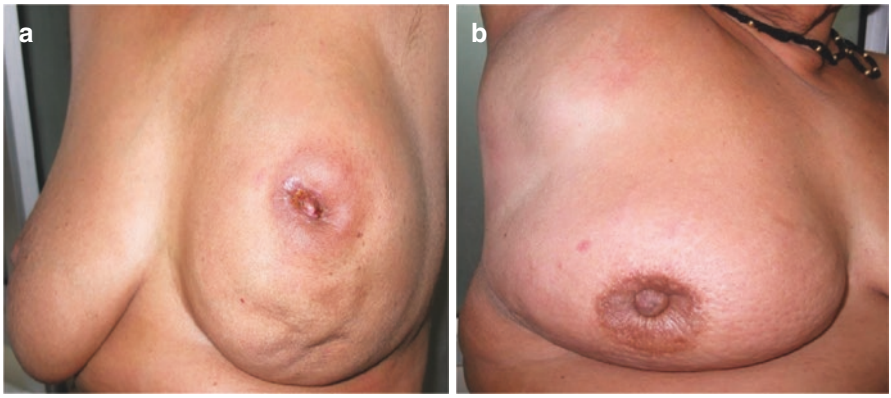


Fig. 16.2 (**a**) Showing Nipple areola complex retraction and destruction. (**b**) showing a large Axillary Lymphadenopathy

16.2 Investigations

Accurate staging of the extent of the primary cancer, regional node involvement, and any evidence of distant disease are important initial steps in the management of LABC

1. Bilateral diagnostic mammogram is essential. Mammography may be inappropriate for patients presenting with bleeding or fungating tumour.
2. Ultrasound (US) may provide additional information regarding breast malignancy and can also be used to evaluate the axilla. US-guided biopsy can be per-

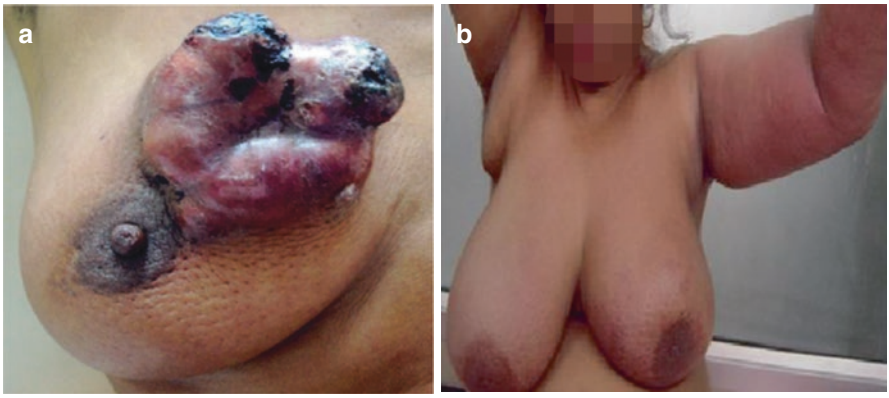


Fig. 16.3 (**a**) Large Fungating mass in with extensive Peud'Orange. (**b**) Swelling of the arm with left breast tumour

formed for enlarged lymph nodes or lymph nodes demonstrating architectural distortion.

3. Magnetic resonance imaging has been increasingly used and recognized as an important tool in evaluating the extent of disease for LABC. It is useful for detecting abnormal lymph nodes, involvement or proximity to chest wall, and contra lateral disease. It may aid in evaluating response to neoadjuvant chemotherapy and determining if a mastectomy is feasible without neoadjuvant therapy [6].
4. Due to the high probability of metastatic disease in patients with LABC, imaging studies including bone scan, and computed tomography (CT) scan of the upper abdomen and chest are useful.
5. For patients with LABC, positron emission tomography (PET) is increasingly used in lieu of CT scan of the chest, abdomen and bone scan [7].
6. The diagnosis of LABC can be confirmed with core needle biopsy or fine needle biopsy. These methods are usually preferable to open biopsy or an attempt at excision biopsy. A core biopsy has the advantage of obtaining sufficient material to characterize the tumour in terms of grade/proliferation status, hormone receptor status (ER, PgR) and HER-2 status. These patients may not be treated surgically and the diagnostic core biopsy may be the only tissue available for testing.

16.3 Metastatic Workup in LABC

- Node-positive breast cancer patients are at risk for metastatic disease. A routine metastatic workup might or might not be necessary for all patients with N2 or N3 diseases. The National Comprehensive Cancer Network guidelines recommend a metastatic workup for patients with T3N1 disease, yet no definitive recommendations are made for N2/N3 diseases.

- In patients with T3/T4 lesions having operable pathologic N2/N3 diseases, a metastatic workup should be considered.
- Chu et al. studied 256 patients with N2 and N3 disease to find out the presence of metastasis at the time of presentation or within one month of diagnosis. There were 158 patients with N2 disease and 98 with N3 disease. Overall, 16% were found to have distant metastasis or stage IV disease (N2 = 15%, N3 = 16%). Incidences of stage IV disease were T0/T1–0%; T2–6%; T3–22%; and T4–36%. Multivariate analysis demonstrated that only T stage and grade were independent predictors of overall survival. They concluded that a metastatic workup is only indicated for N2/N3 patient's withT3 orT4 primary lesions [8].
- Al-Husaini et al. studied 144 patients with LABC. After initial staging investigations, 15 patients (10.4%) were diagnosed as having overt metastatic disease. Confirmatory imaging was carried out on 19 patients, five (3.5%) for unexplained symptoms and 14 (9.7%) due to equivocal baseline imaging. These additional investigations isolated a further four subjects with metastatic disease, bringing the overall prevalence of overt metastases to 13.2% [9].

16.3.1 Investigations for Metastatic Work Up

The most common sites of breast cancer metastasis are bone, lung, and liver, in that order [10].

(a) Bone Metastasis: Serum alkaline phosphatase and calcium measurements if positive may be helpful and increase the suspicion of bony involvement. Imaging options include Bone scanning, CT, MRI, and PET. Bone scintigraphy is exquisitely sensitive to changes in bone metabolism. Plain radiography is of minimal value as a screening modality as it requires 30–50% loss of bone mineral for a metastasis to become visible [11].

The increased sensitivity and improved anatomic detail (including surrounding soft tissues) are factors favouring CT or MRI. MRI compared to scintigraphy has a higher rate of detection of skeletal metastases in the spine, pelvis, limbs, sternum, scapulae, and clavicles [12].

PET and, more recently, PET/CT have been used to evaluate the entire body for metastases, including bone. An emerging consensus is that PET and scintigraphy have a similar sensitivity for detection of metastases, whereas PET shows a definite increase in specificity [13]. There is significantly higher sensitivity with fluorodeoxyglucose (FDG) PET for osteolytic metastases.

Currently, PET and Bone scintigraphy are viewed as complementary imaging modalities for the detection of skeletal metastases.

(b) Lung metastases: Many centres still recommend a Chest X-ray at initial screening; CT is the modality of choice for chest evaluation. PET/CT offers advantages over CT alone in evaluating the mediastinum and as a whole-body survey [14].

(c) Liver metastasis: Can be there. For symptomatic patients and those with clinical evidence of liver involvement, CT and MRI are considered the imaging modalities of choice.
(d) Brain metastasis: It is common and if patients have symptoms, one might have to advise MRI of brain.

16.3.2 Management of LABC

Locally advanced breast cancers are difficult to resect because of their size, extension to chest wall or skin and involvement of regional lymph nodes. There is higher risk of local recurrence and distant metastases in these cases and therefore upfront surgery results in poor outcome.

With this wide spectrum of presentation, management of LABC poses a huge challenge. Management of LABC has evolved from single modality treatment, consisting of radical mutilating surgery or higher doses of radiation in inoperable disease to multimodality management consisting of neoadjuvant chemotherapy, surgery, radiation therapy, with or without hormonal therapy, and this concept has come in practice since early eighties.

Historical results of LABC with surgery and/or radiation alone were poor. A publication in 1951 by Haagensen and Stout [15] noted no benefit with radical mastectomy in patients with skin ulceration, skin edema (peaud' orange) or erythema, satellite skin nodules, or fixation to the chest wall musculature. Patients with operable disease were commonly treated by mastectomy with or without radiation therapy (RT), and inoperable disease was treated by RT alone [16].

The local control in these patients ranged from 50 to 70%. Most of the patients succumbed due to distant metastases. However, there were still 20–50% of patients with 5-year survivors when the patients were treated using definitive radiation with various systemic adjuvant chemotherapies [17]. Retrospective studies suggested that better loco-regional control (LRC) and disease-free survival (DFS) results were obtained with trimodality therapy than with any other combination of therapies [18]. In attempts to improve survival and LRC, a multidisciplinary approach to managing LABC is widely accepted. However, the optimal sequencing of therapies remains an important subject of continued research.

16.3.3 Surgery

Historically, surgery has been the oldest treatment for breast cancer. William Halsted at the end of nineteenth century described a surgical technique for removal of the entire breast and en bloc removal of all axillary lymphatics, the chest wall muscles and at times a part of chest wall as majority of cases used to be locally advanced in that era. With the success of Halstedian mastectomy, this surgery became a standard in the management of breast cancer. However the long-term results were poor with survival ranging from 13 to 20% at 5 years [19].

The pioneering work by McWhirter et al. in the mid twentieth century showed that less mutilating surgery produced results equal to that of radical mastectomy (RM) [20]. The switch from RM to less mutilating surgery came when it was largely recognized that treatment failure from breast cancer was largely due to systemic dissemination prior to surgery [21]. A number of prospective randomized trials comparing RM with modified radical mastectomy (MRM) confirmed the evidence [22, 23]. In twentieth Century NSABP-04 trial showed the path of modified radical mastectomy with similar survival rate to radical surgery.

16.3.4 Radiation Therapy

In 1940s Haagensen & Stout defined criterion of inoperability for carcinoma breast. These included (1) skin ulceration (2) tumour fixation (3) satellite nodules (4) palpable supraclavicular lymph nodes (5) parasternal tumour with internal mammary nodes and (6) clinical picture of positive inflammatory breast cancer [24]. These patients were then treated with RT in order to ablate the tumour. The success was limited.

Bruckman and colleagues (1979) used radical radiotherapy with doses up to 60Gy and showed improvement in survival in women with T3, T4 disease [25].

Higher doses of 80–90 Gy led to higher complications such as cardiac and pulmonary complications, oedema of breast and arm, brachial plexus injury, shoulder stiffness, fibrosis and necrosis of chest wall and the survival rate was dismal.

16.3.5 Combination of Surgery and Radiotherapy

- Adjuvant radiation is used after mastectomy, reduces the risk of loco regional recurrence (LR) by almost two-thirds. This benefit continues for 20 years after radiation therapy. Major trials and groups of trials have demonstrated a moderate but significant reduction in breast cancer mortality.
- The effect on overall survival (OS) has been more difficult to determine. Historically, traditional radiation therapy after mastectomy has increased cardiovascular-related mortality and this has offset the advantage gained in breast cancer–related mortality. Since then, improvements in technology and knowledge in radiation therapy have minimized exposure to the heart and lungs, decreasing risks of cardiovascular and pulmonary toxicities and making radiation therapy after surgery a standard of care.
- Kaae and Johnson (1970) showed significant improvement in local control with surgery followed by radiotherapy [26]. These findings were further confirmed by Danish breast cancer group and British Columbia group. Still there was no increase in overall survival.

16.3.6 Adjuvant Therapy

- A significant proportion of women with LABC experience relapse at distant sites with locoregional therapy (surgery plus radiotherapy) alone. In the absence of systemic therapy, the estimated risk of relapse 15 years after diagnosis in women with LN-positive and LN-negative disease is 70% and 40%, respectively [27].
- Combination of Surgery and Radiation can achieve reasonable local control but survival remains dismal in LABC. There were distant metastases in majority of patients within 24 months [28].
- These relapses have led to the understanding that undetected deposits of disease or micro metastases may remain locally or at distant sites after loco regional treatment. Eliminating micro metastases by giving postoperative or adjuvant chemotherapy or hormonal therapy, or both has proved highly effective in preventing both local and distant relapses and is essential in optimizing the chance for cure.
- Systemic adjuvant therapy (AD) can result in significant adverse effects; therefore, treatment decisions regarding adjuvant therapy are made by estimating an individual's risk of recurrence and the expected benefit of therapy.

16.4 Evolution of Neo-Adjuvant Chemotherapy (NACT) or Pre-Operative or Anterior or Primary Chemotherapy

- The overall survival of LABC still remained dismal after achieving reasonable local control with a combination of surgery and radiation therapy. Distant metastasis was a challenge and invariably there was treatment failure, as it reappeared in majority of patients within a short span.
- It became more and more clear that it is a systemic disease and addressing the systemic component of the disease was more important if good survival rates are to be achieved. This led to the idea of giving chemotherapy prior to surgery or any form of treatment which was termed as Neoadjuvant chemotherapy (NACT). The use of NACT in LABC was based on the rationale that these patients present with a relatively high burden of micrometastasis and therefore it makes sense to initiate systemic therapy upfront at the earliest.

16.4.1 Review of Trials

- The first prospective study for NACT in locally advanced, inoperable breast cancer is dated in 1973, by the European Institute of Oncology and the primary purpose was to downstage the primary tumor in order to achieve surgical resection [29].

- The early 80's and 90's trials that evaluated the role of NACT highlighted the potential of this treatment approach. These trials concluded survival improvement up to 25% at 10 years of follow up [30].
- Recently, many clinical trials have confirmed that NACT could effectively eliminate sub-clinical disseminated lesions of tumor, and consequently improve the long-term and disease-free survival rate of patients with LABC. As a result, neoadjuvant chemotherapy combined with local therapy became a new treatment pattern of LABC [31].
- NSABP B-18 trial findings were encouraging with breast tumour size reduced by 80% and clinical nodal response occurred in 89% of node positive patients. Further studies defined that chemotherapy combinations were more effective with increased rate of breast conservation, better cosmesis and improved survival. The overall survival (OS) and disease free survival (DFS) were 69% and 55% in the NACT group at 9 years.

16.4.2 Advantages of NACT

- Early initiation of systemic treatment
- Opportunity of drugs delivery through intact vasculature
- In vivo assessment of response to administered therapy
- Reduction of microscopic neoplastic dissemination during surgical procedures.
- Inhibition of post-surgical growth spurt
- Down staging of primary tumor and lymph node metastases to facilitate less radical loco regional therapy especially breast conservation surgery or MRM (Fig. 16.4).
- Prognostication based on degree of response.
- Patients with HER2-receptor positive or triple-negative disease may also benefit from early treatment of distant micro metastases due to increased metastatic potential of these disease types.
- Time for genetic counselling
- Can plan breast reconstruction in patients undergoing mastectomy.
- It may allow an opportunity to do SLNB if axilla is cleared by systemic therapy
- Makes an opportunity for less radiotherapy to axilla or breast.

16.4.3 Disadvantages of NACT

- There may be inaccurate pathological staging as size and number of involved nodes cannot be accurately assessed following NACT
- Much greater tumour burden to treat
- Response is not certain and those patients in whom neoadjuvant treatment doesn't bring desired results, there will be a delay in starting curative local therapy;
- Suspicion that it could promote drug resistance
- Risks for surgical complications may also increase [32].

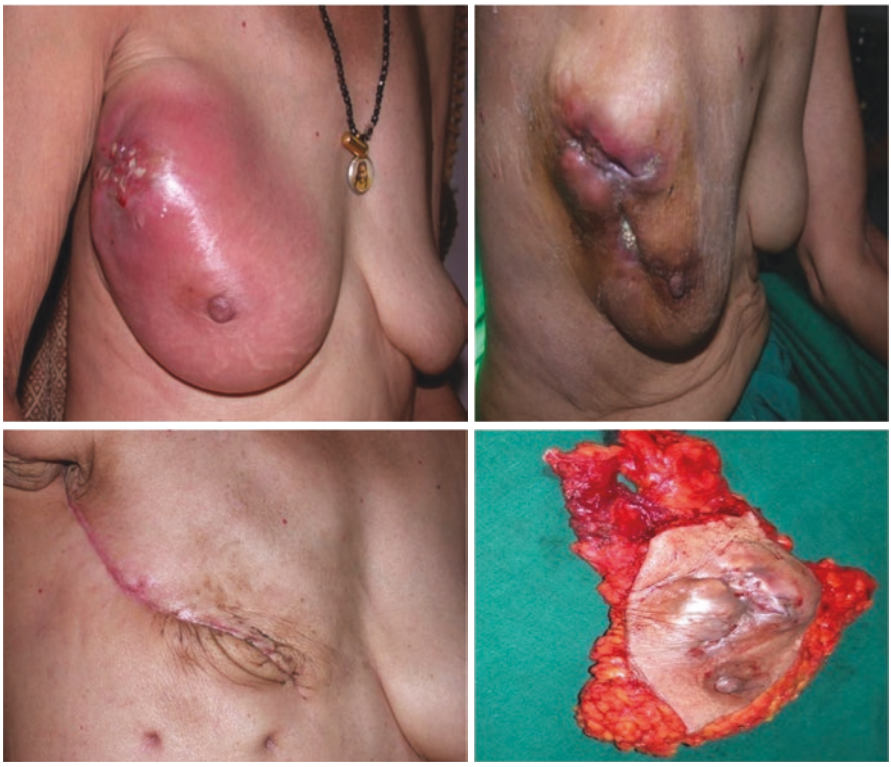


Fig. 16.4 A patient with LABC responded well to NACT and later on underwent MRM (Case of SMB)

16.4.4 Neoadjuvant vs. Adjuvant Chemotherapy

- Despite the potential advantages, NACT has not demonstrated improved survival over adjuvant chemotherapy in randomized trials [27, 33].
- NSABP B-18 in which 1523 patients with primary operable breast cancer were randomized to preoperative doxorubicin and cyclophosphamide (AC) therapy vs. postoperative AC therapy, there was no significant difference in the disease free and overall survival in either group. However the frequency of BCT was greater in the NACT arm (67% for NACT Vs 60% post-operative chemotherapy, $P = 0.002$). Results from B-18 showed no statistically significant differences in DFS and OS between the two groups. However, there were trends in favour of preoperative chemotherapy for DFS and OS in women less than 50 years old (hazard ratio [HR] = 0.85, $P = 0.09$ for DFS; HR = 0.81, $P = 0.06$ for OS). DFS conditional on being event free for 5 years also demonstrated a strong trend in favour of the preoperative group (HR = 0.81, $P = 0.053$).

- In B-27, 784 patients were assigned to receive preoperative AC followed by surgery, 783 patients were assigned to AC followed by Taxanes (T) and surgery, and 777 patients were assigned to AC followed by surgery and then Taxanes. It also demonstrated that the addition of T to AC did not significantly impact DFS or OS. Preoperative T added to AC significantly increased the proportion of patients having pathologic complete responses (pCRs) compared with preoperative AC alone (26% *v* 13%, respectively; $P < 0.0001$). In both studies, patients who achieved a pCR continue to have significantly superior DFS and OS outcomes compared with patients who did not achieve pCR.
- Patients who achieve a pathologic complete response (pCR) to NACT have improved survival compared to patients who do not achieve pCR [34].

16.4.5 Current Approach to Management of LABC: III A and III B

It is important to stage the disease properly. About 2 decades back LABC was divided into operable and inoperable groups. Patients with III A stage was included in operable group while Stage III B was considered as inoperable, this concept is now debatable. Present day, almost all institutions and individual oncologist give NACT or systemic therapy first to all patients of Stage III disease irrespective of it being III A or III B [35].

16.4.6 Pre-Therapy Assessment

- A trucut biopsy is mandatory to know the complete histopathology and hormone receptors status (ER, PgR, HER2) before the initiation of NACT.
- Before starting NACT, size of the tumor needs to be marked to assess response to chemotherapy. Ultrasound/Mammographic guided implantation of metallic clips or coils are used for marking of the tumor; and is considered to be the gold standard.
- Some surgeons would mark the periphery of the tumor also prior to start of NACT. It may be helpful in determining the response to NACT, in case BCS is being contemplated.
- Some surgeons mark the periphery of the tumour by a skin marker and measure the dimensions in two axis by a vernier calliper (Fig. 16.5). The procedure should be done in lying down position and preferably by the same observer so that uniformity is maintained. The measurements should be done a day before chemotherapy and it is better to take photographs.

  This is a practical approach and is recommended for centres who may not have facilities for implantation of clips or coils.

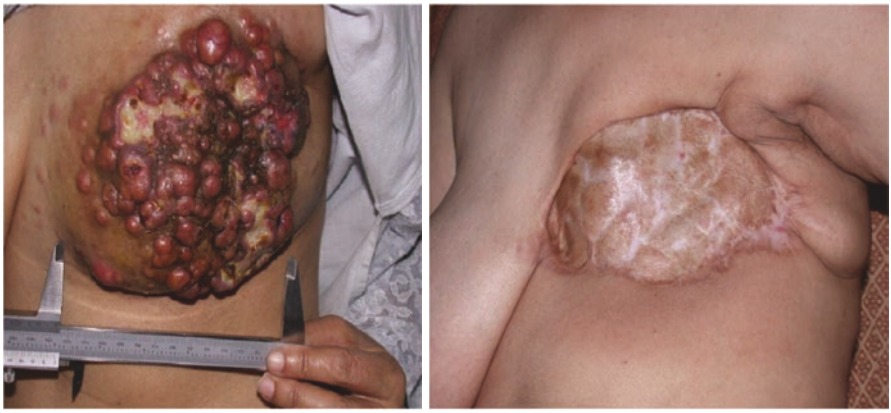


Fig. 16.5 LABC with fungating mass for whom MRM with skin grafting done. This patient had agenesis of a lung, hence was not taken for surgery for years. (Case of SMB)

16.4.7 Evaluation of Chemotherapy Response

- It is done using physical examination, mammography, ultrasound or MRI of breast. Accuracy of MRI in predicting the extent of disease following NACT is in the range of 90%.
- MRI can define additional residual disease and differentiates between chemotherapy induced fibrosis from residual disease, thereby may influence the selection of patient for BCS.
- Recently assessment of response to NACT has been found to be better using sequential magnetic resonance spectroscopic imaging (MRSI).
- It can also be done by 18F-FDG PET/CT.

Several quantitative and categorical methods have been developed to characterize pathologic response to NACT, including residual cancer burden index (RCBI) [36], the Miller-Payne score [37] Or Recist Criteria of Assessment of Pathological Response to Neoadjuvant Chemotherapy [38].

In general, the best single test for evaluating the status of measurable tumour is ultrasonography (preferably done by the same radiologist). The mass often appears larger on physical examination than on ultrasonography, which can more effectively discriminate hypo echoic masses from surrounding stroma or hematoma.

Thus, the purpose of regular size assessment is as follows:

- To exclude continuation of therapy in a patient with a progressive tumour (seen in <5% with the initial treatment)
- To suggest when maximal response of grossly evident disease has been achieved (this may be the optimal time to proceed for surgical resection).

The Response to chemotherapy according to the Response Evaluation Criteria in Solid Tumours published in February 2000 by European Organization for Research and Treatment of Cancer used to evaluate the tumour response and it was documented as follows:

- **Clinical Complete Response** (CCR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
- **Clinical Partial Response (CPR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- **Progressive Disease (CPD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for Partial Response (PR) nor sufficient increase to qualify for Progressive Disease (PD), taking as reference the smallest sum diameters while on study.

16.4.8 Pathological Response

The surgically resected specimen is analysed based on exhaustive microscopic examination of multiple sections from the breast and axillary lymph nodes. Three types of response are noted.

1. **Pathological Complete response (PCR)** if no residual or in situ tumor could be detected in breast and axillary lymph node
2. **Pathological partial response (PPR):** Invasive tumor of maximal diameter less than to that found mammographically and or clinically, tumour cell foci amid fat necrosis and fibrosis with inflammatory cell infiltration and tumour cell vacuolization are all considered as radiation- or chemotherapy- induced microscopic changes of the tumour and breast tissue.
3. **Pathological "No Change" or Progressive Disease (PD)** is considered when clinical response is of the above types together with the presence of infiltrative tumour without evidence of necrosis in microscopy.

Several trials assessing NACT in predominantly operable patients have shown that the amount of residual disease in breast and axilla is inversely related to survival and that pathologic complete response (PCR) is associated with a significantly better prognosis [27, 39].

- Pathological complete response (PCR) is a surrogate marker for evaluating response to NACT and a prognostic marker for survival in many studies, but PCR is not achieved in all patients.

- It would be useful to identify predictive markers to distinguish subgroups of patients with a high or a low probability of response to therapy so that an individualised treatment plan can be implemented. The definition of PCR varies in the literature- PCR can be defined as the absence of any residual invasive cancer of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of NACT; this is adopted by many studies including the NSABP B-27 trial.
- Although patients with Her2-positive or triple-negative breast cancer achieve the highest rates of PCR (31% and 27% respectively), relapse rates in the absence of PCR remain high. In contrast, patients with estrogen receptor positive disease have a better overall prognosis regardless of PCR [40].

16.4.9 Neo-Adjuvant Chemotherapy (NACT)

The choice of the optimal chemotherapy regimen and the duration of treatment have been extensively assessed in induction systemic chemotherapy but no consensus has been developed so far.

The regimen used was CMF (cyclophosphamide, methotrexate and 5-fluorouracil), followed by anthracyclines based regimens like CAF (cyclophosphamide, doxorubicin and 5-fluorouracil). A study done by P Gupta et al. suggested that in LABC a greater proportion of patients can be rendered disease free after neoadjuvant CAF and radiotherapy compared to neoadjuvant CMF and radiotherapy [41].

Then came the taxanes and many combinations of anthracyclines and taxanes have been tried to get a maximum pCR. At present preferred regimen for HER2 negative patients is dose dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks. For LABC patients with HER2 positive status, chemotherapy with targeted agents (trastuzumab/pertuzumab) is used as preoperative/neoadjuvant chemotherapy.

The details of NACT drugs and dosage and various regimens are described in the chapter on Role of Chemotherapy in Breast Cancer.

16.4.10 Loco-Regional Therapy Following NACT

16.4.10.1 Sequencing of Further Treatment

Currently the sequencing of different modalities and their selection is an area of major controversy. This has been a matter of debate and many sequences have been tried following NACT.

Best sequence is supposed to be to complete whole of NACT followed by surgery and RT although many would prefer to administer part of NACT followed by surgery, deliver rest of Chemotherapy followed by RT.

Surgery permits to assess pathological response to NACT, leads to rapid reintroduction of chemotherapy and lower doses of radiotherapy is required for local control. In patients with partial or complete response on imaging, surgery followed by

radiotherapy is standard of care. Subsets of patients having progressive disease on NACT are not suitable candidates for surgery. In these patients change of chemotherapy combination or definitive radiotherapy is preferred treatment modality.

16.4.11 Surgical Approach in LABC

- Surgical options post-NACT include Modified Radical Mastectomy (MRM) or Breast Conservation Surgery (BCS). Approximately 20–23% of patients are candidates for conservative surgery, in view of no difference in survival between MRM and BCS [42].
- For most patients with LABC, mastectomy should be considered the standard of care. BCS can be considered on a case-by-case basis when the surgeon deems that the disease can be fully resected and the patient expresses a strong preference for breast preservation.
- The NCCN recommends that tumours initially staged III a/b/c (except T3N1) with good response be treated with mastectomy or be considered for BCS (plus ALND and RT).
- If the tumour response is good enough for BCS then the extent of tissue to be excised at BCS is the post NACT margins of the tumour and not the pre NACT margins.

BCS has been described in detail in the chapter on management of early breast cancer.

In this Chapter we shall describe MRM in detail.

16.4.12 Technique of MRM (Fig. 16.6)

- Supine position with a thin sandbag under the ipsilateral scapula to facilitate ALND is the preferred choice and if some flap is considered then it may change accordingly. Ipsilateral upper limb should be draped separately in order to keep it free which is helpful during ALND to relax and retract the pectoralis major for dissection of level-III lymph nodes.
- Many variants of the incision are used and it also depends upon the location of the tumour. Most common incision is the transverse elliptical incision encircling the tumour and also incorporating the nipple areola complex along with a skin margin of at least 2 cm (some prefer 4 cm) from the palpable tumour. The incision should extend from lateral sternal edge to the anterior axillary line or the anterior border of latissimus dorsi muscle. It is recommended not to extend the incision beyond the lateral sternal edge or anterior axillary line in order to prevent inadvertent irradiation of heart, lungs and to axilla during adjuvant radiotherapy as the operative scar is included in the field of radiation.
- Breast dissection is started with creating upper and lower flaps. Superior flap is raised first, but it depends on the operator's choice. It is raised up to the subclavius muscle superiorly. The plane is between the subcutaneous fat (smaller) and

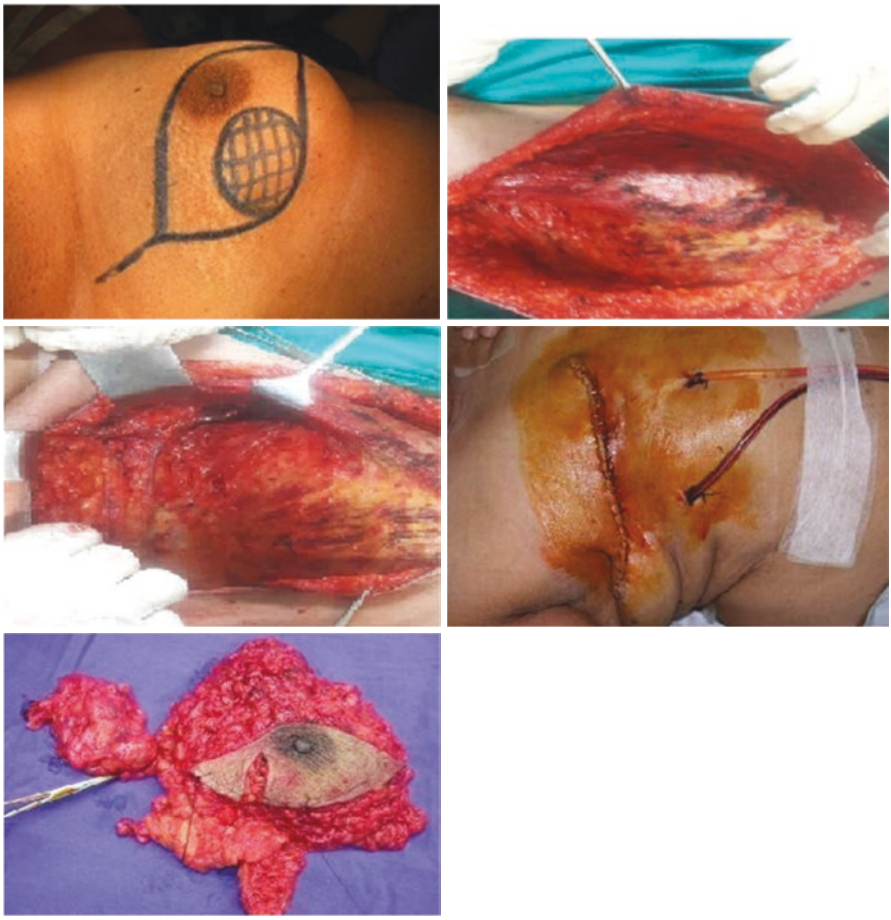


Fig. 16.6 MRM done in a patient with excised specimen (Case of SMB)

breast fat (larger). The lower flap is created 2–3 cm inferior to the presumed infra mammary fold crease. The fibres of abdominal external oblique and serratus anterior muscles are reached in dissection bed. Thickness of flap is important, (about 7–8 mm thick), it should neither be too thin nor thick.

- The breast is then lifted from the pectoralis major (PM) muscle along with the pectoralis fascia, starting from the medial end and gradually moving laterally. One may encounter few medial and some deep perforators which are ligated or cauterized. The fascia over the lateral border of PM is dissected in an upward direction to expose the pectoralis minor muscle. Laterally the axillary vein is identified and the areolar tissue lying between it and the anterior edge of the latissimus dorsi is cleared along with lymph nodes if any (Level (I)).
- The pectoralis minor is dissected further up to the coracoid process. This manoeuvre also exposes the interpectoral space (Rotter's nodes) that is also included in

the level-II group). The medial and lateral pectoral nerves are preserved to prevent atrophy of pectoralis major and minor muscles and the pectorals minor muscle is retracted upwards to facilitate the level-II and III dissection.

- Presently the pectoralis minor muscle is routinely preserved along with pectoralis major. Patey's MRM that involved cutting of the pectoralis minor muscle to facilitate level-III axillary dissection is no longer routinely practiced.
- Axillary dissection up to level-II is adequate in patients with node negative axillae as incidence of involvement of level-III nodes in the absence of level-I disease is less than 2%. If required one may perform level III dissection especially if there are involved nodes in Level II or burden of lymph nodes is high. The limit of level-III dissection is considered to be "Halstead's ligament" or the "Costoclavicular ligament". Axillary vein should not be dissected all around denuding its sheath completely as this may be associated with a higher incidence of axillary vein thrombosis and post- operative lymphedema. Similarly, dissection above the axillary vein should be avoided.
- As the dissection proceeds caudally the Intercosto-brachial nerves are encountered and one must preserve them unless they are involved by the tumour or the lymph node burden is heavy. Their removal will lead to hypoesthesia on the medial aspect of the upper arm. Nerve to serratus anterior lies along the chest wall and needs to be preserved. Tracing the tendon of latissimus dorsi (LD) up to the point where it crosses the axillary vein is also a landmark to find this nerve.
- The thoracodorsal pedicle is very important and it should be preserved particularly if Lattisimus dorsi (LD) flap has to be used for immediate breast reconstruction.
- Closure of the incision with two suction drain(s) in situ, one each for the axilla and flaps; dressing applied.
- The specimen should be oriented and marked with sutures for the pathologist to know its orientation.

16.5 Complications of Modified Radical Mastectomy

- Wound infection: Rates of postoperative infections in breast and axillary incisions have ranged from less than 1% of cases to nearly 20%. A meta-analysis by Platt and colleagues [22] analyzed data from 2587 surgical breast procedures and found an overall wound infection rate of 3.8% [43].
- Seroma formation: About 50% of patients would develop seroma formation. Seroma formation under the skin flaps of axillary or mastectomy wounds impairs the healing process; therefore drains are usually left in place to evacuate postoperative fluid collections. After 1–3 weeks, the skin flaps heal and adhere to the chest wall, as evidenced by diminished drain output.

  Seroma collections that develop after drain removal can be managed by percutaneous aspiration (Fig. 16.7) These procedures can be repeated as frequently as necessary to ensure that the skin flaps become densely adherent to the chest

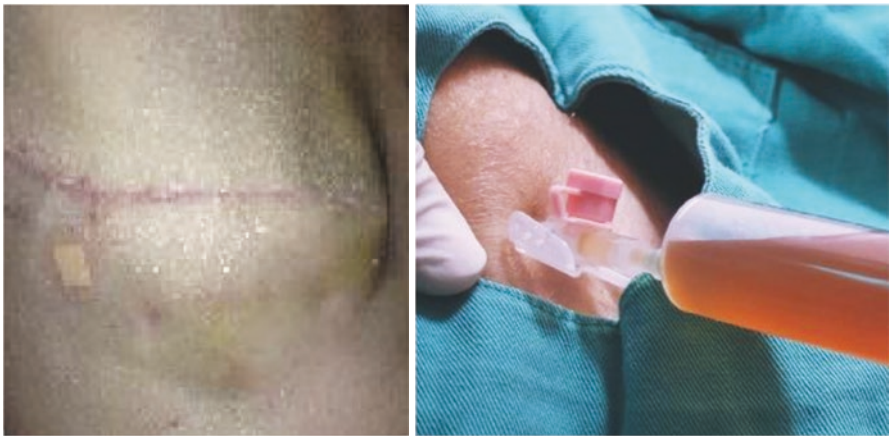


Fig. 16.7 Seroma and aspiration of the same

wall. Seroma aspiration is necessary in 10% to 80% of ALND and mastectomy cases, according to reported series and as reviewed in detail by Pogson and colleagues [44].

Several investigators have studied strategies that might minimize seroma formation to decrease the time that drainage catheters are needed or to obviate their need altogether. Talbot and Magarey subjected 90 consecutive patients undergoing ALND to (1) conventional, prolonged closed-suction drainage; (2) 2-day short-term drainage; or (3) no drainage. There were no differences in the rates of infectious wound complications in the three groups, and at a minimum follow-up of 1 year there were no differences in lymphedema risk [45].

- The number of drains used and the use of low- versus high-vacuum suction do not seem to affect the results achieved with drainage catheters.
- Shoulder immobilization with slings or special wraps to decrease seroma formation has been proposed, but this approach carries the risk of possible long-term range-of-motion limitations and even may increase the risk of lymphedema [46].
- Use of electrocautery is a well-recognized risk factor for increased seroma formation. Two prospective clinical trials have randomly assigned patients who undergo surgery with electrocautery or with scalpel only and have confirmed the lower incidence of seroma formation with the latter technique [47].
- Classe et al. [48] reported successful use of axillary padding in lieu of catheter drains in 207 patients who had breast cancer undergoing ALND and found seroma formation in 22.2%. In contrast, the Memorial Sloan Kettering Cancer Centre conducted a clinical trial that randomly assigned 135 patients undergoing ALND to receive a compression dressing for 4 days or standard wound coverage (all patients had conventional catheter drainage as well). This study found no benefit from compression dressings [49].

- Chemicals like application of tetracycline as a sclerosing agent have been found ineffective. Bovine thrombin similarly has been unsuccessful in this regard. Use of fibrin glues, patches, and/or sealants have seemed promising, but clinical studies in humans have yielded inconsistent results [50].
- Hematoma: Widespread use of electrocautery has dramatically reduced the incidence of hematoma formation in breast surgery, but this complication continues to occur in 2–10% of cases.
- Low-volume haematoma present as extensive ecchymosis and can be managed conservatively. Large hematomas can be quite painful and should be evacuated surgically.
- Chronic pain: A minority of breast cancer patients experience chronic incisional pain that can be quite debilitating and refractory to standard analgesics. The incidence of this chronic pain syndrome has been reported to afflict 20–30% of patients who are specifically queried.
- Injury and thrombosis of axillary vein can also occur. Although we have not witnessed this complication over more than 4 decades while dealing with breast cancer.
- Flap necrosis: Another commonly occurring complication of breast surgery is necrosis of the skin flaps or skin margins. Skin flap necrosis can occur if the skin margins are approximated under tension. Bland and colleagues observed an incidence of 21% for minor and major necrosis of mastectomy skin flaps with associated wound infection.
- Lymphoedema: This complication has generated the most concern after ALND, (Axillary Lymph Node Dissection) because it is a lifelong risk following the procedure and, when it occurs, is quite refractory to treatment. Lymphedema has been reported to develop in 13–27% of patients who have breast cancer [51].
- One of the most feared long-term sequelae of chronic lymphedema is the development of upper extremity angiosarcoma. This condition is also known as "Stewart-Treves syndrome" [52] Lymphoedema has been described in detail in Chap. 25.
- Shoulder dysfunction is another troublesome complication. For prevention of shoulder dysfunction we aggressively encourage patient to move the shoulder (both abduction and adduction including raising both the arms above the shoulder level so that upper arms touch the ears. Patients are encouraged to lift both upper limbs from Postoperative day 1 so that patient knows what needs to be achieved by comparison in normal Vs Operated side.
- Miscellaneous

1. Injury to Nerve to serratus anterior will lead to winging of scapulae
2. Damage to nerve to Latissimus Dorsi will lead to weakening of the internal rotation and abduction of the shoulder.
3. Pectoral muscle atrophy if medial and lateral pectoral nerves are injured.

16.6 Management of Axilla Following NACT

Patients with LABC with clinically positive nodes should undergo a FNAC of palpable lymph node before initiating chemotherapy. Pre-treatment SLNB provides accurate axillary staging, and avoids ALND.

Node-positive patients are benefitted from nodal irradiation. Those with clinically negative nodes may undergo sentinel lymph node biopsy before they start treatment, or else sentinel node determination may be delayed until after treatment is completed.

Theoretically, it should be preferable to perform sentinel node sampling up front, because chemotherapy might eradicate pre-existent disease in the sentinel lymph node and result in a false-negative result or altered lymphatic drainage in large tumours might affect accuracy of the procedure. However, data from the NSABP B-27 trial suggest that the false-negative rate for sentinel lymph node biopsies performed after neoadjuvant chemotherapy is about 11%, comparable to the false-negative rate for patients undergoing initial resection.

Two meta-analyses, one by Xing et al., included 21 studies with a total of 1273 patients and demonstrated that with the use of a single radioactive tracer, SN detection rate can reach 90% [53] and the second performed by Kelly et al. [54] included 20 clinical trials with a total of 1799 BC patients for which neoadjuvant treatment was indicated and their results confirmed a 90% (63–100%) detection rate after neoadjuvant treatment. Hence, SLNB can also be performed after NACT and the patients with positive SN after neoadjuvant treatment should undergo axillary dissection.

Marking abnormal axillary lymph nodes at the time of needle biopsy with either a clip or by tattooing to allow for localization and excision of the known metastatic node following NAC has been suggested as a strategy to reduce the false negative rate.

From a patient and surgeon perspective, the safe avoidance of ALND and the associated lymphedema risk is desirable. With current axillary management strategies for clinically node-negative patients, there is a question as to which approach, initial surgery or NAC, minimizes the likelihood of ALND. In patients undergoing primary breast-conserving surgery, ALND is necessary only for three or more nodal metastases while in patients receiving NAC, the presence of any nodal disease post treatment is an indication for ALND.

16.7 Role of Toilet Mastectomy

Toilet mastectomy is not an accepted terminology and it is loosely applied to the procedure done for palliative purposes to take care of in bleeding, persistent ooze, fungating mass with secondary infection. It should only be done if the patient is not suitable for NACT and if it can improve quality of life (QOL).

Even though the surgical procedure is palliative, it is important to reduce the occurrence of local recurrence developing in the operated area. The tumour should be removed with healthy margins and three dimensionally i.e., at the base as well. At times in order to remove the tumour completely, there is a large defect created (not permitting approximation of the skin margins) and one might require a split skin graft or may be a flap to cover it.

16.8 Radiation Therapy in LABC

- In the past, operable LABC was primarily treated with modified radical mastectomy followed by chemotherapy and postmastectomy radiation therapy (PMRT).
- Treatment options have evolved and now increasingly include the use of NAC followed by surgery (mastectomy or breast conserving surgery in selected cases), with nodal assessment (axillary dissection with ongoing investigation of sentinel node biopsy) and adjuvant radiation to the chest wall/breast and regional lymphatics.
- In combination with chemotherapy and surgery it has shown to reduce loco-regional recurrence and improve survival rates.
- Radiation plays an important and critical role by offering the option of breast conservation treatment for women with locally advanced disease and having a favourable response to neoadjuvant chemotherapy (Fig. 16.8)
- The EBCTG meta-analyses found that postmastectomy RT significantly reduced the 5-year and 10-year recurrence risk in patients with positive nodes. In the same meta-analyses, postmastectomy RT significantly improved 20-year breast cancer mortality (including all subgroups) [55].
- Huang et al. compared 542 patients who received NAC, surgery, and adjuvant RT with 134 patients who did not receive RT. The RT cohort had more advanced disease (73% pre-treatment stage III and 10% stage IV) than those who did not (46% stage III and 4% stage IV). LRR were nonetheless significantly lower for RT patients (11% versus 22%; $p = 0.0001$) [56].

Details of Radiotherapy are given in the Chap. 19.

16.9 Neoadjuvant Radiotherapy

There are two main reasons for this therapy.

1. The rationale for adding Neoadjuvant RT (NART) to NACT before surgery is the expectation to have a combined synergistic lethal effects on tumour cells. It may improve tumour shrinkage and increase the rate of pathologically complete responses (PCR).

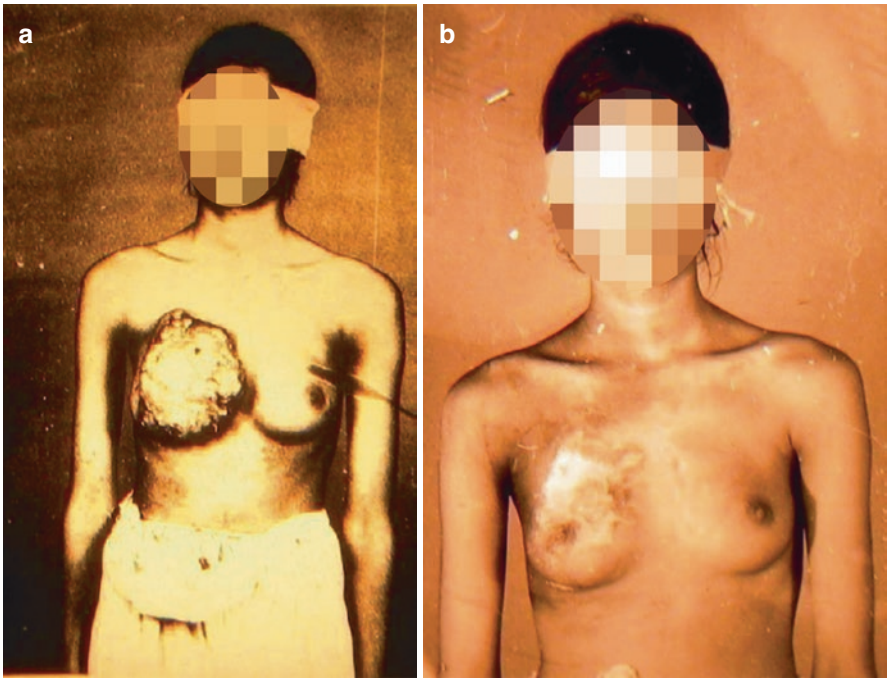


Fig. 16.8 (**a**) A 12 year Girl with Fungating Right Breast Lesion without any family history of breast cancer). (**b**) Post-Neoadjuvant Chemotherapy (CAF), Large tumour with complete clinical response, Patient received radical RT to right breast and axilla. Present consensus is that the patient should undergo MRM

2. NACT alone fails to induce a PCR in three-fourth of patients. Even in patients reaching clinically CR after NACT, up to one third will have pathological evidence of residual disease in the breast and up to one half of them in axillary nodes. Thus, additional RT prior to surgery might be of advantage in T3 or T4 tumours and even in otherwise operable stage I and II, to aim at greater rates of breast preservation.

It is still unknown whether preoperative RT following NACT yields similar results in terms of progression-free survival (PFS), overall survival (OS) and locoregional disease control as compared with adjuvant RT and surgery first after NACT.

The other category of patients is where there is no or poor response to NACT, in such patients alternative strategies should include NART.

For patients who undergo post mastectomy radiotherapy (PMRT) delayed breast reconstructions are preferred due to superior cosmetic outcomes and lower complication rates compared to immediate permanent implant or autologous reconstructions (AR). However, neoadjuvant radiotherapy (NART) prior to surgery allows for definitive oncological surgery to be performed with an immediate AR in a single operation.

Cokelek M et al.'s review demonstrated that this Sequence reversal (SR) i.e. Preoperative RT is a safe technique, which has not lead to an increase in surgical complication rates. Cosmetic outcome has not been affected by NART. SR can achieve a shorter, simpler reconstructive journey for patients [57].

Tran et al. demonstrated that the sequence of postmastectomy breast reconstruction and RT is an important factor which has an impact mainly on late complications of treatment [58]. In patients with TRAM reconstruction followed by RT they observed rates of fat necrosis, flap volume loss, or flap contracture of 43.8%, 87.5%, and 75%, respectively. The corresponding figures in patients with RT before TRAM reconstruction were 8.6%, 0%, and 0%, respectively. In summary, the data point to the following strategy that immediate breast reconstruction should be avoided in patients known to require PMRT and should be delayed until RT is completed [59, 60].

16.10 Neoadjuvant Endocrinal Therapy (NET)

Neoadjuvant endocrine therapy (NAET) is considered an option for patients with hormone receptor-positive LABC. This may be an alternative for older patients and/or existing comorbid conditions. They may not tolerate the chemotherapy due to its cytotoxic effect [61].

In a study of 47 patients with LABC and comorbid illness, after 6 months neoadjuvant tamoxifen treatment, the response rate was reported as 47%, and disease-free survival rate at 40 months was found 49%.

Neoadjuvant aromatase inhibitor study was performed in 239 postmenopausal women with hormone receptor-positive breast cancer, approximately one half of whom had LABC. In this trial, patients randomized to neoadjuvant aromatase inhibitor therapy (anastrozole or exemestan) or chemotherapy (doxorubicin plus paclitaxel). According to the results of the study, there was no difference for clinical response, PCR and disease progression between two groups. Therefore, in neoadjuvant setting for LABC, the optimal use of endocrine therapy seems to be best suited for patients who are older or have comorbidities. Neoadjuvant Aromatase Inhibitor has comparable efficacy to NAC in terms of PCR, ORR, and BCS, suggesting the feasibility of this well-tolerated strategy, mainly for postmenopausal patients [62].

16.11 Concurrent Chemoradiotherapy (CCRT) for LABC

Chemotherapy concurrent with radiation has the potential to offer patients the combined benefits of improved local and distant disease control.

Despite the increasing use of preoperative chemotherapy, rates of pathologic complete response (a surrogate marker for disease-free survival), remain modest in patients with LABC and particularly so when the tumour is estrogen or

progesterone receptor–positive and Her2-negative. In many other solid tumours (for example, rectal, oesophageal, and lung cancers), concurrent chemoradiotherapy (CCRT) is routinely used alike.in neoadjuvant and adjuvant treatment protocols.

Very few prospective studies have addressed the question of benefit from concurrent treatment. Studies looking at 5-fluorouracil infusion-based CCRT in LABC have shown some benefit in the PCR rate and in local control without added toxicity.

Capecitabine based CCRT has also been shown to be beneficial in second-line neoadjuvant (salvage) treatment in anthracycline-resistant LABC 54. The use of taxanes with CCRT is controversial. Toxicity was seen in more than 41% of patients [63].

Ultimately, a randomized controlled trial needs to be designed to evaluate whether the PCR rate is significantly higher with CCRT or with sequential therapy and to determine definitively whether the relationship between PCR and survival persists with the addition of regional therapy modalities such as RT.

A possible disadvantage of CCRT is that reconstructive surgery might not be possible if skin toxicity is more pronounced (no data are yet available to clarify this concern). In contrast, CCRT limits the duration of treatment and the required hospital visits, without compromising quality of life. The cost- effectiveness of the approach also makes it an attractive alternative especially in developing countries, it improves compliance and access to care and reduces the financial burden of cancer care to the country.

16.12 Inflammatory Breast Cancer (IBC)

Inflammatory breast cancer (IBC) is a rare and aggressive clinicopathological entity of breast cancer. It is the most fatal form of breast cancer, and is responsible for up to 7% of all breast cancer-specific mortality.

IBC accounts for 1–6% of all breast cancer diagnoses. In Western countries, the frequency of IBC is low i.e. 1–2% of all breast cancers, but in some parts of the world, such as Northern Africa and Asia (India), it is much higher, for reasons that are not known [64].

Inflammatory breast cancer is associated with younger age at diagnosis (mean age 50–58 years compared with 50–64 years among those diagnosed with noninflammatory breast cancer) [65].

In North Africa, 50% of breast cancer cases present as IBC. The exact reason is not known, an association with obesity and younger age at first giving birth has been suggested [66].

IBC can also develop in a breast that contains a known tumour or that has been previously treated. These “secondary” cases of IBC behave similarly to “primary” cases of IBC, and therefore a diagnosis of IBC cannot be excluded in a woman with a known history of breast cancer [67].

16.12.1 Criteria for Diagnosis of IBC

There are no specific criteria to diagnosis IBC. There are no histological or molecular level specific marker to distinguish it from other non IBC, thus the diagnosis is entirely clinical.

As per the New Edition (seventh) AJCC Staging System for Breast Cancer, the signs and symptoms required for IBC diagnosis are erythema occupying at least one-third of the breast, oedema and/or orange peel appearance of the breast, and/or a warm breast (Fig. 16.9). A palpable mass is present in only one-third of cases. The mass may not be appreciated as something discrete. Indeed, even when a localized mass is apparent in IBC, the true extent of the disease (as shown by performing skin biopsies from the surrounding normal-appearing skin) is usually greater than is apparent on physical examination.

The onset of these signs and symptoms should be rapid; the length of the time taken during its initial presentation should be 3 months [68]. These criteria are important to distinguish the skin changes of IBC (T4d) from the skin changes associated with a neglected noninflammatory breast tumour (T4a-c).

16.12.2 IBC as a Unique Clinical Entity

Despite the absence of a molecular marker to distinguish IBC and from non-IBC at the molecular level, both clinical entities are clearly different distinct in terms of their presentation, natural history and survival. Clinically, the characteristic skin changes have a rapid onset from the time of confirmed diagnosis [69].

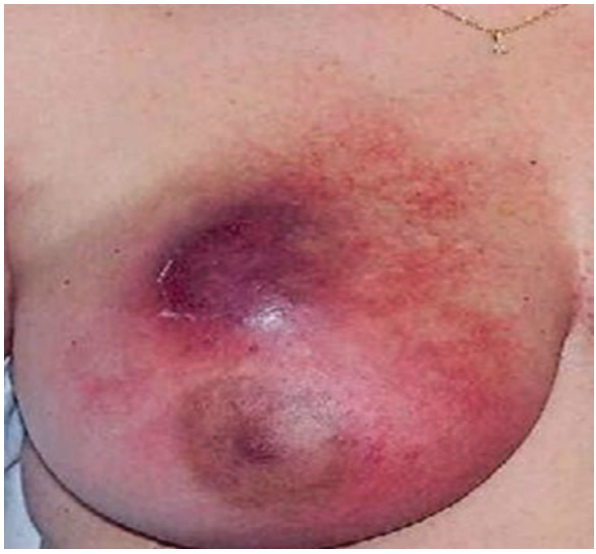


Fig. 16.9 Clinical picture of IBC

Approximately 85% of patients with IBC present with metastasis to the regional lymph nodes, and almost 30% present with distant metastasis at the time of diagnosis [70]. IBC is associated with a 5-year overall survival rate of less than 55% [71]. The name, inflammatory breast cancer is misnomer as it does not demonstrate the histologic characteristics of inflammatory process.

The pathologic hallmark is the presence of microscopic lesions known as lympho-vascular tumour emboli in the subdermal lymphatic vessels. It may be evident on skin biopsy in doubtful cases.

This histologic finding, while not specific, is a useful complement to the clinical diagnosis and may explain some of the clinical manifestations of the disease including its high propensity for spread.

These tumours are more likely to stain negatively by IHC for ER and PR and somewhat more likely to be positive for HER2 over expression. In addition, both angiogenesis and lymphangiogenesis appear to be increased by microvessel density or RNA-based gene expression arrays.

16.13 Management of IBC

16.13.1 Investigations

Mammography is the current standard imaging and one must be careful as compression during the procedure can be painful.

Regional lymph nodes, including axillary nodes and supraclavicular nodes are easily picked up by routine ultrasonography [72].

Breast MRI, has the highest sensitivity in the detection of primary mammary parenchymal lesions and the skin abnormalities. The thickening of the skin is visible in 90–100% of patients with IBC and this finding can be used to differentiate non-IBC LABC patients.

MD Anderson Cancer hospital has demonstrated that for IBC, breast MRI identifies all breast parenchymal lesions and is also useful in monitoring the response to chemotherapy.

16.13.2 Treatment

Historically IBC was treated by surgery and/or radiotherapy. The 5-year overall survivals were under 5% [73].

These days the trimodal therapy consisting of chemotherapy, surgery and radiotherapy has become the standard of care for IBC.

Surgery and radiotherapy are used only to control palliative symptoms.

16.13.3 Chemotherapy

In a study from MD Anderson with 178 IBC patients, anthracycline-based chemotherapy followed by local treatment with irradiation, with or without mastectomy led to an improvement of overall survival rate at 5 years to 40% and 10 years survival to 33% [74]. The integration of taxanes into chemotherapy has shown efficacy in the neoadjuvant treatment of IBC.

Two prospective randomized trials of 68 patients of LABC with IBC, undergoing multimodality therapy revealed the following. Treatment plan consisted of 3 courses of neoadjuvant chemotherapy with CAF (cyclophosphamide/doxorubicin/5-fluorouracil) or CEF (cyclophosphamide/epirubicin/5-FU) followed by surgery and 6 adjuvant courses of CAF or CEF alternated with CMF (cyclophosphamide/methotrexate/5-FU). Radiation therapy was administered at the end of adjuvant treatment. All patients with oestrogen receptor-positive tumours received tamoxifen 20 mg daily for 5 years. Overall survival (OS) rates at 5 and 10 years were 44% and 32%, respectively, and median OS was 4 years (range, 5 months to 14.7 years). Significant prognostic factors for DFS and OS were the number of axillary nodes and residual disease in the breast at surgery. This analysis confirmed that patients with IBC obtained significant long-term survival benefit from combined-modality therapy [75].

HER2 is overexpressed in 36% to 60% of IBC cases. In the NOAH study, which includes IBC patients, the addition of trastuzumab to systemic therapy significantly improved the pathological complete response (PCR) rates (38% versus 19%, P = 0.001) and event-free survival (3-year event free survival 71% versus 56%, HR 0.59, P = 0.013) [76].

The use of double blocking with trastuzumab and pertuzumab in the neoadjuvant setting had improved the rate of PCR. In the NeoSphere and TRYPHAENA trials the PCR rate was 45.8% and 50.7% respectively [77].

16.13.4 Surgery

The standard procedure is a MRM including axillary dissection. The involvement of axillary lymph nodes is noted in 55–85% in IBC at the time of diagnosis. The purpose of the surgery must be complete resection of the residual disease. Conservative surgery and sentinel lymph node biopsy must be avoided. In the metastatic disease, surgery is indicated only for uncontrolled hemorrhage.

Immediate reconstruction is not recommended in patients with IBC.

16.13.5 Radiotherapy

The standard approach for patients with IBC after mastectomy is radiotherapy. A better rate of locoregional control was achieved in the high-dose group than in the standard-dose group (84% vs. 58% at 5 years, 77% vs. 58% at 10 years) [78]. There

is higher risk of developing late complications in the high-dose group than in the standard-dose group (29% vs. 15%, respectively).

Preoperative radiotherapy trials have shown that the rate of complications is higher in patients who receive preoperative radiotherapy and the risk of postoperative complications is dose-dependent [53]. In MD Anderson preoperative trials evaluating local 5-year control and non-distant metastasis-free survival for 42 patients with IBC, the rates were 75% and 20%, respectively, and eight patients survived without distant metastasis for more than 40 months (unpublished data). However, the higher rate of complications has been reported in patients who received preoperative radiation. Preoperative concomitant chemoradiotherapy is not indicated in breast cancer as in other cancers [79].

16.13.6 Surveillance/Follow-Up

Just as the care of the breast cancer patient involves multiple specialists during initial treatment, follow-up strategies require coordination of care to provide high-quality, patient-centered care that meets patient's needs without excessive and unnecessary use of healthcare resources and incremental cost. Appropriate follow-up involves coordinated approach by care providers by prompt evaluation of symptoms that may indicate metastatic recurrence and anticipatory management of long-term possible complications, such as limb edema, loss of bone mineral density.

The follow up protocol has been discussed in the chapter on Follow up and Rehabilitation.

References

1. GLOBOCAN 2012 (IARC), section of cancer surveillance (15/1/2015).
2. Desai PB. Breast cancer profile in India: experiences at the Tata memorial hospital, Bombay. In: AHG P, Lees AW, editors. Fundamental problems in breast cancer. The Hague: Martinus Nijhoff Pub. U.S. Breast cancer Statistics. www.breastcancer.org.
3. Allemani C, Matsuda T, Harewood VDCR, Matz M, Nikšić M, et al., CONCORD Working Group. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018, Mar 17;391(10125):1023–75.
4. Agarwal G, Ramakant P. Breast cancer care in India: the current scenario and the challenges for the future. Breast Care (Basel). 2008;3:21–7.
5. Suhani S, Kazi M, Parshad R, Seenu V, Verma E, Mathur S, et al. An audit of over 1000 breast cancer patients from a tertiary care center of Northern India. Breast Dis. 2020, Jan;39(2):91–9.
6. Yeh E, Slanetz P, Kopans DB, Rafferty E, Georgian-Smith D, Moy L, et al. Prospective comparison of mammography, sonography, and MRI in patients undergoing neoadjuvant chemotherapy for palpable breast cancer. AJR Am J Roentgenol. 2005;184(3):868–77.
7. Groheux D, Espie M, Giacchetti S, Hindie E. Performance of FDG PET/CT in the clinical management of breast cancer. Radiology. 2013;266(2):388–405.
8. Chu QD, Henderson A, Kim RH, Miller JK, Burton G, Ampil F, Li BD. Should a routine metastatic workup be performed for all patients with pathologic N2/N3 breast cancer? J Am Coll Surg. 2012;214(4):456–62.

9. Al-Husaini H, Amir E, Fitzgerald B, Wright F, Dent R, Fralick J, et al. Prevalence of overt metastases in locally advanced breast cancer. Clin Oncol (R Coll Radiol). 2008;20(5):340–4.
10. Huston TL, Osborne MP. Evaluating and staging the patient with breast cancer. In: Ross D, editor. Breast cancer. 2nd ed. Philadelphia: Elsevier Churchill Livingstone; 2005. p. 309–18.
11. Schirrmeister H. Detection of bone metastases in breast cancer by positron emission tomography. PET Clin. 2006;1(1):25–32.
12. Chan Y, Chan K, Lam W, Matreweli C. Comparison of whole body MRI and radioisotope bone scintigram for skeletal metastases detection. Chin Med J (Eng1). 1997;110(6):485–9.
13. Ohta M, Tokuda Y, Suzuki Y, Kubota M, Makuuchi H, Tajima T, et al. Whole body PET for the evaluation of bony metastases in patients with breast cancer: comparison with 99 m Tc-MDP bone scintigraphy. Nucl Med Commun. 2001;22(8):875–9.
14. Dose J, Bleckmann C, Bachmann S, Bohuslavizki KH, Berger J, Jenicke L, et al. Comparison of fluorodeoxyglucose positron emission tomography and "conventional diagnostic procedures" for the detection of distant metastases in breast cancer patients. Nucl Med Commun. 2002;23(9):857–64.
15. Haagensen CD, Stout AP. Carcinoma of the breast. III. Results of treatment, 1935–1942. Ann Surg. 1951;134(2):151–72.
16. Arriagada R, Mouriesse H, Sarrazin D, Clark RM, Deboer G. Radiotherapy alone in breast cancer. I. Analysis of tumor parameters, tumor dose and local control: the experience of the Gustave-Roussy institute and the Princess Margaret hospital. Int J Radiat Oncol Biol Phys. 1985;11(10):1751–7.
17. Huang CJ, Hou MF, Lin SD, Chuang HY, Huang MY, Fu OY, et al. Comparison of local recurrence and distant metastases between breast cancer patients after postmastectomy radiotherapy with and without immediate TRAM flap reconstruction. Plast Reconstr Surg. 2006;118(5):1079–86. discussion 1087-1078
18. Lerouge D, Touboul E, Lefranc JP, Genestie C, Moureau-Zabotto L, Blondon J. Combined chemotherapy and preoperative irradiation for locally advanced noninflammatory breast cancer: updated results in a series of 120 patients. Int J Radiat Oncol Biol Phys. 2004;59(4):1062–73.
19. Halsted WS. The results of operations for the cure of cancer of the breast performed at John Hopkin's hospital from June 1989 to January 1894. John Hopkin's Bulletin. 1894;4(1894-1895):1–60.
20. McWhirter R. The value of simple mastectomy and radiotherapy in the treatment of cancer of the breast. Brit J Radiol. 1948;21:599–610.
21. Robinson D, Van Heerden J, Payne WEA. The primary surgical treatment of carcinoma of the breast. Mayo Clin Proc. 1976;51:433–42.
22. Turner L, Swindell R, Bell W. Radical mastectomy vs MRM for breast cancer. Ann R Coll Surg Engl. 1981;63:239.
23. Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickerham DL, et al. Ten year results of a randomised trial comparing radical mastectomy and total mastectomy + RT. N Engl J Med. 1985;312:674–81.
24. Haagensen CD, Stout AP. Carcinoma of the breast: II. Criteria of operability. Annals Surg. 1943, December;118(6):1032–51.
25. Bruckman JE, Harris JR, Levene MB, Chaffey J, Hellman S. Results of treating stage III carcinoma of the breast by primary radiation therapy. Cancer. 1979;43:985–93.
26. Kaae S, Johansen H. Simple mastectomy plus postoperative irradiation by the method of McWhirter for mammary carcinoma. Ann Surg. 1969;6:895–9.
27. Rustogi A, Budrukkar A, Dinshaw K, Jalali R. Management of locally advanced breast cancer: evolution and current practice. J Cancer Res Ther. 2005 Jan–Mar;1(1):21–30.
28. Hortobagyi GN, Blumenschein GR, Spanos W, Montague ED, Buzdar AU, Yap HY, et al. Multimodal treatment of locally advanced breast cancer. Cancer. 1983, March 1;51:763–8.
29. Bonadonna G. Evolving concepts in the systemic adjuvant treatment of breast cancer. Cancer Res. 1992;52:2127–37.
30. Papadimitriou K, Ardavanis A, Kountourakis P. Neoadjuvant therapy for locally advanced breast cancer: focus on chemotherapy and biological targeted treatments' armamentarium J Thorac Dis. 2013 Aug;5(4):E181. [published correction appears]

31. Ustaalioglu BB, Gumus M, Bilici A, Seker M, Dane F, Salepci T, et al. Neoadjuvant chemotherapy for locally advanced breast cancer: a single center experience. J Med Oncol. 2010, June;27(2):454–8.
32. Liu SV, Melstrom L, Yao K, Russell CA, Sener SF. Neoadjuvant therapy for breast cancer. J Surg Oncol. 2010;15(101):283–91.
33. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19(1):27–39.
34. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and bowel project protocols B-18 and B-27. J Clin Oncol. 2008;26(5):778–85.
35. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol. 2017 Dec 1;28(12):–3111. [Published correction appears]
36. Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H, Valero V, et al. Measurement of residual breast cancer burden to predict survival afterneoadjuvant chemotherapy. J Clin Oncol. 2007;25(28):4414–22.
37. Ogston KN, Miller ID, Payne S, Hutcheon AW, Sarkar TK, Smith I, et al. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. Breast. 2003;12(5):320–7.
38. Nishino M, Jagannathan JP, Ramaiya NH, Van den Abbeele AD. Revised RECIST guideline version 1.1: what oncologists want to know and what radiologists need to know. AJR. 2010;195:281–9.
39. Guarneri V, Broglio K, Kau SW, Cristofanilli M, Buzdar AU, Valero V, et al. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. J Clin Oncol. 2006 March;24(7):1037–44.
40. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010;375:377–84.
41. Gupta P, Bijlani L, Rath GK, Mishra MC, Shukla NK, et al. Neoadjuvant chemotherapy with cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) or cyclophosphamide, methotrexate and 5-fluorouracil (CMF) in 69 cases of locally advanced (stage IIIb) breast cancer. Jpn J Surg. 1991;21(6):637–42.
42. Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol. 1999;17(2):460–9.
43. Audrea H. Szabatura, Amy Hatfield Seung. Early and locally Advanced Breast cancer. Pharmacotherapy Self assessment programme 6th Edition. (Kindly provide complete reference: Attn: Prof. Bose).
44. Platt R, Zucker JR, Zaleznik DF, Hopkins CC, Dellinger EP, Karchmer AW, et al. Perioperative antibiotic prophylaxis and wound infection following breast surgery. J Antimicrob Chemother. 1993;31(Suppl B):43–8.
45. Pogson CJ, Adwani A, Ebbs SR. Seroma following breast cancer surgery. Eur J Surg Oncol. 2003;29(9):711–7.
46. Talbot ML, Magarey CJ. Reduced use of drains following axillary lymphadenectomy for breast cancer. ANZ J Surg. 2002;72(7):488–90.
47. Flew J. The effect of restriction of shoulder movement. Br J Surg. 1979;66:302–5.
48. Porter KA, O'Connor S, Rimm E, Lopez M. Electrocautery as a factor in seroma formation following mastectomy. Am J Surg. 1998;176(1):8–11.
49. Classe J, Dupre P, Francois T, Robard S, Theard JL, Dravet F. Axillary padding as an alternative to closed suction drain for ambulatory axillary lymphadenectomy. Arch Surg. 2002;137:169–72.

50. O'Hea BJ, Ho MN, Petrek JA. External compression dressing versus standard dressing after axillary lymphadenectomy. Am J Surg. 1999;177(6):450–3.
51. Moore M, Burak WE Jr, Nelson E, Kearney T, Simmons R, Mayers L, et al. Fibrin sealant reduces the duration and amount of fluid drainage after axillary dissection: a randomized prospective clinical trial. J Am Coll Surg. 2001;192(5):591–9.
52. Erickson VS, Pearson ML, Ganz PA, Adams J, Kahn KL, et al. Arm edema in breast cancer patients. J Natl Cancer Inst. 2001;93(2):96–111.
53. Grobmyer SR, Daly JM, Glotzbach RE, Grobmyer AJ 3rd. Role of surgery in the management of postmastectomy extremity angiosarcoma (Stewart-Treves syndrome). J Surg Oncol. 2000;73(3):182–8.
54. Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. Br J Surg. 2006;93(5):539–46.
55. Kelly AM, Dwamena B, Cronin P, Carlos RC. Breast cancer sentinel node identification and classification after neoadjuvant chemotherapy – systematic review and meta analysis. Acad Radiol. 2009;16(5):551–63.
56. McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, et al., On behalf of the Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383:2127–35.
57. Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Buzdar AU, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol. 2004;22(23):4691–9.
58. Cokelek M, Chao M, Foroudi F, et al. Sequence reversal: neoadjuvant radiation therapy for locally advanced breast cancer. Int J Radiation Oncol Biol Physics. 2017;99(2):S215–6. (This reference needs to be verified by Prof. Bose)
59. Tran NV, Chang DW, Gupta A, Kroll SS, Robb GL. Comparison of delayed free TRAM flap and breast reconstruction in patients receiving postmastectomy radiation therapy. Plast Reconstr Surg. 2001;108:78–82.
60. Kronowitz SJ, Robb GL. Breast reconstruction with postmastectomy radiation therapy: current issues. Plast Reconstr Surg. 2004;114:950–60.
61. Kronowitz SJ, Feledy JA, Hunt KK, Kuerer HM, Youssef A, Koutz CA, et al. Determining the optimal approach to breast reconstruction after partial mastectomy. Plast Reconstr Surg. 2006;117:1–11.
62. Huang L, Xu AM. Short-term outcomes of neoadjuvant hormonal therapy versus neoadjuvant chemotherapy in breast cancer: systematic review and meta-analysis of randomized controlled trials. Expert Rev Anticancer Ther. 2017;17:327–34.
63. Gaui MF, Amorim G, Arcuri RA, Pereira G, Moreira D, Djahjah C, et al. A phase ii study of second-line neoadjuvant chemotherapy with capecitabine and radiation therapy for anthracycline-resistant locally advanced breast cancer. Am J Clin Oncol. 2007;30:78–81.
64. Mandilaras V, Bouganim N, Spayne J, Dent R, Arnaout A, Boileau JF, et al. Concurrent chemoradiotherapy for locally advanced breast cancer-time for a new paradigm? Curr Oncol. 2015;22(1):25–32.
65. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. J Natl Cancer Inst. 2005;97(13):966–75.
66. Levine PH, Veneroso C. The epidemiology of inflammatory breast cancer. Semin Oncol. 2008;35(1):11–6.
67. Ferdous CS, Islam TM, Meza LA. Review of inflammatory breast cancer: a meta-analysis [abstract]. J Clin Oncol. 2008;26(Suppl):1131.
68. Resetkova E. Pathologic aspects of inflammatory breast carcinoma: part 1. Histomorphology and differential diagnosis. Semin Oncol. 2008;35(1):25–32.

69. Singletary SE, Cristofanilli M. Defining the clinical diagnosis of inflammatory breast cancer. Semin Oncol. 2008;35(1):7–10.
70. Dawood S, Merajver SD, Viens P, Vermeulen PB, Swain SM, Buchholz TA, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Annals Oncol: Official Journal of the European Society for Medical Oncology/ESMO. 2011;22(3):515–23.
71. Walshe JM, Swain SM. Clinical aspects of inflammatory breast cancer. Breast Dis. 2005;22:35–44.
72. Rueth NM, Lin HY, Bedrosian I, Shaitelman SF, Naoto Ueno T, Yu S, et al. Underuse of trimodality treatment affects survival for patients with inflammatory breast cancer: an analysis of treatment and survival trends from the National Cancer Database. J Clin Oncol. 2014;32(19):2018–24.
73. Fouad TM, Kogawa T, Reuben JM, Ueno NT. The role of inflammation in inflammatory breast cancer. Adv Exp Med Biol. 2014;816:53–73.
74. Bozzetti F, Saccozzi R, De Lena M, Salvadori B. Inflammatory cancer of the breast: analysis of 114 cases. J Surg Oncol. 1981;18(4):355–61.
75. Cristofanilli M, Buzdar AU, Sneige N, Smith T, Wasaff B, Ibrahim N, Booser D, et al. Paclitaxel in the multimodality treatment for inflammatory breast carcinoma. Cancer. 2001;92(7):1775–82.
76. Baldini E, Gardin G, Evagelista G, Prochilo T, Collecchi P, Lionetto R. Long-term results of combined-modality therapy for inflammatory breast carcinoma. Clin Breast Cancer. 2004;5(5):358–63.
77. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R. T et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013;24(9):2278–84.
78. Liao Z, Strom EA, Buzdar AU, Singletary SE, Hunt K, Allen PK, et al. Locoregional irradiation for inflammatory breast cancer: effectiveness of dose escalation in decreasing recurrence. Int J Radiat Oncol Biol Phys. 2000;47(5):1191–200.
79. Damast S, Ho AY, Montgomery L, Fornier MN, Ishill N, Elkin E, et al. Locoregional outcomes of inflammatory breast cancer patients treated with standard fractionation radiation and daily skin bolus in the taxane era. Int J Radiat Oncol Biol Phys. 2010;77(4):1105–12.

Recurrent Breast Cancer (Local and Metastatic): Surgical Aspects

17

Sunil Saini, Manisa Pattanayak, and Anshika Arora

17.1 Introduction

Locoregional recurrences (LRR) following surgery [1] are defined as recurrence of invasive/non-invasive disease in

- Breast
- Chest wall (following mastectomy)
- Ipsilateral or parasternal or infra/supraclavicular lymph nodes
- Skin of chest wall (not breast)
- Reconstructed breast
- A second carcinoma (not adenocarcinoma)

LRR are reported in 5–15% of patients following breast conserving surgery or mastectomy and completion of adjuvant radiotherapy and/or chemotherapy [1]. 60–95% recur in the original quadrant after conservative surgery or the chest wall scar following mastectomy [2, 3] but can also occur in another quadrant.

Sunil Saini, MS (✉)
Professor and Head, Department of Surgical Oncology, Himalayan Institute of Medical Sciences, Dehradun, Uttarakhand, India
e-mail: sunilsaini@srhu.edu.in

Manisa Pattanayak, MS
Associate Professor, Department of Surgical Oncology, Himalayan Institute of Medical Sciences, Dehradun, Uttarakhand, India

Anshika Arora, MS
Assistant Professor, Department of Surgical Oncology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, Uttarakhand, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_17

17.1.1 Factors Affecting Locoregional Recurrence

LRR present as either Isolated Locoregional Recurrences (ILR) or distant metastatic disease. ILR accounts for 10–20% and distant metastasis 60–70% of all recurrent breast cancers. Triple Negative and HER2 positive breast cancer have a six to eight times risk of LRR than Luminal A breast cancer; there is increased risk of metastasis and shorter survival in these patients [4].

The majority of data for ILR in breast cancer comes from studies performed in the 1980–90s. Advances like sentinel lymph node biopsy (SLNB), systemic therapy, targeted therapy, partial breast irradiation and down staging of disease with use of neo-adjuvant systemic therapy have changed the presentation of ILR. The highest risk for recurrence is in the first 2–3 years following completion of treatment, decreasing thereafter but never reaching zero [2].

Tumour biology is the main determinant and predictor for ILR. The incidence of ILR/distant metastasis depends on factors like: age of the patient, initial tumour stage, nodal positivity, previous therapy, grade of tumour, margin status, receptor status and the sensitivity of the diagnostic tools used initially [3, 5]. The interval to ILR is longer (almost double) in oestrogen receptor (ER) positive versus negative tumours. The local failure, as well as distant metastasis rate is higher in triple negative tumours as compared to ER positive tumours. Post-lumpectomy margin status bears a significant role on ILR. A study published in 2015 looked at the patterns of ILR following mastectomy and adjuvant systemic treatment [6]. They reported a recurrence rates of 86.7% in node positive and 72.8% in node negative patients in the first 5 years. The median interval to recurrence was 33.2 months, with earliest recurrences seen in triple negative breast cancer molecular subgroups respectively (18.2 months). Addition of whole breast radiation therapy after lumpectomy reduced the 10 year ILR risk from 35 to 19.3% [6].

ILR may be categorized as:

1. Recurrence following breast conserving surgery and radiation therapy
2. Recurrence following mastectomy, axillary dissection and radiation therapy
3. Recurrence following mastectomy and axillary dissection without radiation therapy

17.1.2 Work Up of a Patient with ILR

MRI has higher sensitivity and specificity when compared to mammography and ultrasound alone in identifying locoregional recurrences and is superior to conventional imaging when performed 12–18 months after breast conserving surgery and at greater intervals following breast conserving therapy plus radiotherapy. MRI has shown an extremely high negative predictive value (98.8%) [7].

Once ILR is detected, the three most important issues in the work up of these patients are

1. Re-staging
2. Determination of receptor status
3. Determination of operability

17.1.2.1 Re-Staging

As per current NCCN guidelines all patients with locoregional recurrences must undergo metastatic workup including LFT, Alkaline Phosphatase, Chest & Abdominopelvic CECT Scan & Bone Scan as indicated or FDG PET CT Scan and MRI of brain & spine if clinically warranted. Although re-staging does not confer any survival advantage, it definitely has a bearing on planning of further treatment and may help to avoid unnecessary surgery; and it has been reported that complex surgery could be avoided in 25% patients by detecting distant metastasis [7, 8]. A meta-analysis of 18 studies published in 2005 evaluated the accuracy of ^{18}F-2-deoxy-2-fluoro-D-glucose-positron emission tomography (FDG-PET) scan in breast cancer recurrence and metastasis [9] and concluded that it had a sensitivity of 92.7% and a false positive rate of 11%. If definitive treatment for LRR is being contemplated, FDG PET/CT can be useful in identifying all the sites of recurrence, especially when traditional imaging methods like ultrasound, X-Ray, CT scan and bone scan are equivocal or conflicting. FDG PET/CT can also identify or confirm isolated locoregional recurrence or isolated metastatic disease [10].

17.1.2.2 Determination of Receptor Status

Owing to tumour heterogeneity, almost 30% of recurrent or metastatic disease can have change in receptor status from the initial status. Thus, whenever feasible a core needle biopsy with hormone-receptor expression and HER2 expression determination should be carried out (Cochrane Collaboration 2009: http://www.cochrane.org). A systematic review published in 2012 looked at LRR after breast cancer surgery by receptor phenotype [11]. A total of 12,592 patients' results were analysed from 15 studies, and the authors found that luminal subtype tumours (ER/PR + ve) had the least risk for LRR than both triple-negative and HER2/neu overexpressing tumours following BCT. HER2/neu overexpressing tumours had the highest risk for LRR.

17.1.2.3 Determination of Operability of LRR

Systematic clinical examination in conjunction with mammography or MRI breast are required to differentiate operable from inoperable locoregional recurrences. Additional decisions like salvage mastectomy v/s repeat lumpectomy, axillary remapping and reconstructive options depend on these findings (Fig. 17.1).

17.1.3 General Principles of Management

It is important to differentiate an ipsilateral second tumour from LRR since an ipsilateral second tumour always warrants a curative strategy of management. A long interval since first treatment, different tumour location in breast and different receptor status or tumour grade indicates a second tumour. Different tumour histology may also help in differentiation between LRR and second independent tumour.

ILR is usually treated curatively unless contraindicated [1]. The 5-year overall survival in patients who develop isolated chest wall recurrence (following mastectomy)

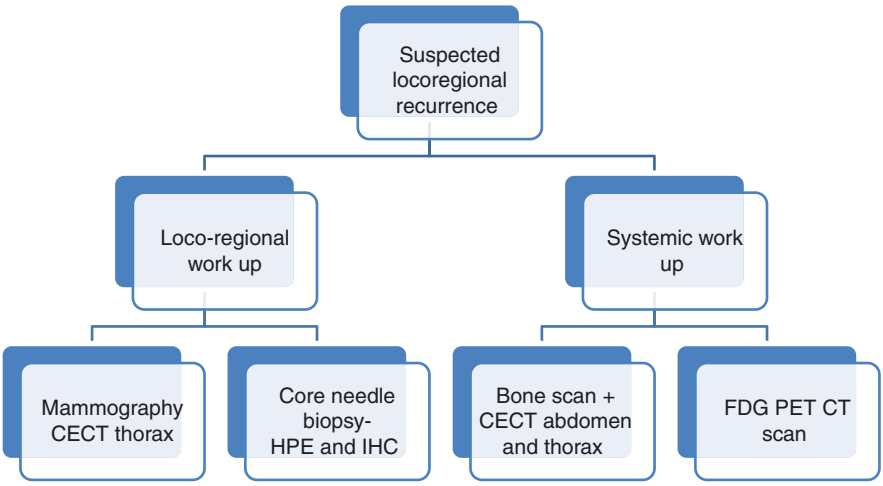


Fig. 17.1 The work up required for locoregional recurrent disease in breast cancer

can be up to 68%; for those with intra-breast recurrence (following breast conserving therapy), up to 81% [2]. Operable recurrent disease in breast, axilla and chest wall should be excised to achieve tumour-free margin status. Although mastectomy is considered as the standard surgery for intra-breast recurrence, repeat breast-conserving surgery may be performed ensuring negative margins in patients opting for breast conservation and cosmetic outcome. The chance of having a second intra-breast recurrence is higher after repeat breast conservation [1] but the implication of this on the overall survival is uncertain [12]. Patients who had not received radiotherapy earlier must be given radiotherapy after revision surgery (Fig. 17.2).

17.1.3.1 Intra-Breast Tumour Recurrence (IBTR) Following Breast Conserving Surgery

The options for treating IBTR are:

1. re-excision (lumpectomy) and
2. mastectomy

In an Italian study published in 1999, IBTR was diagnosed in 209 out of 2544 patients (8.21%) treated with quadrantectomy, axillary dissection and radiotherapy [13]. Out of the 191 patients who underwent surgery, only 57 underwent re-excision and rest underwent salvage-mastectomy. The decision to choose between these two options was based on the following factors- solitary/multifocal recurrence, involvement of skin and subcutaneous/parenchyma or both, localization of the recurrence in relation to previous scar site (<2 cm from scar), relation to subareolar tissue, quadrant/s involved, clinical tumour size and finally, time from initial surgery.

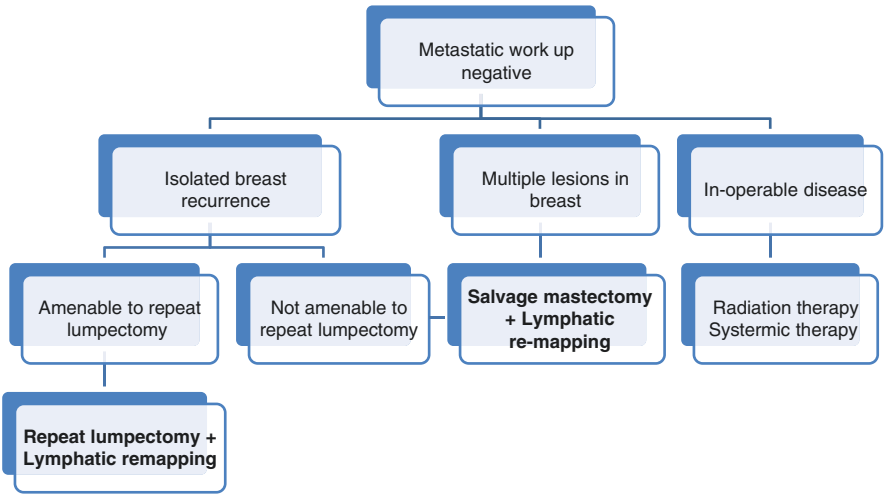


Fig. 17.2 Surgical management strategy for isolated locoregional recurrence following breast conserving therapy

After careful evaluation by clinical examination and imaging (mammography or MRI breast), a repeat lumpectomy may be performed in patients having a single lesion, close to the previous scar, away from subareolar tissue and involvement of only breast parenchyma. The incision should include the old scar, and a wide local excision of the recurrent lesion with a 1–2 cm margin all around should be performed, right down to the pectoralis fascia. The specimen should be palpated for free margins, and additional margins from the breast tissue may be sent for frozen section or histopathology as per institution protocol. The defect may be reconstructed with local tissue or regional flaps. As always, it is important to send the specimen for histopathology in a proper orientation using the standard suture technique, long for lateral and short to indicate superior margin. On the other hand, factors favouring a mastectomy for IBTR are—multicentric lesion, lesion away from previous scar, small breast, and involvement of the skin or fixity to pectoralis muscle. The incision should be elliptical including the nipple-areolar complex and the previous scar. Just like in upfront mastectomy, upper and lower subcutaneous flaps are raised, the breast tissue is then dissected off the pectoralis major muscle including the pectoralis fascia within the specimen, starting medially and working to the lateral border of the pectoralis major muscle. One should take caution regarding deep margin at the site of local recurrence, sometimes due to close proximity or fixity, part of pectoralis major muscle may need to be included in the specimen. The clavi-pectoral fascia is incised at the lateral border of the pectoralis minor muscle to enter the axilla. Axilla may be addressed as per the axillary nodes status on preoperative imaging. Closure may be performed primarily or using local flap\regional flaps or split skin grafting.

17.1.3.2 Recurrence in Skin of Chest Wall Following Mastectomy

Isolated recurrence in the skin following mastectomy is rare, and usually presents as skin thickening, skin oedema, subdermal nodules, redness, erythema, ulceration, or satellite nodules. Skin involvement may be present in relation to the mastectomy scar, away from the scar or may diffusely involve the skin and subcutaneous tissues. It is important from a surgical point of view to assess the limits of recurrent disease as well as the depth of malignant infiltration (limited to the skin and subcutaneous tissue, or going deeper, into the pectoralis muscles or even into the chest wall). Suspected recurrences should always be confirmed with cytology or biopsy since fat necrosis, stitch granuloma following surgery and radiotherapy may present with a similar clinical picture. In the absence of clarity on cytology or core needle biopsy, doubtful operable lesions must always be surgically treated. After evaluation of extent of the lesions and operability, a wide local full thickness excision of the skin recurrence with clear margins is preferred; wound closure may require a variety of procedures ranging from mobilization of local tissue and primary closure, split thickness skin grafting, local rotation flaps to regional pedicled flaps.

Diffuse and progressive skin lesions suspicious of local recurrence in a patient treated earlier for locally advanced and unfavourable histology may not benefit with surgery, and should be treated with other modalities.

17.1.3.3 Chest Wall Tumour Recurrence

Chest wall recurrence after mastectomy is a complex and challenging problem. These can occur after both—mastectomy as well as breast conserving surgery, and can present as a palpable bulge or mass under the skin flap due to recurrence in:

1. Intercostal muscles
2. Serratus anterior muscle
3. Ribs

As many as 30% patients with chest wall recurrence can have synchronous metastasis, thus a metastatic work up is indicated in the form of either PET-CT scan or CECT thorax and abdomen with a bone scan. If the metastatic work up is negative, clinical evaluation and cross-sectional imaging should focus on the delineating extent of involvement of the chest wall, number and length of ribs, soft tissues, parietal pleura and intra-thoracic extension.

Multimodal therapy is the key to managing these patients. For isolated chest wall involvement, a wide local excision with full thickness of the chest wall and negative margins may be performed with a curative intent. As is obvious, patient selection is vital to the success of such major surgical resections. A good candidate would be one with a long duration between treatment completion and recurrence, favourable histology, and early stage of original disease with a negative axilla.

17.1.3.4 Axillary Nodal Recurrence

Patients with recurrence after breast conserving treatment or mastectomy may also have axillary nodal disease. Management of isolated axillary recurrence may require

multimodality treatment including surgery, regional irradiation followed by systemic therapy based on the tumour receptor status in the recurrent disease.

Most patients undergoing BCT have early disease and many of them undergo axillary staging by SLNB. The other group of patients with positive nodes at initial presentation undergo varying degrees of axillary dissection- level I, I/II or I/II/III and axillary irradiation. The issue of aberrant lymphatic drainage following these procedures is significant. Recurrences in interpectoral, internal mammary, infraclavicular and supraclavicular nodes may be inoperable. Thus, operability of nodal recurrence in axilla is limited to the nodes in levels I, II and III without involvement of axillary vein and artery. Axillary remapping with sentinel nodes has been described, but due to the previous surgical procedure and radiation therapy the accuracy of remapping is lower than in patients with no previous axillary surgery. Surgical options include- sentinel remapping with combination of radio-colloid and blue dye, or axillary exploration and clearance of levels I, II and III. Axillary dissection with removal of all visible disease along with fibro fatty tissue is the preferred surgical option in the presence of axillary recurrence.

17.1.4 Prognosis after ILR

In a study published by Chi-Chan Yu et al. [14] in 2020, a retrospective analysis of all overall survival (OS) and distant metastasis free survival (DMFS) following complete excision of ILR for hormone positive breast cancer patients was performed. On multivariate analysis they found that time to ILR <29 months or size of primary tumour >2 cm and grade III tumour were associated with poor OS and DMFS. ILR leads to a higher risk for metastases and lower survival. Depending on tumour characteristics and molecular subtypes, the overall risk and time to metastatic recurrence may vary. In patients that have resectable ILR following mastectomy, multi-modal treatment- comprehensive resection, radiation therapy (if previously unirradiated), and systemic therapy results in 69% and 88% 5 year disease free and overall survival respectively [15].

In a nut shell, management of local and regional recurrence must consider prognostic factors favouring metastatic disease. Personalizing the overall management is important, decision on advising systemic treatment should be based on metastatic risk. All isolated loco-regional recurrences have to be treated with a curative intent. When possible, complete surgical resection is performed. Overall, the "gold standard" is total mastectomy followed by radiation therapy [16].

17.2 Surgical Management of Metastatic Breast Cancer (MBC)

MBC is a problem for all health care systems because these patients are unlikely to be cured by available treatment modalities. Complete remissions are uncommon, and very few patients have a meaningful progression free survival for a prolonged

period. Although the survival in MBC extends from a few months to many years, the overall median survival ranges from 18 to 24 months [17–19].

Metastatic disease in breast cancer may be present at the time of primary presentation or may occur after treatment, often manifesting as polymetastasis and a subset as oligometastasis-characterized by single or few detectable metastases. Literature remains divided on the issue of survival benefit in MBC, and the primary goal of treatment is palliative with emphasis on improving the quality of life. Systemic therapy is the mainstay of treatment in MBC but local management of the primary as well as metastasis-specific local treatment (i.e., metastasectomy, radiofrequency ablation, cryotherapy, and radiation therapy) may palliate symptoms and prevent cancer-related complications [20].

17.2.1 Management of the Local (Primary) Disease in a Metastatic Setup

A large majority of the patients who present with metastatic disease have advanced locoregional disease not amenable for R0 resection. The current recommendations favour systemic treatment as the primary modality in all patients of MBC, with surgical management reserved for patients who require palliation of local symptoms like bleeding, fungation, ulceration and pain [21]. However, surgery for the primary tumour may be performed if there is a possibility of R0 resection and none of the sites of metastasis pose an immediate threat to life. These procedures almost always require some form of reconstruction to facilitate oncological clearance, wound healing and satisfactory cosmetic results.

In the last decade, different prospective studies have addressed the role of primary surgery in metastatic setup [22–24]. A randomised trial by Badwe et al. included 350 women with MBC, out of which 173 were treated with locoregional surgery. They found no benefit in 2 year overall survival (median follow up of 23 months). The only adverse event noted was wound infection related to surgery in one patient in the locoregional treatment group. In another United States registry study in which 94 women who responded to first-line therapy were randomly assigned to local management of the primary, preliminary data suggest no difference in overall survival between the two groups [25].

17.2.2 The Following Scenarios are Usually Encountered in Patients with MBC

Scenario 1. MBC with obvious fungation, ulceration, bleeding or pain—This subgroup of patients benefit from primary surgery in terms of improved quality of life. However, the subsequently decrease in tumour burden does not affect overall survival or response to systemic therapy. Operability and possibility of an R0 resection should be confirmed prior to surgery. Need for a flap cover and other reconstructive

options may be weighed against a prolonged surgery in this group of patients who might otherwise be in a poor general condition.

Scenario 2. MBC with minor ulceration or impending fungation not affecting quality of life—Primary systemic therapy is recommended. Patients who have poor response to systemic treatment or progression of disease may be taken up for surgery if operable.

Scenario 3. MBC with good response to systemic treatment at both primary and metastatic sites—These patients benefit from surgery for the primary site. A modified radical mastectomy is commonly done, because there is limited data on the role of breast conservation and subsequent need for addition of radiation therapy in this subset of patients [26].

Scenario 4. Oligometastatic disease with resectable primary site—A meta-analysis of 28,693 patients from ten studies was reported by Harris et al. in 2013 on the outcomes of primary surgery in operable breast lesions in a metastatic setting. 52.8% of patients who underwent excision of the primary carcinoma had a superior survival at 3 years (40% for surgery versus 22% for no surgery). Subgroup analyses favoured smaller primary lesions, less medical comorbidities and lesser metastatic burden. In the absence of contradictory robust evidence, this meta-analysis provides the evidence base for primary resection in the setting of stage IV breast cancer for patients with small volume or oligometastatic disease [25].

The sum total of available evidence for the role of surgery in metastatic setup suggests benefits in selected case scenarios like resectable disease, and good response to systemic treatment with chemo or endocrine therapy. However, there is a need for further evaluation by means of larger randomized clinical trials that will address the risks and benefits of local therapy while eliminating selection biases. Patient enrolment in such trials is encouraged [27].

17.2.3 Metastatic Site Local Therapy in MBC

There is no available prospective data to suggest that local resection of metastatic sites prolongs overall survival. Therefore, at present, local treatment of metastatic disease aims only at palliation of symptoms like intractable pain, loss of function, or oncologic emergencies like pathological fracture at metastatic site. A tissue diagnosis and IHC from the metastatic site may be valuable in re-establishing receptor status and thereby opening up alternative avenues of treatment [28–30].

In the absence of conclusive evidence, institutional policies and precision therapy tailored to individual patients may guide management decisions. Standard indicators of good prognosis like a good performance status, low tumour burden (oligometastasis), long disease free interval and a high likelihood of R0 resection may be considered when taking individualised decisions [31–34]. The decision should also take into account the availability of relevant expertise as well as patient preferences. An ongoing phase II/III clinical trial (NRG-BR002, NCT02364557) is seeking to assess the impact of aggressive metastasis-specific local therapy on survival.

17.2.4 Site Wise Indications for Resection of Metastatic Disease

17.2.4.1 Liver

Liver metastasis is the most common, occurring in close to half of women with metastatic disease of the breast. The common indication for resection is the presence of pain, bleeding that is refractory to medical therapy, or biliary obstruction. Appropriate candidates include those with isolated liver involvement where resection can be achieved while retaining a sufficient volume of functional liver [35–38]. Patients with hormone-positive disease, normal liver function, good performances status, and a long disease free interval (DFI) are the ones who benefit most. Presence of multiple metastases, bilobar disease and location close to the porta hepatis are considered a contraindication to resection, as is the intraoperative finding of peritoneal or ovarian disease [39–42]. Radio frequency ablation (RFA) and stereotactic body radiotherapy (SBRT) may also be tried in specific indications.

17.2.4.2 Lungs

Solitary pulmonary involvement occurs in 10–25% of patients, most of whom are asymptomatic [40]. Patients with long DFS of 36 months, hormone positive status and good probability of achieving complete resection benefit from surgery [20, 41–43]. RFA and SBRT may be tried for smaller and peripheral lesions. Palliative procedures like insertion of an intercostal drain may be necessary to relieve dyspnoea.

17.2.4.3 Brain

Both open surgery and stereotactic radiosurgery (SRS) have been used to treat patients with recurrent, symptomatic central nervous system (CNS) disease who have stable extracranial disease following their initial treatment for brain metastases [27]. Careful selection of patients is critical. Open surgery may be recommended for solitary and accessible lesions. Patients with lesions <3 cm in size, and with number of lesion <5 do better with SRS. Symptomatic treatment with corticosteroids, anti-epileptics, anti-oedema measures and management and prevention of venous thromboembolic disease forms part of the overall management of brain metastasis.

17.2.4.4 Bones

Resection of an involved bone for an asymptomatic patients without evidence of impending fracture does not result in extending survival, although resection of parasternal/sternal metastasis have been tried [34]. Bony metastasis generally have an indolent course and show good response to systemic therapy [44]. Indications for local management of bone disease are fracture or impending fracture due to a metastasis, significant pain or decreased mobility of a joint, or spinal cord compression. In such cases, short-course palliative radiotherapy is commonly used. Pathologic fractures, pending fractures, or epidural spinal cord or nerve compression may require surgical intervention.

17.2.4.5 Ovaries

Presence of an adnexal mass in a woman with breast cancer poses a diagnostic problem of whether it is metastatic or a second primary. In such cases, a surgical evaluation in the form of salpingo-oophorectomy may be necessary [45, 46]. This would also have an additional therapeutic benefit in premenopausal women with hormone-positive breast cancer. Results of resecting localised ovarian masses diagnosed to be metastatic from a breast primary have only been reported in a small series of 29 cases [32]. In one series of 147 patients with metastatic disease to the ovary (8% of whom had a breast primary), the median overall survival after ovarian metastasectomy was 41 months [33].

In conclusion it may be mentioned that the management of MBC complicated, and presents great challenges in decision making. Although systemic treatment remains the recommended modality of initial management of these patients, surgery for the local disease may benefit a small subset of patients for palliation of distressing local symptoms and improvement in the quality of life.

References

1. Wapnir IL, Anderson SJ, Mamounas EP, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol. 2006;24:2028–37.
2. Kamby C, Ejlertsen B, Andersen J, et al. The pattern of metastases in human breast cancer. Influence of systemic adjuvant therapy and impact on survival. Acta Oncol. 1988;27:715–9.
3. Kamby C, Vejborg I, Kristensen B, Olsen LO, Mouidsen HT. Metastatic pattern in recurrent breast cancer. Special reference to intrathoracic recurrences. Cancer. 1988;62:2226–33.
4. Jeong Y, Kim SS, Gong G, et al. Treatment results of breast cancer patients with locoregional recurrence after mastectomy. Radiat Oncol J. 2013;31:138–46. https://doi.org/10.3857/roj.2013.31.3.138.
5. Jemal A, Thun MJ, Ries LA, et al. Annual report to the nation on the status of cancer, 1975–2005, featuring trends in lung cancer, tobacco use, and tobacco control. J Natl Cancer Inst. 2008;100:1672–94.
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast conserving surgery on 10-year recurrence and 15 year breast cancer death: meta-analysis of 17 randomized clinical trials. Lancet. 2011;378:1707–16.
7. Elfgen C, Schmid SM, Tausch CJ, Montagna G, Güth U. Radiological staging for distant metastases in breast cancer patients with confirmed local and/or Locoregional recurrence: how useful are current guideline recommendations? Ann Surg Oncol. 2019;26:3455–61. https://doi.org/10.1245/s10434-019-07629-9.
8. Sacchini V. Restaging patients with Locoregional relapse: is there any benefit? Commentary on "Radiological staging for distant metastases in breast cancer patients with confirmed local and/or locoregional recurrence: how useful are current guideline recommendations?" by Elfgen. Constanze et al Ann Surg Oncol. 2019;26:3415–7. https://doi.org/10.1245/s10434-019-07642-y.
9. Isasi CR, Moadel RM, Blaufox MD. A meta-analysis of FDG-PET for the evaluation of breast cancer recurrence and metastases. Breast Cancer Res Treat. 2005;90(2):105–12. https://doi.org/10.1007/s10549-004-3291-7.

10. Piva R, Ticconi F, Ceriani V, et al. Comparative diagnostic accuracy of 18F-FDG PET/CT for breast cancer recurrence. Breast Cancer (Dove Med Press). 2017;9:461–71. Published 2017 Jul 4. https://doi.org/10.2147/BCTT.S111098.
11. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat. 2012;133(3):831–41. https://doi.org/10.1007/s10549-011-1891-6.
12. Ma J, Jiang R, Fan L, et al. Isolated locoregional recurrence patterns of breast cancer after mastectomy and adjuvant systemic therapies in the contemporary era. Oncotarget. 2015;6:36860–9. https://doi.org/10.18632/oncotarget.5365.
13. Salvadori B, Marubini E, Miceli R, et al. Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. Br J Surg. 1999;86(1):84–7. https://doi.org/10.1046/j.1365-2168.1999.00961.x.
14. Yu C-C, Kuo W-L, Shen S-C, et al. Prognostic study for isolated local recurrence operated with salvage excision in hormone-receptor-positive patients with invasive breast cancer after primary breast surgery. Biom J. 2020;43:83–93. https://doi.org/10.1016/j.bj.2019.07.002.
15. Harms W, Geretschläger A, Cescato C, Buess M, Köberle D, Asadpour B. Current treatment of isolated locoregional breast cancer recurrences. Breast Care (Basel). 2015;10(4):265–71. https://doi.org/10.1159/000439151.
16. Belkacemi Y, Hanna NE, Besnard C, Majdoul S, Gligorov J. Local and regional breast cancer recurrences: salvage therapy options in the new era of molecular subtypes. Front Oncol. 2018;8:112. https://doi.org/10.3389/fonc.2018.00112.
17. Caswell-Jin JL, Plevritis SK, Tian L, et al. Change in survival in metastatic breast cancer with treatment advances: meta-analysis and systematic review. JNCI Cancer Spectr. 2018;2:pky062. https://doi.org/10.1093/jncics/pky062.
18. Kim H, Choi DH, Park W, et al. Prognostic factors for survivals from first relapse in breast cancer patients: analysis of deceased patients. Radiat Oncol J. 2013;31:222–7.
19. Leung AM, Vu HN, Nguyen KA, et al. Effects of surgical excision on survival of patients with stage IV breast cancer. J Surg Res. 2010;161:83.
20. Pagani O, Senkus E, Wood W, et al. International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? J Natl Cancer Inst. 2010;102:456.
21. Teshome M. Role of operative Management in Stage IV breast cancer. Surg Clin North Am. 2018;98:859–68.
22. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol. 2015;16:1380.
23. King TA, Lyman JP, Gonen M, et al. Prognostic impact of 21-gene recurrence score in patients with stage IV breast cancer: TBCRC 013. J Clin Oncol. 2016;34:2359–65. https://doi.org/10.1200/JCO.2015.63.1960.
24. Soran A, Ozmen V, Ozbas S, et al. Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: protocol MF07-01. Ann Surg Oncol. 2018;25:3141.
25. Harris E, Barry M, Kell MR. Meta-analysis to determine if surgical resection of the primary tumour in the setting of stage IV breast cancer impacts on survival. Ann Surg Oncol. 2013;20:2828.
26. Cady B, Nathan NR, Michaelson JS, et al. Matched pair analyses of stage IV breast cancer with or without resection of primary breast site. Ann Surg Oncol. 2008;15:3384.
27. NCCN guidelines Version 3.2019 Breast Cancer.
28. Van Poznak C, Somerfield MR, Bast RC, et al. Use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2015;33:2695.
29. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4). Ann Oncol. 2018;29:1634.

30. Lindström LS, Karlsson E, Wilking UM, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol. 2012;30:2601.
31. Chua TC, Saxena A, Liauw W, et al. Hepatic resection for metastatic breast cancer: a systematic review. Eur J Cancer. 2011;47:2282.
32. Bigorie V, Morice P, Duvillard P, et al. Ovarian metastases from breast cancer: report of 29 cases. Cancer. 2010;116:799.
33. Li W, Wang H, Wang J, et al. Ovarian metastases resection from extragenital primary sites: outcome and prognostic factor analysis of 147 patients. BMC Cancer. 2012;12:278.
34. Noble J, Sirohi B, Ashley S, et al. Sternal/para-sternal resection for parasternal local recurrence in breast cancer. Breast. 2010;19:350.
35. Selzner M, Morse MA, Vredenburgh JJ, et al. Liver metastases from breast cancer: long-term survival after curative resection. Surgery. 2000;127:383.
36. Maksan SM, Lehnert T, Bastert G, Herfarth C. Curative liver resection for metastatic breast cancer. Eur J Surg Oncol. 2000;26:209.
37. Sadot E, Lee SY, Sofocleous CT, et al. Hepatic resection or ablation for isolated breast cancer liver metastasis: a case-control study with comparison to medically treated patients. Ann Surg. 2016;264:147.
38. Pawlik TM, Izzo F, Cohen DS, et al. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. Ann Surg Oncol. 2003;10:1059.
39. Bortolotto C, Macchi S, Veronese L, et al. Radiofrequency ablation of metastatic lesions from breast cancer. J Ultrasound. 2012;15:199.
40. Planchard D, Soria JC, Michiels S, et al. Uncertain benefit from surgery in patients with lung metastases from breast carcinoma. Cancer. 2004;100:28.
41. Friedel G, Pastorino U, Ginsberg RJ, et al. Results of lung metastasectomy from breast cancer: prognostic criteria on the basis of 467 cases of the International Registry of Lung Metastases. Eur J Cardiothorac Surg. 2002;22:335.
42. Yoshimoto M, Tada K, Nishimura S, et al. Favourable long-term results after surgical removal of lung metastases of breast cancer. Breast Cancer Res Treat. 2008;110:485.
43. Meimarakis G, Rüttinger D, Stemmler J, et al. Prolonged overall survival after pulmonary metastasectomy in patients with breast cancer. Ann Thorac Surg. 2013;95:1170.
44. Briasoulis E, Karavasilis V, Kostadima L, et al. Metastatic breast carcinoma confined to bone: portrait of a clinical entity. Cancer. 2004;101:1524.
45. Alvarado-Cabrero I, Rodríguez-Gómez A, Castelan-Pedraza J, Valencia-Cedillo R. Metastatic ovarian tumors: a clinicopathologic study of 150 cases. Anal Quant Cytopathol Histpathol. 2013;35:241.
46. Quan ML, Fey J, Eitan R, et al. Role of laparoscopy in the evaluation of the adnexa in patients with stage IV breast cancer. Gynecol Oncol. 2004;92:327.

Management of Hereditary Breast Cancer: An Overview

18

Abhay K. Kattepur and K. S. Gopinath

18.1 Introduction [1–5]

Women with genetic or hereditary predisposition to breast cancer constitute 5–10% of all breast cancer cases and represent a special cohort of women with unique disease biology and therapeutic challenges. The genetic abnormalities associated with hereditary predisposition involve (but not limited to) BRCA1 and BRCA2 mutations, constituting 30–40% of hereditary breast cancers. BRCA1, located on chromosome 17 accounts for 35% of hereditary breast cancers with a cumulative risk of breast and ovarian cancer of 44–78% and 18–54% by 70 years of age respectively. Other malignancies associated with BRCA1 mutations include pancreatic cancers, melanomas and male breast cancers. BRCA2, located on chromosome 13 constitutes 25% of hereditary breast cancer and portends a cumulative risk of breast and ovarian cancer of 31–56% and 2.5–20% by 70 years respectively. Other malignancies associated with BRCA2 mutations are male breast cancers and prostate cancers. BRCA mutations are infrequent in the general population (1 out of every 300–800 women), although increased incidence is observed in women with Ashkenazi Jewish ancestry. The clinical syndrome of hereditary breast and ovarian cancer (HBOC) refers to clinical condition associated with BRCA1 or 2 mutations. The following chapter provides an overview approach and management of hereditary breast cancer.

Abhay K. Kattepur, MS, MCh, DNB, MRCS-Ed (✉)
Assistant Professor, Division of Surgical Oncology, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India
e-mail: ambujahc@gmail.com

K. S. Gopinath, MS (Bom), FRCS (Ed.), FAMS, FAIS
Director, HCG Hospital and Bangalore Institute of Oncology, Bengaluru, Karnataka, India

Professor of Surgery and Oncology, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_18

18.2 Approach to a Patient/Individual with Hereditary Breast Cancer

18.2.1 History Taking

The most important aspect in history taking is to document personal and family history of breast cancer.

Family History: [2, 6, 8] A positive or strong family history of breast cancer is defined by (a) two or more cases of breast cancer in women less than 50 years in a family or (b) breast cancer in three women in a family irrespective of age. A positive family history may be or may not be related to BRCA or other high risk mutations and portends 11-fold increase in the personal risk of breast cancer, in the absence of BRCA mutations and twofold increase in contralateral breast cancer risk in these patients. The relative risk (RR) of breast cancer when a parent or sibling is affected is 2. If both, parent and sibling are affected, the RR is 4. In a telephonic survey [9] carried out in the US involving more than 1000 respondents, the estimates for prevalence of breast cancer was 10.9%, 17.9% and 26.4% among any first-degree, any second-degree and either first or second-degree relatives respectively.

The age at diagnosis of breast cancer in the affected individuals within a family is a predictor of disease occurrence in BRCA mutated carriers likely due to polygenic and/or multifactorial predisposition. Survival among breast cancer patients with a strong family history is no different from other breast cancer patients and this was substantiated in a large hospital based cohort study [10] involving 5359 women which showed no relationship in the severity and mortality associated with breast cancer and family history.

Triple Negative Breast Cancer (TNBC) in particular is known to have higher frequency of familial association and it is a common subtype in BRCA mutated women. In a study by Couch et al. [11], 12.2% of women with a positive family history carried BRCA mutations compared to 8.6% without a family history. Other than breast cancer, the presence of ovarian, prostate, tubal cancers and melanomas in the family point towards a high possibility of familial inheritance.

Personal history: A personal history of breast cancer increases the risk of contralateral breast cancer. The age at diagnosis significantly influences the risk of a subsequent ovarian or breast cancer in BRCA carriers. If a 60 year old BRCA2 carrier has a 48% and 3.9% cumulative risk of breast and ovarian cancer respectively at 80 years, the risk is 66% and 12.2% respectively in a similar 30 year old BRCA2 carrier [8]. The US Preventive Services Task Force (USPSTF) recommends thorough evaluation with emphasis on family history during evaluation of women with suspected hereditary breast cancer prior to genetic testing. This is seconded by American Society of Breast Surgeons [6].

Pedigree charts: The pedigree chart should be complete in all aspects with respect to detailed histories of cancer occurrence on both paternal and maternal

sides, for at least 2 generations. The age at diagnosis and outcomes of cancers in every individual should be clearly documented.

18.2.2 Risk Assessment

18.2.2.1 Models in Use [6–8, 12–18]

The goal of risk assessment in breast cancer is to estimate (a) the life-time risk of developing breast cancer in an individual and (b) risk of being positive for high-risk mutations like BRCA1 or 2.

A variety of risk assessment tools are in use to predict the risk of hereditary breast or ovarian cancers in a particular individual. These include (i) Gail model or the Breast Cancer Risk Assessment Tool (BCRAT) (ii) Claus and extended Claus model (iii) BRCAPRO model (iv) Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (v) Tyrer-Cuzick model or the International Breast Cancer Intervention Study (IBIS) model (vi) Breast Cancer Surveillance Consortium (BCSC) breast cancer risk assessment tool and (vii) Penn II and (viii) Rosner & Colditz model.

These models/tools use a combination of demographic and historical data to quantitatively estimate risk of cancer occurrence and are particularly useful in those women who are presumed high risk with no identifiable mutations detected during genetic testing, which can vary from 64 to 87%. All of the mentioned models/tools achieve one or both the goals alluded to earlier. To assess the breast cancer risks temporally with accuracy, all known risk factors need to be available. Some of these tools which are used for estimation of BRCA mutations primarily help is breast cancer risk estimation regardless of the mutation being tested. A 'high risk' individual is one whose estimated life time risk of acquiring cancer is more than 20%. A list of risk assessment models are given below. A recent version of the Gail model includes many parameters such as BMI, weight, HRT, alcohol consumption, diet, physical activity, breast density etc. which overcomes some of the drawbacks of the original model. Table 18.1 below shows the various risk assessment models for breast cancer and/or BRCA mutation risk.

18.2.2.2 Interpretation of Results

These tools estimate the risk of cancer development in the individual tested and risk estimates are usually for 10 years or lifetime. These models can guide or refer patients for genetic counselling if patient carries a high risk of carrying BRCA mutation [6].

18.2.2.3 Drawbacks

None of these models define a numeric threshold or upper limit of risk in order to evaluate the appropriateness of genetic testing in the individual tested [6].

Table 18.1 Various models in breast cancer risk assessment

Name	Components	Comments
Gail/BCRAT	i) Age ii) Age at menarche iii) Age at first life birth iv) Previous breast biopsies v) Ethnicity vi) Number of affected first-degree female relatives vii) Previous ADH	a) Assess eligibility for chemoprevention b) Not suitable for predicting cancer risks in BRCA1/2 mutation carriers c) No information regarding family history of ovarian cancer, paternal history of cancer and history of breast cancer in more distant Maternal relatives d) no assumptions about genetic traits
Claus and Extended Claus	*Claus*: i) Age ii) Age of onset of breast cancer iii) Number of affected first- and second degree female relatives *Extended Claus:* Addition of risk for bilateral disease, ovarian cancer and three or more affected relatives	a) Does not include non-hereditary risk factors b) Discrepancy in results between published tables and computerized versions c) Reflect risk for women in the 1980s in USA d) Extended model estimates risk of contralateral breast cancer and BRCA mutations
Tyrer-Cuzick/ IBIS	i) Age ii) Age at menarche iii) Age at menopause iv) Age at first child birth v) BMI vi) HRT use vii) Bilateral breast cancer viii) Ovarian cancer ix) Age of onset of breast cancer x) Number of affected first- and second degree female relatives xi) Previous breast biopsies xii) Previous ADH/LCIS	a) Assess eligibility for chemoprevention b) Factors in presence of multiple genes of differing penetrance c) Good risk estimation overall d) Estimates risk of BRCA1/2 in family
BRCAPRO	i) Age ii) Age of onset of breast cancer iii) Number of affected first- and second degree female relatives iv) Bilateral breast cancer v) Ovarian cancer vi) Male breast cancer	a) Estimates contralateral breast cancer risk b) Includes information regarding affected and unaffected relatives c) Estimates for likelihood of BRCA1 or BRCA2 mutation d) Doesn't incorporate non-hereditary risk factors e) Accounts for multiple ethnicities f) Accounts for mastectomies in relatives
BOADICEA	i) Age ii) Age of onset iii) Number of affected first-, second- and third-degree female relatives iv) Bilateral breast cancer v) Ovarian cancer vi) Male breast cancer	a) Estimates contralateral breast cancer risk b) Computer based programme c) Non-BRCA mutation risk is estimated d) Useful as a research tool

Table 18.1 (continued)

Name	Components	Comments
BCSC-BCRAT	i) Age ii) Family history iii) Previous biopsies iv) Breast density v) Ethnicity vi) Previous benign breast diseases vii) Polygenic risk score using SNPs	a) Validated in the Mayo mammography health study b) Estimates 5-year risk of cancer c) Not applicable for women younger than 35 or older than 74 years d) Not applicable for those with prior mastectomy or personal H/o breast cancer/DCIS
Penn II	i) Age of onset of cancer in family members ii) Ethnicity iii) Bilateral breast cancer iv) Male breast cancer v) Ovarian/tubal cancer vi) Prostate/pancreatic cancer vii) Age of youngest breast cancer in family viii) First –degree relatives with cancer	a) Assess probability of BRCA mutations b) Doesn't predict breast cancer risk c) Triages for genetic testing d) Involves details from both maternal and paternal lineages
Rosner & Colditz	i) Age ii) Age at menarche iii) Age at and type of menopause iv) Age at first birth v) Age at subsequent births vi) Previous benign breast disease vii) HRT viii) Family history ix) Weight x) BMI xi) Alcohol consumption xii) Oestradiol levels	a) Applicable for women up to 70 years b) Predicts risk of breast cancer at 5 years c) Better than Gail model in risk estimation d) Bio-mathematical model based on incidence of breast cancer and number of breast cancer cell divisions

ADH: atypical ductal hyperplasia; BMI: body mass index; HRT: hormone replacement therapy; LCIS: lobular carcinoma in situ; DCIS: ductal carcinoma in situ; SNP: single nuclear polymorphism

18.2.3 Genetic Testing

18.2.3.1 Definition

It is the study of an individual's DNA to identify genetic differences or assess the susceptibility to particular diseases or abnormalities in DNA sequence or chromosomal structure.

18.2.3.2 Criteria/Indications [1, 3, 6–8, 13, 14, 19–21]

The indications or criteria to perform a genetic test on an individual at risk depends on whether a 'high risk' mutation has already been identified in the family or it. If *BRCA1 or 2 mutations has been detected* in a family, all individuals above the age

of 25 years from that family should undergo genetic testing (if not already tested). If the *mutation is not yet identified*, then the following criteria are used for channeling patients towards genetic testing:

(a) Breast cancer diagnosis at or before 45 years of age
(b) First or second-degree relative with breast cancer diagnosis at or before 45 years of age
(c) Ashkenazi Jews with a family history of breast cancer, diagnosed at any age
(d) Presence of two or more breast primaries: bilateral/multi-centric/synchronous, in a single family member
(e) Presence of breast and/or pancreatic cancer in two or more relatives on the same side of the family
(f) Personal or family history of ovarian, fallopian, or primary peritoneal cancer
(g) Male breast cancers
(h) A diagnosis of TNBC at or before 60 years of age, irrespective of family history
(i) Breast cancer patients with family history of two or more relatives with breast cancer, diagnosed at any age.
(j) Breast cancer patients with family history of ovarian cancer in first-, second-, or third-degree relatives
(k) Breast cancer patients with a male breast cancer relative
(l) Breast cancer patients with family history of pancreatic and/or prostate cancer (Gleason score: ≥7) in two or more first-, second-, or third-degree relatives
(m) If the combined BRCA1 and BRCA2 mutation carrier probability is ≥ to 10%
(n) In patients with BRCA related cancers, to evaluate the need for targeted therapy (PARP inhibitors)

18.2.3.3 Principles [1, 7, 12, 13, 20]

The risk of an individual acquiring mutations within a family depends on:

(i) Causative gene involved
(ii) Penetrance of the gene
(iii) Age and gender of the parents affected with the mutation
(iv) Risk reducing strategies (screening/surgery) adopted by the parents
(v) Death of the affected parent at an early age
(vi) Cancer diagnosis in one or both parents

As BRCA mutations show autosomal dominant mode of inheritance, most individuals acquire the mutations from either parents via germline pathway. Hence, testing of both parents of affected individuals seems prudent to identify from which side of the family the mutation has been passed and therefore at risk. The types of cancers occurring in a particular family may guide to which parent to be tested first. Rarely, both parents may not show the genetic mutation indicating a de-novo appearance of the mutation being tested. In case of BRCA mutations, this is very rare (<5%).

Table 18.2 Relationship to the proband and degree of risk

Name	% risk	Factors involved
Sibling	50%	Genetic status of both parents of the proband
Offspring	50%	Genetic status of both parents of the proband, gender of the offspring and penetrance of the involved gene
Other relatives	Variable	Genetic status of both parents of the proband, relationship with the proband (second/third degree)

The risk of acquiring the mutations by a sibling, offspring or other members of the family is shown in Table 18.2. Cancer development, however, is multifactorial even in the presence of these mutations. Testing of cancer affected individuals within the family ('best test' candidate) increases the probability of a positive result.

All patients who are candidates for genetic testing must be made available to them with inclusion of genetic counselling. The patients and their family members must be appraised about the information and implications about a particular test. Clear cut guidelines for genetic testing for moderate risk genes is lacking. The risk factors, risk estimates and the utility of genetic testing in these patients is not well established.

18.2.3.4 Genetic Counselling [1, 4, 14, 20–23]

An important component of genetic testing is genetic counselling before and after genetic testing. This is recommended whenever there is a clinical suspicion of a hereditary syndrome. The purpose of genetic counselling is (i) to explain the pros and cons of genetic testing (ii) to assess the need for testing the patient/individual in question based on their family/personal history (iii) to assess the risk for developing cancer (iv) to explain regarding the need for early detection and prevention (v) to explain the expenses involved in testing (vi) to provide information regarding reproductive options available and (vii) to offer psychological support to affected individuals.

The pre-test to counselling focusses on the intricate details of genetic testing, the financial and psychological implications of the test and the various options available for likely results. The post-test counselling involves careful interpretation of the results and counselling regarding the risk reducing options available. The type of BRCA mutation detected after testing is important to individualize risk reducing methods among high-risk women: for BRCA1, surgery is preferred over chemoprevention while in BRCA2, options of chemoprevention or surgery or surveillance can be pursued.

The potential advantages of genetic counselling are (a) improved adherence to risk reduction strategies (b) lower distress levels (c) improved surgical decision making with adequate information about surgery (d) better patient satisfaction (e) lower overall costs (f) helps deciding the appropriate time for a genetic test (g) helps in deciding alternative tests for those with no BRCA mutation identified during testing (h) prevents unwanted genetic testing in those with no clear cut indication and (i) decreases the burden on the treating physician who would otherwise had to double up as a counsellor.

Although concerns about the psychological effects of disclosure of results following genetic testing exist, their effects are not clinically evident and do not warrant therapeutic intervention routinely. Most patients show a decline in stress levels by 12 months following the test and faster if genetic counselling had been offered prior to testing. Another area of concern is the protection to patients and families from social and ethical implications of genetic testing that involves patient's guidance to accept their biological and genetic differences, education of genetic responsibility and allay fears of genetic discrimination.

A number of models for genetic counselling are practiced:

(a) ***DNA-direct model***: Telephonic call + written information sheet explaining details of test → BRCA testing → face-to-face counselling by genetic counsellor → options given for further management.
(b) ***Telephone-based counselling model***: Useful in low and middle income countries to provide genetic counselling to people in remote or rural areas. Helps in identifying individuals at need for genetic testing. This is associated with lesser costs.
(c) ***Royal Marsden testing model:*** Involves non genetic healthcare workers to undergo an online training with clear understanding of all protocols → genetic counselling during routine oncology work up → involving trained genetic counsellors if need arises or clarifications are needed.
(d) ***Huntington protocol:*** Involves 2–4 counselling sessions (over a period of 3 months) of unaffected family members/relatives of carriers who wish to undergo genetic testing to determine if they carry the deleterious mutations. Once the counselling is over, the results are conveyed to them.

In developing countries, genetic counselling is most often the responsibility of the treating oncologist as genetic counsellors are not available in routine day-to-day practice. This is referred to as ***mainstreaming*** and involves providing treatment related information in the initial phase by a non-genetics specialist which is proceeded by a formal genetic counselling if patients show positive result on genetic testing and/or have a complex family history of cancer. By this method, autonomy and informed consent is adhered to and stays with the patient while psychosocial issues are simultaneously catered to. Both oncology and genetic counselling platforms should work in tandem to obtain best results that improves patient care. Besides, the availability of up to date information and sophisticated technology can help channeling patients towards clinical trial programmes.

However, not all patients who are candidates for genetic testing end up getting tested or undergo genetic counselling. In a large trial [24] involving 11,159 patients undergoing BRCA testing once a diagnosis of breast cancer was made, only 36.8% of patients underwent genetic counselling. These patients displayed better overall satisfaction towards testing process compared to controls. The various barriers for the same include (i) ignorance about the need for and/or availability of genetic testing (ii) non affordability of undergoing the test (iii) low socioeconomic status and lower education levels (iv) fear of discrimination in

case of positive report (v) lack of trust on or lack of access to healthcare systems and (vi) language and cultural barriers.

18.2.3.5 Testing Platforms [7, 12, 14]

Multiple testing platforms are commercially available (Table 18.3).The factors that are important when choosing a particular platform include: (a) cost of the test (b) ease of use (c) reliability and accuracy of results (d) turnaround time (e) number of genes being tested at a given time (f) rate of obtaining at least one genetic variant of unknown significance (VUS) and (g) whether the test is covered under insurance schemes. Currently there are no recommendations about the type of test used for the given clinical scenario.

Table 18.3 Various genetic testing platforms in clinical use

Name	Genes tested	Utility
Integrated BRACAnalysis™	BRCA1 BRCA2	a) Short turnaround time b) Results for which evidence-based guidelines for clinical application are given c) Low rate of VUS d) Blood or oral rinse sample sufficient
BRCAPlus expanded™	BRCA1 BRCA2 ATM CHEK2 PALB2 CDH1 PTEN p53	a) Uses NGS panel or sanger sequencing b) Single gene testing can also be done c) Helps in breast screening and guides in usage of breast MRI d) Performed in blood or saliva
BreastNext™	17 genes	Uses NGS or sanger sequencing
MyRisk™	35 genes	a) Tests for genes associated with 8 cancers b) Gene selection based on type of cancer, penetrance of gene and clinical significance c) Higher chances of uncertainty with moderate penetrance genes d) Testing done in blood sample
BRAC analysis large rearrangement test (BART).	BRCA1 BRCA2	a) Identifies large genomic arrangements b) Useful in those who have no mutations identified on BRCA testing but are at risk for carrying the gene c) Expensive
Hereditary high-risk breast cancer panel™	8 genes	a) Assess non coding regions as well b) Assess genes that possess well-defined criteria for management c) for hereditary mutations only
BROCA assay	49 genes	a) Detects mutations simultaneously in multiple genes in a single sample b) Used for those who test negative for BRCA c) Tests for melanoma, pancreatic and colon cancers

18.2.3.6 Interpretation of Results [6, 7, 12, 20]

Results obtained from genetic testing may be reported as (a) benign (b) likely benign (c) uncertain significance (d) likely pathogenic and (e) pathogenic. They can also be reported as (a) true positive (b) true negative (c) uninformative and (d) variant of unknown significance (VUS). Uninformative result is a negative test in a family in whom a mutation is yet to be identified. VUS is defined as a genetic change without a proper correlation to actual clinical risk. It includes identification of mutations which may or may not be of clinical importance.

A positive mutation (positive test) of BRCA is an indicator of high likelihood of developing cancer although it doesn't confirm the actual presence of cancer. However, a negative test does not completely eliminate the risk of cancer development as a result of sporadic or non BRCA related genetic mutations.

18.2.3.7 Implications [7, 20, 25]

1. ***For the patient:*** The results of the test influence decision making in at-risk patients, surveillance or risk reducing surgeries. It can have therapeutic implications as well (e.g., use of olaparib as maintenance therapy). For a*t-risk asymptomatic adult relatives*: All at-risk relatives must be counselled and tested for the offending mutation and if found, recommendations for screening or risk reducing strategies must be offered. Those who test negative for the mutation may still be at a higher risk of developing cancer based on personal or family history. Therefore close surveillance is recommended.
2. ***Family planning****:* If the offending mutation is detected in young individuals, they must be offered genetic counselling with emphasis on potential risks to offspring and option of pre-natal genetic testing when pregnancy occurs.
3. ***For* at-risk *asymptomatic relatives < 18 years*:** Genetic testing is not recommended for at-risk young individuals as (a) screening or risk reducing measures begin at 25 years and above and (b) by that time, all of them can take independent decisions regarding the screening or risk reducing options available. Only if the proband in the family is affected at a younger age, then genetic testing at ages below 18 years is recommended.
4. ***DNA banking***: Storing DNA for future research on understanding the genetic basis of disease inheritance and causation is possible.
5. ***Long term follow up***: This is important to look for change in classification status of mutations.

18.2.3.8 Indian Scenario

Data on genetic testing in India is still in its infancy. In a study [26] involving >1000 patients from India being tested for mutations for hereditary breast and ovarian cancer, 30.1% showed a positive result, majority (85%) of which were BRCA1/2 mutations. 75% of those detected were less than 40 years of age and had a first-degree affected relative in breast/ovarian cancer. The authors concluded that a cost effective multi-gene tool for genetic testing can improve screening practices in HBOC in a resource constrained setting. Some of the barriers applicable to Indian context include (a) absence of sufficient number of genetic counsellors (b)

language, social, cultural and financial barriers which prevent routine adaptation in day-to-day practice (c) fear of stigmatization (d) lack of multidisciplinary care clinics and (e) time constraints in a busy OPD. To overcome some of these barriers, some of the recommendations include training of people in genetic counselling, educating people to come forward for genetic testing, incorporating guidelines for genetic testing and counselling in cancer guidelines, improving multi-disciplinary care and provide cost effective genetic testing to all in need [20].

18.3 Screening Strategies

Detection of disease in asymptomatic individuals is called screening and in the setting of HBOC syndrome, screening gains paramount importance in detecting pre-malignant lesions or cancers at an early stage so as to improve survival [6].

18.3.1 Principles [8, 27]

Screening of high risk individuals generally commences in the 3rd decade (see table below) or 5–10 years earlier than the age at diagnosis of the index patient in that family. Screening involves a shared decision making between the health care provider and the patient, so that the pros and cons of the same are clearly understood. It includes a combination of clinical and radiological assessments performed at regular intervals, and compliance to such a schema is necessary to optimize outcomes from screening. Patients with HBOC syndrome are at heightened risk of both breast and ovarian cancers. Although guidelines for breast cancer screening is robust, the same for ovarian cancer is still controversial.

18.3.2 Indications [25]

All known mutation carriers (includes moderate and high risk mutations) should be screened. (i) Women considered at risk of carrying the deleterious mutations, in the absence of genetic test results or (ii) those unwilling for risk reducing surgeries or chemopreventive measures following a positive test result should also be included in screening. The need for a dedicated genetic and breast clinic to manage such women cannot be overemphasized.

18.3.3 Types [14]

There are two types of screening high risk individuals: *family history based* screening and *population based* screening. Though the former is most commonly practiced, the latter is increasingly advocated for those with Ashkenazi Jewish descent. Results from an RCT [28] conducted in the UK looking at family history versus

population based screening involving Ashkenazi Jewish women more than 30 years of age, concluded that 56% additional mutation carriers could be identified, with no impact on quality of life or increase in psychological problems with population based screening. However, the pitfalls of population screening is increased incidence of VUS in the population being tested and cost implications involved considering that incidence of BRCA mutations in the general population is low (BRCA1: 1 in 300 and BRCA2: 1 in 800 prevalence rate).

18.3.4 Methods for Breast Cancer Screening

(a) ***Self-breast examination (SBE):*** or 'breast awareness' starting at 18 years of age is recommended. This includes regular self-examination of both breasts at monthly intervals and reporting of any abnormal feel or palpable lumps noticed in the breast. Any changes in personal or family history must also be reported [27].

(b) ***Clinical breast examination (CBE):*** Though CBE remains controversial in the general population, in high-risk individuals, CBE is recommended from 25 years of age or 10 years earlier than the age of the youngest affected member in the family semi-annually, whichever is earlier [25].

(c) ***Mammography (MMG):*** Screening MMG is recommended between 40 and 49 years at 18 monthly intervals which increases to 3 yearly intervals after 50 years [14]. Moderate risk mutation carriers with no significant family history may be subjected to annual MMG alone [13]. Below 40 years, MMG as a screening tool is not recommended due to (i) higher breast density in younger women that reduces the sensitivity of MMG (ii) potential risk of development of breast cancer from radiation exposure as a result of DNA damage and inability to effectively repair these damages in mutated individuals and (iii) missing of interval cancers as most tumours in this age group are hormone (ER/PR) negative cancers [5, 8, 13, 14, 25, 29]. Availability of breast MRI is a factor which determines the need for MMG screening in young women. However, MMG is useful in detecting DCIS and subtle changes in breast architecture at an early stage [8] and its specificity is higher (>95%) than MRI.

(d) ***Breast MRI:*** Annual breast MRI commencing at the age of 25 remains the standard of care with incorporation of annual MMG after the age of 30 [12, 25]. The indications for breast MRI include (i) women with known hereditary cancer syndromes (ii) first degree relatives of women with deleterious mutations or (iii) life time risk of breast cancer ≥20% or 5-year risk ≥6% by risk assessment tools [5, 13]. Addition of a dedicated breast MRI into the screening algorithm has the following advantages: (i) higher detection of additional cancerous lumps, albeit at an early stage (reduces the incidence of advanced cancers by almost 70%) (ii) detection of more aggressive histologies like TNBCs (iii) absence of ionizing radiation and (iv) at least 2 times more sensitive than MMG (71–100% vs 25–59%) in detecting early lesions [5, 6, 8, 13, 27, 30]. In a Norwegian study [31] evaluating 867 MRIs performed in BRCA carriers, 25

cancers were detected, including 5 interval cancers. The sensitivity of MRI compared to MMG was 86 vs 50%. A meta-analysis evaluating 11 studies depicted an overall sensitivity of 68–100% for MRI [32]. However, MRI has its own limitations namely (i) high false positivity resulting in unnecessary interventions like biopsies (ii) inability to use in claustrophobic patients (iii) need for different positions to obtain image accuracy (iv) need for intravenous contrast (v) restriction of use in renal failure patients (vi) expensive modality and (vi) non availability of MRI guided biopsies at all suites [13, 30]. Besides, neither improved overall survival nor mortality reduction has been achieved using MRI [13, 14, 27]. But in high risk women, improved detection rates clearly outweigh above limitations. The routine use of MRI in women with moderate risk mutations (e.g., ATM, CHEK2) remains controversial [13].

(e) ***Combined MMG and breast MRI:*** at 6 monthly intervals alternatively (MMG-MRI-MMG-MRI-MMG-MRI…so on) helps in detection of interval cancers as patients receive at least one screening modality semi-annually [1, 27]. This combination is more sensitive (80–100%), more cost effective [27] but less specific (73–90%) than either modalities alone, although evidence for the same is lacking [13, 14, 25, 27]. A recent meta-analysis reported that addition of MRI to MMG increased the sensitivity of screening (94.1 vs 38.1%), although the sensitivity of MRI alone was similar to both modalities combined (84.4% vs 94.1%) [33]. Beyond 75 years, the need for screening needs to be individualised [1].

(f) ***Breast USG*:** It serves as an add-on investigation to MMG, especially in centres where breast MRI is not available [25]. It can be used in women of all ages, although its utility remains in younger women. Advantages include absence of ionizing radiation, minimal or no discomfort, inexpensive and can be repeated when necessary. However, quality of reporting lies on the experience of the radiologist performing the scan.

(g) ***Tomosynthesis:*** Although not specifically analyzed in high risk women, the use of tomosynthesis in addition to routine MMG is associated with improved sensitivity (detection of one additional case of invasive cancer for every 1000 women screened) with fewer call back rates. However, the radiation exposure is higher with this modality [13].

(h) ***Tomosynthesis with USG*:** This combination may be useful in younger women with more dense breast, although false positive rates may be higher [13].

(i) ***Contrast mammography:*** It is an upcoming tool which is being tested as a potential substitute for MRI when combined with MMG [13].

18.3.5 Methods for Ovarian Cancer Screening

(a) ***Ovarian symptom index (OSI)*:** This consists of constellation of symptoms such as positive pelvic or abdominal pain, bloating sensation, increased abdominal girth or early satiety occurring more than 12 episodes monthly for <1 year. Each parameter is scored if symptoms are noted and the score is cal-

culated. It serves as a useful triaging tool. However, the specificity and positive predictive value (PPV) of OSI is very low to be used alone [14].

(b) ***CA 125 or Cancer Antigen 125:*** This tumour maker, as a screening tool in isolation in high-risk women is controversial. Being non-specific, values must be correlated with age, smoking habits, menopausal status or presence of conditions such as tuberculosis, pelvic inflammatory disease, endometriosis, all which are likely to give a false positive result. In ovarian cancer, elevated CA 125 levels are seen in only half of the patients affected with early stage disease that lowers specificity [14]. The normal value of CA 125 is 35 U/ml. Though annual measurements has low specificity in average-risk population, elevated levels (≥30 U/mL) serves as a predictor of ovarian cancer, with relative risk at 1 and 5 years of 35.9% and 14.3% respectively.

(c) ***Transvaginal USG (TVUS):*** This modality has demonstrated high sensitivity and specificity as a screening tool for ovarian cancer. It is commended at the age of 30–35 years [12, 29]. According to one study [34], 70% of screen detected cancers using TVUS were in early stages (stages I/II) with a better 5 year survival of 84.6% when compared to 53.7% in unscreened women.

(d) ***TVUS and CA-125:*** This combination is commenced semi-annually or annually at 30–35 years or a decade earlier than the youngest affected individual in the family [4, 8]. In a large screening trial [35] involving more than 34,000 women, after 4 rounds of screening, the positivity rates for TVUS and CA125 respectively were 2.9–4.6% and 1.4–1.8%. However, both tests being positive was extremely low (0.05–0.12%). The rate of biopsy after a positive result on screening was 13.8–33.8%, decreasing with each round of screening. The overall PPV of screening was low (1–1.3%). To translate these trial results into high risk population remains controversial and as such, lack of high quality evidence for the use in high–risk women precludes universal adaptation of screening. Besides, early detection from screening is not guaranteed [21].

(e) ***Combination of the OSI and CA-125:*** This combination is better than either combined in cancer detection.

(f) ***Combining age-specific incidence of cancer and absolute CA-125 levels:*** This combination improves sensitivity (62%–86%) and specificity (98%) [14].

(g) ***Human epididymis protein 4 (HE4):*** Although the sensitivity of this marker is similar to CA 125, its use has been restricted for use as a prognostic marker for recurrence/progression rather than a screening tool [14]. In a study involving 531 women with pelvic masses, an algorithm based on HE4 and CA-125 properly classified 93.8% of high-risk ovarian cancers [36].

18.3.6 Guidelines [7] (Table 18.4)

18.3.7 Screening for Men with BRCA [7, 8, 19, 21]

1. SBE and CBE starting at 35 years and mammography at 40 years
2. Prostate cancer screening at 45 years especially in BRCA2 carriers

Table 18.4 Guidelines on breast and ovarian cancer screening promulgated by various bodies

Organ	Name	Recommendation
Breast	NCCN	1) SBE monthly beginning at age 18 years 2) CBE every 6 to 12 months beginning at age 25 years 3) Annual breast MRI from 25 to 29 years up to 75 years 4) Annual mammogram and breast MRI scan from 30 to 75 years and 5) Consideration of chemoprevention and risk-reducing mastectomy 6) USG screening is not recommended
	NHS	1) Annual breast MRI starting at age 25 years 2) MMG every 18 months between ages 40 and 49 years and 3) MMG every 3 years starting at age 50 years
	ACS	Breast MRI for any woman with a lifetime risk of ≥20%
	ESMO	1) CBE every 6–12 months starting at age 25 or 10 years before the youngest affected member in the family, whichever is earlier 2) Annual screening MRI starting at age 25 with the addition of annual MMG at age 30
		Presence of other (non BRCA)high- or moderate risk mutations: Screening CBE every 6–12 months starting at 20–25 years with annual breast MRI between 20 and 75 years (with mammography considered if MRI is not available) [5, 20, 24]
Ovary	NCCN	CA 125 (after day 5 of menstrual cycle) + TVUS (on D1 and D10 of menstrual cycle) every 6 months commencing between 30 and 35 years or 5 to 10 years earlier than the youngest diagnosis of ovarian cancer in the family. However, routine screening is not recommended
	USPTF	Potential harms of general population screening for ovarian cancer outweigh any potential benefits (recommended against screening)

NCCN: National Comprehensive Cancer Network; ACS: American College of Surgeons; ESMO: European Society of Medical Oncology; USPTF: United State Preventive Services Task Force; NHS: National Health Scheme

18.3.8 Screening for Breast Cancer After Ovarian Cancer Diagnosis/Treatment [13]

The appearance of a subsequent breast cancer in the first 2–5 years after ovarian cancer diagnosis is low. Beyond 5 years, breast cancer risk exceeds the risk of ovarian cancer recurrence at 2–6%. In general, 10% of BRCA carriers develop a metachronous breast cancer within 10 years. Studies by Vencken et al. [37] and Domchek et al. [38] have both reported 11% risk of primary breast cancer (with a 7% risk of contralateral breast cancer in the former study) at 10 years of follow up. Hence, screening becomes imperative after 5 years of ovarian cancer diagnosis. However, breast cancer specific mortality is low and prognosis (stage, remission status) of the ovarian cancer determines the need and intensity for subsequent screening. MMG and breast MRI are most commonly used for screening. The psychological quotient of individuals must also be catered to as appearance of a second cancer can be emotionally and financially taxing.

- Early stage ovarian cancer at diagnosis: aggressive screening after 2 years of diagnosis

- Advanced stage ovarian cancer under remission: screening at 2–5 years
- Advanced stage ovarian cancer not under remission: no screening recommended
- Individuals keen on continuing screening must be offered irrespective of stage/prognosis

18.4 Risk Reduction Strategies

18.4.1 Prophylactic or Risk Reducing Mastectomy

18.4.1.1 Introduction

Prophylactic or risk reducing mastectomy is an important risk reducing surgery in high risk women. When performed as a primary preventive procedure, it is referred to as *'bilateral prophylactic mastectomy'* and when performed as a secondary preventive procedure (i.e. once cancer is diagnosed on one side), *'contralateral prophylactic mastectomy'* [21]. Studies on prophylactic mastectomy have reported an increase in utilization over the years. A SEER analysis in 2007 showed an increase in prophylactic mastectomy rates from 1.8 to 4.5% over a 5 year period from 1998 to 2003 [39]. This increase has been attributed to various reasons namely (a) increased use of genetic testing tools to identify hereditary breast cancers or high risk mutations (b) overestimation of risk of developing contralateral breast cancer which is around 0.5–1% in average risk women and 4% in high risk women (c) increased utilization of pre-operative MRI which is associated with higher detection of multifocal lumps within the index or contralateral breast that increases the need for mastectomy and (d) better cosmesis and symmetry obtained with bilateral breast reconstruction performed in same sitting [30].

18.4.1.2 Rationale

Women with moderate-high risk mutations are at heightened risk of bilateral or contralateral breast cancers during follow up. Among BRCA1 and BRCA2 carriers, the risk of contralateral breast cancer is estimated to be 83% and 62% respectively by the age of 70. This risk estimate is age dependent: if the initial tumour is diagnosed before 40 years, the 25-year risk of contralateral breast cancer approaches 63%. If the same is diagnosed beyond 50 years, the risk drops down to <20% [13, 40]. Another study by Biglia et al. [41] demonstrated a 10 year risk of contralateral breast cancer to be 27% and 19% respectively in BRCA 1 and BRCA 2 carriers. Furthermore, BRCA1 associated cancers are mostly aggressive TNBC histology in whom chemoprevention is unlikely to be beneficial while in BRCA2, hormone receptor positive tumours are common and therefore prophylactic mastectomy is advisable in the former and may be optional in the latter [8].

18.4.1.3 Indications

Women with moderate and high risk mutations that increases their risk of acquiring breast cancer are candidates for prophylactic mastectomy. As effective screening tools for breast cancer are already in place, the need for prophylactic mastectomy

must be personalized with respect to each patient based on age of patient, type of at risk mutation, preference, personal and family history and prognosis of the index cancer at presentation [4, 5, 13, 27, 29, 30, 40]. However, robust evidence of efficacy of these procedures is lacking [5]. The age at which prophylactic mastectomy is recommended is at 25–30 years, when greatest benefit in survival is possible [27]. Others have quoted a meagre absolute benefit of 3% when performed at 40 years [13]. Hence an ideal patient for prophylactic bilateral or contralateral mastectomy would be a young BRCA1 carrier with or without an early, node negative breast cancer on one side. Likewise, patients with widely metastatic or advanced index cancers with poor response to systemic therapy are not candidates for bilateral mastectomy.

18.4.1.4 Techniques [1, 3, 8, 14, 25, 27, 29, 40]

The goal in prophylactic mastectomy is to completely remove all breast parenchyma with its lymphatics. A concept of '*conservative mastectomy'* was propounded by Nava et al. [42] who emphasized the need for preservation of appearance of the breast, biomechanical balance, adequate restoration of volume and symmetrical scarring in oncoplastic surgery. A number of techniques that can be utilized are (a) simple/total mastectomy (TM) (b) nipple sparing mastectomy (NSM) and (c) skin sparing mastectomy(SSM). Immediate whole breast reconstruction (flap/implant based) is performed routinely. On the contrary, subcutaneous mastectomy which leaves behind a considerable amount of breast parenchyma is not advisable. Although TM is easy to perform and removes >95% of breast parenchyma, it is associated with poor cosmetic outcomes and thus not recommended. Both NSM and SSM have good cosmetic outcomes and are safe with respect to breast cancer recurrences when compared with TM. The rate of local recurrence is 3.5–5.5% at the end of 5 years. One caveat when performing NSM is that tissue posterior to the nipple areola complex must be completely cleared off breast tissue as it could become a source of residual breast tissue and cancer. However, one must note that no procedure is completely fool proof to be able to remove breast tissue completely from the chest wall. For any technique being adopted, the pros and cons of each must be carefully discussed with the patient including psychological outcomes. Axillary staging is not necessary as nodal metastases is exceedingly rare.

18.4.1.5 Benefits

The most important benefit of prophylactic mastectomy is a reduction in the life time risk of breast cancer to the tune of 90% [1, 4, 5, 8, 13, 14, 21, 25, 27, 29, 40]. Addition of RRSO to prophylactic mastectomy increases to 95% [5, 40]. By decreasing the risk of subsequent breast cancer, the need for radiation and chemotherapy as treatment modalities is also lessened [27] and need for frequent surveillance of the breasts reduces. There is reduction in levels of anxiety among operated women [13]. However, whether this reduction in cancer risk translates to improved survival, especially after contralateral mastectomy is controversial [13, 19, 21, 25]. A few studies have reported gain in life expectancy (LE) from prophylactic mastectomy in BRCA carriers. Schrag et al. [43] and Grann et al. [44] respectively reported

2.9–5.3 years and 3.5 years absolute gain in life expectancy in those undergoing prophylactic mastectomy. When stratifying with respect to age at which mastectomy is performed, Kurian et al. [45] demonstrated 13% gain at 25 years compared to just 2% gain at 40 years in life expectancy in BRCA1 carriers and 8% vs 1% at same ages in BRCA2. Sigal et al. [46] concluded that delaying mastectomy by 5–10 years lead to reduction in LE by 1–9.9 years and 0.5–4.2 years in BRCA1 and 2 carriers respectively.

18.4.1.6 Implications

1. ***Occult cancer*:** The breast tissue removed after a prophylactic mastectomy could harbor occult malignancy is <5% [3, 25] although others have reported a risk of 5–10% [29]. A Japanese study evaluated women with BRCA mutations undergoing prophylactic mastectomy with pre-operative image based evaluation (MMG, USG and MRI) followed by serial pathological examination on resected breast specimen. The authors reported 11.3% risk of occult cancers in specimen in spite of thorough pre-operative radiological assessment and recommend detailed histological evaluation of specimen [47].
2. ***Psychological and psychosocial effects*** [13, 25]: Many studies evaluating psychological effects after prophylactic mastectomy have reported favourable outcomes at both short and long term follow up periods. Most women who opt for prophylactic mastectomy generally perceive a higher risk of cancer development to choose surgery over other risk reducing measures. Furthermore, loss of both breasts at same sitting can be emotionally taxing. Additionally, reconstructive outcomes if not satisfactory to patient's expectations or complications arising thereof could bring in feelings of guilt, depression and negative self-image and sexuality in emotionally labile patients. In a survey [48] conducted in high risk women who had opted for prophylactic mastectomy, few patients had feelings of regret, although all respondents demonstrated a sense of relief with lower anxiety levels with respect to breast cancer risk and screening. Similar results were obtained in another study [49] involving 14 women post prophylactic mastectomy who reported lower anxiety and high degree of satisfaction regarding their decision making. Issues regarding self-image, intimacy and physicality were also observed in the immediate post-surgery period.
3. ***Need for counselling*** [40]: A dedicated breast clinic with a comprehensive discussion about the benefits, reconstructive options available, complications arising due to surgery or reconstruction (e.g., sensory loss over the flaps and the nipple areola complex), perceived changes in cosmetic and body image, need for follow up and risk of occult cancer in the resected breast(s) should be explained preferable in the presence of a key male member of the family. Multiple counselling sessions may be warranted and queries arising thereof must be adequately addressed. They must be forewarned that there is no complete elimination of cancer at risk despite surgery.
4. ***Cost implications*** [40]: When the surgical costs are compared to costs associated with surveillance, it has been demonstrated that prophylactic mastectomy is more cost effective and associated with higher quality-adjusted life years

(QALY) in BRCA mutated women. To prevent one contralateral breast cancer development, 6 prophylactic mastectomies need to be performed (1:6). In non BRCA mutated women, cost implications depend on the QOL outcomes after mastectomy versus surveillance.

18.4.1.7 Drawbacks and Bias

Although the rate of utilization of prophylactic mastectomy has increased over time with improvement in survival among surgically treated women, this is related to a *selection bias*: women who are healthier, more conscious about their own health, financially sound (insurance schemes in place) and having better access to health care facilities are more likely to adopt for prophylactic mastectomy than the others which can reflect as improved survival in these women as shown in various studies. Besides, QOL issues are yet to be addressed [3, 30]. Additional points to be remembered when interpretation of survival results are *performance bias* (no objective conformation of the type of risk reducing surgery performed from medical records), *attrition bias* (differences in follow up among operated and non-operated women that can result in differing pick up rates of cancer during follow up) and *detection bias* (differences in screening tools and procedures adopted for operated and non-operated women), that can skew the results [3].

Prophylactic mastectomy for non BRCA mutated women with moderate risk gene (e.g. ATM, CHEK2) mutations has not been explored completely and hence use in these patients is controversial with no survival benefit [13, 40]. The same is with BRCA patients who have been diagnosed and treated for ovarian cancer is limited where survival advantage after mastectomy is questionable. However, if the patient is disease free after 2 or 5 years depending on the aggressive ness of the ovarian cancer, option of surveillance versus mastectomy may be offered to these patients [13]. Prophylactic mastectomy is not recommended in men with BRCA mutations as cancer risk in this particular subset of patients is lower than average risk women [8].

18.4.1.8 Complications

Prophylactic mastectomy is not without its attendant complications. The rate of complications increases proportionately to the type of reconstruction offered. The most common complications reported are hematoma formation, wound related morbidity and capsular contraction or other implant related issues, if implant based reconstruction has been performed. In one study [50], the rate of complications was 17.3% at end of 12 months and 30% by 60 months, implying that longer follow up is necessary to correctly measure the rate of complications. In another study [51], the complication rate was almost 50% with more than half of patients needing re-surgeries for the same. Manning et al. reported 7.3% skin flap or nipple areola related complication after nipple sparing mastectomy. Skin desquamation, hematoma formation and surgical site infections were 38.4%, 1.7% and 4% respectively [52]. Surgical morbidity is also associated with psychological problems and poor satisfaction towards the procedure, besides additional costs for interventions.

18.4.1.9 **Evidence** (Tables 18.5 and 18.6)

The conclusions [66] from the above studies are:

1. Prophylactic mastectomy reduces incidence of breast cancer significantly
2. There is an improvement in breast cancer specific survival over time, more profound in younger patients with no prior exposure to chemotherapy
3. There is a reduction in breast cancer specific mortality (48–65%) over time
4. The incidence of contralateral breast cancer is significantly reduced
5. Survival benefit for contralateral mastectomy is controversial; depends on the stage of the index cancer and timing of the contralateral mastectomy
6. Surgical morbidity can by substantial and is to be considered when evaluating psychological outcomes after prophylactic mastectomy

Table 18.5 Various studies of prophylactic mastectomy in breast cancer

Author	Year	Population studied	n	F/U(mo.)	PM group	Control group	CA breast incidence (%)	Other findings
Heemskerk-Gerritsen [51]	2007	HBOC	358	54.0	358	–	0	OCA: 0.84%
Manning [52]	2015	BRCA1/2	89	28, 26	89	–	0	OCA: 0% BCSM:1.1% ACM:2.2%
Hartmann [53]	1999	+ve family history	639	168	214	403	1.4 vs 38.7	OCA: 0.1% BCSM:28.6%
Hartmann [54]	2001	BRCA1/2	26/214	160.8	26	–	0	RRed:89.5–100% ACM: 3.7%
Meijers-Heijboer [55]	2001	BRCA1/2	139	34.8	76	63	0 vs 12.7	OCA: 0% BCSM:12.5%
Heemskerk-Gerritsen [56]	2019	BRCA1/2	2857	123.6	1128	1729	1 vs 27 & 0 vs 19 for BRCA 1 and 2	BCSS (65 year): *BRCA1*–99.7 vs 93% *BRCA2*–100 vs 98% BCSM: *BRCA1*–1 vs 20 (HR:0.4); *BRCA2*–0 vs 7(HR:0.45)
Rebbeck [57]	2004	BRCA1/2	483	76.8	102	378	1.9 vs 48.7	RRed: 95%

(continued)

Table 18.5 (continued)

Author	Year	Population studied	n	F/U(mo.)	PM group	Control group	CA breast incidence (%)	Other findings
Domchek [58]	2010	BRCA1/2	2482	43.8, 51.5	257	1372	0 vs 7.1	*RRSO*: OC-1.1%; BC-11.4%; mortality-3% *No RRSO*: OC-5.8%; BC- 19.2%; mortality:10%
Geiger [59]	2005	High risk	472	123.6 74.4	276	196	0.4 vs 4	HR for BC:0.05 BCSM: 0 vs 0.2% OCA: 4.3%
Metcalfe [60]	2004	BRCA1/2	491	110.4	116	–	0.68 vs 28.9	10 year CBC risk: 29.5% (32 vs 24.5% for BRCA1 vs BRCA2); RRSO: 59% reduction in BC
Van Sprundel [61]	2005	BRCA1/2	148	42	79	69	1.26 vs 8.7	Reduction in CBC: 91% 5 year OS: 94 vs 77%
Peralta [62]	2000	CPM	246	NA	64	182	0 vs 19.8	15 year DFS: 55 vs 28% 15 year OS: 64 vs 48%
Herrinton [63]	2005	Breast cancer U/L	56, 400	68.4, 57.6	1072	–	0.5 vs 2.7	BC: 12.4%; BCSM: 8.1 vs 11.7% (HR:0.57) ACM:13 vs 25%
Boughey [64]	2010	+ve family history with EBC	770	207.6	385	385	0.5 vs 8.1	10 year OS:83 vs 74% Better DFS in PM group

PM: prophylactic mastectomy; F/U: follow up; BCSM: breast cancer specific mortality; OCA: occult cancer; BCSS: breast cancer specific survival; ACM: all-cause mortality; RRed: risk reduction; LE: life expectancy; +ve: positive; mo.: months; OC: ovarian cancer; BC: breast cancer; RRSO: risk reducing salpingooophorectomy; CBC: contralateral breast cancer; EBC: early breast cancer; OS: overall survival; DFS: disease free survival; CPM: contralateral prophylactic mastectomy

Table 18.6 Various end points of the meta-analysis (From Ref. [65])

Parameter	Studies	Results
Breast cancer specific mortality	21 studies	Reduction
Contralateral breast cancer: Incidence	26 studies	Reduction
Contralateral breast cancer: DFS	26 studies	Inconsistent result
	7 studies	No survival benefit
Psychosocial parameters	20 studies	High levels of satisfaction with decision, reduction in worry; reduced body image satisfaction, reduced sexual feelings
Morbidity of surgery	17 studies	4–64% (with and without reconstruction)

18.4.1.10 Follow Up

Post-surgery, patients are followed annually with clinical examination. If flaps have been used for reconstruction, addition of single-view mammography or breast USG is recommended [27, 40]. At the end of the first year, breast MRI may be performed to identify the presence of any residual breast tissue [40].

18.4.1.11 Guidelines (Table 18.7) [7, 13]

All major guidelines have incorporated prophylactic mastectomy as part of risk reduction strategy in high risk women after thorough discussion given that effective screening protocols are in place already.

18.4.2 Risk Reducing Salphingo-Oophorectomy (RRSO)

18.4.2.1 Introduction

RRSO is an important risk reducing surgery in women with high risk mutations.

18.4.2.2 Rationale

Screening tools for ovarian cancer diagnosis is controversial. Although CA 125 and TVUS has been recommended by some for screening, their reliability is questionable. Advanced ovarian malignancy has poor prognosis despite treatment. These factors substantiate removal of ovaries which can prevent development of cancer in future in BRCA carriers [21].

18.4.2.3 Indications

All BRCA mutation carriers (especially BRCA1 mutations) should be counselled for RRSO after completion of family or childbearing. The ideal time to do so is around 35–40 years [1, 3, 4, 8, 12, 14, 21, 27, 29]. Around 65% of BRCA1 mutation carriers are estimated to undergo RRSO before natural menopause [67].

Table 18.7 Guidelines on prophylactic mastectomy promulgated by various bodies

Name	Recommendation
NCCN	Prophylactic mastectomy provides a high degree of protection against breast cancer in women with a *BRCA1/2* mutation and therefore recommended
USPSTF	Prophylactic mastectomy compared to none among high-risk women and mutation carriers reduced breast cancer incidence by 85–100% and breast-cancer mortality by 81–100%
SSO	Indications for bilateral prophylactic mastectomy include mutations in *BRCA1*, *BRCA2* or other strongly predisposing breast-cancer susceptibility genes or, in the absence of data on mutations, a hereditary breast-cancer syndrome
NICE	Appropriate only for a small proportion who are from high-risk families and must be managed by a multidisciplinary team; should be raised as a risk-reducing strategy option with all women at high risk

NCCN: National Comprehensive Cancer Network; USPTF: United State Preventive Services Task Force; NICE: National Institute for Health and Care Excellence; SSO: Society of Surgical Oncology

However, if the age of the index patient at diagnosis in the family is at a younger age or if the woman can completed family, then earlier the better. In BRCA2 carriers, as the onset of ovarian cancer is a decade later than BRCA1 carriers, RRSO at 40–45 years is also acceptable (risk of ovarian cancer by 50 years is around 1% in BRCA2), provided breast cancer prevention is underway [8, 13, 29]. However, delaying RRSO may decrease the extent of benefit of reduction in breast cancer risk [13]. Salphingo-oophorectomy rather than oophorectomy alone is indicated because (i) mutation carriers are at risk of fallopian tube cancers over time and (ii) the postulated origin of serous ovarian cancers is actually from the tubal fimbriae rather than the ovaries. Patients with RAD51 mutations are also candidates for RRSO [40].

18.4.2.4 Methods

RRSO can be performed by open or minimally invasive techniques, though the latter is preferred. The entire abdomen is inspected carefully to look for tell-tale signs of ovarian cancer (peritoneal nodules, metastases in liver) in the absence of which saline is instilled into the pelvis and washings are taken. *Bilateral Salphingo-oophorectomy* is then performed with ligation of the infundibulopelvic ligaments at least 2 cm proximal to the ovaries. The ovary and tube must be removed in entirety and subjected to thorough histological evaluation to rule out presence of STIC (serous tubal intraepithelial cancer) or occult cancer. The SEE-FIM protocol (Sectioning and Extensively Examining the FIMbriated end) is used for evaluation [8]. Performing a *hysterectomy* simultaneously is justifiable after childbearing, as future therapy with tamoxifen for breast cancer prevention in many BRCA carriers runs the risk of endometrial hyperplasias and cancer [8]. Use of *salpingectomy alone* with delayed oophorectomy is also being evaluated to reduce the risks of surgical menopause, albeit with no robust data at present backing it [8]. Similarly, *tubal ligation* has been shown by a meta-analysis to reduce the risk of ovarian cancer by 34% in the general population and some benefit may exist even for BRCA individuals [4, 7].

18.4.2.5 Benefits

RRSO has been reported to reduce the risk of ovarian cancer by 70–95%, breast cancer by 50–90% and fallopian tube cancer by 80% in BRCA carriers when performed in premenopausal women [1, 4, 7, 12–14, 19, 27, 29, 40, 67]. Both RRSO and prophylactic mastectomy if performed together, reduces breast cancer risk by 95% [1]. It reduces the all-cause mortality (around 77%), with a trend in reduction in ovarian cancer specific and breast cancer specific mortality rates in BRCA carriers [4, 8, 13, 14, 19, 21, 27]. Additionally, it can reduce the ovarian cancer incidence in post -menopausal women [14] and the risk of both ipsilateral and contralateral tumour recurrences in patients with breast cancer [19]. A reduction in cancer-related worry in 80% and satisfaction in decision taken for surgery in 95% has been reported [8].

18.4.2.6 Occult Cancer

The presence of occult cancer after RRSO is around 5% [29].

18.4.2.7 Drawbacks

Despite RRSO, BRCA carriers are at risk of primary peritoneal cancers, risk being 1–4.5% [4, 21, 29]. The implications are that continued gynecological surveillance is mandatory during follow up even after RRSO [29]. Also there are attended complications of surgical menopause namely osteoporosis, cardiovascular complications, hot flushes, reduced libido, dyspareunia, night sweats and cognitive effects [8, 27]. Some of these side effects may be ameliorated using topical oestrogen preparations. Reduction in breast cancer mortality has not been uniformly demonstrated which could be related due to selection bias [27].

18.4.2.8 Evidence (Tables 18.8 and 18.9)

The conclusions from the above mentioned evidence are:

1. RRSO reduces the risk of a subsequent breast (by 50%) and ovarian cancer (by 80%) significantly
2. It also results in significant reduction in ovarian cancer (by 95%), breast cancer (by 90%) and all-cause mortality (by 76%).
3. Risk of subsequent development of PPC still exists, despite the above advantages

18.4.2.9 Use of HRT Post RRSO

Use of hormone replacement therapy (HRT) after RRSO helps to ameliorate menopausal symptoms and improve QOL with no added risk of breast cancer development in BRCA mutation carriers who do not have a personal history of breast cancer. The duration and dose of HRT should be short term (till the age of natural menopause) and low dose [8, 12, 21].

Table 18.8 Published studies on risk reducing salpingo-oophorectomy

Author	Year	n	F/U(mo.)	RRSO group	Controlgroup	OC risk (%)	BC risk (%)	Other findings
Domchek [68]	2006	666	37.2, 25.2	155	271	1.3 vs 5.9	HR: 0.36	ACM (HR: 0.24) BCSM (HR: 0.1) OCSM (HR:0.05)
				188	478	–	–	ACM (HR:0.28) Not associated with BCSM or OCSM
Rebbeck [69]	2002	551	98.4, 106.8	259 99	292 142	2.3 + 0.8 vs 19.9	21.2 vs 42.3	–
Finch [70]	2006	1828	42	1045	783	1.73 vs 4.1	–	Risk of PPC: 4.3% at 20 years RRed: 80%
Kauff [71]	2008	1079	34–40, 38	509	283	0.59 vs 4.24	–	85% reduction in OC in BRCA1; 72% reduction in BC in BRCA2
Kauff [72]	2002	170	24.2	98	72	1 vs 7	3.06 vs 11.1	HR for either BC/ OC: 0.25
Rocca [73]	2006	4780	30, 31.2	2390	2390	–	–	HR:1.67 for ACM in RRSO before 45 years
Domchek [58]	2010	1370	36	336	1034	–	HR: 0.54	ACM (HR: 0.4)
Finch [74]	2014	3841	67.2	2507	1334	3.1 vs 8.1	–	ACM (HR: 0.23)
Mavaddat [75]	2013	988	24	309	679	–	HR:0.62	–
Kramer [76]	2005	98	198	33	65	–	HR:0.38	–

ACM: all-cause mortality; OC; ovarian cancer; BC: breast cancer; BCSM: breast cancer specific mortality; OCSM: ovarian cancer specific mortality; HR: hazard ratio; PPC: primary peritoneal cancer; RRed: risk reduction

Table 18.9 Main outcomes/results from the meta-analysis (from Ref. [77])

Parameter	Studies	n	Population studied	Results
Breast cancer outcomes	3 studies 4 studies 3 studies	5703	BRCA1 or 2 BRCA1 BRCA2	HR:0.49 HR:0.47 HR:0.47
Gynecological cancer outcomes	3 studies 1 study	2840	BRCA1 or 2 BRCA1	HR:0.21 Insufficient data

HR: hazard ratio

Table 18.10 Guidelines on risk reducing salpingo-oophorectomy and salpingectomy promulgated by various bodies

	Recommendations	
Name	Bilateral salpingo-oophorectomy	Salpingectomy alone
NCCN	Recommend typically between 35 and 40 years, and upon completion of child bearing	**Not the standard of care** and is discouraged outside a clinical trial. The concern is that women are still at risk for developing ovarian cancer
USPTF	Decreased breast cancer incidence by 37–100%, ovarian cancer by 69–100% and All-cause mortality by 55–100%	
Society of gynecologic oncology	The most proven method for the prevention of ovarian cancer with *BRCA1* or *BRCA2* mutation; prospective studies have reported a 70% to 85% reduction in ovarian cancer; recommended between the ages of 35 and 40 years	Can be considered in women at increased genetic risk of ovarian cancer **who do not agree to Salpingo-oophorectomy.** However, this is not a substitute for oophorectomy, which should still be performed as soon as the woman is willing to accept menopause, preferably by the age of 40 years

NCCN: National Comprehensive Cancer Network; USPTF: United State Preventive Services Task Force

18.4.2.10 **Guidelines** (Table 18.10)

18.4.3 Chemoprevention

18.4.3.1 Introduction

The use of drugs to prevent the development of cancer is termed as chemoprevention [27]. Chemoprevention is an important risk reducing strategy in high risk women who want to adopt non-surgical methods for risk reduction. The drugs commonly used in chemoprevention are

(a) Selective Estrogen Receptor Modulators (SERMs): tamoxifen, raloxifene
(b) Aromatase inhibitors (AI): exemestane, anastrozole
(c) Oral contraceptive pills (OCP)
(d) Hormone replacement therapy (HRT)

18.4.3.2 Indications

For patients with an increased risk of breast cancer electing not to pursue surgical intervention, the use of chemoprevention is a valuable non-surgical option [1, 2, 4].

18.4.3.3 Usage [5, 21, 27]

(a) SERMs: pre and post-menopausal carriers for 5 years (except raloxifene in post-menopausal women only)
(b) AIs: post-menopausal women for 5 years
(c) OCPs: avoid in young women
(d) HRT: premenopausal women with no comorbidities [40]

18.4.3.4 Benefits

(a) SERMs: Tamoxifen offers 50 and 62% reduction in risk of breast cancer in those with moderate- high risk mutations and BRCA2 mutations respectively [1, 4, 5, 7, 27]. There is also reduction in the risk of contralateral breast cancers, some with BRCA1 mutations also reaping the benefit (? reduction in TNBC) [4, 21].
(b) AIs: post-menopausal women for 5 years
(c) OCPs: Reduce risk of ovarian cancer by 50–60% in both BRCA1 and 2 mutation carriers [8, 13, 21, 27]. Others have quoted a reduction ranging from 14 to 38% depending on the duration of usage [7].
(d) HRT: Helps in mitigating menopausal symptoms and improve quality of life and reduce all-cause mortality after RRSO in those with no personal history of breast cancer. However, risk assessment based on a number of parameters must be taken into account [27, 67].

18.4.3.5 Drawbacks

(a) SERMs: Not useful in BRCA1 women as tumours are TNBCs (oestrogen receptor negative) [1, 4, 5, 27]. Also, mortality benefit has not been demonstrated from studies [5, 27]. Besides, tamoxifen is associated with risk of thromboembolism and endometrial cancers when used in post-menopausal women [27]. The benefit of tamoxifen as part of primary prevention strategy has not been conclusively demonstrated [21].
(b) AIs: Increased risk of osteoporosis and bone loss.
(c) OCPs: risk of breast cancer is controversial and especially in BRCA1 may be avoided if intent is solely chemoprevention for ovarian cancer especially in young women [14, 21]. The risk is higher before 20 years of age and before first pregnancy or use of 5 or more years. Progesterone only pills increase risk of endometrial cancers when used in BRCA1 carriers [67].
(d) HRT: long term use is associated with increased risk of breast cancer especially in younger women with early onset of use.

18.4.3.6 Evidence (Table 18.11) [2, 4, 5, 12, 13, 19, 27, 29, 67]

(a) *SERMs and AIs:* The evidence for SERMs and AIs for breast cancer prevention is well documented and depicted in table below.

Table 18.11 Various studies on chemoprevention in breast cancer

Name of study	n	Population	Arms	F/U (mo.)	Results
NSABP-P1/ BCPT [78]	13,338	High risk for breast cancer	Tamoxifen vs placebo	69	49% reduction in invasive cancers (HR: 0.51)
NSABP-P2/ STAR [79]	19,747	High risk for breast cancer (post-menopausal)	Raloxifene vs tamoxifen	81	Risk ratio—for invasive cancer:1.24; for non-invasive cancer: 1.22 (raloxifene)
IBIS-I [80]	7152	High risk for breast cancer +/− HRT use	Tamoxifen vs placebo	50	32% reduction in breast cancer, (HR of 0.68)
Map.3 [81]	4560	High risk for breast cancer (post-menopausal)	Exemestane vs placebo	35	65% reduction in breast cancer (HR: 0.35), for both invasive and non-invasive cancers
IBIS-II [82]	3864	High risk for breast cancer (post-menopausal)	Anastrozole vs placebo	131	49% reduction in breast cancer; higher in first 5 years; 54% and 59% reduction in invasive cancer and DCIS

BCPT: breast cancer prevention trial; HR: hazard ratio; DCIS: ductal carcinoma –in-situ; mo.: months

(b) *OCPs*: A large number of studies and meta-analyses have evaluated the role of OCPs and breast cancer risk. In the Oxford meta-analysis [83] conducted in 1996 which evaluated 54 epidemiological studies involving 50,000 breast cancer women, the authors reported 24% increase (RR: 1.24; 95% CI: 1.15–1.33) in the risk of breast cancer with current use of OCPs which remained sustained until 9 years of discontinuation with no risk beyond 10 years or longer duration of discontinuation (RR: 1.01; 95% CI: 0.96–1.05). Women who started OCP usage prior to 20 years of age demonstrated higher risk. In another meta-analysis [84] of 13 prospective cohort studies involving 11,722 women with breast cancer and 859,894 controls, the relative risk for breast cancer was 1.08 (95% CI: 0.99–1.17) that showed incremental increase by 14% with prolonged (every 10 years) usage. Bethea et al. [85] reported that OCP use within last 5 years was associated with increase in hormone positive, hormone negative and triple negative cancers with sustained risk even beyond 15–20 years of cessation and higher with hormone negative subtypes (OR:1.57–1.78). In a recent population based study [86] conducted in Denmark involving 1.8 million women, the relative risk of breast cancer with OCP use was 1.2 which increased to 1.38 with more than 10 years of use. In spite of discontinuation, the risk of breast cancer remained elevated in those who has used OCPs for 5 years or more. However, a large study involving 4500 women with breast cancer and equal controls reported no increase in risk of breast cancer with current of prior usage of OCPs [87]. Similarly, another study with 4200 women with breast cancer showed no association with breast cancer mortality and OCP use irrespective of duration or age of start of use [88].

(c) *HRT*: In a study [89] conducted in 872 BRCA1 carriers, the use of HRT after oophorectomy was not associated with an increased risk (HR: 0.97). However, after 10 years of follow up, the cumulative incidence of breast cancer was higher with combined pills compared to estrogen only pills (22 vs 12%). Domcheket al. [90] prospectively evaluated >1800 BRCA carriers from the PROSE study database for HRT use and breast cancer risk. They reported that in BRCA carriers undergoing RRSO, use of HRT was not associated with increased risk of breast cancer compared to those who hadn't undergone RRSO. In fact, HRT use in BRCA1 carriers irrespective of RRSO was associated with reduced breast cancer risk (HR: 0.29 [no RRSO] and 0.52 [RRSO]).

The conclusions from available evidence are:

1. The role of tamoxifen for primary prevention in BRCA mutation carriers is controversial as data is limited.
2. The efficacy of tamoxifen is higher in BRCA2 (compared to BRCA1) carriers, given the higher hormone positive cancers associated with this mutation.
3. None of the trials have evaluated chemoprevention solely in BRCA carriers. Most trials included BRCA carriers as part of other 'high risk' women.
4. Data on preventive efficacy of AIs is also limited. They have been studied in trials involving high risk women, rather than sole BRCA carriers.
5. Use of OCPs have produced conflicting results with respect to breast cancer risk, and contrary, may increase cancer risk in younger women.
6. Use of short term HRT may be instituted in those who have undergone surgical menopause. Long term use, however, is associated with increased breast cancer risk.
7. There is no data to support routine chemoprevention in non BRCA associated mutation carriers.

18.4.3.7 Guidelines

The USPSTF and ASCO recommend chemoprevention in women having a 5 year risk of breast cancer of at least 1.7% with a 3% cut off for post-menopausal women. The benefit should clearly outweigh the risks involved. The ACOG 2018 guidelines have reported low risk of breast cancer after OCP usage, although caution has to be exercised for progesterone based OCPs where risk of breast cancer needs further evaluation.

18.4.4 Lifestyle Modifications [40]

(a) Breast feeding: Breast feeding for at least 1 year should be encouraged. Studies have shown breast cancer reduction in BRCA women.
(b) Physical activity: Maintaining a regular exercise or fitness regime and a healthy body weight are important parameters as well.
(c) Reduction in alcohol consumption

18.5 Managing the Index Cancer

18.5.1 Surgery

The principles of surgical management of the index cancer in high risk mutation carriers parallel those with no mutations [1, 4]. An exception to this caveat is the performance of breast conservation surgery (BCS). As the risk of ipsilateral breast tumour recurrences (IBTR) and contralateral breast cancers are higher in these women (ranging from 20 to 40%), compared to sporadic cancers, pursuing conservation remains a matter of debate, although mastectomy has shown some survival benefit [1, 21].

A number of studies evaluating conservation in BRCA carriers have reported higher incidence of IBTR at longer follow up period. In a study by Pierce et al. [91] who evaluated 655 patients with BRCA mutations to BCS versus mastectomy, the rate of IBTR at 15 years was 23.5% compared to 5.5% in the mastectomy group. However, breast cancer specific survival was similar at 15 year follow up in this study. Contralateral breast cancer risk is also higher in mutation carriers compared to controls, with the risk being 40% or more at longer follow ups. Young patients (<50 years), BRCA1 carriers and presence of a positive family history increases the risk further. Table 18.12 depicts the studies on the role of index surgery and outcomes in hereditary breast cancers.

A systematic review of surgical management of BRCA (Table 18.13) associated cancers reported no difference in the risk of IBTR in BRCA carriers. However, there was a three- to fourfold increased risk of contralateral breast events in mutation carriers. The use of adjuvant chemotherapy and oophorectomy significantly lowered IBTR risks while oophorectomy, tamoxifen use and older age at first breast cancer were protective for contralateral breast events. The authors concluded that use of BCS in BRCA mutation carriers is a reasonable option. However, the NCCN guidelines have recommended against the use of BCS in BRCA carriers in view of higher local recurrence rates.

18.5.2 Radiotherapy [19, 29]

Two important caveats to be considered for radiotherapy administration in BRCA women are (i) the radio sensitivity of the tumour and (ii) risk of malignancy as a result of radiotherapy to adjacent normal tissues which lack normal DNA repair mechanisms. Cancers arising in the setting of BRCA mutations are known to be radiosensitive and at present, there is no concrete evidence to suggest heightened risk for development of second malignancy after radiotherapy usage in BRCA carriers compared to sporadic cancers. This was reported in a study by Pierce et al. [99] on 71 BRCA mutated women undergoing radiotherapy. The authors found no differences in acute or chronic morbidity involving the skin, subcutaneous tissues, lung or bone with similar survival rates when compared to non-mutated controls. They concluded that there was no deleterious effects of radiotherapy in BRCA mutation carriers. As a result, the indications for radiotherapy remains the same as that of sporadic breast cancers.

Table 18.12 Published literature on the role of index surgery in hereditary breast cancers

Author	Year	n	F/u(mo)	BRCA + ve	IBTR	Findings
Pierce [91]	2010	655	98.4, 107	100%	23.5 vs 5.5% at 15 years (BCS vs mastectomy)	15 year CSS: 91.7 vs 92.8% (BCS vs mastectomy) BRCA1: 1.8X higher CBC
Robson [92]	2004	496	116	11.3%	12 vs 8% at 10 years (mutation vs no mutation)	10 year CSS: 62 (BRCA1) vs 84 (BRCA2) vs 86% (no mutation) 10 year mortality: 33 vs 14% (mutation vs no mutation)
Pierce [93]	2006	605	94.8, 80.4	26.5%	12 vs 9% at 10 years (mutation vs no mutation); HR:1.99 if oophorectomy patients excluded	10 year CBC: 26 vs 3% (mutation vs no mutation); tamoxifen reduced this risk
Seynaeve [94]	2004	200	73.2, 72	13%	30% vs 16% (mutation vs no mutation)	Overall survival similar
Haffty [95]	2002	127	144	17.3%	49 vs 21% at 12 years (mutation vs no mutation)	Contralateral breast events:42 vs 9% (mutation vs no mutation)
Metcalfe [96]	2011	810	138	100%	NA	15 year CBC: 36.1 (BRCA1) vs 28.5% (BRCA2); higher in those less than 50 years and positive family history
Graeser [97]	2009	2020	NA	100%	NA	25 year CBC: 47.4%; higher in BRCA1,those <50 years and index patients

IBTR: ipsilateral breast tumour recurrence; CSS: cancer specific survival; HR: hazard ratio; RR: relative risk; NA: not available; F/u: follow up; CBC: contralateral breast cancer

18.5.3 Chemotherapy

18.5.3.1 Standard Chemotherapy

BRCA associated breast cancers are associated with faulty DNA repair mechanisms. Therefore, chemotherapeutic agents which result in DNA damage (*anthracycline)* or inhibit DNA replication (*platinum compounds*) are shown to be effective in them [19, 100].

Table 18.13 Main results/outcomes of meta-analysis on surgery and outcomes in hereditary breast cancer (From Ref. [98])

Variable	Groups	n	Result	RR	Conclusion
IBTR	BRCA vs none	526 vs 2320 10 studies	17.3 vs 11%	1.45	No difference
	BRCA1 vs 2	405 vs 203 4 studies		0.76	No difference
	BCS vs MRM	302 vs 353 1 study	23.5 vs 5.5%		Higher after BCS
CBC	BRCA vs none	807 vs 3163 7 studies	23.7 vs 6.8%	3.56	Higher risk in BRCA
	BRCA1 vs 2	1532 vs 950 7 studies	21.1 vs 15.1%	1.42	Higher in BRCA1
BCSS	BRCA vs none	2 studies	One study: Higher risk; another: No difference		
	C/LPM vs TM	2 studies	HR:0.78; no difference		
OS	BRCA vs none	2 studies	No analysis done due to insufficient data		
	C/LPM vs TM	1 study	94 vs 77%	Negated by oophorectomy	

IBTR: ipsilateral breast tumour recurrence; BCSS: breast cancer specific survival; RR: relative risk; CBC: contralateral breast cancer; OS: overall survival; C/LPM: contralateral prophylactic mastectomy; TM: therapeutic mastectomy; BCS: breast conservative surgery; MRM: modified radical mastectomy; HR: hazard ratio

Platinum agents have been studied both in the neoadjuvant and metastatic setting and exert cytotoxicity by damaging DNA which can be repaired only using homologous recombination, missing in BRCA individuals [21, 101]. Pathological complete response (pCR) is a surrogate marker for survival used in most studies involving BRCA mutated cancers and platinum agents are known to improve pCR rates over and above standard chemotherapy [100] platinum agents have been approves in the neoadjuvant and metastatic setting [21].

Response to *taxanes* is variable and depends on prior or concurrent platinum exposure. BRCA1 mutations have lower response to taxanes compared to BRCA2. BRCA mutations predict resistance to taxane based chemotherapy [19, 101]. This resistance has been confirmed by pre-clinical studies on mice. However, overall prognosis is similar to sporadic breast cancers when *anthracycline and taxanes* are administered together which augments taxane response [19, 100, 101].

Various chemotherapy trials (Table 18.14) have been depicted below. The prognosis of BRCA mutated cancers are similar to sporadic cancers. This was evaluated in the POSH trial [102] evaluating 2733 women. The overall survival at 10 years was 73.4 vs 70.1% in the BRCA mutated and sporadic cancers respectively. However, TNBCs associated with BRCA mutations demonstrated better survival (95vs 91% HR: 0.59) at 2 years.

The main conclusion from these trials are:

1. Use of platinum agents as NACT is associated with higher pCR in those with BRCA.
2. Higher pCR is seen both in TNBCs as well as hormone receptor positive tumours
3. For early stage BRCA mutated cancers, addition of chemotherapy is associated with improved survival.

Table 18.14 Published studies on role of chemotherapy in hereditary breast cancer

Author	Year	n	Setting	BRCA1/ BRCA2	Drugs/groups	End Points	Findings
Platinum agents							
Arun [103]	2011	317	NACT	18% /7%	Anthracycline + taxane	pCR OS	46 vs 13% (BRCA1 vs 2) Similar
Byrski [104]	2010	102	NACT	100% /0%	Cisplatin CMF Anthracycline + taxane AC+/− F	pCR	83% 7% 8% 22%
Byrski [105]	2014	107	NACT	100% /0%	4# cisplatin	pCR	61%
TBCRC008 [106]	2016	48/62	NACT in TNBC ER+ ve +/− HRD	46%	Carboplatin+ nab-paclitaxel X 12wks vs Carboplatin+ nab-paclitaxel+ vorinostat X 12 wks	pCR	50 vs 7.7% (with HRD and no HRD) in both ER + ve and TNBC
Narod [107]	2013	379	Stage I EBC	100% /0%	Chemotherapy vs no chemotherapy	15 year OS	89.4 vs 73.1% (HR: 0.53)
Byrski [108]	2012	20	MBC: Her-2 –ve, ER + ve	100% /0%	6# cisplatin	ORR TTP	80% (CCR: 45%) 12 mo.
TBCR009 [109]	2015	86	MBC: TNBC	12.8%	Cisplatin vs carboplatin	ORR	32.6 vs 18.7%; 54.5% with BRCA
Taxanes							
Byrski [110]	2008	85	NACT TNBC	51.76% /0%	Docetaxel+ doxorubicin AC+/-F CMF Vinorelbine + doxorubicin	pCR PR ORR	9.1 vs 4.9% 80 vs 95% (Mutation vs no mutation) 40 vs 100% (docetaxel based, in mutation vs no mutation)

(continued)

Table 18.14 (continued)

Author	Year	n	Setting	BRCA1/ BRCA2	Drugs/groups	End Points	Findings
TNT trial [111]	2015	376	TNBC	8.2% /3.2%	Carboplatin vs docetaxel	ORR PFS	31.4 vs 34% 68 vs 33% (BRCA mutation) 3.1 vs 4.4 mo. 6.8 vs 4.4 mo. (BRCA mutation)
Seynaeve [112]	2010	135	MBC: TNBC	23.7%/9.6%	Docetaxel Paclitaxel Taxane+ Trastuzumab	ORR PFS	25 vs 38% (BRCA1 vs no mutation) 75 vs 36% (BRCA2 vs no mutation) 2 vs 4.5mo. (BRCA1 vs no mutation)
Boughey [113]	2016	124/130	NACT in high risk stage I-III	3.1%/9.2%	Taxane + AC/ FEC	RR pCR	47.3 vs 66.7% (mutation vs no mutation); higher in BRCA2 50 vs 31.3% (mutation vs no mutation)
Fasching [114]	2015	1956	NACTTNBC	15.8%	4# cyclo-phosphamide + epirubicin f/b 4# docetaxel +/− bevacizumab	pCR	50 vs 31.1% (mutation vs no mutation) pCR predicted better DFS in all patients

(continued)

Table 18.14 (continued)

Author	Year	n	Setting	BRCA1/ BRCA2	Drugs/groups	End Points	Findings
Platinum + Taxanes combination							
Gepar-Sixto [115]	2014	295	NACTTNBC	11.9%/1%	Paclitaxel + liposomal doxorubicin + /−carboplatin	pCR	57.9 vs 40.2% (mutation vs no mutation) +25 vs +14% with platinum addition
Sharma [116]	2017	190	NACT: Stage I-III TNBC	16%	Carboplatin + docetaxel	pCR	59 vs 56% (mutation vs no mutation)
Lurbinectedin							
Cruz [117]	2018	89	MBC	60.7%	7 mg or 3.5 mg/ m2 q3 weeks	ORR PFS	41 vs 9% (mutation vs no mutation) 26 vs 61% (BRCA1 vs BRCA2) 3 vs 5.9 vs 2.5 mo. (BRCA1 vs BRCA2 vs no mutation)

NACT: neoadjuvant chemotherapy; MBC: metastatic breast cancer; ORR: objective response rate; PFS: progression free survival; OS: overall survival; pCR: pathological complete response; RR: radiological response; f/b: followed by; FEC: 5-flurouracil, epirubicin and cyclophosphamide; AC: Adriamycinand cyclophosphamide; TTP: time to tumour progression; EBC: early breast cancer; RR: response rate

4. Response to cisplatin is better than carboplatin for TNBCs
5. Taxane based chemotherapy is associated with lower ORR and shorter PFS in BRCA1 mutated cancers, both in the neoadjuvant and in the metastatic setting
6. Use of taxanes in BRCA2 is associated with good response rates compared to sporadic cancers
7. Combination of taxane and platinum improves the pCR rates.

18.5.3.2 Poly Adenosisne Ribose Phosphate (PARP) Inhibitors

Rationale

Normally when DNA damage occurs → PARP gets activated → histone proteins undergo ribosylation, chromatin re-modelling enzymes activated → favourable state

achieved for DNA repair via base excision (BER) and nucleotide excision repairs (NER). In BRCA mutated individuals, BER and NER are the only pathways of DNA repair as homologous recombination is deficient. Adding PARP inhibitors →inhibition of PARP activity by preventing formation of ADP-ribose polymers at areas of DNA strand breaks→single stranded breaks lead to formation of double stranded breaks →no homologous recombination activity→cell death occurs. This is called synthetic lethality where two lethal mechanisms or pathways are used to achieve the goal [19, 101].

Drugs and Mechanism of Action

These include **olaparib, veliparib, rucaparib, niraparib and talazoparib**. Excepting for veliparib, which acts by inhibition of catalytic activity of PARP, others lead to PARP trapping on DNA thereby leading to its non-availability for DNA repair. While platinum compounds and taxanes are synergistic with veliparib, alkylating agents synergize with other agents.

Dosage, Route of Administration and Approved Indications (Table 18.15)

Evidence (Table 18.16)

18.5.3.3 Other Drugs

Several novel agents such as *Trabectedin*, *Lurbinectedin* and *Eribulin* have been studied in BRCA associated breast cancers in phase II and III trials. All these agents act by augmenting DNA damage that is irreparable in those with homologous recombination repair deficiency [101]. Most of these agents are being used in the platinum resistant setting. *Methotrexate* has also been studied in BRCA deficient cells with some benefit.

18.5.4 Immunotherapy

Newer drugs including PDL1 inhibitors like *Pembrolizumab* have been evaluated in metastatic TNBCs. The TOPACIO phase II trial evaluated the combination of niraparib plus pembrolizumab in this setting, which included BRCA mutated patients (22%). The overall response rate was 29% in all patients, and higher in BRCA mutated carriers [4].

Table 18.15 Various PARP inhibitors and their utility

Name	Dose	ROA	Indications for use
Olaparib	300-400 mg BD	Oral	Ovarian cancer, breast cancer
Veliparib	600 mg BD	Oral	Melanoma, breast cancer, glioblastoma, ovarian cancer
Rucaparib	600 mg BD	Oral	Ovarian cancer, breast cancer
Niraparib	300 mg BD	Oral	Ovarian cancer
Talazoparib	1 mg OD	Oral	Breast cancer

ROA: route of administration

Table 18.16 Published studies and ongoing trials on the role of PARP inhibitors in breast cancer

Author/Trial	Year	Drug	n	Setting	Chemo used if any	Findings
BASKET [118]	2015	Olaparib	298	Recurrent BRCA +ve cancers (breast/ ovary/pancreas)	Platinum (ovary); gemcitabine (pancreas); >3 prior chemo (breast)	ORR:26.2% (overall) and 12.9% (breast); SD:42%
Gelmon [119]	2011	Olaparib	90	TNBC & advanced ovarian cancer	Nil	No ORR in breast cancer
OlympiA [120]	2017	Olaparib Adjuvant	1836	High risk Her-2– ve breast cancer	Olaparib vs placebo X 12mo	Results awaited
OlympiAD [121]	2019	Olaparib	205	Advanced Her-2 –ve BRCA +ve breast cancer	Capecitabine/ Vinorelbine or eribulin	OS:19.3 vs 17.1 mo.; 42% reduction in risk of disease progression or death with olaparib
GeparOLA [122]	2019	Olaparib Neoadj	102	Early HER2 – ve breast cancer with HRD	Olaparib + paclitaxel f/b EC vs paclitaxel + carboplatin f/b EC	pCR: 55% vs 49%
Somlo [123]	2014	Veliparib	44	Metastatic BRCA +ve breast cancer	Carboplatin	PR: 17 vs 23% (BRCA1 vs 2) TTF: 2 vs 5.1 mo.
Drew [124]	2011	Rucaparib	17/41	Advanced or metastatic breast + ovarian cancer	Nil	ORR:5%; SD:26% for 4 mo.; CBR:32%
ABRAZO [125]	2019	Talazoparib	84	Advanced breast cancer	Platinum/non platinum agents	ORR: 23 vs 33% (BRCA1 vs 2); 26% (TNBC)
EMBRACA [126]	2020	Talazoparib	431	Locally advanced/ metastatic Her-2 –ve breast cancer	Capecitabine/ eribulin/ Gemcitabine or vinorelbine	PFS: 8.6 vs 5.6 mo. OS: 44.9 vs 36.8 mo. (NS)
TALA [127]	2018	Talazoparib Neoadjuvant	20	Her-2 –ve, BRCA +ve breast cancer	Adjuvant as per physician choice	RCB:59%

(continued)

Table 18.16 (continued)

Author/Trial	Year	Drug	n	Setting	Chemo used if any	Findings
TBB [128]	2019	Talazoparib	20	Advanced Her-2 –ve breast cancer with HRD	Prior platinum	ORR: 25%
BrighTNess [129]	2018	Veliparib	634	Stage I-III TNBC	Paclitaxel vs carboplatin + paclitaxel vs veliparib + paclitaxel + carboplatin all f/b AC X4 cycles	pCR: 31 vs 58 vs 53%

ORR: objective response rate; mo.: months; PR: partial response; SD: stable disease; TTF: time to failure; PFS: progression free survival; OS: overall survival; NS: not significant; RCB: residual cancer burden; HRD: homologous recombinant deficiency; AC: Adriamycinand cyclophosphamide; pCR: pathological complete response; +ve: positive; −ve: negative; f/b: followed by; EC: epirubicin with cyclophosphamide

18.6 Special Considerations

18.6.1 Hereditary Breast Cancer in Men [8, 27]

Hereditary breast cancer in men accounts for 10% of all male breast cancers (which in turn is 1% of all breast cancers) and is commonly encountered in BRCA2 mutations (life time risk of 5–10%) and less frequently with BRCA1. The cumulative risk at 70 years for breast cancer development is 1% and 7% respectively for BRCA1 and BRCA2 mutation carriers. They are usually hormone receptor positive tumours akin to sporadic male breast cancers. A study from the SEER database from 1973 to 2005 observed that only 7.6% of breast cancers in men were TNBCs highlighting a relatively low prevalence of TNBCs in men. At presentation, majority of these cancers are locally advanced, resulting in poorer overall survival (5 year OS: 35–65%) when compared to the female counterparts. Given the frequency of genetic predisposition involved, genetic counselling is recommended for all male patients with breast cancer. Screening in high risk men involves SBE and CBE starting at 35 years annually with addition of prostate cancer screening starting at 40 years. However, there is no data to support imaging for screening. Unlike women BRCA carriers, there is no role for prophylactic mastectomy in men as the risk of developing breast cancer is lower than them.

18.6.2 BRCA-X [21]

Women without identifiable BRCA mutations despite a strong family history of malignancy are labelled as BRCA-X and possess a three- to fourfold risk of developing breast cancer, but not ovarian cancer. The life time risk of breast cancer after

25 years is more than 20–25%. The screening of women with BRCA-X mutations follow the same pattern as BRCA carriers. Use of risk assessment models help in facilitating the screening guidelines.

References

1. Caso R, Beamer M, Lofthus AD, Sosin M. Integrating surgery and genetic testing for the modern surgeon. Ann Transl Med. 2017;5(20):399.
2. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. Breast Cancer. 2019;11:151–64.
3. Hahnen E, Hauke J, Engel C, Neidhardt G, Rhiem K, Schmutzler RK. Germline mutations in triple-negative breast cancer. Breast Care. 2017;12:15–9.
4. Murthy P, Muggia F. Women's cancers: how the discovery of BRCA genes is driving current concepts of cancer biology and therapeutics. eCancer. 2019;13:904.
5. Jatoi I. Risk-reducing options for women with a hereditary breast cancer predisposition. Eur J Breast Health. 2018;14(4):189–93.
6. Casaubon JT, Grewal US, Regan JP. BRCA 1 and 2. StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2020.
7. Petrucelli N, Daly MB, Pal T, Adam MP, Ardinger HH, Pagon RA, et al. BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. In: GeneReviews® [Internet]. Seattle: University of Washington; 1993–2020. 1998 Sep 4 [updated 2016 Dec 15].
8. Hartmann LC, Lindor NM. The role of risk-reducing surgery in hereditary breast and ovarian cancer. N Engl J Med. 2016;374:454–68.
9. Mai PL, Garceau AO, Graubard BI, et al. Confirmation of family cancerhistory reported in a population-based survey. J Natl Cancer Inst. 2011;103:788–97.
10. Melvin JC, Wulaningsih W, Hana Z, Purushotham AD, Pinder SE, Fentiman I, et al. Family history of breast cancer and its association with disease severity and mortality. Cancer Med. 2016;5(5):942–9.
11. Couch FJ, Hart SN, Sharma P, Toland AE, Wang X, Miron P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015;33:304–11.
12. Shiovitz S, Korde LA. Genetics of breast cancer: a topic in evolution. Ann Oncol. 2015;26:1291–9.
13. Peters ML, Garber JE, Tung A. Managing hereditary breast cancer risk in women with and without ovarian cancer. Gynecol Oncol. 2017;146(1):205–14.
14. Zeichner SB, Stanislaw C, Meisel JL. Prevention and screening in hereditary breast and ovarian cancer: page 2 of 2. Oncology (Williston Park). 2016;30(10):896–904.
15. Engela C, Fischer BC. Breast cancer risks and risk prediction models. Breast Care (Basel). 2015;10(1):7–12.
16. Louro J, Posso M, Boon MH, Román M, Domingo L, Castells X, et al. A systematic review and quality assessment of individualized breast cancer risk prediction models. Br J Cancer. 2019;121:76–85.
17. Evans GDR, Howell A. Breast cancer risk-assessment models. Breast Cancer Res. 2007;9(5):213.
18. Lindor NM, Johnson KJ, Harvey H, Pankratz VS, Domchek SM, Hunt K, et al. Predicting BRCA1 and BRCA2 gene mutation carriers: comparison of PENN II model to previous study. Fam Cancer. 2010;9(4):495–502.
19. Lee A, Moon BI, Kim TH. BRCA1/BRCA2 pathogenic variant breast cancer: treatment and prevention strategies. Ann Lab Med. 2020;40:114–21.
20. Verma A, Nag S, Hasan Q, PriyaSelvakumar VP. Mainstreaming genetic counseling for BRCA testing into oncology clinics—Indian perspective. Indian J Cancer. 2019;56:S38–47.
21. Llort G, Chirivella I, Morales R, Serrano R, Sanchez AB, Teule A. SEOM clinical guidelines in hereditary breast and ovarian cancer. Clin Transl Oncol. 2015;17:956–61.

22. Sayani A. Inequities in genetic testing for hereditary breast cancer: implications for public health practice. J Community Genet. 2019;10:35–9.
23. Kinney AY, Howell R, Ruckman R, McDougall JA, Boyce TW, Vicuñ B, et al. Promoting guideline-based cancer genetic risk assessment for hereditary breast and ovarian cancer in ethnically and geographically diverse cancer survivors: rationale and design of a 3-arm randomized controlled trial. Gue Contemp Clin Trials. 2018;73:123–35.
24. Armstrong J, Toscano M, Kotchko N, Friedman S, Schwartz MD, Virgo KS, et al. Utilization and outcomes of *BRCA* genetic testing and counseling in a national commercially insured population: the ABOUT study. JAMA Oncol. 2015;1:1251–60.
25. Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO clinical practice guidelines for cancer prevention and screening. Ann Oncol. 2016;27(S5):103–10.
26. Singh J, Thota N, Singh S, Padhi S, Mohan P, Deshwal S, et al. Screening of over 1000 Indian patients with breast and/or ovarian cancer with a multi-gene panel: prevalence of BRCA1/2 and non-BRCA mutations. Breast Cancer Res Treat. 2018;170(1):189–96.
27. Pederson HJ, Padia SA, Grobmyer MM. Managing patients at genetic risk of breast cancer. Cleve Clin J Med. 2016;83(3):199–206.
28. Manchanda R, Loggenberg K, Sanderson S, Burnell M, Wardle J, Gessler S, et al. Population testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish community: a randomized controlled trial. J Natl Cancer Inst. 2014;107(1):379.
29. Yamauchi H, Takei J. Management of hereditary breast and ovarian cancer. Int J Clin Oncol. 2017;23(1):45–51.
30. Jatoi I. Bilateral mastectomy for unilateral breast cancer: a perplexing trend. Indian J Surg Oncol. 2015;6(4):387–9.
31. Hagen AI, Kvistad KA, Maehle L, Holmen MM, Aase H, Styr B, et al. Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. Breast. 2007;16(4):367–74.
32. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med. 2008;148:671–9.
33. Phi XA, Houssami N, Obdeijn IM, Warner E, Sardanelli F, Leach MO, et al. Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age ≥50 years: evidence from an individual patient data meta-analysis. J Clin Oncol. 2015;33(4):349–56.
34. van Nagell JR Jr, Miller RW, DeSimone CP, Ueland FR, Podzielinski I, Goodrich ST, et al. Long-term survival of women with epithelial ovarian cancer detected by ultrasonographic screening. Obstet Gynecol. 2011;118(6):1212–21.
35. Partridge E, Kreimer AR, Greenlee RT, Williams C, Xu JL, Church TR, et al. Results from four rounds of ovarian cancer screening in a randomized trial. Obstet Gynecol. 2009;113(4):775–82.
36. Shah CA, Lowe KA, Paley P, Wallace E, Anderson GL, McIntosh MW, et al. Influence of ovarian cancer risk status on the diagnostic performance of the serum biomarkers mesothelin, HE4, and CA125. Cancer Epidemiol Biomarkers Prev. 2009;18:1365–72.
37. Vencken PM, Kriege M, Hooning M, Menke-Pluymers MB, Heemskerk-Gerritsen BA, van Doorn LC, et al. The risk of primary and contralateral breast cancerafter ovarian cancer in BRCA1/BRCA2mutation carriers: implications for counselling. Cancer. 2013;119:955–62.
38. Domchek SM, Jhaveri K, Patil S, Stopfer JE, Hudis C, Powers J, et al. Risk of metachronous breast cancer after BRCA mutation-associated ovarian cancer. Cancer. 2013;119:1344–8.
39. Tuttle TM, Habermann EB, Grund EH, Morris TJ, Virnig BA. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol. 2007;25(33):5203–9.
40. Mau C, Untch M. Prophylactic surgery: for whom, when and how? Breast Care. 2017;12:379–84.
41. Biglia N, D'Alonzo M, Sgro LG, TomasiCont N, Bounous V, Robba E. Breast cancer treatment in mutation carriers: surgical treatment. Minerva Ginecol. 2016;68:548–56.

42. Nava MB, Rocco N, Catanuto G. Conservative mastectomies: an overview. Gland Surg. 2015;4(6):463–6.
43. Schrag D, Kuntz KM, Garber JE, Weeks JC. Decision analysis—effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. N Engl J Med. 1997;336:1465–71.
44. Grann VR, Jacobson JS, Thomason D, Hershman D, Heitjan DF, Neugut AI, et al. Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: an updated decision analysis. J Clin Oncol. 2002;20:2520–9.
45. Kurian AW, Sigal BM, Plevritis SK. Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers. J Clin Oncol. 2010;28:222–31.
46. Sigal BM, Munoz DF, Kurian AW, Plevritis SK. A simulation model to predict the impact of prophylactic surgery and screening on the life expectancy of BRCA1 and BRCA2 mutation carriers. Cancer Epidemiol Biomarkers Prev. 2012;21:1066–77.
47. Yamauchi H, Okawa M, Yokoyama S, Nakagawa C, Yoshida R, Suzuki K, et al. High rate of occult cancer found in prophylactic mastectomy specimens despite thorough pre-surgical assessment with MRI and ultrasound: findings from the hereditary breast and ovarian cancer registration 2016 in Japan. Breast Cancer Res Treat. 2018;172:679–87.
48. Kwong A, Chu AT. What made her give up her breasts: a qualitative study on decisional considerations for contralateral prophylactic mastectomy among breast cancer survivors undergoing BRCA1/2 genetic testing. Asian Pac J Cancer Prev. 2012;13:2241–7.
49. Lodder LN, Frets PG, Trijsburg RW, Meijers-Heijboer EJ, Klijn JGM, Seynaeve C, et al. One year follow-up of women opting for pre-symptomatic testing for BRCA1 and BRCA2: emotional impact of the test outcome and decisions on risk management (surveillance or prophylactic surgery). Breast Cancer Res Treat. 2002;73:97–112.
50. Gabriel SE, Woods JE, O'Fallon WM, Beard CM, Kurland LT, Melton LJ. Complications leading to surgery after breast implantation. N Engl J Med. 1997;336:677–82.
51. Heemskerk-Gerritsen BAM, Brekelmans CTM, Menke-Pluymers MBE, van Geel AN, Tilanus-Linthorst MMA, Bartels CCM, et al. Prophylactic mastectomy in BRCA1/2 mutation carriers and women at risk of hereditary breast cancer: long-term experiences at the Rotterdam family cancer clinic. Ann Surg Oncol. 2007;14(12):3335–44.
52. Manning AT, Wood C, Eaton A, Stempel M, Capko D, Pusic A, et al. Nipple-sparing mastectomy in patients with BRCA1/2 mutations and variants of uncertain significance. Br J Surg. 2015;102:1354–9.
53. Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med. 1999;340(2):77–84.
54. Hartmann LC, Sellers TA, Schaid DJ, Frank TS, Soderberg CL, Sitta DL, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst. 2001;93:1633–7.
55. Meijers-Heijboer H, van Geel B, van Putten WLJ, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MBE, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345(3):159–64.
56. Heemskerk-Gerritsen BAM, Jager A, Koppert LB, Obdeijn AIM, Collée M, Meijers-Heijboer HEJ, et al. Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat. 2019;177(3):723–33.
57. Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, van't Veer L, Garber JE, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE study group. J Clin Oncol. 2004;22:1055–62.
58. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304:967–75.
59. Geiger AM, Yu O, Herrinton LJ, Barlow WE, Harris EL, Rolnick S, et al. Apopulation-based study of bilateral prophylactic mastectomy efficacy in women at elevated risk for breast cancer in community practices. Arch Intern Med. 2005;165:516–20.

60. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2004;22:2328–35.
61. van Sprundel TC, Schmidt MK, Rookus MA, Brohet R, van Asperen CJ, Rutgers EJ, et al. Risk reduction of contralateral breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers. Br J Cancer. 2005;93:287–92.
62. Peralta EA, Ellenhorn JD, Wagman LD, Dagis A, Andersen JS, Chu DZ, et al. Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer. Am J Surg. 2000;180:439–45.
63. Herrinton LJ, Barlow WE, Yu O, Geiger AM, Elmore JG, Barton MB, et al. Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project. J Clin Oncol. 2005;23:4275–86.
64. Boughey JC, Hoskin TL, Degnim AC, Sellers TA, Johnson JL, Kasner MJ, et al. Contralateral prophylactic mastectomy is associated with a survival advantage in high-risk women with a personal history of breast cancer. Ann Surg Oncol. 2010;17:2702–9.
65. Lostumbo L, Wallace J, Ko H. Risk reducing mastectomy for the prevention of primary breast cancer. Cochrane Database Syst Rev. 2018;4(4):CD002748.
66. Alaofi RK, Nassif MO, Al-Hajeili MR. Prophylactic mastectomy for the prevention of breast cancer: review of the literature. Avicenna J Med. 2018;8:67–77.
67. Kotsopoulos J, Gronwald J, Karlan BY, Huzarski T, Tung N, Moller P, et al. Hormone replacement therapy after oophorectomy and breast cancer risk among BRCA1 mutation carriers. JAMA Oncol. 2018;4(8):1059–65.
68. Domchek SM, Friebel TM, Neuhausen SL, Wagner T, Evans G, Isaacs C, et al. Mortality after bilateral salpingo-oophorectomyin BRCA1 and BRCA2 mutationcarriers: a prospective cohort study. Lancet Oncol. 2006;7:223–9.
69. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, van't Veer L, Garber JE, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2mutations. N Engl J Med. 2002;346:1616–22.
70. Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 mutation. JAMA. 2006;296:185–92.
71. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2- associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol. 2008;26:1331–7.
72. Kauff ND, Satagopan JM, Robson ME, , Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346(21):1609–1615.
73. Rocca W, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ III. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 2006;7:821–8.
74. Finch AP, Lubinski J, Møller P, Singer CF, Karlan B, Senter L, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014;32:1547–53.
75. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst. 2013;105:812–22.
76. Kramer JL, Velazquez IA, Chen BE, Rosenberg PS, Struewing JP, Greene MH. Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of BRCA1 mutation carriers. J Clin Oncol. 2005;23:8629–35.
77. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with RRSO in BRCA1 or BBRCA2 mutation carriers. J Natl Cancer Inst. 2009;101(2):80–7.
78. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and bowel project P-1 study. J Natl Cancer Inst. 1998;90:1371–88.
79. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project study of tamoxifen and Raloxifene (STAR) P-2 trial: preventing breast cancer. Cancer Prev Res (Phila). 2010;3:696–706.

80. Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, Coates A, et al. First results from the international breast cancer intervention study (IBIS-I): a randomized prevention trial. Lancet. 2002;360(9336):817–24.
81. Goss PE, Ingle JN, Ales-Martinez J, Cheung AM, Chlebowski RT, Wactawski-Wende J, et al. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011;364:2381–91.
82. Cuzick J, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 2015;16:67–75.
83. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet. 1996;347:1713–27.
84. Zhu H, Lei X, Feng J, Wang Y. Oral contraceptive use and risk of breast cancer: a meta-analysis of prospective cohort studies. Eur J Contraception Repr Health Care. 2012;17:402–14.
85. Bethea TN, Rosenberg L, Hong CC, Troester MA, Lunetta KL, Bandera EV, et al. A case-control analysis of oral contraceptive use and breast cancer subtypes in the African American Breast Cancer Epidemiology and Risk Consortium. Breast Cancer Res. 2015;17:22.
86. Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med. 2017;377: 2228–39.
87. Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR, et al. Oral contraceptivesand the risk of breast cancer. N Engl J Med. 2002;346(26):2025–32.
88. Wingo PA, Austin H, Marchbanks PA, Whiteman MK, Hsia J, Mandel MG, et al. Oral contraceptives and the risk of death from breast cancer. Obstet Gynecol. 2007;110(4):793–800.
89. Kotsopoulos J, Gronwald J, Karlan BY, Huzarski T, Tung N, Moller P, et al. Hormone replacement therapy after oophorectomy and breast cancer risk among BRCA1 mutation carriers. JAMA Oncologia. 2018;4(8):1059–65.
90. Domchek SM, Friebel T, Neuhausen SL, Lynch HT, Singer CF, Eeles RA, et al. Is hormone replacement therapy (HRT) following risk-reducing salpingo-oophorectomy (RRSO) in BRCA1 (B1) and BRCA2 (B2)-mutation carriers associated with an increased risk of breast cancer? J Clin Oncol. 2011;29(S15):1501.
91. Pierce LJ, Phillips KA, Griffith KA, Buys S, Gaffney DK, Moran MS, et al. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. Breast Cancer Res Treat. 2010;121(2):389–98.
92. Robson ME, Chappuis PO, Satagopan J, Wong N, Boyd J, Goffin JR, et al. A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. Breast Cancer Res. 2004;6(1):R8–R17.
93. Pierce LJ, Levin AM, Rebbeck TR, Ben-David MA, Friedman E, Solin LJ, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapyin BRCA1/2-associated stage I/II breast cancer. J Clin Oncol. 2006;24(16):2437–43.
94. Seynaeve C, Verhoog LC, van de Bosch LM, van Geel AN, Menke-Pluymers M, Meijers-Heijboer EJ, et al. Ipsilateral breast tumour recurrence in hereditary breast cancer following breast-conserving therapy. Eur J Cancer. 2004;40(8):1150–8.
95. Haffty BG, Harrold E, Khan AJ, Pathare P, Smith TE, Turner BC, et al. Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status. Lancet. 2002;359(9316):1471–7.
96. Metcalfe K, Gershman S, Lynch HT, Ghadirian P, Tung N, Kim-Sing C, et al. Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer. 2011;104(9):1384–92.
97. Graeser MK, Engel C, Rhiem K, Gadzicki D, Bick U, Kast K, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2009;27(35): 5887–92.
98. Valachis A, Nearchou AD, Lind P. Surgical management of breast cancer in BRCA-mutation carriers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014;144(3):443–55.

99. Pierce LJ, Strawderman M, Narod SA, Oliviotto I, Eisen A, Dawson L, et al. Effect of radiotherapy after breast-conserving treatment in women with breast cancer and germline BRCA1/2 mutations. J Clin Oncol. 2000;18:3360–9.
100. Turk A, Wisinski KB. PARP inhibition in BRCA-mutant breast cancer. Cancer. 2018;24(12):2498–506.
101. Parkes A, ArunBK LJK. Systemic treatment strategies for patients with hereditary breast cancer syndromes. Oncologist. 2017;22:655–66.
102. Copson ER, Maishman TC, Tapper WJ, Cutress RI, Greville-Heygate S, Altman DG, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol. 2018;19(2):P169–80.
103. Arun B, Bayraktar S, Liu DD, Gutierrez Barrera AM, Atchley D, Pusztai L, et al. Response to neoadjuvant systemic therapy for breast cancer in BRCA mutation carriers and non-carriers: a singleinstitution experience. J Clin Oncol. 2011;29:3739–46.
104. Byrski T, Gronwald J, Huzarski T, Grzybowska E, Budryk M, Stawicka M, et al. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. J Clin Oncol. 2010;28:375–9.
105. Byrski T, Huzarski T, Dent R, Marczyk E, Jasiowka M, Gronwald J, et al. Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients. Breast Cancer Res Treat. 2014;147:401–5.
106. Connolly RM, Leal JP, Goetz MP, Zhang Z, Zhou XC, Jacobs LK, et al. TBCRC 008: early change in 18F-FDG uptake on PET predicts response to preoperative systemic therapy in human epidermal growth factor receptor 2-negative primary operable breast cancer. J Nucl Med. 2015;56:31–7.
107. Narod SA, Metcalfe K, Lynch HT, Ghadirian P, Robidoux A, Tung N, et al. Should all BRCA1 mutation carriers with stage I breast cancer receive chemotherapy? Breast Cancer Res Treat. 2013;138(1):273–9.
108. Byrski T, Dent R, Blecharz P, Foszczynska-Kloda M, Gronwald J, Huzarski T, et al. Results of a phase II open-label, non-randomized trial of cisplatin chemotherapy in patients with BRCA1-positive metastatic breast cancer. Breast Cancer Res. 2012;14:R110.
109. Isakoff SJ, Mayer EL, He L, Traina TA, Carey LA, Krag KJ, et al. TBCRC009: a multicenter phase II clinical trial of platinum monotherapy with biomarker assessment in metastatic triple-negative breast cancer. J Clin Oncol. 2015;33:1902–9.
110. Byrski T, Gronwald J, Huzarski T, Grzybowska E, Budryk M, Stawicka M, et al. Response to neo-adjuvant chemotherapy in women with BRCA1-positive breast cancers. Breast Cancer Res Treat. 2008;108:289–96.
111. Tutt A, Ellis P, Kilburn L, Gilett C, Pinder SC, Abraham J, et al. The TNT trial: a randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients withmetastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer. Cancer Res. 2015;75(suppl 9):S3-01a.
112. Seynaeve C, Jager A, Hooning M, Van Deurzen CH, Blom J, Collee M, et al. Activity of taxane chemotherapy for metastatic breast cancer (MBC) in BRCA1 and BRCA2 mutation carriers compared to sporadic BC patients. J Clin Oncol. 2010;28:1020a. https://doi.org/10.1200/jco.2010.28.15_suppl.1020.
113. Boughey JC, Kalari KR, Suman VJ, McLaughlin SA, Moreno-Aspitia A, Moyer AM, et al. Role of germline BRCA status and tumor homologous recombination (HR) deficiency in response to neoadjuvant weekly paclitaxel followed by anthracycline based chemotherapy. Cancer Res. 2016;76(suppl 4):P3-07-29a.
114. Fasching PA, Loibl S, Eidtmann H, Tesch H, Untch M, Hilfrich J, et al. BRCA mutations, therapy response and prognosis in the neoadjuvant GeparQuinto study. Cancer Res. 2016;76(suppl 4):S5-06a.
115. Minckwitz GV, Hahnen E, Fasching PA, Hauke J, Schneeweiss A, Salat C, et al. Pathological complete response (pCR) rates after carboplatin-containing neoadjuvant chemotherapy in patients with germline BRCA (gBRCA) mutation and triple-negative breast cancer (TNBC): results from GeparSixto. J Clin Oncol. 2014;32:1005a.

116. Sharma P, López-Tarruella S, García-Saenz JA, Ward C, Connor CS, Gómez HL, et al. Efficacy of neoadjuvant carboplatin plus docetaxel in triple-negative breast cancer: combined analysis of two cohorts. Clin Cancer Res. 2017;23(3):649–57.
117. Cruz C, Llop-Guevara A, Garber JE, Arun BK, Pérez Fidalgo JA, Lluch A, et al. Multicenter phase II study of lurbinectedin in BRCA-mutated and unselected metastatic advanced breast cancer and biomarker assessment sub-study. J Clin Oncol. 2018;36(31):3134–43.
118. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33(3):244–50. https://doi.org/10.1200/jco.2014.32.15_suppl.1005.
119. Gelmon KA, Tischkowitz M, Mackay H, Swenerton K, Robidoux A, Tonkin K, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triplenegative breast cancer: a phase 2, multicentre, open-label, non-randomized study. Lancet Oncol. 2011;12:852–61.
120. Tutt A, Kaufman B, Garber J, Gelber RD, McFadden E, Goessl CD, et al. OlympiA: a randomized phase III trial of olaparib as adjuvant therapy in patients with high-risk HER2-ne9S5gative breast cancer (BC) and a germline BRCA1/2 mutation (gBRCAm). Ann Oncol. 2017;28(S5):v43–67.
121. Robson ME, Tung N, Conte P, Im SA, Senkus E, Xu B, et al. OlympiAD: final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol. 2019;30(4):558–66.
122. Fasching PA, Jackisch C, Rhiem K, Schneeweiss A, Klare P, Hanusch C, et al. GeparOLA: a randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel/carboplatin followed by epirubicin/cyclophosphamide as neoadjuvant chemotherapy in patients (pts) with HER2-negative early breast cancer (BC) and homologous recombination deficiency (HRD). J Clin Oncol. 2019;37:506. https://doi.org/10.1200/JCO.2019.37.15_suppl.506.
123. Somlo G, Frankel PH, Luu TH, Ma C, Arun B, Garcia A, et al. Phase II trial of single agent PARP inhibitor ABT-888 (veliparib [vel]) followed by postprogression therapy of vel with carboplatin (carb) in patients (pts) with stage BRCA-associated metastatic breast cancer (MBC): California Cancer Consortium trial PHII-96. J Clin Oncol. 2014;32:1021a. https://doi.org/10.1200/jco.2014.32.15_suppl.1021.
124. Drew Y, Ledermann JA, Jones A, Hall G, Jayson GC, Highley M, et al. Phase II trial of the poly(ADP-ribose) polymerase (PARP) inhibitor AG-014699 in BRCA 1 and 2–mutated, advanced ovarian and/or locally advanced or metastatic breast cancer. J Clin Oncol. 2011;29:3104a. https://doi.org/10.1200/jco.2011.29.15_suppl.3104.
125. Turner NC, Telli ML, Rugo HS, Mailliez A, Ettl J, Grischke EM, et al. A phase II study of Talazoparib after platinum or cytotoxic non-platinum regimens in patients with advanced breast cancer and germline BRCA1/2 mutations (ABRAZO). Clin Cancer Res. 2019;25(9):2717–24.
126. Litton JK, Rugo HS, Ettl J, Hurvitz HA, Gonçalves A, Lee KH, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med. 2018;379:753–63.
127. Litton JK, Scoggins M, Hess KR, Adrada B, Barcenas CH, Murthy RK, et al. Neoadjuvant talazoparib (TALA) for operable breast cancer patients with a BRCA mutation (BRCA+). J Clin Oncol. 2018;36:508. https://doi.org/10.1200/JCO.2018.36.15_suppl.508.
128. Gruber JJ, Afghahi A, Hatton A, Scott D, McMillan A, Ford JM, et al. Talazoparib beyond BRCA: a phase II trial of talazoparib monotherapy in BRCA1 and BRCA2 wild-type patients with advanced HER2-negative breast cancer or other solid tumors with a mutation in homologous recombination (HR) pathway genes. J Clin Oncol. 2019;37(S15):3006. https://doi.org/10.1200/JCO.2019.37.15_suppl.3006.
129. Loibl S, O'Shaughnessy J, Untch M, Sikov WM, Rugo HS, McKee MD, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol. 2018;19:497–509.

Role of Radiotherapy in Breast Cancer

19

Suresh Chander Sharma and Rakesh Kapoor

19.1 Introduction

Cancer is one of the major health problems in the world. 18.1 million new cancer cases were diagnosed in 2018 and 9.6 million die from this disease. Lung cancer and breast cancer are commonest (2,093,876 and 2,088,849 cases respectively) each making 11.6% of total cancer cases. 1,761,007 of lung cancer and 626,279 of breast cancer cases died during the year [1]. Inspite of having almost same number of cases, mortality is higher for lung cancer in comparison to breast cancer because later can be treated more effectively with present day treatment.

In our country nearly 1.62 million cancer cases were diagnosed in 2018 and 0.87 million died from disease. Breast cancer is the commonest cancer among women, makes 14% of all cancer cases. Almost 1,62,468 new breast cancer cases are diagnosed every year and 87,090 die from disease, making 11.1% of all cancer deaths. Prevalence of breast cancer is 4,05,456 cases all ages over 5 years [2]. Breast cancer forms 24–32% of all cancers in women in different parts of the country. It was second most common cancer among women, 10 years back carcinoma cervix used to be leading one. But in last one decade, breast cancer has taken over carcinoma cervix. Breast cancer is on the rise. This rise is commonly seen in urban areas rather than rural areas where incidence is low and remains static. The incidence of breast cancer varies between 24–33 per 100.000 of population in urban

Suresh Chander Sharma, MD (✉)
Former Senior Professor and Head, Department of Radiotherapy, PGIMER, Chandigarh and MM Institute of Medical Sciences, Mullana, Ambala, Haryana, India
e-mail: Sharmasc49@gmail.com

Rakesh Kapoor, MD, FICRO
Former Professor, Department of Radiotherapy, PGIMER, Chandigarh, India

Director, Homi Bhabha Cancer Hospital and Research Center, Mullanpur and Sangrur, Punjab, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_19

areas and 7–12 per 100,000 in rural areas as per Cancer Registry Project Report of ICMR, government of India, 2016. Highest incidence is seen in Delhi followed by Mumbai, Kolkata, Bengaluru and Chennai. Lowest incidence of 12cases per 100,000 population has been observed in rural population based tumour registry at Barsi, Maharashtra [3]. Incidence in India is much less than that of western countries where it is more than 120 per 100,000. Because of large population, India has more number of total cases. In USA 1 in 8 women develop breast cancer but in India 1 in 18 women develop this disease.

Histological confirmation of breast cancer is best and easily done by FNAC or core biopsy from local lump or metastatic lymph node. Biopsy is rarely required but if needed it should always be excision biopsy. Following histological confirmation, investigations are undertaken for staging and for assessment of the patient. Marker studies are must and should be done on tissue from Core biopsy or from surgical specimen. These not only are indicative of prognosis but also help in the total management of the patient.

Treatment of carcinoma breast is based on multidisciplinary approach to give patient best possible loco-regional and systemic control of disease and hence best disease free and overall survival. It requires judicious combination of surgery and radiation for best local control and systemic therapies for systemic control of disease.

19.2 Role of Radiation in Carcinoma Breast

Radiation plays a very important role in the treatment of both early and advanced disease. It is used in following ways:

A. Post-operative Adjuvant radiation following Modified Radical Mastectomy (MRM) in early stage disease when indicated
B. Radiation as part of primary local therapy following Breast Conservation Surgery (BCS) in early stage disease.
C. Surgery (MRM or BCS) plus Post-operative Radiation in locally advanced breast cancer after down staging of tumour following Neo-adjuvant chemotherapy
D. Radiation for palliation in metastatic disease

A. Postoperative Adjuvant Radiotherapy Following MRM

MRM is one of the standard surgical techniques for local control of early breast cancer and presently is supposed to be the best surgical procedure for this purpose. In India, MRM is done in 70% of the cases compared to western countries where it is performed in 30% of cases only. MRM alone gives cure rate of 60–70% in early breast cancer. But 20–40% of cases fail either due to local recurrence or due to distant metastasis. Local recurrence used to be seen in 16% in stage I and 41% in stage II [4, 5] following Radical Mastectomy (RM) which used to be the preferred surgical technique in 1950–1960s. MRM was introduced in 1960s due to its advantages

over RM but with same control rate, large number of studies done since then showed that local recurrence rate following MRM are 10% to 25% in early stage disease. Local recurrence is a function of T stage, Axillary status, margin status, Grade, Age and status of markers—e.g. ER, PR and Her-2 neu. Increasing size of tumour, positive axilla and positive margins, high grade tumour, triple negative cancer and young age increase chances of local recurrence.

Hence, post-operative radiation was introduced in 5th decade of last century and delivered post-operatively for better local control of disease and continued to be used since then. Various studies done over almost 80 years have shown that local, post-operative radiation reduces local recurrence from 25% to less than 10% in early stages of breast cancer, however, there was no significant increase in the survival in most of the series. Radiation may not add to the survival but it definitely leads to better quality of life by avoiding local recurrence, which is otherwise difficult to treat [6–9].

Radiation is not indicated in each and every patient after MRM. Should be delivered to those patients who are at high risk to develop local recurrence. Radiation is delivered to chest wall alone or chest wall + draining lymph node areas. Following are indications for post- operative radiation:

1. Pathologicaly 4 or more lymph nodes positive or clinical involvement (N1) or unknown histology of axilla
2. Grade 2 and 3 tumour
3. Lymphatic invasion positive
4. Tumour >4 cm in size
5. Tumour at or near resection line
6. Tumour in central or medial quadrant
7. Extra capsular extension in axillary nodes
8. Localizes skin or muscle invasion on histology
9. Sometime if only simple mastectomy is done
10. Very young age of ≤35
11. Triple negative tumour
12. Surgeon not satisfied with clearance

All of above are indications not only for chest wall irradiation but for irradiation of ipsilateral axilla and supra clavicular lymph node areas also. Axilla may not be irradiated if full and adequate dissection of axilla is done and if only 1–3 lymphnodes are positive with favourable features. Sometimes, addition of radiation to axilla even in patients with 1–3 lymph nodes positivity and showing cellular and genetic poor prognostic features has shown better control of disease. Internal mammary lymph nodes are not usually irradiated because it unnecessarily gives more dose to lungs and heart and does not add significantly to control rate. Only 1% of patients show clinically positive internal mammary lymph node metastases. However if disease is present in central or medial quadrant with positive axilla and other poor prognostic features, irradiation to internal mammary lymph nodes may be considered in such patients.

B. Breast Conservative Surgery & Radiation

The aims of breast conservative surgery in early breast cancer are to preserve the breast so as to preserve dignity of women, cosmetic superiority and function and it gives same disease free control and total survival as that given by MRM. BCS requires excision of tumour with margin of safety all around the tumour along with dissection of axilla. This surgery should be carried out in good institutions by an experienced surgeon so as to give best control and survival. It is indicated in stage I& II disease, particularly in young patients who desire preservation of their breasts. It is not indicated in situations when chances of local failures are high.

Details have been given in the chapter on early breast cancer.

Initially, radiation was not added routinely to BCS. Local recurrence rate upto 40–60% was observed [10]. Addition of radiation brought down recurrence to below 10%. Randomized trials were carried out by Verronesi et all in Milan,1983, Italy [11], Hayward,1983 UK [12] and Bernard Fisher in USA, 1983, 1989 [13, 14]. These trials compared MRM with BCS + radiation and concluded after long follow up period of 10–20 years that results were similar in terms of local control and survival with added advantage of preservation of near normal breast. Large numbers of randomized studies have been reported over last 40 years with similar results [15, 16].

Addition of radiation following BCS/MRM and adjuvant chemotherapy, not only reduced chances of local recurrence below 10% but Danish study, [17, 18] and British Columbia study [19, 20] have shown increase in both disease free as well as overall survival. Hence BCS + Radiation has become preferred standard of care for best local control of disease in early stage breast cancer. However, this modality requires very good compliance of patient as treatment time is long and willingness of patient for having radiation plus close follow up are must.

Radiation following BCS requires irradiation of whole breast followed by boost to bed of lumpectomy cavity. Irradiation of lymph nodal areas is considered if indicated. The indications are same as given above under Post-operative radiation after MRM.

Boost: is delivered after completion of external radiation to whole breast. Aim of boost is to reduce local recurrence further. Randomized studies have shown that boost to the lumpectomy cavity can reduce the chance of recurrence to or below 3% [21–23] compared to omission of boost.

C. Accelerated Partial Breast Irradiation (APBI)

Like surgeons, Radiation Oncologist are also practising conservative approach now and has introduced Accelerated Partial Breast Irradiation (APBI) in which only lumpectomy cavity is irradiated with margin of safety of 2 cm all around and rest of the breast is spared, an alternative to whole breast radiation to make BCS a realistic and palatable option for more women. Rationale is that 80% of local recurrences are seen within 2 cm of margin of cavity [24, 25]. The concept that irradiation of the immediate vicinity of the primary tumor is adequate to achieve local control of early-stage breast cancer was used to initiate numerous clinical trials involving APBI to show equivalence and non-inferiority of APBI. Due to small volume, high

radiation can be delivered in short time of one week. Patient's compliance is likely to be more [25–30]. APBI is indicated only in elderly patients ≥45 years, with T1 / T2 ≤ 3 cm tumour invasive tumour with negative margins and negative axilla as per ASCO/ABS guidelines. There are various techniques of delivering APBI which are described later in the chapter. This is still an evolving modality of treatment.

Radiation is not without side effects. Patients develop acute toxicity, like radiation dermatitis and esophagitis leading to difficulty in swallowing. These are temporary effects and are reversed completely within a week of completion of radiation therapy. 5–10% of patients do develop late or chronic effects. Two commonly seen effects are Radiation pneumonitis [31–33] and cardiac toxicity [34–37] particularly if disease is present on left side. With present day highly sophisticated radiotherapy techniques, radiation energy and Dose, Time and Fractionation regimens, the chances of long term toxicity has been reduced and has made it highly safe modality of breast cancer treatment.

D. Role of Radiation in Locally Advanced Breast Cancer (LABC)

Locally advanced breast cancer (LABC) is a stage of breast cancer characterized by advanced local breast tumour in the absence of distant metastasis. U.S. National Comprehensive Cancer Network describe LABC as a AJC stage III breast cancer [38]; the definition includes breast cancer that fulfils any of the following criteria in the absence of distant metastasis:

- Tumours more than 5 cm in size (T3, T4) with regional lymphadenopathy (N0–3)
- Tumours 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 advanced lymphadenopathy—clinically fixed or matted axillary lymph nodes, or any of infraclavicular, supraclavicular, or internal mammary lymphadenopathy regardless of tumour stage.

LABC forms 10–20% [39] and 40–60% [40] of all breast cancers in US and India respectively. LABC is a very heterogeneous group and requires multimodality approach for its treatment. LABC is further divided into "operable" or "inoperable", In some centres operable cases first undergo initial surgery followed by post-operative radiation and adjuvant systemic therapy as described above for early stage disease.

However, at present Neoadjuvant chemotherapy (NACT) followed by surgery and radiation is treatment of choice for all cases of LABC. ± adjuvant systemic therapy.

Neoadjuvant chemotherapy does not improve overall or disease-free survival [41–43] compared to adjuvant chemotherapy but response to neo-adjuvant therapy is the best surrogate prognostic marker. Neo-adjuvant chemotherapy has following advantages

1. Down stage the disease and can make inoperable patient into operable one.
2. Takes care of distant metastases.

3. pCR (Pathological complete response), possible in up to 30% of cases or PR (Partial response) with residual tumour less than 3 cm, can allow BCS, particularly in young patients, if the patient so desires.
4. Degree of response to NACT helps to tailor further adjuvant systemic therapy, particularly in selection of chemo drugs.

Disadvantages:

1. Possible over treatment (as exact pathological stage is unknown)
2. Possible under treatment (especially undertaking BCS in case of good response in LABC)
3. Possible disease progression if no response, as main loco-regional therapy is delayed .

Surgery after NACT: 2–4 courses of chemotherapy are given when clinical assessment of response is done. If CR or PR of more than 80% is achieved, patient should be taken up for Surgery. Mostly MRM is done. 30% of cases may undergo BCS [44, 45] if patient is desirous of preservation of breast and is young. Rest of chemotherapy is completed after surgery in adjuvant setting and after that post-operative radiation is delivered to all patients of LABC.

Radiation after NACT and Surgery: Local recurrence rate following NACT + Surgery in LABC varies between 30–60% [46] as reported in the literature, hence, all patients should receive post- operative radiation following both MRM and BCS. Radiation does not add to survival but it reduces local recurrence by 2/3 and hence improves quality of life [47, 48]. Good response to neo-adjuvant chemotherapy help in planning further systemic therapy [48].

Radiation techniques and dose schedules are same following MRM and BCS in LABC as described below for early stage breast cancer.

NACT in early stage breast cancer: NACT has been tested in early stage patients also. Evaluation of such studies have shown that NACT is not superior but equivalent to adjuvant chemotherapy in term of disease free and overall survival but may be considered due to added advantages of NACT. It may increase chances of BCS [49]. NACT may be considered in patients with early stage operable breast cancer with poor prognostic features e.g. high ratio of tumour volume to breast, lymph node-positive disease, biological features of primary cancer- high grade, hormone receptor-negative, HER2-positive, triple negative cancer (TNBC) and younger age [50, 51]. This modality of treatment is still under investigation.

Neo-adjuvant Chemo-radiation in LABC: NACT is treatment of choice for LABC and is being used for long time due to its benefits. But rates of pathologic complete response, a surrogate marker for disease-free survival remain modest following NACT, more so when the tumour is estrogen or progesterone receptor–positive and Her2-negative [52].

Due to success of chemoradiation in other solid tumours e.g. cancer cervix, head & neck cancer, anal canal cancer, chemo-radiation is being tested in LABC in

neo-adjuvant setting with aim of further improving control rate and survival. Chemotherapy usually with single drug or combinations including e.g. 5-Fluorouracil or Paclitaxel or Vinorelbin or Doxorubicin is concurrently given with radiation delivering a dose of 40–46 Grays in 4–41/2 weeks. Chemoradiation demonstrated its benefit of increased pCR of around 27% and BCS is possible in 69% of cases in LABC. But chemoradiation has higher grade 4 toxicity of >20% [53–58] This modality is still under investigation. Treatment of large number of patients with long follow up will determine efficacy and usefulness of chemoradiation in future.

19.3 Radiation Techniques and Dosage

Radiation is used post-operatively either following MRM or BCS. Different radiation parameters are discussed below.

1. **Choice of energy of radiation**: External radiation to chest wall ± drainage area is delivered by photons of either Cobalt beam of 1.25 MeV energy or X-ray beam of 6 MeV energy from Linear Accelerator. External radiation with Electron beam can also be delivered in post MRM patients for treatment of chest wall/Flap and drainage area. Energy of 6–12 MeV electron beam depending on thickness of chest wall is used for irradiation and 12–16 MeV for lymph node areas depending on depth of lymph nodes. Main advantage of electron beam is that radiation goes up to a particular depth and then there is rapid fall off dose and hence tissue beyond can be spared. Dose to lungs and heart can be very low and therefore less lung and cardiac toxicity. Both photon and electron beams have same efficacy, however electron beam is not usually preferred as it is very difficult to achieve dose homogeneity and has high late skin radiation toxicity like skin fibrosis and telengectagia. Electron beam is not used for whole breast irradiation following BCS as cosmesis will be compromised severely due to above mentioned toxicity, however electron beam is useful for boost in BCS after external radiation.
2. **Position of patient for external radiation**: Patient is treated in supine position. Chest wall is a curved region, hence Breast Board (Fig. 19.1) is must for treatment of both chest wall and whole breast. Breast board by adjusting the angle, makes chest wall parallel to the couch and it is easier to position the radiation beams (Fig. 19.2). Patient is positioned both for planning CT and on treatment machine couch with breast board.

Arm is abducted at 90 ° to the neck and head is turned to the opposite side. Arm rests on the board are used for better positioning, reproducibility and comfort of the patient. Some centers do use prone position with special couch to treat breast after BCS.

Fig. 19.1 Breast Board

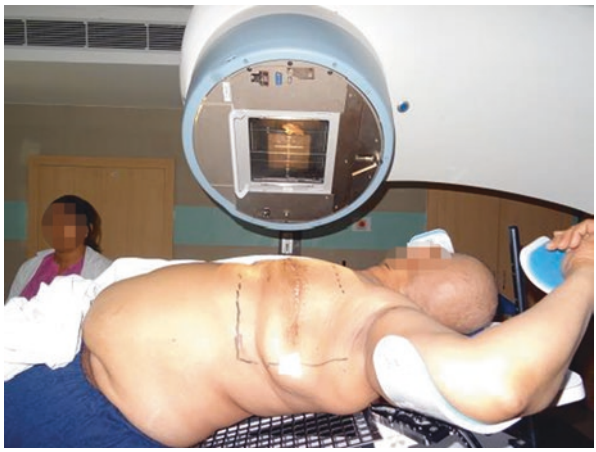


Fig. 19.2 Patient in treatment position on Breast Board with markings for post MRM treatment

19.3.1 Radiotherapy Techniques

Whole chest wall/flap following MRM or whole breast following BCS and lymph node drainage areas—axilla, supraclavicular ± internal mammary are to be irradiated. Various radiotherapy techniques are used for irradiation of both chest flap following MRM or whole breast following BCS as given below:

19.3.1.1 Conventional Technique

This technique is being used for almost last 80 years. Chest wall/flap and is still considered best Whole breast following BCS or chest wall after MRM is irradiated using two parallel opposing tangential fields to avoid excessive irradiation of underlying lung and a direct anterior fields to irradiate axilla & supracluvicular area and a separate direct anterior field to irradiate internal mammary lymph nodes. Extent of these fields are given below

1. **Two parallel opposing Tangential fields to chest wall or whole breast**
   Upper border—second inter costal space (angle of Louis) when supraclavicular (S/C) field is used and when S/C field not used– head of clavicle
   Medial border—at or 1 cm across midline
   Lateral border—2–3 cm beyond all palpable breast tissue or along mid axillary line
   Lower border—2 cm below opposite infra mammary fold

Angle of tangential field is determined for individual patient by doing simulation on conventional or CT simulator. A angle of 55 ° of medial tangent is good for almost 80% of cases. Central lung distance which determines the depth of lung included in the field should not be more than 3.5 cm.

2. **Anterior axillary and supraclavicular field**
   Should cover axilla and lower 2/3rd of neck
   Field borders –
   Upper border: thyro-cricoid groove
   Medial border: at or 1 cm across midline extending upward following medial border of SCM (sternocleidomastoid muscle) to thyrocricoid groove
   Lateral border: insertion of deltoid muscle
   Lower border: matched with upper order of tangential fields
3. **Internal mammary field:**
   Medial boarder—2–3 cm across midline on opposite side
   Lateral border—4 cm lateral to midline on same side
   Superior border—To match Supraclavicular field or at lower part of sternal notch
   Inferior border—At sixth costal cartilage or in fourth intercostals space on left side to avoid radiation to heart
   Ipsilateral internal mammary chain may also be irradiated by including in tangential field taking medial tangential field 2 cm across midline on opposite side
4. **Posterior axillary field**: Is indicated when thickness of axilla is more than 12 cm
   Borders:
   Medial border—To allow 1.5–2 cm of lung on the portal film
   Inferior border—at same level of inferior border of S/C field
   Lateral border—just blocks fall off across post axillary fold
   Superior border—splits the clavicle
   Superiolaterally—shields or splits humeral head
   Centre—at acromial process of scapula
   Junctions between fields need to be managed properly to avoid overlapping.
   Wedges as compensators—The intact breast is conical organ. When radiation is delivered by two tangential fields, apex or breast- areola and nipple get more dose due to obliquity of breast and base of breast get less, hence dose inhomogenity. To achieve uniform dose distribution in whole breast irradiation after BCS, a device called Wedge filter (Fig. 19.3) is used as compensator during irradiation so that dose variation is minimal. A 30° wedge filter is commonly used. Some time a appropriate compensator may to used to take care of oblique contour of breast.

Fig. 19.3 Wedge filter used with Cobalt beam

Fig. 19.4 Wax Bolus

Bolus—is a tissue equivalent material. Megavoltage radiation when enters the body, gives 100% dose at 0.5 cm depth in Cobalt beam and at 1.2 cm for photon beam of 6 MeV below skin, hence skin is spared. In MRM patients, radiation should give adequate dose to skin otherwise there is risk of developing recurrence, hence 0.5 cm and 1.2 cm universal wax bolus (Fig. 19.4) or commercially

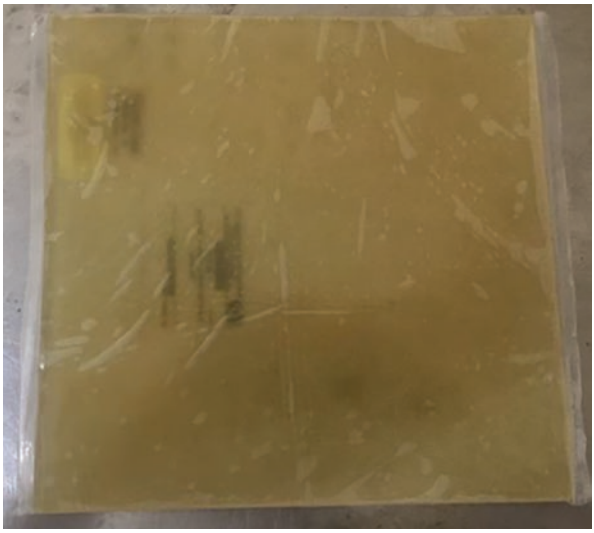


Fig. 19.5 Synthetic Bolus—Superflab

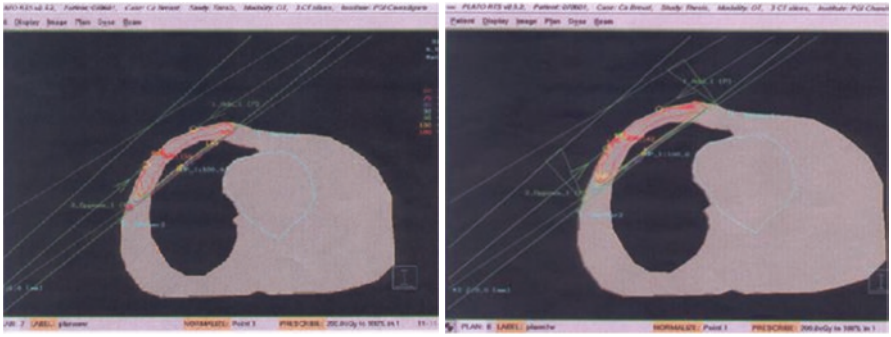


Fig. 19.6 showing isodose distribution of two tangential fields for irradiation of chest wall following MRM with and without wedge filter

available synthetic bolus (Fig. 19.5) should be used with Cobalt or Linear Accelerator beam of 6 MeV respectively. This brings 100% percent dose to the surface and skin is adequately irradiated. Size of bolus should be 20x20 cm so that whole of chest flap can be covered.

Treatment planning and dose calculations; After verification of field markings on the simulator, patient is planned to treat either by SSD or SAD technique. Dose calculations can be done manually or by TPS. Advantage of computer calculation is that isodose disrtribution can be drawn in 2D format as shown in Fig. 19.6. Incident dose per field is calculated using PDD or TAR tables and time to deliver that dose is calculated as per out put tables.

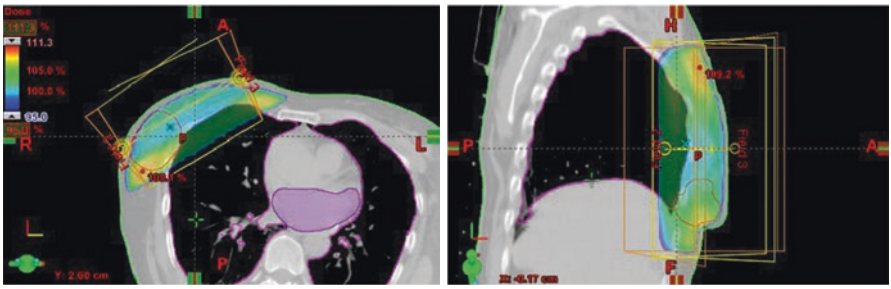


Fig. 19.7 Shows dose distribution of two tangential fields for treatment of whole breast with 3D CRT

19.3.1.2 3D Conformal Therapy (3D CRT)

3D CRT is a technique in which multileaf collimated 2 or more fields are used delivery same uniform dose from each field. This is technique of choice at present. It is similar to conventional technique and uses two tangential fields for chest wall/flap radiation and direct fields for treatment of drainage areas. However, it involves 3D conformal planning which gives better idea of homogeneous coverage of target and reduced irradiation of normal tissues with use of multileaf collimator. Figure 19.7 shows dose distribution of 3D CRT plan. 3 D CRT significantly reduces late radiation toxicity.

19.3.1.3 Intensity Modulated Radiation Therapy (IMRT)

IMRT is a radiotherapy technique where 2 or more multleaf collimated fields are used and different dose is delivered thorough each field and intensity of dose can also vary across same field. This helps in more conformal dose distribution according to size and shape of tumour and also effectively spares normal tissues. It is not used routinely in treatment of breast cancer but it is useful technique when normal tissues like lung and heart tissue are getting more dose with 3D CRT. This technique is good for post BCS patients. IMRT is delivered either as Classical IMRT or Volumetric modulated arc based radiotherapy (VMAT). VMAT is being used with increasing frequency as it takes less time for planning and treatment time is less and hence, better efficiency of machine. There are no junctional problems. Figures 19.8 and 19.9 shows dose distribution of each technique.

IMRT can also deliver simultaneous boost to lumpectomy cavity in post BCS patients. IMRT is laborious and time consuming technique. It takes long time for planning and delivery of IMRT and efficiency of machine is reduced.

19.3.1.4 Image Guided Radiation Thearpy (IGRT)

Breast is a mobile organ due to respiration. Therefore errors may creep in during radiation treatment following BCS and reproducibility of treatment plan done initially may be disturbed. IGRT is useful for correcting the same. In IGRT, onboard CT-Scan is done when patient is lying in treatment position on the treatment couch,

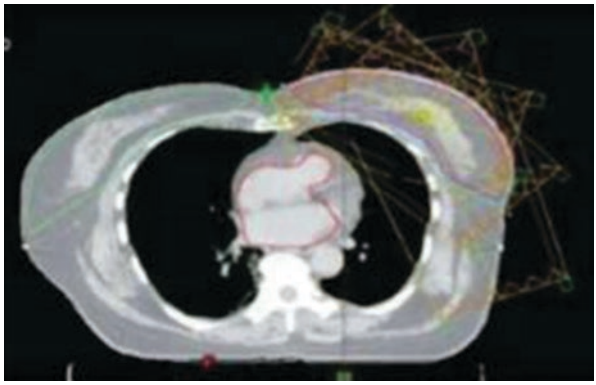


Fig. 19.8 Multiple fields classical IMRT dose distribution

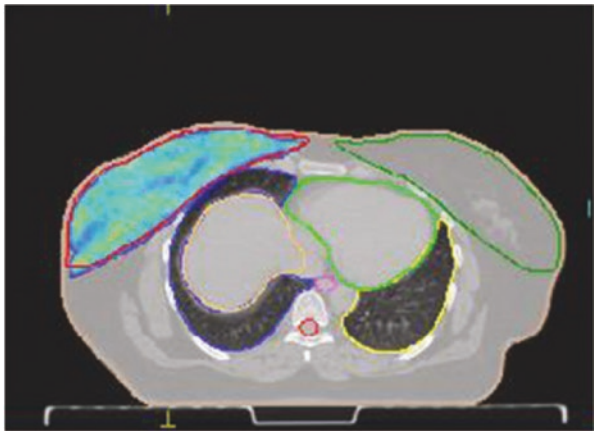


Fig. 19.9 VMAT arc IMRT dose distribution

immediate planning is done and is compared with pre-treatment planning and if both simulates, treatment is continued otherwise patient needs to be simulated again and re-planning is done. Motion management methods are used to take care of movements of breast due to respiration for precise and accurate delivery of radiation .

19.3.2 Dose, Time and Fractionation

Standard radiation dose of 50 Grays is delivered in 25 fractions in 5 weeks time. This gives best control of disease with minimum late radiation morbidity.

Hypofractionated regimen is gaining popularity now a days. In this regimen, a dose of 40–42.5 Gys is delivered in 15 fractions in 3 weeks. Advantages of this regimen are short treatment time, hence better compliance and comfort, less costly and radiation reactions appear after completion of radiation and hence no interruption of treatment.

Randomized trials START (Standardisation of Breast Radiotherapy) A & B on hypofractionation regimen of 40 -42.5 Gys from UK [59, 60] and a trial from Canada [61, 62] have shown that hypofractionation gives same local control and survival when compared with conventional regimen of 50 Gys; and similar or lower late radiation toxicity. A number of trials since have proved efficacy of hypofractionation in the treatment of breast cancer and is standard of care in most of centers now.

19.3.3 Boost Techniques

Boost radiation is given after completion of external radiation after BCS to raise the total dose to the cavity to 65–70 Gys. For best control of disease.

Initially deep X-ray therapy beam was used and some centers also used Cobalt-60 beam at low SSD. Both these beams gave high skin and lung toxicities and therefore these are not used any more. Following two techniques are standard of care for boost therapy at present.

A. **Electron beam therapy:** It is most commonly used technique. Direct single field radiation is given. Electron energy of 9–18 MeV is selected depending on size of breast and depth of lumpectomy cavity. Dose of 10–20 Gys has been practiced by different centers. Advantage of this technique are, easy availability and ease of delivery. Late toxicity include talengectegia and de-pigmentation of skin which may lower cosmosis slightly.
B. **Interstitial Brachytherapy:** This is considered to be ideal technique for boost therapy as it gives conformal dose distribution and delivers 1.5 to 2 times more dose in the centre than the prescribed dose. Implant can be given intra-operatively immediately after lumpectomy by the surgeon. Or it can be given after completion of external radiation. Identification of cavity is a problem when implant is given after external radiation and therefore surgeon should implant clips in the wall of the cavity. 2–4 plane implant is given depending on size of cavity and breast. Brachytherapy can be practiced with low dose rate (LDR) using Iridium-192 wire delivering dose of 10–15 Gys but at present high dose rate (HDR) brachytherapy is used where same equivalent dose is delivered using after loading brachytherapy machine with Iridium-192 or Cobalt- 60 source. Procedure of implant is shown below from Figs. 19.10, 19.11, 19.12, 19.13, and 19.14. A dose of 3–4 Gys per fraction is delivered to a total of 15–20 Gys and patient is treated twice a day, a gap of 6–8 h between 2 fraction on same day. Treatment is completed in 3–5 days time, This technique requires facilities for brachytherapy and experienced radiation oncologist for doing implant. It is invasive procedure. It is time consuming and labour intense technique. Few patients may develop scars at entry and exit of implant catheters and fibrosis in implanted area and may compromise cosmetic appearance slightly.

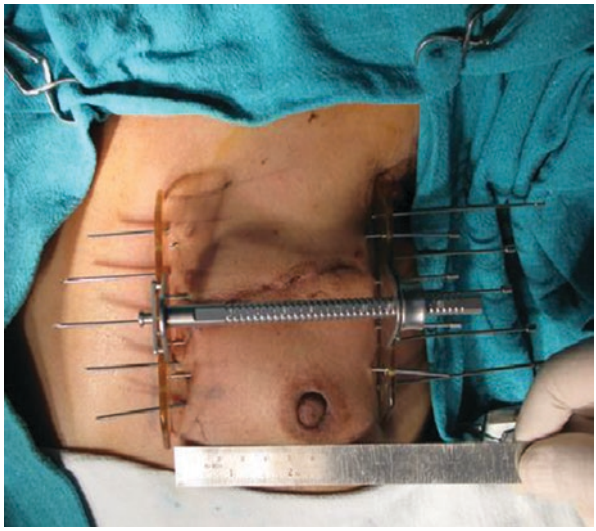


Fig. 19.10 Interstitial Implant first done with metal needles. Template being used to ensure parallelism of needles

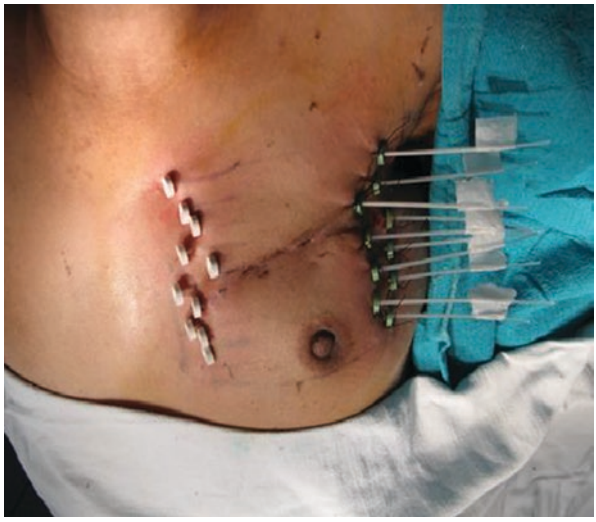


Fig. 19.11 Metal needles are replaced with plastic catheters

19.3.4 Techniques for APBI

There are number of techniques for delivery of APBI. They are described below

1. **Brachytherapy:** This is most commonly used technique. It delivers high dose of radiation in short time biologically more effective and gives better control with excellent cosmetic outlook. Brachytherapy is practised in following two ways
   (a) **Interstitial Implant:** Lumpectomy and implant are planned together. Surgeon will do the lumpectomy and Radiation Oncologist will implant the

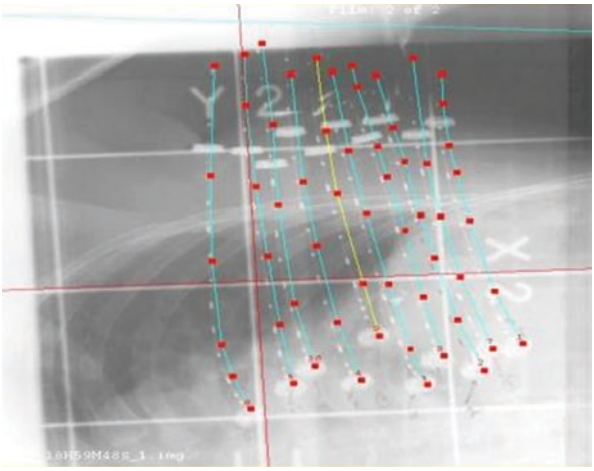


Fig. 19.12 Simulation image of implant for calculations of dose

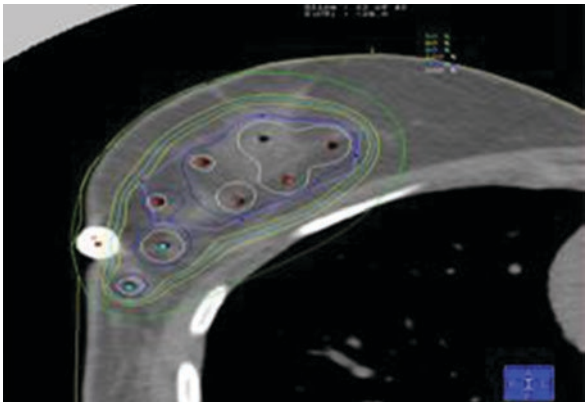


Fig. 19.13 Radiation dose distribution on CT - Simulation Image

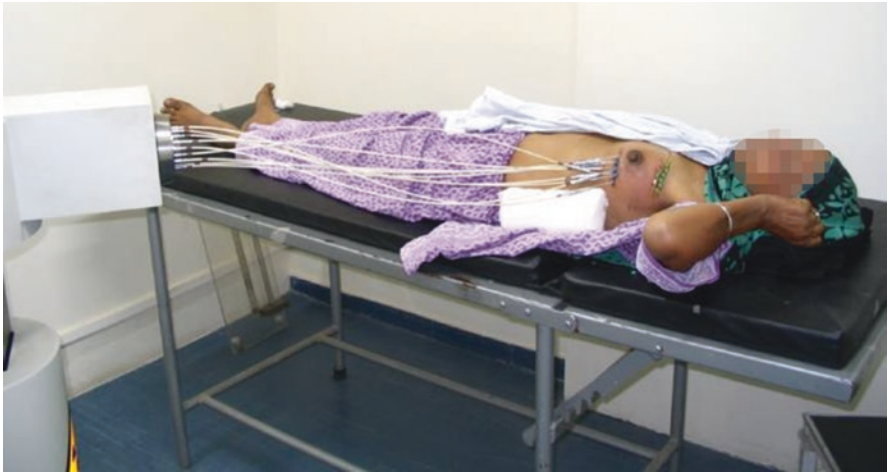


Fig. 19.14 Patient is being treated on HDR machine

cavity with margin of safety using 2–4 planes using low dose rate (LDR) or high dose rate (HDR) technique as described above for boost therapy. Dose of 60 Gys with LDR or equivalent Hypo-fractionated regimen of 34 Gys in 10 fraction is delivered with HDR treating patient twice a day with 6–8 h interval and total dose is delivered in short period of 5 days. This technique gives excellent control of tumour locally but is a invasive procedure.

(b) **Mammocyte Balloon Brachytherapy:** A specially designed balloon with capacity of 30–70 cc is known as Mammocyte with one central or multiple catheters is used. Later gives better distribution of dose.

It is placed inside the cavity immediately after lumpectomy. It can be used with HDR brachytherapy only. Dose of 34 Gys is delivered in 10 fractions over a time of one week. Uniformity of dose distribution is poor with Mammocyte than interstitial brachytherpy and it is not presently available in India.

2. **External radiation Techniques:** 3 D CRT or IMRT with 6 MeV Linear Accelerator beam is used. Both these techniques give better dose homogeneity, are non-invasive and allows evaluation of final histology. This technique is practised by some centers but it is still under going evaluation. Similarly Proton beam IMRT can also be used for APBI. Hypofractioned regimen is used. Total dose of 34–38.5Gys. at 3.4–3.85 Gys per fraction is given in 10 fractions over 5 days and patient is treated twice a day with 6–8 h interval between 2 fractions in a day. Treatment is completed in short period of 5 days. Figure 19.15 shows dose distribution of 3D CRT plan.
3. **Intra-operative radiation Techniques**: Intra-operative technique have also been used for APBI. Initially, Electron beam was used but Linear Accelerator has to be in the operation theatre and hence cumbersome. Mobile small linear accelerator (Mebatron and Novac −7) have been developed with beam energies of 4–12 MeV. Results were not better than brachytherapy. However this modality is

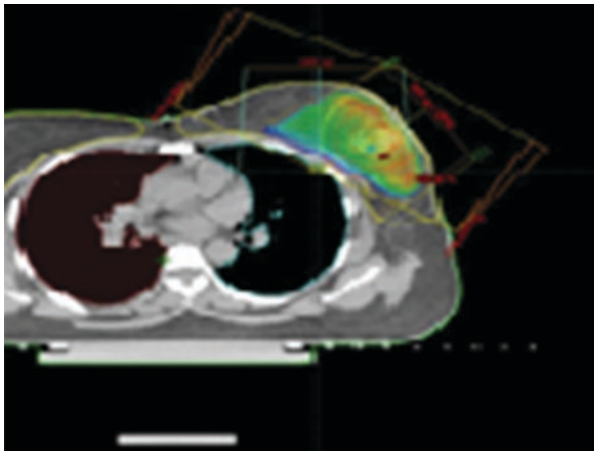


Fig. 19.15 3 Fields 3D CRT Dose distribution localised to lumpectomy cavity only

still under investigation. A low energy X-ray machine with 50 KeV beam energy (Intrabeam from Carl Zeiss Meditec AG, Jena, Germany) has been developed with intra-operative applicators of different sizes to deliver APBI. Early results have shown promise and this modality is still under evaluation.

In conclusion among all the techniques, Interstitial brachytherapy and 3D CRT are best for practice of APBI at present in Indian setup.

19.4 Role of Radiation in Metastatic and Advanced Breast Cancer

Radiation is used as supportive and palliative treatment to systemic therapy of metastatic and advanced disease with aims of

1. Relief of pain particularly in bone metastases.
2. Control of pressure symptoms.
3. Control of bleeding or fungation from breast tumour.

Indications for palliative radiation are:

1. Bone metastases—Localised or disseminated.
2. Brain metastases.
3. Extradural spinal deposits.
4. Soft tissue metastasis.
5. Choroidal metastases
6. Impending fracture.
7. Large local growth with pain, ulceration, bleeding.
8. Fixed nodal recurrences.
9. Liver and lung metastasis
10. For ovarian ablation.

1. **Radiation in Bone metastases:** Bone is most common site for metastases in breast cancer. 20–85% of patients of breast cancer develop bone metastases. Bone metastasis are usually associated with a poor prognosis with median survival rates are limited to few months. Localized Involvement of any bone can be seen but commonly involved bones are lumber and thoracic vertebrae, pelvis, ribs, long bones and skull. Metastases may be at single or multiple sites. Some patients have diffuse involvement of whole skeletal. Pain is most common symptom at site of metastases which is best relieved by radiation. It also avoids impending fractures and provide strength to bone. Patient may require radiation to one site or multiple sites. Patients may require radiation at one time or number of times in the follow up as and when metastases appear. Radiation gives pain control in 50–80% of bone metastases [63].

   Radiation parameters: External radiation is given either with Cobalt- 60 beam or Linear Accelerator beam of 6 MeV X-rays.

Commonly convention technique or 3D CRT using single or two parallel opposing fields are used. Some time IMRT may be used in vertebral metastases to avoid irradiation of spinal cord. SRS (Stereotactic radio-surgery) in single treatment or SRT or SBRT (Stereotactic radiotherapy or stereotactic body radiotherapy) in multiple treatments can also be used for such sites.

Dose of Radiation—there is no agreement on optimal dose for bone metastasis. Large number of dose time fractionation regimens are used e.g. 8 Gys in single fraction, 20 Gys in 5 fractions, 30 Gys in 10 fractions in 2 weeks or 35–40 Gys in 3 weeks [64]. All dose regimens give almost same control of pain which may range from 50–85%. Younger patients, those with localized single or few metastases sites, with possibility of long survival and in good general condition should be treated with fractionated regimens of 2–3 weeks to avoid late toxicity.

Patients with diffuse disseminated bone metastases can be treated with Hemi- body radiation for pain relief or with radio-isotopes such as Phosphorus -P32 or Stronsium- Sr 89. These techniques are rarely used as more effective systemic Chemotherapy is available at present

2. **Radiation for Brain Metastatses**: Upto 20% of breast cancer patients are likely to develop brain metastases, which may be single or multiple, later is more common. 1% of patients may have spread to meninges. Systemic therapy of any kind is of little help in brain metastases due to blood brain barrier. Radiation is treatment of choice. Most of these patients present with symptoms of raised intracranial tension. Patients should immediately be started on decompressive therapy with high doses of steroids and anticonvulsants before starting radiation.

   Patients are given whole brain iradiation (WBI) due to multiplicity of metastases. Conventional or 3D CRT techniques are used with Cobalt-60 or Linear Accelerator beam of 6 MeV. Dose of 30 Gys in 10 fractions in 2 weeks. is delivered in 2 weeks time. IMRT Or VMAT can also be used. Modern IMRT techniques allow for sparing of the hippocampus with acceptable target coverage and homogeneity. Theses techniques are most useful in patients who has longer chance of survival.

   Pateint who has better chance of survival may be given more protracted course of 35–40 Gys in 15 fractions. Patient with poor performance status may be given single dose of 8Gys. Large volume of literature is available on efficacy of WBI.

   Stereotactic Radio-surgery (SRS) is preferred now a days for well defined single or multiple metastases. Upto 10 lesions can be treated delivering dose of 20–30 Gys in a single fraction to each lesion [65].

3. **Radiation in Spinal Cord Compression:** 15–25% cases of cord compression are due to breast cancer metastases., Pain is most common symptoms in 90% of cases followed by compression symptoms of paraparesis or paraplegia. With or without involvement of sphincters. Most of the time compression is due to frac-

ture of vertebra or paravertebral space involvement. It can be due to extra-dural deposits and rarely due to intramedulary metastases. Surgery is treatment of choice if patient presents within 24–48 h of onset. Surgery in form of laminectomy, has maximum chance of recovery of compressive symptoms. If surgery is not feasible because of late presentation or patient's refusal, then radiation is the treatment for these patients. Radiation should also be given post- operatively to get best control of disease. Radiation modalities are same as given above. Dose of radiation is 30Gys in 2 weeks. Patients with favourable parameters may be given 35–45 Gys in 3–4 weeks. Conventional or 3D CRT IMRT can be used for spinal cord compression. De-compressive therapy with high dose steroids should be started before radiation. Stereotactic body radiation therapy (SBRT) is being used with excellent results [66, 67]. The most common and ideal indications for spine SBRT are in patients with no prior history of radiation, oligometastatic disease, limited or no epidural disease and no spinal instability. Results of radiation treatment are best in ambulatory followed by non-ambulatory or paraplegic patients.

4. Radiation is also considered for all other indications given above, A single dose of 8 Gys or short course of 20–30 Gys is given. Conventional technique or 3D CRT is used but small localized metastatic deposits in lung and liver can also be treated with SRS or SBRT [68]

19.5 Radiation in Locally Recurrent Disease

Local recurrence after MRM or BCS is significant clinical problem. Patient is started on systemic therapy as there are high chances of distant metastases. Local treatment of local recurrence is important for best local control which chemotherapy can not provide. It also adds to quality of life by avoiding associated complications e.g. pain. Fungation, bleeding. Following two types of patients are seen with recurrences. Radiation plays important role in both .

(a) Patients with no prior post –operative radiation after MRM: These patients are treated with radiation to whole chest wall with and without regional lymphnode areas. Same technique and dose is given as described above in this chapter for post-operative radiation. Boost with electrons may be added to area of localized recurrence.

(b) Patients with prior post-operative radiation:
   1. Post BCS patient: Surgery is treatment of choice if operable, mostly MRM is done. No further radiation.
   2. Post MRM recurrence on chest wall: Localized recurrences can be considered both for surgery and for radiation. One of the following radiation modalities can be choosen for treatment of such patients.
      - **Interstitial Implant**—is of choice as described in this chapter above and it can deliver high dose of radiation in short time and hence better control of disease. Near radical dose can be delivered if recurrence has occurred

after 2 or more years. Implant gives best chance of control but require good experience. It also spares underlying lung.

- **Mould Therapy:** This is also one of the best treatment modalities of brachytherapy with same advantages as with implant. Near radical dose can be given but is laborious and time consuming. Underlying lung is completely spared
- **Electron Beam Therapy:** Appropriate electron energy is selected depending on thickness of lesion. It spares the lung but total dose delivered is limited so control rate is poor.
- **Cobalt or Linaear Accelerator Beam:** can also be used with small localized field using 3D CRT or even IMRT technique but again dose delivered is limited and control rate poor with high chance of pulmonary or cardiac toxicity.

19.6 Conclusions

1. Radiation plays an important role in overall management of breast cancer.
2. In post operative adjuvant setting after MRM or BCS, it provide best local control with least morbidity by reducing local recurrences and also adds to survival in early stage patients.
3. In locally advanced patients, radiation improves the local control but no significant effect on survival and hence improves quality of life.
4. Radiation produces worthwhile palliation in recurrent and metastatic breast cancer by controlling pain and compressive symptoms in bones, brain or spinal metastases.
5. Various techniques of radiation are available for irradiation of breast cancer. An individualized approach should be used to select best technique for a particular patient.
6. Late radiation toxicity is very low more so if conformal techniques like 3D CRT or IMRT and Hypofractionation regimen are used.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Asthana S, Labani PS, Labani S. Epidemiology of breast cancer in Indian women. Asia Pac J Clin Oncol. 2015;4:150–4.
3. Tumour Registry Report, ICMR, 2016.
4. Paterson R, Russel MH. Breast cancer; evaluation of postoperative radiotherapy. J Fac Radiol. 1959;10:174–80.
5. Easson EC. Post-operative radiotherapy in breast cancer. In: Forrest APM, Kunkler PB, editors. Prognostic factors in breast cancer. Edinburgh: E. & S. Livingstone; 1968. p. 1.

6. Cuzick J, Stewart H, Peto R, Baum M, Host H, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. Cancer Treat Rep. 1987;71:15–29.
7. Early Breast Cancer Trialist Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of randomized trials. N Engl J Med. 1995;333:1444–55.
8. Fletcher G, McNeese M, Oswald M. Longrange results of patients treated by radical mastectomy and post-operative radiation without adjuvant chemotherapy: an update. Int J Radiat Oncol Biol Phys. 1989;17:11.
9. Vallagusa P, Bonadonna G, Veronesi U. Pattern of relapse and survival following radical mastectomy: an analysis of 716 concecutive cases. Cancer. 1986;41:1170.
10. K. Guidolin, M. Lock, K. Vogt, J.A. McClure, J. Winick-Ng, , C. Vinden, M. Brackstone. (2019) Recurrence and mortality after breast-conserving surgery without radiation, Curr Oncol, 26, 6, 380-388. https://doi.org/10.3747/co.26.5225.
11. Veronesi U, del Vecchio M, Greco M, et al. (1983) results of quadrantectomy, axillary dissection and radiotherapy (QUART) in T1 no patients. In: Harris JR, Hellman S, Silen W, editors. Conservative management of breast cancer. Philadelphia: Lippincott; 1983. p. 91–9.
12. Hayward JL. The guy's hospital trials on breast conservation. In: Harris JR, Hellman S, Silen W, editors. Conservative management of breast cancer. Philadelphia: Lippincott; 1983. p. 77–90.
13. Fisher B, Margoleser BM, et al. Five-year results of a randomised clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med. 1985;312:665–73.
14. Fisher B, Redmond C, Poisson R. Eight year results of a randomized clinical trial comparing total mastectomy and lumpectomy with and without irradiation on the treatment of breast. N Engl Med. 1989;320:822–8.
15. Joop A, van Dongen JA, Voogd AC AC, Fentiman IS IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of cancer 10801 trial. JNCI. 2000;92:1143–50.
16. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, Cutter D, Davies C, Ewertz M, Godwin J. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378:1707–16.
17. Overgaard M, Hansen PS, Overgaard J, Rose C, Anderson M, Bach F, et al. Postoperative radiotherapy in high risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish breast cooperative 82b trial. N Engl J Med. 1997;337:949–55.
18. Overgaard M, Jensen MB, Overgaard J, Rose C, Andersson M, et al. Postoperative radiotherapy in high risk post menopausal breast cancer patients given adjuvant tamoxifen. Danish breast cancer cooperative group DBGC 82 c randomized trial. Lancet. 1999;353:1641–8.
19. Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med. 1997;337:956–62.
20. Ragaz J, Olivotto IA, Spinell JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;97:116–26.
21. Bartelink H, Maingon P, Poortmans P, Weltens C. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015 Jan;16:47–56.
22. Bartelink H, Horiot J, Poortmans P, et al. Impact of radiation dose on local control, fibrosis and survival after breast conserving treatment: 10-year results of the EORTC trial 22881-10882. Proceedings from the 2006 annual San Antonio Breast Cancer Symposium. Oral presentation December 14, 2006.
23. Kindts I, Laenen A, Depuydt T, Weltens C. Tumour bed boost radiotherapy for women after breast-conserving surgery. Cochrane Data Base Syst Rev. 2017;11:CD011987.
24. Sanders ME, Scroggins T, Ampil FL, Li BD. Accelerated partial breast irradiation in early-stage breast cancer. J Clin Oncol. 2007;25:996–1002.

25. Njeh CF, Saunders MW, Langton CM. Accelerated partial breast irradiation (APBI): a review of available techniques. Radiat Oncol. 2010;5:1–28.
26. Jalali R, Singh S, Budrukkar A. Techniques of boost irradiation in conservative therapy; current evidence and suggested guidelines. Acta Oncol. 2009;46:879–92.
27. Shah C, et al. The American brachytherapy society consensus statement for accelerated partial breast irradiation. Brachytherapy. 2013;12(4):267–77.
28. Mannino M, Yarnold J, Offersen BV, et al. Accelerated partial breast irradiation as part of breast conserving therapy of early breast carcinoma: a systematic review. Radiother Oncol. 2009;90(1):1–13.
29. Shah C, et al. The American Brachytherapy Society consensus statement for accelerated partial-breast irradiation. Brachytherapy. 2018;17(1):154–70.
30. Correa C, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. Pract Radiat Oncol. 2017;7:73–9.
31. Oie Y, Saito Y, Kato M, et al. Relationship between radiation pneumonitis and organizing pneumonia after radiotherapy for breast cancer. Radiat Oncol. 2013;8:56.
32. Takigawa N, Segawa Y, Saeki T, Kataoka M, Ida M, Kishino D, Fujiwara K, Ohsumi S, Eguchi K, Takashima S. Bronchiolitis obliterans organizing pneumonia syndrome in breast-conserving therapy for early breast cancer: radiation-induced lung toxicity. Int J Radiat Oncol Biol Phys. 2000;48:751–5.
33. Vasiljevic D, Arnold C, Neuman D. Occurrence of pneumonitis following radiotherapy of breast cancer – a prospective study. Strahlenther Onkol. 2018;194(6):520–32.
34. Cuzick J, Stewart H, Rutqvist L, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol. 1994;12:447.
35. Rutqvist LE, Lax I, Fornander T, Johansson H. Cardiovascular mortality in a randomized trial of adjuvant radiotherapy versus surgery alone in primary breast cancer. Int J Radiol Oncol Biol Phys. 1992;22:887–96.
36. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368:987.
37. Cheng YJ, Nie XY, Ji CC, et al. Long-term cardiovascular risk after radiotherapy in women with breast cancer. J Am Heart Assoc. 2017;6:5.
38. National Comprehensive Cancer Network (nccn). NCCN clinical practice guidelines in oncology: breast cancer. Fort Washington, PA: NCCN; 2015. Ver. 2
39. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics. CA Cancer J Clin. 2019;2019:1. https://doi.org/10.3322/caac.21583.
40. Aggarwal G, Ramakant P. Breast cancer Care in India: the current scenario and the challenges for the future. Breast Care. 2008;3:21.
41. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and bowel project protocols B-18 and B-27. J Clin Oncol. 2008;26:778.
42. van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of cancer trial 10902. J Clin Oncol. 2001;19(22):4224.
43. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19(1):27.
44. Singltery SE, MacNeese MD, Hortobagyi GN. Feasibility of breast conservation surgery after induction chemotherapy for locally advanced breast cancer. Cancer. 1992;69:2849–52.
45. Parmar V, Krishnanurthy A, Hawaldar R, Nadkarni MS, Sarin R, Chenoy R, et al. Breast conservation treatment in locally advanced breast cancer – experience from a single institution. Int J Surg. 2006;4:106–17.
46. Yadav BS, Sharma SC, Singh R, Singh G. Pattern of relapse in locally advanced breast cancer treated with neo-adjuvant chemotherapy followed by surgery and radiotherapy. J Cancer Res Ther. 2007;3:75–80.

47. Raina V, Kunjanhari M, Shukla SK, Deo SV, Sharma A, Mohanty BK. Outcome of combined modality treatment including neo-adjuvant chemotherapy of 128 cases of locally advanced breast cancer – data from a tertiary cancer center in northern India. Indian J Cancer. 2011;48:80–5.
48. von Minckwitz G, Blohmer JU, Costa SD, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013;31:3623–35.
49. Coates S, Winer EP, Goldhirsch A, Gelber RD, Gnan M, Piccart-Gebhart M, et al. Tailoring therapies—improving the management of early breast cancer: St Gallen international expert consensus on the primary therapy of early breast cancer 2015. Ann Oncol. 2015;26:1533.
50. Loibl S, Pagan O, Graziottin A, et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer. 2012;48:3355.
51. Petros Charalampoudis P, Karakatsanis A. Neoadjuvant chemotherapy for early breast cancer. Lancet Oncol. 2018;19:128.
52. Adams S, Chakravarthy AB, Donach M, et al. Preoperative concurrent paclitaxel–radiation in locally advanced breast cancer: pathologic response correlates with five-year overall survival. Breast Cancer Res Treat. 2010;124:723.
53. Toledano A, Azria D, Garaud P, et al. Phase iii trial of concurrent or sequential adjuvant chemoradiotherapy after conservative surgery for early-stage breast cancer: final results of the Arcosein trial. J Clin Oncol. 2007;25:405.
54. Ellerbroek N, Martino S, Mautner B, Tao ML, Rose C, Botnick L. Breast-conserving therapy with adjuvant paclitaxel and radiation therapy: feasibility of concurrent treatment. Breast J. 2003;9:74.
55. Formenti SC, Volm M, Skinner KA, et al. Preoperative twice-weekly paclitaxel with concurrent radiation therapy followed by surgery and postoperative doxorubicin-based chemotherapy in locally advanced breast cancer: a phase i/ii trial. J Clin Oncol. 2003;21:864.
56. Kao J, Conzen SD, Jaskowiak NT, et al. Concomitant radiation therapy and paclitaxel for unresectable locally advanced breast cancer: results from two consecutive phase i/ii trials. Int J Radiat Oncol Biol Phys. 2005;61:1045.
57. Bollet MA, Sigal-Zafrani B, Gambotti L, On behalf of the Institut Curie Breast Cancer Study Group, et al. Pathological response to preoperative concurrent chemo-radiotherapy for breast cancer: results of a phase II study. Eur J Cancer. 2006;42:2286.
58. Kosma L, Koukourakis M, Skarlatos J, et al. Hypofractionated radiotherapy with 5-fluorouracil radiosensitization for locally "far advanced" breast cancer. Am J Clin Oncol. 1997;20:562.
59. The START Trialists' Group. The UK standardisation of breast radiotherapy (START) trial a of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 2008;9:331–41.
60. The START Trialists; Group. The UK standardisation of breast radiotherapy (START) trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 2008;371:1098–107.
61. Wheelan J, Pignol JP, Levine MN, et al. Long-term results of Hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362:513–20.
62. Bhattacharyya T, Mahajan R, Ghoshal S, Yadav BS, Rai B. Hypofractionated radiotherapy in carcinoma breast: what we have achieved? J Cancer Res Ther. 2015;11:259–63.
63. van der Velden JM, van der Linden YM, Versteeg AL, et al. Evaluation of effectiveness of palliative radiotherapy for bone metastases: a prospective cohort study. J Radian Oncol. 2018;7:325–33.
64. Sze WM, Shelley M, Held I, Mason M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy – a systematic review of the randomised trials. Cochrane Database Syst Rev. 2004;2:CD004721.
65. Nieder C, Grosu A, Gaspar LE. Stereotactic radiosurgery (SRS) for brain metastases: a systematic review. Radiat Oncol. 2014;9:1–9.

66. Gerszten PC, Mendel E, Yamada Y. Radiotherapy and radiosurgery for metastatic spine disease: what are the options, indications, and outcomes? Spine. 2009;34:S78–92.
67. Choi CY, Adler JR, Gibbs IC, et al. Stereotactic radiosurgery for treatment of spinal metastases recurring in close proximity to previously irradiated spinal cord. Int J Radiat Oncol Biol Phys. 2010;78:499–506.
68. Mahadevan A, Blanck O, Lanciano R, Peddada A, Sundararaman S, D'Ambrosio D, et al. Stereotactic body radiotherapy (SBRT) for liver metastasis – clinical outcomes from the international multi-institutional research patient registry. Radiat Oncol. 2018;13:26.

Role of Chemotherapy in Breast Cancer

20

Pramod Kumar Julka, Ishu Gupta, and Romila Tiwari

20.1 Introduction

Successful treatment of breast cancer requires elimination of all cancer cells whether at primary site, extended to loco-regional areas or metastatic to other regions of the body. Hence, multimodality treatment approaches are adopted involving surgery to eradicate the disease localised to the breast and/or axilla in early stages; radiation therapy to eradicate micro-metastatic disease in early stages; systemic therapy for the treatment of locally advanced disease (neo-adjuvant) or micro-metastatic (adjuvant) disease in early stages as well as palliation for the extension of survival in stage IV disease.

A significant improvement in the survival of women with breast cancer has been witnessed over the past few decades due to the introduction of chemotherapy, endocrine therapy and human epidermal growth factor receptor 2 (HER2) directed therapies.

Chemotherapy involves use of drugs either as a single agent or in combinations for killing cancerous cells and is administered in fixed schedules known as treatment Cycle. Each treatment Cycle is generally composed of 21 days and drugs are administered at different time-points (e.g., Day 1, Day 8, Day 15 etc.) to achieve maximum response. After 21 days, next treatment Cycle is initiated and the same schedule is repeated. On an average a patient receives 4–6 treatment Cycles; however, the

Pramod Kumar Julka, MD, FAMS (✉)
Former Professor and Head, Department of Oncology, AIIMS, New Delhi, India

Senior Director, Max Institute of Cancer Care, New Delhi, India
e-mail: pkjulka18@yahoo.co.in

Ishu Gupta, MBBS, MD
Senior Resident, Department of Medical Oncology, VMMC, Safdarjung Hospital, New Delhi, India

Romila Tiwari, MBBS
Specialist Medical Officer, Max Institute of Cancer Care, New Delhi, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_20

continuation or termination of chemotherapy purely depends upon the response to the treatment. Though, chemotherapy is mostly administered as an infusion into the vein (intravenously), some drugs can be taken in the form of pill or capsule as well.

Based on the stage of disease, the hormonal receptor status and Her2/neu status of the tumour, systemic management of breast cancer can be divided into three broad categories;

(a) **Adjuvant systemic therapy in early and locally advanced stage disease**
   1. Adjuvant Chemotherapy
   2. Adjuvant hormonal therapy
   3. Adjuvant Targeted therapy

(b) **Neo-adjuvant Chemotherapy in early and locally advanced stage disease**

(c) **Therapeutic systemic therapy in metastatic disease**
   1. Chemotherapy
   2. Hormonal/endocrine therapy
   3. Targeted therapy

Chemotherapy and hormonal therapy may be used as single modality or these may be combined in receptor positive patients but given sequentially. Targeted therapy is always combined with either chemotherapy or hormonal therapy or both when patient is Her2/neu positive. In this chapter we will discuss role of chemotherapy in adjuvant and neo-adjuvant settings both in early and locally advanced breast cancer.

20.2 Adjuvant Systemic Therapy in Early and Locally Advanced Stage Disease

Adjuvant therapy is indicated for early as well as locally advanced operable breast cancer after primary treatment with surgery in the form of either Modified Radical Mastectomy (MRM) or Breast conservative surgery (BCS). The main goal of adjuvant systemic therapy is to prevent the recurrence of breast cancer by eliminating occult, micro metastatic deposits present at the time of diagnosis thereby leading to an improvement in the survival. Experience over the last 50 years have shown that, it achieves both the aims by reducing the risk of relapse by approximately one third.

Administration of polychemotherapy (duration usually ranges from 3 to 6 months) reduces the annual death rate due to breast cancer by about 38% in women <50 years of age, and about 20% in those aged between 50–69 years. Most patients with early breast cancer undergo surgery upfront. This is followed by adjuvant systemic therapy (chemotherapy/hormone therapy/immunotherapy). Until recently, the standard of care for adjuvant chemotherapy was one-size-fits-all approach for all patients.

With the introduction of genomic tests, a personalized approach to adjuvant treatment has evolved in the past decade. The activity of a group of genes in the

form of genomic tests has been evaluated to reliably predict how a cancer is likely to behave and respond to treatment. One such test, Oncotype DX [1], analyses the activity of 21 genes to predict the recurrence as well as benefits from chemotherapy for HER2 negative, node negative (in premenopausal women) or node positive (in post menopausal women) early-stage, estrogen-receptor-positive breast cancer. Depending upon the age, the test assigns a recurrence score between 0 and 100 to early-stage breast cancer. For women older than 50 years of age, a score of 0–25 denote a low risk of recurrence (the benefits of chemotherapy do not outweigh the risks of side effects) whereas a score of 26–100 denotes a higher risk of recurrence (the benefits of chemotherapy are greater than the risks of side effects). For women aged 50 years and younger, a score of 0–15 denotes a low risk of recurrence (the benefits of chemotherapy do not outweigh the risks of side effects), a score of 16–20 denotes a low to medium risk of recurrence (the benefits of chemotherapy do not outweigh the risks of side effects), a score of 21–25 denotes a medium risk of recurrence (the benefits of chemotherapy are greater than the risks of side effects) and a score of 26–100 denotes a high risk of recurrence (the benefits of chemotherapy are greater than the risks of side effects). For scores of more than 16 in patients younger than 50 years of age, benefits of adjuvant chemotherapy have been demonstrated. Another genomic test, MammaPrint [2], looks at the activity of 70 genes to predict a recurrence score that is either low risk or high risk.

Adjuvant systemic therapy is considered for following categories of patients:

1. Nearly all women with positive axillary lymph nodes in early stage—more so if 4 or more lymph nodes are involved.
2. Tumour size more than 1 cm.
3. Undifferentiated tumour.
4. Lymphovascular invasion present.
5. Young and premenopausal patient.
6. Surgical margin positive or unknown.
7. Postmenopausal women with ER PR and Her2 negativity.
8. All patients of stage III disease who undergo surgery first.

Node negative patients with sufficient high risk features as follows are also given adjuvant chemotherapy:

1. Hormone receptor negative status, high grade or poorly differentiated tumours.
2. HER2 over expressing tumours
3. Tumours with markers of increased proliferation like mitotic index, high Ki-67 or elevated S phase fraction
4. Evidence of angio-lymphatic invasion
5. High risk recurrence score based on Oncotype DX assay
6. High risk disease based on Mamma Print analysis
7. Young age (*below 35 years*)

Based on the above consideration, three systemic treatment approaches are widely used as adjuvant therapy for early-stage breast cancer. These include

1. Adjuvant Chemotherapy
2. Adjuvant hormone therapy in receptor positive patients
3. Adjuvant Targeted therapy in Her2 positive patients

20.3 Adjuvant Chemotherapy

In 1950 and 1960 single drug either Cyclophosphamide or Melphalan were used as adjuvant systemic therapy with small increases in survival. It was in late 1970 that combination chemotherapy regimen CMF (Cyclophosphamide + Methotrexate +5-Fluorouracil) was developed in Milan, Italy by Bonadona et al., [3] which significantly added to the survival of breast cancer. Hence, it became a standard treatment in the early1970's. Systemic adjuvant chemotherapy therapy of breast cancer has evolved with a brisk pace since then. Bonadona et al. in late 1970 published results of anthracycline based regimen FAC or CAF (5-Fluorouracil + Adriamycin + Cyclophosphamide) which further added to the survival. Addition of taxanes in 1990 also added to survival and hence anthracycline and or taxane based regimen are standard of care now in the systemic adjuvant chemotherapy of breast cancer.

Adjuvant chemotherapy recommendations include multiple cycles (4 to 8) of taxanes and anthracyclines-based regimens for patients with node-positive and higher risk node-negative tumours. The American Society of Clinical Oncology guideline adaptation of the Cancer Care Ontario Clinical Practice guidelines [4] recommend the use of a regimen containing anthracyclines and taxanes as an optimal adjuvant chemotherapy strategy for patients who are deemed to be at high risk. A 15-year meta-analysis comprising 100,000 women treated across 123 randomized trials [5] demonstrated a reduction in 10-year breast cancer mortality by one-third with anthracycline-based chemotherapy regimens as compared to no chemotherapy. However, anthracycline-based regimens were associated with increased risk of cardiac mortality, myelodysplastic syndromes and treatment-related leukemia. To prevent anthracycline toxicities, several trials (USOR9735 [6], NSABP B-46 [7], Plan B [8], Success C [9]) have evaluated the role of non-anthracycline regimes in patients with early breast cancer and demonstrated that anthracycline-based regimens be used only in patients with four or more positive lymph nodes. However, this currently should not be considered as a standard of care except in patients with high risk of cardiac toxicity.

Taxanes in adjuvant settings have additional benefits, as strongly suggested by multiple clinical trials [10, 11]. The study CALGB 9344 demonstrated that the addition of sequential paclitaxel therapy improved both disease free survival (DFS) and overall (OS) among women with node-positive breast cancer,

Table 20.1 Chemotherapeutic agents for breast cancer

Anthracyclines (*e.g.* Doxorubicin, Epirubicin, Pegylated Liposomal Doxorubicin)
Taxanes (*e.g.* Paclitaxel, Docetaxel, Nanoparticle Albumin-Bound Paclitaxel)
Cyclophosphamide, Gemcitabine
Platinum salts (*e.g.* Cisplatin, Carboplatin)
Methotrexate (MTX)
5-Fluorouracil or oral Capecitabine)

compared to women receiving four cycles of cyclophosphamide plus doxorubicin chemotherapy. Dose dense therapies (every-2-week) with growth factor support studied in a large clinical trial (CALGB 9741) [12] have shown a 26% improvement in DFS and a 31% improvement in OS for women with lymph node positive breast cancer as compared to those receiving the same every-3-week (q3w) without growth factor support.

Breast cancer is sensitive to large number of chemotherapeutic agents given in the Table 20.1.

Single drug therapy has no place at present in adjuvant chemotherapy of breast cancer. Combination regimens are of choice due to their high response, low toxicity and less chance of drug resistance. Various combinations used in adjuvant setting are given below.

20.4 Dosing Schedule of Common Adjuvant Chemotherapy Regimen

1. ***AC followed by weekly Paclitaxel (dose-dense)***
   Doxorubicin 60 mg/m^2 IV push on Day 1
   Cyclophosphamide 600 mg/m^2 IV over 30 min on Day 1,
   Repeat cycle every 2 weeks for 4 cycles followed by
   Paclitaxel 175 mg/m^2 IV over I-hr infusion on Day 1 every 2 weeks
   or
   Paclitaxel 80 mg/m^2 by 1-h IV infusion weekly for 12 weeks
2. ***AC followed by Docetaxel (dose-dense)***
   Doxorubicin 60 mg/m^2 IV push on Day 1
   Cyclophosphamide 600 mg/m^2 IV over 30 min on Day 1
   Repeat cycle every 2 weeks for 4 cycles followed by
   Docetaxel 75 mg/m^2 IV over 60 min on Day 1
   Repeat cycle every 2 weeks for 4 cycles
3. ***CMF (IV regimen)***
   Cyclophosphamide 100 mg/m^2 P.O. on day 1–14
   Methotrexate 40 mg/m^2 IV day 1 & 8
   5- Fluorouracil 600 mg/m^2 IV on day 1& 8

Repeat cycle every 21 days for total of 6 cycle
Or
Cyclophosphamide 600 mg/m^2 IV on day 1
Methotrexate 40 mg/m^2 IV day 1
5- Fluorouracil 600 mg/m^2 IV on day 1
Repeat cycle every 21 days for total of 6 cycle

4. ***FAC or FEC x 4*** followed by
   Paclitaxel 175 mg/m^2 IV over I-hr infusion on Day 1
   Repeat cycle every 3 weeks for 4 cycles
5. ***CAF or FAC***
   Cyclophosphamide 600 mg/m^2 IV on day 1
   Doxorubicin 60 mg/m^2 IV day 1
   5- Fluorouracil 600 mg/m^2 IV on day 1
   Repeat cycle every 21 days for total of 6 cycles
6. ***FEC***
   5- Fluorouracil 500 mg/m^2 IV on day 1
   Epirubicin 100 mg/m^2 IV day 1
   Cyclophosphamide 500 mg/m^2 IV on day 1
   Repeat cycle every 21 days for total of 6 cycles
7. ***AC***
   Doxorubicin 60 mg/m^2 IV on Day 1
   Cyclophosphamide 600 mg/m^2 IV over 30 min on Day 1 + growth factor support
   Repeat cycle every 3 weeks for 4–6 cycles);
8. ***EC***
   Epirubicin 100 mg/m^2 IV push on Day 1
   Cyclophosphamide 830 mg/m^2 IV over 30 min on Day 1
   Repeat cycle every 3 weeks for 8 cycles
9. ***TAC***
   Paclitaxel 150 mg/m^2 IV day 1
   Doxorubicin 60 mg/m^2 IV day 1
   Cyclophosphamide 600 mg/m^2 IV day 1
   Repeat cycle every 21 days for total of 6 cycle

20.5 Adjuvant Chemotherapy Is Not Indicated in the Following Conditions

(a) Non-invasive carcinoma in situ (CIS) of any size in women of any age.
(b) Very small primary tumours (< 0.5 cm; T1a) and axillary lymph node negative status, irrespective of the hormonal status.
(c) Estrogen receptor (ER) positive cases with lymph-node negative status and low risk recurrence score based on Oncotype DX assay.
(d) Potential unacceptable adverse effects or existing co-morbid medical conditions that make the survival of the patients unlikely beyond 5 years.

20.6 Recent Advance in Systemic Adjuvant Therapy in Breast Cancer

Started as a standard of care in the late 1970's and early 1980's, systemic adjuvant therapy of breast cancer has evolved with a brisk pace. Currently, the adjuvant therapy is based on the stage as well as the genetic expression classification of breast cancer, which is as follows:

1. Luminal A
   - ER-positive
   - HER2-negative
   - Ki67 low
   - PR high
   - Low-risk molecular signature (if available)
2. Luminal B
   - Luminal B (HER2-negative)
   - ER-positive
   - Ki67 high or PR low of high-risk molecular signature (if available)
   - Luminal B-like (HER2-positive)
   - ER-positive
   - Any Ki67
   - Any PR
3. HER2-positive
   - HER2-positive (non-luminal)
   - ER and PR-negative
4. Basal
   - Triple negative
5. Normal breast-like
   - Claudin-low

Based on the gene expression profiling classification, the adjuvant treatment of breast cancer is as shown below in Table 20.2.

As indicated in Table 20.3, the recommendations for adjuvant treatment in premenopausal women include multidrug chemotherapy. For estrogen receptor positive patients, addition of endocrine therapy (Tamoxifen) after completion of chemotherapy (for at least 5 years to 10 years) has shown to improve the overall survival (OS). Similarly, for HER2 overexpressing tumours, addition of anti-HER2 therapy (Trastuzumab ± Pertuzumab) to the multidrug chemotherapy ± endocrine therapy depending upon the estrogen receptor positive status is associated with substantial survival benefit. For postmenopausal women with more than one positive lymph node, multidrug chemotherapy followed by addition of endocrine therapy (aromatase inhibitors or tamoxifen) for estrogen receptor positive patients has shown to improve the OS. Endocrine therapy alone may be used in postmenopausal women with a more favourable prognosis (based on Oncotype DX). Studies have shown superiority of Aromatase inhibitors over Tamoxifen in HER2/neu-positive

Table 20.2 Gene expression profiling classification for adjuvant treatment of breast cancer

Luminal A	Endocrine therapy in most cases; Chemotherapy if there is a high tumour burden (i.e., if >T3, >4 nodes involved)
Luminal B-like HER2 negative	Chemotherapy followed by hormone therapy in most cases
Luminal B HER2 positive	Chemotherapy + anti-HER2 therapy followed by hormone therapy
HER2-positive	Chemotherapy + anti-HER2 therapy
Basal	Adjuvant chemotherapy

Table 20.3 Enumerates the suggested adjuvant treatment approaches in breast cancer

Lymph node status	Hormone receptor status (ER)	HER2 status	Adjuvant treatment recommendations	
			Premenopausal women	Postmenopausal women
Positive	Negative	Negative	Multidrug chemotherapy	Multidrug chemotherapy
Negative	Negative	Negative	Multidrug chemotherapy	Multidrug chemotherapy
Any	Positive	Negative	Multidrug chemotherapy + endocrine therapy (tamoxifen)	*Lymph node status: Positive* Endocrine therapy (aromatase inhibitors and tamoxifen) with or without chemotherapy *Lymph node status: Negative* Endocrine therapy (aromatase inhibitors and tamoxifen)
Any	Positive	Positive	Multidrug chemotherapy + endocrine therapy (tamoxifen) + Trastuzumab[a]	*Lymph node status: Positive* Endocrine therapy (aromatase inhibitors and tamoxifen) with or without chemotherapy + Trastuzumab[a] *Lymph node status: Negative* Endocrine therapy (aromatase inhibitors and tamoxifen) + Trastuzumab[a]
Any	Negative	Positive	Multidrug chemotherapy + endocrine therapy (tamoxifen) + Trastuzumab[a]	Multidrug chemotherapy + Trastuzumab[a]

[a]Trastuzumab and Pertuzumab for stage II and III disease

tumours in postmenopausal women whereas Tamoxifen has shown equivalent efficacy in women who are obese. Similarly, for HER2 overexpressing tumours, addition of anti-HER2 therapy (Trastuzumab ± Pertuzumab) to the multidrug chemotherapy ± endocrine therapy is associated with substantial survival benefits.

20.7 Neoadjuvant or Preoperative Chemotherapy in Breast Cancer

Neoadjuvant chemotherapy is used to deliver systemic chemotherapy before definitive surgery in order to contain the spread of disease with an ultimate aim to improve the long-term survival. Patients with newly diagnosed locally advanced breast cancer (LABC) and inflammatory breast cancer (IBC) should be evaluated for neoadjuvant chemotherapy prior to definitive surgery and radiotherapy. Neoadjuvant chemotherapy is often used to 'downstage' the tumour so that more women become eligible for breast conservation therapy or with an intention to make inoperable locally advanced non metastatic breast cancers operable. Neoadjuvant chemotherapy should be considered for patients who fall into one of the following categories:

1. Locally advanced disease at presentation
2. Triple negative breast cancer (TNBC)
3. HER2/neu receptor positive breast cancer

In post-menopausal women, available data suggests that neoadjuvant endocrine therapy is associated with similar response rates and rates of breast-conserving surgery (BCS) as that of neoadjuvant chemotherapy, with lower toxicity, although survival data with neoadjuvant endocrine therapy are not yet available [13].

The drug regimens used in neoadjuvant settings are quite the same as those of adjuvant settings and include anthracycline and a taxane. The clinical response rate is good (60–80%) and about 15–25% women experience a pathologic complete remission (pCR) after neoadjuvant chemotherapy [14, 15]. However, even amongst the women with pCR, LABC or IBC subsets have higher risks of recurrence and do not show an improved survival as compared to early-stage breast cancer. In Her2/neu receptor positive breast cancer, Pertuzumab has been shown to provide additional benefit when combined with Trastuzumab in the neoadjuvant setting.

The most commonly used regimens for neoadjuvant therapy in breast cancer are as follows:

1. ***In Her2/neu receptor negative cases***, AC x 4 cycles every-2-week (q2w) followed by Paclitaxel x 4 cycles every-2-week (q2w) as dose-dense regimen or a conventional every-3-week schedule of AC (q3w) x 4 cycles followed by Paclitaxel (q3w) x 4 cycles or weekly Paclitaxel x 12 doses. This is the commonest used regimen.
2. ***In TNBC with BRCA mutations***, AC x 4 cycles every-2-week (q2w) as dose-dense regimen or a conventional every-3-week schedule followed by Paclitaxel x 4 cycles every-2-week (q2w) or every-3-week (q3w) or weekly Paclitaxel x 12 doses + Platinum (Carboplatin) x 4 cycles every-3-week (q3w) or weekly x 12 doses.

3. ***In Her2/neu receptor positive cases***, TCH regimen is used which comprises Docetaxel + Carboplatin + Trastuzumab x 6 cycles followed by maintenance Trastuzumab over a period of one year.
4. ***In Her2/neu receptor positive cases***, where T size ≥ T2 and nodal status is ≥ N1, Pertuzumab containing regimen is used. TCH is given every 3 weeks (q3w) for 6 cycles and 4 doses of Pertuzumab are given along with the first 4 cycles of TCH.

The tumour response is routinely assessed clinically with each neoadjuvant therapy whereas radiological response is assessed after 4–6 cycles of treatment in order to plan for surgery. Neoadjuvant chemotherapy is followed by definitive surgery and radiotherapy (RT) and hormonal therapy (HT) in case of hormone status positive cases. For Her2/neu receptor positive tumours, Trastuzumab is included in the treatment regimen and continued for a total of one year duration. In certain cases, if a very good response is seen, then the patient undergoes surgery and the remaining chemotherapy is given as adjuvant chemotherapy post-surgery (The so-called sandwich treatment).

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [16] conducted a meta-analysis of 10 randomized trials to investigate the long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer.Overall, 15-year local recurrence was seen more frequently with neoadjuvant chemotherapy as compared to adjuvant chemotherapy. Hence, surgery upfront followed by, if required, adjuvant chemotherapy/radiation/hormone therapy is the standard of care in early breast cancer. However, no difference was noted between the two groups for distal tumour recurrence or death.

20.8 Chemotherapy in Metastatic Breast Cancer

Although the combination of systemic and local therapy can achieve long term remissions in patients with localized breast cancer, nearly one third of them develop metastatic disease at some point in time. Furthermore, *de novo* metastatic disease at the time of presentation ranges between 3–5% in Europe and United States and 10–25% in Asian population [17, 18]. With a median survival of less than 3 years, metastatic breast cancer has a very dismal prognosis. Systemic therapy remains the cornerstone for the overall disease management of metastatic disease and the choice of therapy depends upon the overall medical condition of the patient, considerations for local therapy, hormone receptor status and Her2/neu receptor status of the tumour. Since, the intent of systemic therapy is mostly palliative; the risk of potential toxicities should be weighed against the expected response rates.

20.9 Systemic Chemotherapy for Metastatic Breast Cancer

Multiple systemic chemotherapeutic agents have shown activity in metastatic breast cancer. These include anthracyclines, alkylating agents, taxanes, and antimetabolites. The choice of a polychemotherapy combination depends upon whether or not adjuvant chemotherapy was administered to the patient. Though the patient treated with CMF regimens in the adjuvant setting may respond to same regimen in the metastatic setting as well, the treating physician may choose the drugs that were not being used earlier. In order to avoid the cumulative toxicity, patients who have progressed on polychemotherapy are treated with single agent belonging to the class of anthracyclines, alkylating agents, taxanes, antimetabolites etc. Amongst the taxanes, a nanoparticle Albumin-bound Paclitaxel (Abraxane) is found to be effective, although Docetaxel may be superior to Paclitaxel. In patients with HER2/neu overexpressing tumours, a combination of Trastuzumab with Paclitaxel can improve both the response rates as well as survival. The addition of Bevacizumab (Avastin) to Paclitaxel has shown to improve the response rate as well as duration of response as compared to Taxane alone. Similarly, Gemcitabine, Capecitabine, Vinorelbine, oral Etoposide, Epothilones, Vinca alkaloids has shown good response in previously treated patients. In the heavily pretreated patients, autologous bone marrow transplantation combined with high doses of single agents can produce objective responses with limited benefits. Carboplatin has shown significant objective response rate in BRCA mutant metastatic breast cancer. Intrathecal methotrexate has a role in leptomeningeal metastasis and is used for the management of same.

In patients having metastatic disease involving bony sites, local radiotherapy is administered in order to relieve the symptoms of metastatic disease. Similarly concomitant use of Bisphosphonates (Zoledronate, Palmidronate) or Denosumab a complete human monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL) has a role in cases of skeletal metastases and is used to reduce the bone pain and pathological fractures.

In summary, the therapies used in a metastatic breast cancer setting can be broadly divided into three categories:

(a) Hormone receptor positive candidates: In this subset of patients, sequential endocrine therapy forms the main line of treatment which includes AI/Fulvestrant + Palbociclib + Everolimus.
(b) Triple negative candidates: Sequential single agent chemotherapy:
    - Anthracyclines (Doxorubicin, Epirubicin or Liposomal Doxorubicin)
    - Taxanes (Paclitaxel, Docetaxel, or Abraxane)
    - Capecitabine or Vinorelbine
    - Other agents: Gemcitabine, Platinoids, Vinblastine, Eribulin, Irinotecan, Mitomycin, Ixabepilone, Carboplatin
    - Bevacizumab

(c) HER2 positive candidates: Pertuzumab and Trastuzumab + systemic chemotherapy, Lapatinib, T-DM1, Trastuzumab Deruxtecan, Tucatinib with Capecitabine and Trastuzumab, Lapatinib with Capecitabine etc.

Common drugs effective against metastatic breast cancer and their dose schedule is summarized below:

1. Capecitabine (1000–1250 mg/m^2 orally twice daily), Days 1–14, repeat cycle every 3 weeks (q3w)
2. Carboplatin (AUC 6 IV over 30 min), Day 1, repeat cycle every 3 (q3w) or 4 weeks (q4w)
3. Cisplatin (75 mg/m^2 IV over 60 min), Day 1, repeat cycle every 3 weeks (q3w)
4. Doxorubicin (60–75 mg/m^2 IV push), Day 1, repeat cycle every 3 weeks (q3w) or 20 mg/m^2 IV push, Day 1, repeat cycle weekly
5. Liposomal Doxorubicin (40–50 mg/m^2 IV), Day 1, repeat cycle every 4 weeks (q4w)
6. Eribulin (1.4 mg/m^2 IV push), Day 1 and 8, repeat cycle every 3 weeks (q3w)
7. Gemcitabine (800–1200 mg/m^2 IV over 30 min), Day 1, 8, 15, repeat cycle every 4 weeks (q4w)
8. Paclitaxel (175 mg/m^2 IV over 3 h), Day 1, repeat cycle every 3 weeks (q3w) or 80 mg/m^2 IV over 60 min, Day 1, repeat cycle weekly
9. Albumin-bound paclitaxel (260 mg/m^2 IV over 30 min) Day 1, repeat cycle every 3 weeks (q3w) or 100 mg/m^2 IV over 30 min, Day 1, 8, 15, repeat cycle every 4 weeks (q4w) or 125 mg/m^2 IV over 30 min, Day 1, 8, 15, repeat cycle every 4 weeks (q4w)
10. Vinorelbine (25 mg/m^2 over 5–10 min), Day 1, repeat cycle weekly
11. Cyclophosphamide (50 mg orally once daily), Day 1–21, repeat cycle every 4 weeks (q4w)
12. Docetaxel 60–100 mg/m^2 IV over 60 min, Day 1, repeat cycle every 3 weeks (q3w) or 35 mg/m^2 IV over 60 min, Days 1,8,15,22,29,36, repeat cycle every 8 weeks (6 weeks on-followed by 2 weeks off-treatment)
13. Epirubicin (60–90 mg/m^2 IV push), Day 1, repeat cycle every 3 weeks (q3w)
14. Ixabepilone (40 mg/m^2, maximum 88 mg IV over 3 h), Day 1, repeat cycle every 3 weeks (q3w)
15. Pertuzumab (840 mg IV over 60 min on cycle 1, then 420 mg IV over 30 min starting with cycle 2), Day 1 + Trastuzumab (8 mg/kg IV over 90 min on cycle 1, then 6 mg/kg IV over 30 min starting with cycle 2) Day 1+ Docetaxel (75 mg/kg IV over 60 min on cycle 1, then 75–100 mg/m^2 over 60 min starting with cycle 2), Day 1, repeat cycle every 3 weeks (q3w)
16. Pertuzumab (840 mg IV over 60 min on cycle 1, then 420 mg IV over 30 min starting with cycle 2), Day 1 + Trastuzumab (8 mg/kg IV over 90 min on cycle 1, then 6 mg/kg IV over 30 min starting with cycle 2) Day 1+ Paclitaxel (80 mg/kg IV over 60 min), Days 1, 8, 15, repeat cycle every 3 weeks (q3w)

17. Adotrastuzumab emtansine (3.6 mg/kg IV over 90 min on cycle 1, then 3.6 mg/kg over 30 min beginning with cycle 2) Day 1, repeat cycle every 3 weeks (q3w)
18. Atezolizumab (840 mg IV over 60 min), Days 1 and 15 followed by Albumin-bound Paclitaxel (100 mg/m^2 IV) Days 1, 8, 15, repeat cycle every 4 weeks (q4w)
19. Olaparib (300 mg orally twice daily), days 1–28, repeat cycle every 4 weeks (q4w)
20. Talazoparib (1 mg orally once daily), days 1–28, repeat cycle every 4 weeks (q4w)

20.10 Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer

In patients with hormone receptor-positive disease hormonal drugs (AI) are always preferred. In subsequent lines mTOR pathway inhibitors like Everolimus is added to hormone therapy to overcome the resistance. In ER positive and HER2 negative metastatic breast cancer, the CDK4/6 inhibitors namely Palbociclib, Ribociclib and Abemaciclib in combination with AIs as first-line treatment or with Fulvestrant as second line treatment constitutes an optimal treatment strategy. Treatment with CDK4/6 inhibitors is associated with anaemia, thrombocytopenia, fatigue, nausea, neuropathy, mucositis, alopecia, diarrhoea, vomiting, weakness, anorexia etc. Endocrine therapy for metastatic breast cancer is covered in details under the subheading of Hormonal or Endocrine Therapy. In patients with metastatic hormone receptor positive breast cancer with VISCERAL CRISIS (defined as severe organ dysfunction, which involves severe symptoms and rapid disease progression) it is advised to start chemotherapy rather than hormone therapy.

20.11 Metastatic Triple-Negative Breast Cancer

For triple negative breast cancer chemotherapy is the treatment of choice. Recently, the FDA has approved an antibody-drug conjugate (ADC) Sacituzumab govitecan-hziy (Trodelvy) for the treatment of metastatic triple-negative breast cancer who has already received at least two treatments. Treatment with Trodelvy is associated with neutropenia, diarrhoea, nausea and vomiting, and allergic reaction.

20.12 BRCA1 or BRCA2 Gene Mutation

A novel class of agents targeting DNA repair, poly-ADP ribose polymerase (PARP) inhibitors such as Olaparib and Talazoparib can be used as an alternative to chemotherapy in patients with metastatic HER2-negative breast cancer along with a

BRCA1 or *BRCA2* gene mutation. Common adverse effects of PARP inhibitors include fatigue, anaemia, nausea, vomiting, diarrhoea, decreased appetite, alopecia etc.

20.13 HER2-Positive Metastatic Breast Cancer

In patients with Her2/neu positive disease with hormone receptor positive disease a combination of hormonal and HER2-targeted therapy with either Trastuzumab or Lapatinib is preferred. In patients with Her2/neu positive and hormone receptor-negative disease a combination of anti Her2/neu and systemic chemotherapy is usually administered. Since anti Her2/neu therapy is not able to cross the blood-brain barrier, HER2-positive metastatic breast cancer with brain metastases is often treated with surgery and/or radiation therapy. Lapatinib a tyrosine kinase inhibitor of HER2 and EGFR may be able to enter into the brain, and could be an option for HER2-positive breast cancer that has spread to the brain. Treatment with Lapatinib is associated with diarrhoea, hand-foot syndrome (Palmar-plantar erythrodysesthesia or PPE) -skin rash, swelling, redness, pain and/or peeling of the skin on the palms of hands and soles of feet, anaemia, nausea and vomiting and elevated liver enzymes.

The first-line treatment of Her2/neu positive disease is usually a combination of Pertuzumab and Trastuzumab, and systemic chemotherapy (Taxane). Pertuzumab with trastuzumab has shown significantly higher OS as compared to trastuzumab alone. In this subset of patients, anthracyclines are avoided mostly to avoid cardiotoxicity due to the addition of trastuzumab/pertuzumab. T-DM1 (a novel antibody-drug conjugate ado-trastuzumab emtansine) is used as a second-line anti Her2/neu agent following progression on Trastuzumab, Taxane and Lapatinib. The most common adverse effects of T-DM1 include *fatigue*, *nausea*, arthralgias and myalgias, anaemia, thrombocytopenia, headache, constipation, nerve damage and hypokalaemia. Third-line or higher treatment for patients who have already received T-DM1 and Pertuzumab include Trastuzumab Deruxtecan, Tucatinib with Capecitabine and Trastuzumab, Lapatinib with Capecitabine etc. Lapatinib is active with Capecitabine in patients whose disease has progressed on Trastuzumab. The most common adverse effects of Trastuzumab Deruxtecan include nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anaemia, neutropenia, diarrhoea, leukopenia, cough, and thrombocytopenia whereas treatment with Tucatinib is associated with diarrhoea, hand-foot syndrome, nausea, fatigue and vomiting.

20.14 Immunotherapy in Breast Cancer

Immunotherapy, also called as biologic therapy refers to the use of medicines to stimulate a person's own immune system in order to effectively recognize and destroy cancer cells. Tests such as Tumour Mutational Burden (TMB), Microsatellite Instability (MSI) and PD-L1 are biomarkers for immunotherapy and can help

identify patients that may respond to Immuno-Oncology (I-O) therapy. Atezolizumab (Tecentriq) is one of the approved Immune checkpoint inhibitors to treat breast cancer. Atezolizumab in combination with Abraxane (nab-paclitaxel) is indicated for the first line treatment of unresectable locally advanced or metastatic triple-negative, PD-L1-positive (≥1) breast cancer. *The* IMpassion130 trial [19] compared Atezolizumab in combination with Abraxane versus placebo and Abraxane in previously untreated metastatic triple-negative breast cancer with a prolonged PFS in Atezolizumab and Abraxane arm. Pembrolizumab (Keytruda) is another immunotherapy that is approved for the treatment of metastatic cancer or cancer that cannot be treated with surgery having a molecular alteration MSI-high (MSI-H) or DNA mismatch repair deficiency (dMMR). Common side effects associated with immunotherapy include skin reactions, flu-like symptoms, diarrhoea, and weight changes.

20.15 Management of Adverse Drug Reactions

Monitoring of side effects is essential in order to ensure the safety of patients. A good strategy to monitor the side effects of chemotherapy include clinical evaluation of patients on every visit along with clinical laboratory evaluation (CBC, LFT, KFT etc.) before every treatment cycle. Most of the side effects associated with chemotherapy go away shortly with the medications prescribed to manage them. The international guidelines recommend primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) in patients receiving myelosuppressive chemotherapy. According to the ASCO guidelines, cancer patients with low risk of complications should be treated with a combination of oral fluoroquinolones (ciprofloxacin or levofloxacin) and amoxicillin/clavulanate (or clindamycin in patients allergic to penicillin) for the management of febrile neutropenia. In the younger women who wish to preserve the ovarian function, use of GnRH agonist therapy immediately before and throughout the duration of adjuvant or neoadjuvant chemotherapy can help improve the long-term menstruation and fertility.

20.16 Conclusion

1. Although the incidence of breast cancer is increasing the mortality from the disease has shown a decline during the last four decades due to the improvements in the treatment modalities. Adjuvant systemic therapy significantly increase both disease free and overall survival.
2. Chemotherapy plays predominant role in adjuvant therapy while addition of hormone or anti Her2 neu therapy in case of markers positive patient further adds to the survival.
3. Small number of receptor positive patients with favourable prognostic factors may be given only hormone therapy
4. Neoadjuvant chemotherapy in locally advanced patients down stage the disease which can make some patients suitable for breast conservation surgery.

Neoadjuvant chemotherapy may add to the survival and also add to the quality of life.

5. Systemic therapy with all the three modalities provides good palliation in metastatic disease.
6. Having breast cancer is nothing to be ashamed about or feel embarrassed and by taking an active role in the treatment of this aggressive disease a woman can improve her chances of survival with a better quality of life.

References

1. Markopoulos C. Overview of the use of Oncotype DX(®) as an additional treatment decision tool in early breast cancer. Expert Rev Anticancer Ther. 2013 Feb;13(2):179–94.
2. Soliman H, Shah V, Srkalovic G, Mahtani R, Levine E, Mavromatis B, et al. Mamma print guides treatment decisions in breast cancer: results of the IMPACt trial. BMC Cancer. 2020 Jan 31;20(1):81.
3. Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnatelli L, Brambilla C, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med. 1976 Feb 19;294(8):405–10.
4. Denduluri N, Somerfield MR, Eisen A, Holloway JN, Hurria A, King TA, et al. Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2) -negative and adjuvant targeted therapy for HER2-positive breast cancers: an American Society of Clinical Oncology Guideline Adaptation of the Cancer Care Ontario Clinical Practice Guideline. J Clin Oncol. 2016 Jul 10;34(20):2416–27.
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, Godwin J, Gray R, Pan HC, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012 Feb 4;379(9814):432–44.
6. Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US oncology research trial 9735. J Clin Oncol. 2009 Mar 10;27(8):1177–83.
7. Blum JL, Flynn PJ, Yothers G, Asmar L, Geyer CE Jr, Jacobs SA, et al. Anthracyclines in early breast cancer: the ABC trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG oncology). J Clin Oncol. 2017 Aug 10;35(23):2647–55.
8. Nitz U, Gluz O, Clemens M, Malter W, Reimer T, Nuding B, et al. West German study plan B trial: adjuvant four cycles of Epirubicin and cyclophosphamide plus docetaxel versus six cycles of docetaxel and cyclophosphamide in HER2-negative early breast cancer. J Clin Oncol. 2019 Apr 1;37(10):799–808.
9. Rack B, Andergassen U, Neugebauer J, Salmen J, Hepp P, Sommer H, et al. The German SUCCESS C study – the first European lifestyle study on breast cancer. Breast Care (Basel). 2010;5(6):395–400.
10. Poole C. Adjuvant chemotherapy for early-stage breast cancer: the tAnGo trial. Oncology (Williston Park). 2004 Dec;18(14 Suppl 12):23–6.
11. Henderson IC, Berry DA, Demetri GD, Cirrincione CT, Goldstein LJ, Martino S, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol. 2003 Mar 15;21(6):976–83.

12. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of intergroup trial C9741/cancer and leukemia group B trial 9741. J Clin Oncol. 2003 Apr 15;21(8):1431–9.
13. Spring LM, Gupta A, Reynolds KL, Gadd MA, Ellisen LW, Isakoff SJ, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. JAMA Oncol. 2016 Nov 1;2(11):1477–86.
14. Cianfrocca M, Gradishar WJ. Controversies in the therapy of early stage breast cancer. Oncologist. 2005 Nov-Dec;10(10):766–79.
15. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 1998 Aug;16(8):2672–85.
16. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018 Jan;19(1):27–39.
17. Lim SE, Back M, Quek E, Iau P, Putti T, Wong JE. Clinical observations from a breast cancer registry in Asian women. World J Surg. 2007 Jul;31(7):1387–92.
18. Sant M, Allemani C, Berrino F, Coleman MP, Aareleid T, Chaplain G, et al. Breast carcinoma survival in Europe and the United States: a population-based study. Cancer. 2004 Feb 15;100(4):715–22.
19. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018 Nov 29;379(22):2108–21.

Hormonal and Targeted Treatments in Breast Cancer

21

Sandeep Kumar, Sudeep Gupta, Ajeet Pratap Maurya, Rajender Singh, and Shashank Nigam

21.1 Introduction

Breast cancer has a saga of being considered a local disease with end-organ derangement and treated by radical mastectomy for almost 100 years. A major paradigm shift took place in breast cancer treatment and rhetoric that wider local treatment was associated with greater chances of cure was challenged and lesser treatments like simple mastectomy, wide local excision combined with cyto-toxic agents and radiotherapy to chest wall and lymph node basin became the standard of care. There remained an unpredictable behavior of breast cancer and traditional histo-morphology, lymph node involvement, extent of surgery and combined treatment with chemotherapy and

Sandeep Kumar, MS FRCS, PhD, MMSc (✉)
Former Professor, Department of Surgery, King George's Medical University, Lucknow, Uttar Pradesh, India

Founder Director, AIIMS, Bhopal, Madhya Pradesh, India
e-mail: profsandeepsurgeon@gmail.com

Sudeep Gupta, MD DM
Director, Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Mumbai, Maharashtra, India

Professor of Medical Oncology, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

Ajeet Pratap Maurya, MS
Associate Professor, Department of Surgery, AIIMS, Bhopal, Madhya Pradesh, India

Rajender Singh, PhD
Principal Scientist, Male Reproductive Biology Laboratory, Endocrinology Division, Central Drug Research Institute, Lucknow, Uttar Pradesh, India

Shashank Nigam, MS, MRCS, DNB, MNAMS
Consultant in Surgical Oncology, Lucknow, Uttar Pradesh, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_21

radiotherapy left almost a third or half the patients who failed early. In the last 2 decades much knowledge has been gained in the molecular and the genetic variations. One of which was a luminal classification based on quantitative and qualitative presence of hormone receptors viz.; estrogen and progesterone receptors and human epidermal growth factor-2 (*Her2 neu)* in the tumor tissue. This also enabled to specifically use certain treatments now known as targeted treatments. Also, genomic studies started discovering certain patterns called gene signatures which were mostly predictors of prognosis and have so far not provided with any therapeutic agent. There is a quest to continued search both in the direction of finding new targets to treat breast cancer and prognostic markers—through proteomic and genomic methods. That breast cancer has some environmental predilection and it is preventable has not come out despite yeoman epidemiological studies in the past half a century. Epigenetic studies may unravel some of these mysteries as to how environmental, genetic and translational factors have bearing on this most common cancer in women in the world. This chapter will gleam over most recent hormonal and targeted treatments that are in vogue. There may be a large number of researches in this area which may bring out effective treatment that have not been the part of description here.

About 75% of breast cancers express estrogen receptors (ERs). Receptor positivity is more common in cancers from postmenopausal women than premenopausal women. Estrogen and progesterone are main regulators of breast tissue growth and differentiation. Endocrine therapy deprives the tumor of estrogen by blocking the receptor by an antagonist. George T Beatson performed oophorectomy in premenopausal patients with unresectable breast cancer in 1895 and demonstrated beneficial effect of hormone deprivation in breast cancer. Isolation of estrogen receptors in 1967 and development of technique of quantitative measurement of receptors in tissues was another milestone in hormone therapy. Hormone therapy is now being widely used as chemoprevention and adjuvant therapy for breast cancer in early breast cancer.

Her2 is a trans-membrane tyrosine kinase receptor, involved in cell proliferation, angiogenesis and invasiveness. It is over expressed in nearly 20–30% of breast cancer patients and carries poor prognosis. This can be targeted by specific monoclonal antibodies. Assessment of both hormone receptor status and *Her2* over expression is thus standard of care in breast cancer management as it helps in tailoring appropriate adjuvant/neo-adjuvant therapy. In addition to hormone receptor status and *Her2* over expression other molecular markers and pathways also affect breast cancer outcome. Multiple gene-based tests have also been developed which assess the risk of recurrence and thus help in individualizing the adjuvant treatment.

21.2 Estrogen Receptors

The relation between ovarian hormones and size of breast tumors are known since nineteenth century [1]. Estrogen receptors can be of two basic types, ERα and ERβ. These are encoded by ESR1 and ESR2 genes respectively, present at separate chromosomes [2]. Important role of ERα in normal breast development have been

demonstrated by knockout studies. Estrogen through its receptor regulates gene transcription and thereby controls cell proliferation and differentiation. ERα expression in normal breast tissue is at low to intermediate level and limited to non-proliferating epithelial tissue. High level of ERα expression is seen in proliferative benign disease especially with atypia, carcinoma in situ and invasive breast cancer. About 54% of patients with high ERα expression have gene amplification at ESR1 [3]. Estrogen receptors belong to nuclear receptor family of transcription factors. Estrogen receptor has a central DNA binding domain which is most conserved part and involved in DNA recognition and binding. Ligand binding domain is at COOH-terminal. Two activation functions AF-1 and AF-2 help in transcriptional activation by recruiting co-regulatory protein complexes to DNA bound receptors [4]. Through classical mechanism of action estrogen binds to its nuclear receptors. This hormone receptor complex in turn binds to estrogen response element sequences in promoter region of estrogen responsive genes with recruitment of co-activators or co-repressors to promoter resulting in increased or decreased levels of mRNA and associated physiological response. Yet another mechanism of estrogen action is through ER at plasma membrane resulting in activation of kinases by increasing the cellular level of Ca and NO [5].

21.2.1 Mechanism of Estrogen Carcinogenesis

Prolonged exposure of estrogen and increase in number of menstrual cycles is associated with higher risk of breast cancer. Age at onset of regular menstrual cycles is important in deciding the risk of breast cancer rather than age at menarche. Estrogen window hypothesis proposed by Korenman in 1980, proposes that unopposed estrogen stimulation due to deficient luteal phase (resulting in decreased level of progesterone) is favourable for tumor development [6]. Obesity also leads to increased risk of breast cancer as a result of increased production of estrogen by the aromatase enzyme present in adipose tissues. Levels of ERα are found to be increased in most breast cancers while the levels of ERβ are decreased. In culture estrogen increases the number of cells in phase G0/G1 entering into cell cycle [7]. Mitogenic effect of estrogen has been explained by two hypotheses. Estrogen—hormone receptor complex stimulates proliferation of mammary cells and increases the target cell number and also inhibits the apoptosis. Increased cell division and DNA synthesis increases the replication error. According to other hypothesis toxic metabolites of estrogen can directly damage the DNA. Estrogen 3,4 quinone, metabolite of estrogen can form unstable adducts with adenine and guanine in DNA and cause depurination and mutation [8].

21.2.2 Resistance to Anti-Estrogens

About 40% of breast cancers are resistant to endocrine therapy. Resistance to endocrine therapy may be de-novo or acquired. De-novo resistance is chiefly due to lack

of expression of ER. Aberrant methylation of its CpG island is associated with lack of ERα gene expression [9]. Mutations causing the cancer may also render them non-responsive to endocrine therapy. Loss of ER occurs in about 20% of patients treated with endocrine therapy [10]. Long term use of hormones may lead to selection of resistant tumor cells. Up-regulation of HER2 has been shown in some tumors and may provide alternate survival pathway. Prolonged exposure to ERα antagonist leads to estrogen hypersensitivity and tumors respond to very low level of estrogen. Some tumors become estrogen supersensitive on prolonged estrogen deprivation by AI and apparently become ligand independent. Increased growth factor signalling may promote tumor growth in prolong estrogen deprivation [11].

21.2.3 Endocrine Therapy for Chemoprevention

Tamoxifen when used as adjuvant therapy in breast cancer has demonstrated reduction in incidence of second primary cancer in contralateral breast [12]. Selective estrogen receptor modulators (SERMs), Tamoxifen and Raloxifene, and aromatase inhibitor (Exemestane) are in use as chemo preventive agents against breast cancer in high risk healthy women. In the National Surgical Adjuvant Breast and Bowel Project P-1 (NSABP-P1) trial 13,388 healthy women more than 60 years of age and age group 35–59 years with 5-year predicted risk for breast cancer 1.66% (using Gail's model) or more and women with history of lobular carcinoma were randomized into placebo or Tamoxifen (20 mg/day) arm for 5 years [13]. There was reduction in risk of invasive breast cancer in Tamoxifen group by 49%. At 69 months of follow up cumulative incidence of invasive breast cancer in placebo and Tamoxifen arms were 43.4 versus 22.0 per 1000 women respectively. The risk of non-invasive breast cancer was also reduced by 50% in the Tamoxifen group. Similarly, risk reduction of 56% was observed in women with history of lobular carcinoma in situ and 86% in atypical hyperplasia. These risk reductions were seen only in estrogen positive tumors while no difference was observed in estrogen negative tumors. The Tamoxifen group however had higher rate of endometrial cancer (RR 2.53; 95% CI 1.35–4.97). The risk of stroke, deep vein thrombosis and pulmonary embolism were higher in Tamoxifen group. Tamoxifen and Raloxifene are US-FDA approved for breast cancer chemoprevention.

Randomized trial from Italy included 5408 healthy women with history of hysterectomy, who were randomized into Tamoxifen (20 mg/day) or placebo groups for 5 years. At 11 years of follow up rates of breast cancer in two groups were similar in women with bilateral oophorectomy and those at low risk for hormone receptor positive disease. In women at high risk, rate of breast cancer was lower in Tamoxifen group (RR 0.24, 95% CI 0.10 to 0.59), cumulative incidence being 1.50 per 1000 women-years in Tamoxifen arm and 6.26 per 1000 women years in placebo arm [14]. Extended follow up of the IBIS-1 trial reported breast cancer risk reduction (hazard ratio [HR] 0.71 [95% CI 0.60–0.83], $p < 0.0001$) in women who were at high risk. The risk reduction was seen in ER positive tumors only. This study also demonstrated long term protection after treatment cessation [15].

The NSABP "study of Tamoxifen and Raloxifene" STAR P-2 trial compared the efficacy and safety of Tamoxifen (20 mg/day) and Raloxifene (60 mg/day) in chemoprevention of breast cancer in post-menopausal women at high risk for breast cancer [16]. Raloxifene was found to be equally effective as Tamoxifen in reducing the risk of invasive breast cancer (incidence in Tamoxifen arm 4.30 per 1000 versus 4.41 per 1000 in the Raloxifene group; RR 1.02). Rate of non-invasive breast cancer was higher in the Raloxifene group than the Tamoxifen (2.11 versus 1.51 per 1000). Risk of thromboembolic event and cataract was however lower in Raloxifene group. The rate of endometrial cancer was also 38% lower in the Raloxifene group as compared to Tamoxifen group. The "National Cancer Institute of Canada Clinical Trials Group Mammary Prevention.3 trial" (NCIC CTG MAP.3) studied the use of Exemestane, an aromatase inhibitor, as chemo-preventive agent for breast cancer [17]. At 35 months of follow-up there was 65% relative reduction in incidence of invasive breast cancer in comparison to placebo. There was no significant difference in two groups with respect to cardiovascular events, other cancers or treatment related deaths.

21.2.4 Endocrine therapy for Carcinoma in situ: Tamoxifen and DCIS

Tamoxifen has been used as adjuvant treatment for invasive breast cancer and for primary prophylaxis in healthy women at high risk. With the increased use of mammography, ductal carcinoma in situ (DCIS) now accounts for 20–30% of all breast cancers. Breast conserving surgery is standard of care for DCIS. The role of Tamoxifen after DCIS excision was examined in the National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial where 1804 women with DCIS including resected samples with margins involved with tumor, were randomized into lumpectomy, radiotherapy (50 Gy) and placebo or lumpectomy, radiotherapy and Tamoxifen (20 mg/day for 5 years) groups [18]. At a median follow up of 74 months breast cancer related events were fewer in Tamoxifen group than placebo (8.2 versus 13.4%, $p = 0.0009$). Rate of endometrial cancer was higher in Tamoxifen group than placebo (1.53 versus 0.45 per 1000 patients per year). Subsequent analysis of ERs revealed that patients with ER positive DCIS demonstrated significant decrease in breast cancer in the Tamoxifen arm (HR, 0.60; $p = 0.003$). ER negative DCIS showed no significant benefit. UK/ANZ DCIS trial included 1701 patients with complete excision of lesion who were randomised into 4 groups: radiotherapy alone, Tamoxifen alone, both radiotherapy and Tamoxifen or none [19]. With a median follow up of 52 months patients receiving radiotherapy had a lower incidence of ipsilateral invasive disease (HR 0.45, CI 0.24–0.85; $p = 0.01$) as well as ipsilateral ductal carcinoma in situ (HR 0.36, CI 0.19–0.66; $p = 0.0004$). In the Tamoxifen group there was no reduction in ipsilateral invasive group but recurrence of DCIS was decreased (HR 0.68 [0.49–0.96]; $p = 0.03$). Long term result of this study showed that benefit for Tamoxifen is in reducing incidence of all new breast events (HR 0.71, 95% CI 0.58–0.88; $p = 0.002$), decreased

recurrent ipsilateral DCIS (0.70, 0.51–0.86; p = 0.03) and contralateral tumours (HR 0.44, CI 0.25–0.77; p = 0.005), while there was no effect on invasive disease on ipsilateral side [20]. In a double blinded randomised controlled trial on post-menopausal women with ER positive DCIS, Anastrazole was compared with Tamoxifen [21]. At median follow up of 7 years the difference between the two groups was not statistically significant. Thus, in patients with contraindications to Tamoxifen, Anastrazole can be an alternate option.

21.2.5 Endocrine Therapy for Early Breast Cancer

Interfering with the estrogen production or its action on the receptor has been associated with prolonged disease free and overall survival in patients with breast cancer. Generally, anti-estrogens are better tolerated in comparison to chemotherapy.

21.2.5.1 Tamoxifen

Tamoxifen is a non-steroidal anti-estrogen which has been extensively studied as adjuvant endocrine therapy for early breast cancer. One of the earliest trials was conducted by Nolvadex Adjuvant Trial Organisation (NATO), which randomised 1285 women treated by total mastectomy and axillary node clearance into either receiving Tamoxifen (10 mg twice daily for 2 years) or no further treatment. At 66 months of follow up there was significant reduction in risk of an event ($X^2 = 17.69$, p = 0.0001). Relative risk of an event was 0.64 suggesting 36% reduction in risk for Tamoxifen treated patients. The reduction in relative risk of death from all causes was 29% for Tamoxifen treated group [22]. A meta-analysis by Early Breast Cancer Trialists Collaborative Group (EBCTCG) showed highly significant reduction in recurrence rate and breast cancer death rate in trials of 1–2 years of Tamoxifen versus 5 years of Tamoxifen [23]. Tamoxifen for 1–2 years was found to be less effective than 5 years (p < 0.00001 for recurrence, p = 0.0001 for breast cancer mortality). In women with ER positive disease on 5 years of Tamoxifen, the annual recurrence rate was half and breast cancer mortality was reduced by a third irrespective of age or use of chemotherapy. Absolute reduction in recurrence risk was similar for younger and older women, but it was significantly greater for patients with node positive disease in comparison to node negative disease. National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 Randomized Trial evaluated the 5 years versus more than 5-years Tamoxifen for lymph node negative breast cancer [24]. At 7 years of follow up no additional benefit was seen from Tamoxifen administered beyond 5 years in ER positive and node negative breast cancer. Concurrent Tamoxifen with chemotherapy has better disease-free survival (DFS) (HR 0.76, 95% CI 0.64–0.91; p = 0.002) than Tamoxifen alone with statistically non-significant improvement in survival [25]. Worldwide Adjuvant Tamoxifene: Long Against

Shorter (ATLAS) trial on 12894 women with early breast cancer completed 5-years of Tamoxifen were randomly allocated to continue for 10 years or stop showed that 10 years of Tamoxifen can halve breast cancer mortality in the second decade after diagnosis [26].

21.2.5.2 Aromatase Inhibitors (AI)

Aromatase enzymes are present in adipose tissue, breast tissue, breast tumor cells, and other sites and convert hormone androstenedione into estrone. AIs are used in post-menopausal women as they are not able to suppress ovarian functions completely in premenopausal or peri-menopausal women. "Arimidex, Tamoxifen Alone or in Combination (ATAC)" trial compared Anastrazole with Tamoxifen [27]. Disease free survival at 4 years was higher in Anastrazole group compared with Tamoxifen group (86.9% versus 84.5%, respectively, HR 0.86, P = 0.03). DFS benefit was higher in patients with hormone receptor positive tumors. Reduction in incidence of primary contralateral breast cancer was higher in Anastrazole group than with Tamoxifen (n = 25 vs. n = 40; OR, 0.62; 95% CI, 0.38–1.02; P = 0.06). Side effects like endometrial cancer (P < 0.007), cerebrovascular events (P < 0.001), venous thromboembolic events ($P < 0.001$), and hot flashes ($P < 0.001$) were less common in the Anastrazole group as compared to Tamoxifen group.

Use of AI after adjuvant Tamoxifen therapy for 5 years has been studied. A randomized trial comparing AI after Tamoxifen therapy in postmenopausal women versus placebo reported four-year DFS of 93% and 83% respectively (P < 0.001) [28]. Low grade hot flashes, arthralgia and myalgia were more common in the Letrozole group.

21.2.5.3 Ormeloxifene

Ormeloxifene is a non-steroidal selective estrogen receptor modulator (SERM) that was developed as an oral contraceptive at Central Drug Research Institute Lucknow and marketed as *Saheli* or *Novex*. It has a long half-life with once week dosage and literally no side effects. It primarily functions as an estrogen antagonist in many organs including breast tissue. In a randomised trial it was shown to abrogate benign breast nodularity and pain effectively [29].

It interacts with both ER subtypes, demonstrating more selectivity and higher affinity towards ERα (8.8%) as compared to ERβ (3%). This SERM role of Ormeloxifene makes it a choice anti-cancer agent for the treatment and prevention of breast cancers especially when ER functions are up regulated. In addition, similar to many SERMs, this agent also modulates various other signalling pathways independent of ER expression to regulate growth in cancer cell [30]. A phase II study on Centchroman or racemic form of Ormeloxifene in advanced breast cancer showed beneficial effect [31].

21.2.5.4 Ovarian Ablation and Suppression

Beatson reported oophorectomy as systemic therapy of metastatic breast cancer in premenopausal women in 1896. EBCTCG meta-analysis evaluated the effect of ovarian ablation by surgery or irradiation or ovarian suppression by luteinising-hormone releasing-hormone (LHRH) inhibitors [23]. There was beneficial effect of ovarian ablation or suppression on recurrence ($P < 0.00001$) and breast cancer mortality ($P < 0.004$). The effects of ovarian treatment were smaller in trials where both groups received chemotherapy. Early Breast Cancer Overview group reported meta-analysis of 16 trials [32]. LHRH agonist as only adjuvant treatment shows non-statistically significant reduction in recurrence (relative reduction 28%. $P = 0.08$) or death after recurrence (relative reduction 17.8%, $P = 0.49$) in hormone receptor positive cancers. Hormone receptor negative tumors showed no response to LHRH agonists.

21.3 HER2: Human Epidermal Growth Factor or CerB2/neu

Human epidermal growth factor receptor (HER-2) or erb-B2/neu protein is the product of erb-B2 gene located on chromosome 17. HER2 is a member of Erb-B family (HER1/EGFR, HER2, HER3 and HER4) of plasma membrane bound receptor tyrosine kinases. These receptor tyrosine kinases are involved in cell proliferation, angiogenesis, invasiveness and resistance to apoptosis [33]. These receptors have an extracellular ligand binding domain and intracellular kinase domain. Ligand binding causes dimerization and activation of intracellular kinase domain. Over-expression of HER2 is involved in breast, stomach, ovarian and endometrial cancers. HER2/erb-B2 is over-expressed/amplified in 15–20% of breast cancers. Over expression of HER2 predicts poor prognosis and poor response to non-Anthracycline, non-Paclitaxel chemotherapy in breast cancer. Over expression of HER2 is identified by immunohistochemistry (IHC) and scored on a scale 0 to 3+. Fluorescent in situ hybridization (FISH) detects gene copy number (ratio between HER2 gene copy number and number of chromosome 17 centromeres [34]. IHC score of 0 and 1+ represents HER2 negative and 3+ is HER2 positive, while 2+ presents uncertainty and needs further investigation.

21.3.1 Anti-HER2 Based Chemotherapy: Adjuvant

Trastuzumab is humanized monoclonal antibody and it binds to extracellular portion of *Her2* receptor. Trastuzumab induces antibody dependent cell mediated cytotoxicity and suppresses *Her2* signalling. Trastuzumab inhibits *Her*2 signalling either by internalization and degradation of the *Her*2 receptor, by destabilizing *Her*2 heterodimers or by blocking the proteolytic cleavage site in the juxtamembrane region and activation of intracellular kinase domains [35]. Trastuzumab

can be used as single agent or in combination with chemotherapy. The combination therapy shows biologic synergy.

Her2 over expression is seen in about 15–20% of patients with invasive breast cancer and is associated with aggressive behaviour of tumor. Trastuzumab has beneficial effect in *Her*2 positive metastatic breast cancer. Role of Trastuzumab in early breast cancer after completion of chemotherapy was examined in Herceptin Adjuvant (HERA) trial [36]. Patients were randomized into Trastuzumab for 1 year, Trastuzumab for 2 years and observation groups. At one year follow up HR for an event in Trastuzumab group was 0.54 (95% CI, 0.43 to 0.67; P < 0.0001). Cardiotoxicity was seen in 0.5% of patients in Trastuzumab group. At 8 years follow up of HERA trial in one-year Trastuzumab versus observation group HR for DFS was 0.76 (95% CI 0.67–0.86, p < 0.0001), and 0.76 (0.65–0.88, p = 0.0005) for overall survival. Nearly equal events of DFS was observed in 1-year and 2-year Trastuzumab group (HR 0.99, 95% CI 0.85–1.14, p = 0.86). Frequencies of adverse events were more in 2-year Trastuzumab group [37]. Combined result of two trials (NSABP B-31 and NCCTG N9831) comparing adjuvant chemotherapy with or without concurrent Trastuzumab in women with *Her*2 positive breast cancer [38]. Patients in Trastuzumab group had fewer breast cancer related events than control group (HR, 0.48; P < 0.0001). Difference in DFS between Trastuzumab and control group was 12% at 3 years. Incidence of congestive heart failure and death from cardiac cause was 4.1% in B-31 trial. Overall survival at 8.4 years was 37% higher in Trastuzumab with chemotherapy group than chemotherapy alone group (HR, 0.63; 95% CI, 0.54 to 0.73; P < 0.001) [39]. Disease free survival improved by 40% in Trastuzumab with chemotherapy group (HR, 0.60; 95% CI, 0.53 to 0.68; P < 0.001). Addition of Pertuzumab to Trastuzumab and Docetaxel for *Her*2 positive metastatic breast cancer was studied in phase 3 randomized trial CLEOPATRA), 808 patients were randomized to receive Docetaxel plus Trastuzumab plus Pertuzumab or Docetaxel plus Trastuzumab plus placebo [40]. There was crossover of 50 patients from placebo to Pertuzumab group. At median follow up of 99.9 months median overall survival was 57.1 months in Pertuzumab group and 40.8 months in placebo group (HR 0.69, 95% CI 0.58–0.82).Most common adverse event was neutropenia (49% vs. 46%).

21.3.2 Anti-HER2 Based Chemotherapy: Neo-Adjuvant

Trastuzumab has potential use as neoadjuvant therapy in *Her*2 positive locally advanced breast cancers. Significantly higher rate of complete pathologic response (66.7% vs. 25% for Trastuzumab plus chemotherapy and chemotherapy alone respectively) has been shown after neo-adjuvant therapy with Trastuzumab [41]. The NeoAdjuvant Herceptin (NOAH) trial compared one-year treatment with Trastuzumab (used as neo-adjuvant and adjuvant therapy) and chemotherapy alone, in patients with *Her*2 positive locally advanced or inflammatory breast cancer [42]. Event free survival was significantly better in Trastuzumab group (71% vs. 56%, HR 0.59 [95% CI 0.38–0.90]; p = 0.013). Pathologic complete response was present

in 45 patients with Trastuzumab (n = 117) and 23 patients in chemotherapy (n = 118) alone group. Benefit in event free survival persisted with time in Trastuzumab-containing neoadjuvant therapy followed by adjuvant Trastuzumab group [43].

21.4 Molecular Sub-types of Breast Cancer

Breast cancers have been classified into molecular subtypes (Table 21.1); viz. Luminal A (ER/PR positive, HER2 negative/low Ki67), Luminal B (ER/PR positive, HER2 negative/High Ki-67), *Her2*-positive luminal B (ER and/or PR-positive/HER2 over-expression/any Ki-67), non-luminal *Her*2-positive (ER and PR absent/*Her2* over-expression), and triple negative (ER and PR absent/HER2-negative) [44]. Hormone receptor and Her2 receptor is routinely used as predictive marker of breast cancer outcome. Molecular markers are used to select adjuvant systemic therapy and predict tumour response to treatment.

21.5 Prognosis in Breast Cancer: Treatment Determination

In addition to hormone receptor and HER2 status, multiple other genes have been used to predict tumour response to systemic therapy. The *Oncotype DX* (Genomic Health Inc., Redwood City, CA) is a clinically validated genomic assay. *Oncotype DX* uses 16 cancer related genes and 5 reference genes and can be used on formalin fixed paraffin embedded tumour samples. The test generates recurrence score 0–100. Recurrence score is categorised as low risk (0–17), intermediate risk

Table 21.1 Molecular subtypes of breast cancer

Subtype	Phenotype—IHC	Disease free/ Overall Survival	Treatment option
Luminal A 50–60%	ER^{strong} + PR+ Her2−/ CK 18 +, low protein Ki 67	75/90	SERM Palbociclib, Ribociclib
Luminal B 15%	ER^{weak} + PR+/− Her2+ CK8/18/12 +, high protein Ki 67 low protein Ki 67	47/40	SERM Palbociclib, Ribociclib ER/PR can be weak +ve, Her2 Neg or 2+
HER2 Enriched 08%	ER− PR− Her3+ or FISH detects gene copy number chromosome 17	34/31	Her2 enriched Trastuzumab/ Pertuzumab
Basal like or Triple Negative 10–20%	ER− PR− Her2− Cytokeratin 5/6 + EGFR+	18/00	Atezolizumab
Unclassified 2–5% *?Contamination of normal mammary cells*	ER− PR− Her2− Cytokeratin 5/6 − EGFR−		
BRCA 1/BRCA 2	Positive/negative		Talazoparib, Olaparib

(18–30) and high risk (>30). Recurrence score predicts recurrence at 10 years [45]. *MammaPrint* assay (Agendia BV, The Netherlands) is another microarray based multi-gene assay to determine the prognosis in breast cancer. It uses 70 gene signatures to develop risk profile. *MammaPrint* assay uses fresh tissue samples or tissues collected into an RNA preservation solution. *MammaPrint* assay results are reported as either low or high risk of recurrence [46]. Another IHC based prognostic test *Can-Assist-Breast* test uses expression levels of five biomarkers (CD44, N-cadherin, pan-cadherin, ABCC4and ABCC11) and tumor size, tumor grade and nodal status to calculate a risk score and stratify patients into low or high risk of recurrence [47].

21.6 Gene Expression Patterns

The pattern of gene expressions in breast cancer determines tumor behaviour and response to treatment. Complementary DNA (cDNA) microarray analysis of 8102 human genes in breast tumour specimens revealed a characteristic molecular pattern of each tumour [48]. Hierarchical clustering method of gene grouping (1753 out of 8102 genes) shown that tumours have significant variation in patterns of gene expression and different sets of genes show independent patterns of variation. Expression of proliferation cluster was largest and well correlated with mitotic index. Breast has two types of epithelial cells basal and epithelial. These two are separately identified by IHC. ERα gene expression variation correlated with ER over tumour samples. Tumours are classified into subgroups based on patterns of gene expression and serves as a prognostic marker. Based on 456 cDNA of intrinsic gene sets breast tumours were sub-classified into 5 subgroups [49]. Basal like and ERBB2+ subtype (both characterized by low ER gene expression) and ER+/luminal group was further sub-classified into three subgroups luminal A (highest expression of ERα gene) and luminal B and C (with low to moderate expression of ER cluster). Basal like and ERBB2+ subtype had TP53 mutation in 70–80% of tumor samples. Survival analysis showed poor survival in Basal like and ERBB2+ subtypes. An integrated genomic analysis of breast cancer showed molecular subtypes [50]. Copy number aberrations (CNAs) and single nucleotide polymorphisms (SNPs) affect expression variation. Limited number of genomic regions may contain driver genes like ZNF703, a luminal B specific driver. Integrated subtype identification proves breast cancer heterogeneity and shows possible further subdivisions of subtypes.

Prognosis in breast cancer varies greatly among different molecular subtypes. Integrative cluster (IntClust) based subtypes have been evaluated and compared with IHC based subtypes as prognostic marker. In a study (n = 3240) patients were assigned into IHC subtypes (ER+/HER2+, ER+/HER2−, ER−HER2+ and ER−/HER2−), 5 intrinsic gene expression subtypes (PAM50 subtypes) and 11 IntClust subtypes [51]. ER− patients had high risk of recurrence and death in first five years. ER− IntClust subgroups have marked difference in their recurrence pattern. Similarly, different IntClust subgroups in ER+ patients have variable prognosis. IntClust sub-typing improved the predictive value than obtained by clinical information and IHC subtypes.

21.7 Anti-Body Drug Conjugates

Systemic chemotherapy is mainstay of treatment in metastatic breast cancer. However, dose and response of systemic chemotherapy is limited by toxicity. Targeted delivery of chemotherapeutic agents has been developed in the form of antibody-drug conjugates (ADC). Monoclonal antibody, drug and a linker are three important components of ADCs. Monoclonal antibody specifically binds to antigen expressed by tumor cells. After binding antigen-ADC complex is internalized and with the help of lysosomal enzymes drug is released. Drug needs to be highly potent at nano-molar concentration as only very small amount of drug can be delivered. Two groups of drugs are used one is Calicheamicin which acts by breaking down double stranded DNA and other group is microtubule disrupting anti-mitotic agents Auristatins and Maytansine [52].

Ado-Trastuzumab Emtansine (T-DM1) an ADC used for breast cancer is prepared by conjugation of lysine amino groups of Trastuzumab to sulfhydryl group of the maytansinoid DM1. An average of 3.5 molecules of DM1 conjugates per molecule of antibody. EMILIA randomized controlled trial randomized 991 patients with HER2 positive advanced breast cancer, who had already received Trastuzumab and a taxane, into receiving either T-DM1 or Lapatinib plus Capecitabine groups [53]. Median progression free survival was 9.6 months with T-DM1 and 6.4 months in Lapatinib plus Capecitabine group (HR 0.65; 95% CI, 0.55 to 0.77; $P < 0.001$). Median overall survival was 30.9 months for T-DM1 group vs. 25.1 months for Lapatinib plus Capecitabine group (HR 0.68; 95% CI, 0.55 to 0.85; $P < 0.001$). Incidence of adverse events was higher with Lapatinib plus Capecitabine group.

Trastuzumab Deruxtecan another ADC with cytotoxic topoisomerase 1 inhibitor was evaluated in patients with HER2 positive metastatic breast cancer previously treated with Trastuzumab Emtansine (T-DM1) [54]. At median follow up of 11 months response to treatment was found in 60.9% of patients.

21.8 Targeted Therapy for Triple Negative Breast Cancer

Triple negative breast cancer is an aggressive tumor with poorer prognosis compared with other sub-types. Pembrolizumab is an anti-programmed death ligand 1 (PD-L1) monoclonal antibody. Neoadjuvant use of Pembrolizumab in early triple negative breast cancer was evaluated in a phase 3 trial [55]. Patients were randomized into receiving Pembrolizumab plus Paclitaxel plus Carboplatin group or placebo plus Paclitaxel plus Carboplatin group. Pathological complete response was seen in 64.8% of Pembrolizumab with chemotherapy group compared to 51.2% in placebo-chemotherapy group ($P < 0.001$). At a median follow up of 15.5 months 7.4% (58 of 784) in Pembrolizumab with chemotherapy and 11.8% (46 of 390) had disease progression. Although there is no evidence yet that immune check-point

inhibition will improve long-term outcome in patients with triple negative breast cancer, this is a promising therapeutic avenue.

Metastatic triple negative breast cancer is usually associated with poor outcome and sequential single agent chemotherapy is often the mainstay of treatment. "Trophoblast cell surface antigen (Trop-2)" is a transmembrane calcium signal transducer, expressed in nearly 85% of triple negative breast cancers. Sacituzumab Govitecan-hziy is an ADC in which SN-38 (topoisomerase 1 inhibitor) is conjugated with anti-Trop-2 monoclonal antibody hRS7 IgG1κ. Sacituzumab Govitecan-hziy when used in 108 patients with triple negative breast cancer previously treated with chemotherapy [56], a response rate was 33% (3 complete and 33 partial responses) was seen. Median duration of response was 7.7 months while the Progression free survival was 5.5 months. Anaemia and neutropenia were common adverse events.

Programmed death ligand 1 (PD-L1) are expressed over tumor infiltrating immune cells and inhibit anti-tumor immune response. Atezolizumab is a monoclonal antibody against PD-L1. Addition of chemotherapy can have synergistic effect. In a phase 3 trial, patients with metastatic triple negative breast cancers were assigned to receive Atezolizumab or placebo with nanoparticle albumin bound (nab) Paclitaxel [57]. At a median follow up 12.9 months median progression free survival was 7.2 months with Atezolizumab plus nab-Paclitaxel versus 5.5 months with placebo plus nab-Paclitaxel (HR 0.80; 95% CI, 0.69 to 0.92; P = 0.002). Median overall survival was 21.3 months in Atezolizumab plus nab-Paclitaxel group versus 17.6 months in placebo plus nab-Paclitaxel group (HR 0.84; 95% CI, 0.69 to 1.02; P = 0.08). Survival was better in patients with PD-L1 positive tumors.

21.9 Targeted Therapy for BRCA Positive Tumors

Germline BRCA mutations are present in 5% of breast cancer patients. BRCA1 and BRCA2 are tumor suppressor genes and are involved in repair of double strand DNA breaks via homologous recombination pathway. Polyadenosine diphosphate-ribose polymerase (PARP)-1 is a DNA repair enzyme involved in repair of single strand DNA breaks. Inhibition of PARP-1 enzyme will cause accumulation of single strand breaks and stalling and collapse of replication fork resulting in double strand breaks [58]. In normal cells these double strand breaks are repaired by homologous recombination. Unrepaired double strand breaks will lead to cell death. In cells with BRCA1/2 mutation with defective homologous recombination pathway, inhibition of PARP1 will prevent repair of single strand breaks and consequently lead to cell death (synthetic lethality) [59]. Patients with wild type BRCA1/2 but with defective homologous recombination pathway will have similar effect with PARP1 inhibitors (BRCAness). PARP inhibitors induce PARP-DNA complexes and replication arrest (PARP trapping). Tumors develop resistance to PARP1 inhibitors by down regulation of PARP1 and MDR1/glycoprotein-1 mediated drug efflux. PARP trapping will

have synergistic effect with DNA alkylating agents and topoisomerase 1 inhibitors [60]. In a phase 3 randomized controlled trial Olaparib, a PARP-1 inhibitor, was compared with standard chemotherapy in patients with *Her*2 negative metastatic breast cancer with germline BRCA mutation [61]. Patients were assigned into 2:1 ratio in either Olaparib (300 mg twice daily) group or chemotherapy group. Median progression free survival was 7.0 months in Olaparib group and 4.2 months in chemotherapy group (HR 0.58; 95% CI, 0.43 to 0.80; $P < 0.001$). The response rate was also higher in Olaparib group than chemotherapy group (59.9% vs. 28.8%). There was no significant difference in overall survival. Talazoparib is another PARP-1 inhibitor with high PARP-trapping activity. Phase 3 randomized trial comparing Talazoparib and standard chemotherapy in patients with advanced breast cancer with germline mutation, showed median progression free survival of 8.6 months in Talazoparib group and 5.6 months in standard chemotherapy group (HR 0.54; 95% CI, 0.41 to 0.71; $P < 0.001$) [62]. Objective response rate was 62.6% in Talazoparib group and 27.7% in chemotherapy group (OR, 5.0; 95% CI, 2.9 to 8.8; $P < 0.001$). Hematologic adverse events were higher in Talazoparib group than chemotherapy group (55% vs. 38%).

21.10 Cyclin-Dependent Kinase 4/6 Inhibitors

Cyclin-dependent kinase (CDK) 4 and 6 are member serine-threonine kinase family and regulate progression of cell cycle from G0/G1 to S phase. Cyclins are regulatory subunit and control the activity of CDKs. Retinoblastoma (Rb) is a tumor suppressor gene and acts by preventing progression of cell cycle to S phase by sequestering E2F transcription factors. Resting cells synthesize cyclin D1 in response to mitogenic signals [63]. Cyclin D1-CDK4/6 complex leads to phosphorylation and inactivation of Rb protein and allows progression of cell cycle to S phase. Dysregulated cyclin D1-CKK4/6 complex is involved in initiation and progression of multiple cancers. Cyclin D1 over-expression is a common and early finding in breast cancer pathogenesis. Cyclin D1 and CDK4 amplification is high in luminal B and HER2 positive tumors. Estrogen acts by up-regulating cyclin D1level and CDK4/6 activity. Cyclin D1-CDK4/6 pathway has a role in endocrine therapy resistance.

In a phase 3 randomized trial post-menopausal women with ER positive HER2 negative breast cancer were assigned in to either Palbociclib plus Letrozole group or placebo plus Letrozole group [64]. Median progression free survival was higher (24.8 months vs. 14.5 months) in Palbociclib plus Letrozole group than placebo plus Letrozole group (HR 0.58; 95% CI, 0.46 to 0.72; $P < 0.001$). Neutropenia was markedly higher in Palbociclib-Letrozole group (66.4% vs. 1.4%). PATRICIA phase 2 trial is an ongoing study evaluating Palbociclib in combination with Trastuzumab in patients with HER2 positive metastatic breast cancer [65]. Patients were assigned into 3 cohorts: cohort A (ER negative), cohort B1 (ER positive) and cohort B2 (ER positive with Letrozole). Progression free survivals at 6 months were 33.3%, 40% and 53.3% in cohorts A, B1 and B2 respectively. Progression free

survival was higher in luminal disease in comparison to non-luminal disease (12.4 vs. 4.1 months). Clinical benefit rate at 6 months was 73% in luminal compared to 31% non-luminal (P = 0.031). Grade 3/4 toxicities were seen in 84.4% of patients, most commonly neutropenia and thrombocytopenia.

21.11 PIK3CA Mutation: Alpelisib

Phosphatidylinositol-4,5-bisphosphate 3- kinase catalytic subunit α (PIK3CA) is a central element of a signalling pathway involved in cell proliferation, survival and growth. Mutations in this pathway results in enhanced PI3K signalling, which is associated with oncogenic cellular transformation and cancer. This mutation is found in 30–40% of breast cancer. Alpelisib is a targeted therapy called a PI3K inhibitor, specifically for advanced breast cancer patients (postmenopausal women and men), whose tumor has the mutation and is estrogen receptor positive and Her2neu negative. This has been FDA approved for use in patients who have progressed on Aromatase inhibitors, based on the results of SOLAR-1 trial [66].

21.12 Epigenetics and Breast Cancer

Until the early 2000s, cancer was known to be a disease caused by multiple mutations in the genome. It was believed that a single mutation would cause cancer only if it is in the primary gene regulating cell division; otherwise, cancer requires several mutations across the genome to come together to result in malignancy. Mutations in oncogenes and tumor-suppressor genes, chromosomal translocations, copy number variations, loss and gain of function mutations and structural re-arrangements in DNA can lead to increased breast cancer risk of cancer risk in general. However, massive research in the epigenetics area in the first decade of 2000 led to the identification of a number of epigenetic factors that play a crucial role in predisposition, disease onset and metastasis of cancer, including breast cancer. DNA methylation is one of the epigenetic modifications most commonly studied in breast cancer. In fact, altered DNA methylation has been identified in several cancer types including breast, prostate, gastric, liver, lung and leukemia. Among the first reports was the global hypomethylation at CpG sites of DNA repetitive elements identified in tumor cells. Currently several drugs that work by modifying epigenome are undergoing preclinical and clinical trials [67].

Among epigenetic modifiers, targeting DNA methylation was the first approach. Inhibitors of DNA methylation (DNMTi) have been developed to re-activate tumor suppressors silenced by DNA methylation [68]. US FDA has approved two DNMT inhibitors (DNMTi) for high-risk myelodysplastic syndrome, and the results are encouraging [69]. 5-Azacytidine (5-aza-CR), is a nucleoside analogue that incorporates into DNA and RNA. Similarly, 5-aza-2'deoxycytidine (5-aza-CdR) incorporates into DNA. The incorporation of these inhibitors in the DNA traps DNMTs and does not allow DNA methylation [70]. Irradiation in combination with 5-aza-CR

has been shown positive results in breast cancer cells [71]. 5-aza-CR is now being tried in solid tumors including breast cancer [72]. It seems the best way to use such inhibitors is in combination with chemotherapy or irradiation [69]. Alterations in DNA methylation would make the cells more sensitive to chemotherapy and irradiation.

Histone deacetylases are the enzymes, which play important roles in gene expression by way of affecting histone modifications. Two HDAC inhibitors, Vorinostat and Romidepsin, have been approved by the US FDA for treating cutaneous T-cell lymphoma [73]; however, none of them has been approved for breast cancer. However, HDAC inhibitors with mTOR inhibitors have been shown to have effect on breast cancer cells [74]. Similarly, HDAC inhibitor, Trichostatin, with DNMT inhibitor, 5-aza-CdR has been shown to show promise in breast cancer cells [75]. In ER negative breast cancer cells, HDACi entinostat or Valporic have been tested and shown to restore ERα expression and sensitivity to anti-estrogen therapy [76, 77].

HDAC inhibitors with DNMT inhibitors demethylate ER-α promoter and restore its expression, which makes the cells sensitive to Tamoxifen in ER-negative breast cancer cells [78, 79]. Similarly, this combination along with other drugs such as retinoid acid derivatives has also shown promise [80]. The Ten Eleven Translocation—TET enzymes are now well known to regulate DNA methylation and de-methylation and appear to be attractive candidates for epigenetic modulating drugs, but the first TET inhibitor or activator is yet to be tested for breast cancer treatment.

Another mechanism of epigenetic gene regulation is mi-RNA expression, which ultimately changes the expression of a number of target genes. A number of such important mi-RNAs that regulate the breast cancer cells proliferation have been identified. For example, miR200a inhibits cell proliferation [81], and the suppression of miR-21 expression increases sensitivity of breast cancer cells to Topotecan and Paclitaxel [82, 83]. Similarly, miR-155 knockdown leads to apoptosis and increased chemo-sensitivity [84]. In this category, miR-30 family regulates the growth of breast cancer cells and miR200a inhibits cell proliferation and can be an attractive target [85].

A general drawback of the epigenetic modifiers is their non-specificity with respect to genes and organs. Therefore, they have to be monitored very carefully for side-effects. While epigenetic modifiers have shown great promise in hematological malignancies, their use in solid tumors remains challenging with little success. Nevertheless, it appears that these modifiers can yield exciting results in combination with chemotherapy and irradiation. Since these inhibitors affect the expression of a number of housekeeping genes as well, they are toxic and need close monitoring vis-à-vis benefits. It must be remembered that in addition to activating tumor suppressor genes, these inhibitors also demethylate and activate pro-metastatic genes. Since DNMTs are not tissue specific and so is DNMT inhibitors, they have more general effects and are not specific in action.

21.13 Conclusions

The outcome of patients with early and metastatic breast cancer has improved considerably in the past two decades. The greatest improvement has been seen in patients with HER2 positive breast cancer due to the routine use of HER2 targeted therapy and considerable improvement in those with ER positive disease. Similarly CDK 4/6 inhibitors have shown great promise in hormone receptor positive Her2 negative breast cancer in metastatic disease and its role in adjuvant setting for high risk tumors is being evaluated. Triple negative breast cancer continues to pose a considerable challenge, especially in patients with metastatic disease. There are several promising drugs, including antibody-drug conjugates and immunotherapeutic agents, which are likely to positively impact the outcomes in the near future.

References

1. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment with illustrative cases. Lancet. 1896;2:104–7.
2. Herynk MH, Fuqua SA. Estrogen eceptor mutations in human disease. Endocr Rev. 2004;25:869–98.
3. Holst F, Stahl PR, Ruiz C, Hellwinkel O, Jehan Z, Wendland M, Lebeau A, Terracciano L, Al-Kuraya K, Janicke F, et al. Estrogen receptor alpha (ESR1) gene amplification is frequent in breast cancer. Nat Genet. 2007;39:655–60.
4. Heldring N, Pike A, Andersson S, Matthews J, Cheng G, Hartman J, Tujague M, Strom A, Treuter E, Warner M, Gustafsson JA. Estrogen receptors: how do they signal and what are their targets. Physiol Rev. 2007;87(3):905–31.
5. Deroo BJ, Korach KS. Estrogen receptors and human disease. J Clin Invest. 2006;116(3):561–70.
6. Korenman SG. Oestrogen window hypothesis of the aetiology of breast cancer. Lancet. 1980;1(8170):700–1.
7. Doisneau-Sixou SF, Sergio CM, Carroll JS, Hui R, Musgrove EA, Sutherland RL. Estrogen and antiestrogen regulation of cell cycle progression in breast cancer cells. Endocr Relat Cancer. 2003;10:179–86.
8. Yager JD, Davidson NE. Mechanisms of disease: estrogen carcinogenesis in breast cancer (2006). N Engl J Med. 2006;354:270–82.
9. Ottaviano YL, Issa JP, Parl FF, Smith HS, Baylin SB, Davidson NE. Methylation of the estrogen receptor gene CpG island marks loss of estrogen receptor expression in human breast cancer cells. Cancer Res. 1994;54:2552–5.
10. Encarnacion CA, Ciocca DR, McGuire WL, et al. Measurement of steroid hormone receptors in breast cancer patients on Tamoxifen. Breast Cancer Res Treat. 1993;26:237–46.
11. Normanno N, Di Maio M, De Maio E, et al. Mechanisms of endocrine resistance and novel therapeutic strategies in breast cancer. Endocr Relat Cancer. 2005;12(4):721–47.
12. Gierach GL, Curtis RE, Pfeiffer RM, et al. Association of adjuvant tamoxifen and aromatase inhibitor therapy with contralateral breast cancer risk among US women with breast cancer in a general community setting. JAMA Oncol. 2017;3(2):186–93.
13. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 1998;90:1371–88.

14. Veronesi U, Maisonneuve P, Rotmensz N, et al. Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. J Natl Cancer Inst. 2007;9(9):727–37.
15. Cuzick J, Sestak I, Cawthorn S, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 2015;6(1):67–75.
16. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of Tamoxifen vs Raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;296(24):2926.
17. Goss PE, Ingle JN, Ales-Martinez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, McTiernan A, Robbins J, Johnson KC, Martin LW, Winquist E, Sarto GE, Garber JE, Fabian CJ, Pujol P, Maunsell E, Farmer P, Gelmon KA, Tu D, Richardson H. NCIC CTG MAP.3 Study Investigators: exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011;364:2381–91.
18. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet. 1999;353(9169):1993–2000.
19. Houghton J, George WD, Cuzick J, et al. Radiotherapy and Tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet. 2003;362:95–102.
20. Cuzick J, Sestak I, Pinder SE, et al. Effect of Tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol. 2011;12(1):21–9.
21. Forbes JF, Sestak I, Howell A, et al. Anastrazole versus Tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. Lancet. 2016;387(10021):866–73.
22. Controlled trial of Tamoxifen as a single adjuvant agent in the management of early breast cancer. 'Nolvadex' Adjuvant Trial Organisation. Br J Cancer. 1988;57(6):608–11.
23. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687–717.
24. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of Tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor positive tumors. J Natl Cancer Inst. 1996;88:1529–42.
25. Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of Tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. Lancet. 2009;374:2055–63.
26. Davies C, Pan H, Godwin J, et al. Long term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor posititive breast cancer: ATLAS, randomised trial. Lancet. 2013;381(9869):805–16. https://doi.org/10.1016/S0140-6736(12)61963-1.
27. Baum M, Buzdar A, Cuzick J, et al. Anastrazole alone or in combination with Tamoxifen versus Tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer. 2003;98(9):1802–10.
28. Goss PE, Ingle JN, Martino S, et al. A randomized trial of Letrozole in postmenopausal women after five years of Tamoxifen therapy for early-stage breast cancer. N Engl J Med. 2003;349(19):1793–802.
29. Sandeep K, Rai R, Agarwal GG, Dwivedi V, Kumar S, Das V. A randomised double blind placebo controlled clinical trial of centchroman (ormeloxifene) in breast pain and nodularity (benign breast disorder). Natl Med J India. 2013;26:69–74. http://www.nmji.in/archives/Volume-26/Issue-2/Original-Article-I.pdf
30. Gara RK, Sundram V, Chauhan SC, Jaggi M. Anti-cancer potential of a novel SERM ormeloxifene. Curr Med Chem. 2013;20(33):4177–84.

31. Misra NC, Nigam PK, Gupta R, Agarwal AK, Kamboj VP. Centchroman - a non-steriodal anti-cancer agent for advanced breast cancer: Phase II study. Int J Cancer. 1989;43:781–3.
32. LHRH-agonists in Early Breast Cancer Overview group, Cuzick J, Ambroisine L, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet. 2007;369(9574):1711–23.
33. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist. 2009;14:320–68.
34. Schramm A, De Gregorio N, Widschwendter P, Fink V, Huober J. Targeted therapies in HER2-positive breast cancer – a systematic review. Breast Care (Basel, Switzerland). 2015;10:173–8.
35. Schmitz KR, Ferguson KM. Interaction of antibodies with ErbB receptor extracellular regions. Exp Cell Res. 2009;315(4):659–70.
36. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353:1659–72.
37. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant Trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013;382(9897):1021–8.
38. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673–84.
39. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744–52.
40. Swain SM, Miles D, Kim SB, et al. Pertuzumab, Trastuzumab, and Docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21(4):519–30.
41. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with Trastuzumab, paclitaxel, and epirubicinchemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol. 2005;23(16):3676–85.
42. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with Trastuzumab followed by adjuvant Trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010;375(9712):377–84.
43. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant and adjuvant Trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort [published correction appears in Lancet Oncol. 2018 Dec;19(12):e667]. Lancet Oncol. 2014;15(6):640–7.
44. Wang H, et al. The prognosis analysis of different metastasis pattern in patients with different breast cancer subtypes: a SEER based study. Oncotarget. 2017;8(16):26368–79.
45. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of Tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004;351(27):2817–26.
46. Slodkowska EA, Ross JS. MammaPrint 70-gene signature: another milestone in personalized medical care for breast cancer patients. Expert Rev Mol Diagn. 2009;9(5):417–22.
47. Attuluri AK, Prakash VSC, Gunda A, et al. Analytical validation of CanAssist-Breast: an immunohistochemistry based prognostic test for hormone receptor positive breast cancer patients. BMC Cancer. 2019;19(1):249.
48. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747–52.
49. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98:10869–74.
50. Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012;486:346–52.

51. Rueda OM, Sammut SJ, Seoane JA, et al. Dynamics of breast-cancer relapse reveal late-recurring ER-positive genomic subgroups. Nature. 2019;567:399–404.
52. Lambert JM, Chari RVJ. Ado-Trastuzumab emtansine (T-DM1): an antibody-drug conjugate (ADC) for HER2-positive breast cancer. J Med Chem. 2014;57:6949–64.
53. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer [published correction appears in N Engl J Med. 2013 20;368(25):2442]. N Engl J Med. 2012;367(19):1783–91.
54. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al. Trastuzumab deruxtecanin previously treated HER2-positive breast cancer. N Engl J Med. 2020;382:610–21.
55. Schmid P, Cortes J, Pusztai L, McArthur H, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020;382:810–21.
56. Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab Govitecan-hziy in refractory metastatic triple-negative breast cancer. N Engl J Med. 2019;380(8):741–51.
57. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379:2108–212.
58. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434:917–21.
59. Dedes KJ, Wilkerson PM, Wetterskog D, Weigelt B, Ashworth A, Reis-Filho JS. Synthetic lethality of PARP inhibition in cancers lacking BRCA1 and BRCA2 mutations. Cell Cycle. 2011;10:1192–9.
60. Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med. 2016;8:362ps17.
61. Robson M, Im S-A, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017;377:523–33.
62. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med. 2018;379(8):753–63.
63. Finn RS, Aleshin A, Slamon DJ. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. Breast Cancer Res. 2016;18:17.
64. Finn RS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375:1925–36.
65. Ciruelos E, et al. Abstract PD3-03: SOLTI-1303 PATRICIA phase II trial (STAGE 1)–Palbociclib and Trastuzumab in postmenopausal patients with HER2-positive metastatic breast cancer. Cancer Res. 2019;79:PD3–PD03.
66. Andre F, Ciruelos E, Rubovszky G, Campine M, for the SOLAR-1 Group, et al. Alpelisib for PIK3CA-mutated. hormone receptor-positive advanced breast cancer. N Engl J Med. 2019;380:1929–40. https://doi.org/10.1056/NEJMoa1813904.
67. Byler S, Goldgar S, Heerboth S, et al. Genetic and epigenetic aspects of breast cancer progression and therapy. Anticancer Res. 2014;34:1071–7.
68. Chik F, Szyf M. Effects of specific DNMT gene depletion on cancer cell transformation and breast cancer cell invasion; toward selective DNMT inhibitors. Carcinogenesis. 2011;32:224–32.
69. Kelly TK, De Carvalho DD, Jones PA. Epigenetic modifications as therapeutic targets. Nat Biotechnol. 2010;28:1069–78.
70. Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis. 2010;31:27–36.
71. Chang HW, Wang HC, Chen CY, et al. 5-azacytidine induces anoikis, inhibits mammosphere formation and reduces metalloproteinase 9 activityin mcf-7 human breast cancer cells. Molecules. 2014;19:3149–59.
72. Chik F, Machnes Z, Szyf M. Synergistic antibreast cancer effect of a combined treatment with the methyl donor S-adenosyl methionine and the DNA methylation inhibitor 5-aza-2′ deoxycytidine. Carcinogenesis. 2014;35:138–44.
73. Cody JJ, Markert JM, Hurst DR. Histone deacetylase inhibitors improve the replication of oncolytic herpes simplex virus in breast cancer cells. PLoS One. 2014;9:e92919.
74. Wilson-Edell KA, Yevtushenko MA, et al. mTORC1/C2 and pan-HDAC inhibitors synergisticallyimpair breast cancer growth by convergentAKT and polysome inhibiting mechanisms. Breast Cancer Res Treat. 2014;144:287–98.

75. Al-Rayyan N, Litchfield LM, Ivanova MM, et al. 5-Aza-2-deoxycytidine and trichostatin A increase COUP-TFII expression in antiestrogen resistant breast cancer cell lines. Cancer Lett. 2014;347:139–50.
76. Fortunati N, Bertino S, Costantino L, et al. Valproic acid restores ER alpha and antiestrogen sensitivity to ER alpha-negative breast cancer cells. Mol Cell Endocrinol. 2010;314:17–22.
77. Sabnis GJ, GoloubevaO CS, et al. Functional activation of the estrogen receptor-alpha and aromatase by the HDAC inhibitor entinostat sensitizes ER-negative tumors to Letrozole. Cancer Res. 2011;71:1893–903.
78. Yang X, Phillips DL, Ferguson AT, et al. Synergistic activation of functional estrogen receptor(ER)-alpha by DNA methyltransferase and histonedeacetylase inhibition in human ER-alpha negative breast cancer cells. Cancer Res. 2001;61:7025–9.
79. Sharma D, Saxena NK, Davidson NE, Vertino PM. Restoration of Tamoxifen sensitivity in estrogen receptor-negative breast cancer cells: tamoxifen-bound reactivated ER recruits distinctive corepressor complexes. Cancer Res. 2006;66:6370–8.
80. Mongan NP, Gudas LJ. Valproic acid, in combination with all-trans retinoic acid and 5-aza-20-deoxycytidine, restores expression of silenced RARbeta2 in breast cancer cells. Mol Cancer Ther. 2005;4:477–86.
81. Yao J, Zhou E, Wang Y, et al. MicroRNA-200a inhibits cell proliferation by targeting mitochondrial transcription factor A in breast cancer. DNA Cell Biol. 2014;33:291–300.
82. Si ML, Zhu S, Wu H, Lu Z, Wu F, Mo YY. miR-21-mediated tumor growth. Oncogene. 2007;26:2799–803.
83. Mei M, Ren Y, Zhou X, et al. Down regulation of miR-21 enhances chemotherapeutic effect of taxol in breast carcinoma cells. Technol Cancer Res Treat. 2010;9:77–86.
84. Kong W, He L, Coppola M, et al. MicroRNA-155 regulates cell survival, growth, and chemosensitivity by targeting FOXO3a in breast cancer. J Biol Chem. 2010;285:17869–79.
85. Ouzounova M, Vuong T, Ancey PB, et al. Micro RNA miR-30 family regulates non attachment growth of breast cancer cells. BMC Genomics. 2013;14:139.

Oncoplastic and Reconstructive Surgery for Breast Cancer

22

Prabha Yadav and Dushyant Jaiswal

22.1 Introduction

Breast is the most revered symbol of the feminine. Before and long after their main function of lactation, they continue to serve as an important part of body image and sexuality. Cancer ablative surgery in the form of total removal (mastectomy) or partial removal (Breast Conservative Surgery, BCS) leads to a deformity with potential adverse impact on body image perception and psychosexual wellbeing, having an adverse impact on the quality of life [1, 2] Fig. 22.1. Reconstruction using plastic surgery principles is now safe, proven and well established. Oncoplastic Breast Surgery (OBS) is an approach where plastic surgery principles are used in synchrony with established oncological caveats to achieve good cosmetic outcomes [3–5]. Term OBS is generally used to refer to reconstructive surgery interventions done with BCS. Reconstruction after mastectomy, Whole Breast Reconstruction (WBR), can be accomplished using autologous tissue, synthetic implants or a combination of the two. The aim of all reconstructive endeavour is to achieve an outcome acceptable to the patient, aligned with her perception of size, symmetry, site and proportions. In absence of WBR or OBS, the breast deformities are a constant reminder of the disease long after oncological treatment has attained purpose. Reconstruction cannot free the patient of the disease but free their minds off these

Prabha Yadav, MS (✉)
Director and Professor, Department of Plastic and Reconstructive Surgery, Sir H N Reliance Foundation Hospital, Mumbai, India

Former Professor and Head, Department of Plastic and Reconstructive Surgery, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India
e-mail: drprabhatata@gmail.com

Dushyant Jaiswal, MS, MCh
Professor, Department of Plastic and Reconstructive Surgery, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_22

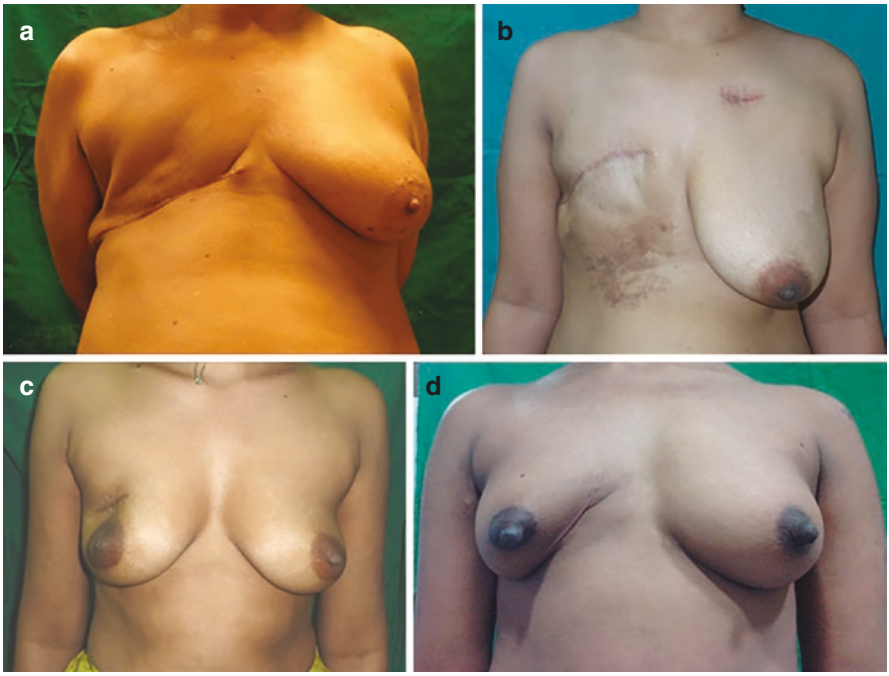


Fig. 22.1 (**a**, **b**, **c**, **d**): Deformity after mastectomy and breast conservative surgery without reconstruction

reminders. It per se doesn't affect the disease biology and should not interfere with timely delivery of chemotherapy and radiation therapy [6]. Follow-up for cancer recurrence is not hindered by reconstruction in the era of modern imaging modalities of mammography, CT scan and MRI.

Patient Autonomy in Reconstruction All forms of breast reconstruction are essentially cosmetic. The patient has a full right to choose a life with a deformed or an absent breast. An open and inclusive approach in decision making is highly recommended. All possible options of type of reconstruction, donor site and timing (primary or secondary) with advantages & disadvantages must be explained to the patient before a decision is made [7]. Even an option of an external prosthesis, a post-mastectomy brassiere, for camouflage must be offered to the patient.

The Opposite Breast An assessment of the opposite breast is the first and most important element in planning reconstruction. It serves as the baseline template which reconstruction tries to match. If the patient wishes to modulate the normal breast, the reconstructive end points change. A large and/or ptotic breast can be subjected to reduction or mastopexy procedure, a small breast can be augmented with an implant or a lipofilling procedure. The willingness of a patient to undergo a symmetrising procedure often eases the reconstructive effort and yields a better cosmetic and symmetrical result.

22.2 Whole Breast Reconstruction: Implant Based

Implant based reconstructions after mastectomy (they are not usually used an option after BCS) offer the absolute advantage of not needing any additional donor site scars or morbidity. They are an option when patient doesn't have any suitable donor site with abundant skin and fat or doesn't wish an additional scar on her body. In western nations they also have a short-term cost advantage [8].

Breast implants and expanders are made of medical grade silicone. The shell is of silicone, core is empty in 'Saline implants' and again of silicone in 'Silicone implants". Surfaces are round as textured implants now withdrawn due to association with BIA-ALCL [9]. 'Implants' are of a fixed size. 'Expanders' can be increased or decreased in size, accessed by a 'port' on the device or remote and connected to it Fig. 22.2.

Implant Pocket The implant or expander needs space, a 'pocket', to fit in. The pocket needs to be robust in morphology and vascularity to cover and isolate it from the environment. The pocket options are,

(a) Subcutaneous: The device is placed just below the mastectomy flaps
(b) Submuscular: The device is placed below the pectoralis major muscle totally covered; no surface is in contact with the under surface of skin.
(c) Dual plane: the upper part of implant is submuscular, lower part subcutaneous [10].

The lower half of the subcutaneous implant coverage can be augmented or buttressed by, acellular dermal matrix (ADM), de epithelised dermal flap remnant from a wise pattern skin reduction, serratus anterior or LD muscle flap or a rectus fascia turnover flap.

The quality of the skin flaps, thickness and vascularity, after mastectomy are one of the most important determinants of outcome of any reconstruction [11]. If the pocket is suspect, reconstruction can be delayed to observe (temporary expander placement), pocket changed or augmented (muscle or fascial flap or ADM). Sometimes the pocket is outright deficient in skin and the defect needs to be plugged with an autologous tissue flap, Latissimus Dorsi flap is the most common choice.

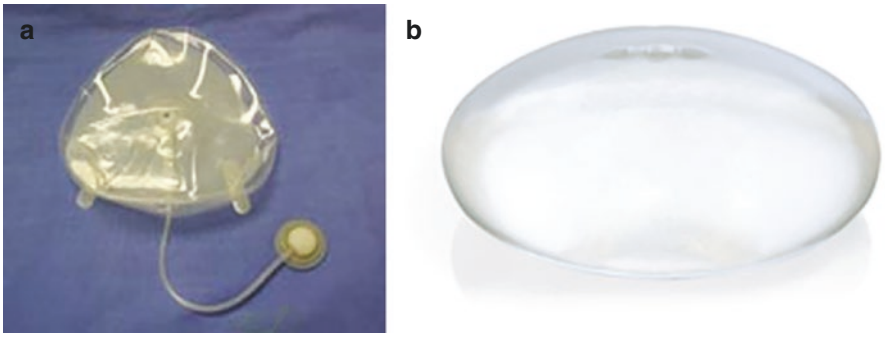


Fig. 22.2 (**a**) Expander with remote port for breast. (**b**) Silicone breast implant

Need for Expander Commonly arises in two situations.

(a) *Secondary reconstruction*—The mastectomy has been done prior and skin pocket is contracted like a flat sheet compared to a hemisphere of a normal breast before mastectomy. Tissue expansion reverses this process to enable an implant placement.
(b) *Primary reconstruction* with postoperative radiation requirement—In this scenario the chest needs to be flat for ease of radiation delivery and expanded later to accommodate the implant.

Long Term Complications The implant is inert, however, it being a foreign material, doesn't integrate with the body in a biological way. Biofilm formation happens, starting the process of infection, exposure and extrusion. Capsular contracture is a major concern in nearly 25–30% of patients [12]. Most complications with implants are insidious and unravel over long term. This often gives a false sense of comfort about the safety of implant-based reconstruction, and necessitates adequate long-term follow-up of these patients.

Additional Concerns Implants come with an element of fear of the unknown. The PIP controversy happened where a manufacturer used industrial grade silicone instead of medical grade, prompting implant removal or exchange in thousands of women in Europe [13]. The recent concerns with BIA—ALCL (Breast Implant Associated—Anaplastic Large Cell Lymphoma) also places a seed of doubt. The Incidence of BIA-ALCL is extremely low as of now and associated with only textured implants [14]. These concerns also come with the fear of something yet unknown cropping up in the future.

Indian Perspective Young patients often present with advanced primary necessitating skin excision and subsequently a LD flap when an implant is planned after mastectomy Fig. 22.3. Tissue expander is often needed prior to an implant. In addi-

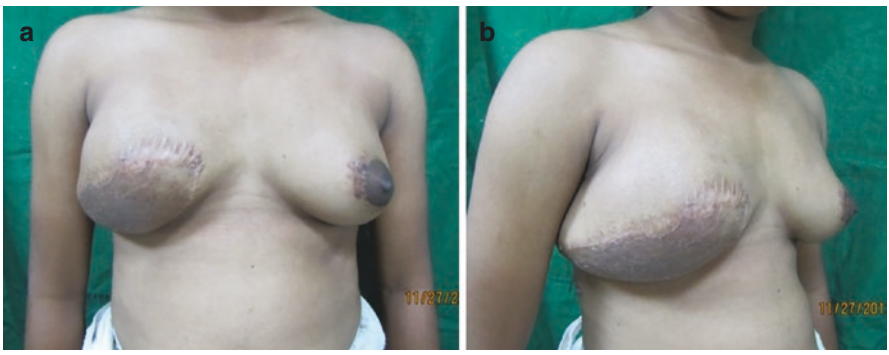


Fig. 22.3 (**a**, **b**): Follow up of breast reconstruction with LD flap & expander, followed by insertion of an implant after completion of radiotherapy. Note the scar stretching and skin changes in the LD skin island due to radiation

tion, the nodal burden, usually necessitates postoperative radiation which prolongs the whole process till a result is achieved and also pulls the cosmetic results a notch lower in long term. The repeated follow up (for tissue expansion) and multiple visits to operating room (expander to implant change) push up the costs and present additional logistics issues. The availability of a spectrum of implants and expander to choose from is also an issue, especially in non-metro cities and towns.

22.3 Whole Breast Reconstruction with Autologous Tissue

Autologous reconstruction implies patients own tissues are used to reconstruct the 'neo faux breast' from her donor sites, most commonly abdomen and less frequently back, thighs, buttocks or flanks. This tissue could be varying combinations of skin, fat and muscle in the form of a pedicle flap, a free flap or lipofilling of suctioned fat. These tissues integrate with the body in breast location (unlike an implant / expander), feel, behave and age as they would in the native donor site (even gaining and losing weight as they would at the native site). Autologous reconstruction can have some short-term complications or failure with flaps but the incidence is very low (1–2%). Long-term complications with successful autologous reconstruction are extremely low [15]. They are all associated with a donor site cost; scar and its sequalae, rarely morbidity due to muscle loss or weakness, herniation and cosmetic deformity of the donor site. With the current state of autologous reconstruction, microvascular surgery, range of donor site options and predictability with modern imaging techniques, it is a very safe, robust and reliable option to choose.

Decision to choose autologous tissue for WBR should be preceded by a thorough examination of the possible donor sites and opposite breast Fig. 22.4. Patient's willingness to symmetrise the opposite breast, should be taken into account. Clinical examination gives an approximate idea of options of donor sites, which have required amount of fat and skin needed to reconstruct the breast without significant morbidity. These technically feasible options, matched to the comfort level of the surgeon, need to be discussed with the patient before a final decision is made. The autologous free flap options need the blood vessels of the flap to be anastomosed to a donor set of vessels, requiring microvascular expertise, longer operative time and more cost. The donor sites which can be utilised in order of most common to rarer ones are described below Fig. 22.5.

22.3.1 Abdomen-Pedicle TRAM to the DIEP Flap

Lower abdomen skin and fat offer the closest match to the breast morphologically. It can look and feel almost like the normal breast tissue. In addition, it gives a donor site gain rather than morbidity in form of a 'cosmetic abdominoplasty' or a free "tummy tuck". When available, it is the first choice as a donor site.

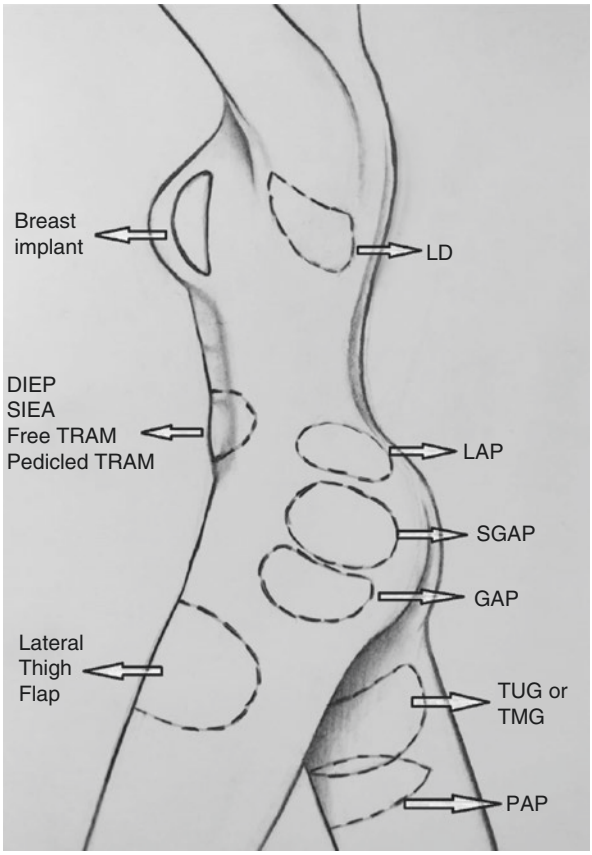


Fig. 22.4 Possible flap donor sites for Autologous whole breast reconstruction

Pertinent Anatomy The Rectus Abdominis (R.A.) muscle has a codominant blood supply from the Superior Epigastric Artery (SEA, continuation of the Internal Mammary Artery) and Deep Inferior Epigastric Artery Fig. 22.6. These two vessels anastomose with each other in the rectus abdominis muscle. The dominant supply of the lower abdominal pannus is the deep inferior epigastric artery & vein (DIEA&V), via the perforators traversing the RA muscle and rectus sheath. Innervation of the RA muscle is from anterior rami of thoracic 6–12 spinal nerves, which begin as intercostal nerves, in a segmental manner entering the muscle laterally.

Pedicled TRAM Flap This was first performed (on suggestion of a patient!), standardised and popularised by Carl Hartrampff [16]. This pedicle flap utilises the

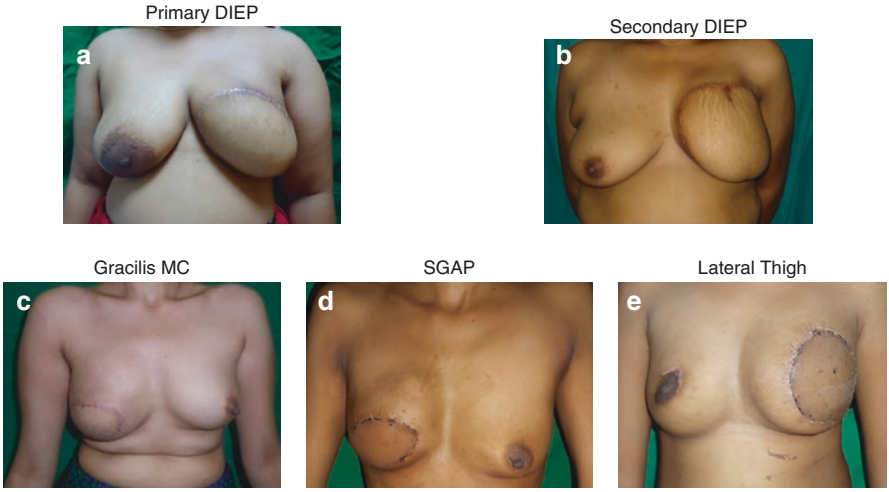


Fig. 22.5 Autologous reconstruction—different paths to same destination, (**a**) primary Deep inferior epigastric perforator (DIEP flap), (**b**) Secondary DIEP flap, (**c**) Gracilis myocutaneous flap, (**d**) Superior Gluteal artery perforator flap (SGAP), (**e**) Lateral thigh flap

lower abdominal pannus based on the SEA communicating with the DIEA, within the RA muscle. Many variations in skin island design, mode of inset of the flap, use of bilateral flaps and delay techniques have been described.

This flap can produce excellent results in selected cases Fig. 22.7. It is but plagued by a high rate of partial flap necrosis and fat necrosis in the late postoperative period. The reason for this is the unpredictable nature of communications between the SEA and DIEA, sometimes few, rarely absent and occasionally the choke vessels are present but don't open up. This problem is compounded in obese, smokers and patients with comorbidities where the peripheral circulation is compromised [17, 18].

The other problem is donor site morbidity due to loss of the RA muscles and rectus sheath, resulting in abdominal wall weakness, bulges, hernia and backache due to muscle imbalance.

Free TRAM and Free DIEP Flap The ischemic complications drove the change to use the, lower abdomen pannus based on the dominant DIEA/V, harvested with the corresponding RA muscle and rectus sheath called Free TRAM flap (first described by Holmstrom) [18]. This transfer is as a free flap with need for microvascular tech-

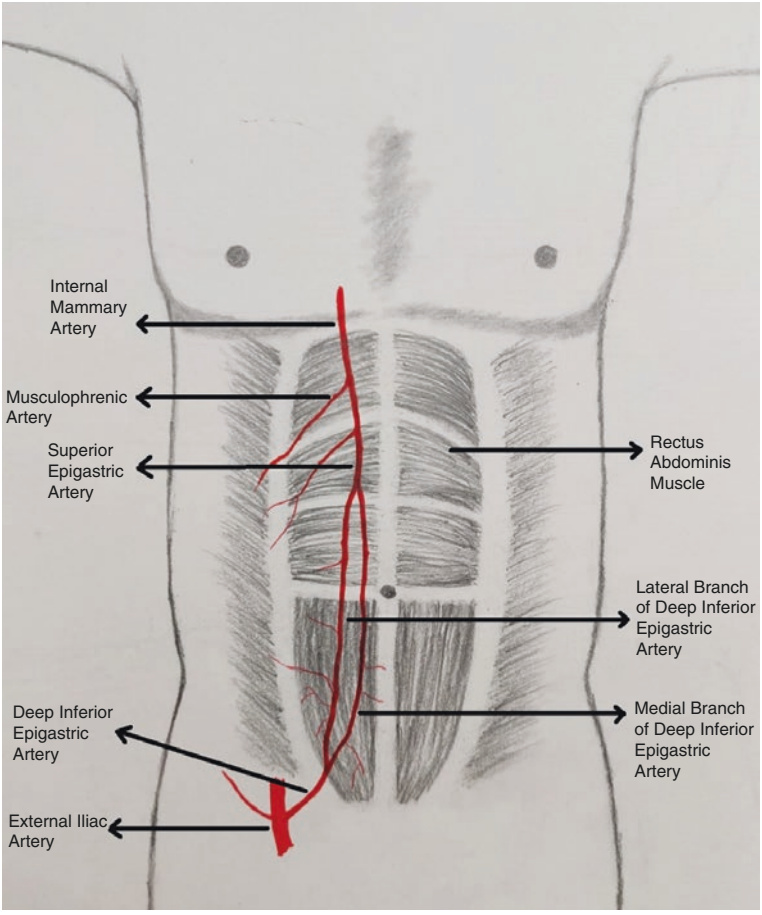


Fig. 22.6 Pertinent anatomy of flaps from the abdomen

nique to anastomose the DIEA/V to a donor pedicle of Thoracodorsal or Internal mammary vessels. Free TRAM flap took care of the ischemic problems of Pedicle TRAM but the donor morbidity remained an issue.

The *Free DIEP flap* is the current 'gold standard' of autologous breast reconstruction against which all other are compared [19] Figs. 22.8, 22.9 and 22.10. It utilises the lower abdominal pannus with the DIEA/V vessels based on a single or few perforators only sparing the Rectus muscle, its innervation and rectus sheath completely. This in principle reduces the morbidity. It was first described for a different indication by Isao Koshima, by Robert Allen for breast reconstruction and popularised by the early work of Phillip Blondeel [18, 20]. CT Angiogram or MR

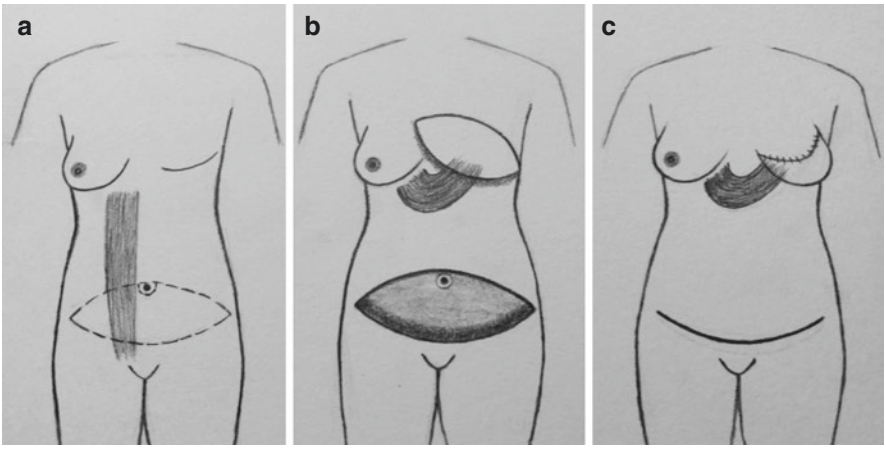


Fig. 22.7 Pedicled TRAM flap for breast reconstruction. (**a**) Defect and the flap marking. (**b**) Harvested pedicle for TRAM and donor defect. (**c**) Post operative views

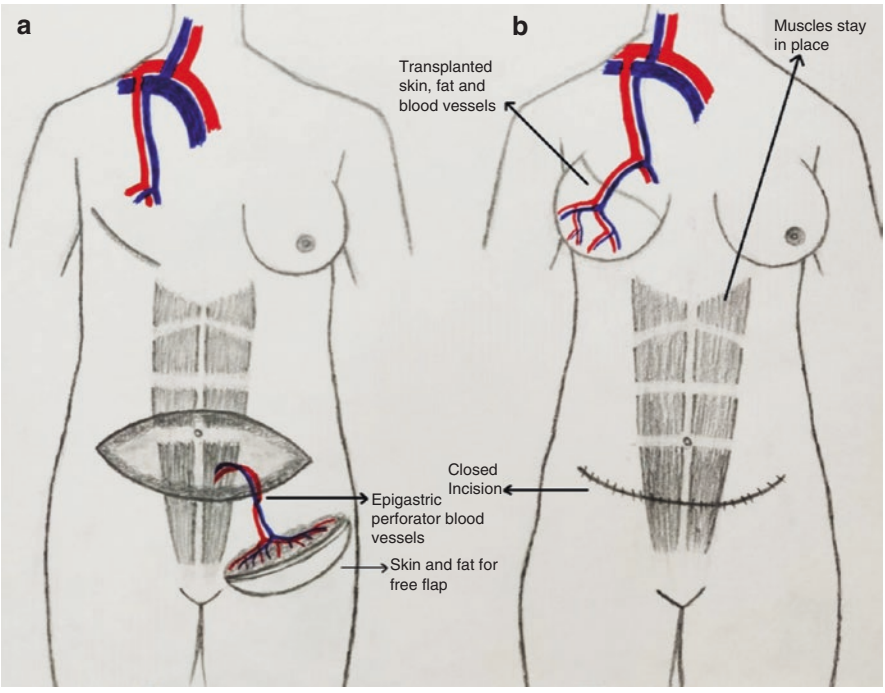


Fig. 22.8 DIEP flap for Whole Breast Reconstruction. (**a**) Defect after mastectomy and harvested flap showing perforator and pedicle (**b**) transplanted DIEP flap for breast reconstruction; rectus sheath primarily closed

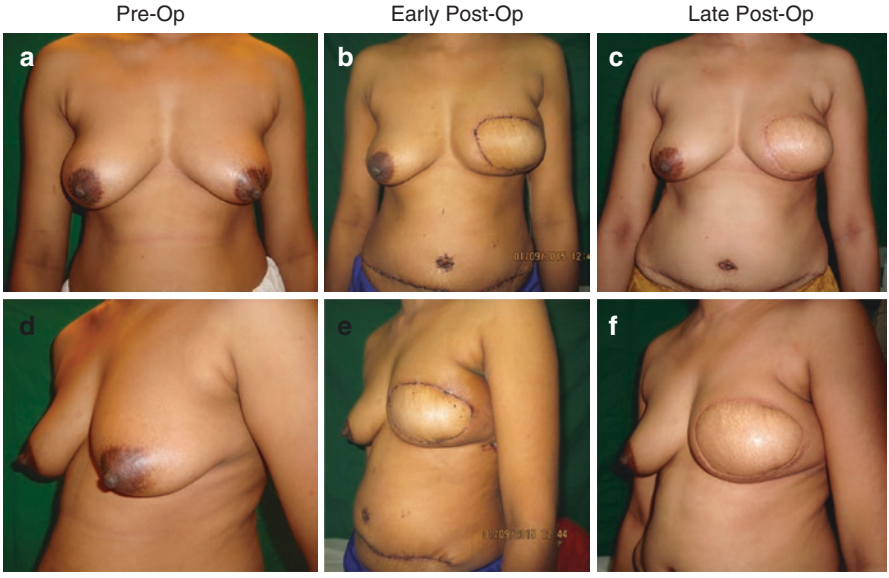


Fig. 22.9 (**a** & **d**) Preoperative, (**b** & **e**) early postoperative and (**c** & **f**) late postoperative post radiation images of patient in Fig. 22.9, front and semi lateral views

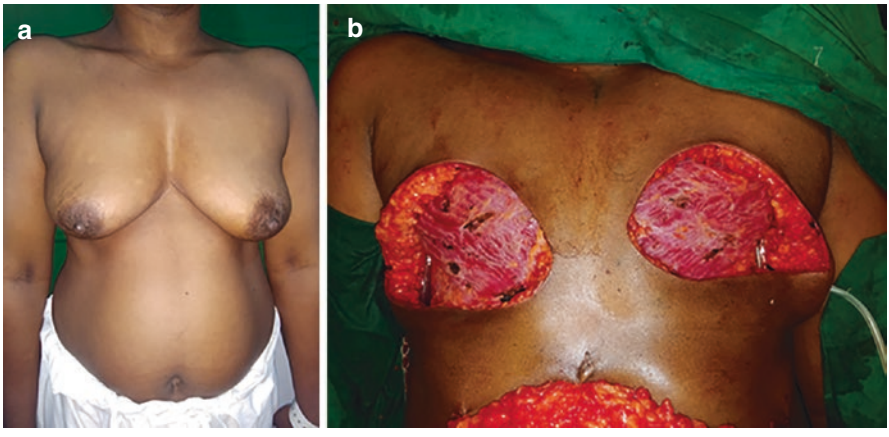


Fig. 22.10 Bilateral mastectomy with Bilateral DIEP flap (clockwise), (**a**) Preoperative, (**b**) Bilateral mastectomy with skin defects, (**c**) Bilateral DIEP flap marking, (**d**) The two harvested flaps, (**e**) Under surface of both flaps showing one perforator each with pedicle, (**f**) At completion of surgery with flap inset and abdominoplasty (**g**, **h** and **i**) Follow up after completion of radiation

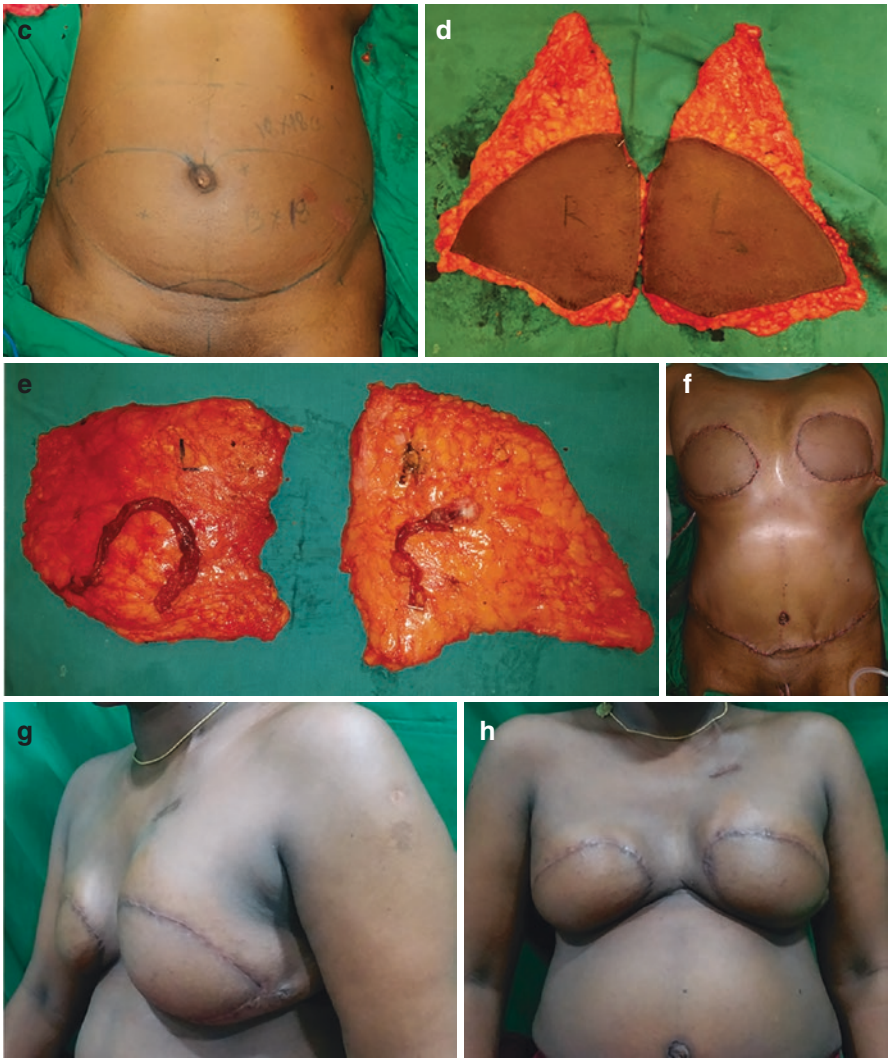


Fig. 22.10 (continued)

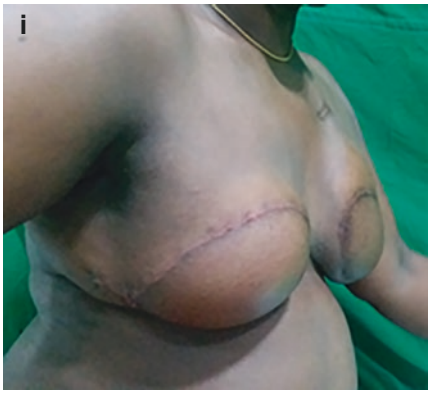


Fig. 22.10 (continued)

Angiogram, to identify the most suitable perforator or their combinations (size, arborisation, communications, likely area perfused and their course through muscle), represent the next major step in evolution [21, 22].

Previous surgery with any scars or nulliparity is not an absolute contraindication to use of abdomen. Imaging can identify and assure about the intact vascular basis of the flap [23].

22.3.2 Back- Latissimus Dorsi Myocutaneous Flap

LD flap can be used to reconstruct the whole breast in selected cases Fig. 22.11. The morphology, texture and feel of the back fat is close to the breast, though not as good as abdominal tissue [18]. Patients with small to moderate size breast, with a wide trunk and adequate fat in the back are ideal candidates. (See section on OBS for anatomy details).

The LD flap skin island can be larger than needed from anterior axillary line till the midline. The LD muscle atrophies significantly after transfer and should be discounted when assessing the volume of the flap needed. The flap should be seen as a skin and fat harvest with muscle being just the carrier. This ensures good long-term volume retention. Extra fat can be harvested beyond the skin island. This version of the flap is popularly called the '*Extended LD flap'*. This harvest should be restricted to the deep layer of the fat between the superficial fascia and the muscle [24]. This deep fat layer is perfused by minor perforators from the pedicle. The fat above this fascia is perfused dermis down, and is likely to necrose if harvested and likely to result in donor site complications. Persistent seroma is usually the sequala of this excess harvest. The donor site complications of dehiscence and skin necrosis are often the result of overenthusiastic fat harvest. The donor site availability and complications with excessive harvest, limit the utility and indications of LD flap for WBR.

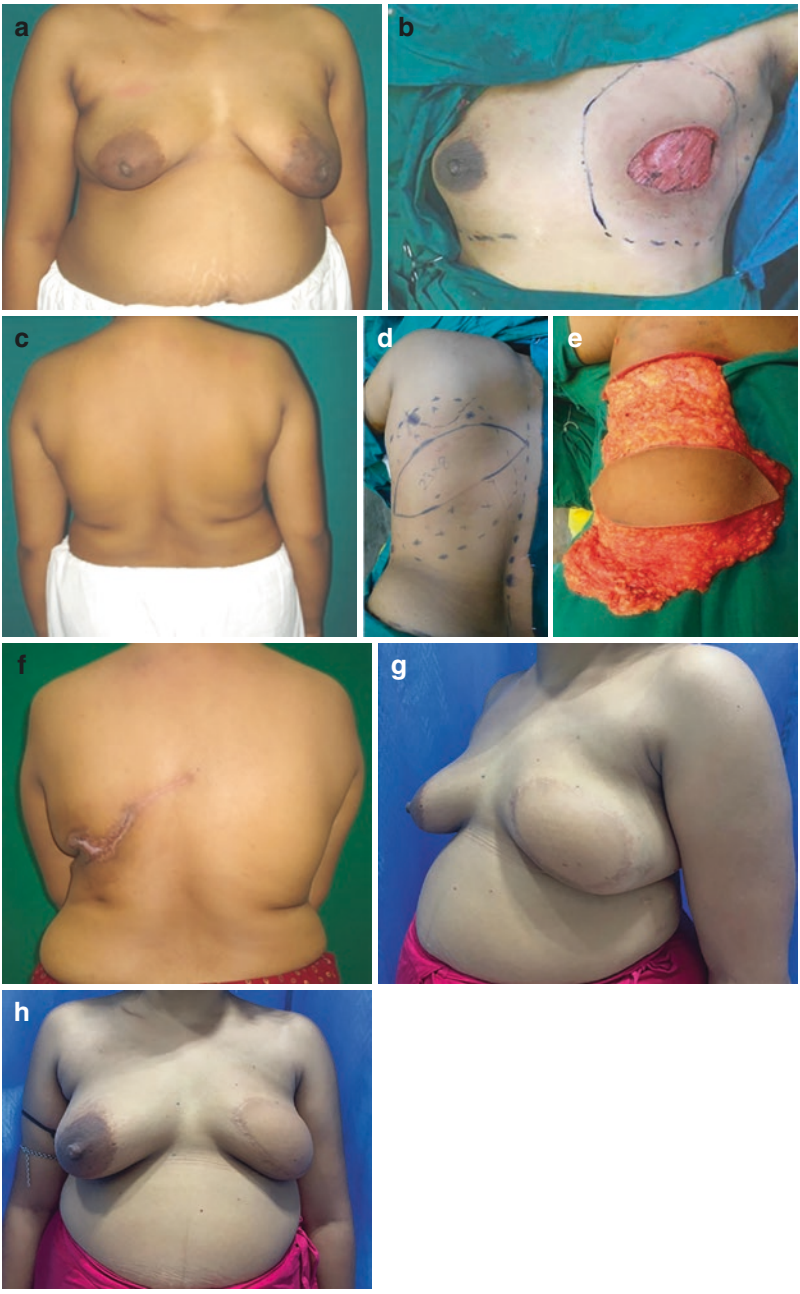


Fig. 22.11 Whole breast reconstruction with Extended LD flap, (**a**) Preoperative Left breast IDC, (**b**) Mastectomy defect, (**c**) Preoperative abundant fat in back, (**d**) Flap marking, (**e**) Harvested flap with extended fat harvest, (**f**, **g**, **h**) 2 year postoperative, note scarring of the donor site following delayed healing due to skin necrosis and dehiscence

22.3.3 Alternative Free Flaps for WBR

They come into picture if the abdomen has been used for a flap, violated by abdominoplasty or liposuction or doesn't have adequate fat. A pear-shaped body habitus lends itself well to flaps from lower part of the body. These flaps generally have a low skin to fat/volume ratio and are best suited when skin envelope is preserved and the requirement is small to moderate. The fat texture is firmer and skin thicker compared to breast tissue or abdominal tissue. These flaps are often technically challenging to harvest and anastomose.

The upper medial thigh tissue above the Gracilis muscle, is used as a free flap based on the medial circumflex femoral vessels called the *Transverse Upper Gracilis myocutaneous* flap (TUG) [25, 26]. The medial to posterior upper and midthigh tissue can be also based on the perforators of profunda femoris (Deep femoral) vessels as the *Profunda Artery Perforator flap* (PAP) [27]. The lateral upper thigh tissue can be harvested based on the transverse branch of the Lateral circumflex femoral vessels as the *Lateral thigh flap or TFL perforator flap* [28]. The buttock skin and fat can be harvested based on perforators originating from Superior or Inferior gluteal vessels as *Superior or Inferior Gluteal Artery Perforator flaps (SGAP & IGAP)* [29]. The posterior flank tissue above the iliac crest can be harvested based on the lumbar perforating vessels as *Lumber Artery Perforator flap (LAP)* [30].

22.4 Oncoplastic Breast Surgery

The term Oncoplastic Breast Surgery (OBS) refers to an approach where plastic surgery principles are used in synchrony with oncological principles to achieve a good cosmetic outcome after breast conservative surgery. The term is conventionally used for plastic surgery after BCS. The choice of incisions for resection of the primary tumour to cosmetically acceptable locations such as peri areolar, radial or in IMF can be the first step in an oncoplastic approach. The two main approaches to OBS are described below.

22.5 Volume Displacement Techniques

These are procedures when no tissue is added to the breast but remoulding and reshaping of the remnant breast tissue is done based on principles of rotation flap, mastopexy or reduction mammoplasty template or its modification as per the defect size and location.

22.5.1 Disc Rotation or Donut Mastopexy

Ideal indication for this is a small defect in a moderately sized breast, other than the retroareolar area.

The breast parenchymal tissue is mobilised from both sides, rotated and advanced into the defect and sutured [31]. Biplanar mobilization of breast tissue leading to lack of dermal contact with parenchyma and mobilisation from the chest wall, predisposes these flaps to ischemia and fat necrosis. It is the most common 'oncoplasty' procedure but often not well understood and poorly applied.

A variant of this flap is a rotation flap of the lower pole of the breast for lower inner quadrant defects Fig. 22.12. Here the flap is dermo glandular, hence of robust vascularity and safe.

The Grissoti flap is also a rotation flap modification for central quadrant tumours, with a retained skin island to create the neo areola Fig. 22.13.

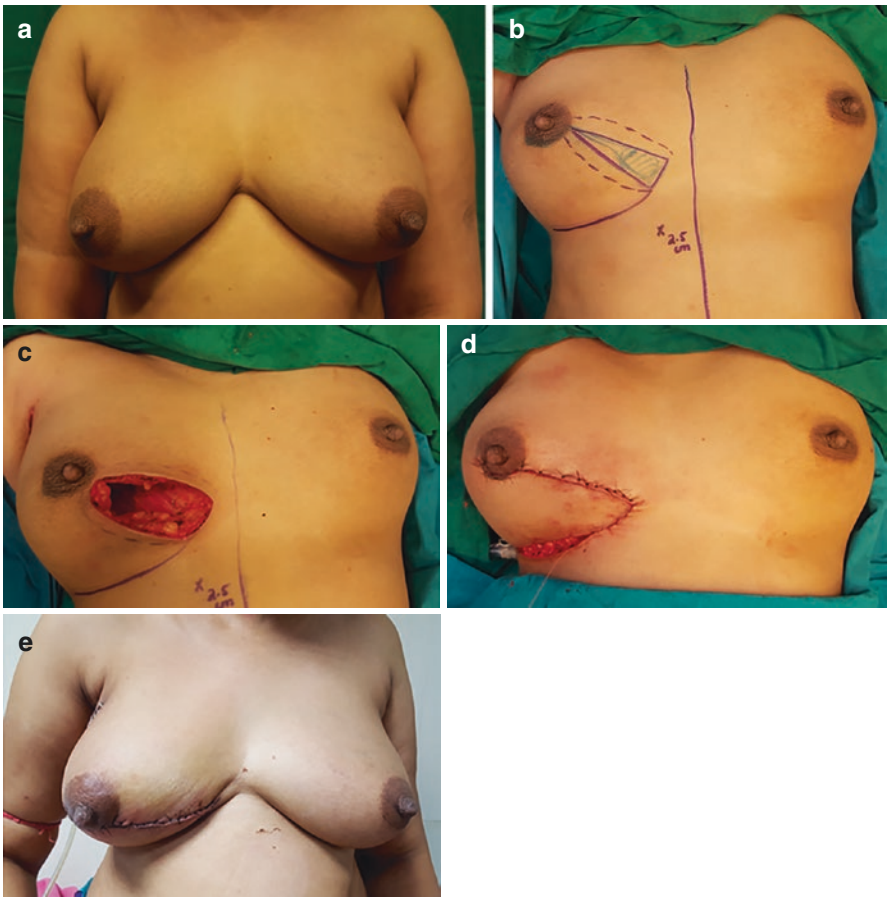


Fig. 22.12 Rotation flap for lower inner quadrant defect, (**a**) Preoperative, (**b**) Marking of skin and gland excision, (**c**) defect after BCS, (**d**) Rotation flap with incision in inframammary fold, (**e**) Early postoperative. Case courtesy, Dr. Shalaka Joshi Professor, Breast Services, Tata Memorial Centre, Mumbai

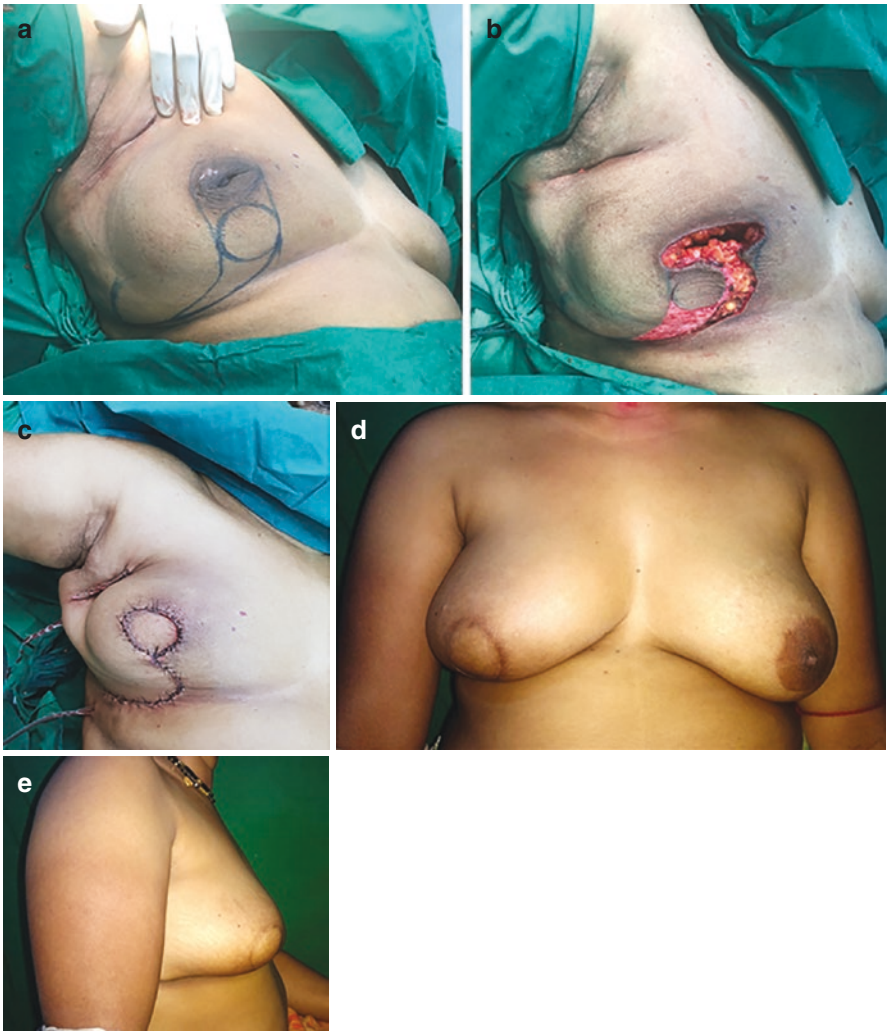


Fig. 22.13 Grisotti flap for central defect, (**a**) flap marking note the epithelial island at the leading edge, (**b**) NAC central quadrant defect with elevated flap, (**c**) Flap sutured in place with donor site closed, (**d** and **e**). Follow Up Case courtesy, Dr. Shalaka Joshi Professor, Breast Services, Tata Memorial Centre, Mumbai

22.5.2 Mastopexy and Reduction Mammoplasty Templates

Mastopexy is a procedure where the breast ptosis and shape are modified with minimal or no reduction in volume. *Reduction mammoplasty* is a mastopexy with significant reduction in the volume of the breast.

These two surgeries are not distinct entities but represent a continuum with the same three basic principles:

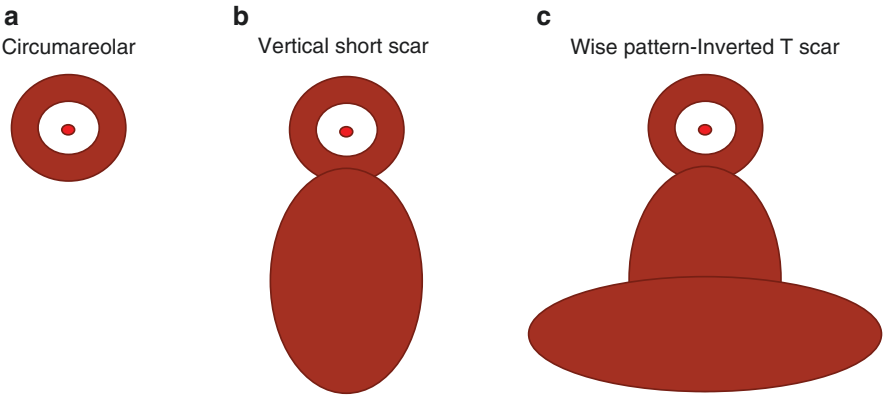


Fig. 22.14 Basic skin resection and access pattern's for OBS, (**a**) Cicumareolar skin incision can be extended to skin excision also, (**b**) Vertical short scar, combination of circumareolar and vertical ellipse, (**c**) Wise pattern skin excision, combination of a vertical short scar pattern and horizontal ellipse in inferior part of breast

1. *Skin resection pattern selection*—this could be needed for access or reduction of the skin envelope Fig. 22.14. Depending on the size of breast, access needed and amount of tissue to be resected, choice could be made from
   (a) *Peri areolar*
   (b) *Vertical short scar* (combination of peri areolar and vertical ellipse inferiorly)
   (c) *Wise pattern* (combination of peri areolar, vertical ellipse inferiorly and horizontal ellipse at IMF)

   However, often skin resection patterns may have to be modified depending upon the incisions planned for primary resection.
2. *Nipple Areola modulation*—the NAC complex can be resized, re-located and needs to be retained. The NAC can be used as a free graft or retained on vascularised dermo glandular pedicles most commonly superomedial or inferior or rarely a glandular central pedicle Fig. 22.15.
3. *Parenchyma resection*—needed for resizing the breast, this could follow the skin resection pattern or differ from it slightly.

   In all these procedures, what is left behind of the breast tissue is more important than how much and from where is it removed. Numerous combinations of pedicles and skin resection patterns have been historically described.

   These procedures lend themselves beautifully to OBS Figs. 22.16 and 22.17. Each of the above procedures needs excision of some breast parenchyma. When BCS is done and resection falls in one of these templates' excision, nothing more needs to be done. In other cases, which is more often the case, the skin resection patterns and parenchyma resections can be modulated. The breast tissue which would otherwise be removed can be utilised for filling the BCS cavities as dermo glandular flaps based on named or visible perforators or supply based on dermal and subdermal plexus.

   The radical rearrangement of breast tissue can make the planning radiotherapy difficult, especially when boost needs to be delivered. All OBS procedures

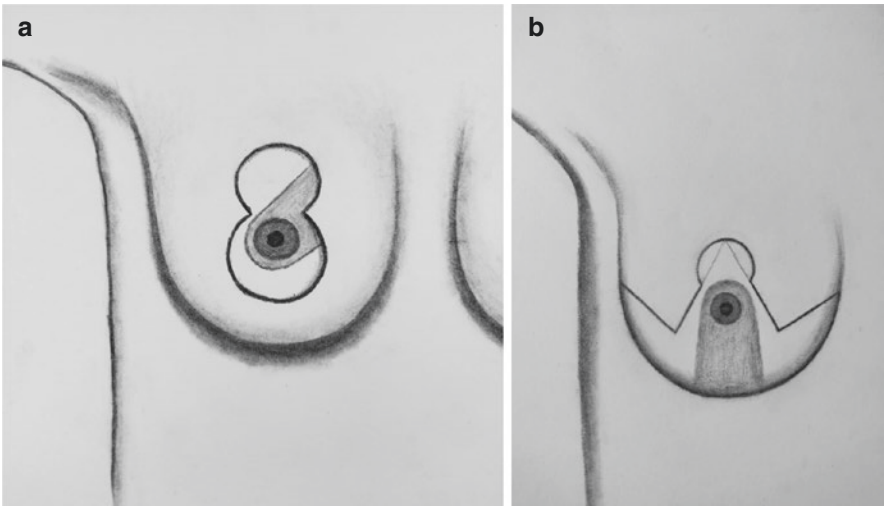


Fig. 22.15 Most common dermoglandular pedicle options to preserve NAC in breast reduction based OBS, both combine well with a wise pattern skin resection. (**a**) Superomedial pedicle, (**b**) Inferior pedicle

should be documented and photographed for ease of communication with the radiation oncologist. Surgical clips should be appropriately applied for cavity delineation to help in delivery of radiation boost which significantly impacts local recurrence rates. Inability to boost the primary cavity and need of mastectomy for local recurrence is detrimental to the primary goal of aesthesis and breast conservation.

22.6 Volume Replacement Techniques

These are procedures where tissues from outside the breast are bought into it by way of local, perforator, regional pedicle, or rarely free flaps. They are indicated when the defect is large compared to the remnant breast, usually in a small to moderate sized breast, when only breast reshaping would not serve the purpose and additional tissue is required for adequate cosmesis.

22.6.1 Latissimus Dorsi Myocutaneous Flap

It is the workhorse and most often done flap for breast restoration in partial breast reconstruction or volume replacement techniques in OBS Fig. 22.18. The safety of LD flap is well proven in early as well as locally advanced breast cancer with respect to oncological outcomes.

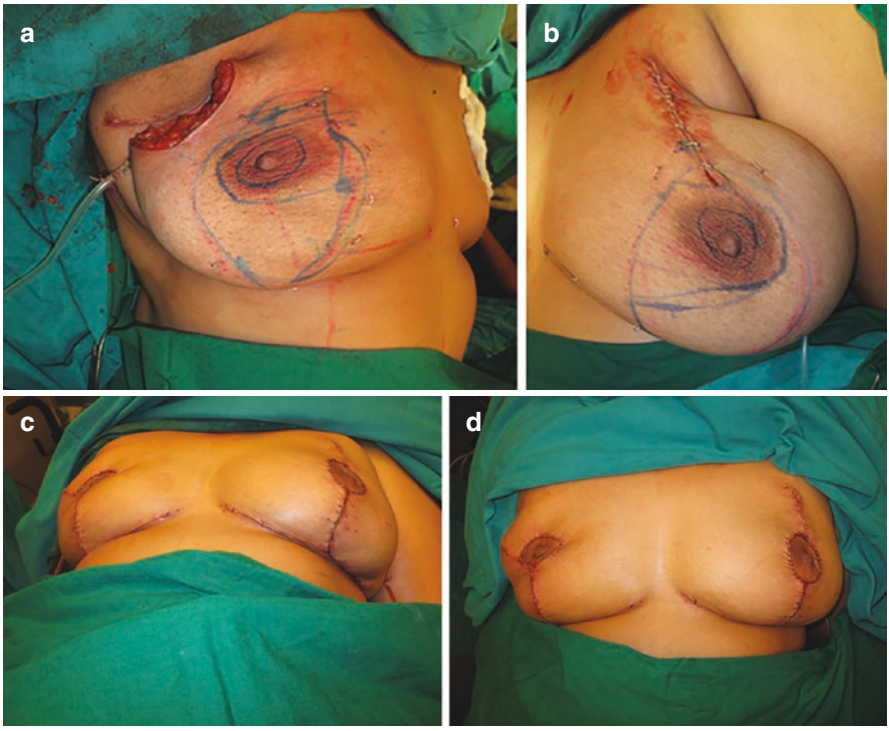


Fig. 22.16 Bilateral IDC breast treated with BCS on both sides, (**a**) R- modified Wise pattern skin resection with superomedial dermoglandular pedicle for NAC, (**b**) L- Wise Pattern skin resection with primary closure superiorly and medial dermoglandular pedicle for NAC, (**c** and **d**) At completion of surgery

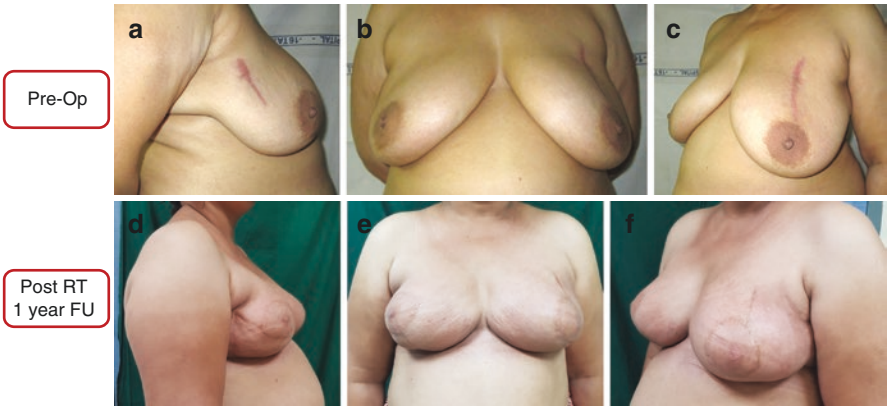


Fig. 22.17 (**a**, **b** and **c**) Preoperative, (**d**, **e** and **f**) Follow up at one year after radiation therapy of case in figure

LD is a large muscle on the back just below the subcutaneous tissue. The flap is based on the Thoracodorsal artery and vein, branches of the subscapular vessels. The vessel divides into a descending and transverse branch within the substance of the muscle and gives numerous perforator branches to the overlying fat, some of the larger ones reaching the dermis and supplying the skin. Any skin island located on

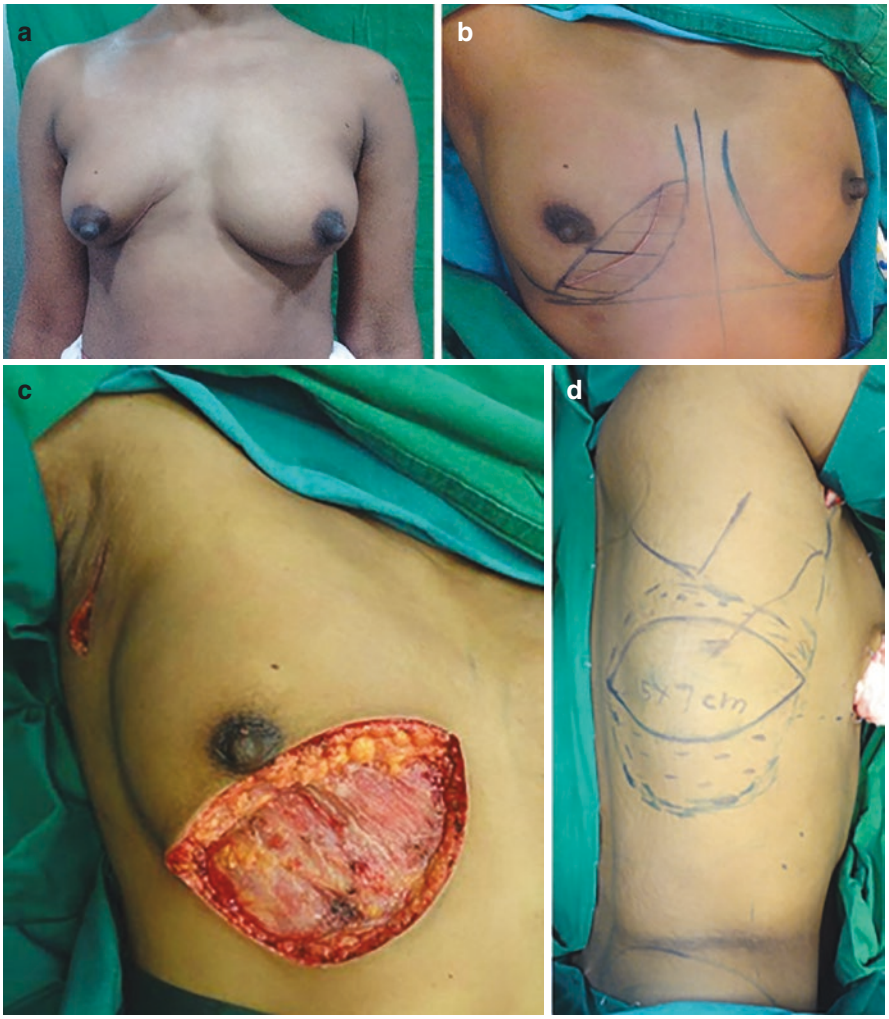


Fig. 22.18 LD myocutaneous flap for partial breast defect, (**a**) Deformed breast after excision, (**b**) Further scar revision required for margins, (**c**) Defect in lower inner quadrant, (**d**) Marking of the LD flap with intended fat harvest, (**e**) Harvested flap, (**f**) Flap rotated anteriroly into the defect, (**g**) LD flap skin island sutured in to defect, (**h**) Follow up

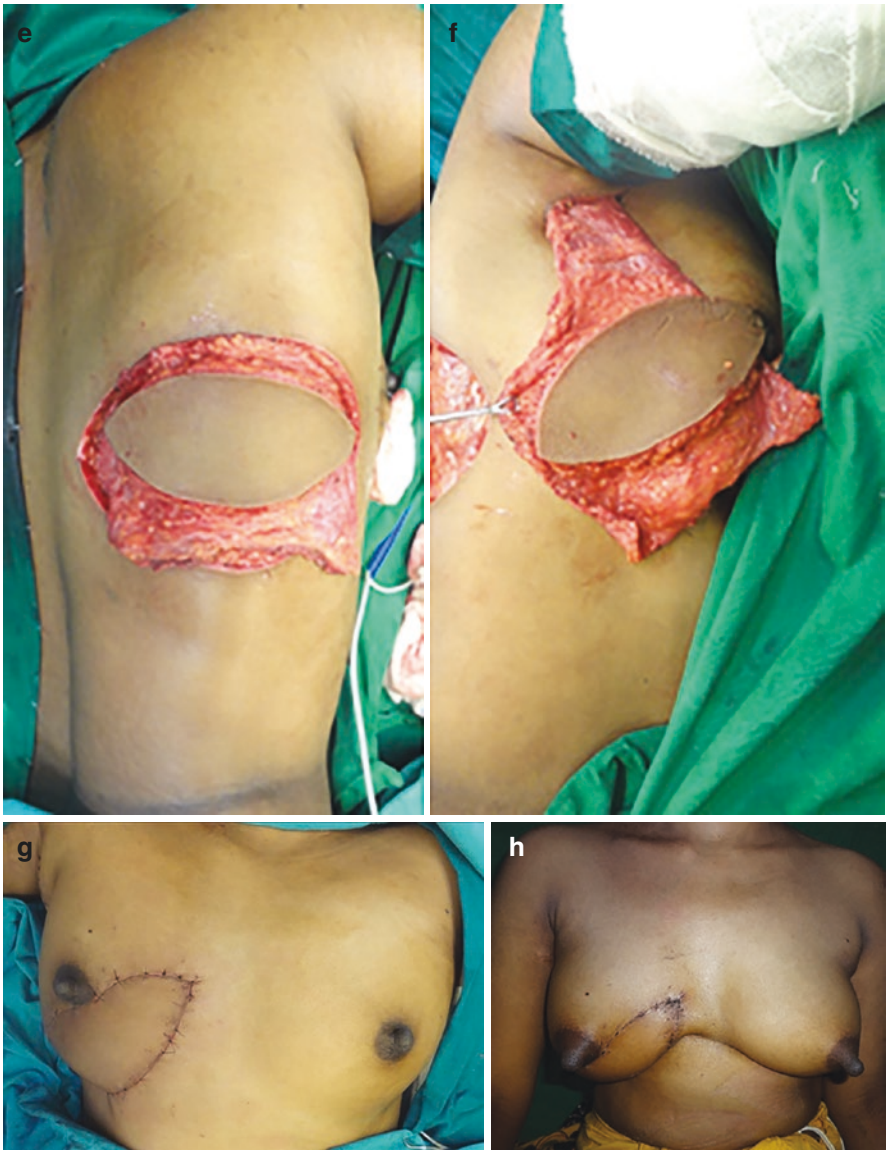


Fig. 22.18 (continued)

the muscle can be presumed to be safe vascularity wise, especially on the proximal two third of the muscle.

The transverse skin island at the level of the inframammary fold is the most used and gives the most concealed scar in Indian clothing. Only as much flap as needed should be harvested to limit donor site morbidity, most common being pain, persistent seroma formation and rarely dehiscence of suture line.

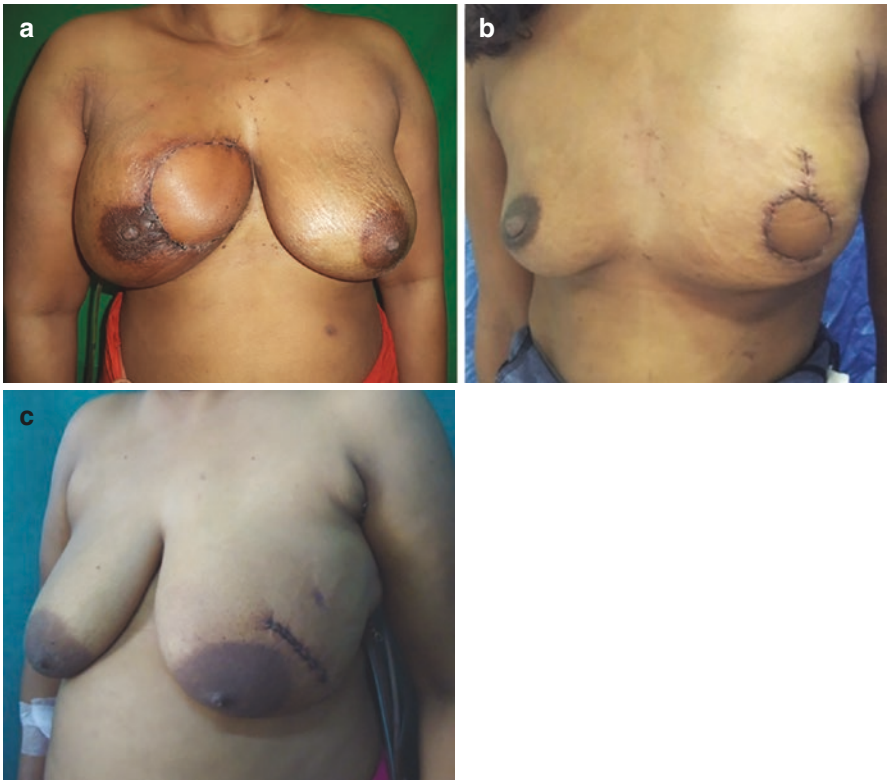


Fig. 22.19 LD flap reaches anywhere in the breast, (**a**) Inner quadrant, (**b**) Central quadrant, (**c**) Total flap deepithelised and buried for outer and central quadrant

The LD flap can reliably reach any quadrant of the breast safely Fig. 22.19. Cutting the tendinous insertion of LD into the humerus and ligating serratus muscle and chest wall branches gives extra length of the pedicle, allowing further reach and greater liberties in inset and contouring.

The vascular anatomy and innervation allow certain muscle preserving approaches. Segmental LD flap can be harvested based on one of the branches, preserving the innervation of the remnant muscle.

TDAP (Thoracodorsal Artery Perforator) Flap Can be harvested where the entire LD muscle and its innervation is spared, harvesting only the skin and fat as per requirement [32] Fig. 22.20. The vascularity of the remaining LD muscle is maintained by secondary segmental pedicles i.e., paraspinal and intercostal perforators. This offers a thinner flap of robust vascularity, amenable to contouring in all three dimensions with the muscle preserved and functional, reach is variable but the flap generally feasible for outer and central quadrant defects. It can also be used as a dermo-glandular turnover flap for peripheral outer quadrant defects with no skin requirement.

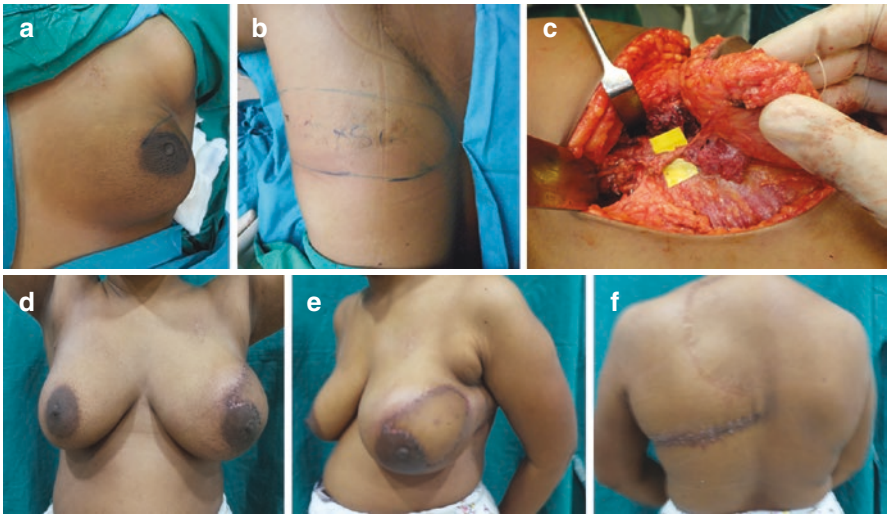


Fig. 22.20 TDAP flap for UOQ defect in a case of previous spinal surgery requiring LD muscle function for using crutches, (**a**) Recurrent IDC with scar, (**b**) Flap planned guided by the doppler signal, (**c**) Perforator dissected sparing the nerves, (**d**) Healed donor site, (**e** and **f**) Follow up

22.6.2 Other Perforator-Based Flaps: SEAP/LTAP/AICAP/LICAP

Some local perforator flaps are now popular [33]. Most of used variants of these are not true islanded perforator flaps but dermo glandular or glandular turnover, VY advancement or transposition flaps based on the supply of the perforators. The ones generally suitable for outer upper and outer lower quadrant are TDAP, LICAP (Lateral Intercostal Artery Perforator flap) and LTAP (Lateral Thoracic Artery Perforator flap), for lower inner quadrant SEAP (Superior Epigastric Artery Perforator flap) and AICAP (Anterior Intercostal Artery Perforator flap) for lower central and outer quadrant defects Figs. 22.21, 22.22 and 22.23. Most of these flaps do well when performed for defects at the edge of the breast mound, no skin replacement and only filler is needed. However, use of magnification becomes necessary while harvesting these true islanded perforator-based flaps and an initial learning curve may be steep.

22.7 Just Cover Needed

At least 30% patients in India present with locally advanced tumours where large skin resection is indicated. In some patients after mastectomy, primary closure of skin is not possible. A robust skin cover is still desired to ensure timely delivery of radiotherapy with a stable wound peri RT. In these patients, following options can be utilised depending on the donor site expendability and microvascular expertise available.

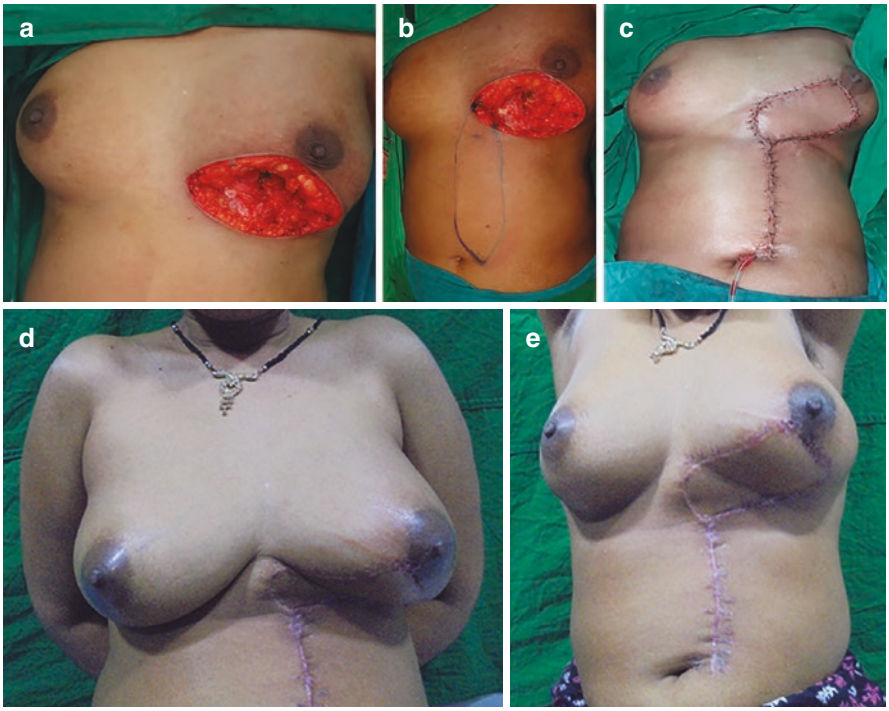


Fig. 22.21 SEAP flap, (**a**) Lower inner quadrant defect with injured LD pedicle (clock wise), (**b**) Flap planned around a robust audio Doppler signal and perforator visualisation from the defect, (**c**) flap harvested, inset with donor site primary closure, (**d** and **e**) Follow up after radiation

1. Latissimus Dorsi flap with a skin island. When a large skin island is needed the donor site might not close primarily and skin graft to the back might be needed Fig. 22.24. Large skin grafts to the back are troublesome to manage postoperatively. Only LD muscle with skin graft can also be utilised in rare cases where post-mastectomy radiation therapy is not indicated.
2. Free Anterolateral Thigh (ALT) flap offers an excellent donor site when large amounts of tissue are needed, up to half the circumference of the thigh can be harvested in the full length.
3. Pedicle TRAM, VRAM or free DIEP can also be utilised to cover these defects, especially when abdomen is not very thick but very pliable, allowing easy donor site closure.

22.8 Nipple-Areola Reconstruction

There is a plethora of local flap designs described for the reconstruction of the nipple. Most of them suffer from loss of volume with time especially when reconstruction is done from breast tissue or abdominal skin of the flap with low dermis content.

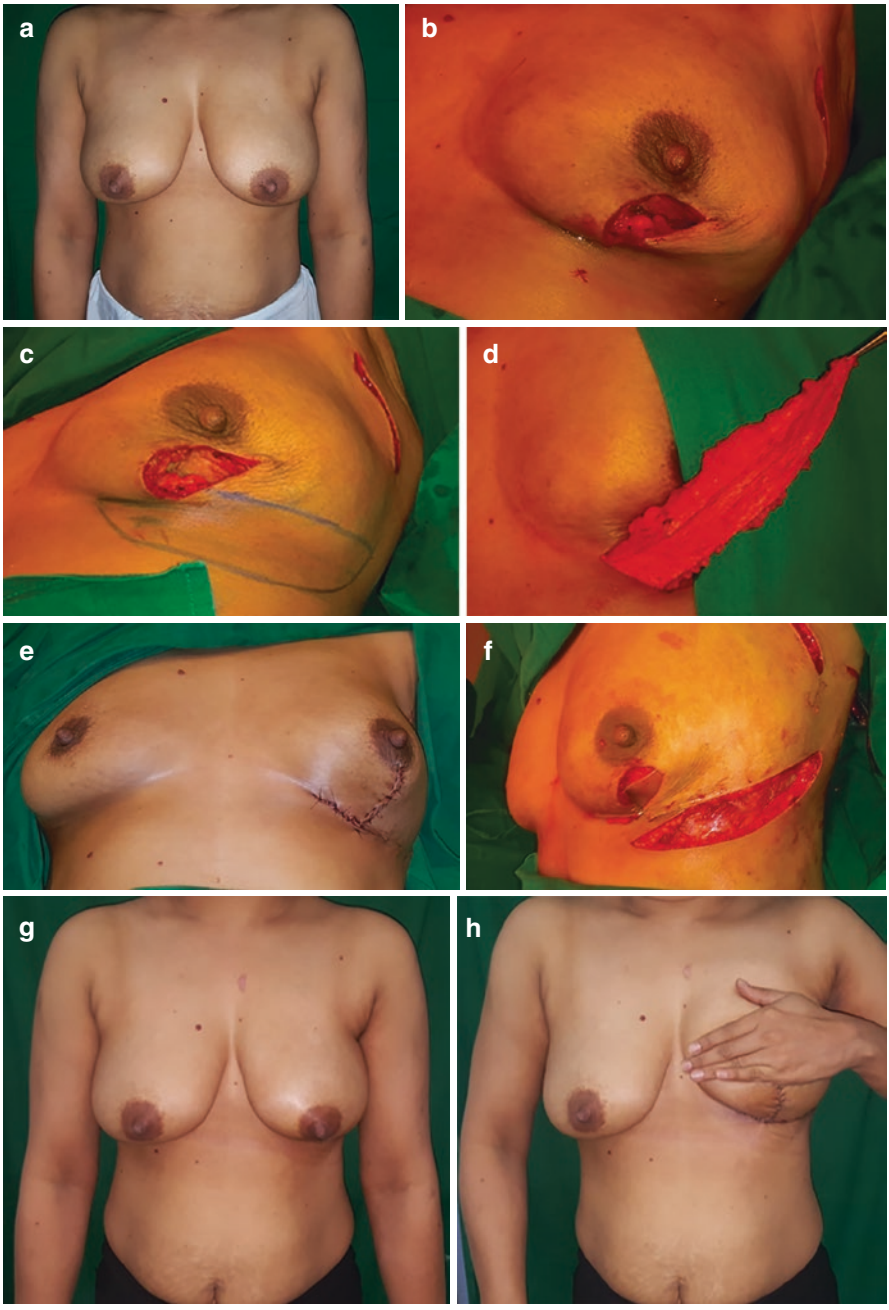


Fig. 22.22 AICAP flap (Anterior Intercostal artery perforator flap) (**a**) Preoperative, (**b**) Defect in lower central quadrant, (**c**) flap marked around doppler signal, (**d**) flap elevated and deepithelised, (**e**) flap moved in place, (**f**) flap sutured in place and skin closure, (**g** and **h**) post operative

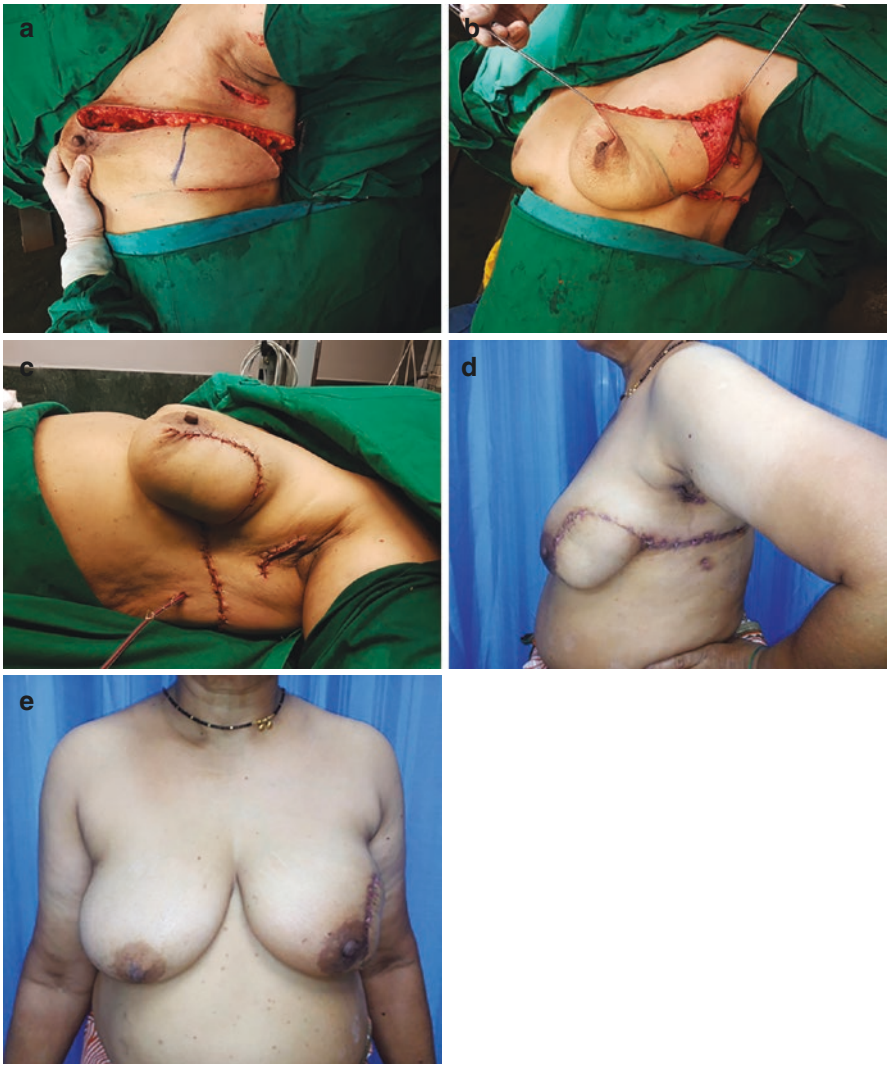


Fig. 22.23 Transposition flap for outer quadrant defect, (**a**) Outer quadrant defect with flap marking, (**b**) Transposition flap elevated and rotated, (**c**) Flap sutured in position and donor site closed, (**d** and **e**) Follow up images front and lateral views. Case courtesy, Dr. Shalaka Joshi Professor, Breast Services, Tata Memorial Centre, Mumbai

Even with use of dermis or cartilage fillers with flaps for nipple volume, long term results are not encouraging. LD flap with thick dorsal skin with higher dermal thickness does better in terms volume retention of the nipple. Authors recommend a simple modified C-V flap design to reconstruct the nipple [34] Fig. 22.25.

Nipple reconstruction can also be done by a nipple sharing procedure. Part of the opposite nipple, if large enough, is harvested in full thickness and grafted on the breast mound.

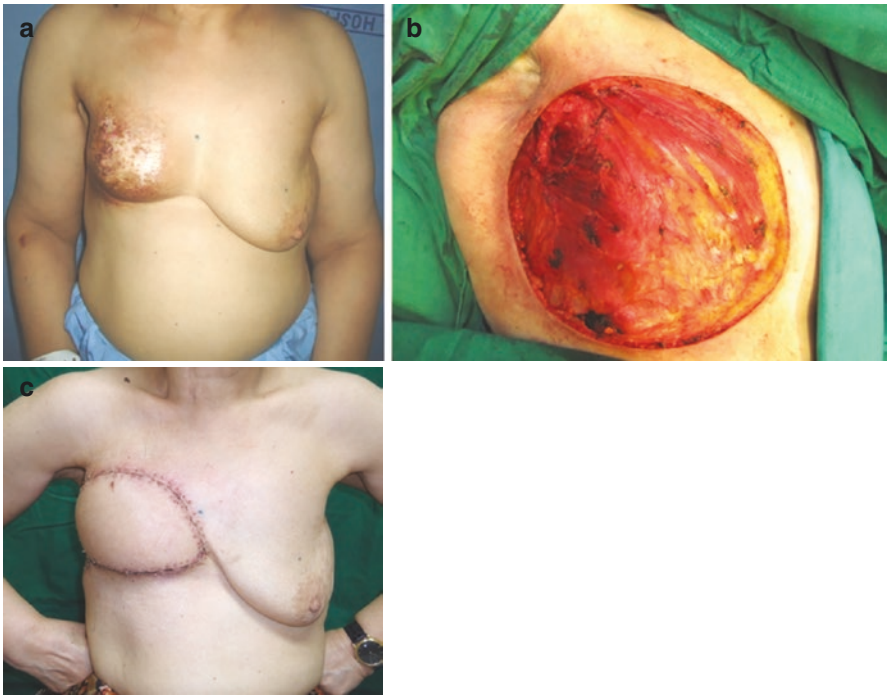


Fig. 22.24 LD Myocutaneous flap for chest wall coverage (clockwise), (**a**) Recurrent carcinoma breast after surgery and radiation, (**b**) Skin defect after excision, (**c**) LD myocutaneous flap after inset

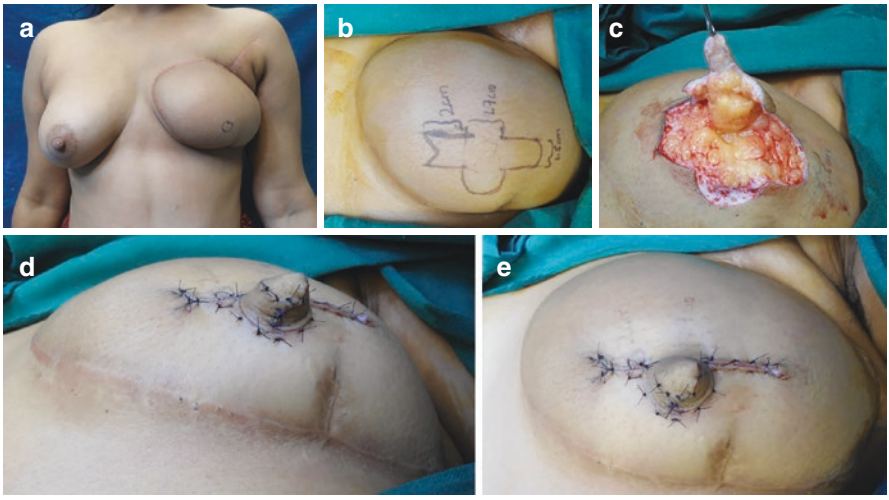


Fig. 22.25 Nipple reconstruction with CV flap (clock wise), (**a**) Nipple marking in standing position, (**b**) Markings of the CV flap, (**c**) Elevated flap, note fat in the centre of the flap, (**d** and **e**) the three flaps, two wings and lid sutured in position

Areola reconstruction can be done with grafting of opposite areola if a symmetrising procedure is done on the opposite side or grafting skin of darker matching complexion from medial thigh or the labia. Tattooing of the areola produces excellent results in good hands, even an illusion of nipple can be created by good expert tattoo artist. Some patients opt for an artistic tattoo instead of NAC to camouflage the deficit!

22.9 Radiation and Breast Reconstruction

Radiotherapy is an integral part of Breast Conservative Therapy (BCT). With mastectomy too, radiation is often required depending on tumour size, skin involvement and nodal status. Radiation affects the reconstructed and the conserved part of the breast. The changes might range from minimal skin colour and texture changes to extremes of volume loss, a stony hard breast, wound dehiscence, and very rarely, osteoradionecrosis of ribs. The severity of manifestations is dependent on the vascularity of the conserved and reconstructed element of breast, radiotherapy dosage and technique employed and individual patient susceptibility. The skin can get hyperpigmented, develop a leathery texture and contract to a variable degree. The parenchyma and fat of breast can have ischemic changes rarely progressing to necrosis manifesting as discharging sinuses, abscess, or firm to stony texture of 'fat necrosis'. Any shortcoming in the vascularity of the fat and parenchyma of reconstructed and conserved breast often confounds and amplifies the ill effects of radiation. From a decision-making point of view, flap or procedure choices must be made which are based on robust vascularity, 'highly unlikely to have a problem' taking precedence over 'might just work'. Modern methods of radiotherapy delivery and hypo fractionated regimens combined with predictability in reconstruction aided by a preoperative imaging and a wide array of donor sites have resulted in freeing reconstructive choices from the fear of radiation to a large extent.

Secondary breast reconstruction in a radiated field can also be safely done. The extra skin requirement and radiated vessels sometimes pose a technical challenge but are rarely a deterrent. Once a reconstruction has been successfully done the results are stable and predictable over the long term, as there is no further radiation.

Breast implant-based reconstruction and radiation have a way more troubled relationship. Robust envelopes of breast skin, muscle or a flap need to be preserved or reconstructed to protect the implants. The long-term complications especially capsular contracture is much higher.

22.10 Indian Perspective on Breast Reconstruction

In the authors' experience, breast reconstruction in India has some peculiar challenges. Breast cancer has now surpassed cancer of the cervix and oral cavity squamous cell carcinoma to be the most common cancer of India [35]. Because of the middle heavy population pyramid of the country, majority of the patients presenting with breast cancer are in late 40s or early 50s unlike the West where the median age at presentation is 60. The younger patients are more likely to present with advanced

and aggressive disease necessitating mastectomy. Offering them reconstruction can substantially improve their quality of life. Reconstructive surgeons need to keep up with the pace of increasing number of breast cancer patients in urban India.

The idea that breast can be reconstructed after removal is met with surprise by few patients. The awareness about reconstruction is still low, but in the era of internet, google searches, multiple social media, and digital platforms this deficiency should be bridged in the future. The primary surgeons too often presume patients non inclination to reconstruction.

The decision of reconstruction is often taken by or is influenced by the spouse or other family members. Some patients leave the ball in the cancer or reconstructive surgeons' court. The authors recommend counselling until the patient voluntarily takes an informed decision regarding reconstruction. An unmotivated patient with unfortunate complication is a very adverse situation to be in!

In the authors experience, our patients do choose reconstruction and a symmetrising procedure too, when offered early, counselled appropriately, given some time to decide and communication is concordant between the cancer and reconstructive surgeon. They also respond best when they can interact with long term follow up cases who have undergone a similar procedure. The acceptance for autologous reconstruction and scars is also high. Cost is often the deciding factor. Surprisingly in India autologous reconstruction is often cheaper in the long term than implant-based reconstruction.

22.11 Conclusion

Breast reconstruction and oncoplastic breast surgery in the current era are desired and safe. The earliest attempts at breast reconstruction included transferring a thigh lipoma to the chest! We have evolved to a point where implants can substitute for breast tissue or tissue from a range of donor sites in the body can be harvested with minimal donor site morbidity and transferred with predictability using microvascular skills. The future might be in lipofilling or bioprinted breasts! [36]. The reconstructive surgery skill set availability, interaction and cooperation between the reconstructive and cancer surgeon are vital in delivering reconstructive services to patients. Every woman undergoing surgery for breast cancer has a right to be offered the best possible reconstruction options available and the free will to choose or refuse it. Its duty of the doctors involved to facilitate this.

References

1. Zehra S, Doyle F, Barry M, Walsh S, Kell MR. Health-related quality of life following breast reconstruction compared to total mastectomy and breast-conserving surgery among breast cancer survivors: a systematic review and meta-analysis. Breast Cancer. 2020;
2. Zhang C, Hu G, Biskup E, Qiu X, Zhang H, Zhang H. Depression induced by Total mastectomy, breast conserving surgery and breast reconstruction: a systematic review and meta-analysis. World J Surg. 2018;42(7):2076–85.

3. Clough KB, Ihrai T, Oden S, Kaufman G, Massey E, Nos C. Oncoplastic surgery for breast cancer based on tumour location and a quadrant-per-quadrant atlas. Br J Surg. 2012;99(10):1389–95.
4. Audretsch W, Rezai M, Kolotas C, et al. Tumour-specific immediate reconstruction in breast cancer patients. Semin Plastic Surg. 1998;11:71–99.
5. Macmillan RD, McCulley SJ. Oncoplastic breast surgery: what, when and for whom? Curr Breast Cancer Rep. 2016;8:112–7.
6. El-Sabawi B, Sosin M, Carey JN, Nahabedian MY, Patel KM. Breast reconstruction and adjuvant therapy: a systematic review of surgical outcomes. J Surg Oncol. 2015;112(5):458–64.
7. Ashraf AA, Colakoglu S, Nguyen JT, Anastasopulos AJ, Ahmed BS, Ibrahim MS, Yueh JH, Lin SJ, Tobias AM, Lee BT. Patient involvement in the decision-making process improves satisfaction and quality of life in postmastectomy breast reconstruction. J Surg Res. 2013 September;184(1):665–70.
8. Scurci S, Parecco J, De La Cruz L, Chatterjee A. Abstract P8: Nationwide cost comparison of autologous vs implant-based Postmastectomy reconstruction. Plast Reconstr Surg Glob Open. 2017;5(4 Suppl):107.
9. Daniels AU. Silicone breast implant materials. Swiss Med Wkly. 2012;142:w13614.
10. Swanson E. Dual plane versus subpectoral breast augmentation: is there a difference? Plast Reconstr Surg Glob Open. 2016;4(12):e1173.
11. Robertson SA, Jeevaratnam JA, Agrawal A, Cutress RI. Mastectomy skin flap necrosis: challenges and solutions. Breast Cancer (Dove Med Press). 2017;9:141–52.
12. Iwuagwu FC, Frame JD. Silicone breast implants: complications. Br J Plast Surg. 1997;50(8):632–6.
13. Berry MG, et al. The PIP mammary prosthesis: a product recall study. J Plastic Reconstr Aesthet Surg. 2012;65(6):697–704.
14. Jones JL, Hanby AM, Wells C, et al. Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL): an overview of presentation and pathogenesis and guidelines for pathological diagnosis and management. Histopathology. 2019;75(6):787–96.
15. Massenburg BB, Sanati-Mehrizy P, Ingargiola MJ, Rosa JH, Taub PJ. Flap failure and wound complications in autologous breast reconstruction: a National Perspective. Aesthet Plast Surg. 2015 Dec;39(6):902–9.
16. Hartrampf CR, Scheflan M, Black PW. Breast reconstruction with a transverse abdominal island flap. Plast Reconstr Surg. 1982 Feb;69(2):216–25.
17. Jones G. The pedicled TRAM flap in breast reconstruction. Clin Plastic Surg. 2007;34(1):83–104.
18. Uroskie TW, Colen LB. History of breast reconstruction. Semin Plast Surg. 2004;18(2):65–9.
19. Nahabedian M. Defining the "gold standard" in breast reconstruction with abdominal tissue. Plastic Reconstr Surg. 2004;114:804–6.
20. Koshima I, Soeda S. Inferior epigastric artery skin flaps without rectus abdominis muscle. Br J Plast Surg. 1989;42(6):645–8.
21. Masia J, Clavero JA, Larrañaga JR, Alomar X, Pons G, Serret P. Multidetector-row computed tomography in the planning of abdominal perforator flaps. J Plast Reconstr Aesthet Surg. 2006;59:594–9.
22. Gurtner GC, Jones GE, Neligan PC, et al. Intraoperative laser angiography using the SPY system: review of the literature and recommendations for use. Ann Surg Innov Res. 2013;7(1):1.
23. Santanelli F, Longo B, Cagli B, Pugliese P, Sorotos M, Paolini G. Predictive and protective factors for partial necrosis in DIEP flap breast reconstruction. Ann Plastic Surg. 2015 January;74(1):47–51.
24. Chang DW, Youssef A, Cha S, Reece GP. Autologous breast reconstruction with the extended latissimus dorsi flap. Plast Reconstr Surg. 2002;110(3):751–61.
25. Park JE, Alkureishi LW, Song DH. TUGs into VUGs and friendly BUGs: transforming the Gracilis territory into the best secondary breast reconstructive option. Plast Reconstr Surg. 2015;136(3):447–54.
26. Buchel EW, Dalke KR, Hayakawa TE. The transverse upper gracilis flap: efficiencies and design tips. Can J Plast Surg. 2013;21(3):162–6.

27. Allen RJ, Lee Z-H, Mayo JL, Levine J, Ahn C. The Profunda Artery Perforator (PAP) flap experience for breast reconstruction. Plast Reconstr Surg. 2016;138(5):968–75.
28. Tuinder SMH, Beugels J, Lataster A, de Haan MW, Piatkowski A, Saint-Cyr M, van der Hulst RRWJ, Allen RJ. The lateral thigh perforator flap for autologous breast reconstruction: a prospective analysis of 138 flaps. Plast Reconstr Surg. 2018 February;141(2):257–68.
29. Granzow JW, Levine JL, Chiu ES, Allen RJ. Breast reconstruction with gluteal artery perforator flaps. J Plast Reconstr Aesthet Surg. 2006, June;59(6):614–21.
30. Hamdi M, Antoniazzi E. Lumbar artery perforator flap for breast reconstruction. In: Mayer H, editor. Breast reconstruction. Cham: Springer; 2020.
31. Chatterjee A, Dayicioglu D, Khakpour N, Czerniecki B. J. Oncoplastic surgery: keeping it simple with 5 essential volume displacement techniques for breast conservation in a patient with moderate- to large-sized breasts. Cancer Control. 2017;24(4):1073274817729043. https://doi.org/10.1177/1073274817729043.
32. Hamdi M, Van Landyut K, Hijjawi JB, Roche N, Blondeel P, Monstery S. Surgical technique in Pedicled Thoraco dorsal artery perforator flaps: a clinical experience with 99 patients. Plast Reconstr Surg. 1632;121:2008.
33. Van Landuyt K, Hamdi M, Blondeel P, Monstrey S. Autologous breast augmentation by pedicled perforator flaps. Ann Plast Surg. 2004;53(4):322–7.
34. Nimboriboonporn A, Chuthapisith S. Nipple-areola complex reconstruction. Gland Surg. 2014;3(1):35–42.
35. Globocan 2018: India fact sheet.
36. Simonacci F, Bertozzi N, Grieco MP, Grignaffini E, Raposio E. Autologous fat transplantation for breast reconstruction: a literature review. Ann Med Surg. 2016, December;12:94–100.

Non-Surgical Management of Metastatic Breast Cancer and Palliative Care

23

Firuza Patel and Suresh Chander Sharma

23.1 Introduction

The definition of advanced breast cancer is not uniform across centres as it is a very heterogeneous group of patients with a varied spectrum of presentation. However it can broadly be divided into three categories:

1. **Locally Advanced Inoperable or Recurrent Breast Cancer**—These include T4,N 0-3, M0, tumours and locally recurrent tumour after curative primary therapy has been undertaken earlier. First group consists of T4 lesions. Advanced patients who have fixed local disease to chest wall and/or multiple skin nodules or those with ulcerated and bleeding lesions (Fig. 23.1) with and without fixed axillary lymph nodes or those with supraclavicular or internal mammary lymph node metastases. This group constitutes ≤10% in the west but 10–15% of total cases in our country.
2. **Metastatic breast cancer**—Second group of advanced patients are those who present with distant metastatic disease with and without primary disease in the breast or local recurrent disease. 10% of patients in USA [1] have distant metastases at presentation and it is about 20% in our country. Rest of the patients are

Firuza Patel, MD (✉)
Former Professor, Department of Radiotherapy, PGIMER, Chandigarh, India

Mentor and In-charge, Chandigarh Hospice and Palliative Care Service, Chandigarh, India
e-mail: firuzapatel@gmail.com

Suresh Chander Sharma, MD
Former Senior Professor and Head, Department of Radiotherapy, PGIMER, Chandigarh and MM Institute of Medical Sciences, Mullana, Ambala, Haryana, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_23

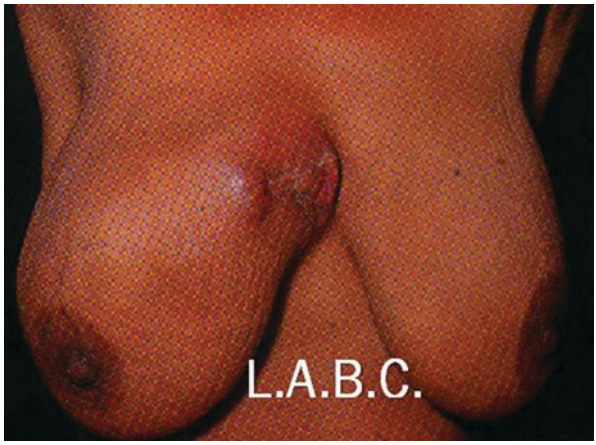


Fig. 23.1 Locally advanced case of carcinoma breast with direct skin invasion and ulceration (Case of SMB)

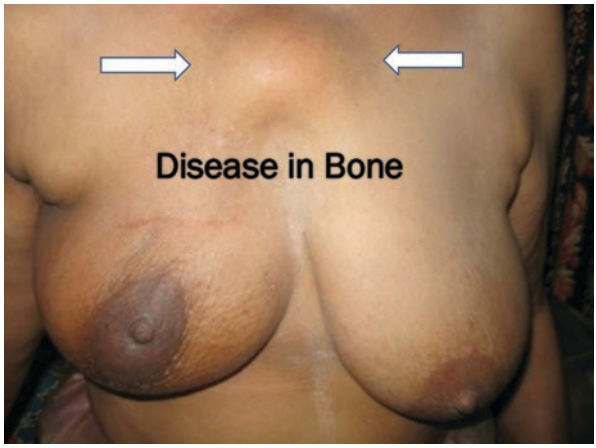


Fig. 23.2 Metastasis in sternum about 4 years following breast Conservative Surgery (Case of SMB)

those who develop metastases in the follow up after primary curative therapy given earlier. Rate of metastasis is less than 20% in early stages and up to 50% in advanced stages of disease [2]. Common sites of metastases are bones, (Fig. 23.2) lungs, liver, opposite breast, lymph nodes and brain; however, sporadically metastases have been seen at any site or organ in the body (Fig. 23.3) shows multiple subcutaneous metastases, following modified radical mastectomy about 7 years earlier. Such small sized secondaries are usually missed on physical examination and are also not picked up by usual investigations. Almost all patients are treated for palliation as chance of long term survival and cures are low in metastatic breast cancer.

3. **Inflammatory carcinoma breast:** This type of cancer is rare but is highly aggressive and carries poor prognosis in spite of administration of multimodality treatment. Only palliation is achieved in most of the cases after systemic and local treatment.

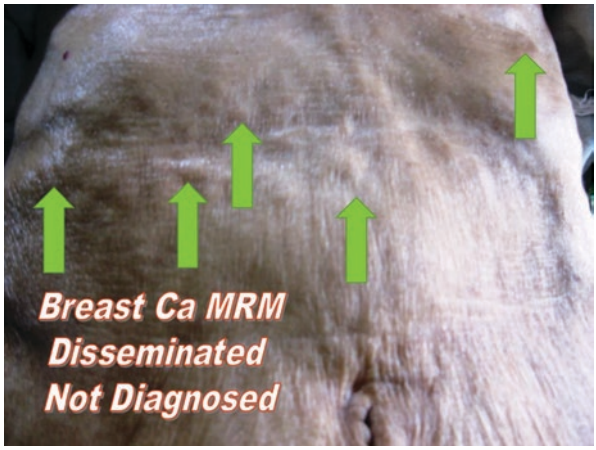


Fig. 23.3 Multiple subcutaneous metastatis (Case of SMB)

23.2 Investigative Work Up of Advanced Metastatic Patient

Symptoms and signs of advanced metastatic disease will depend on site of disease presentation. Locally advanced patients may present with symptoms related to disease in the breast and those with metastases will have symptoms and signs related to the site of metastasis. Advanced breast cancer patients are investigated to assess exact extent of dissemination on following lines.

1. **Blood Tests**: Hemogram to assess general status, kidney function tests to assess status of kidneys and liver function tests to assess involvement of liver.
2. **X-ray chest** to rule out or detect chest metastases
3. **Ultrasound of whole abdomen** to assess involvement of liver, ovaries abdominal lymph nodes and peritoneum.
4. **Bone Scan** to assess bone metastases, but now done only if PET-Scan is not available
5. **CT-Scan** of Lung, Liver, Spine or Brain to confirm suspected metastases and also to assess volume of disease which has bearing on response to treatment.
6. **MRI** is ideal for detecting and confirming brain and spinal metastases.
7. **FNAC/Core biopsy/excision Biopsy** of primary in the breast for confirmation only in those patients who present with metastases. All others usually have biopsy confirmation at first presentation.
8. **Marker studies**: Ideally all patients should have ER, PR and Her2 neu testing that help in selection of appropriate systemic therapy. Even if their status is known but still they should have marker studies again on metastatic tissue as there may be a change in their status. Appropriate molecular marker may be considered for testing if targeted therapy/immunotherapy related to that target is considered.
9. **PET—CT Scan** is must in advanced breast cancer to detect metastasis (Fig. 23.4) or sites of subclinical metastases and to assess response to treatment and is also important in the follow up of patient.

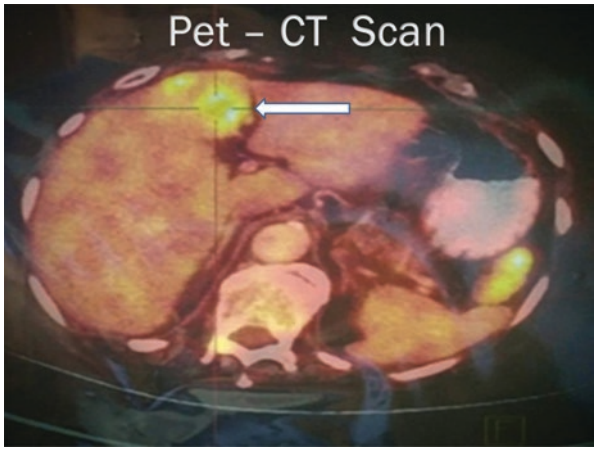


Fig. 23.4 Metastasis in liver seen on Pet-CT -Scan (Case of SMB)

23.3 Treatment of Advanced Disease

Advanced metastatic breast cancer is a heterogeneous local and systemic disease. It requires an individualized approach for its treatment. Aim of treatment is

(a) To get maximum control of symptoms.
(b) To prevent serious complications.
(c) To increase survival without compromising quality of life.

Systemic therapy with either Cytotoxic drugs and/or Hormones and/or Molecular/Targeted drugs and/or Immunotherapy are treatment of choice in advanced metastatic carcinoma breast, however, multimodality approach is more appropriate to get best control, palliation and survival of these patients. Judicious combination of systemic therapy as well as local therapy with radiation and/or surgery when indicated is the best approach. Those patients who are too advanced for any specific therapy are best treated with palliative care for their pain and symptom control so that they can die with dignity (Table 23.1).

23.3.1 Systemic Therapies

23.3.1.1 Chemotherapy

Chemotherapy treatment of metastatic/recurrent/locally advanced breast cancer is highly challenging more so when patient of early stage disease have already received adjuvant chemotherapy. Such patients already have low tolerance to chemotherapy and also have problem of resistance. Breast cancer is a chemo-sensitive cancer. Number of cytotoxic agents are active against breast cancer [3]. First line drugs are—Methotrexate, 5-Flurouracil, Cyclophosphamide, Anthracyclines (Adriamycin or Doxorubicin, Lysomal Doxorubicin, and Epirubicin), Taxanes (Paclitaxel, Nano-Paclitaxel and Docetaxel). Second line drugs are—Venorelbine, Vinblastin,

Table 23.1 Shows different modalities of treatment for advanced metastatic breast cancer

1. Systemic Therapies
Chemotherapy
Hormone therapy
Molecular or Targeted therapy
Immunotherapy
2. Local Therapies
Radiotherapy
Surgery
3. Supportive Therapies
4. Palliative Care and Symptom Management

Capcetabine, Gemcitabine, Cisplatin, Carboplatin, Paclitaxel, Etoposide, Mitoxantron. Anti Her2 neu agents are Trastuzumab and Pertuzumab.

Both single drug or combination chemotherapy are practiced in advanced metastatic disease. Response to single cytotoxic therapy is 30–40% and 5–15% for Trastuzumab alone but 60–80% for combination chemotherapy; and hence combination chemotherapy is preferred. Combination chemotherapy will give more number of complete or partial responses and improves quality of life of more number of patients compared to single drug therapy. Overall survival is not any different in locally advanced and metastatic disease when treated by either single drug or combination chemotherapy, hence some advocate use of single drug to reduce toxicity to the patient. Older patients with poor performance status and previously heavily treated patients are candidates for single drug therapy. Rest all should have combination chemotherapy.

Large number of combinations of above mentioned drugs are available both for first and second line chemotherapy. Line of chemotherapy depends on previous use of adjuvant chemotherapy, ER,PR positivity, Her2 neu positivity (20–30% are positive) and triple negative status of breast cancer.

First Line Chemotherapy

- Patients who present with metastases or recurrence or locally advanced inoperable cancer and have not received any chemotherapy previously are given first line chemotherapy which gives best response and control of disease.
- Even those patients who have received adjuvant chemotherapy but have relapsed after long disease free interval of 4–5 years or more can also be given same first line chemotherapy with good response and survival.
- Various regimen are CMF, AC, FAC/CAF, AP, AD or TAC ± Trastuzumab if Her2 is positive [4]. Anthracycline and Taxol based regimens are preferred as response rate is as high as 80%. 5–15% of patients are likely to achieve complete remission leading to long disease free survival [5].
- Same regimens are useful in triple negative cancer also but combination of Gemcitabine plus Carboplatin/Cisplatin has slight edge over all other regimens [6].
- Triple negative disease which is common in India, carry poor prognosis and it is highly challenging to treat this disease entity [7]

Second Line Chemotherapy

- All those patients who have failed after first line therapy or have relapsed within 2–3 years of primary therapy including adjuvant chemotherapy are given second line chemotherapy.
- Various combination of second line drugs have been developed. More than 30 combinations of various second line drugs with each other have been developed and used by different institutions or workers [8–14].
- The response to second line therapy is 30–60%, very few patients achieve complete remission and have low progression free and overall survival.
- Trustuzumab is added to these combinations if patient is Her2 neu positive. The response rates vary from 30% to 80% for the patients who receive Trastuzumab with different drug combinations [15, 16].

Third Line Chemotherapy

- Those patients who fail with second line chemotherapy, may be considered for third line chemotherapy if they are in good general condition and have good haematological tolerance and are willing for the same.
- Tolerance to third line therapy is likely to be poor and will have high chance of toxicity. Combination of either of these drugs can be used—Etoposide, Vinblastin, Mitomycin, nab Paclitaxel and Mitoxantron. These patients requires support of bone marrow rescue factors. Response rates are poor with very low PFS and OS.
- These patient may also be considered for Stem cell or autologous transplant but results are poor and carry high toxicity and even mortality.

23.3.2 Targeted Therapy

Various molecular pathways are involved in the proliferation of tumour. Blocking one or more of these pathways with drugs can achieve regression of tumour. Various drugs have been developed which are used for treatment of advanced breast cancer as described below.

23.3.2.1 Anti- Her2 neu Therapy

20–30% patient of breast cancer show amplification and overexpression of Her2 neu oncogene. Its positivity signifies poor prognosis. Recombinant humanized monoclonal antibody has been developed against Her2 neu oncogene and used for treatment of breast cancer both in adjuvant and therapeutic setting in positive patients and give better control and survival of breast cancer [17, 18]. First drug was Trastuzumab and second is Partuzumab. Both are in clinical use. These are always used along with chemotherapy. Dosage schedules are as below;

Trastuzumab- Initial dose of 4 mg/kg IV in 90 min infusion followed by 2 mg/kg IV in 60 min infusion weekly; or initial dose of 8 mg/kg IV in 90 min infusion followed by 6 mg/kg IV in 90 min infusion every 3 weeks.

Pertuzumab- 840 mg initial dose IV in 90 min infusion followed by 420 mg IV in 60 min infusion every 3 weeks.

Addition of Trastuzumab to first line chemotherapy in advanced metastatic breast cancer adds to response rate, progression free survival and overall survival [15, 16, 19]. Combination of trastuzumab and Pertuzumab with Docetaxel gives better control rate of disease with no added toxicity in metastatic disease [20]. Targeted therapy in metastatic disease is continued till progression of disease. In those few who achieve CR, targeted therapy may be continued for 1 year.

23.3.2.2 Vascular Endothelial Growth Factor (VEGF)

Bevacizumab (Avastin)- is a, a targeted VEGF molecule which was approved in February 2008 by the U.S. Food and Drug Administration (FDA) in combination with Taxol—Paclitaxel (weekly Paclitaxel—90 mg/m^2 on days 1, 8, and 15 every 4 weeks alone or in combination with Bevacizumab—10 mg/kg on days 1 and 15 to treat metastatic HER2-negative breast cancer who haven't yet received chemotherapy for metastatic breast cancer. Approval was withdrawn in 2010 because of its safety concern.

Further studies done showed that toxicity profile of Bevacizumab when used with Paclitaxel is similar to other combination chemotherapy [21], hence its approval was restored. Bevacizumab has increased progression free survival but has not increased overall survival [22, 23].

23.3.2.3 Epidermal Growth Factor Receptor and Their Inhibitors

45% of breast cancer has EGFR positivity. Cetuximab, Gefitinib, Erlotinib, Neratinib, Afatinib have been used in metastatic breast cancer. Use of these molecules have shown good response in combination with chemotherapy and are still under investigations.

23.3.2.4 Dual Inhibitors of EGFR and HER2

Lapatinib in combination with vinorelbine showed moderate efficacy in metastatic breast cancer patients with over expression of HER2. Combination of lapatinib plus trastuzumab showed higher response in metastasis to brain compared with a single drug treatment [24].

23.3.3 Immunotherapy

Combination of nab Paclitaxel with Atezolizumab, an immunotherapy agent, in the treatment of PD-L1 positive cases of metastatic breast carcinoma has shown better response and median progression free survival compared to nab Paclitaxel alone. Immuno check point inhibitors—Atezolizumab and Pembrolizumab have also shown good response as monotherapy.

Various other molecular drugs like PARP and AKT inhibitors, CDK 4/6 PI3K and mTOR inhibitors are also under investigations for treatment of advanced metastatic breast cancer. CDK 4/6 inhibitors like Palbocicli, Ribociclib and Bemaciclib have shown better control of disease when used with hormone therapy in postmenopausal women [25].

23.3.4 Hormone Therapy (HT)

Breast cancer is hormone dependent. Hormone receptor status determines the use of hormone therapy. Patients who are ER, PR positive respond to various types of hormone manipulations. On an average 30–45% of breast cancers show receptor positivity but postmenopausal and elderly women have higher positivity up to 75%. Response to hormone therapy varies from <10% in ER, PR negative to 70–75% in ER PR positive patients [26, 27]. Patients with ER value of >30 fmol/mg have response rate of ≥70%.

Hormone therapy is used if both ER and PR or even if any one of them is positive. ER PR should be done before starting any treatment. ER PR status is not changed by either chemo or surgery but biology of disease itself can change it during course of this disease.

Hormone therapy is a cytostatic treatment but produce good response and regression of breast cancer but may not eradicate it. It is least toxic therapy.

Hormone therapy is used as adjuvant in early breast cancer but as therapeutic agent in advanced metastatic cancer. In advanced metastatic cancer it can be used either alone or in combination with chemotherapy or targeted therapy, either concurrently or sequentially.

Goal of hormone therapy in advanced metastatic disease is to reduce burden of disease, improve symptoms with fewer toxic effects. Modern day hormone therapy can produce better progression free survival and it can also add to overall survival. Few of the patients may be cured but majority of them will achieve good palliation only. General impression is that all patients with advanced metastatic disease should be treated primarily with chemotherapy but hormone therapy is indicated as primary therapy in all those patients who are ER PR positive with bone metastases or soft tissue disease and are postmenopausal and elderly with long latent period of more than 2 years and had previous response to hormone therapy. All others should receive chemotherapy more so if they have visceral metastases and are young. Two types of patients are seen. One who have already received adjuvant hormone therapy or those who have not, which determines the type of hormone therapy to be given to a patient.

In olden days ablative procedures like Bilateral Ophrectomy, Bilateral Adrenalectomy or Hypophysectomy were practiced as hormonal therapies in metastatic breast cancer. These are practised no more except B/L Ophrectomy which is done some time in metastatic disease along with oral drug therapy in very young pre-menopausal women who have to be ER & PR positive.

Large number of drugs have been developed for hormone therapy over the years. Their indications and dosage are discussed below:

(a) Antiestrogens or Select Estrogen Receptor Modulators (SERMS):
    (i) Tamoxifen: This is most commonly used drug. It lowers the estrogen levels and blocks the estrogen receptor. It is first line drug for both premenopausal and postmenopausal patients with ER PR positivity in advanced metastatic breast cancer. It can be used in combination with chemotherapy

or other hormones either concurrently or sequentially. It is continued till progression of disease. Response rate varies from 15% to 53% in receptor positive patients in different series reported in the literature [28]. Tamoxifen with oophorectomy in premenopausal women may give better control. Median duration of response is 2.5 to 36 months when used alone. Important side effects are hot flashes, weight gain, vaginal bleeding, hypercalcaemia, endometrial carcinoma. Dose: 20 mg P.O. O.D.

(ii) Toremifene: It is less potent than Tamoxifen but is useful as second line therapy in patients treated previously with adjuvant Tamoxifen [29] Dose: 60 mg P.O., O.D.

(iii) New Generation SERMS: Include Raloxifene (200–300 mg per day) and Arzoxifene (20 or 50 mg per day) are still under investigations and may be available in future.

(b) Aromatase Inhibitors (AIs): They are first line therapy in advanced metastatic receptor positive breast cancer in post-menopausal women. The commonly used drugs are Letrazole, Anastrazole and Exmestane. Large number of studies have shown that AIs are superior to Tamoxifen in postmenopausal women and all AIs are equally effective. AIs give better response and survival compared with Tamoxifen and are of choice in postmenopausal women. AI are not useful in premenopausal women as they fail to block ovarian estrogens. They act on estrogens produced by adrenal or from fat source which are sources of estrogens in postmenopausal women. Combination of Letrazole with Tamoxifen have also shown superior results. Drugs are used till progression of disease. Toxicity profile is similar to Tamoxifen except that the development of uterine cancer is supposed to be less with AIs. Any of following AI drugs can be used. Dosage of these drugs are as follows.

(i) Letrazole—2.5 mg P.O.,O.D.

(ii) Anastrazole—1 mg P.O, O.D.

(iii) Exmestane—25 mg P.O,O.D.

(c) Lutenizing Hormone Releasing Hormone (LHRH): It produces reversible chemical castration. It is used in premenopausal or perimenopausal women as second line therapy in metastatic bone disease. Response rate is 39% this drug is usually used when Tamoxifen fails.

Drug and dosage is: Gosereline -Dose 3.6 mg S/C every 4 weeks.

Other two LHRH drugs are Buserelin and Leuprolide but are not in common use.

(d) Additive hormone therapies:

Progestines: Magesterol Acetate and Medroxy progesterone acetate are most commonly used in metastatic breast cancer in post-menopausal women as second line. Progestin can give response up to 27% with complete remission of 5%. It is continued till progression of disease. Dosage is as follows:

Megesterol acetate—160 mg P.O. O.D.

Medroxyprogesterone acetate—1000 mg P/O/, O.D.

Estrogens: Diethyl estradiol and Ethinylestradiol is effective in advanced breast cancer as third line therapy. Dose of 15 mg PO, OD is useful. It can give response of 65% in ER PR positive patients. 10% can have flair of disease.

Androgen: Testosterone and other related drugs have been used in advanced breast cancer with response up to 46% in receptor positive patients.

(e) Selective estrogen receptor down regulators:

Fulvestrant: has steroidal structure similar to naturally occurring estradiol, differing only in side light chain, hence useful in treatment of receptor positive metastatic breast cancer. Results of Two trials [30, 31] have shown fulvestrant as a novel hormone therapy with results similar to Anastrazole. Dose; 250 mg I/M once in a month.

(f) Hormone Therapy Plus Targeted Therapy:

Post-menopausal receptor positive, Her2 negative patients who progress 12 months or more after the end of adjuvant hormone therapy and patients who present with de novo metastatic breast cancer are eligible for first-line endocrine treatment. Aromatase inhibitor or Fluvestrant are first line agents in such patients as described above. Combination of hormones and targeted therapy may be an alternative option for them or as second line therapy. Recent studies have shown that cyclin-dependent kinase (CDK) 4/6 inhibitor with an aromatase inhibitor (AI) can provide better results. Any of AIs or Fulvestrant when combined with cyclin dependent kinase inhibitor e.g., Palbocicli, Ribociclib and Abemaciclib can provide best response and survival in advanced breast cancer [25]. Immune checkpoint inhibitors have also been tested in HR-positive MBC. Hormone drugs are used in their standard doses while the dose schedule of CDK 4/6 inhibitors is as follows:

(i) Palbociclib: 125 mg PO qDay for Days 1–21 of each 28-day cycle.
(ii) Ribociclib: 600 mg PO qDay for 21 consecutive days followed by 7 days off treatment resulting in a 28-day cycle.
(iii) Abemaciclib: 150 mg PO BID.

Combination of hormone and targeted therapy is still under investigation and may be treatment of choice in future.

23.3.5 Local Therapy

23.3.5.1 Role of Radiation in Advanced Metastatic Disease

Radiation plays an important role in advanced in-operable and metastatic breast cancer and produces worthwhile palliation by controlling pain, compression symptoms in metastatic disease and palliation of local bleeding or fun gated tumour. The details of palliative radiation are described in a chapter on “Role of Radiotherapy in Breast Cancer”.

23.3.6 Supportive Therapy in Breast Cancer

Breast cancer with locally advanced disease with fixity to skin or chest wall and those with metastasis to different sites may present with various kinds of manifestations or symptoms such as pain, large fixed local tumour, compressive symptoms as seen in brain and spinal metastases, and brachial plexus compression due to lymph node metastases. Pleural and pericardial effusions and ascites are common. Symptoms due to hyper calcium due to extensive bone metastases should also be kept in mind. Treatment also leads to side effects which need to be managed. All these signs and symptoms require additional treatment apart from specific therapy called Supportive Therapy.

23.3.6.1 Supportive Drug Therapy

(a) **Steroids for decompression:** are very important for managing compressive symptoms in brain, spinal cord and brachial plexus involvement and also in locally advanced disease with hypercalcemia. Following two drugs are commonly used. Inj. Dexamethasone 8 mg I/V stat and 4 mg 4–6 hourly, or Tab. Prednisolone 30–100 mg O.D. in divided doses depending on severity of symptoms.

(b) **Bis-phosphonates**: are useful in bone metastases and for treatment of hyper calcium. In bone disease besides reducing pain they also reduce skeletal related events (SRE) by 30–50%. Inj. Zoledronic Acid 4 mg I/V infusion over 1–2 h every four weeks for 6–12 months is the drug of choice as it is more potent than Inj. Pamidronate which is used at a dose of 90 mg I/V infusion over 2 h every 4 weeks. Oral Bis- phosphonates may also be used but are poorly absorbed and hence less effective. Clodronate (800–1600 mg P.O. O.D. depending on creatinine clearance) or Ibandronate (150 mg P.O. every month or 3 mg I/V every 3 months) are also available.

(c) **Anti-emetics**: Nausea and vomiting are common side effect of chemotherapy. These needs to be managed with anti-emetic drugs effectively. Commonly used drugs are:

  (i) Granisetron (5-HT3 receptor antagonists.)—10 μg/kg I/V 30 min before chemotherapy and oral dose 2 mg P.O.one hour before chemotherapy and then 1 mg B.D.

  (ii) Onadesetron (5-HT3 receptor antagonists.)—32 mg I/V 30 min before chemotherapy or 8 mg P. O BD. First dose is given 30 min before chemotherapy.

  (iii) Dexamethasone (Glucocorticoid Steroid)—8-12 mg I/V before chemotherapy and 4 mg I/V every 4–6 h.

  Orally 4 mgs 4–6 hourly for 4–6 doses, First dose 1 h before chemotherapy.

(iv) Metoclopramide (Substituted Benzamine)—2-3 mg/kg I/V 30 min before chemotherapy and then 20–40 mg P.O. every 4–6 h.
(v) Prochlorperazine (Phenothiazine)—5-25 mg I/M or I/V or orally every 4–6 h starting before chemotherapy. It can also be given per rectum 12 mg 12 hourly.

(d) **Bone marrow rescue**: Granulocyte- colony stimulating factor (G-CSF recombinant form) is used with cancer chemotherapy to accelerate recovery and to reduce mortality from neutropenia allowing higher-intensity treatment regimens. It stimulates the production, maturation, and activation of neutrophils. It also stimulates the release of neutrophils from the bone marrow. It is used both for prophylaxis and therapy of neutropenia. It can be given as prophylaxis immediately after first cycle of chemotherapy (Primary Prophylaxis) or with subsequent cycles when there is chance of neutropenia (Secondary Prophylaxis). It can be used to treat already established neutropenia after cytotoxic chemotherapy. It is available in two forms:
(i) Filgrastim—short acting, single use prefilled syringe of 300 mg per 0.5 ml or 480 mg per 0.8 ml is available. It is given S/C from day two of chemotherapy for next 4–5 days.
(ii) Pegylated—Filgrastim—long acting, available as single dose of 6 mg per 0.6 ml in a prefilled syringe and one dose given S/C day after the chemotherapy.

23.3.6.2 Treatment of Effusions

Pleural and pericardium are sites of metastases in breast cancer and usually present with pleural and pericardial effusion. Some patients even develop ascites following liver or peritoneal metastases.

1. **Pleural Effusion:** is seen in 2–20% of metastatic breast cancer and 75–80% are due to pleural infiltration. Patient can present with acute to chronic pulmonary symptoms e.g. cough, difficulty in breathing. Some time symptoms are highly distressing and need immediate relief. The effusion can be managed as follows:
   (a) **Thoracocentesis** or tapping of pleural fluid. It is both therapeutic and diagnostic. Fluid cytology confirms the diagnosis. Sometime pleural biopsy may also be done. Recurrences are common after chest aspiration but it gives quick relief of symptoms.
   (b) **Tube Thoracostomy**: in fast filling recurring effusion, 28–32 French tube is introduced in the pleural cavity under local anaesthesia called tube thoracostomy for continuous drainage. It may also lead to spontaneous pleurodesis.
   (c) **Sclerotherapy for pleurodesis:** Many agents have been instilled into pleural cavity to produce pleurodesis both chemicals like Talc or Cytotoxic

agents like Mustine, Thiotepa (both best for pleurodesis but are not available). Cisplatin, Bleomycin are available but results are not very good.

(d) **Surgical intervention;** in form of pleurectomy, Surgical approach is rarely used as it carries high mortality and morbidity.

2. **Pericardial Effusion:** about 5–10% patients of metastatic disease develop pericardial effusion. Only 50% of effusions are malignant. It needs immediate treatment because of ensuing cardiac complications which are usually fatal, more so if patient has cardiac tamponade. Control of pericardial effusion is best achieved by pericardiocentasis by placing single or multiple catheters in pericardial cavity under echocardiography by cardiologist for continuous drainage. Cytology for malignancy should be done of the aspirated fluid. Sclerotherapy with Tetracycline, Doxycycline, Bleomycin or Thiotepa may be considered in recurrent effusion. If done by experienced hand, complications are few.
3. **Ascites:** is seen in patient with liver and peritoneal metastases. Treatment of malignant ascites requires complete drainage of fluid till dry followed by sclerosis by any of the cytotoxic agents—Mustine, Thiotepan, Bleomycin or Cisplatin.

   In patients with repeated refilling (which is usually the case) addition of low-dose oral diuretics in the outpatient setting is helpful. The usually recommended initial dose for diuretic regimen is a combination of a single daily dose of 100 milligrams of spironolactone and 40 milligrams of furosemide.

23.4 Palliative Care, Pain and Symptom Management

Cancer does not affect the patient alone, but has an impact on the entire family. Palliative Care is therefore the active total care of patients and their families facing the problems associated with life-threatening illness, when the disease is no longer responsive to curative or life prolonging treatment. At this stage, the focus of care is prevention of suffering and overall improvement in quality of life.

A large number of women diagnosed with breast cancer in financially poor countries present with locally advanced breast cancer or metastatic breast cancer. Common sites for metastases are bone, brain, liver, and lung; and less common sites being intra-abdominal and skin. While cure is not a realistic outcome, for metastatic disease, supportive care, and palliative care can achieve meaningful outcomes and improve the quality of life. Palliative Care offers a support system to help patients live as actively and creatively as possible until death, thereby promoting autonomy, personal integrity and self-esteem and; it offers a support system to help families cope during the patient's illness and in bereavement. Pain management (including access to morphine) and psychosocial and spiritual services are core components of palliative care.

23.5 Evaluation and Management of Common Physical Symptoms

23.5.1 Pain

Pain is reported at diagnosis by 20–50 of cancer patients and by 75% of those with advanced disease. In 85% of patients the pain is due to the cancer itself and in 17% it is due to the anticancer treatment that the patient has received. However general illness & debility associated with disease, and concurrent disorders may also be the cause of the pain. The concept of **total pain** emphasizes that pain is not due to physical causes alone, there may be non-physical causes also like psychological factors (e.g., depression), social factors (e.g., familial estrangement), and spiritual or existential (e.g., loss of meaning in life) which can contribute and exacerbate pain [32]. It is not possible to control pain successfully without addressing all the other sources of suffering.

The commonest cause of pain in breast cancer patients is

- Bone Metastases. Vertebrae are the most common sites of bony metastases with more than two-thirds of vertebral metastases being located in the thoracic spine; lumbo sacral and cervical metastases account for ~20% and 10%, respectively.
- Though patients with bone- only metastases have a longer survival than those with visceral metastases, the symptom burden in these patients is more as they can develop fractures, spinal cord compression and hypercalcemia.
- Chest wall infiltration, brachial plexopathy, headache from brain metastases or leptomeningeal metastases, and abdominal pain from hepatic capsular distension are the other causes of pain.

Therefore a proper pain assessment is the first step in treating these patients. The first thing to decide is if the pain is "nociceptive" pain (caused by tissue damage) or "neuropathic" pain (caused by dysfunction of the nervous system). The next is to assess the site and severity of the pain. A body chart should be used to record the site of different pains as 70% of patients generally have more than one pain. For knowing the severity of the pain Verbal Descriptor Scale of mild, moderate, severe should not be used as it is subjective. It is best to use the Visual Analogue Scale, or Numerical Rating Scale on a scale of 0–10 where 0 = no pain and 10 = worst pain possible. Most of our patients understand the Rupee scale more easily.

For proper pain management one should aim at progressive pain relief. First one should try to relieve the pain at night so that the patient can sleep comfortably. Next one should plan for relief at rest during the day. Relief on movement is not always completely possible.

In 1986, the World Health Organization (WHO) developed a three-step conceptual model called the WHO Ladder to guide the management of cancer pain [33]. The WHO Ladder is effective in relieving pain for 90% of cancer patients and in 75% of patients who are terminally ill. It provides a simple, well-tested approach for

the rational selection, administration, and titration of analgesics depending on the severity of the pain.

1. ***First Step:*** Mild pain: non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen with or without adjuvants

   The nonopioid analgesics that characterize step 1 of the WHO ladder all have a ceiling effect to their analgesia. Acetaminophen is an effective step 1 analgesic. Chronic doses >4.0 g/24 h or acute doses >6.0 g/24 h are not recommended as they cause hepatic injury. Non-steroidal anti-inflammatory drugs (NSAID) are effective step 1 analgesics and may also be useful coanalgesics. However they can have significant adverse effects that include gastropathy, renal insufficiency, and platelet inhibition.
2. ***Second Step:*** Moderate pain: weak opioids, hydrocodone, codeine, tramadol with or without non-opioid analgesics, and with or without adjuvants

   Medications for step 2, include tramadol and combination formulations of acetaminophen or aspirin with weak opioids like codeine. Tramadol is a bridge between weak and strong opioid and has some effect in neuropathic pain also. Combination formulation tablets should preferably not be used because if you need to increase the dose of opioid it is not possible to do that without increasing the dose of the non-opioid too and this can increase the risk of hepatotoxicity. Do not change from one weak opioid to another, if optimum dose of a weak opioid is inadequate, change to strong opioid. Always remember to prescribe laxatives prophylactically to all patients as long as they are on opioids. One third of the patients on opioids will also need an antiemetic for the first few days for nausea and then it can be discontinued as unlike constipation it is self-limiting.
3. ***Third Step:*** Severe and persistent pain: potent opioids morphine, methadone, fentanyl, oxycodone, buprenorphine, with or without non-opioid analgesics, and with or without adjuvants.

   Adjuvants refer either to medications that are co-administered to manage an adverse effect of an opioid, e.g. constipation, nausea, or to so-called adjuvant analgesics that are added to enhance analgesia e.g. antidepressants including tricyclic antidepressants (TCAs) such as amitriptyline.
   - For mild pain (1–3/10 on a numerical analogue scale), start at step 1.
   - For moderate pain (4–6/10), start at step 2.
   - For severe pain (7–10/10), start at step 3.
   - It is not necessary to traverse each step sequentially; a patient with severe pain may need to have step 3 opioids right away.
   - Whenever possible give the drugs orally. In cancer pain there is no role for SOS or on demand prescription. The prescription interval must follow the pharmacokinetic characteristics of the drugs, in order to maintain analgesic concentration in the blood.
   - Step 2 and 3 analgesics involve opioids that act at opioid receptors. These receptors are found both peripherally and centrally, but the central receptors in the spinal cord and brain are most important for controlling pain.

23.5.2 Neuropathic Pain

For neuropathic pain related to metastases or treatment, adjuvant analgesics such as antidepressants i.e., the tricyclics amitriptyline, and anticonvulsants i.e., gabapentin or pregabalin are first-line therapies in conjunction with opioids. Start with a low dose and increase every 3–14 days as tolerated.

23.5.3 Fatigue

Fatigue is a major cause of distress to both patients and their family members. The underlying causes may be tumor burden, anemia, infection, fever, dehydration, electrolyte imbalance, cachexia, depression, sleep disturbance, and centrally acting sedating medications.

The first step is to correct the correctable e.g. anemia, dehydration etc. The next is to plan daily activities or prioritizing activities to be undertaken at times of least fatigue and when patient has maximal energy. In order to restore the energy patient should have good rest, nutrition and to relieve stress patient should undertake meditation, relaxation etc. Physical exercise has been endorsed as a useful approach in many clinical trials [34].

The level of physical exercise needs to be tailored to the underlying performance status and general well-being of the patients. Though steroids are not useful in the long-term management of fatigue, they may have a role to play in the short-term management. Dosing options include: Dexamethasone, 4 mg PO q am or Prednisone, 20 mg PO daily [35].

23.5.4 Dyspnoea

The major causes of breathlessness are due to airway obstruction, pleural effusion, pericardial tamponade, or thick secretions. Lung metastasis may occur in up to 70% of breast cancer patients with metastatic disease. Pulmonary lymphangitis carcinomatous is common in breast cancer patients and pulmonary infiltrates causing dyspnea may be associated with treatments such as radiation induced pneumonitis or after chemotherapy especially with taxanes [36]. The gold standard for diagnosis of dyspnea is patient self-report. The therapeutic goal of symptomatic management of dyspnea is to relieve the patient's sense of breathlessness by using both nonpharmacological and pharmacological approaches [37]. Help the patient sit as upright as possible and increase the air flow over the face by using a fan or by opening a window. Large symptomatic pleural or pericardial effusions should be drained and some patients may require pleuradesis or a permanent drainage device. Opioids are the preferred symptomatic therapy for dyspnea at the end-of-life. In the opioid naïve patient, a low dose of oral (5–10 mg) or parenteral morphine (2–4 mg) may be adequate for most. Despite this if patient remains anxious diazepam 2–5 mg may be given. Oxygen is helpful in patients who are hypoxic and is best given by nasal prongs (4 L/min).

Death rattle is seen in 30–50% of patients who are close to death and it is very distressing for the relatives. It is due to secretions in the hypopharynx. Hyoscine hydrobromide 0.4–0.6 mg subcutaneously should be given stat and the rattle is reduced in 1/2 to 2/3 of patients.

23.5.5 Psychological Symptoms

Delirium, depression and anxiety are the commonest Psychological disorders seen in cancer patients. Delirium is a common complication of advanced cancer. Incidence estimates range from 43% in the general cancer population to 85% in patients in the terminal stages of their illness. Common precipitating events include sepsis, medication side effects, brain metastases, or cerebrovascular events and metabolic aberrations (particularly hypercalcemia, hyponatremia, uremia, dehydration,). Less common causes include leptomeningeal metastases or status epilepticus. Delirium is a medical emergency that must be managed with compassion, reassurance, and clear explanation of the impact of pharmacological and nonpharmacological strategies to improve symptom control. Medications include antipsychotics and the newer agents such as olanzapine, are less likely to be associated with extrapyramidal side effects unlike the earlier generation antipsychotics such as haloperidol.

Cancer patients and their families commonly experience anxiety over anti-cancer therapies, their ability to live life as they have known it, and uncertainty about their future. Anxiety often co-occurs with depression. Common symptoms seen in depression, such as loss of appetite, decreased libido, and insomnia, may also be part of anxiety states [38]. Good communication skills are required as the majority of patients and their families will be receptive to compassionate exploration of the specific issues that are causing or exacerbating their anxiety. Concerns about anti-cancer therapy, finances, family conflicts, future disability, dependency, existential questions, and dying will not resolve with medication. Instead, they will benefit from counselling and supportive therapy. During the discussions, provide the patient with an improved understanding of his or her prognosis, potential treatments, and outcomes. These may help the patient put perceptions, into a different perspective. Benzodiazepines are usually the medications of choice for the short-term management of acute anxiety reactions when immediate relief is desired.

Major depression is an episode during which the patient complains or is noted to have depressed mood or the loss of interest or pleasure in nearly all activities for a period of at least 2 weeks. Patients also experience a host of other symptoms, including changes in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty in thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal plans, or attempts. Depression is often viewed by patients as something to be ashamed of, or as a sign of weakness and is a source of intense suffering. Persistent depression is not normal for patients with a serious illness or at the end-of-life. It is a myth that feeling helpless, hopeless, depressed, and/or miserable are inevitable consequences of advanced

life-threatening illnesses [39]. The principal medications used for the treatment of depression include tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), psychostimulants, and other classes of antidepressants. With all antidepressant medications, "start dosing low and go slow." Titrate the dose to effect and tolerability. Warn patients about possible adverse effects, which will usually ameliorate within a few days. SSRIs are recommended over TCAs as: (1) they are almost as effective antidepressants, (2) their onset of action is usually faster, and (3) they have much less risk of adverse effects.

Readers can go through the psychological aspects in the chapter "Psychosocial Aspects Of breast Cancer".

23.6 Local Recurrence

Local recurrence may be the only form of disease recurrence and when this occurs, it should be treated aggressively with surgery and/or radiation with or without systemic therapy. Although the goal of treatment is to control the disease, this is not always possible as patients present with ulcerated or fungating lesions which can be devastating to patients and families. Loss of vascularity is a major source of problem associated with these wounds. Because of the loss of tissue viability and consequent necrosis, anaerobic and aerobic bacteria proliferate in these conditions and is probably the cause of malodour and exudates that are commonly associated with these wounds. The primary aim is to promote comfort (as opposed to healing) and the enhancement of quality of life. There are numerous commercially available products for cleaning and dressing. However the dressing needs to be changed often and in a poor country vaseline gauze or a simple dressing material (like old saree or dhoti) which can be sterilized in a •pressure cooker• at home are the best affordable options. Debridement removes necrotic tissue and bacteria and is the primary treatment for malodorous fungating wounds. Use of Plermin, Sumag, Acriflavine with glycerine, Magsuph can be found helpful in removal of necrotic slough. Good dressings by a doctor or nurse are essential for cleaning the ulcerated growth. The antibiotic most commonly used is topical preparation of Metronidazole powder. Activated charcoal kept by the patient's bedside is also very helpful as it acts by adsorbing the volatile odour causing molecules. Recently sugar paste and honey has come back into use, mainly due to the emergence of many antibiotic resistant strains of bacteria, as both have antibacterial and debriding properties. Natural live yoghurt also helps in wound debridement and prevents the growth of bacteria, thereby ensuring healing.

23.7 Conclusion

Since the survival of women with metastatic breast cancer is often prolonged, the care for women with metastatic breast cancer is a major challenge for oncologists and palliative care teams. Antineoplastic treatment can modify and relieve physical

manifestations of the disease. However with the passage of time and sequential lines of treatment, the therapeutic window narrows down and the likelihood of achieving substantial benefit from disease-modifying therapies is diminished until such a time that further trials of disease-modifying treatments are either no longer helpful or have greater likelihood of harm than benefit, at which point palliation and support become the central focus of care. Good communication with the patient and family are crucial at this stage and patient's needs should come first as the aim of treatment should focus on improving the quality of life. When cure is not possible, as often it is not, the relief of suffering is the cardinal goal of medicine. This is an issue that affects us all because we would like our lives and the lives of those we love to end peacefully & comfortably.

References

1. Redig AJ, McAllister SS. Breast cancer as a systemic disease: a view of metastasis. J Intern Med. 2013;274:113–26.
2. Jamal A, Tewari RC, Murray T, et al. Cancer statistics, 2004. CA Cancer J Clin. 2004;54:8–29.
3. Carlson RW, Anderson BO, Berstein HJ, et al. NCCN clinical pracrtice guidelines – invasive breast cancer. J Natl Cancer Netw. 2007;5(3):246–312.
4. Greenberg PA, Hartobagyi GN, Smith TI, et al. Long term followup of patients with complete remission following combination chemotherapy in metastatic breast cancer. J Clin Oncol. 1996;14:217.
5. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel and combination ofdoxorubicin and paclitaxelas front line cmeotherapy for metastaic breast cancer. J Clini Oncologia. 2003;21:588.
6. Li CH, Karantza V, Aktan G, Mallika L. Current treatment landscape for patients with locally recurrent inoperable or metastatic triple-negative breast cancer: a systematic literature review. Breast Cancer Res. 2019;21:143.
7. Al-Mehmood S, Sapiezynski J, Garbuzenko OB. Metastatic and triple-negative breast cancer: challenges and treatment options. Drug Deliv Transl Res. 2018;8:1483–507.
8. Pentheroudakis G, Razis E, Athanassiadis A, Pavlidis N, Fountzilas G. Paclitaxel-carboplatin combination chemotherapy in advanced breast cancer. Med Oncol. 2006;23:147–60.
9. Chen XS, Nie XQ, Chen CM, Wu JY, Wu J, Lu JS, et al. Weekly paclitaxel plus carboplatin is an effective nonanthracycline-containing regimen as neoadjuvant chemotherapy for breast cancer. Ann Oncol: Official Journal of the European Society for Medical Oncology/ESMO. 2010;21:961–7.
10. Laessig D, Stemmler HJ, Vehling-Kaiser U, Fasching PA, Melchert F, Kolbl H, et al. Gemcitabine and carboplatin in intensively pretreated patients with metastatic breast cancer. Oncology. 2007;73:407–14.
11. Karachaliou N, Ziras N, Syrigos K, Tryfonidis K, Papadimitraki E, Kontopodis E, et al. A multicenter phase II trial of docetaxel and capecitabine as salvage treatment in anthracycline- and taxane-pretreated patients with metastatic breast cancer. Cancer Chemother Pharmacol. 2012;70:169–76.
12. Roy V, LaPlant BR, Gross GG, Bane CL, Palmieri FM. Group NCCT Phase II trial of weekly nab (nanoparticle albumin-bound)-paclitaxel (nab-paclitaxel) (Abraxane) in combination with gemcitabine in patients with metastatic breast cancer (N0531). Ann Oncol: Official Journal of the European Society for Medical Oncology/ESMO. 2009;20:449–53.
13. Kim JS, Park IH, Lee KS, Ro J. Outcomes of palliative weekly low-dose gemcitabine-cisplatin chemotherapy in anthracycline-and taxane-pretreated metastatic breast cancer patients. J Breast Cancer. 2014;17:339–43.

14. Fan Y, Xu B, Yuan P, Wang J, Ma F, Li Q, et al. Prospective study of vinorelbine and capecitabine combination therapy in Chinese patients with metastatic breast cancer pretreated with anthracyclines and taxanes. Chemotherapy. 2010;56:340–7.
15. Robert N, Leyland-Jones B, Asmar L, Belt R, Ilegbodu D, Loesch D, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol. 2006;24:2786–92.
16. Crown J, Kennedy MJ, Tresca P, Marty M, Espie M, Burris HA, et al. Optimally tolerated dose of lapatinib in combination with docetaxel plus trastuzumab in first-line treatment of HER2-positive metastatic breast cancer. Ann Oncol: Official Journal of the European Society for Medical Oncology/ESMO. 2013;24:2005–201.
17. Bramati A, Girelli S, Torri V, Farina G, Galfrascoli E, Piva S, et al. Efficacy of biological agents in metastatic triple-negative breast cancer. Cancer Treat Rev. 2014;40:605.
18. Slamon DJ, Leland-Jones B, Shak S. Use of chemotherapy monoclonal antibody against her 2 for metastatic breast cancer which expresses Her2. N Eng J Med. 2001;344:793.
19. Marty M, Cognetti F, Maraninchi D. Randomized phase II trial of efficacy and safety of trastuzumab combined with doectaxel in patients with human epidermal growth factor receptor2 positive metastatic breast cancer administered as first line treatment. J Cnin Oncol. 2005;23:4265.
20. Baselga J, Cortés J, Kim SB, Im SA. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366:109–19.
21. Smith IE, Pierga JY, Biganzoli L, Cortes-Funes H, Thomssen C, Pivot X, et al. First-line bevacizumab plus taxane-based chemotherapy for locally recurrent or metastatic breast cancer: safety and efficacy in an open-label study in 2,251 patients. Ann Oncol. 2011;3:595–602.
22. Valachis A, Polyzos NP, Patsopoulos NA, Georgoulias V, Mavroudis D, Mauri D. Bevacizumab in metastatic breast cancer: a meta-analysis of randomized controlled trials. Breast Cancer Res Treat. 2010;122:1.
23. Kontopodis E, Kentepozidis N, Christophyllakis C, Boukovinas I, Kalykaki A, Kalbakis K, et al. Docetaxel, gemcitabine and bevacizumab as salvage chemotherapy for HER-2-negative metastatic breast cancer. Cancer Chemother Pharmacol. 2015;75:153–60.
24. Fujita Y, Mizuta N, Sakaguchi K, Nakatsukasa K, Imai A, Umeda Y, et al. A case of effective lapatinib/capecitabine therapy for HER2-positive breast cancer with multiple brain metastases. Gan to Kagaku Ryoho Cancer & Chemotherapy. 2012;39:1699–702.
25. Cynthia X Ma, Sparano, JA, Sparano DF, Vora, SR. Treatment approach to metastatic hormone receptor-positive, HER2-negative breast cancer: Endocrine therapy and targeted agents. Up to date, 2020: March.
26. Wittliff JL. Steroid hormone receptors in breast cancer. Cancer. 1984;53:630.
27. McGuire WL, Chamness GC, SAW F. Mini review estrogen receptor variants in clinical breast cancer. Mol Endocrinol. 1991;5:1571.
28. Kiiang DT, Kennedy BJ. Tamoxifen in advanced breast cancer. Ann Intern Med. 1977;87:68.
29. Stenbygaard LE. Tormefen and tamoxifen in advanced breast cancer: a double blind cross over trial. Breast Cancer Res Treat. 1993;25:57.
30. Howell A, et al. Fulvestrant, formely ICI 182 780, is as effective as Anastrazole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol. 2002;20:1.
31. Osborn CK, et al. Double blind, randomizedtrial comparing the efficacy and tolerability of fulvestrant versus anastrazole in postmenopausal women on prior endocrine therapy: results of north American trial. J Clin Oncol. 2002;20:1.
32. Saunders C. Care of patients suffering from terminal illness at St. Joseph's Hospice. Nurs Mirror February. 1964;14:7–10.
33. World Health Organization. Cancer pain relief. 2nd ed. Geneva: WHO; 1996.
34. Juvet LK, Thune I, Elvsaas IKØ, et al. The effect of exercise on fatigue and physical functioning in breast cancer patients during and after treatment and at 6 months follow-up: a meta-analysis. Breast. 2017;33:166–77.

35. Miaskowski C, Portenoy RK. Update on the assessment and management of cancer-related fatigue. In: Principles and practice of supportive oncology updates, vol. 1. Philadelphia: Lippincott-Raven Publishers; 1998. p. 1–10.
36. Nagata S, Ueda N, Yoshida Y, et al. Severe interstitial pneumonitis associated with the administration of taxanes. J Infect Chemother. 2010;16:340–4.
37. Kloke M, Cherny N. Treatment of dyspnoea in advanced cancer patients:ESMO clinical practice guidelines. Ann Oncol. 2015;26(Suppl 5):v169–73.
38. Payne DK, Massie MJ. Anxiety in palliative care. In: Breitbart W, editor. Handbook of psychiatry in palliative medicine. New York: Oxford University Press; 2000. p. 435.
39. Wilson KG, Chochinov HM, de Faye BJ, Breitbart W. Diagnosis and management of depression in palliative care. In: Chochinov HM, Breitbart W, editors. Handbook of psychiatry in palliative medicine. New York: Oxford University Press; 2000. p. 435.

Breast Cancer with Associated Problems

24

Chintamani, Megha Tandon, and Jaya Ghosh

24.1 Introduction

The treatment of breast cancer is an art. It is a holistic approach where the focus is not only on the cancer but on the person suffering from it. This also is one of the commonest cancers afflicting women with comorbidities because of its high incidence. Comorbid conditions may affect the drug pharmacokinetics, or the side effects of systemic therapy may be aggravated. As the goal of treatment is to help the patient to live better and longer, the therapy needs to be tailored both as per tumour characteristics and patient's underlying co morbid conditions. This chapter aims to focus on some of the common comorbid conditions and the consideration of systemic therapy thereof.

24.2 Acknowledging the Presence of Comorbid Conditions

The most important first step is to document all the comorbid conditions and the concomitant medications the patient is on. This often involves an active history taking into individual comorbidities rather than a generic question as to whether they

Chintamani, MS, FRCS, FACS, FICS (✉)
Professor and former Head, Department of Surgery, VMMC, Safdarjang Hospital, New Delhi, India

President, Asian Society of Mastology, Kolkata, West Bengal, India
e-mail: chintamani7@gmail.com

Megha Tandon, MS, MRCS (Ed.), DNB
Associate Professor, Department of Surgery, VMMC, Safdarjang Hospital, New Delhi, India

Jaya Ghosh, MD, DM
Professor, Department of Medical Oncology, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_24

have any other ailments to which many patients reply is in negative. A detailed documentation of all concomitant medications and going into the details of the combination drug used is essential as they may have an interaction with the systemic therapy. Also, the compliance to medication for comorbid condition during chemotherapy needs to be ensured. This history is essential and forms the basis of all modifications needed in systemic therapy.

The presence of comorbidities have an impact upon the stage of the breast cancer and also on the outcome, morbidity and treatment options [1–7]. There is enough evidence to suggest that the comorbidities are more prevalent as the age advances, increasing from less than 10% in women that are less than 50 years to beyond 40% in those that are more than 80 years of age. There is also an increased all-cause mortality reported if there is associated comorbidity [1–7].

With a better understanding of the biological behaviour and evolution of management strategies, women with breast cancer now live longer and are also candidates for development of various comorbidities, therefore, the issue needs a special addressal. Most guidelines for detection and management of breast cancer are based on studies that rarely include and in fact exclude patients with comorbidities leading to often an under-representation of this sub-group. While it may seem like common sense that the outcome in this subgroup should be worse than their counterparts without any comorbidities but that is not always true, and it may be worthwhile to study this sub-group with greater keenness. With improved survival a lot of these patients now may live long enough to get these comorbidities needing a tailored management.

There are many studies that have shown a negative impact of pre-existing diseases on cancer survival and treatment outcomes. A few recent data have suggested that the breast cancer patients with significant comorbidities tend to develop increased treatment related complications and higher risk of overall as well as cancer related mortality [8, 9]. However, there are conflicting results regarding the association between rate of metastases and risk of recurrence in this subgroup, Studies have reported that the breast cancer patients with comorbidities have similar risk of recurrence, though may have higher mortality [10]. On the other side, a study has shown worse treatment outcomes even in early breast cancer following omission of appropriate adjuvant therapies in patients with significant comorbidities [11].

The optimal treatment of breast cancer patients with comorbidities is a challenge for most clinicians in various ways. Most agree that optimally managing the comorbidities, involving multiple disciplines, tailoring treatment options and informed decision making with patients and understanding their realistic expectations out of their treatment should be the best way to manage this subset of patients.

24.3 Grading of Comorbidities

In order to address the issue of standardizing yet individualizing the management it is mandatory to grade the severity of comorbidities. Most commonly used scales are ASA (American Society of Anesthesiologist), OARS (Older American Resources and Services) Multidimensional functional assessment questionnaire (OARS MFAQ) and Charlson Comorbidity Index etc. Since breast cancer is mostly

diagnosed over 65 years of age, especially in the west, a substantial number of patients are elderly. In practice, data from younger, healthier populations are usually extrapolated for the elderly population when making adjuvant treatment recommendations which may not be the best approach. Compared to younger ladies, even healthy elderly women are at greater risk of early treatment discontinuation [12]. But since the management of breast cancer should be tailored to a particular patient, one needs clearer information on indices that may describe a specific morbidity and outcome of breast cancer in respective patients.

24.4 Correlating Comorbidities with Outcome and Impact on Therapy

A better understanding of the relationship between co-morbid conditions, hematologic toxicities, treatment-related mortality, and treatment-associated toxicity in the adjuvant setting is mandatory to tailor a therapy to an individual patient. This would also improve informed decision making about the risks and benefits of adjuvant chemotherapy for older women with breast cancer.

For surgical management, axillary nodal addressal or nodal staging is minimised or omitted in elderly patients with severe comorbidities. And as opposed to this a mastectomy is often preferred over limited resection/breast conservation to minimise/avoid the morbidity of adjuvant radiation to the chest wall. There are studies to show a significantly higher use of mastectomies as compared to breast conservation in patients with severe comorbidities [13].

Functional status and pre-existing comorbidities also influence the choice of adjuvant treatment in these patients. The decision of omitting adjuvant therapies in patients with comorbidities may be a double-edged sword. On one hand, these patients may be vulnerable to serious adverse effects of systemic therapies while on the other, there is a concern about compromising optimum oncological treatment as suboptimal use of the systemic therapies can increase the rates of recurrence and mortality. On the flip side, there are also studies to suggest that there is no difference in treatment related adverse effects simply based on comorbidity profile of patients undergoing systemic treatment [8, 9]. The author discusses some common comorbidities encountered by clinicians in management of breast cancer patients although in most cases multiple comorbidities may co-exist.

Underlying comorbidities are expected to influence the outcome in breast cancer patients for various obvious reasons. Most studies include comorbidities with pre-existing cancer being an important one besides diabetes. Others include myocardial infarction, congestive heart failure, renal, cardiac or respiratory failure, cerebrovascular disease, connective tissue disease and ulcer disease etc. There are limited studies on potentially confounding factors, such as smoking or obesity. The perceived risk of dying due to some of these comorbidities like renal, cardiac, or respiratory failure may actually jeopardise the optimum management leading to inadequate treatment with an inferior outcome and increased mortality. Also, these comorbidities may not let the patient live long enough to survive the benefits of present day improved breast cancer specific therapy protocols [1–7].

24.5 Impact of Whether the Comorbidity Is Recent or Old

Patients with more recent comorbidities i.e. those happening within 5 years of the diagnosis of breast cancer have a higher risk of dying than those in whom the comorbidity had occurred more than 5 years back except hemiplegia where a reverse trend has been observed in most studies [1–6].

24.6 Evidence Based Management of Breast Cancer Patients with Comorbidities

The guidelines and data regarding the ideal management of these patients are limited and there is a desperate need to study this sub-group more effectively. There are many studies that suggest that a higher comorbidity score is associated with increased Breast Cancer Specific Mortality (BCSM) besides a higher risk of dying from these comorbidities. The lower scores may also reduce the likelihood of receiving guideline therapy leading to a poorer outcome [1, 3–7].

Studying the definitive correlation between a specific comorbidity and breast cancer related outcome is therefore mandatory so that one may tailor the therapy to a particular patient in a standardized and evidence-based manner. In most published literature there are studies that have compared the outcome in terms of overall and breast cancer specific mortality (BCSM) and the expected impact of adjuvant therapy in these patients. No significant increase in BCSM could be observed in those with prior myocardial infarction, congestive heart failure or diabetes mellitus, cerebrovascular accident (CVA), or connective tissue disorder. As expected, there was definitely an increase in the myocardial diseases with radiotherapy especially in left sided cancers. One may conclude based on these observations that it should be possible to adhere to a similar protocol of adjuvant therapy in this subgroup that is applicable to patients without any comorbidities [1].

24.7 Correlating the Outcome with Specific Morbidity

There are very few studies that have indeed addressed the association between specific comorbidity and breast cancer related mortality. One such study included more than 64,000 breast cancer patients that were diagnosed at a median age of 75 years, taken from SEER (Surveillance Epidemiology and End Results) Medicare data base Patnaik et al. [1]. Prior cancer and diabetes mellitus (DM) were found to be the most common pre-existing comorbidities (13% of patients). It was observed that each of these comorbidities was associated with a poorer outcome in terms of mortality and overall survival. When compared with non-diabetic women, patients with pre-existing diabetes were found to have greater risk of death and also a greater probability of presenting with a delayed disease and receiving a changed treatment protocol [1–8]. It has been reported by The Danish Breast Cancer Cooperative Group (DBCG) that Charlson's Comorbidity Index at the time of breast cancer diagnosis is

an independent prognostic factor (adverse) for mortality after breast cancer. Thus comorbidities are considered as important predictors of a poorer outcome [1].

24.8 Effect of Adjuvant Treatment on Breast Cancer Mortality in Those with Comorbidities

In most studies the effect of adjuvant therapy has been observed to be similar in those with or without comorbidities. It has however been observed that patients with dementia and receiving chemotherapy have a four times increased risk of dying.

Radiotherapy (RT) leads to an increased risk of myocardial infarction especially when the cancer is left sided. The risk increases further in those with pre-existing ischaemic heart disease [14, 15]. Anthracycline or Taxane based chemotherapy or targeted therapy like trastuzumab which are known to be cardiotoxic can also in addition predispose to increased cardiotoxicity following RT [1].

Breast cancer mortality has not been found to increase significantly in patients with prior myocardial infarction (MI), congestive heart failure, cerebrovascular disease, connective tissue disorder, ulcer disease and DM. It has also been observed that the effect of adjuvant treatment is similar between those with and those without comorbidities. This therefore clearly indicates the importance of following the standard guideline therapy in all patients regardless of any comorbidity to the extent possible [1–10].

24.9 Effect of Comorbidities on the Management of Breast Cancer

24.9.1 Age as a Comorbidity

There is increased vulnerability of dying from breast cancer with increasing age which may also be considered a stand-alone comorbidity besides being associated with other comorbidities.

Postmenopausal women that may have other comorbidities and a later stage at presentation (screening and other factors being contributory), especially in those that are more than 70 years of age, guidelines need to be worked out and more data is needed. Since there is heterogeneity of individuals even in this age group, one may argue against age being a factor while making decisions regarding management of breast cancer. There are other issues relating to the optimum and tolerable treatment for this subgroup [2–5].

Issues like the role of axillary lymph node dissection, adjuvant chemotherapy and radiotherapy especially for women in 80s or those in 70s but with a poor performance status are important to consider. Also, in view of these cancers generally not being aggressive (*especially in women more than 70 years of age*), the significance of aggressive approach may be questionable. Response to chemotherapy, optimum role of hormone therapy and guidelines for using adjuvant therapy are not

adequately documented especially for older women. An additional effort is required in these age groups focussing on early detection, optimum management and long term follow up including the supportive care [1–5].

Age and associated comorbidities also pose restrictions in use of various diagnostic modalities and treatment options especially in elderly women (more than 70 years of age. There, is an overall increase in comorbidities occurring with increasing age, thus age besides itself being a comorbidity further increases the risk of development of other comorbidities.

24.10 Diabetes Mellitus

24.10.1 Diabetes and its Association with All-cause Mortality with Breast Cancer

Diabetes Mellitus (DM) per say is not considered significant, however complicated DM especially with vascular complications may lead to a higher mortality as associated peripheral vascular disease is known to increase mortality in breast cancer. Since most important complications of diabetes happen due to associated vascular complications, it may be a significant comorbidity. A correlation between DM with congestive heart failure and breast cancer related mortality has also been observed in most studies [1–5].

Diabetes is essentially associated with microangiopathy which may predispose to macroangiopathy like atherosclerosis, cerebrovascular accidents and myocardial infarction. This, therefore may be leading to higher breast cancer related mortality. In most studies however this was not observed to be significant and especially if the disease was non-insulin dependent and more than 5 years old from the time of breast cancer diagnosis [1, 10–13, 16, 17].

24.10.2 Diabetes Mellitus and Breast Cancer

DM has attained the status of global pandemic and is a major public health problem. It affects up to one-third of patients with breast cancer [17]. Women with breast cancer and DM have a 40% higher risk of mortality versus those without it [14, 15, 17, 18]. On one hand while the overall outcome and prognosis is also poorer in breast cancer patients with co-existing DM, these patients also have higher treatment related complications and morbidities [19].

The effect of DM on breast cancer is multidimensional and complex. It is associated with multiple factors that influence risk of breast cancer like obesity, metabolic syndrome etc. It directly impacts the breast cancer occurrence and contributes to cancer risk at molecular levels. Several mechanisms are proposed that link DM to breast cancer risk like endogenous sex hormone regulation especially oestrogen and activation of IGF (insulin like growth factor) and insulin signalling pathways [14].

24.10.3 Impaired Glucose Regulation and Breast Cancer

Hyperglycaemia is the hallmark for DM and results both from insufficient insulin production in pancreatic βcells, as in Type 1Diabetes (T1DM), and from the increase of systemic insulin resistance, as in Type 2Diabetes(T2DM). Both are associated with increased risk of breast cancer. However, other cancers associated with these two types are different suggesting different mechanisms involved. Several studies have investigated the role of sustained hyperglycaemia, hyperinsulinemia, insulin resistance (IR), and hyperinsulinemia-related increase of insulin-like growth factor-1 (IGF-1) in cancer promotion and progression [19–24].

24.10.4 Summary of Various Mechanisms by which DM increases Risk of Breast Cancer

1. *Hyperglycemia*: Some authors believe that hyperglycaemia has a direct effect on cancer initiation, proliferation, migration, and invasiveness [25]. However, several studies have supported that Hyperinsulinemia (a feature of T2DM) rather than hyperglycaemia is major culprit. Extensive research is presently available supporting a causative link between impaired glucose tolerance/T2DM and breast cancer [25–30].
2. *Oxidative stress*: Poor glycaemic control leading to a dysregulated metabolism is responsible for a long-term pro-inflammatory condition. This chronic inflammation-induced oxidative stress may concur with impaired glucose-associated conditions to promote tumour progression [30, 31].
3. *Hyperinsulinemia*: Type 2 DM (T2DM) in contrast to type 1is characterised by hyperinsulinemia and has late onset of hyperglycaemia. One of the mechanisms leading to increased risk of breast cancer in T2DM patients, is by causing reduction in concentration of circulating sex hormone binding protein (SHBG) by high insulin levels [32], which in turn causes increased levels of bio-active oestrogens responsible for proliferation of both breast and endometrial cells and, this may possibly enhance the hormonal carcinogenesis [29]. Furthermore, insulin and IGF-1 cause enhanced expression of aromatase leading to increased levels of oestrogen. Indeed, in obese T2DM subjects, oestrone and oestradiol are overproduced in adipose tissue by intense activity of aromatase [29], expressed both in breast and tumour tissues, and may accelerate the cancer growth [30]. IGF-1 also participates oestrogen receptor signalling via IGF-1 receptor/ER interaction and cooperates with oestrogens to regulate proliferation, apoptosis, and differentiation of breast epithelial cells in a bi-directional way [33].

IGF-1 and 17β-estradiol complex interplay results in the proliferation of breast carcinoma cells. It may therefore be inferred that insulin and oestrogen might have a mutual inter-relationship leading to higher risk for endocrine-related cancers, especially in postmenopausal women [31].

24.10.5 Management Challenges in Breast Cancer Patients with Diabetes Mellitus

24.10.5.1 Surgical Management of Breast Cancer with DM

Although, DM may not alter the planned surgical management the associated comorbidities like obesity, dyslipidaemia, metabolic syndrome along with advanced age etc. should be taken into consideration when planning treatment options like breast conservation, breast oncoplasty, use of implant or tissue reconstructions and axillary dissection. The decision should be tailored according to the patient profile, tumour characteristics, severity of comorbidities and functional assessment.

Optimisation of blood glucose levels and monitoring the blood sugar via HbA1c is desirable before surgery. Uncontrolled hyperglycaemia has a detrimental impact on wound healing due to a delayed response to injury and impaired functioning of immune cells. Evidence suggests that these impairments may be the result of an inherent (genetic) defect and/or decreased insulin availability plus increased blood glucose concentration [31, 32, 34]. Peri-operative shift to insulin will usually be required in patients on oral hypoglycaemic drugs.

Therapeutically targeting the associated dyslipidaemia has been found to be promising in retarding the tumour growth. it has been shown that cancer cell proliferation and migration can be inhibited by:

(a) Inhibiting lipid synthesis.
(b) Blocking the lipid uptake by cancer cells.
(c) Blocking the intracellular lipolysis.
(d) Restricting the lipid utilisation [35].

24.10.5.2 Anti-Diabetic Drugs and Breast Cancer

24.10.5.2.1 Insulin

Insulin and its analogues confer anti-diabetic effect by controlling hyperglycaemia but cause an increase in circulating levels of insulin which as discussed earlier may have implication in increasing the risk of developing breast cancer and its progression [26, 27].

24.10.5.2.2 Insulin Sensitizers: Thiozolidiones (TZDs, Rosiglitazone, Pioglitazone)

Studies show that they do not affect breast cancer risk and progression when used alone or in combination with adjuvant therapies [33, 36, 37].

24.10.5.2.3 Insulin Sensitisers Biguanide (Metformin)

Metformin, a widely used and accepted drug for DM has been extensively studied for its anti-neoplastic potential and has shown promising results in risk reduction [38, 39]. Diabetic postmenopausal women on metformin have lower

incidence of invasive cancer vs those patients that are on other oral hypoglycaemic agents (OHA). Breast cancer patients on concurrent metformin for DM may show higher rates of "pathological complete response" with neo-adjuvant chemotherapy [40]. Analysis from adjuvant Lapatinib/Transtuzumab treatment optimisation (ALTTO)has shown that Her2 neu positive diabetic patients on metformin experience improved disease free and overall survival [41]. However, the positive effect of metformin may be restricted to hormone positive breast cancer patients [39]. Although larger studies may be required to substantiate the claim and providing additional support for use of metformin in future cancer treatment regimen. Ongoing clinical trials are determining therapeutic advantage of using metformin in breast cancer patients independent of diabetic status of individuals [42–44].

24.10.6 Chemotherapy and Diabetic Breast Cancer Patient

In diabetic women chemotherapy dose intensity may be compromised [19] e especially if there is poor glycaemic control or presence of concurrent cardiac morbidities [45]. Diabetic end organ damage and presence of higher rates of chemotherapy induced toxicities [19] may result in suboptimal doses or reduced cycles of chemotherapy. The decision of the chemotherapy regimen should be based on individual risk benefit ratio.

The presence diabetes and diabetic end organ damage may affect the side effect profile of several chemotherapeutic drugs also these drugs may adversely affect the control of diabetes. Presence of underlying diabetic neuropathy is important to note especially in patients undergoing therapy with drugs causing peripheral neuropathy like Paclitaxel and Cisplatin [46]. As around half of the survivors who have received Paclitaxel based therapy continue to experience some neuropathic symptoms [47, 48], this compounded with diabetic neuropathy may affect the quality of life. In such situations, drugs with less neurotoxicity like Docetaxel [46] may be considered. Dexamethasone used as antiemetic increases blood sugars in pre-existing diabetes or those with borderline diabetes may become frankly diabetic, especially in weekly chemotherapy protocols using dexamethasone. Some of the newer targeted therapies like mTOR inhibitors (everolimus) or PIK3CA inhibitors (alpelisib) also cause hyperglycaemia [49, 50]. Thus, blood sugars need to be monitored during treatment and compliance to antidiabetic drugs ensured.

24.10.7 Radiotherapy and Diabetes Mellitus

In patients with diabetes, concomitant underlying cardiovascular risks would be factored in the decision regarding radiotherapy especially in those with left sided tumors [50].

24.10.8 Hormonal Therapy and Diabetes Mellitus

Although only a limited number of studies have looked at the impact of hormone therapy on glucose and insulin metabolism in women with BC, it appears that a negative effect is the most common observation. Hormone therapy may increase the risk of developing DM in breast cancer survivors.

According to a cohort study, Hormone therapy with tamoxifen was associated with a more than two-fold increase in the risk of diabetes and aromatase inhibitors were associated with more than fourfold increase [51]. Thus lifestyle modifications are important in breast cancer survivors to prevent diabetes [51].

24.11 Hypertension

As a component of metabolic syndrome, hypertension (HTN) was shown to increase postmenopausal breast cancer risk in a meta-analysis [52]. Though the mere presence of hypertension does not merit a change of systemic therapy, control of hypertension during treatment is necessary. Drugs like anthracyclines and trastuzumab which affect cardiac function may have increased adverse effects with an underlying uncontrolled hypertension [53]. Dexamethasone is a part of the antiemetic chemotherapy protocol, so monitoring of their blood pressure regularly during treatment is mandatory. The use of anti- hypertensives which include thiazide diuretics may aggravate hyponatremia especially with chemotherapy agents like platinum or cyclophosphamide [54]. In the evaluation of a patient with hyponatremia on chemotherapy the history of use of diuretics is often forgotten. Thus, a well-controlled blood pressure and a knowledge of the anti-hypertensive medications is needed for optimal patient management. HTN is a modifiable risk factor and hence measures like diet modification, healthy lifestyle etc. go a long way in prevention and decreasing risk of breast cancer.

24.12 Nephropathy

When considering the presence of impaired renal function not only should one look at serum creatinine but also estimate the glomerular filtration rate (GFR). Also, routine urine examination to look for proteinuria, casts, red blood cells gives important indicators of renal function. Among cancer patients almost half of those with normal serum creatinine have renal insufficiency when the GFR is estimated [55]. The most common method of estimation of creatinine clearance used in oncology is the Cockcroft-Gault formula which takes into account the patients gender, age, body weight apart from body weight [56]. The GFR estimation is especially relevant when administering drugs like Cisplatin and Carboplatin (the dose of which itself is based on GFR). However, at the same time one needs to remember that in patients with low serum albumin and extremes of age Cockcroft-Gault formula may not be accurate [57]. Several other drugs like Capecitabine and cyclophosphamide,

bisphosphonates and low molecular weight heparin may need dose modification depending upon degree of renal impairment [56, 58–60]. Bisphosphonates can cause renal injury (acute tubular necrosis, focal segmental glomerular sclerosis) [61] especially with long term use in metastatic breast cancer where almost 11% may develop renal failure [62]. Hence renal function must be monitored during bisphosphonate use and appropriate dose adjustment made [58]. During the course of cancer treatment patients receive several nephrotoxic drugs including chemotherapy and antibiotics also many drugs need dose modification in the presence of renal impairment, hence early detection would help in both optimal drug dosing and preventing further decline in renal function.

24.13 Heart Disease

Heart disease is the second most common cause of death after breast cancer itself, especially in older postmenopausal women [63]. These include coronary artery disease, cardiomyopathy, arrhythmias and valvular disease. In India rheumatic heart disease, continues to remain an important cause of heart disease [64] and may remain undiagnosed till late. In women with co-existing heart disease especially with early-stage breast cancer the risk of breast cancer mortality must be weighed against cardiac cause of mortality. A careful history into not only underlying cardiac disorder but also into cardiovascular risk factors like hypertension, diabetes, dyslipidaemia, obesity and smoking should also be taken into account [53]. Patients with cardiac dysfunction or at high risk for same especially in those receiving cardiotoxic drugs should undergo baseline evaluation and monitoring for cardiac function by ECG and echocardiogram [53]. In the ECG apart from looking for any signs of ischemic heart disease, rhythm abnormalities the QTc interval should be evaluated [65]. Echocardiogram provides useful information on LVEF, any regional wall motion abnormality and valvular heart disease. Another important parameter in echocardiogram is the global longitudinal strain (GLS) which can detect subclinical cardiac dysfunction even when the LVEF is normal [65]. It would thus help in early detection and institution of treatment and prevention of cardiac dysfunction. The MUGA (multi gated acquisition) can also be used to monitor LVEF and is more objective but is limited by availability and need of radioisotope [54].

Drugs like anthracyclines (doxorubicin, epirubicin) cause cardiotoxicity by the generation of reactive oxygen species which lead to myofibrillar disarray, myocyte damage and cell death. This is irreversible and cumulative dose dependent (Type I Cancer Therapeutic related cardiac dysfunction-CTRCD) [66, 67]. The risk of cardiac toxicity increases with increasing dose, ≥7% at 200 mg/m^2, ≥16% at 400 mg/m^2 and ≥ 20% at 500 mg/m^2 [65]. It is also important to note that some of the cardiac toxicity may manifest late [65]. Thus, there is increased risk of cardiac dysfunction in patients receiving Doxorubicin (>250 mg/m^2) or Epirubicin (>600 mg/m^2) or a lower dose but with 2 or more cardiovascular risk factors, older age (>60 years), compromised LV function (borderline LV function LVEF-50-55%), history of myocardial infarction, moderate valvular dysfunction, or anthracyclines

followed by trastuzumab [53]. This cardiac risk is also increased in those receiving radiotherapy especially to the left side, though better techniques have reduced this risk [53]. Hence limiting the dose of anthracyclines used (e.g. doxorubicin Cyclophosphamide (AC) 4 cycles, cumulative dose 240 mg/m^2 compared to 6 cycles −360 mg/m^2) may reduce the risk of subsequent cardiotoxicity. In node positive or high risk node negative disease 3–4 cycles of anthracycline followed by taxane, apart from reducing risk of relapse also has less potential for subsequent cardiac toxicity compared to 6 cycles of anthracyclines [68, 69]. In patients with high risk of cardiac dysfunction careful judgement on the need and type of chemotherapy must be made depending on stage and breast cancer subtype. In patients with early stage strongly hormone positive breast, HER 2 negative cancer the benefit of adjuvant chemotherapy should be weighed against risk of cardiovascular mortality, and may consider treatment with adjuvant hormone therapy alone if cardiovascular risk is higher than risk of breast cancer relapse. In those who do need chemotherapy other non-anthracycline based regimens may be considered like TC -Docetaxel and cyclophosphamide [70, 71] or CMF -cyclophosphamide and methotrexate [72] (if no previous history of ischemia). In HER2 positive cancers non anthracycline options include TCH (Docetaxel, Carboplatin,trastuzumab) [73] or 12 cycles of Paclitaxel and trastuzumab followed by trastuzumab maintenance for a year (early stage cancers, node negative only) [74].

HER 2 directed therapy like Trastuzumab cause reversible cardiac dysfunction due to HER2 inhibition in cardiomyocytes [75]. This is a reversible type II cardiac dysfunction. The incidence of cardiac toxicity after a year of adjuvant trastuzumab is around 4%, and less with shorter duration (9–12 weeks or 6 months) of trastuzumab and higher around 25% in those with metastatic disease [65, 66]. If there is a drop in LVEF to less than 50% and greater than 10% drop from baseline then trastuzumab needs to be stopped for 3 weeks and LVEF rechecked and trastuzumab can be restarted if the LVEF improves to ≥50% or to 45–49% and is less than 10% lower from baseline [67]. Other anti HER2 agents like Lapatinib, Pertuzumab and TDM1 also need cardiac evaluation and monitoring. In a recent prospective SAFE HEaRT study the safety of trastuzumab, pertuzumab and TDM1 use in patients with LVEF 40–49% with close cardiology consultation and use of β blockers and ACE inhibitors has been shown, though the sample size was small [76]. Thus, anti HER 2 agents which causes reversible dysfunction could be considered even in those with minimally impaired cardiac function.

Cardiovascular protective agents like ACE inhibitors, angiotensin receptor blockers and β blockers are used for the treatment of heart failure and cardiac dysfunction caused by anti-cancer agents [65]. They prevent cardiac remodelling and left ventricular enlargement and dysfunction. Their role in primary prevention is still debated [65, 77].

5FU can lead to coronary vasospasm and should be avoided in those with coronary artery disease [78]. Paclitaxel should be avoided in patients with arrythmias as it can lead to bradycardia or asymptomatic left bundle-branch block and non-sustained ventricular tachycardia, and can rarely ischemia [79, 80]. Drugs like 5HT3 receptor blockers (ondansetron) used as antiemetics, tamoxifen and ribociclib (CDK4/6 inhibitor) can prolong QTc [81, 82]. Thus, care needs to be taken to check

serum electrolytes, other conditions like hypothyroidism and other drugs causing prolonged QTc [81].

In patients with cardiac dysfunction or in those with high risk for the same the use of cardiotoxic medicines should be minimized or avoided if alternative regimens can be used without compromising cancer specific outcomes. Thus, early detection of heart disease, cardiovascular risk factors and monitoring of survivors would lead to optimal patient and forms the basis of the emerging field of cardio oncology [83].

24.14 Pulmonary Disease

Pre-existing pulmonary disease and the severity of may affect the patients' ability to tolerate adjuvant chemotherapy. Chemotherapy and radiotherapy may increase the incidence of interstitial pneumonitis [84]. Among the chemotherapy drugs used in breast cancer, Paclitaxel, gemcitabine, mTOR inhibitors (everolimus) have been implicated in the development of interstitial pneumonitis [50, 85, 86]. Though this is a rare complication of Paclitaxel [85, 87], however one must be aware of it, to detect it early. Patients may present with persistent dry cough, subsequently with breathlessness and it is important to exclude ILD in them [87]. This may be more common in those receiving weekly paclitaxel and in elderly patients [84, 85]. Early diagnosis and treatment with corticosteroids may reverse it [87]. Thus, prompt diagnosis and treatment are the key to reversal of this rare but debilitating toxicity.

24.15 Psychiatric Comorbidities

Diagnosis and treatment of breast cancer have a significant psychological bearing. Breast being a secondary sexual organ is usually linked as a feature of feminity and its removal has significant implications on quality of life. It has been observed in various studies that some amount of psychiatric morbidity has been observed at some point of breast cancer treatment in almost all patients. Presence of pre-existing psychiatric ailment complicates the treatment and should be considered while planning the management. Counselling, family support, peer groups go a long way in providing mental and emotional support in these patients [88–90].

24.16 Pregnancy Associated Breast Cancer (PABC)

PABC is defined as breast cancer diagnosed during pregnancy or within one year of delivery is an extremely rare and challenging situation. It demands multi-disciplinary care including oncologist, obstetrician and foetal medicine expert to balance oncological and the pregnancy outcomes. The incidence is rising due to and one of the important reasons is delayed childbearing which is a neo -norm for various reasons. Among the PA cancers, breast cancer (1 in 3000) is the commonest. Delayed

diagnosis (between 1 to 13 month) due to lack of awareness is common and leads to upstaging of the disease [91].

The management is stage and trimester dependent and merits attention towards the pregnancy induced physiologic changes which may alter the pharmacokinetics of various drugs. Furthermore, the foetus and amniotic fluid act as a third space, and drugs enter to foetal circulation from the mother. These anti-cancer agents are teratogenic and are absolutely contraindicated during the first trimester [91, 92]. However, long term data ensured the safety of standard chemotherapy drugs (anthracycline based) in second and third trimester and not found associated with perinatal complications/deaths [91, 93]. Adriamycin is preferred (Adriamycin and cyclophosphamide -AC) as it does not cross blood placental barrier being a larger molecule [94]. The data about the safety of taxanes is limited though the emerging data is more reassuring, still caution needs to be practised [91, 92, 95]. Targeted therapy like trastuzumab, hormonal therapy like tamoxifen and radiotherapy are teratogenic and must be used only in post-partum settings and only when indicated [91, 92]. Surgery can be executed in all the trimesters; however, breast conservation needs appropriate planning for subsequent need of radiation therapy.

The PABC registry study from India aimed to evaluate the epidemiological aspects, demographics, and outcomes [95]. The stage-by-stage short-term oncologic and obstetric outcomes in 104 patients registered, remain comparable in this study as well as in some other studies and children born to antenatal mothers attained normal milestones till the last follow up recorded [96].

Thus, patients with pregnancy associated breast cancer need to be reassured. For those diagnosed in the first trimester a discussion regarding termination of pregnancy especially if diagnosed early in first trimester versus waiting till second trimester and initiating treatment if an early-stage cancer is diagnosed late in first trimester and the patient is very keen to continue pregnancy. Those diagnosed in second and third trimester can safely continue pregnancy and receive neoadjuvant or adjuvant chemotherapy. Breast cancer surgery can be planned in the second trimester or post-partum. It is important to closely collaborate with the obstetrician and monitor the patient and foetus before each cycle of chemotherapy. There should be a gap of preferably two to three weeks between the last cycle of chemotherapy and delivery to allow for blood counts to recover. Growth factors may be safely used during pregnancy. The use of other supportive medications during pregnancy should be carefully monitored. The obstetric plan should remain independent of the diagnosis of breast cancer with the goal of trying to achieve full term delivery. The risk of foetal malformation is not significantly increased.

24.17 Conclusion

Thus, in patients with breast cancer the morbidity due to comorbidities and causes of non-breast cancer mortality must be weighed against breast cancer mortality when taking treatment decisions. Special consideration needs to be given in situation such as pregnancy. The ultimate goal being to provide optimal care to improve survival.

References

1. Hong CC, Ambrosone CB, Goodwin PJ. Comorbidities and their management: potential impact on breast cancer outcomes. Adv Exp Med Biol. 2015;862:155–75.
2. Silliman RA, Balducci L, Goodwin JS, Holmes FF, Leventhal EA. Breast cancer care in old age: what we know, don' t know, and do. J Natl Cancer Inst. 1993;85:190–9.
3. Silliman RA, Troyan SL, Guadagnoli E, Kaplan SH, Greenfield S. The impact of age, marital status, and physician patient interactions on the care of older women with breast carcinoma. Cancer. 1997;80:1326–34.
4. Silliman RA, Guadagnoli E, Weitberg AB, Mor V. Age as a predictor of diagnostic and initial treatment intensity in newly diagnosed breast cancer patients. J Gerontol. 1989;44:M46–50.
5. Trimble EL, Carter CL, Cain D, Freidlin B, Ungerleider RS, Friedman MA. Representation of older patients in cancer treatment trials. Cancer. 1994;74:2208–14.
6. Global Burden of Disease Cancer Collaboration. The global burden of cancer 2013. JAMA Oncol. 2015;1(4):505–27.
7. Søgaard M, Thomsen RW, Bossen KS, Sørensen HT, Norgaard M. The impact of comorbidity on cancer survival: a review. Clin Epidemiol. 2013;5(Supplement 1 Comorbidity and Cancer Survival):3–29.
8. Dehal A, Abbas A, Johna S. Comorbidity and outcomes after surgery among women with breast cancer: analysis of nationwide in-patient sample database. Breast Cancer Res Treat. 2013;139:469–76.
9. Kiderlen M, de Glas NA, Bastiaannet E, et al. Impact of comorbidity on outcome of older breast cancer patients: a FOCUS cohort study. Breast Cancer Res Treat. 2014;145:185–92.
10. Land LH, Dalton SO, Jensen M, et al. Impact of comorbidity on mortality: a cohort study of 62,591 Danish women diagnosed with early breast cancer, 1990–2008. Breast Cancer Res Treat. 2012;131:1013–20.
11. Gold HT, Do HT, Dick AW. Correlates and effect of suboptimal radiotherapy in women with ductal carcinoma in situ or early invasive breast cancer. Cancer. 2008;113(11):3108–15.
12. Muss HB, Berry DA, Cirrincione C, et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the cancer and leukemia group B experience. J Clin Oncol. 2007;25:3699–704.
13. Han J, Lee HB, Lee ES, et al. The treatment outcomes and the use of adjuvant therapies in breast cancer patients with severe co-morbidities. PLoS One. 2017;12(3):e0173721. Published 2017 Mar 21
14. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA. 2008;300(23):2754–64.
15. Luo J, Hendryx M, Virnig B, et al. Pre-existing diabetes and breast cancer prognosis among elderly women. Br J Cancer. 2015;113(5):827–32.
16. Klepin HD, Pitcher BN, Ballman KV, et al. Comorbidity, chemotherapy toxicity, and outcomes among older women receiving adjuvant chemotherapy for breast cancer on a clinical trial: CALGB 49907 and CALGB 361004 (alliance). J Oncol Pract. 2014;10(5):e285–92.
17. Peairs KS, Barone BB, Snyder CF, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. J Clin Oncol. 2011;29(1):40–6.
18. Zhao XB, Ren GS. Diabetes mellitus and prognosis in women with breast cancer: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95(49):e5602.
19. Srokowski TP, Fang S, Hortobagyi GN, Giordano SH. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol. 2009;27(13):2170–6.
20. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B. Diabetes mellitus and breast cancer. Lancet Oncol. 2005;6(2):103–11.
21. Pollak M. The insulin and insulin-like growth factor receptor family in neoplasia: an update. Nat Rev Cancer. 2012;12(3):159–69.

22. Orgel E, Mittelman SD. The links between insulin resistance, diabetes, and cancer. Curr Diab Rep. 2013;13(2):213–22.
23. Noto H, Goto A, Tsujimoto T, Osame K, Noda M. Latest insights into the risk of cancer in diabetes. J Diabetes Investig. 2013;4(3):225–32.
24. Baxter RC. IGF binding proteins in cancer: mechanistic and clinical insights. Nat Rev Cancer. 2014;14(5):329–41.
25. Muti P, Quattrin T, Grant BJB, et al. Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev. 2002;11(11):1361–8.
26. Lawlor DA, Smith GD, Ebrahim S. Hyperinsulinaemia and increased risk of breast cancer: findings from the British women's heart and health study. Cancer Causes Control. 2004;15(3):267–75.
27. Gunter MJ, Hoover DR, Yu H, et al. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 2009;101(1):48–60.
28. Chodick G, Zucker I. Diabetes, gestational diabetes and the risk of cancer in women: epidemiologic evidence and possible biologic mechanisms. Womens Health. 2011;7(2):227–37.
29. Formica V, Tesauro M, Cardillo C, Roselli M. Insulinemia and the risk of breast cancer and its relapse. Diabetes Obes Metab. 2012;14(12):1073–80.
30. Weiderpass E, Gridley G, Persson I, Nyrén O, Ekbom A, Adami H-O. Risk of endometrial and breast cancer in patients with diabetes mellitus. Int J Cancer. 1997;71(3):360–3.
31. Kabat GC, Kim M, Caan BJ, et al. Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer. Int J Cancer. 2009;125(11):2704–10.
32. Arcidiacono B, Iiritano S, Nocera A, et al. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. Exp Diabetes Res. 2012;2012:12.
33. Fierz Y, Novosyadlyy R, Vijayakumar A, Yakar S, LeRoith D. Insulin-sensitizing therapy attenuates type 2 diabetes-mediated mammary tumor progression. Diabetes. 2010;59(3):686–93.
34. Weichhaus M, Broom J, Wahle K, Bermano G. A novel role for insulin resistance in the connection between obesity and postmenopausal breast cancer. Int J Oncol. 2012;41(2):745–52.
35. Suba Z. Interplay between insulin resistance and estrogen deficiency as co-activators in carcinogenesis. Pathol Oncol Res. 2012;18(2):123–33.
36. Hawsawi Y, El-Gendy R, Twelves C, Speirs V, Beattie J. Insulin-like growth factor—oestradiol crosstalk and mammary gland tumourigenesis. Biochim Biophys Acta. 2013;1836(2):345–53.
37. Majuri A, Santaniemi M, Rautio K, et al. Rosiglitazone treatment increases plasma levels of adiponectin and decreases levels of resistin in overweight women with PCOS: a randomized placebo-controlled study. Eur J Endocrinol. 2007;156(2):263–9.
38. Kurtzhals P, Schäffer L, Sørensen A, Kristensen C, Jonassen I, Schmid C, Trüb T. Correlations of receptor clinical use. Diabetes. 2000;49(6):999–1005.
39. Hatoum D, McGowan EM. Recent advances in the use of metformin: can treating diabetes prevent breast cancer? Biomed Res Int. 2015;2015:548436.
40. Jiralerspong S, Palla SL, Giordano SH, et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol. 2009;27(20):3297–302.
41. Sonnenblick A, Agbor-Tarh D, Bradbury I, et al. Impact of diabetes, insulin, and metformin use on the outcome of patients with human epidermal growth factor receptor 2-positive primary breast cancer: analysis from the ALTTO phase III randomized trial. J Clin Oncol. 2017;35(13):1421–9.
42. Xu H, Aldrich MC, Chen Q, et al. Validating drug repurposing signals using electronic health records: a case study of metformin associated with reduced cancer mortality. J Am Med Inform Assoc. 2015;22(1):179–91.
43. Chlebowski RT, McTiernan A, Wactawski-Wende J, et al. Diabetes, metformin, and breast cancer in postmenopausal women. J Clin Oncol. 2012;30(23):2844–52.
44. Camacho L, Dasgupta A, Jiralerspong S. Metformin in breast cancer - an evolving mystery. Breast Cancer Res. 2015;17(1):88. Published 2015 Jun 26

45. Lega IC, Austin PC, Fischer HD, Fung K, Krzyzanowska MK, Amir E, Lorraine L. Lipscombe. Diabetes Care. 2018, Apr;41(4):755–76.
46. Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of chemotherapy-induced peripheral neuropathy. Int J Mol Sci. 2019;20(6):1451.
47. Bao T, Basal C, Seluzicki C, Li SQ, Seidman AD, Mao JJ. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. Breast Cancer Res Treat. 2016;159(2):327–33.
48. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. N Engl J Med. 2019;380(20):1929–40.
49. Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. N Engl J Med. 2011;366(6):520–9.
50. Hamood R, Hamood H, Merhasin I, Keinan-Boker L. Diabetes after hormone therapy in breast cancer survivors: a case-cohort study. J Clin Oncol. 2018;36(20):2061–9.
51. Han H, Guo W, Shi W, et al. Hypertension and breast cancer risk: a systematic review and meta-analysis. Sci Rep. 2017;7:44877. Published 2017 Mar 20
52. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2017;35(8):893–911.
53. Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. Oncologist. 2012;17(6):756–65.
54. Launay-Vacher V, Oudard S, Janus N, Gligorov J, Pourrat X, Rixe O, et al. Prevalence of renal insufficiency in cancer patients and implications for anticancer drug management. Cancer. 2007;110(6):1376–84.
55. Casal MA, Nolin TD, Beumer JH. Estimation of kidney function in oncology. Clin J Am Soc Nephrol. 2019;14(4):587.
56. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.
57. Dhesy-Thind S, Fletcher GG, Blanchette PS, Clemons MJ, Dillmon MS, Frank ES, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2017;35(18):2062–81.
58. Hendrayana T, Wilmer A, Kurth V, Schmidt-Wolf IG, Jaehde U. Anticancer dose adjustment for patients with renal and hepatic dysfunction: from scientific evidence to clinical application. Sci Pharm. 2017;85:1–16.
59. Shaikh SA, Regal RE. Dosing of enoxaparin in renal impairment. P T. 2017;42(4):245–9.
60. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. Kidney Int. 2008;74(11):1385–93.
61. Brufsky AM, Sereika SM, Mathew A, Tomifumi O, Singh V, Rosenzweig M. Long-term treatment with intravenous bisphosphonates in metastatic breast cancer: a retrospective study. Breast J. 2013;19(5):504–11.
62. Yancik R, Wesley MN, Ries LAG, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA. 2001;285(7):885–92.
63. Negi PC, Sondhi S, Asotra S, Mahajan K, Mehta A. Current status of rheumatic heart disease in India. Indian Heart J. 2019;71(1):85–90.
64. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol. 2020;31(2):171–90.
65. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2014;27(9):911–39.

66. Jones AL, Barlow M, Barrett-Lee PJ, et al. Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. Br J Cancer. 2009;100(5):684–92.
67. Lynce F, Barac A, Geng X, Dang C, Yu AF, Smith KL, et al. Prospective evaluation of the cardiac safety of HER2-targeted therapies in patients with HER2-positive breast cancer and compromised heart function: the SAFE-HEaRt study. Breast Cancer Res Treat. 2019;175(3):595–603.
68. Roché H, Fumoleau P, Spielmann M, Canon J-L, Delozier T, Serin D, et al. Sequential adjuvant Epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 trial. J Clin Oncol. 2006;24(36):5664–71.
69. Blum JL, Flynn PJ, Yothers G, Asmar L, Geyer CE Jr, Jacobs SA, et al. Anthracyclines in early breast cancer: the ABC trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG oncology). J Clin Oncol. 2017;35(23):2647–55.
70. Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US oncology research trial 9735. J Clin Oncol. 2009;27(8):1177–83.
71. Bonadonna G, Moliterni A, Zambetti M, Daidone MG, Pilotti S, Gianni L, et al. 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study. BMJ: British Med J. 2005;330(7485):217.
72. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant Trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273–83.
73. Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med. 2015;372(2):134–41.
74. Crone SA, Zhao YY, Fan L, Gu Y, Minamisawa S, Liu Y, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med. 2002;8(5):459–65.
75. Eiger D, Franzoi MA, Pondé N, Brandão M, de Angelis C, Schmitt Nogueira M, et al. Cardiotoxicity of trastuzumab given for 12 months compared to shorter treatment periods: a systematic review and meta-analysis of six clinical trials. ESMO Open. 2020;5(1):e000659.
76. Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, et al. Multidisciplinary approach to novel therapies in cardio-oncology research (MANTICORE 101–breast): a randomized trial for the prevention of Trastuzumab-associated cardiotoxicity. J Clin Oncol. 2017;35(8):870–7.
77. Südhoff T, Enderle MD, Pahlke M, Petz C, Teschendorf C, Graeven U, et al. 5-fluorouracil induces arterial vasocontractions. Ann Oncol. 2004;15(4):661–4.
78. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol. 1993;20(4 Suppl 3):1–15.
79. Shah K, Gupta S, Ghosh J, Bajpai J, Maheshwari A. Acute non-ST elevation myocardial infarction following paclitaxel administration for ovarian carcinoma: a case report and review of literature. J Cancer Res Ther. 2012;8(3):442–4.
80. Coppola C, Rienzo A, Piscopo G, Barbieri A, Arra C, Maurea N. Management of QT prolongation induced by anti-cancer drugs: target therapy and old agents. Different algorithms for different drugs. Cancer Treat Rev. 2018;63:135–43.
81. Porta-Sánchez A, Gilbert C, Spears D, Amir E, Chan J, Nanthakumar K, et al. Incidence, diagnosis, and management of QT prolongation induced by cancer therapies: a systematic review. J Am Heart Assoc. 2017;6(12):e007724.
82. Campia U, Moslehi JJ, Amiri-Kordestani L, Barac A, Beckman JA, Chism DD, et al. Cardio-oncology: vascular and metabolic perspectives: a scientific statement from the American Heart Association. Circulation. 2019;139(13):e579–602.
83. Christensen S, Pedersen L, Grijota M, Kornum JB, Beiderbeck A, Sørensen HT. Incidence of interstitial pneumonitis among breast cancer patients: a 10-year Danish population-based cohort study. Br J Cancer. 2008;98(11):1870–5.

84. Taghian AG, Assaad SI, Niemierko A, Kuter I, Younger J, Schoenthaler R, et al. Risk of pneumonitis in breast cancer patients treated with radiation therapy and combination chemotherapy with paclitaxel. J Natl Cancer Inst. 2001;93(23):1806–11.
85. Skeoch S, Weatherley N, Swift AJ, Oldroyd A, Johns C, Hayton C, et al. Drug-Induced interstitial lung disease: a systematic review. J Clin Med. 2018;7(10):356.
86. Khan A, McNally D, Tutschka PJ, Bilgrami S. Paclitaxel-induced acute bilateral pneumonitis. Ann Pharmacother. 1997;31(12):1471–4.
87. İzci F, İlgün AS, Fındıklı E, Özmen V. Psychiatric symptoms and psychosocial problems in patients with breast cancer. J Breast Health. 2016;12(3):94–101.
88. Ganz PA. Psychological and social aspects of breast cancer. Oncology (Williston Park). 2008 May;22(6):642–646. discussion 650, 653.
89. Schmid-Büchi S, Halfens RJ, Dassen T, van den Borne B. A review of psychosocial needs of breast-cancer patients and their relatives. J Clin Nurs. 2008 Nov;17(21):2895–909.
90. Ruiz R, Herrero C, Strasser-Weippl K, Touya D, St Louis J, Bukowski A, et al. Epidemiology and pathophysiology of pregnancy-associated breast cancer: a review. Breast. 2017;35:136–41.
91. Bajpai J, Surappa S. Pregnancy-associated breast cancer: controversies and consensus! Oncobiol Targets. 2016;3:6.
92. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019;30(8):1194–220.
93. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol. 2004;5(5):283–91.
94. Cardonick E, Bhat A, Gilmandyar D, Somer R. Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. Ann Oncol. 2012;23(12):3016–23.
95. Bajpai J, Dandekar S, Simha V, Shylasree T, Sarin R, Bansal V, et al. 117P pregnancy-associated breast cancer (PABC): demographics and outcome analysis from a lower and middle income country (LMIC). Ann Oncol. 2020;31:S55.
96. Murthy RK, Theriault RL, Barnett CM, Hodge S, Ramirez MM, Milbourne A, et al. Outcomes of children exposed in utero to chemotherapy for breast cancer. Breast Cancer Res. 2014;16(6):500.

Management of Lymphoedema in Breast Cancer

25

Hari Venkatramani, R. Raja Shanmugakrishnan, and S. Raja Sabapathy

25.1 Introduction

Breast cancer is the most common cancer among women in India (27.7%) and is also the most common cancer among both men and women (14%) combined [1]. With the recent advances in the management of breast cancer, the 5-year survival is about 90% [2]. Hence, the quality of life has become very important for breast cancer survivors. Lymphoedema that can occur in the process of breast cancer management is a chronic complication. Lymphoedema significantly reduces the quality of life as it is functionally incapacitating, affects the psychosocial balance of individuals, increases the cost of treatment, and many are uncomfortable with the prolonged treatment.

Hari Venkatramani, MS, MCh (Plastic), DNB (Plastic) (✉)
Senior Consultant, Division of Plastic, Hand, Reconstructive Microsurgery and Burns, Ganga Hospital, Coimbatore, Tamil Nadu, India
e-mail: drhariv@gmail.com

R. Raja Shanmugakrishnan, MS, MRCS, DNB (Plastic)
Consultant, Division of Plastic, Hand, Reconstructive Microsurgery and Burns, Ganga Hospital, Coimbatore, Tamil Nadu, India

S. Raja Sabapathy, MS, MCh, DNB, FRCS
Director and Chairman, Division of Plastic, Hand, Reconstructive Microsurgery and Burns, Ganga Hospital, Coimbatore, Tamil Nadu, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_25

25.2 Pathophysiology of Breast Cancer Related Lymphoedema

Lymphoedema is defined as the collection of protein-rich lymphatic fluid in the interstitial space. Lymphoedema occurs when there is an obstruction to the flow of lymphatic fluid and when the lymphatic load exceeds the transport capacity of the lymphatic system (Fig. 25.1).

The most common cause of lymphoedema in breast cancer is due to therapy associated with breast cancer, such as surgery, radiotherapy, and post surgical infection. Surgery is an integral part in the management of operable breast cancers. Sentinel lymph node biopsies and axillary lymph node dissection for staging and treating the axilla. Lymphoedema develops in 5–7% of cases with sentinel lymph node biopsies, 13–44% of cases when axillary dissection is done, 8.3% with axillary radiotherapy and 38.3% when axillary clearance and axillary radiotherapy are combined [3, 4]. Due to the high incidence of lymphoedema,axillary radiotherapy should be avoided in all individuals with axillary lymph node dissection. The pathophysiology of radiation-induced lymphedema has not been established fully but is believed to be related to fibrosis affecting the lymph nodes causing constriction of the lymphatic channels. Certain risk factors not directly associated with breast cancer such as obesity, weight gain after diagnosis, minor upper extremity infections, injury or trauma to the affected limb and overuse of the limb can increase the risk of lymphoedema. Inflammation, infection, and high body mass index (BMI) are the main predictors of lymphoedema besides treatment-related risk. Women who had

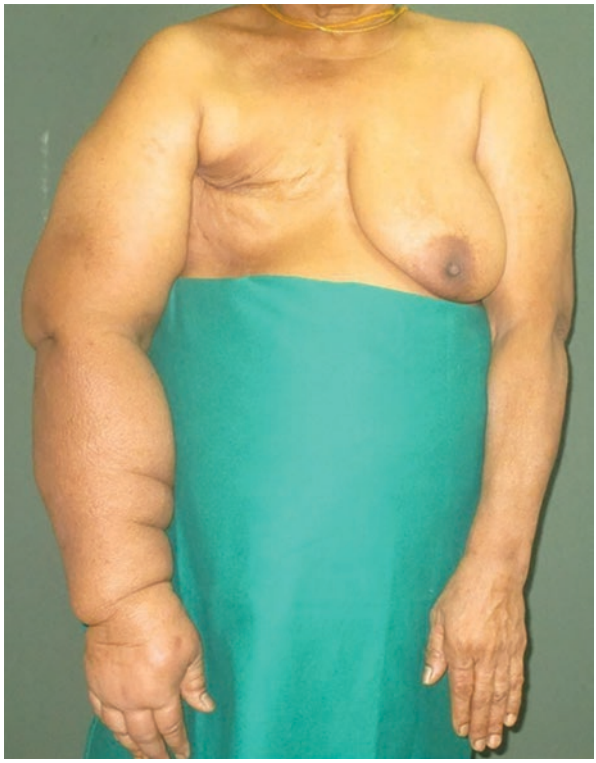


Fig. 25.1 Lady with right side post mastectomy lymphoedema

previous inflammation-infection in the breast or upper extremity were 3.8 times more predisposed to develop lymphoedema [5]. Survivors with each increase of 1 kg/m^2 in their BMI were 1.11 times more at risk for developing lymphoedema [6]. In severe cases of breast cancer, breast cancer-associated lymphoedema (BCAL) occurs due to the obstruction of the lymphatic channels or lymph nodes, or due to infiltration with tumour cells (lymphangitic carcinomatosis).

25.3 Symptoms

Two forms of lymphoedema associated with breast cancer have been described. Early lymphoedema occurs within 2 months of therapy for breast cancer and is usually transient. It results from acute lymphatic overload probably due to wound complications. Late lymphoedema occurs after 6 months and is usually progressive. Early assessment of symptoms for lymphoedema is essential as they can occur months or years before overt swelling occurs. The symptoms to look for in lymphoedema are swelling, heaviness, tightness, firmness, pain/aching/soreness, numbness, tingling, stiffness, limb fatigue, limb weakness and impaired limb mobility. These symptoms indicate increasing interstitial pressure with lymphoedema. With further increase in interstitial pressure due to lymphatic obstruction, the limb may become visibly swollen with a noticeable increase in limb size. In long-standing cases of lymphoedema, chronic oedema and fibrosis result in skin changes such as thickening of the skin, multiple skin folds, warty outgrowths, and ulcers. The multiple crevices in the skin of patients with lymphoedema act as nidus of infection if they are not cleaned well and frequently results in cellulitis of the upper limb.

25.4 Staging

The most commonly used staging for lymphoedema is the International Society of Lymphology staging [7]. This is as follows.

- **Stage 0**: Latent or subclinical lymphoedema where swelling is not evident despite impaired lymph transport and changes in subjective symptoms.
- **Stage I:** Limb swelling with pitting oedema which reduces on elevation.
- **Stage IIA:** Limb swelling with pitting oedema which does not reduce on elevation.
- **Stage IIB:** Limb swelling with non-pitting oedema which does not reduce on elevation. This occurs as excess subcutaneous fat and fibrosis develop.
- **Stage III:** Limb swelling with skin changes characteristic of fibrosis such as acanthosis, thickening of skin and warty overgrowths.

25.5 Diagnosis and Investigations

Although there is inconsistency in the criteria defining lymphoedema, lymphoedema has been arbitrarily defined in research studies as a 2 cm increase in arm circumference, 15 cm above the lateral epicondyle, a 200 ml or more increase in limb

volume or a 10% or greater change in the limb volume [8]. Investigations are done for lymphoedema to document the changes in the limb volume and to map the lymphatic flow, which would help in the treatment of breast cancer.

25.6 Investigations to Document the Changes in Limb Volume

There are multiple methods to measure the volume of the limb. A chosen method is used to measure the size of the limb each time the patient comes. This helps us to assess the condition of the patient, the efficacy of the therapy and the compliance of the patient.

(a) **Water displacement method:**
The water displacement method is generally considered as the gold standard method for assessing the volume of the limb. Patients submerge the affected limb up to 15 cms above the lateral epicondyle in a container filled with water and the water overflown is measured. However, this method is seldom used clinically as this can be messy and cumbersome. Furthermore, it does not provide data about the localisation of oedema and the shape of the extremity. This method is also contraindicated with open skin lesions.

(b) **Sequential Circumferential Arm Measurements**
A flexible non-stretch tape is used to measure the circumference of the upper limb every four cms starting from the wrist up to the axilla. The volume of each segment is calculated by using the Truncated Cone formula. If C1 and C2 are the circumferences at the end of the segment and h is the distance between each segment, the volume of each segment V is given by the formula.

$$V = h\left[C1 \times C1 + C1 \times C2 + C2 \times C2\right] / 12 \times \pi$$

The volume of each segment is added to give the size of the entire upper limb. The formulas can be fed into an Excel sheet and the volume of the limb can be easily calculated. This is the most commonly used method to calculate the volume of the limb with the standard error of measurements ranging between 10 ml and 70 ml. The volume of the hand is however not measured by this method.

(c) **Infrared Perometry**
Infrared perometry is an optoelectric device which uses infrared rays to measure the volume, shape, and circumference of the upper limb. The advantage of this method is that it is very accurate, and it does not touch the skin of the limb. So, it can be used to measure the volume of limbs that are of different shapes and with multiple skin changes like ulcers.

(d) **Bioelectrical impedance analysis**
Bioelectrical impedance analysis measures the impedance and resistance of the extracellular fluid using a single frequency below 30 kHz. The ratio between the impedance values of the unaffected and the affected limb called as the Lymphoedema Index, termed as L-Dex ratio is calculated. A L-Dex ratio of

more than 7.1 helps to identify the breast cancer survivorswho may lymphoedema with 80% sensitivity and 90% specificity [9]. This method helps to identify limbs at risk for lymphoedema. This technique is however not appropriate in assessing bilateral lymphoedema.

25.7 Investigations to Map the Lymphatics

Investigations for lymphatic mapping are undertaken to know the position of the lymphatic channels and lymph nodes, to know the level of obstruction and plan surgery for lymphoedema. These investigations also help to differentiate lymphoedema from other causes of leg swelling such as chronic venous insufficiency, hypoalbuminemia, cellulitis, and arthritis.

(a) **Lymphangiography**

This technique used iodinated oil-based contrast to inject and visualise the lymphatics. However, this method has largely been abandoned because

(i). Difficulty in the cannulation of large lymphatic draining collectors through tiny skin lymphatics

(ii). Damage to the lymphatic endothelial lining by the contrast medium

(iii). Risk of oil(fat) embolism

(b) **Lymphoscintigraphy**

In this method, a radiopharmaceutical such as technetium Tc 99 m–filtered sulphur colloid is injected into the web spaces of the hand. This radiopharmaceutical enters and travels through the lymphatic system and emits radioactive energy which is captured by a special gamma camera, also known as scintillation camera. This test helps to identify the lymphatic pathways, lymph nodes, collateral lymph channels, dermal backflow, and clearance time of the radiopharmaceutical. This is a safe and accepted method to diagnose lymphoedema with a sensitivity of 73–97% and specificity nearing 100% [10].

(c) **Magnetic Resonance Lymphangiography (MRL)**

A mixture of paramagnetic contrast medium containing gadobenate dimeglumine and lignocaine is injected intradermally in the webspaces of the hands and MRI is performed [11]. MRL helps to grade the lymphoedema based on the lymphatic drainage pattern and delay in drainage and helps to understand the course of the lymphatic channel in relation to the nearby venules, skin, and lymph nodes. The highlight of this method is that it offers better spatial orientation of the lymphatics and it does not need radiotherapy. However, MRL is costly, not freely available and can be time consuming.

(d) **Indocyanine Green (ICG) Lymphangiography**

This is presently commonly used and is becoming more popular. Indocyanine green is a water-soluble biliary excreted dye which is injected intradermally in the web spaces of the hand. The ICG is then taken by the lymphatic vessels. When LASER light is shown on the part containing the ICG, the molecules get excited and emit infrared rays which is captured by the camera and shown on the screen [12]. ICG lymphangiography helps us to know the position of the lymphatic channels. When there is no obstruction of lymphatics, and when

there are healthy lymphatic channels, the lymphatic channels are shown as a linear pattern. With increasing levels of obstruction and with more dermal backflow, the pattern appears as splash, stardust and diffuse respectively (Fig. 25.2).

Knowledge of the pattern of lymphatics is essential as lymphovenous anastomosis (LVA) should be done only when the ICG lymphatic pattern is linear. ICG lymphangiography is used intra operatively also to find out the position of the lymphatic and can also help to ascertain the patency of lymphovenous anastomosis.

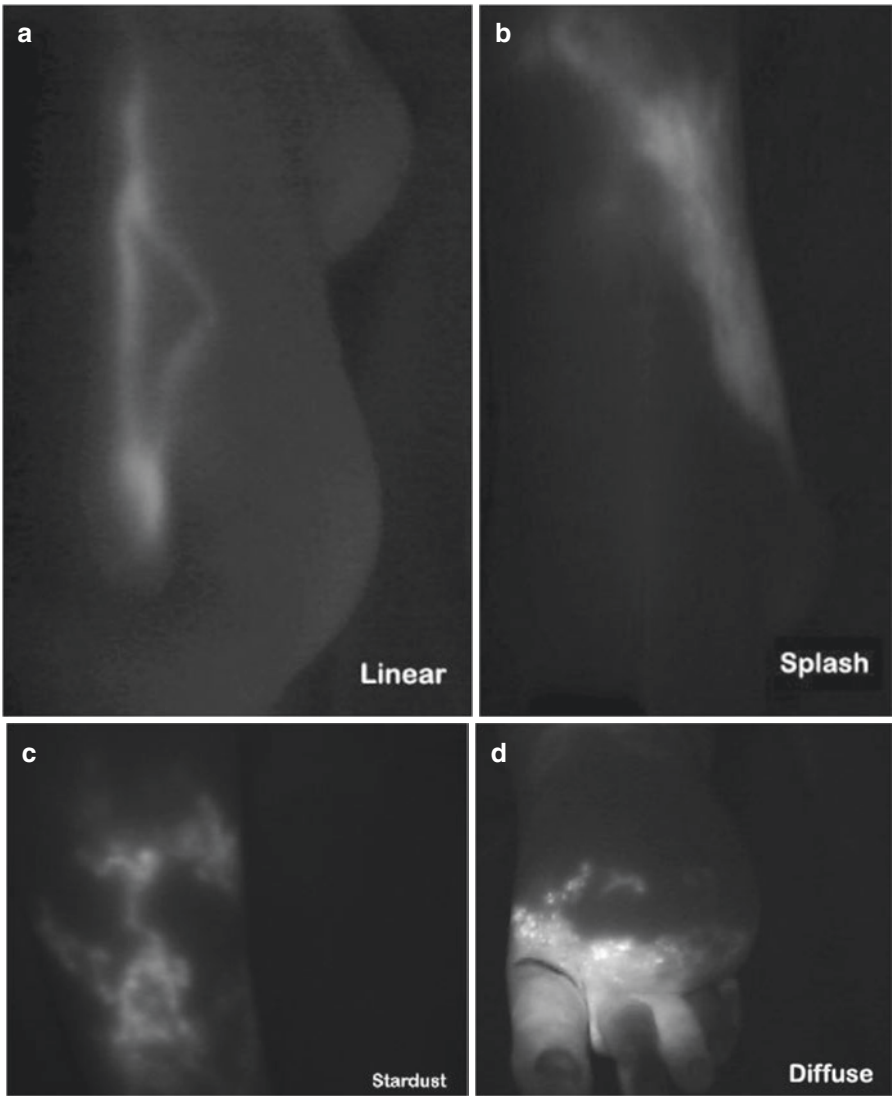


Fig. 25.2 ICG lymphangiography patterns (**a**) Linear pattern (**b**) Splash pattern (**c**) Stardust pattern (**d**) Diffuse pattern

25.8 Management of Lymphoedema

25.8.1 Nonsurgical Management

The management of lymphoedema starts with a good history, clinical examination and investigations as described above. The treatment of lymphoedema should start with nonsurgical modalities. Nonsurgical modalities are important as they not only reduce the amount of swelling in lymphoedema, but also make the skin soft and pliable which helps to facilitate further surgeries. Compliance to the nonsurgical management can be a problem as they can be time consuming, uncomfortable, and costly. Hence the importance of the nonsurgical management must be emphasized clearly to the patient before initiation of nonsurgical management. Patients should be encouraged to avoid gaining weight and losing weight could improve their symptoms. The non-surgical management of lymphoedema is done by a process called as Complete Decongestive Therapy (CDT) [13]. This includes:

(a) **Manual Lymphatic Drainage (MLD):**
Manual lymphatic drainage is skin stretching massage of the skin performed to open the lymphatics in unaffected regions to drain fluid from the affected regions and increase lymphatic drainage

(b) **Compression:**
Compression therapy is used to mobilise the lymphatics and reduce the swelling. Bandage application causes high pressure during activity and relatively low pressure in the limb while resting.

(c) **Exercises:**
Exercises help to pump lymph out of the swollen area and prevents stiffness in the shoulder, elbow, wrist, and the fingers

(d) **Deep Breathing exercises:**
Deep breathing exercises help to augment the venous and lymphatic flow.

(e) **Skin and Nail Care:**
The skin is kept clean and moisturised to prevent dry skin. The nails should be trimmed appropriately. The web spaces in the hand and the crevasses in the folds of skin need to be kept dry to prevent fungal infections.

The CDT regimen is divided into 2 phases namely

(a) **Acute or Reduction phase**
This phase aims to get rid of the excess lymphatic fluid in the upper extremity. This phase can last for about 3–8 weeks, depending on how long it takes to bring down the swelling in the upper extremity. The patient should see a trained lymphoedema therapist at least five times in a week. The therapist would do Manual Lymphatic Drainage (MLD) and exercises. They would bandage the upper extremity with short stretch compression bandages which needs to be worn all times of the day except while taking a shower and doing MLD.

(b) **Maintenance Phase**

This phase aims to maintain the results of the initial phase. Skin and nail care are emphasized. Well-fitting compression garments should be worn throughout the day, and soft bandages are to be worn in the night. The patients are to avoid injuries to the limb. Exercise should be done within the compression garments.

25.8.2 Surgical Management

Surgery for lymphoedema should be contemplated only when the non-surgical management fails or has not produced the expected decrease in swelling of the limb. Surgery is not an answer to the poor compliance of non-surgical management. Good results are obtained only when surgery is followed up with good non-surgical management. ICG lymphangiography is done for all patients. If there are good lymphatic channels as evidenced by linear streaks in ICG lymphangiography, Lymphovenous anastomosis (LVA) can be done. LVA is a physiological procedure in which lymphatic channels are anastomosed to veins to promote an alternative flow in the lymphatics. If the ICG lymphangiography shows dermal backflow and obstruction to the flow of lymphatics as evidenced by splash, stardust, or diffuse patterns in the ICG lymphangiography, Vascularised lymph node transfer (VLNT) or surgical debulking or a combination of them are done. If the swelling in the upper extremity is due to excess fat, then liposuction can be done [14].

25.8.2.1 Lymphovenous Anastomosis (LVA)

Lymphovenous Anastomosis (LVA) is a microsurgical procedure in which lymphatic vessels lesser than 0.8 mm are connected to the subdermal venules using fine microsurgical sutures, instruments, and high-resolution magnification microscopes [15] (Fig. 25.3).

LVA is used to treat early lymphoedema (Stage 1&2) as LVA needs good functional lymphatic channels and minimal fibrosis for it to be effective. In later stages LVA can be combined with other procedures such as Vascularised lymph node transfers or surgical debulking. Small subdermal venules less than 1 mm in size with no backflow are preferably chosen as they have low intravascular pressure. Larger veins with backflow are associated with higher intravascular pressure and obstruction of the anastomotic site. Hence LVA is more commonly performed in the distal part of the limb where there are smaller venules and the lymphatic pressure is more.

LVA can be done under regional or general anaesthesia under tourniquet control, or it can be done with a local anaesthetic containing adrenaline to limit the bleeding from the dermal edges. LVA is best done using Indocyanine green (ICG) lymphangiography as they help to easily locate the position of the lymphatic channels. The position of the lymphatic channel is easily marked using a pen on the skin. A 3 cm incision is made near the lymphatic vessel and then the anastomosis is done. If ICG is not available, 5–10 incisions can be made on the medial and lateral side of the affected extremities as the lymphatics are more common in these areas. Isosulfan

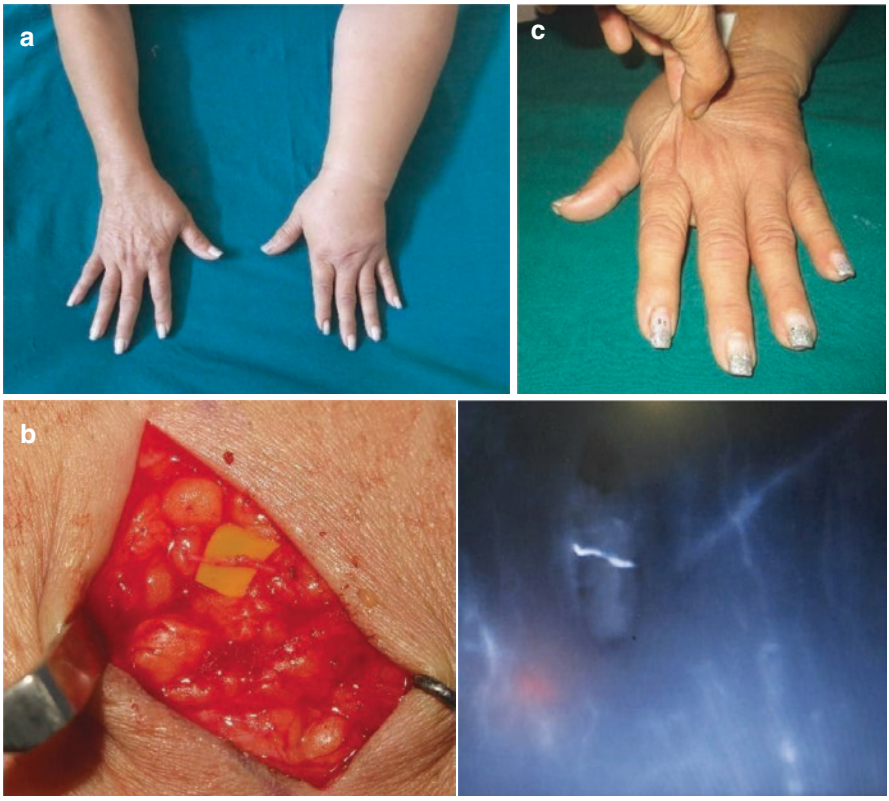


Fig. 25.3 (**a**) Left side upper limb lymphoedema (**b**) LVA done and confirmed by ICG. (**c**) Post op result showing resolution of lymphoedema

Blue or Lymphazurin (Covidien) is injected just distal to the incision site. The dye easily gets absorbed into the lymphatic channels and facilitates easy visualisation of the lymphatic channels. Once the appropriate lymphatic vessels and veins are identified, anastomosis is done between the lymphatic channel and venule. As the lymphatic channel and venule are exceedingly small, this can be technically challenging. High resolution microscopes with a magnification of 20X to 30X, fine sutures such as 10-0 or 11-0 and special instruments are needed to perform this procedure. Although there is no consensus on the number of anastomoses to produce a significant reduction of lymphoedema, it is believed that increasing the number of LVA can improve the outcome. As the incisions are only skin deep, the patient usually has only mild pain and can go home the same day or the next day. Bandages are applied until the wounds heal. Compression stockings are used 3 weeks after the operation and continued for at least 6 months after the procedure. Best results are obtained when the compression is continued for lifetime. After analysing 18 studies containing 939 patients, Scaglioni et al. have noted that all studies show that LVA with or without compression treatment resulted in the improvement of both

subjective and objective outcomes of lymphoedema [16]. Several studies also show a striking reduction in the episodes of cellulitis post-surgery [17, 18].

25.8.2.2 Vascularised Lymph Node Transfer (VLNT)

Vascularised lymph node transfer is a surgical procedure used to treat lymphoedema in which missing lymph nodes of an affected extremity is replaced by harvesting healthy vascularised lymph nodes from one part of the body and transplanting them to the affected area using microsurgery. VLNT can be done in Stage II & III when the ICG lymphangiography shows splash, stardust and diffuse patterns indicating significant backflow. For better outcome, VLNT can be combined with LVA in some situations where good lymphatic channels are available.

The mechanism of action of VLNT is not fully understood and several theories have been postulated regarding this

(i) VLNT acts like a "Lymphatic Wick" between the proximal and distal lymphatic vessels in the recipient site. This is specifically attractive in women affected with lymphoedema due to breast cancer wherein the axillary lymph nodes are removed [19].
(ii) High levels of Vascular Endothelial Growth Factor-C are produced by the transferred lymph nodes which induces lymphangiogenesis and facilitates recanalization between the recipient and transferred lymph nodes [20].
(iii) Placing healthy vascularised tissue instead of the scar which hinders lymphatic flow helps to facilitate lymphatic drainage [14]
(iv) VLNT act like a "lymphatic pump". The strong arterial pulsations in the flap provide a strong hydrostatic force in the flap. The flap veins which have low pressure act like a suction drawing the lymphatic fluid into the capillaries [21].
(v) The lymphatic collection is predominantly distal due to gravity. VLNT when placed distally seems to have a "catchment effect" thus improving lymphatic drainage [22].

VLNT can be harvested from many donor sites namely the groin, thoracic area, submental, supraclavicular, mesentery and omental lymph nodes. Each donor site has its own advantages and disadvantages which is given in Table 25.1.

The VLNT can be placed both proximally and distally in the limb. For women with lymphoedema due to breast cancer, the most preferred VLNT is using the DIEP (Deep Inferior Epigastric Artery Perforator) flap with accompanying groin lymph nodes (Fig. 25.4).

This flap not only helps in lymphoedema, but also helps to reconstruct the missing breast at the same time. The flap is taken as caudally as possible along with groin lymph nodes and superficial circumflex iliac vessels. The flap is turned 180 degrees and the Superficial circumflex iliac vessels are anastomosed to the thoracodorsal vessels and the main pedicle of the DIEP flap is anastomosed to the internal mammary vessels. The major concern about this flap is about donor site lymphoedema in the lower extremity. The donor site lymphoedema in the lower limb can be prevented by harvesting groin lymph nodes lateral to the femoral vessels and by reverse

Table 25.1 Advantages and Disadvantages of various types of Vascularised Lymph Node Transfers (VLNT)

Vascularised Lymph node flaps	Advantages	Disadvantages
Groin	Preferred for lymphoedema secondary to breast cancer; Can be taken with DIEP flap along with breast reconstruction; well concealed scar; good cosmesis;	Donor site lower limb lymphoedema
Omentum	No donor site lymphoedema; rich source of lymphatic tissue;	Laparoscopy/laparotomy needed; poor cosmesis. Complications due to laparotomy; adhesions; hernias; DVT
Submental	Less donor site lymphoedema	Injury to marginal mandibular branch of facial nerve; pedicle is short and vessel is small; few nodes in the flap
Supraclavicular	Less donor site lymphoedema	Vessel is small; few nodes; damage to brachial plexus and lymphatic duct
Lateral thoracic	Commonly used for lower limb lymphoedema	Donor site upper limb lymphoedema; damage to the thoracodorsal nerve; not used often for upper limb lymphoedema

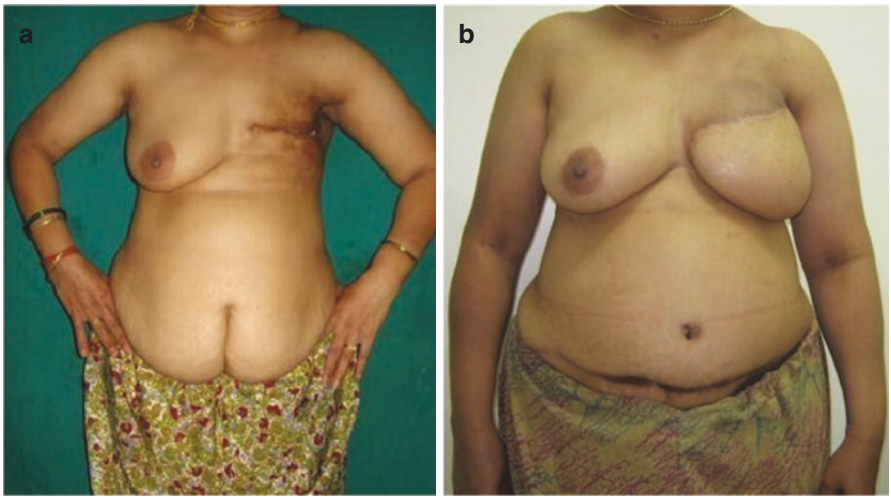


Fig. 25.4 (**a**) Post mastectomy left side lymphoedema (**b**) VLNT using DIEP flap

lymphatic mapping. In reverse lymphatic mapping two different methods are used to evaluate the lymphatic drainage of the flap to be harvested and the potential donor site area [23]. Technetium injections are injected in the web spaces of the foot and ICG is injected intradermally in the lower abdomen. A gamma probe helps to identify the groin lymph nodes which are avoided.

25.8.2.3 Liposuction

It has been noticed that in long standing cases of lymphoedema, there is excess deposition of fat in the limbs probably due to the chronic inflammation and impaired lymphatic drainage associated with lymphoedema. In lymphoedema, there is accumulation of both excess fat and lymphatic fluid. The excess lymphatic fluid is removed by conservative techniques like Complete Decongestive therapy (CDT), Lymphovenous Anastomosis (LVA) and Vascularised Lymph Node Transfers (VLNT). After removal of the excess lymphatic fluid by these techniques, the accumulated fat is removed by liposuction. Liposuction is a technique to remove only fat and should be done after the excess lymphatic fluid is removed by the above conservative or microsurgical methods [24]. The absence of lymphatic collection is confirmed when the limbs are not pitting even on applying pressure on them for a minute. It is for these patients that liposuction should be done. A sterile tourniquet is applied proximally in the upper limb. Stab incisions are made, and liposuction cannulas are used to suck out the excess fat. Compression bandages are applied after the surgery. For good results, compression garments should be worn throughout life.

25.8.2.4 Surgical Debulking

Surgical debulking is done in late stages of lymphoedema with skin changes, pendulous skin (Fig. 25.5) and in places where microsurgical facilities are unavailable Earlier, the skin and subcutaneous tissue was excised circumferentially in the upper limb and skin grafts were applied over the deep fascia. However, this resulted in poor cosmesis, associated bottle neck deformity and distal lymphoedema. This procedure can be combined with VLNT as this will reduce distal lymphoedema [25]. To prevent application of skin grafts, staged subcutaneous excision beneath skin flaps can be done [26]. In this, the excess skin and subcutaneous tissue is excised from either the medial or lateral side and then closed. 3 months later, the procedure is repeated over the other side. With techniques such as doppler and CT scan, the position of the perforators is known. This helps us to raise flaps and debulk aggressively in the rest of the areas. This is called Radical reduction of lymphoedema with preservation of perforators [27].

25.9 Lymphoedema Risk Reduction

25.9.1 Axillary Reverse Mapping

Blue dye is injected subcutaneously in the arm and Technetium sulphur colloid is injected subareolarly while doing Sentinel lymph node biopsies and axillary dissection. The lymph nodes detected by the gamma probe represent the nodes draining the breast and those nodes coloured blue represent the nodes draining the arm. During axillary dissection, all nodes detected by the gamma probe draining the breast is removed leaving behind the nodes coloured blue which drain the arm. This helps to avoid lymphoedema [28].

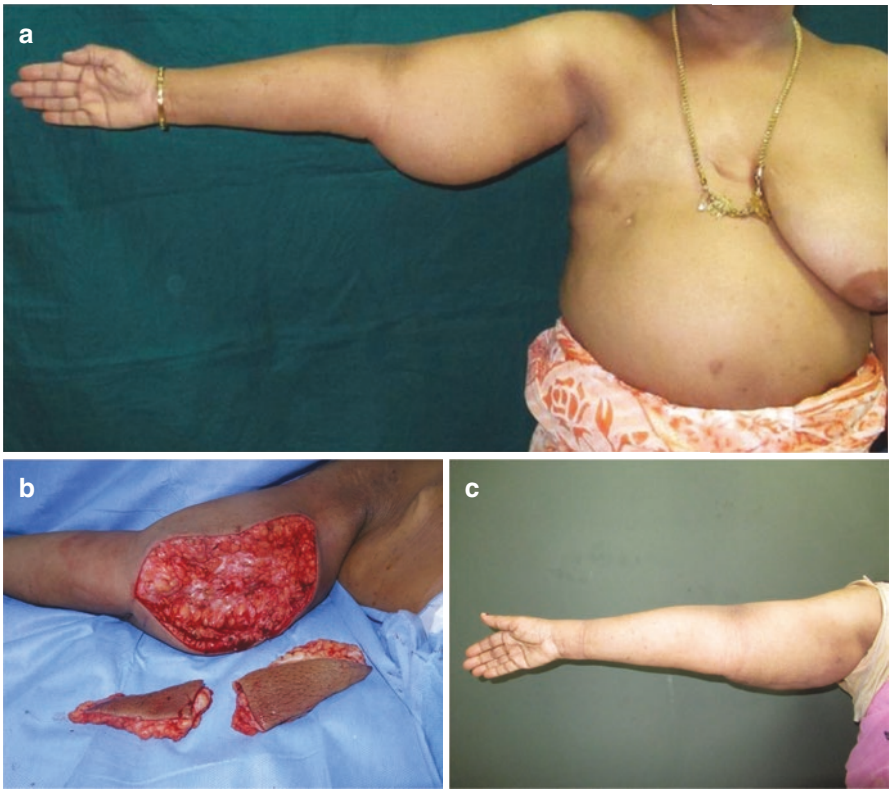


Fig. 25.5 (**a**) Post mastectomy left side lymphoedema. (**b**) Surgical debulking done to remove the pendulous part of the arm. (**c**) Post op result of surgical debulking

25.9.2 Lymphatic Microsurgical Preventive Healing Approach (LYMPHA)

In this procedure, one or more lymphatic channels that are transected during axillary dissection is anastomosed to a nearby vein. This helps to prevent lymphoedema. A recent study has reported an incidence of lymphoedema of 14.1% and 2.1% without and with LYMPHA respectively after axillary dissection [29].

25.9.3 Education of Lymphoedema Patients

Educating the lymphoedema patients about what to do and what not to do is particularly important to ensure compliance and prevent complications like cellulitis which can even worsen the lymphoedema. A card with some Dos and DONTs for lymphoedema should be given and explained to them. An example of this is given in Table 25.2.

Table 25.2 DOs and DON'Ts for Lymphoedema

Do's
1. Keep the skin meticulously clean and frequently check for any cracks, fungal infections, or rashes
2. Use a moisturising soap to take a shower or a bath.
3. Elevate the lymphoedematous limb as much as possible
4. Wear the compression stockings or garments given throughout the day.
5. Exercise as much as possible as discussed with the physiotherapist.
6. To visit the doctor if there is increasing pain, redness, and fever
Dont's
1. Avoid tight clothing such as a tight blouse, undergarments, or socks
2. Avoid wearing bangles, watches and rings in the limb affected with lymphoedema.
3. Keep the nails short. In the same time avoid having short nails.
4. Try to avoid injections in the limb affected with lymphoedema
5. No piercing or tattoos in the limb with lymphoedema
6. Avoid adding weight. It makes the lymphoedema worse.
7. Avoid hot showers.

25.10 Conclusion

With many advancements in the treatment of lymphoedema, lymphoedema needs a holistic multimodal approach in diagnosis, investigations, and treatment of lymphoedema. With good physiotherapy, nonsurgical management, microsurgical and non-microsurgical approaches, patients with lymphoedema can be treated well and their quality of life can be improved.

References

1. The Global Cancer Observatory. Gobocan 2018: India factsheet. 2018 September. http://cancerindia.org.in/globocan-2018-india-factsheet/.
2. National Cancer Institute. Surveillance, epidemiology and End results program. Cancer stat facts: female breast cancer. https://seer.cancer.gov/statfacts/html/breast.html.
3. Husted Madsen A, Haugaard K, Soerensen J, et al. Arm morbidity following sentinel lymph node biopsy or axillary lymph node dissection: a study from the Danish breast cancer cooperative group. Breast. 2008;17(2):138–47.
4. Kissin MW, Rovere GQD, Easton D, Westbury G. Risk of lymphoedema following the treatment of breast cancer. Br J Surg. 1986;73(7):580–4. https://doi.org/10.1002/bjs.1800730723.
5. Mak SS, Yeo W, Lee YM, Mo KF, Tse KY, Tse SM, Ho FP, Kwan WH. Predictors of lymphedema in patients with breast cancer undergoing axillary lymph node dissection in Hong Kong. Nurs Res. 2008;57:416–25.
6. Paskett ED, Naughton MJ, McCoy TP, Case LD, Abbott JM. The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. Cancer Epidemiol Biomark Prev. 2007;16:775–82.
7. Executive Committee. Consensus document of the international society of lymphology. Lymphology. 2016;49:170–84.
8. Armer JM, Stewart BR. A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. Lymphatic Res Bio. 2005;3:208–17.

9. Fu MR, Cleland CM, Guth AA, Kayal M, et al. L-dex ratio in detecting breast cancer related lymphoedema: reliability, sensitivity, and specificity. Lymphoology. 2001;34:2–11.
10. Ter SE, Alavi A, Kim CK, Merli G. Lymphoscinitigraphy: a reliable test for the diagnosis of lymphoedema. Clin Nucl Med. 1993;18:646–54.
11. Mazzei FG, Gentili F, Guerrini S, Cioffi SN. MR lymphangiography: a practical guide to perform it and a brief review of literature from a technical point of view. Biomed Res Int. 2017;2017:2598358.
12. Griffiths M, Chae MP, Rozen WM. Indocyanine green-based fluorescent angiography in breast reconstruction. Gland Surg. 2016;5(2):133–49.
13. Koul R, Dufan T, Russell C, et al. Efficacy of complete decongestive therapy and manual lymphatic drainage on treatment-related lymphedema in breast cancer. Int J Radiat Oncol Biol Phys. 2007;67(3):841–6.
14. Venkatramani H, Shanmugakrishnan RR, Kumaran MS, Sabapathy SR. Surgical debulking, lymphatico venous anastomosis, vascularised lymph node transfer in lower limb lymphoedema. Plast Aesthet Res. 2020;7:19.
15. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. J Reconstr Microsurg. 2000;16:437–42.
16. Scaglioni MF, Fontein DBY, Arvanitakis M, Giovanoli P. Systematic review of lymphovenous anastomosis (LVA) for the treatment of lymphedema. Microsurgery. 2017;37:947–53.
17. Chen WF, Zhao H, Yamamoto T, Hara H, Ding J. Indocyanine green lymphographic evidence of surgical efficacy following microsurgical and supermicrosurgical lymphedema reconstructions. J Reconstr Microsurg. 2016;32:688–98.
18. Yamamoto T, Koshima I. Supermicrosurgical anastomosis ofsuperficial lymphatic vessel to deep lymphatic vessel for a patient with cellulitis-induced chronic localized leg lymphedema. Microsurgery. 2015;35:68–71.
19. Honkonen KM, Visuri MT, Tervala TV, Halonen PJ, Koivisto M, et al. Lymph node transfer and perinodal lymphatic growth factor treatment for lymphedema. Ann Surg. 2013;257:961–7.
20. Saaristo AM, Niemi TS, Viitanen TP, Tervala TV, Hartiala P, et al. Microvascular breast reconstruction and lymph node transfer for postmastectomy lymphedema patients. Ann Surg. 2012;255:468–73.
21. Lin CH, Ali R, Chen SC, Wallace C, Chang YC, et al. Vascularized groin lymph node transfer using the wrist as a recipient site for management of postmastectomy upper extremity lymphedema. Plast Reconstr Surg. 2009;123:1265–75.
22. Patel KM, Lin CY, Cheng MH. From theory to evidence:long-term evaluation of the mechanism of action and flap integration of distal vascularized lymph node transfers. J Reconstr Microsurg. 2015;31:26–30.
23. Dayan JH, Dayan E, Smith ML. Reverse lymphatic mapping: a new technique for maximizing safety in vascularized lymph node transfer. Plast Reconstr Surg. 2015;135:277–85.
24. Brorson H. Liposuction in arm lymphedema treatment. Scand J Surg. 2003;92:287–95.
25. Sapountzis S, Ciudad P, Lim SY, Chilgar RM, Kiranantawat K, et al. Modified Charles procedure and lymph node flap transfer for advanced lower extremity lymphedema. Microsurgery. 2014;34:439–47.
26. Miller TA, Wyatt LE, Rudkin GH. Staged skin and subcutaneous excision for lymphedema: a favourable report of long-term results. Plast Reconstr Surg. 1998;102:1486–98.
27. Salgado CJ, Sassu P, Gharb BB, Spanio di Spilimbergo S, Mardini S, et al. Radical reduction of upper extremity lymphedema with preservation of perforators. Ann Plast Surg. 2009;63:302–6.
28. Ochoa D, Korourian S, Boneti C, Adkins L, Badgwell B, Klimberg VS. Axillary reverse mapping: five-year experience. Surgery. 2014;156(5):1261–8. https://doi.org/10.1016/j.surg.2014.05.011.
29. Agarwal S, Garza RM, Chang DW. Lymphatic microsurgical preventive healing approach (LYMPHA) for the prevention of secondary lymphoedema. Breast J. 2020;26:721–4.

Management of Chemotherapy Infusion Extravasation in Breast Cancer

26

Prabha Yadav and Saumya Mathews

26.1 Introduction

Extravasation is defined as the unintentional leakage of intravenous drugs into the surrounding perivascular tissue or subcutaneous spaces with subsequent tissue damage.

Chemotherapy is a mainstay in the treatment of breast cancer. Administration of chemotherapeutic agent is done via central or peripheral intravenous access; however, extravasation of chemotherapeutic agents may lead to devastating complications. Although guidelines have been laid down for the administration of chemotherapeutic agents to prevent this complication, it does happen occasionally and needs urgent recognition and management.

26.2 Recognition of I.V. Extravasation

The importance of timely recognition of IV extravasation cannot be stressed enough. Most instances of irreversible damage to tissue can be prevented by early recognition [1].

Prabha Yadav, MS (✉)
Director and Professor, Department of Plastic and Reconstructive Surgery, Sir H N Reliance Foundation Hospital, Mumbai, India

Former Professor and Head, Department of Plastic and Reconstructive Surgery, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India
e-mail: drprabhatata@gmail.com

Saumya Mathews, MS, MCh
Assistant Professor, Department of Plastic and Reconstructive Surgery, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_26

Symptoms and signs of IV extravasation may include:

1. Patient complains of discomfort, tightness or burning sensation in the areas surrounding the infusion site
2. Change in IV flow rate
3. Swelling due to leakage of fluid from injection site into the tissue
4. Erythema, induration or blanching of skin

26.3 Classifying Severity of Extravasation

National Institutes of Health & National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 has devised a 5-point grading system for extravasation (Table 26.1).

26.4 Identification of the Agent

The propensity for damage and the subsequent management of an infiltration insult is highly dependent upon the physiochemical characteristics of the extravasated agent. Hence identification of the agent and knowledge of subsequent effects are paramount [3].

Intravenously administered drugs can be classified into five categories according to their damage potential (Table 26.2).

26.5 Management of Extravasation

All units administering chemotherapy should ideally have access to Chemotherapy Extravasation Prevention and Management Kits which contains disposable syringes and cannulas, cold-hot packs, gauze pads, adhesive plaster, gloves, and antidotes [6].

26.5.1 Emergent Management

26.5.1.1 Termination of Infusion

The primary management in any case of chemo extravasation should be immediate termination of infusion. The cannula or port should be removed with gentle aspiration with a 10 cc syringe. In case an antidote is to be administered the cannula should be left in situ and removed thereafter.

Table 26.1 Grading system for extravasation [2]

Grade 1 painless edema
Grade 2 erythema with associated symptoms (e.g., edema, pain)
Grade 3 ulceration or necrosis; severe tissue damage; operative intervention indicated
Grade 4 life-threatening consequences; urgent intervention indicated
Grade 5 death

Table 26.2 Classification of drugs based on tissue damage potential [4, 5]

Type	Classification	Drugs	Effects on soft tissue
1.	Vesicants	***Anthracyclines*****:** Doxorubicin, Epirubicin ***Taxane*****:**Paclitaxel ***Vinca alkaloid*****:** Vincristine	Tissue necrosis or formation of blisters
2.	Exfoliants (partial vesicants)	Cisplatin, Adriamycin, paclitaxel, Aclarubicin, cisplatin, docetaxel, Floxuridine, Oxaliplatin, Topotecan	Inflammation and shedding (peeling off) of skin without causing underlying tissue death
3.	Irritants	Carboplatin, etoposide, liposomal anthracyclines	Inflammation, pain or irritation at the extravasation site, without any blister formation
4.	Inflammitants	5-fluorouracil, methotrexate, rituximab, etoposide phosphate	Mild to moderate inflammation, painless skin erythema and elevation (flare reaction) at the extravasation site
5.	Neutrals	Rituximab, Eribulin, gemcitabine, Trastuzumab, Pertuxumab	Neither cause inflammation nor damage upon extravasation

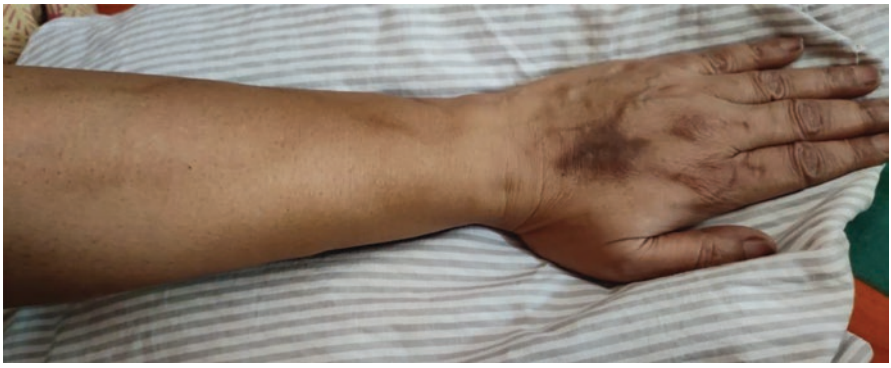


Fig. 26.1 Presentation of extravasation with thrombosis and mild edema

26.5.1.2 Photography

Digital photographs of the affected area must be taken in order to document extent of damage and also to monitor the progress (Figs. 26.1 and 26.2).

The next step in management is guided by the quantity of drug that has extravasated, whether high or low volume extravasation. Unfortunately, there is no defined volume of what constitutes a high-volume extravasation.

In the presence of intense pain, tightness and swelling the following methods of management should be instituted.

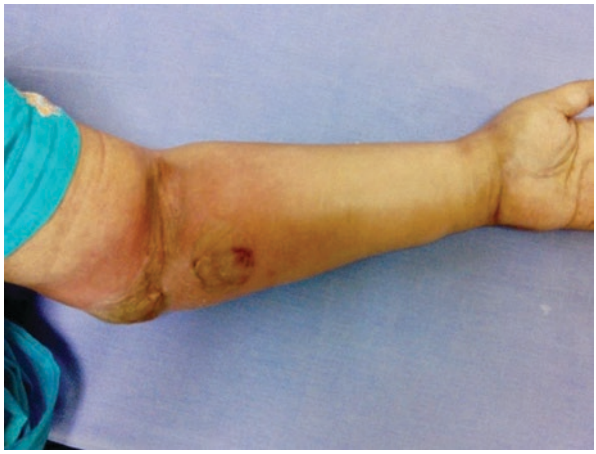


Fig. 26.2 I.V. extravasation with formation of blebs on forearm around injection site

26.5.1.3 Initial Non-pharmacologic Management

Saline Dilution

Saline dispersion via a large bore catheter is useful in mitigating the effects of a vesicant. Sterile saline is infiltrated at subcutaneous level within and around the lesion—20–30 ml for hand; 20–50 ml for forearm; 40–90 ml for antecubital fossa. The next step is application of steroid cream. The standard protocol is infiltration 3 times a week and up to 6 infiltrations every 3 days in severe cases [7].

Saline Dispersion and Aspiration

In this method, isotonic saline is infiltrated through a liposuction cannula (avg. 400 ml) and the fluid is then removed by careful suction through the cannula. This procedure is repeated until 300–500 mL has been removed in total within 6 hours of the extravasation injury. Higher aspiration pressure must be avoided to prevent further damage [8].

Since this method is invasive it should be performed in sterile conditions and not in an ambulatory regimen.

Saline Dilution and Aspiration with Use of Hyaluronidase

This technique was first described by Gault (1993). Local anaesthetic infiltration with 1% plain lidocaine is followed by subcutaneous infiltration of 1500 IU of hyaluronidase. Four stab incisions are made around the periphery of the extravasation site. A blunt- tipped catheter or needle is used via one of the incisions to flush 500 ml of saline through the subcutaneous tissue and out via the other three incisions [9].

Napoli described a technique using approximately 10 small incisions and tunnels are created with 2-mm cannulas to allow aspiration, followed by a second irrigation with normal saline [10]. A variation of this procedure described is a single stab

incision made outside the zone of injury and a cannula is tunnelled subcutaneously into the affected area to allow irrigation with saline [11].

Squeeze Method

Squeeze method with or without multiple puncture procedure, involve using an 18-gauge needle to make 5–8 fenestrations at the peri-insertion area, followed by compression proximal to the extravasation to liberate the vesicant [12, 13].

Liposuction

A small incision is made adjacent to the area of extravasation. A blunt- ended liposuction cannula with side holes is used to aspirate the extravasated material and fat within subcutaneous channels as in conventional liposuction. This is often used with hyaluronidase and is effective when done within 1 to 2 hours [14–17].

This should always be followed by limb elevation as it aids in reducing the hydrostatic pressure of the limb

Warm and Cold Compresses

These methods must be used with caution as there are clear indications for their application. However, the effectiveness of this method is anecdotal and is at best demonstrated to have a soothing effect for the patient.

Types of compresses for chemotherapy extravasation [18].

Type of compress	Indication	Contraindication
Warm	Vinca alkaloids Epipodo-phyllotoxins	–
Cold	Anthracycline Paclitaxel Docitaxel	Vasopressors, vinca alkaloids, and epipodo—phyllotoxins (etoposide)

26.5.1.4 Pharmacological Management [19–22]

Dexrazoxane Hydrochloride

Pharmacology: Bisdioxopiperazine family.

Mechanism of action: It is an analogue of chelatorethylenediaminetetraacetic acid that strongly binds iron and chelates it from anthracycline. It also plays a role in reducing the oxidative stress caused by anthracyclines by exerting a catalytic inhibition of topoisomerase 2, the main target of anthracyclines.

Uses: treatment of Anthracycline, mainly doxorubicin <5 ml extravasation via peripheral or port-a-cath.

Dosage: 1–2 h intravenous Infusion for 3 consecutive days through a large caliber vein in an unaffected limb. The first dose of 1000 mg/m^2 immediately, followed by 1000 mg/m^2 on day 2, and 500 mg/m^2 on day 3.

Side effects*:* transient neutropenia.

Contraindications: Patients less than 18 years old, pregnant, hepatic or renal insufficiency, recent inoculation with a live vaccine.

Dexrazoxane should be made available at all centers that administer anthracycline chemotherapy as Doxorubicin is one of the most widely used drugs with the highest potential and risk for extravasation. The average efficacy of dexrazoxane is 98%. It should *not* be used in combination with topical DMSO. It is recommended by ESMO guidelines to control symptoms from mediastinitis or pleuritis in case of chest wall post site extravasation.

Hyaluronidase

Mechanism of action: Degrades glycosaminoglycans and hyaluronic acid, with increases in tissue permeability and dispersion of extravasated agent.

Uses*:* Extravasation due to etoposide, taxanes (ie paclitaxel, docetaxel, and cabazitaxel), and vinca alkaloids.

Dosage: Multiple subcutaneous injections of hyaluronidase 150–100 IU given as five 0.2 mL injections. It is most often used in conjunction with mechanical aspiration procedures in high volume extravasation.

Dimethyl Sulfoxide

Pharmacology: Organosulfur solvent.

Mechanism of action: Improves absorption of the extravasated solvent and has free-radical scavenging properties.

Uses: anthracyclines extravasation cooling.

Dosage: A dropper is usually used to instill drops over the affected skin, four drops per 10 cm^2 to twice the size of the extravasation area

Sodium Thiosulfate

Four to 8 ml of 10% sodium thiosulfate is mixed with 6 ml of sterile water and injected subcutaneously in a pinwheel fashion around the affected tissue for the treatment of extravasation of doxorubicin, epirubicin, vinblastine, mitomycin C and concentrated cisplatin. It is said to promote accelerated wound healing.

Other Pharmacological Agents

Local injection of corticosteroids and granulocyte macrophage colony-stimulating factor has been hypothesized to accelerate wound healing and prevent ulcer formation in cases of anthracycline extravasation.

26.5.1.5 Wound Care in Patients with Extravasation

In cases of breach of intact skin due to ischemic necrosis, the area of injury should be protected with a nonadherent dressing, which provides a protective barrier. Topical antimicrobials or a wound gel must be used to promote a moist wound environment. Regular and repeated reassessments by a plastic surgery team is paramount to avoid progression of injury (Fig. 26.3).

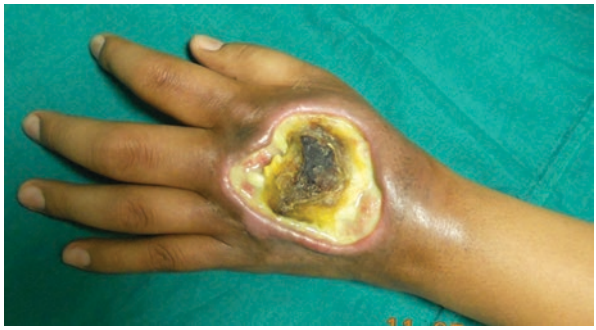


Fig. 26.3 IV extravasation with necrosis of overlying skin and soft tissue over dorsum of hand

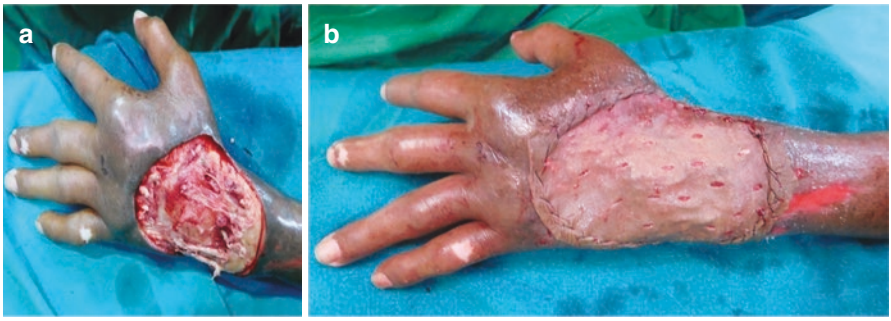


Fig. 26.4 (**a**) Wound post debridement, (**b**) Wound coverage with split thickness skin graft

26.5.1.6 Surgery in Extravasation

The most common site of extravasation is dorsum of hand or forearm. However, in occasional patients, extravasation may occur in the subcutaneous tissue of the chest wall or neck, or in the mediastinum.

1. Indications for surgery:
   (a) Full-thickness skin necrosis
   (b) Chronic ulcer
   (c) Persistent pain
2. Timing: The patient's overall physical condition is a factor in the timing of surgery. Immediate debridement followed by wound closure must be taken to prevent delay in further treatment (Fig. 26.4a and b). However, in patients with metastatic disease, neutropenia and quality of life issues must be considered [23].
3. Procedure: All necrotic tissue must be removed until bleeding occurs and only healthy tissue left for wound coverage. Intra-operative use of fluorescent dye injection to detect doxorubicin HCl in tissues is not well supported by evidence.
4. Wound coverage choices—Split thickness skin graft is recommended for soft tissue coverage for non-critical areas or when paratenon is preserved. If there is a need for secondary tendon or nerve reconstruction, flap cover must be performed after assessing the ECOG status of the patient (Table 26.3).

Table 26.3 Wound cover options based on site [23, 24]

Site	Flap	Disadvantage
Forearm Dorsum hand	Pedicled groin	Patients hand is placed into uncomfortable position Ambulation of the patient is delayed due to persistent hip flexion. Flap donor site may require skin grafting in some cases
	Pedicled hypogastric	Requires 2–3 weeks delay before division
	Reverse radial forearm flap	Retrograde flow through the radial artery should be confirmed Skin graft over donor site
Antecubital fossa	Lateral arm fasciocutaneous flap Pedicled radial forearm flap Posterior interosseous artery flap	Split-thickness skin graft on donor site Possible thrombosis of adjacent veins
Axillary and infraclavicular regions Chest wall	Latissimus dorsi, scapular Parascapular flaps Pectoralis major muscle	Patency of vascular pedicle must be confirmed
All sites	Free tissue	Venous thrombosis often occurs proximal to the site of injury due to the long-term presence of indwelling catheters, the surgeon must confirm the patency of the local venous system

26.5.1.7 Physical Therapy [24]

Physical therapy is an integral part in the treatment of extravasation injuries involving the hand and upper extremities to prevent development of a flexion contracture at the level of the elbow, a fixed extension contracture at the wrist, or a metacarpophalangeal joint. These deformities are extremely difficult to treat secondarily and often require multiple surgical procedures. Therapy should be pursued aggressively with adequate analgesia for the local pain that accompanies physical therapy (Figs. 26.5 and 26.6).

26.5.1.8 Adjuncts to Surgical Treatment

1. **Negative pressure wound Therapy (NPWT)—**Negative pressure is applied to the wound. The mechanism of action is by aspiration of vesicant and providing a moist clean environment that promotes neovascularization and granulation tissue formation. In an experimental animal study there were smaller extravasation areas in rabbits subjected to NPWT, but no histological difference was observed when compared to control rabbits [25].
2. **Hyperbaric oxygen therapy** [26]: Hyperbaric oxygen therapy (HBO) is defined by the Undersea and Hyperbaric Medical Society as a therapy consisting of

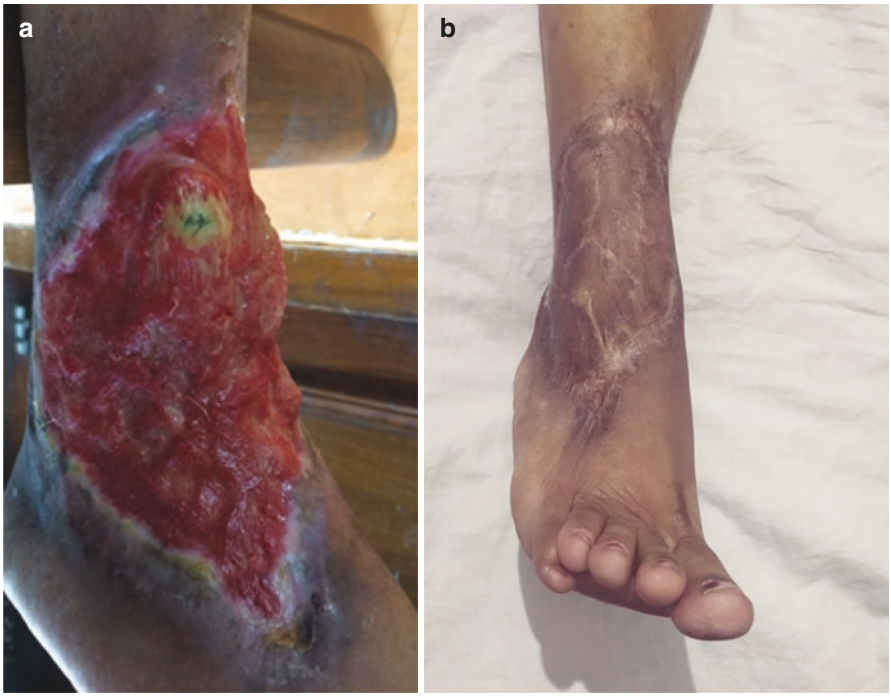


Fig. 26.5 Large granulating wound on the foot following chemotherapy agent extravasation. Case of SMBose. (**a**) Granulating tissue at the site of extravasation (**b**) Wound healed up following split skin graft

intermittent breathing 100% oxygen in a chamber whose pressure is greater than atmospheric pressure. HBO increases production of oxygen free radicals and thus can aid in wound healing [27].

26.6 Recall Phenomenon

It is a rare occurrence attributed to the ability of doxorubicin to produce re-ulceration and tissue necrosis in areas that previously have sustained either extravasation or irradiation injury. The treating physicians must be aware of this rare possibility in cases of repeated wound break down [28].

26.7 Practical Management

The guidelines detailed in this chapter are with the assumption of an ideal situation in which there is immediate recognition of extravasation and subsequent referral. However, in most instances the authors have encountered patients in whom the necrosis of the tissues has already been established or the limb has become stiff due

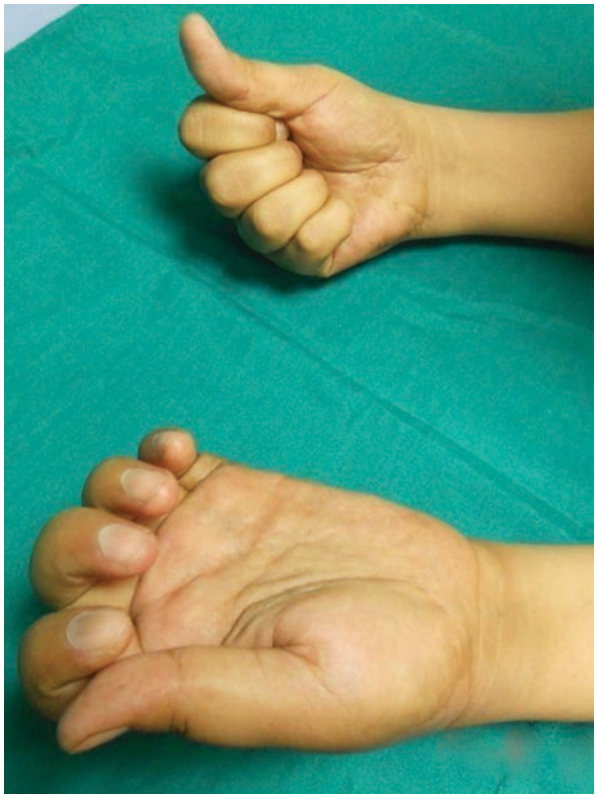


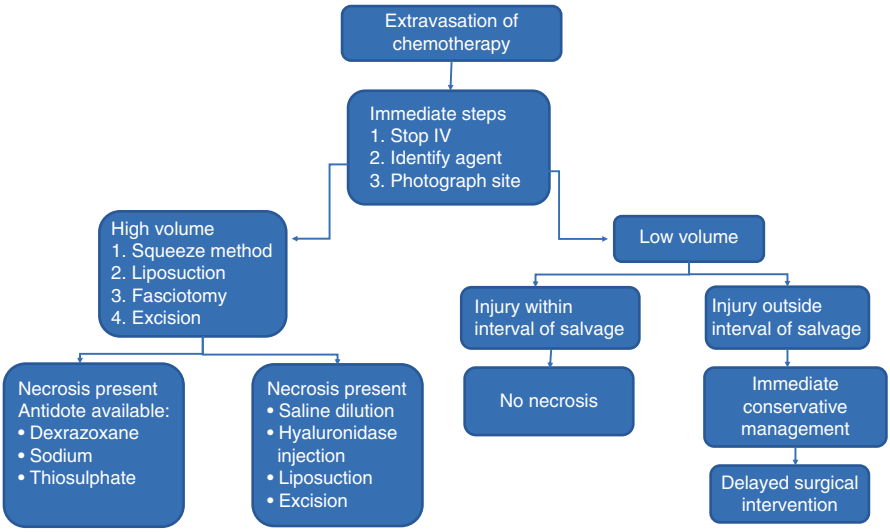
Fig. 26.6 Stiffness caused in left hand due to lack of early intervention

to inactivity. Under such circumstances if the treatment is ongoing we can only offer conservative treatment which includes active wound care (minor debridement, dressing), splintage and physiotherapy with pain management. Definitive wound cover is deferred till cancer treatment is complete.

26.8 Conclusion

In conclusion chemotherapeutic agent extravasation is an accidental and unfortunate complication in the course of treatment of a breast cancer patient. This chapter attempts to provide an overview of the available evidence for its management. The number of cases in which surgical intervention is required is steadily decreasing due to preventive protocols and increased awareness of immediate management to mitigate serious complication [8, 26, 29, 30].

Flowchart for management of IV extravasation of chemotherapeutic agent.



References

1. Maly C, Fan KL, Rogers GF, et al. A primer on the acute Management of Intravenous Extravasation Injuries for the plastic surgeon. Plast Reconstr Surg Glob Open. 2018;6(4):e1743. https://doi.org/10.1097/GOX.0000000000001743.
2. Larson DL. What is the appropriate management of tissue extravasation by antitumor agents? Plast Reconstr Surg. 1985;75(3):397–405. https://doi.org/10.1097/00006534-198503000-00017.
3. US. Department of Health and Human Services, National Institute of Health, National Cancer Institute. Common terminology criteria for adverse events (CTAE) 2017.
4. Al-Benna S, O'Boyle C, Holley J. Extravasation injuries in adults. ISRN Dermatol. 2013;2013:856541. https://doi.org/10.1155/2013/856541.
5. Kreidieh FY, Moukadem HA, El Saghir NS. Overview, prevention and management of chemotherapy extravasation. World J Clin Oncol. 2016;7(1):87–97. https://doi.org/10.5306/wjco.v7.i1.87.
6. Allwood M, Stanley A, Wright P, editors. Cytotoxics handbook. 4th ed. Oxford: Radcliffe Medical Press; 2002.
7. Dychter SS, Gold DA, Carson D, Haller M. Intravenous therapy: a review of complications and economic considerations of peripheral access. J Infus Nurs. 2012;35(2):84–91. https://doi.org/10.1097/NAN.0b013e31824237ce.
8. Onesti MG, Carella S, Fioramonti P, Scuderi N. Chemotherapy extravasation management: 21-year experience. Ann Plast Surg. 2017;79(5):450–7. https://doi.org/10.1097/SAP.0000000000001248.
9. Giunta R. Early subcutaneous wash-out in acute extravasations. Ann Oncol. 2004;15(7):1146–7. https://doi.org/10.1093/annonc/mdh271.
10. Gault DT. Extravasation injuries. Br J Plast Surg. 1993;46:91–6.

11. Napoli P, Corradino B, Badalamenti G, Tripoli M, Vieni S, Furfaro MF, Cordova A, Moschella F. Surgical treatment of extravasation injuries. J Surg Oncol. 2005;91(4):264–8; discussion 268-9. https://doi.org/10.1002/jso.20248.
12. Steiert A, Hille U, Burke W, et al. Subcutaneous wash-out procedure (SWOP) for the treatment of chemotherapeutic extravasations. J Plast Reconstr Aesthet Surg. 2011;64(2):240–7. https://doi.org/10.1016/j.bjps.2010.04.040.
13. Tsai YS, Cheng SM, Ng SP, Yang FS, Shih SL, Sheu CY, Huang JK. Squeeze maneuver: an easy way to manage radiological contrast-medium extravasation. Acta Radiol. 2007;48:605–7. https://doi.org/10.1080/02841850701324094.
14. Thigpen JL. Peripheral intravenous extravasation: nursing procedure for initial treatment. Neonatal Netw. 2007;26:379–84. https://doi.org/10.1891/0730-0832.26.6.379.
15. Harrold K, Gould D, Drey N. The efficacy of saline washout technique in the management of exfoliant and vesicant chemotherapy extravasation: a historical case series report. Eur J Cancer Care (Engl). 2013;22(2):169–78. https://doi.org/10.1111/ecc.12023.
16. Vandeweyer E, Heymans O, Deraemaecker R. Extravasation injuries and emergency suction as treatment. Plast Reconstr Surg. 2000;105:109–10. https://doi.org/10.1097/00006534-200001000-00019.
17. McBride A. Management of chemotherapy extravasations. US Pharm. 2009;34(Oncology suppl):3–11.
18. Doellman D, Hadaway L, Bowe-Geddes LA, Franklin M, LeDonne J, Papke-O'Donnell L, Pettit J, Schulmeister L, Stranz M. Infiltration and extravasation: update on prevention and management. J Infus Nurs. 2009;32:203–11. https://doi.org/10.1097/NAN.0b013e3181aac042.
19. Langer SW. Dexrazoxane for the treatment of chemotherapy-related side effects. Cancer Manag Res. 2014;6:357–63. https://doi.org/10.2147/CMAR.S47238.
20. Jordan K, Behlendorf T, Mueller F, Schmoll HJ. Anthracycline extravasation injuries: management with dexrazoxane. Therapeutics and clinical risk management. 2009; 5:361. Ther Clin Risk Manag. 2009;5(2):361–6. https://doi.org/10.2147/tcrm.s3694.
21. El-Saghir N, Otrock Z, Mufarrij A, Abou-Mourad Y, Salem Z, Shamseddine A, Abbas J. Dexrazoxane for anthracycline extravasation and GM-CSF for skin ulceration and wound healing. Lancet Oncol. 2004;5(5):320–1. https://doi.org/10.1016/S1470-2045(04)01470-6.
22. Hong WK, Bast RC, Hait WN, Kufe DW, Pollock RE, Weichselbaum RR, Holland JF. Cancer medicine, vol. 8. Shelton: PMPHUSA Ltd; 2010.
23. Salunke AA, Nambi GI, Sudhakar N. Post chemotherapy extravasation injuries: hypogastric flap for reconstruction of wounds over dorsum of hand. J Cancer Res Ther. 2015;11(4):835–9. https://doi.org/10.4103/0973-1482.144589.
24. Shenaq SM, Abbase EH, Friedman JD. Soft-tissue reconstruction following extravasation of chemotherapeutic agents. Surg Oncol Clin N Am. 1996;5(4):825–45.
25. Isci E, Canter HI, Dadaci M, Atilla P, Cakar AN, Kecik A. The efficacy of negative pressure wound therapy on chemotherapeutic extravasation ulcers: an experimental study. Indian J Plast Surg. 2014;47(3):394–400. https://doi.org/10.4103/0970-0358.146611.
26. Goutos I, Cogswell LK, Giele H. Extravasation injuries: a review. J Hand Surg Eur Vol. 2014;39(8):808–18. https://doi.org/10.1177/1753193413511921.
27. Gill AL, Bell CN. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. QJM. 2004;97(7):385–95. https://doi.org/10.1093/qjmed/hch074.
28. Cohen SC, Dibella NJ, Michalak JC. Letter: recall injury from adriamycin. Ann Intern Med. 1975;83(2):232. https://doi.org/10.7326/0003-4819-83-2-232_1.
29. Langstein HN, Duman H, Seelig D, Butler CE, Evans GR. Retrospective study of the management of chemotherapeutic extravasation injury. Ann Plast Surg. 2002;49(4):369–74. https://doi.org/10.1097/00000637-200210000-00006.
30. D'Andrea F, Onesti MG, Nicoletti GF, et al. Surgical treatment of ulcers caused by extravasation of cytotoxic drugs. Scand J Plast Reconstr Surg Hand Surg. 2004;38(5):288–92. https://doi.org/10.1080/02844310410027383.

Psychosocial Aspects of Breast Cancer

27

Krishan Kumar and S. K. Mattoo

27.1 Introduction

Despite complete recovery in a few, and good treatment outcome in some others, cancer continues to set in negative thoughts and emotions in most people. This is understandable considering that in most cases cancers and their treatments lead to a shorter life span and have a variable impact on the remaining life. It was believed earlier that Indian women because of their culture and traditional values do not care about the mutilation or loss of their breasts but a study done by Mattoo et al., 1985 [1–3] showed very different results and found that Indian women were very conscious of their physical attributes, irrespective of their status (age, education, financial status, urban or rural habitation), post removal of the breast their social and sexual attitudes had changed drastically, some of them had even suicidal tendencies [4–6]. As a matter of fact, the surgeon Prof. S.M Bose from PGIMER Chandigarh, who was associated with this study, got so much convinced that he started undertaking Breast Conservation Surgery, which was not in fashion in the country in early eighties.

Advances in screening and medical treatments have changed the face of breast cancer from a terminal illness to a chronic illness [7]. Yet, the diagnosis of cancer affects not only the patients but also their care givers and in several ways; [5] reduced quality of life, [7] depression, anxiety, insomnia [8] are commonly reported; in addition to death, dependency, disfigurement, and physical disabilities [9, 10].

Krishan Kumar, PhD
Assistant Professor (Clinical Psychology), Department of Psychiatry, PGIMER, Chandigarh, India

S. K. Mattoo, MD (✉)
Professor and Head, Department of Psychiatry, PGIMER, Chandigarh, India
e-mail: skmattoo@ymail.com

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_27

Western and Asian societies are markedly different in structure, familial organization, and the social support from Government and other agencies. In India the principal caregivers during illness including cancers are family members and close relatives [11]. Often the family members have to give up their work and earnings permanently, leading to a significant lowering of quality of life (QOL) and finances [12]. Yet, compared to cancer patients, the psychological distress of their caregivers has received limited attention in India [13, 14]. Studies have shown the interventions like psycho-education, supportive, and cognitive behavioral therapies (CBT), and family and group therapies are efficacious among cancer patients as well as their caregivers [2, 14].

27.2 Psycho Social Adjustment: Indian Perspective

Psychosocial adjustment to and treatment of breast cancer in India may differ from what has been reported in the developed countries. The reason for this expectation is that Indian women are, in general, characterized by low literacy, greater economic dependence and less psychological sophistication; with little understanding of etiological factors and available treatment options; in addition, our religious and philosophical belief systems are very different [15].

27.2.1 Factors Contributing to Psychological Adaptation to Breast Cancer

To identify those who are most vulnerable to the adverse physical and psychosocial impact of breast cancer and its treatments, it is important to understand the factors that mediate this impact. Such understanding will help in promoting positive adjustment and reduce distress among cancer patients and their survivors.

1. **Awareness:** Breast cancer starts with some bodily changes/symptoms (breast lump, bleeding, skin changes, retraction of nipple). Initial suspicion may be for just any disease or even a cancer. The awareness until the diagnosis of cancer is finalized is called the recognition process. [16] This process involves a state of hyper alertness that eventually leads to seeking medical help—from initial check-up to final treatment. It has been reported [14] that in breast cancer cases 92 % had heard of cancer, 67 % didn't know anything or any 'effective' treatment for cancer, 29 % had not known of cancer involving the breast, 21 % had met breast cancer patient/s, and 29% and 4 % respectively had heard of operation and medications as treatment options
2. **Treatment seeking behaviour:** How quickly an intervention is sought depends on several factors, including symptom awareness, and the level of motivation of an individual based on pain or discomfort [16, 17] and previous experiences with diseases and cancer within self and family. Factors that can lead to delays are financial constraints, non-availability of and negative feelings about health care services, and fears of dependence and disfigurement. Family members with similar beliefs may promote or delay treatment seeking activities. One study [4, 6]

reported that while 62.5% of breast cancer subjects had been symptomatic for more than 6 months, only 33% had sought medical consultation within 1 month of first symptom. The main reasons for delay were reluctance (87.5%), followed by shame and financial constraints. The treatments taken before the index hospitalization included medical (21%, including indigenous system) home remedies (17%, mainly diet and poultices) and faith healers (4.2%).

3. **Willingness for acceptance of treatment:** The biggest barrier to seeking care is the diagnosis of cancer itself; in addition, the immense self-image issues (breast removal), lifestyle changes, considerations of post-operative life span and family members' reactions are some of the reasons for delay to seek care [18, 19]. One study reported that even when patients are well informed about the importance of removal of breast for better and full recovery 21% cases denied that the breast would be removed; major anxiety towards seeking treatment or surgery reported by 42% participant in study was due to the threat posed to life (42%) and disfigurement (29%) [15].
4. **Psychiatric co-morbidity:** Distress is related to pain, discomfort and dysfunction, as also the awareness of the risk of mortality/poor prognosis. Epidemiological research has established this distress converting into psychiatric diagnoses of depression and anxiety disorders in 20–60% of cases [20–22]. Depression was also contributed by uncontrolled pain and low performance status, whereas anxiety was observed to be a part of depression. Both were variably related to a normal stress response, adjustment disorder, poor communication with health professionals, increased costs of treatment, future of family, lack of adequate response to treatment, and worry about other unfinished businesses of life. Compared to general female population, depression and anxiety among women with breast cancer were twice as common, especially during the first year after diagnosis [23]. One study also reported anxiety in 87.5% (moderate severity in 37.5%), and sadness in 75% (moderate severity in 21%) subjects, with occasional suicidal ideas in 1 case (4.2%) [15]. Another study with cancer patients reported psychiatric disorders in 48% cases, including adjustment disorders in 44% in a general hospital, while in a cancer hospital psychiatric disorders were identified in 53% (including depressive diseases in 22%, and sleep disorders in 15%) [19].

27.2.2 Factors Mediating Adjustment in Women with Breast Cancer and Its Treatment

27.2.2.1 Communication with Patients

Breaking the bad news, an integral part of cancer care, is a skill often not focused on in the training of nurses, and doctors, including psychiatrists [24]. Communication with patients with cancer may be very difficult, especially in eastern cultures. An Indian study noted that despite frequent visits for care to a hospital with cancer in its name, 46% patients were not aware of or denied having cancer [19]. When aware, not wanting to disturb the peace of mind of the other side due to the diagnosis of cancer, patients and the family members both may advise the doctors to not disclose/discuss the cancer diagnosis to/with the other side [25]. Dealing sensitively with and declining (the advice for) such collusion is important to preserve the trust

and communication among the patients and family members—without the conspiracy of silence.

Life threatening nature of cancer contributes to psychological distress. Breasts being sign of a woman's grace, sexuality and motherhood, breast cancer related scarring, bleeding, mis-shaping, and therapeutic breast amputation to be more specific, scars a woman's self-image of physical beauty, self-esteem and femininity [25, 26]. A trained nurse who underwent mastectomy said, "Mutilation was more traumatic……." [27, 28]. As a result depression, anxiety, feelings of humiliation, shame and social withdrawal are common psychological manifestations [28, 29].

To identify those who are most vulnerable to the adverse physical and psychosocial effects of breast cancer and its treatment, it is important to understand the factors mediating the psychosocial impact. This understanding will help in promoting adjustment and reducing distress. Of the five mediating factors discussed below, the first two are valuable for addressing and identifying those who are at higher risks of developing the disease, and the latter three help in identifying and formulating effective intervention strategies:

27.2.2.2 Disease and Socio-Demographic Variables

Younger women have been reported to experience more distress and experience a greater threat to their lives in the future, and manifest poorer mental health, [25, 26] while older women have less fear of disease recurrence [6]. Some studies found surgically-related symptoms or physical disability to be associated with more depression [30] or poorer psychosocial adjustment, [31] while others found more advanced disease to be associated with greater psychological distress [30, 32]. Race, marital status, educational level, or financial stability have not been alluded to affect adjustment among breast cancer patients.

27.2.2.3 Personality Factors

While personality characteristics were reported to be associated with how disease and its treatment are perceived for their impact, [17] two years after mastectomy, lower neuroticism and depression were found to be associated with less distress and better emotional adjustment [33–35].

27.2.2.4 Information Processing

Disclosure of information about the diagnosis, treatment, and rehabilitation to cancer patients has increased significantly over the years, [36, 37] and the resulting involvement of patient in the treatment and clear understanding of diagnosis has been found to improve both a desire for open communication and detailed information being shared, and short-term hopefulness and later adjustment, [38] less evidence of depression in those offered a choice in deciding various treatment options [39].

27.2.2.5 Coping Style

Half of the variance in psychosocial adjustment to breast cancer has been shown to be due to individual variables, [40] most patients using multiple coping modes and

changing coping processes over time [32, 41]. Three coping styles, beliefs about personal control, avoidance/denial, and active information-seeking have been associated with positive adjustment and reduced post-mastectomy distress [40, 42].

27.2.2.6 Social Support

Adverse effect of breast cancer on marital, family and social life and resultant social isolation are well documented [25, 41]. By reducing isolation and providing practical assistance towards emotional aid; social support can act as a buffer to the stress of disease and treatment, [28] and improve adjustment and emotional well-being, [28, 43] and reduced fear of recurrence. Family cohesiveness and amount of social contact have been identified as indicators of social support-perception [39].

A good understanding of these mediating factors lays the foundation for interventions for improving psychosocial status of cases with breast cancer.

27.3 Psychological/Psychosocial Interventions

1. **Family Therapy and Counseling**

   Family therapy focuses on sharing roles and responsibilities, and improving communication. The role of caregiver is the most crucial at stages of advanced illness and in home-based care, when family issues, especially assistance to the family become more crucial and a vital aspect of care [44]. Effectively dealing with caregivers' stress and burden may become central theme of family therapy, focusing on their unmet needs for social, personal, psychological and physical health [45]. Psycho-educational and problem-solving approaches have been found efficacious for this.
2. **Social Support**

   Psychotherapy, especially group psychotherapy, provides a new social network with the common bond of facing similar problems, helps members feel a sense of mastery over their lives, improves self-esteem, and gives meaning to an otherwise meaningless tragedy [42]. It facilitates emotional expression to address head-on the negative thoughts of death, anxiety and worries. Direct discussion of death anxiety helps to divide the fear of death into a series of smaller easier-to-tackle problems: loss of control over treatment decisions, fear of separation from loved ones, anxiety about pain, etc. Reorganizing life priorities and living in the present are important aspects of social group counseling which help these individuals to realistically evaluate the future and make the best use of remaining time [44, 45].
3. **Effective Crisis Management**

   The crises usually occur around initial symptoms, first diagnosis, early or major treatment, and change in illness status or treatment, and result in a transient sense of vulnerability and distress. Time-limited counseling at these periods focuses on overcoming the crisis without exploring the underlying personal or psychological problems [45]. The focus is on quick regaining of equilibrium and improved coping ability; problem-solving and restructuring the perception

of the crisis are the cognitive techniques used. This approach shows some success in supporting, enhancing satisfaction and decreasing the costs of mental health services [46, 47].

4. **Sexual Counseling**

   Women with breast cancer often experience problems in sexual self-image and sexual function, manifest as reduced libido and desire, reduced lubrication, and painful intercourse, and avoidance etc. These issues may be a consequence of the illness or side effects of cancer treatment, and may require active participation of the woman and her partner in the counseling sessions [48, 49].

5. **Cognitive and Behavioral Interventions**

   Cognitive and behavioral interventions help in addressing and altering underlying thoughts, feelings and behaviors through techniques of distraction, cognitive-restructuring, guided imagery, and coping. These approaches are particularly valuable for pain relief, control of chemotherapy related anticipatory nausea and vomiting, and enhancing emotional well-being [50]. Behavioral techniques of progressive muscle relaxation and autogenic training improve pain, sleep problems and positive mental health. Kabat-Zinn, a mindfulness-based meditation, can be learnt with a therapist and then practiced using an audiotape or a self induced state [51].

6. **Grief Therapy**

   Grief counseling helps the client grieve in a healthy way through the stages of grief cycle (Denial, Anger, Bargaining, Depression, Acceptance), [52, 53]; and aim at complete acceptance of the present condition and finding a way to move on—both for the cancer patient and the carers.

27.4 Provision of Services

Breast cancer cases see numerous barriers obstructing appropriate care: inadequate medical and health care facilities and policies, limitations of physical and social resources, and lack of health care/coordination among multiple specialists (e.g., surgeons, radiation oncologists, medical oncologists) [54, 55]. Fragmented care adds to psychological burden. Patients and care takers often do not know what to expect from psychosocial interventions, and feel shame, guilt, and fear that disclosing their feelings may impair their emotional status [56, 57]. The most commonly perceived barrier for the patients may be related to receive adequate support from elsewhere and a lack of perceived need for specific psychosocial care. Health insurance coverage adds to the burden, especially for mental health issues. Stigma associated with mental health issues adds to the worries. Another barrier is information, sometimes contradictory, from different psychosocial services [58]. In addition to the physicians' failure to ask patients about distressing emotional symptoms, the lack of simple and rapid screening instruments for psychosocial distress adds to overlooking of/delayed recognition and therefore early addressing of psychological problems. Thus early recognition and addressing is vital for resolution of psychosocial complications of breast cancer [58].

References

1. Gorji MA, Bouzar Z, Haghshenas M, Kasaeeyan AA, Sadeghi MR, Ardebil MD. Quality of life and depression in caregivers of patients with breast cancer. BMC Res Notes. 2012;5:310.
2. Siddharth R, Gupta D, Narang R, Singh P. Knowledge, attitude and practice about breast cancer and breast self-examination among women seeking out-patient care in a teaching hospital in Central India. Indian J Cancer. 2016;53:226.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2016;66:7–30.
4. Mattoo SK, Verma VK, Bose SM. Psycho-social adjustment to breast cancer pre-operative assessment-preliminary report. Bulletin PGI. 1983;17:121–5.
5. Agarwal G, Pradeep PV, Aggarwal V, Yip CH, Cheung PS. Spectrum of breast cancer in Asian women. World J Surg. 2007;31:1031–40.
6. Mattoo SK, Verma VK, Bose SM. Psycho-social adjustment to breast cancer post-operative assessment. Bulletin PGI. 1985;19:19–24.
7. Takiar R, Nadayil D, Nandakumar A. Projections of number of cancer cases in India (2010-2020) by cancer groups. Asian Pac J Cancer Prev. 2010;11:1045–9.
8. Mor V, Allen S, Malin M. The psychosocial impact of cancer on older versus younger patients and their families. Cancer. 1994;74:2118–27.
9. Hodges LJ, Humphris GM, Macfarlane G. A meta-analytic investigation of the relationship between the psychological distress of cancer patients and their carers. Soc Sci Med. 2005;60:1–2.
10. Harrison PA, Srinivasan K, Binu VS, Vidyasagar MS, Nair S. Risk factors for breast cancer among women attending a tertiary care hospital in southern India. Int J Collaborative Res. 2010;2:10–4.
11. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the caregiver health effects study. J Am Med Assoc. 1999;282:2215–9.
12. Kamath R, Mahajan KS, Ashok L, Sanal TS. A study on risk factors of breast cancer among patients attending the tertiary care hospital, in Udupi district. Indian J Community Med. 2013;38:95.
13. Nijboer C, Tempelaar R, Sanderman R, Triemstra M, Spruijt RJ, van den Bos GA, et al. Cancer and caregiving: the impact on the caregiver's health. J Psychol Soc Behav Dimens Cancer. 1998;7:313.
14. Fallowfield U. Psychosocial adjustment after treatment for early breast cancer. Oncology. 1990;4:89–96.
15. Kiebert GM, Haes JCJM, Velde CJH. The impact of breast-conserving treatment and mastectomy on the quality-of life of early-stage breast cancer patients. J Clin Oncol. 1991;9:1059–70.
16. Nail LM. I'm coping as fast as I can: psychosocial adjustment to cancer and cancer treatment. Oncol Nurs Forum. 2007;28:967–70.
17. Mood DW. The diagnosis of cancer: a life transition. Cancer Nurs. 1996:298–314.
18. Glajchen M. Psychosocial issues in cancer care. In: Miaskowski C, Buchsel P, editors. Oncology nursing: assessment and clinical care. St. Louis, MO: Mosby; 1999. p. 305–17.
19. Chaturvedi SK. Exploration of concerns and the role of psychosocial intervention in palliative care. Ann Med. 1994;23:756–60.
20. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psycho-oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer. 2001;10:19–28.
21. Chaturvedi SK, Uchitomi Y. Psychosocial and psychiatric disorders. Clinical Psycho-oncology. 2012;18:58.
22. Derogatis LR, Morrow GR, Fetting J, et al. The prevalence of psychiatric disorders among cancer patients. J Am Med Assoc. 1983;249:751–7.
23. Harter M, Reuter K, Aschenbrenner A, Schretzmann B, Marschner N, Hasenburg A, Weis J. Psychiatric disorders and associated factors in cancer: results of an interview study with patients in inpatient, rehabilitation and outpatient treatment. Eur J Cancer. 2001;37:1385–93.

24. Chandra PS, Chaturvedi SK, Channabasavanna SM, Reddy BK, Anantha N, Sharma S. Psychological well being in patients receiving radiotherapy—a prospective study. Qual Life Res. 1998;7:495–500.
25. Malvia S, Bagadi SA, Dubey US, Saxena S. Epidemiology of breast cancer in Indian women. Asia Pac J Clin Oncol. 2017;13:289–95.
26. Sarin R. Landscape of cancer in India overview of Indian institutions and possible collaborations director, advanced Centre for treatment research and education in cancer. Mumbai: Tata Memorial Centre Mumbai India; 2009.
27. Asken MJ. Psycho emotional aspects of mastectomy: a review of recent literature. Am J Psychiatry. 1975;132(1):56–9.
28. Harrel HC. Nurses perceptions of early breast cancer and mastectomy, and their psychological implications, and of the role of health professionals in providing support. Int J Nurs Stud. 1972;21:101–11.
29. Polivy J. Psychological effects of mastectomy on a woman's feminine self-concept. J Nerv Ment Dis. 1977;164:77–87.
30. Vinokur AD, Threatt BA, Vinokur-Kaplan D, Satariano WA. The process of recovery from breast cancer for younger and older patients. Changes during the first year. Cancer. 1990;65:1242–54.
31. Taylor SE, Lichtman RR, Wood JV. Attributions, beliefs about control, and adjustment to breast cancer. J Pers Soc Psychol. 1984;46:489–92.
32. Morris T, Greer HS, White P. Psychological and social adjustment to mastectomy: a two-year follow-up. Cancer. 1977;77:2381–7.
33. Jamison KR, Wellisch DK, Pasnau RO. Psychosocial aspects of mastectomy: I. The woman's perspective. Am J Psychiatr. 1978;135:431–6.
34. Chandra PS, Akhileswaran R, Chaturvedi SK, Shinde U. Caring at home: frequently asked questions by persons with advanced cancers and their caregivers. Bangalore: BHT Center for Palliative Care Education; 1999.
35. Siminoff LA. Cancer patient and physician communication: Progress and continuing problems. Ann Behav Med. 1989;11:108–12.
36. McIntosh J. Processes of communication, information-seeking, and control associated with cancer. Soc Sci Med. 1974;8:167–87.
37. Cassileth BR, Zupkis RV, Sutton-Smith K, March V. Information and participation preferences among cancer patients. Ann Intern Med. 1980;92:832–6.
38. Fallowfield U, Hall A, Maguire GP, Baum M. Psychological outcomes of different treatment policies in women with early breast cancer outside a clinical trial. Br J Med. 1990;301:575–80.
39. Weisman AD, Worden JW. The existential plight in cancer: significance of the first 100 days. Int J Psychiatry Med. 1976;7:1976–7.
40. Beadle GF, Silver B, Botnick L, Hellman S, Harris JR. Cosmetic results following primary radiation therapy for early breast cancer. Cancer. 1984;54:2911–8.
41. Woods NF, Earp JA. Women with cured breast cancer a study of mastectomy patients in North Carolina. Nurs Res. 1978;27:279–85.
42. Spiegel D. Cancer patients: psychotherapy. Editors-in-Chief. 2002;1:35–9.
43. Gotay CC. The experience of cancer during early and advanced stages: the views of patients and their mates. Soc Sci Med. 1984;18:605–13.
44. Vos PJ, Visser AP, Garssen B, Duivenvoorden HJ, Haes HC. Effectiveness of group psychotherapy compared to social support groups in patients with primary, non-metastatic breast cancer. J Psychosoc Oncol. 2007;25:37–60.
45. Schachter S, Coyle N. Palliative home care. Impact on families. In: Holland JC, editor. Psychooncology. New York: Oxford University Press; 1998. p. 1004–5.
46. Houts PS, Nezu AM, Nezu CM, Bucher JA. A problem-solving model of family caregiving for cancer patients. Patient Educ Couns. 1996;27:63–73.
47. Loscalzo M. Brief crisis counseling. In: Psycho-Oncology. New York: Oxford University Press; 1998. p. 662–75.

48. Schover LR. The impact of breast cancer on sexuality, body image, and intimate relationships. Cancer J Clin. 1991;41:112–20.
49. Fobair P, Spiegel D. Concerns about sexuality after breast cancer. Cancer J. 2009;15:19–26.
50. Sheppard LA, Ely S. Breast cancer and sexuality. Breast J. 2008;14:176–81.
51. Kabat-Zinn J, Massion AO, Hebert JR, Rosenbaum E. Meditation. In: Holland JC, editor. Textbook on Psycho-oncology. Oxford: Oxford University Press.
52. Kessler D, Kubler-Ross E. On grief and grieving. Finding the meaning of grief through the five stages of loss. 2005.
53. Koocher GP, Pollin I. Preventive psychosocial intervention in cancer treatment: implications for managed care. Washington, DC: Psychosocial Interventions for Cancer; 2001.
54. Goldman W, McCulloch J, Sturm R. Costs and use of mental health services before and after managed care: six years of data show that managed behavioral health care has reduced mental health care costs for one large employer. Health Aff. 1998;17:40–52.
55. Jacobsen PB, Meade CD, Stein KD, Chirikos TN, Small BJ, Ruckdeschel JC. Efficacy and costs of two forms of stress management training for cancer patients undergoing chemotherapy. J Clin Oncol. 2002;20:2851–62.
56. Coughlan R. Stigma, shame, and blame experienced by patients with lung cancer: health promotion and support groups have a role. Br Med J. 2004;329:402–3.
57. Dilworth S, Higgins I, Parker V, Kelly B, Turner J. Patient and health professional's perceived barriers to the delivery of psychosocial care to adults with cancer: a systematic review. Psycho-Oncology. 2014;23:601–12.
58. Sharpe M, Walker J, Hansen CH, Martin P, Symeonides S, Gourley C, Wall L, Weller D, Murray G. SMaRT (symptom management research trials): integrated collaborative care for co-morbid major depression in patients with cancer: a multicentre randomized controlled effectiveness trial. Lancet. 2014;384:1099–108.

Follow Up and Rehabilitation in Breast Cancer

28

Firuza Patel

28.1 Introduction

The trajectory of a breast cancer patient goes through diagnosis, treatment and finally survivorship. With more patients diagnosed at an early stage, breast cancer today has become a survivable chronic disease. Most patients remain at risk indefinitely for local or systemic recurrences, and also the side effects of the previous treatment that they have received. Long term follow up is important as survivorship is the main priority for them now and it must include a plan for rehabilitation. However the cost of long-term follow up must be supported by improvements in outcome. While there are many definite evidence based studies for the diagnosis and treatment of breast cancer there are few guidelines for lifelong follow-up care after primary treatment. The American Cancer Society/American Society of Clinical Oncology (ACS/ASCO Guidelines) Breast Cancer Survivorship Care Guideline 2015 was developed to recommend and better manage potential long term and late effects of treatment and to provide timely and appropriate screening and surveillance to improve the overall health and Quality of Life (QoL) of breast cancer survivors [1]. ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances, and facilities available. However it has been observed that for the asymptomatic survivor not following the guidelines results in follow-up that is 2.2–3.6 times more costly than guideline compliant follow up as otherwise unnecessary tests and investigations tend to be ordered.

The clinical practice guideline addresses five key areas of breast cancer survivorship. (1) surveillance for breast cancer recurrence, (2) screening for second primary

Firuza Patel, MD (✉)
Former Professor, Department of Radiotherapy, PGIMER, Chandigarh, India

Mentor and In-charge, Chandigarh Hospice and Palliative Care Service, Chandigarh, India
e-mail: firuzapatel@gmail.com

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_28

cancers, (3) assessment and management of physical and psychosocial long-term and late effects of breast cancer and treatment, (4) health promotion, (5) care coordination and practice implications.

28.2 Recommended Breast Cancer Surveillance

28.2.1 Frequency of Follow-Up

Although most recurrences occur within the first 36 months after primary treatment some tumors may remain dormant only to recur after 20 years or more. In a study of 177 patients of recurrent breast cancer it was found that 29% of the recurrences were found in the first year after treatment, 30% during the second year, 13% during the third year, 27% during the fourth through eleventh year, and 5% at 12 years or later [2]. As 60–80% of all breast cancer recurrences are detected in the first 3 years after primary treatment, scheduling of surveillance visits should be more frequent during that period of time. Hence follow up should be performed every 3 to 6 months for the first 3 years after primary therapy, every 6 to 12 months for the next 2 years, and annually thereafter. No study has demonstrated the benefits of more frequent follow up visits. A meta-analysis of 12 studies involving 5045 patients found that 40% of patients with locoregional recurrences were diagnosed during routine clinic visits or routine testing whereas approximately 60% developed symptomatic recurrence between their scheduled visits [3]. This emphasizes the importance of patient education regarding the signs and symptoms of possible recurrence (e.g. new lumps mainly in underarm or neck, rash or skin changes on the chest wall or breast, changes in the shape or size of the breast, swelling of the arm, bone pains, dyspnoea or vomiting and persistent headaches) and the need to seek medical advice immediately.

28.2.2 Clinical Evaluation

Most recurrences are detected by history and physical examination. When an asymptomatic patient comes for a follow-up visit it is very important to take a detailed history to make sure that she is indeed asymptomatic. In a review of 1125 patients with recurrent breast cancer at MD Anderson Cancer Centre, symptoms, were the first indicator of relapse in 57.6% of patients. In 32.1% of patients recurrence was detected by self-examination or physical examination and in only 10.3% of patients recurrence was detected by radiological or serological testing [4].

28.2.3 Screening the Breast for Local Recurrence or a New Primary Breast Cancer

Mammography along with history and physical examination is the only imaging modality recommended for asymptomatic patients. The first mammography should

be done not earlier than 6 months after definitive radiation therapy. Subsequently, mammography should be performed yearly on the breast treated by breast conserving therapy (BCT) and on the intact contralateral breast. More frequent mammography is only warranted for evaluation or follow-up of a suspicious finding. In a radio-dense breast after BCT sometimes mammography may be unable to detect a local recurrence and an ultrasound may be helpful.

MRI is more sensitive than mammography, but there can be false-positive findings on MRI leading to unnecessary tests and biopsies. Hence it should be restricted to women who are at a high risk which is defined as a woman with a lifetime risk of more than 20% of developing a second primary breast cancer, such as a woman with BRCA1/BRCA2 mutation, or a very strong family history of breast cancer [5]. Early detection of metastatic breast cancer has not been shown to have a significant impact on survival. In contrast, early diagnosis of a second primary breast cancer in the conserved breast or in the contralateral breast offers great potential to improve survival. Therefore routine breast examination & mammography studies remain among the most important components of the follow-up of breast cancer patient.

28.2.4 Laboratory Tests and Imaging

The ASCO panel recommends that tests and imaging should only be done if they can demonstrate a positive impact on the improvements in overall or disease free survival, improvement in quality of life, reduced toxicity or is cost effective. However in clinical practice it is seen that blood tests, x-ray chest, ultrasound of liver, bone scan etc. are routinely ordered. If a patient is asymptomatic routine testing with blood biochemistry, tumor markers or imaging studies (e.g., bone scan, chest x-ray, positron emission tomography-computed tomography [PET-CT] scans, MRI scans) SHOULD NOT be performed for screening purposes, because they have not been shown to improve survival outcomes or QoL in asymptomatic patients. Two prospective studies evaluating surveillance with regular clinical visits and mammography (standard follow-up), versus the same surveillance program plus scheduled laboratory and other imaging studies (intensive surveillance), failed to show a survival benefit between the two groups [6]. The mortality rate at 5 years was 19.5% in the standard arm and 18.6 in the intensive surveillance group. Patients monitored intensively had shorter relapse free survival however the 5 years survival was not significantly different. Thus it is difficult to establish that earlier detection translates into survival benefit. Chest x-rays and advanced body imaging (e.g. PET, MRI, positron emission tomography-PET, bone scan) and blood tests should be ordered only if disease recurrence is suspected [7].

28.2.5 Genetic Counselling

To identify those women with breast cancer who have a high risk of a second primary breast cancer and/or may have a genetic susceptibility to cancer that may

affect other family members, a detailed family history, should be obtained. Genetic testing should be recommended for the following breast survivors: patient younger than age 50 years at diagnosis, ovarian cancer at any age in patient or any first or second degree relative, any first degree relative diagnosed with breast cancer before the age of 50, two or more first or second degree relatives diagnosed with breast cancer at any age, patient or relative with bilateral breast cancer, history of breast cancer in a male relative, or patient diagnosed at age 60 or younger with triple negative breast cancer. However Genetic testing should be preceded by consultation with a counsellor or other trained professional to assure full discussion of the risks and benefits.

28.2.6 Endocrine Treatment

Endocrine therapy is known to reduce the risk of recurrence and improve the overall survival hence at every follow-up the importance of continuing the endocrine treatment must be stressed as some woman discontinue the treatment due to the cost, adverse effects or other reasons.

28.2.7 Screening for Other Cancers

It is important to screen these survivors like the general population for other primary cancers like cervix, colorectal, endometrium, ovary and lung. Women who are taking tamoxifen should be advised to report any vaginal spotting or bleeding, because these drugs slightly increase the risk of endometrial cancer in postmenopausal women. An annual gynaecological examination must be done, however periodic imaging is not of any value in an asymptomatic patient as it may lead to unwarranted biopsies [8].

28.3 Assessment and Management of Physical and Psychosocial Long-Term and Late Effects of Breast Cancer and Treatment

Long-term effects are medical problems that develop during active treatment and persist after the completion of treatment, whereas late effects are medical problems that develop or become apparent months or years after treatment is completed.

28.3.1 Lymphedema

All breast cancer patients who undergo surgery and radiotherapy are at risk of developing some amount of edema either of the arm, breast or chest wall. A difference in circumference of more than 2 cm between the arms has clinical significance.

Education, regarding methods to prevent/reduce the risk of lymphedema e.g. arm elevation, pumping etc. should be taught at the earliest. Patients should also be instructed regarding skin care, avoidance of venipuncture or finger pricks and constrictive pressure on the affected arm. They should be instructed on the correct method of manual lymphatic drainage. Patients with clinical symptoms of swelling suggestive of lymphedema should be referred to a specialist for decongestive therapy and exercises. Once the edema has stabilized compression garments with pressure of 30–60 mm of Hg is advised.

28.3.2 Cardiotoxicity

Radiation, chemotherapy, and hormonal/endocrine therapy with aromatase inhibitors have been associated with an increased risk of cardiovascular disease in patients with breast cancer [9]. Hence it is advisable to monitor lipid levels and provide cardiovascular monitoring. Also breast cancer patients who experience treatment-related early menopause may be at higher risk for heart disease than age-matched women in the general population. Therefore it is important to educate survivors on healthy lifestyle modifications, (diet, exercise), potential cardiac risk factors, and when to report relevant symptoms, that is shortness of breath or fatigue to their health care provider. However, routine screening or testing for cardiovascular disease in asymptomatic patients beyond careful history and physical examination are not warranted.

28.3.3 Cognitive Impairment

Up to 75% of breast cancer patients on treatment and 35% after treatment report cognitive impairment, including problems with concentration, executive function, and memory [10]. Hence the physician must ask the patient if they are experiencing cognitive difficulties and listen to the family members also reporting any symptoms that the patient may be having. The causes of cognitive impairment are thought to be multifactorial and may include treatable conditions, such as fatigue, insomnia, and depression. Cognitive impairment can also have detrimental effects on the survivor's role within the family, in the workplace, and in society and can lead to distress and impaired QoL. If required the patient should be referred for neurocognitive assessment and rehabilitation.

28.3.4 Fatigue

Cancer-related fatigue is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Cancer-related fatigue is very common and the estimated

prevalence is 28–91% [11]. For some, fatigue lasts long after treatment and can significantly interfere with QoL. Therefore treatable causes of fatigue like anemia, thyroid dysfunction, and cardiac dysfunction along with some contributing factors like mood disorders, sleep disturbance, and pain, which may be present should also be addressed. A regular exercise regimen can reduce fatigue, help survivors feel better physically and emotionally, and help them cope.

28.3.5 Bone Health

Up to 80% of breast cancer patients experience bone loss. All postmenopausal breast cancer survivors should have a baseline dual-energy x-ray absorptiometry (DEXA) scan. Repeat DEXA scans should be done every 2 years, for women who are taking an aromatase inhibitor, premenopausal women who are taking tamoxifen and/or a gonadotropin-releasing hormone (GnRH) agonist, and women who have chemotherapy induced premature menopause. To reduce the morbidity associated with bone loss, survivors should include physical activity and regular weight-bearing exercise. Also calcium supplements should be considered to achieve a total intake of 1200 mg/day and vitamin D3 600–1000 IU/day. For patients with osteoporosis at baseline or during follow up bisphosphonate therapy should be considered.

28.3.6 Musculoskeletal Health

The shoulder and arm show maximum musculoskeletal symptoms. Problems may include swelling in 25%, weakness in 25%, limited range of movement in 30%, and stiffness in 40%. Also 25–60% of breast cancer survivors experience chronic pain as a result of the treatments received, including surgery, radiation therapy, chemotherapy, and endocrine therapy. Upto 50% of postmenopausal women receiving aromatase inhibitors report arthralgias and myalgias that are severe enough in 20% of women to lead to treatment discontinuation. Neuropathy, including numbness, tingling, and burning pain, is also common. It is particularly common after surgery and after treatment with taxane-based or platinum-based chemotherapy regimens and is reported in 30–40% of patients. At 3 or 15 months after surgery, approximately 80% of patients continue to report at least one problem. Ideally patients should be evaluated pre-operatively for strength and range of motions. Exercises for range of motion (ROM) should start on first postoperative day. Recovery is faster in patients who begin shoulder flexion to 40° on day 1 and 90° on day 4 than in those who have a delayed start of ROM exercises. Exercises, such as wall climbing, and use of pulley should be added for stretching.

28.3.7 Infertility, Sexual Issues and Premature Menopause

Cancer breast is now being diagnosed in patients at a younger age making infertility an issue for the young survivors. Premenopausal women who desire pregnancy and are having difficulty conceiving for 6 months or more, or who have had more than one miscarriage should be referred to a fertility specialist. Sexual complaints are a common problem among breast cancer survivors, yet sexual assessment and counselling are not routinely provided in the oncology setting, although in one study approximately 80% of women had a strong desire to discuss sexual matters but did not make inquiries [12]. Asking open-ended questions regarding sexual function is a first step to revealing a range of symptoms [13]. Sexual dysfunction in breast cancer survivors is complicated as it involves multiple dimensions. It may result from psychological and body-image factors or directly to the treatment of breast cancer, such as vaginal dryness leading to dyspareunia as an effect of hormonal therapy. A comprehensive assessment of breast cancer survivors at the end of primary treatment found that 34% of women treated with mastectomy and chemotherapy lacked sexual interest. Women can experience menopausal symptoms like hot flushes if chemotherapy results in premature cessation of ovarian function or as an adverse effect of endocrine therapies. For younger women on endocrine therapies 50–70% will likely experience hot flushes while on tamoxifen and this can significantly impact their QoL.

28.3.8 Body Image Concerns

At follow-up the physician must assess for patient body image concerns as 31–67% of survivors have major concerns regarding their body image [14]. Women are concerned regarding loss of a breast, scarring and/or lymphedema after surgery, hair loss, skin changes from radiation, and weight gain. All these changes have a negative impact on the quality of life of these patients, and they also have poor self-esteem [15]. Breast-reconstructive surgery should be considered in women who do not feel comfortable with the results of their initial breast surgery, whether lumpectomy or mastectomy, because there may be ways to improve symmetry or appearance. For those who do not want surgery, breast prostheses or bras are available options.

28.3.9 Distress, Depression, and Anxiety

Psychosocial distress is a continuum ranging from normal distress levels such as fear, grief etc. up to high levels of distress and psychiatric comorbidity. The highest prevalence for mental disorders was found in patients with breast cancer and the most commonly reported needs include help in coping with anxiety, depression, and

fear of recurrence or progression, help with better communication, and support for relatives, families, or spouses [16]. A more probing assessment should be done for patients at a higher risk of depression e.g., young patients, and those with a history of prior psychiatric disease. A good tool for initial assessment is the distress thermometer (NCCN.org), with scores from 0 (no distress) to 10 (extreme distress) [17]. A score of 4 or higher suggests a level of distress that has clinical significance. These patients should be offered counselling and/or pharmacotherapy and may need to be referred to specialists. Quality of life and functional status of the patients may be substantially reduced, and patients and their families are faced with many challenges in terms of coping and adjustment.

28.3.10 Health Promotion

The majority of cancer patients can look forward to a long life after diagnosis and treatment. Thus, enhancing the length and quality of life is an important goal in the care of patients. It is important to counsel the survivors to achieve or maintain a healthy weight. Strength training should be emphasized for women who are treated with adjuvant chemotherapy or hormone therapy and they should avoid inactivity and return to normal daily activities as soon as possible after diagnosis. They should also be instructed regarding the importance of controlling co-morbidities like hypertension, diabetes, hyperlipidemia, and osteoporosis.

28.4 Summary

Early detection of metastatic breast cancer has not been shown to have a significant impact on survival; in contrast, early diagnosis of a second primary breast cancer in the conserved breast or in the contralateral breast offers great potential to improve survival. Therefore routine breast examination & mammography studies remain among the most important components of the follow-up of breast cancer patients. Rehabilitation to improve the QoL of these survivors is also important so that they can live as normal a life as possible.

References

1. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. J Clin Oncol. 2016;34:611–35.
2. Romsdahl M, Eckles N. Posttreatment evaluation of breast cancer. In: Breast cancer: early and late. Chicago, IL: Year Book Medical Publishers; 1970. p. 291–9.
3. de Bock GH, Bonnema J, van der Hage J, et al. Effectiveness of routine visits and routine tests in detecting isolated locoregional recurrences after treatment for early-stage invasive breast cancer: a meta-analysis and systematic review. J Clin Oncol. 2004;22:4010–8.
4. Pivot X. A retrospective study of first indicators of breast cancer recurrence. Oncology. 2000;58:185.

5. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57:75–89.
6. Del Turco M, Palli D, Cariddi A, et al. Intensive diagnostic follow-up after treatment of primary breast cancer: a randomized trial. JAMA. 1994;271:1593–7.
7. Salani R, Andersen BL. Gynecologic care for breast cancer survivors: assisting in the transition to wellness. Am J Obstet Gynecol. 2012;206:390–7.
8. Smith RA, Manassaram-Baptiste D, Brooks D, et al. Cancer screening in the United States, 2015: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2015;65:30–54.
9. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368:987–98.
10. Janelsins MC, Kohli S, Mohile SG, et al. An update on cancer- and chemotherapy-related cognitive dysfunction. Current status. Semin Oncol. 2011;38:431–8.
11. Jacobsen PB, Hann DM, Azzarello LM, et al. Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course, and correlates. J Pain Symptom Manage. 1999;18:233–42.
12. Krychman ML, Pereira L, Carter J, Amsterdam A. Sexual oncology: sexual health issues in women with cancer. Oncology. 2006;71:18–25.
13. Ganz PA. Monitoring the physical health of cancer survivors: a survivorship-focused medical history. J Clin Oncol. 2006;24:5105–11.
14. Falk Dahl CA, Reinertsen KV, Nesvold IL, et al. A study of body image in long-term breast cancer survivors. Cancer. 2010;116:3549–57.
15. Partridge AH. Cancer survivorship and the young breast cancer patient: addressing the important issues. Oncologist. 2013;18:e19–20.
16. Sutherland G, Hill D, Morand M, Pruden M, McLachlan S-A. Assessing the unmet supportive care needs of newly diagnosed patients with cancer. Eur J Cancer Care (Engl). 2009;18:577–84.
17. Patel D, Sharpe L, Thewes B, et al. Using the distress thermometer and hospital anxiety and depression scale to screen for psychosocial morbidity in patients diagnosed with colorectal cancer. J Affect Disord. 2011;131:412–6.

Screening, Self-Examination and Awareness in Breast Cancer

29

Anita Dhar Bhan and Jnaneshwari Jayaram

29.1 Introduction

Breast cancer is a major non communicable public health problem among females in India and worldwide. In India, it is ranked as the most common cancer among females in large cities [1].

Breast cancer rates in India show considerable variation with cases in urban India being almost twice that of rural India (National Cancer Registry Program) [2]. This disease if detected in early stage and treated effectively has good outcome. This is possible by means of raising awareness about breast health through various effective breast cancer screening programmes.

29.2 Breast Awareness

It is defined as, 'a woman becoming familiar with her own breasts and the way that they will change throughout her life, 'this helps the women to seek early medical care for changes in her breast.

Awareness can be discussed in three categories [2]:

- *First*: knowledge of breast cancer (BC),
- *Second:* Factors preventing early recognition of BC and
- *Third*: Approach to health care services.

Anita Dhar Bhan, DNB, FCLS, PhD (✉)
Professor, Department of Surgical Disciplines, AIIMS, New Delhi, India
e-mail: dranitadharbhan@gmail.com

Jnaneshwari Jayaram, MS
Senior Resident, Department of Surgical Disciplines, AIIMS, New Delhi, India

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_29

In India which is low income country, there is lack of well organized breast cancer screening services. To know about the existing knowledge of people about breast cancer, Anita Gadgil et al., conducted a programme for urban community in Mumbai for the women aged between 30 and 69 years to understand their awareness about breast cancer through a postal survey. They found that women in both low and high income groups were aware of entity called breast cancer, however low income group lacked awareness about its signs and symptoms as compared to higher income group [3].

The same group mailed breast awareness brochures yearly from June 2013 to June 2016 for a cohort of 22,500 eligible women who were receiving universal health care from health care schemes such as primary health centres and referral secondary care hospitals. They compared socio-demographic information and tumour characteristics between pre and post awareness period and found that early breast tumours increased from 74 to 81%and axillary node negative incidence increased from 46 to 53%. More patients opted for breast conserving surgery with decreased numbers receiving chemotherapy [4].

29.2.1 Knowledge and Perception

Dey et al., by conducting focussed group discussions attempted to understand the knowledge of BC and its perception in women from rural and urban area. First and foremost, many women are not aware of the term breast cancer. Surprisingly even literate women are new to this term. Many women know it as just a "lump". This information is from media, either through newspapers and television or through relatives and close friends [2].

Many women are not aware of symptoms of breast cancer. People think pain is the most common symptom and is one of the main reasons for patients presenting late to the outpatient department. In early stage of the disease, pain is not associated with the lump. There is also a wrong perception of incurability of breast cancer even if detected early.

Majority of women from low socioeconomic status think BC is a contagious disease, but literate women do not think it that way. Even educated people, who undergo regular health check-ups, are not aware of breast cancer screening because mammogram is not a part of regular health check-up. They only get mammogram done on recommendation of a doctor.

It would help to define alarming facts regarding incidence and mortality about breast cancer in India, common age at presentation and to highlight that it is now occurring in younger age group also and that men too can get it.

29.2.2 Factors Preventing Early Recognition of BC and Causing Delayed Approach to Health Services

Many behavioural factors are the reasons for women not reaching the health care facility. Breast is a reproductive organ which develops during puberty and matures

during pregnancy and lactation. It brings feminity and grace to females. Women hesitate, non-prioritising their health over their family members (husband's, children's health). Lack of family support is again one of the reasons for non-prioritising. They feel embarrassed and feel shy when they have to discuss with other women, elders of family and especially male individuals. Ladies feel shy to consult a male doctor for this disease, hence hesitate to seek advice. Poverty is the main reason for most of the families neglecting their (women) health. Daily wage workers hesitate to reach to doctor in fear of hospital bills, medicines and loss of wages for a particular day of their consultation with doctor, and the thought that this may make their children starve.

29.2.3 Myths Surrounding Breast Cancer

Some of the myths surrounding breast cancer are fear of cancer and associated death, breast cancer presents with pain and that it is a contagious disease. It is believed by many that breast cancer is common with regular use of tight inner garments (tight/underwired/puffed). Post surgery absence of breast is embarrassing and is considered as a social stigma.

29.3 Breast Cancer Screening

29.3.1 Principles of Cancer Screening

Screening tests differ from diagnostic tests-screening tests are done in asymptomatic women while diagnostic tests are done in symptomatic women for breast health. Positive screening tests are followed by diagnostic tests to confirm the disease and its further characterization. Screening tests should be safe, cost effective and with minimal side effects. There should be treatment available if lesions are detected by screening modalities. Screening should decrease the morbidity and mortality of the particular disease. As described by Pace, the condition for which screening programme is described should be an important health problem, whose natural course can be well understood, recognised in early or latent stage. Disease should have facilities available for its treatment, with an agreed policy [5].

29.3.1.1 Need for Breast Cancer Screening

Breast cancer is becoming a leading cause of morbidity and cancer related death in both - developing and developed countries. Most women seek medical advice when the tumour is in an advanced stage. Screening detected lesions are small, early stage tumours, and the rationale behind screening programmes is that early detection of tumour reduces cancer related morbidity and mortality. High risk individuals need screening for any breast lesion at an early age compared to the normal population.

Screening asymptomatic women for BC detects impalpable lesions, and helps its further characterization by diagnostic mammography. Effective treatment can be given with curative intent.

29.3.2 Benefits and Harm of Breast Cancer Screening Program

29.3.2.1 Benefits

The benefit of screening is to detect cancer early, when it is easier to treat, morbidity and disfigurement are low and survival rates are better. Early diagnosis of breast cancer/any lumps can be coordinated by health workers with whom patients are familiar, which can result in early approachability and expression of patient's problems. Screening methods like Clinical Breast Examination (CBE) done in villages by health workers is definitely better than not doing anything and it is also very cost effective.

29.3.2.2 Harm

Any lesion detected induces anxiety until it is proven by further diagnostic methods, and to characterise the lesion, recalling of the patients will be needed. Repeat mammogram can cause pain and increased radiation exposure. The requirement of MRI breast if any doubtful lesion is not characterised by repeat mammogram can cause additional financial burden. Biopsy of benign lesions can cause unnecessary intervention procedure and pain. A systematic assessment done by Pace and Lydia et al., reported over-diagnosis associated with screening mammography at the rate of 19% [5]. Detection of ductal carcinoma in situ (DCIS) in MRI, may be over diagnosed as such lesions may not actually show up in natural course and never be harmful during lifetime [6].

29.3.3 Impact on Life Expectancy

Cancer localised to breast is a potentially curable condition. Screening mammogram done above 50 years has been noted to reduce breast cancer mortality by 20–25% since women diagnosed with impalpable, early lesions which are not metastatic, carry good prognosis of 5 year survival of 95%. Screening reduces the incidence of advanced stage breast cancer but it may not have impact on life expectancy [7, 8]. Long term follow up trials are required to minimise the concern of over diagnosis and its approximate estimation.

29.3.4 Role of Screening in High Risk Women

Risk of breast cancer is high in women with BRCA 1, BRCA 2 gene mutation, Li-Fraumeni syndrome, Cowden's syndrome and women whose life time risk of breast cancer is above 25% (women with strong family history of breast or ovarian cancer, women with Hodgkin's lymphoma treated with chest mantle radiation). In the above categories screening for breast cancer should begin at early age compared to average risk population in terms of SBE, CBE, Mammogram and if required, MRI of breast at regular intervals.

29.4 Breast Cancer Screening Modalities

- Mammography
- Ultrasound
- Magnetic Resonance Imaging(MRI breast)
- Clinical Breast Examination (CBE)
- Self-Breast Examination (SBE)

29.5 Screening Mammography

As breast cancer is a disease of elderly most of the times (exception of familial/hereditary), breast cancer screening with screening mammography in women aged 40 and above reduces the mortality by early detection of asymptomatic disease. In younger women, whose breast tissue is made up of dense fibrous stroma and epithelium and less fat, mammography produces an image without proper delineation; as age advances breast tissue is replaced by fat that absorbs relatively less x rays allowing lesions to be made clearly visible.

Mammography techniques have revolutionized from screen film mammography to digital mammography. Conventional mammogram delivers 0.1 cGy per study. In screening mammography, two views [craniocaudal (CC) view and mediolateral oblique (MLO)] of the breast are obtained.

Standard mammogram has limitations of parenchymal density and superimposition of breast tissue masking lumps or making normal structures appearing abnormal thereby reducing sensitivity of mammogram. To overcome this limitation, *digital breast tomosynthesis (DBT)* technology was developed. Tomosynthesis was approved by the U.S. Food and Drug Administration (FDA) in 2011 to be used in combination with standard digital mammography in breast cancer screening. The total radiation dose when tomosynthesis is added is about twice the current dose of digital mammography alone but remains well below the limits set by the FDA [9]. If any abnormality is found on screening mammogram, diagnostic mammogram is done for further characterization such as 90° lateral view and spot compression views.

The first RCT to understand the importance of screening mammogram was conducted from 1963 to 1966; it enrolled women between 40 and 64 years and they were randomised to screening versus no screening groups. Intervention/screening group (30,239 women) underwent two view mammography annually and clinical breast examination (CBE) every 3 years. This trial demonstrated a 30% reduction in mortality after screening mammogram [10].

Cochrane data base reviewed the usefulness of mammographic method of breast cancer screening [11]. Seven RCTs (including 600,000 women, ranging from 39 to 74 years) were included which compared screening with and without mammogram. The pooled results showed that mammogram did not reduce breast cancer mortality after 13 years, all cancer related mortality after 10 years, and all cause mortality after 13 years. Instead, all interventions, total number of lumpectomies and

mastectomies, chemotherapy and radiotherapy were significantly higher in screened groups. Hence it was concluded that on 10 years screening of 2000 women, the rate of over diagnosis and overtreatment would be 30% with avoiding one women from dying of breast cancer and 10 healthy women would be treated unnecessarily [12].

The standard guidelines of NCCN, WHO, ACS advises to begin mammogram from the age of 40 years and to continue annually for average risk women. NCCN recommends beginning SBE and CBE from the age of 20, and repeat once in three years till age 40 and then annually. WHO does not recommend SBE and CBE [13].

Screening mammography is reported to reduce breast cancer related mortality by 20–35% in women of the age group 50–69 years, and slightly less in women between the ages of 40–49 years at 14 years of follow-up [14].

29.5.1 In India

Breast cancer screening is part of multi-disease screening programme that covers five non communicable diseases. The programme was launched as a National programme by the Ministry of Health and Family Welfare on 16th May 2017, covering age group 30–65 years. Breast cancer incidence is seen to be increasing in younger age group of less than 50 years (39–49). It has been noticed that Indian women present with breast cancer one decade earlier compared to western world. This assumption is based on 8 trials conducted between 2001 and 2008 and hence suggests that mammographic screening is beneficial in younger age groups of 40–49 years [15].

29.6 Ultrasound (USG)

Ultrasound acts as critical adjunct for screening mammography, once the lesions are detected in mammogram to characterise the type of lesions. There is a rapid increase in trend for the use of USG as screening modality in younger women who has dense breasts reported on mammogram. The disadvantage is that it is operator dependent, thus having marked inter-observer variation, unnecessary biopsies, anxiety in participants, and over-diagnosis.

The largest trial known as ACRIN 666, compared the addition of screening ultrasound to mammography in women with dense breasts and at least one extra risk factor of malignancy and demonstrated a detection rate of 4.3 additional cancer cases per 1000 women screened. The results were increase in biopsy rate from 2 to 5% in women both screened with mammography and ultrasound. Among these, only 7.4% were positive for malignancy, thus suggesting a high false positive rate [16].

As of early 2013, legislation has been passed in the states of Connecticut, Texas, Virginia, New York, and California to mandate that women with mammographically dense breasts be informed that they may be at higher than average risk for developing cancer, and that they may benefit from supplemental screening tests such as whole-breast ultrasound [17].

No studies have demonstrated the clinical effectiveness of ultrasound screening in asymptomatic women with dense breasts who lack other risk factors.

29.7 Magnetic Resonance Imaging (MRI)

MRI of the breast is more sensitive than mammography and therefore is of importance in women with higher than average risk of malignancy. The sensitivity for detecting cancers in these high risk individuals, range from 71–100% in comparison to mammogram, which has sensitivity of 16–40%. American cancer society provides guidelines of MRI breast in high risk women [18]. (Ref to Table 29.1).

Addition of MRI in the screening tool algorithm for women who are at higher risk adds a considerable cost by over U.S. $50,000 per cancer by adding MRI to mammography [19].

The cost increases considerably as risk of developing cancer decreases. This forms rationale for performing MRI only in women with higher risk of developing breast cancer [18].

The high risk women are:

(a) women with BRCA1 and 2 genetic mutation, first degree relatives with known BRCA mutation
(b) Li-Fraumeni syndrome
(c) Cowden syndrome
(d) Women with personal history of lobular carcinoma in situ, atypical ductal hyperplasia, dense breast tissue
(e) Women with history of radiation to chest wall in between 10 and 20 years
(f) The less penetrant gene mutation involving ATM, CHEK2, CDH1, STK11, PALB2

Table 29.1 American Cancer Society recommendation for MRI breast for screening

Recommendation for high risk women to start at age 30
(a) Women who have life time risk of breast cancer of about 20–25%
(b) Known BRCA 1 or BRCA 2 gene mutation
(c) Untested first degree relative with BRCA1/2 mutation
(d) H/O radiation therapy to the chest in between age group of 10–30 years
(e) Li-Fraumeni syndrome, Cowden syndrome, or Bannyan-Riley-Ruvalcaba syndrome or first degree relatives with one of these syndromes
Recommendation against MRI breast
(a) Life time risk of breast cancer less than 15%
No evidence for or against MRI
(a) Personal history of breast cancer
(b) Ductal carcinoma in situ (DCIS)
(c) Lobular carcinoma in situ (LCIS)
(d) Atypical ductal hyperplasia (ADH)
(e) Atypical lobular hyperplasia (ALH)
(f) Dense breasts

NCCN recommends to begin screening at the age of 30 and to continue annually. MRI breast is to be done after discussing with health care provider which can be begun from the age of 25 years [20].

29.8 Self-Breast Examination (SBE)

Self-breast examination means in simple words "women does her own breast examination." Most of the lumps of the breast are self-detected. Women need to be aware of normal appearance of their own breasts. Any deviation from normal can be detected early to be reported to a health care provider. Even though it is not as effective as mammography and CBE, SBE can still be considered as one of the screening method where there is no easy facility to outreach for mammogram. Educating women about knowledge of their breasts help in women developing positive health seeking behaviour.

Dr. Cushman Haagensen first introduced SBE in 1990 [21]. Nottingham Centre in the UK and the Canadian National Breast Screening Study (CNBSS) conducted study on this showed that practising SBE could help to decrease breast cancer mortality [22] but now it is felt that SBE does not reduce the mortality rate but may help in early detection .

In 2017, a Cochrane data base [11] review was conducted on the effectiveness of screening programmes in seventeen malignancies. A systematic review of two large population based studies conducted in Shanghai and Russia, comparing SBE with no intervention [23]. Statistically no significant difference in breast cancer mortality between two groups was found. In the Russian study, more cancers were detected than in control group whereas the Shanghai study did not find any difference. They also found that rate of biopsies were doubled. Hence the Cochrane review concluded that there was no benefit from using SBE screening method, rather would cause increased harm due to the number of benign lesions identified and their further unnecessary biopsies. Hence, SBE is no longer recommended for screening.

The US Preventive Services Task Force (USPSTF) and ACS, no longer recommend SBE as screening test due to very low sensitivity of SBE (20–30%). However, in countries where breast cancer lumps at presentation continue to be large and places that lack screening programme, this method might help to recognise these lumps at smaller size.

29.8.1 When to Perform SBE

SBE should be performed from age 20 years, once a month, 4–5 days after end of menstrual cycle. In postmenopausal or post hysterectomy, women are advised to perform SBE each month on a fixed day of their choice [24].

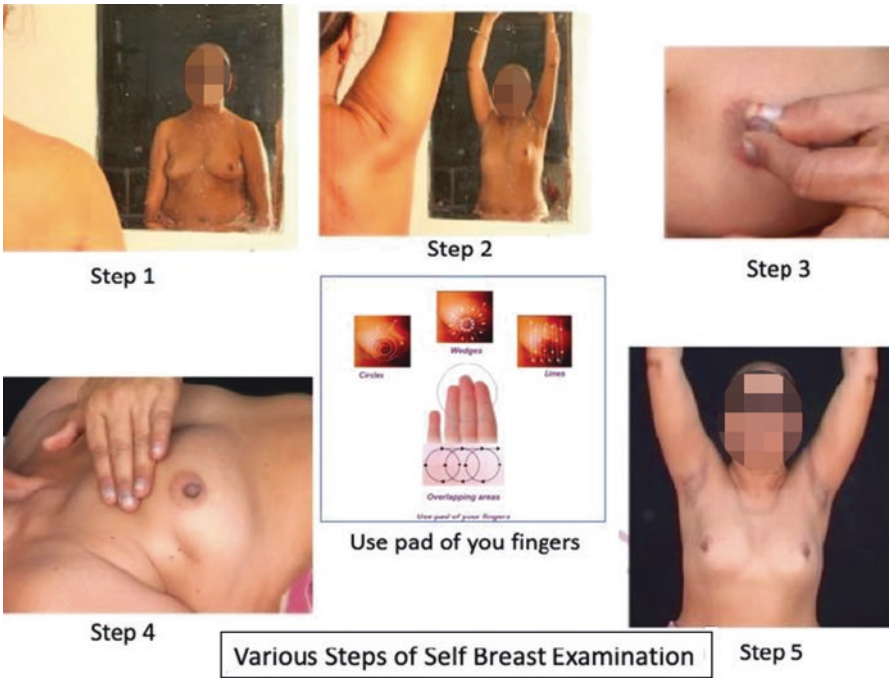


Fig. 29.1 Steps of Self Breast Examination with BC information

29.8.2 Method of Performing SBE

SBE is done in following few steps (Fig. 29.1):

- **Step 1**: In privacy, should stand in front of the mirror with both breasts exposed and hands on the hips. She has to look for variations in both breasts in size, shape, dimpling and puckering.
- **Step 2**: Raises her hands above head to observe same findings.
- **Step 3**: With thumb and index finger role the nipple and gently squeeze to look for discharge and its colour.
- **Step 4**: Examine the breast in lying down position, each breast at a time with opposite hand using pad of fingers. Place a small pillow below the scapular region of the same side to elevate the breast (Fig. 29.2).
- **Step 5**: Breast can also be examined while taking bath with slippery/soapy fingers, palpation becomes easier including axillae.

SBE is one of the methods of breast cancer screening program that can be used in places where mammography is not easily available. SBE is cost effective, non-invasive procedure and can be easily taught and performed at home, the only requirement is awareness and motivation towards breast health.

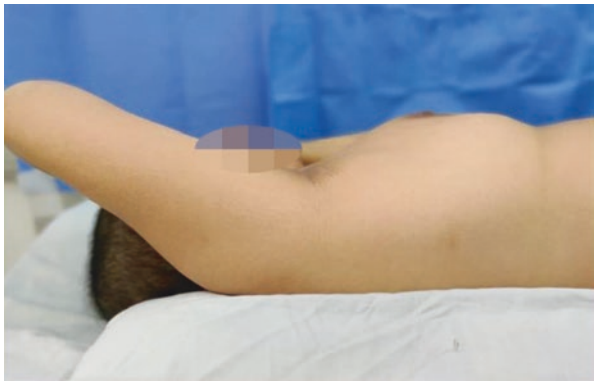


Fig. 29.2 Showing position of patient for palpation of lateral half of breast by making patient roll to opposite side under a pillow (Note: examination of the medial half of breast done in a neutral supine position)

29.9 Clinical Breast Examination (CBE)

CBE is done once the patient consults the health worker. It has to be done effectively to detect any abnormality like breast lumps, nipple discharge, changes in breast skin, axillary lymphadenopathy etc. CBE is considered as an effective screening tool for confirming the presence of a breast lump or any abnormality. This includes examination of both breasts, and both axillae in systematic way in the order of inspection and palpation [25]. In Asian countries, screening mammography is not available at many places, therefore CBE is the only modality of diagnosing a breast lump and helping in further planning. Mitra et al. found that CBE was effective as combined modality with mammography [26].

Miller et al. found that adding mammography to CBE did not influence breast cancer mortality as it was highlighted by Canadian National breast cancer screening studies in ladies aged 40–59 years [27]. Elmore found the sensitivity of CBE as screening tool to vary between 40 and 69%. The Health Insurance Plan (HIP) project in 1960 was first to evaluate effectiveness of CBE plus mammography compared to CBE alone [28].

When we consider cost, and the lack of easy accessibility for mammogram in developing countries, CBE may still be considered as the best modality for early assessment of patients for breast symptoms. So, World Health Organisation and Global Health Initiative recommended CBE as a screening method [29, 30].

The method of conducting CBE is also equally important. There are various methods of performing CBE such as dial of a clock (Fig. 29.3), vertical strips (Fig. 29.4), quadrant-wise, concentric circles method. *Methods of axilla examination are* conventional and open book (Fig. 29.5).

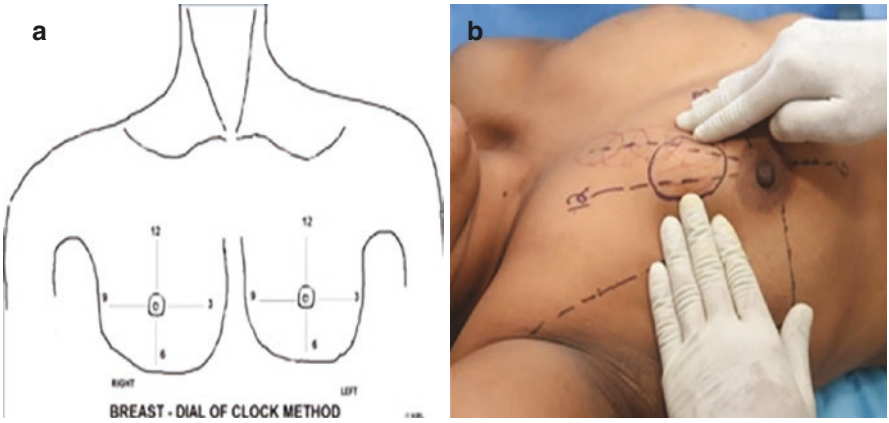


Fig. 29.3 Dial of a clock search pattern (**a**) Schematic diagram (**b**) Dial of a clock search pattern being demonstrated

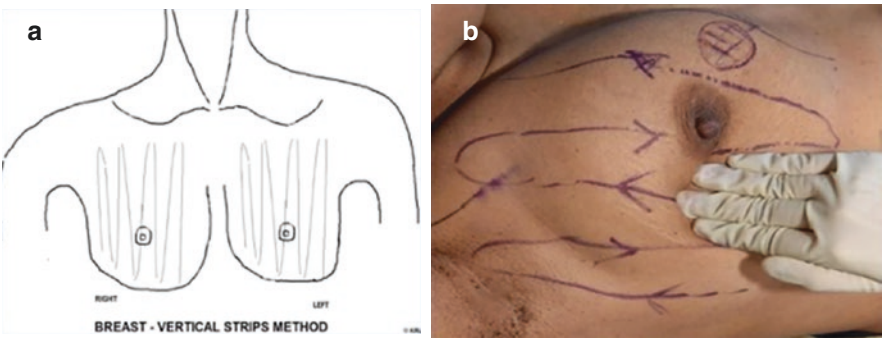


Fig. 29.4 Vertical strips search pattern (**a**) Schematic diagram (**b**) Vertical strips search pattern being demonstrated

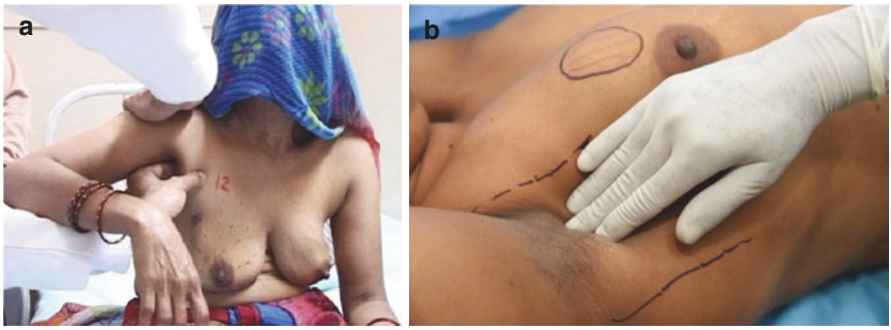


Fig. 29.5 Methods of examination of axilla (**a**) Conventional (**b**) Abduction or "Open book-method

29.10 Breast Examination

29.10.1 Inspection

Inspection of breast in various positions:

(a) Sitting position with arms by side.
(b) Arms raised over the head position to see for any prominence in any part of the breast, nipple areolar distortion, skin changes, dimpling, and puckering.

29.10.2 Palpation

Examination should start from normal breast. Important methods have been described here.

Palpation is to be done in supine position with arms abducted for medial half of breast and roll onto opposite direction for lateral half. Palpation is to be carried out by first fixing the breast with one hand and palpating with other by making circular movements of the pads of middle three fingers (index, middle and ring) with the palm of hand held in slightly bowed position. Around each point, 3 circles with increasing pressure (light, medium and deep) have to be applied without lifting the fingers. Palpation should be performed meticulously by applying one of the search patterns until entire breast is examined (Fig. 29.6).

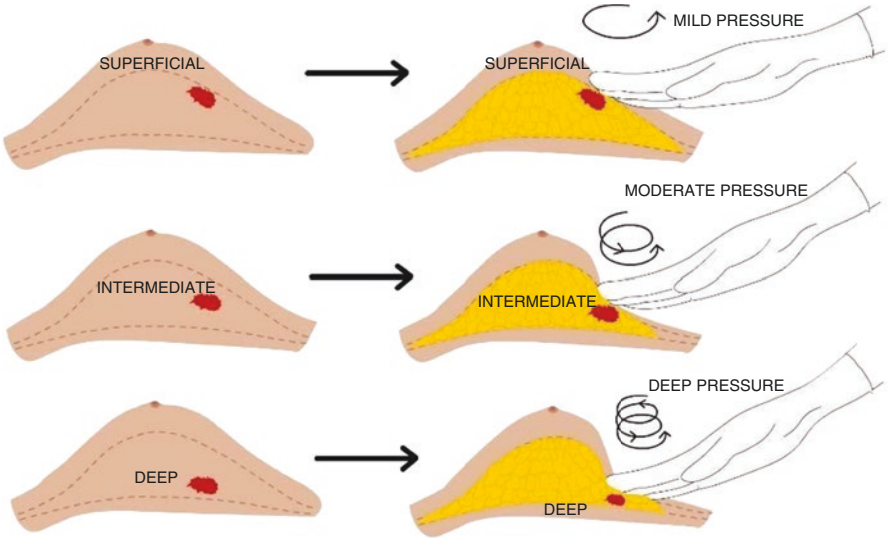


Fig. 29.6 Circular or rubbing finger movement technique with varying degrees of pressures for CBE

29.11 Conclusion

Breast cancer is a leading cause of morbidity and mortality among women across the world. It has a good outcome if detected early and treated effectively. Many women lack knowledge and awareness about breast cancer, therefore there is delay in seeking medical advice. By raising awareness and through various screening programmes breast cancer can be detected at early stage leading to less associated morbidity and mortality. The screening modalities available are SBE, CBE, mammogram and MRI breast, in selected cases. CBE is effective as combined modality with mammography. SBE is a feasible option to be practiced by women. Early recognition of the disease makes the treatment to be cost effective for the family and has direct impact on outcome of the breast cancer.

References

1. Dahiya N, Basu S, Singh MC, Garg S, Kumar R, Kohli C. Knowledge and practices related to screening for breast cancer among women in Delhi, India. Asian Pac J Cancer Prev. 2018;19:155–9. https://doi.org/10.22034/APJCP.2018.19.1.155. PMID: 29373907; PMCID: PMC5844610.
2. Dey S, Sharma S, Mishra A, Krishnan S, Govil J, Dhillon PK. Breast cancer awareness and prevention behaviour among women of Delhi, India: identifying barriers to early detection. Breast Cancer Basic Clin Res. 2016;10:147–56.
3. Gadgil A, Sauvaget C, Roy N, Grosse Frie K, Chakraborty A, Lucas E, Bantwal K, Haldar I, Sankaranarayanan R. Breast cancer awareness among middle class urban women-a community-based study from Mumbai. India Asian Pac J Cancer Prev. 2015;16:6249–54. https://doi.org/10.7314/apjcp.2015.16.15.6249.
4. Gadgil A, Sauvaget C, Roy N, Muwonge R, Kantharia S, Chakrabarty A, Bantwal K, Haldar I, Sankaranarayanan R. Cancer early detection program based on awareness and clinical breast examination: interim results from an urban community in Mumbai. India Breast. 2017;31:85–9. https://doi.org/10.1016/j.breast.2016.10.025. Epub 2016 Nov 6.
5. Pace LE, Keating NL. A systematic assessment of benefits and risks to guide breast cancer screening decisions. JAMA. 2014;311:1327–35.
6. Tosteson ANA. An abbreviated MRI protocol for breast cancer screening in women with dense breasts: promising results, but further evaluation required prior to widespread implementation. JAMA. 2020;323:719–21.
7. Nagtegaal ID, Duffy SW. Reduction in rate of node metastases with breast screening: consistency of association with tumor size. Breast Cancer Res Treat. 2013;137:653–63.
8. Etzioni R, Gulati R, Mallinger L, Mandelblatt J. Influence of study features and methods on Overdiagnosis estimates in breast and prostate cancer screening. Ann Intern Med. 2013;158:831.
9. Friedewald SM, Rafferty EA, Rose SL, Durand MA, Plecha DM, Greenberg JS, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. JAMA. 2014;311:2499–507.
10. Glasziou P, Houssami N. The evidence base for breast cancer screening. Prev Med. 2011;53:100–2.
11. Bueno ATP, Capelasso VL, Pacheco RL, COC L, Castria TB, Pachito DV, Riera R. What do Cochrane systematic reviews say about the clinical effectiveness of screening and diagnostic tests for cancer? Sao Paulo Medical J. 2017;135:401–10. https://doi.org/10.1590/1516-3180.2017.0171110717.

12. Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. Cochrane Database Syst Rev. 2013;6:CD001877.
13. Helvie MA, Bevers TB. Screening mammography for average-risk women: the controversy and NCCN's position. J Natl Compr Canc Netw. 2018;16:1398–404. https://doi.org/10.6004/jnccn.2018.7081.
14. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, et al. Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2018;68:297–316.
15. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L, et al. Screening for breast cancer: an update for the U.S. preventive services task force. Ann Intern Med. 2009;151:727–37.
16. Berg WA, Zhang Z, Lehrer D, Jong RA, Pisano ED, Barr RG, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA. 2012;307:1394–404.
17. Freer PE. Mammographic breast density: impact on breast cancer risk and implications for screening. Radiographics. 2015;35:302–15.
18. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57:75–89.
19. Griebsch I, Brown J, Boggis C, Dixon A, Dixon M, Easton D, et al. Cost-effectiveness of screening with contrast enhanced magnetic resonance imaging vs X-ray mammography of women at a high familial risk of breast cancer. Br J Cancer. 2006;95:801–10.
20. Daly MB, Pilarski R, Yurgelun MB, et al. NCCN guidelines insights: genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 1.2020. J Natl Compr Cancer Netw. 2020;18:380–91. https://doi.org/10.6004/jnccn.2020.0017.
21. Thornton H, Pillarisetti RR. 'Breast awareness' and 'breast self-examination' are not the same. What do these terms mean? Why are they confused? What can we do? Eur J Cancer. 2008;44:2118–21.
22. Miller AB. Practical applications for clinical breast examination (CBE) and breast self-examination (BSE) in screening and early detection of breast cancer. Breast Care. 2008;3:17–20.
23. Kösters JP, Gøtzsche PC. Regular self-examination or clinical examination for early detection of breast cancer. Cochrane Database Syst Rev. 2003;2:CD003373.
24. Shah TA, Guraya SS. Breast cancer screening programs: review of merits, demerits, and recent recommendations practiced across the world. J Microsc Ultrastruct. 2017;5:59–69.
25. Organization WH, Mediterranean RO for the early detection of cancers common in the eastern Mediterranean region [internet]. World Health Organization, Regional Office for the Eastern Mediterranean; 2017 [cited 2020 May 7]. Available from: https://apps.who.int/iris/handle/10665/258889.
26. Mittra I. Breast screening: the case for physical examination without mammography. Lancet. 1994;343(8893):342–4.
27. Miller AB, To T, Baines CJ, Wall C. Canadian national breast screening study-2: 13-year results of a randomized trial in women aged 50-59 years. J Natl Cancer Inst. 2000;92:1490–9.
28. Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. JAMA. 2005;293:1245–56.
29. Tsu VD, Jeronimo J, Anderson BO. Why the time is right to tackle breast and cervical cancer in low-resource settings. Bull World Health Organ. 2013;91:683–90.
30. Anderson BO, Yip C-H, Smith RA, Shyyan R, Sener SF, Eniu A, et al. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the breast health global initiative global summit 2007. Cancer. 2008;113(8 Suppl):2221–43.

Organisation of Breast Cancer Management Group

30

Vani Parmar

30.1 Introduction

Breast cancer in India is the most common cancer in women and accounts for more than 160,000 new cancer cases every year [1]. Not only has it gained importance in public health activities, Breast Oncology has become an important subspecialty of Oncology, for the last two decades, with research and treatment in breast cancer advancing at a rapid rate globally. Keeping abreast with the newer treatments interventions and novel discoveries has also become challenging. These are required to enable the advances in treatment and management to be delivered to the final beneficiary, i.e., the patient.

30.2 Multidisciplinary Team

It was in the mid 80's that the concept of multidisciplinary teams in care of chronic non-communicable diseases started in the UK [2], followed by US and Europe [3]. These mainly addressed diabetes, stroke and neurological rehabilitation, chronic obstructive pulmonary disease, and coronary heart disease. Multidisciplinary team based cancer care started much later.

The main purpose of a multidisciplinary team approach was to bring together medical and health personnel to address and manage a specific disease condition, such as cancer in a defined organ system, in a disciplined, systematic, evidence-based, timely manner for best treatment outcomes, and impacting on better patient safety, satisfaction, improved survival and a better quality of life and job satisfaction

Vani Parmar, MS, DNB (✉)
Professor, Department of Surgical Oncology, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India
e-mail: vaniparmar@gmail.com

S. M. Bose et al. (eds.), *Breast Cancer*,
https://doi.org/10.1007/978-981-16-4546-4_30

on health care providers [4, 5]. It has been well explained as a system of communication platform among different specialties of cancer care, facilitating complex decisions and individualized personalized treatment plans for patients. In fact it allows for better patient-doctor interaction in treatment decisions based on current updated evidence [6].

Breast cancer is treated primarily by multimodality treatment protocols. Best outcomes are obtained when timelines of treatment are adhered to and delivered. It has been proven that shorter the gap between presentation to the breast clinic, diagnosis, and surgery with early initiation of systemic therapy and radiation therapy, results in best outcomes. Delays in adjuvant therapy, beyond 90 days from surgery, have detrimental impact on outcomes [7, 8]. A focused, well-coordinated effort by the dedicated specialties involved in multimodality cancer care such as surgeons, medical and radiation oncologists, genetic counsellors, and nurses, etc., ensures timely treatments and best results.

30.3 Disease Management Group

This was the main basis on which the concept of *'Disease Management Groups'* (DMG) was created. Instead of the patient moving to different departments for availing each modality of treatment, the concept of 'one stop-one level management' was born. This not only made it practically easier and faster for cross references, it also reduced the movement of patients from one level to another just for cross-consultations and hence reducing crowding at various levels and waiting period for initiation of essential treatment. Spatially centralizing the patient management meant reduced waiting time, shorter transit time, fewer places to navigate, even fewer schedules to keep track of, with less chance of getting lost, and for the patient, more valued time and mind that can be spent outside of cancer care with supportive family and friends.

The important prerequisite to this was another major change in the oncology practice, necessitating the specialists to choose their primary area of interest with respect to cancer to treat. A new breed of Breast Oncosurgeons, Breast Medical Oncologists, Pathologists, Radiation oncologists were born. There were, however, still overlaps in utilization of certain common facilities such as Plastic Reconstructive surgeons, basic researchers, physiotherapists, anaesthetists, psychologists [8], intensive care physicians and intervention radiologists. But over a period of time, there are now dedicated disease specific faculties even in these facilities for each DMG.

As is always the case, any such change in paradigm is not accepted easily. The initial phase of formation of these disease management groups was wrought with resistance, reluctance, anxiety and feeling of being denied freedom of work and apprehension regarding reduced scope of work. It was not surprising eventually that it actually turned out to be the most progressive radical move in the history of the cancer care. With a narrower area of work focus, the in-depth knowledge improved, more productive research was initiated to better the quality of care provided, advances in treatment delivery and timelines, eventually translating into better patient care.

30.4 Functioning of DMG

The management and smooth functioning of such a Disease Management Group is dependent on certain core areas as listed below:

1. A good leadership, by a senior 'Lead' or 'Convener' assisted in the regular duties by the Secretary of DMG. And basing all decisions by consensus of members.
2. Having a clear agenda and functional roles defined for each member within each specialty, covering areas of awareness, screening, diagnosis, treatment, follow up, research, rehabilitation, survivorship, and palliation.
3. Follow evidence-based guidelines for uniformity in cancer care within the group. Such guidelines should be drafted and printed. And re-looked at regular intervals for updates and audits for continued benefits. Timelines of treatment to be defined based on evidence and institutional infrastructure to ensure timely interventions for best outcomes.
4. Any proposed change in standard of care to be brought to the whole group to discuss in detail, debate and discourse before dispensing to the patient after reaching a consensus from majority.
5. Support regular tumor board activities and active participation. These are demanding on time and attention of busy oncologists but are mandatory towards the strength of the DMG.
6. Regular meetings of the Group every month with clear pre-set agenda. Maintaining quorum for the meeting is very essential from all specialties and should be predefined.
7. Appropriate logging of all discussions and documentation of decisions taken.
8. All new results from research and new treatments to be discussed in the DMG before incorporating and adopting as standard of care.
9. All new proposals for research within DMG by member faculties to be discussed with inputs from rest of DMG taken.
10. Resolving issues and concerns of day-to-day functioning of DMG.
11. All functioning with common goal of improved patient care and service.
12. Annual meetings and regular teaching or educational sessions to share the experiences and expertise with the evidence-based management policies.
13. Feedback from patients at regular intervals and audits for quality checks. Patient engagement and empowerment in multidisciplinary teams should improve patient satisfaction and outcomes. Patient-reported outcome measures will improve multidisciplinary teams' insights into their patients' problems and symptoms and can improve patient outcomes
14. All aspects of DMG to be externally peer-reviewed every 5 years to identify any areas of lacunae and improvements in fields of service, research and education in cancer.
15. Very important to have institutional support and inputs for smooth functioning of DMG.

16. Have a separate DMG financial account to allow for independent functioning in select areas including some research funding.
17. Raising funds and donations from Corporate Social Responsibility funds ({CSR}) or other sources has more credibility as a Group rather than as individual faculty.
18. Any honorarium or advisory fee paid to a member for their role as representatives of DMG is added to the DMG funds to build on the reserves.
19. DMG must have their own dedicated secretarial and coordinator staff for the day to day functioning of the Group and other research and administrative activities.
20. The tenure of the Convener and Secretary are by far fixed for definite period, say a 3-year tenure, where the Secretary automatically takes over from the exiting Convener and a new secretary is then appointed from the member faculty. This ensures that all will get their turn as administrators in the DMG and will contribute actively to the combined growth and expansion of scope of activities of the DMG.
21. The Convener finally has the last word in the DMG as the lead or head of the Group and is a representative of the whole Group. All DMG's in various cancers report eventually to the Director of the institute.
22. Other crucial members of DMG include Nurse practitioners (Breast Care Nurse), Psychologists, allied health professionals and administrators.
23. Working closely with dedicated NGO's improves the quality of care, psychosocial well-being of patients and rehabilitation and overall compliance to treatment.
24. Effective DMG functioning requires policy support from administration, national and regional health authorities, scientific societies and patients' organizations.

Having a multidisciplinary team caring for the patient also improves number of cases recruited into clinical trials. This increases the participation and involvement of patient in clinical decisions. Also due to regular monitoring and adherence to predefined protocols, participation in clinical trials has shown to enhance patient safety and improved patient care translating into improved patient survival [9, 10]. Of course in addition, there is a perceived better quality of evidence generated from the clinical trial and generation of evidence-based medicine—a complete win-win situation.

Thus, the formation of a DMG in cancer care has resulted in improved disease management, better communication with the patient regarding their disease status, and available treatment options, specific outcomes, along with appropriate improved emotional, psychological and financial support ensuring better compliance to treatment and translating into overall improved outcomes of treatment and reduced financial burden. All these are a positive step towards improved patient-centric health care. Having focused teams of Disease Management Groups is the way forward in the current times and is being widely accepted in larger institutes and Cancer Centres in India.

References

1. India: Globocan 2018. International agency for research in cancer and world health organization. The Global Cancer Observatory, May 2019.
2. Gross GE. The role of the tumor board in a community hospital. CA Cancer J Clin. 1987;37(2):88–92.
3. van Nes JGH, van de Velde CJH. The multidisciplinary breast cancer care team: promoting better care. Ned Tijdschr Geneeskd. 2005;149(35):1929–31.
4. Gabel M, Hilton NE, Nathanson SD. Multidisciplinary breast cancer clinics: do they work? Cancer. 1997;79(12):2380–4.
5. Epstein NE. Multidisciplinary in-hospital teams improve patient outcomes: a review. Surg Neurol Int. 2014;5:S295–303.
6. Jacobson JO. Multidisciplinary cancer management: a systems-based approach to deliver complex care. J Oncol Pract. 2010 Nov;6(6):274–5. https://doi.org/10.1200/JOP.2010.000164.
7. Bleicher RJ. Timing and delays in breast cancer evaluation and treatment. Ann Surg Oncol. 2018;25:2829–38.
8. Horlait M, Dhaene S, Van Belle S, Leys M. Multidisciplinary team meetings in cancer care: is there a psychologist in the house? Int J Integrated Care. 2019;19(S1):A131, pp 1–8. https://doi.org/10.5334/ijic.s3131.
9. Vrijens F, Stordeur S, Beirens K, Devriese S, Van Eycken E, Vlayen J. Effect of hospital volume on processes of care and 5-year survival after breast cancer: a population-based study on 25 000 women. Breast. 2012;21:261–6.
10. Houssami N, Sainsbury R. Breast cancer: multidisciplinary care and clinical outcomes. Eur J Cancer. 2006;42:2480–91.