INTERNATIONAL JOURNAL OF PHARMA PROFESSIONAL'S RESEARCH

Innovations in Breast Cancer Surgery: Minimally Invasive Techniques and Reconstruction

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ABSTRACT

Specifically focused on minimally invasive procedures and breakthroughs in reconstruction, this review article investigates the most recent developments in breast cancer surgery. Oncoplastic surgery and robotic-assisted operations are two examples of minimally invasive approaches that have gained popularity in recent years due to their capacity to shorten the amount of time needed for recovery and to improve the appearance of the patient's appearance. This is in response to the growing focus placed on the preservation of quality of life in conjunction with advanced cancer therapy. Within the context of typical surgical procedures, the paper investigates the efficacy of these techniques, focusing on the impact that they have on patient satisfaction and survival rates. In addition to this, it goes into the ever-evolving subject of breast reconstruction, examining various choices such as autologous tissue reconstruction and implant-based reconstruction, as well as contemporary technology that improves surgical precision and cosmetic outcomes. This study aims to assess how developments in breast cancer surgery are redefining treatment paradigms and improving the entire patient experience. This review will accomplish this by combining current research and clinical practices.

Keywords: *Breast cancer, innovations, Oncoplastic surgery, minimally invasive techniques and reconstruction*

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Volume 15, Issue 3, 2024, Received: *31 March 2024,* ***Accepted:*** *10 June 2024,* ***Published:*** *30 July 2024,*
DOI: 10.69580/IJPPR.15.3.2024.18-34

1. Introduction

Breast cancer is the second leading cause of death in the United States attributable to cancer. It is also one of the most common forms of cancer in females. The good news is that breast cancer can be entirely cured if it is detected at an extremely early stage so that it can be treated. Because no known cause of breast cancer can be prevented, the single factor that is considered to be the most important in reducing the death rate and the amount of treatment that is required is the discovery of breast cancer at an early stage by screening.[1] Every year, thousands of women are detected with breast cancer in the early stage, even before they begin to feel any lump (that is, before it is palpable). This is made possible by the improved screening facilities that are available. Nevertheless, the situation is much different in the countries that are considered to be developing or third-world countries.[2] As a result of the high expense of screening tests, many women are unable to afford frequent screening, which ultimately leads to their death. This is because by the time the tumor is found or diagnosed, or even when surgery is performed, the root of the cancer has already progressed far further. Apart from the fact that they are cost-effective, the screening methods that are now available have a few other downsides. Every nation can't afford such systems because of the complex nature of their operation and the requirement for highly skilled experts to operate them.[3] This is because there is a shortage of technically skilled workers. In addition, the tension that arises from the struggle between detail and sensitivity is important. However, the majority of the currently available procedures are quite sensitive, but they are not precise enough, which results in an alarmingly high proportion of false positive cases. As a consequence of this, the rate of needless biopsies has also grown as a result of the increased number of false positive results. Some technologies are even incapable of diagnosing tumors that are mm in size or at the cellular level. In light of this, it is possible that breast tumors will not be detected in an early, curable stage, even if screening tests are performed regularly.[4]

1.2 Classification of breast cancers

The classification of breast cancers according to the molecular profile of gene expression patterns has improved the fundamental understanding and the rational strategy of research and treatment of patients with breast cancer. Breast cancers have been classified into 5 subtypes: luminal-A, luminal-B, Her2-enriched, basal-like, and claudin low. The alternative but practical classification using immunohistochemical staining of estrogen receptor (ER), progesterone receptor (PgR), and Her2 protein has been used worldwide. Hormone dependency is a well-known and important characteristic of breast cancer. Therefore, the actual treatment of patients with breast cancer has often been based on the cancer subtype classification.[5,6]

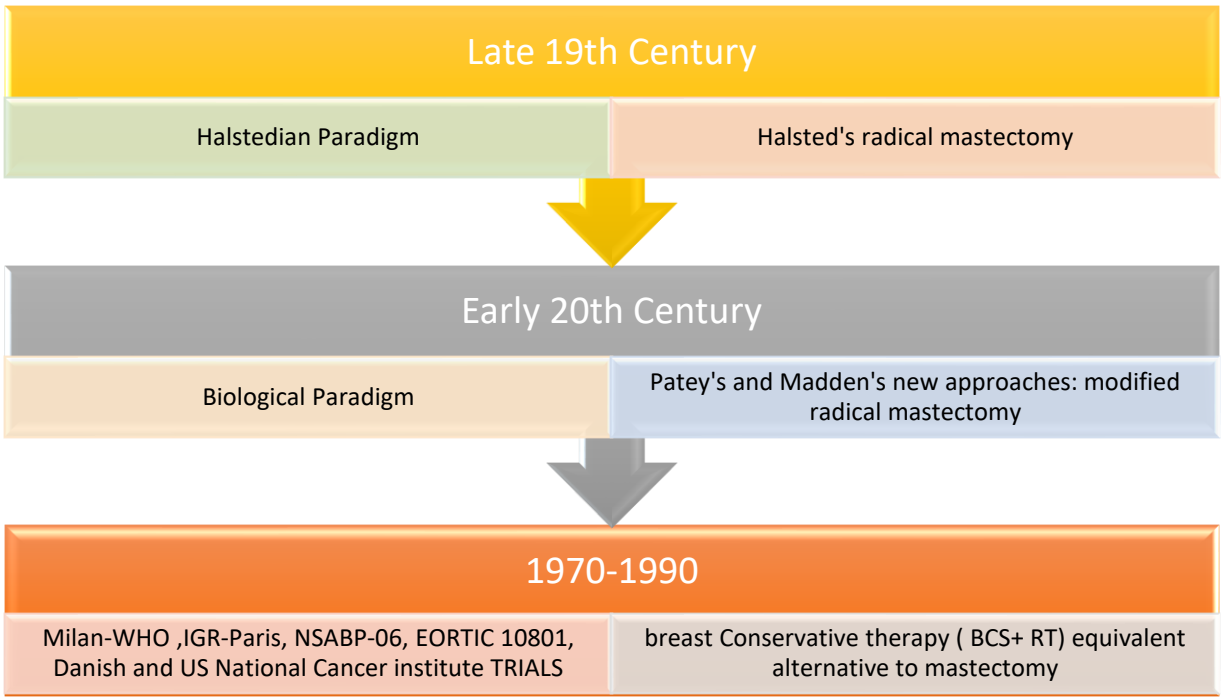

Figure 1: Evolution of breast cancer (BC) surgery

2. Minimally Invasive Techniques

2.1 Lumpectomy

Breast-conserving surgery is referred to by several different names, such as quadrantectomy, lumpectomy, or partial mastectomy. Others include partial mastectomy. In terms of technique, these phrases may differ slightly from one another, but the end goal of breast preservation remains the same. When dealing with non-palpable tumors, it is necessary to employ image-guided localization procedures, which are outlined in the section on equipment that was just mentioned. Quadrantectomy is a surgical procedure that involves the removal of the tumor, along with a margin of two to three centimeters, the pectoralis fascia, and the skin that is overlaying it. In contrast, a lumpectomy has a margin of one centimeter and involves a less extensive removal of tissue. It is not necessary to do a quadrantectomy on the vast majority of early-stage cancers; hence, this procedure will not be detailed in more depth.

When performing a lumpectomy, the incision that is used is determined by several different criteria. A radial incision may be performed, particularly in the case of a big tumor, or it may be positioned inside the Langer lines over the mass, whenever it is physically or visually feasible to do so. It is essential to carry in mind the likelihood of a subsequent mastectomy, regardless of the site of the incision. Subcutaneous flaps are generated around the tumor after the incision has been

complete. Following the removal of the specimen, it is of the utmost importance to orient it, particularly if a subsequent excision is required in the future. To confirm the existence of the biopsy clip and any markers that were put before the operation, intraoperative specimen imaging is then carried out. An extra 0.5 to 1.0 cm of tissue will be removed along with the specimen by many surgeons if a narrow margin is detected or indicated. To reduce margin positivity and maybe re-excision rates, it has been demonstrated that "shave margins," which involve the removal of an additional one millimeter of tissue, are effective. The placement of radiopaque clips within the cavity of the tumor is another common practice that is used to guide subsequent radiation treatment as well as imaging procedures. Subsequently, the incision is closed by the surgeon in successive layers. It is common practice to apply an absorbable suture while working on the skin. [7]

2.2 Mastectomy

Since the historic radical mastectomy described by William Halsted in the 1890s, which entailed bloc removal of the entire breast, pectoralis major reduction, and lymphadenectomy, mastectomy procedures have undergone a significant transformation. This method was associated with a high morbidity rate as well as substantial cosmetic abnormalities. John Madden offered a description of the modified radical mastectomy in the year 1972, and this method is still utilized in contemporary medical practice. During this treatment, an elliptical incision was made, which included the excision of the nipple-areolar complex as well as the removal of all breast tissue and the pectoralis major fascia. In addition, the removal of level I-III axillary lymph nodes is a component of a modified radical mastectomy. On the other hand, a simple mastectomy eliminates all of the breast tissue without the need for a full dissection of the axillary nodes.

In most cases, a mastectomy is performed by making an elliptical incision and then raising uniform flaps. Although the thickness of these flaps can vary, they normally fall somewhere in the range of 5 millimeters to one centimeter. The ideal situation is one in which all of the breast tissue is removed while the blood flow to the skin that overlays the breast is maintained. These flaps extend to the clavicle on the superior side, the lateral border of the sternum on the medial side, the inframammary fold on the inferior side, and the anterior edge of the latissimus dorsi on the lateral side.

Two other types of mastectomy can be performed. These include mastectomies that spare the skin and those that spare the nipple. When these treatments are carried out, immediate reconstruction is conducted. To verify that the nipple-areolar complex on the ipsilateral side of the tumor is uninvolved and, as a result, can be spared during the resection, it is essential to remember to send a frozen slice of the complex. [8]

2.3 Sentinel Node Biopsy

Patients with early-stage breast cancer who are clinically node-negative are typically candidates for the sentinel lymph node biopsy, which is a crucial component of the staging process. Short-

acting neuromuscular blocking agents are preferred during induction in both sentinel and axillary lymph node dissection. This is done to ensure that patients are not paralyzed during the procedure. This enables the correct identification of the thoracodorsal, long thoracic, medial, and lateral pectoral nerves, which helps to prevent accidental injury. When it comes to the identification of nodes, the majority of surgeons favor a dual tracer approach the majority of the time because it has the maximum sensitivity. To begin, a radioactive tracer consisting of a technetium-99m sulfur colloid is administered intradermally into the area of the tumor or the areolar subdermal plexus. This is done to detect the presence of the tumor. In the following step, the surgeon may inject isosulfan blue or methylene blue dye that has been diluted to assist in the identification of the sentinel lymph nodes. Another common application of this dye involves injecting it into the subdermal plexus of the areola. Following this, a gamma probe is utilized to ascertain the precise location of the likely sentinel node. After making a tiny incision, the tissue is dissected down to the fascia of the clavipectoral region. The gamma probe is then utilized to determine the node that is the hottest. This node has been removed. Next, the gamma probe is used to assist in the identification of any additional sentinel nodes. These nodes are eliminated if they account for more than ten percent of the total counts of the sentinel node, are blue, or are suspicious. Following the careful removal of these nodes, the surgeon may choose to perform either a frozen section or a permanent section, depending on his or her preference. [9]

2.4 Axillary Node Dissection

It is currently standard of care to perform axillary node dissection on a select group of patients, as indicated above. First, the surgeon palpates the pectoralis major and forms a “lazy S” incision using a scalpel. Next, electrocautery is used to both dissect through the subcutaneous tissue as well as raise skin flaps. The inferior skin flap should be raised to the level of the 5th rib. The borders of the axilla include the axillary vein, the pectoralis major and minor as well as the latissimus dorsi muscle. The lateral border of the pectoralis major gets elevated to expose the interpectoral (Rotter’s) nodes, which are dissected off the pectoralis minor muscle. Next, the axillary fascia gets divided to free up the lateral edge of the pectoralis minor. This step will expose the nodal tissue to be excised with the specimen. In bulky disease, the pectoralis minor muscle may require division to improve the exposure of the upper axillary lymph nodes. The wound should be irrigated, and hemostasis assured. A single drain should be placed and lie inferior to the axillary vein. The incision is typically closed using deep dermal 3-0 absorbable sutures followed by skin adhesive or absorbable sutures.[10]

3. Reconstruction Techniques

3.1 Oncoplastic surgery

Oncoplastic surgery is a specialized approach in breast surgery that combines oncological and plastic surgical techniques to treat breast cancer while preserving or enhancing the aesthetic

appearance of the breast. This method allows for the excision of larger tumors without compromising the cosmetic outcome, making it a viable option for many patients who might otherwise face mastectomy.[11]

Oncoplastic surgery can be broadly categorized into two main types:

i. **Volume Displacement Techniques**: These involve rearranging the remaining breast tissue to fill the defect left by tumor removal. Techniques in this category include:

- **Glandular or local tissue rearrangement**: This includes procedures like crescent mastopexy and doughnut mastopexy, where minimal amounts of tissue (up to 20-50%) are removed.
- **Reduction mammoplasty**: This is used when larger volumes of tissue need to be excised, often requiring symmetry procedures on the contralateral breast for aesthetic balance.[12]

ii. **Volume Replacement Techniques**: These techniques are employed when significant tissue removal is necessary, typically exceeding 50% of the breast volume. They involve:

- **Autologous tissue reconstruction**: Using tissue from another part of the body (e.g., latissimus dorsi flap).
- **Implant-based reconstruction**: Utilizing implants to restore breast volume after substantial tissue removal.[13]

3.2 Techniques

Oncoplastic surgery encompasses a variety of surgical techniques tailored to the individual patient's needs based on tumor size and location. Some common techniques include:

- **Therapeutic Mammoplasty**: This combines breast reduction and cancer removal, allowing for significant tumor excision while achieving a more favorable breast shape.[14]
- **Mastopexy**: This technique lifts and reshapes the breast, often used in conjunction with tumor removal to maintain aesthetic integrity.[15]
- **Local Flaps**: Techniques such as the latissimus dorsi myocutaneous flap or other regional flaps are employed to cover larger defects post-excision.
- **Symmetry Procedures**: Often, a symmetry operation on the opposite breast is performed to ensure aesthetic balance, particularly when significant tissue is removed from one side.[16]

3.3 Outcomes

The outcomes of oncoplastic surgery are generally favorable, both oncologically and aesthetically. Studies indicate that:

- **Local Recurrence Rates**: The local recurrence rates in patients undergoing oncoplastic surgery are comparable to those seen in traditional mastectomy, with rates reported around 3-9% over several years of follow-up.[17]
- **Aesthetic Satisfaction**: Many patients report high satisfaction levels with their aesthetic outcomes, as oncoplastic techniques are designed to minimize visible scarring and maintain breast shape. However, aesthetic outcomes can vary based on the extent of tissue removed and the specific techniques used.[18]
- **Overall Survival**: Long-term studies have shown that patients undergoing oncoplastic surgery have survival rates similar to those undergoing more traditional surgical approaches, reinforcing the safety and efficacy of this method in managing breast cancer.[19]

4. Implant-based breast reconstruction

Implant-based breast reconstruction (IBBR) IBBR is the most common breast reconstruction method in the world, and its application is increasing. In a longitudinal trend analysis of the National Inpatient Sample database from 1998-2008, the rate of implant reconstructions increased by 11% yearly.[20,21] A seven-year population-based cohort study also showed that between 2007 and 2014, immediate implant reconstruction increased from 30% to 54%. This technique is often preferred by patients who want to avoid scars and pain in the chest region, such as the abdomen and back. Capsular contracture and implant failure are common complications of breast reconstruction with implants and expanders (e.g., rupture, deflation, and malposition).[22,23]

5. Autologous breast reconstruction (ABR)

Autologous breast reconstruction (ABR) is a surgical technique that utilizes the patient's own tissue to reconstruct the breast following mastectomy, offering several advantages over implant-based reconstruction. One of the primary benefits of ABR is its ability to provide excellent long-term results, resulting in a natural appearance and feel that many patients prefer. Additionally, ABR often allows for better sensory restoration and higher aesthetic satisfaction, as studies have shown that patients report greater satisfaction with the overall reconstructive treatment compared to those who opt for implants.[24,25] Furthermore, ABR has been associated with a longer time to recurrence of breast cancer, enhancing its appeal as a viable option for many patients. Common donor sites for the tissue used in ABR include the abdomen, back, and thighs, each offering unique benefits and considerations. While ABR can lead to higher health costs and requires additional surgery to harvest the tissue, it remains a highly regarded option for breast reconstruction. Ultimately, the decision between ABR and implant-based reconstruction depends on individual patient preferences, anatomical considerations, and the expertise of the surgical team, making it essential for patients to engage in thorough discussions with their healthcare providers to determine the best

approach for their needs.[26,27] The indications, complications, advantages, disadvantages, and prognosis of IBBR and ABR are presented in Table 1.

Table 1: Comparison of different flaps

Autologous flaps	Indications	Complications
DIEP	patient preference, failed implant, and severe soft tissue damage	fat necrosis (high), abdominal bulging/hernia (low), and venous congestion (high)
SIEA		abdominal bulging/hernia (low), wound infection (high)
TRAM		fat necrosis (low in fTRAM), abdominal bulging/hernia (high in pTRAM and low in fTRAM), and flap loss (high in pTRAM)
LD	patient preference, insufficient tissue volume, impaired abdominal blood supply, a history of abdominal surgery, and postoperative deformities that need correction	seroma (high), shoulder pain, and dysfunction (high)
TAP		seroma (low), shoulder pain, and dysfunction (low)

6. Autologous fat grafting

Implants are generally inserted to improve the volume, but as they have many associated problems, the use of fat grafting has become popular. In this technique, fat is collected from fat-rich areas of the body, such as the thighs, abdomen, and buttocks, through negative pressure liposuction. Then, the fat particles are purified and filled evenly in the depressed areas of the breasts.[28,29] The combined implantation of the implant and autologous-fat granule for breast reconstruction after a radical mastectomy is a simple operation and has better aesthetic outcomes and safety. It satisfies the aesthetic needs of patients with resected lesions, and it does not alter the surgical effects of modified radical mastectomy.[30]

7. Technological Advancements in Imaging and Surgery

7.1 Imaging Techniques

7.1.1 3D Mammography

3D mammography, also known as digital breast tomosynthesis, is an advanced imaging technique that enhances breast cancer detection. It works by taking multiple X-ray images of the breast from different angles, which are then reconstructed into a three-dimensional image. This method improves the visibility of breast tissue, particularly in women with dense breasts, and has been shown to detect cancers earlier than traditional 2D mammograms. Studies indicate that 3D mammography can reduce the need for follow-up imaging and decrease the number of false positives, thus lowering patient anxiety and healthcare costs.[31,32]

7.1.2 MRI and Ultrasound

Magnetic Resonance Imaging (MRI) and ultrasound are complementary to mammography. MRI is particularly useful for assessing breast tissue in women at high risk for breast cancer or those with dense breast tissue. It provides detailed images without radiation exposure but is more expensive and time-consuming compared to mammography. Ultrasound, on the other hand, uses sound waves to create images and can detect some cancers that mammograms may miss, especially in dense breast tissue. When used together, these imaging techniques enhance the overall effectiveness of breast cancer screening.[33,34]

7.1.3 Impact on Surgery

The integration of advanced imaging techniques into surgical practices has significantly improved outcomes. Enhanced imaging aids surgeons in accurately locating tumors and planning surgical approaches, which can lead to less invasive procedures and better preservation of surrounding tissues. This precision translates to improved recovery times and overall patient satisfaction.[35,36]

7.2 Surgical Tools and Devices

7.2.1 Innovations

Recent innovations in surgical tools and devices include the development of minimally invasive instruments and advanced visualization technologies. These innovations allow surgeons to perform complex procedures with smaller incisions, leading to reduced trauma, shorter hospital stays, and quicker recoveries for patients. Additionally, enhanced imaging technologies, such as intraoperative ultrasound and 3D visualization, provide real-time feedback during surgery, improving decision-making and outcomes.[37,38]

7.2.2 Impact on Precision and Safety

The advancements in surgical tools have markedly increased the precision and safety of surgical procedures. For instance, robotic-assisted surgeries enable greater dexterity and control, allowing for intricate maneuvers that would be challenging with traditional techniques. This precision reduces the risk of complications and enhances the overall safety of surgical interventions.[39]

7.3 Robotics in Surgery

7.3.1 Current State

Robotic surgery has gained traction in various fields, including urology, gynecology, and cardiothoracic surgery. Current robotic systems provide surgeons with enhanced visualization and precision through 3D imaging and robotic arms that mimic human movements. These systems have been shown to reduce blood loss, minimize pain, and shorten recovery times compared to conventional surgery.[40,41]

7.3.2 Future Potential

The future of robotics in surgery looks promising, with ongoing advancements in artificial intelligence and machine learning. These technologies are expected to enhance robotic systems' capabilities, making them even more intuitive and responsive to surgeons' needs. Future developments may include fully autonomous surgical procedures, which could further revolutionize surgical practices and improve patient outcomes.In summary, technological advancements in imaging techniques, surgical tools, and robotics are transforming the landscape of healthcare, leading to improved diagnostic accuracy, enhanced surgical precision, and better patient outcomes.[42]

8. Patient Outcomes and Quality of Life

8.1 Survival Rates and Recurrence

8.1.1 Data and Statistics

Survival rates for patients undergoing surgical interventions, particularly for cancers such as breast, colorectal, and prostate cancer, have improved significantly over the past few decades. According to recent statistics, the five-year survival rate for breast cancer has increased to approximately 90%, largely due to advancements in early detection and treatment options. Recurrence rates vary by cancer type and treatment modality; for example, breast cancer recurrence rates can be as low as 10-15% with appropriate adjuvant therapy, while certain aggressive forms may have higher rates.[43,44]

8.1.2 Comparative Analysis

Comparative analyses of treatment modalities reveal that patients who undergo minimally invasive surgeries often experience lower recurrence rates and better survival outcomes compared to those who have traditional open surgeries. Studies indicate that robotic-assisted surgeries, for instance, can lead to fewer complications and improved long-term results, enhancing overall patient survival and quality of life.[45,46]

8.2 Aesthetic Outcomes

8.2.1 Patient Satisfaction

Aesthetic outcomes are increasingly recognized as critical components of patient satisfaction, particularly in surgeries involving visible areas such as breast reconstruction or facial procedures. Surveys indicate that patients who receive reconstructive surgeries report high levels of satisfaction, with many noting improved body image and self-esteem post-surgery. The use of advanced techniques, such as oncoplastic surgery, has further enhanced aesthetic results in breast cancer patients.[47]

8.2.2 Psychological Impact

The psychological impact of aesthetic outcomes is profound, as positive surgical results can lead to improved mental health and quality of life. Patients often experience reduced anxiety and depression levels when they are satisfied with their surgical outcomes. Conversely, poor aesthetic results can lead to dissatisfaction and emotional distress, highlighting the importance of discussing aesthetic goals during pre-operative consultations.[48]

8.3 Functional Outcomes

8.3.1 Range of Motion

Functional outcomes, including range of motion, are critical for assessing the success of surgical interventions, particularly in orthopedic and reconstructive surgeries. For instance, patients undergoing shoulder surgery often experience significant improvements in range of motion post-operatively, with many regaining full functionalities within months. Rehabilitation protocols that include physical therapy are essential for optimizing these outcomes.[49]

8.3.2 Pain Management

Effective pain management is crucial for enhancing functional outcomes and overall patient satisfaction. Advances in pain management techniques, including multimodal analgesia and regional anesthesia, have significantly improved post-operative pain control. Studies have shown that patients who receive comprehensive pain management strategies report lower pain levels and quicker recoveries, enabling them to return to daily activities sooner.[50]

8.4 Recovery and Rehabilitation

8.4.1 Techniques

Recovery and rehabilitation techniques have evolved to support patients in their post-operative journeys. Evidence-based practices, such as early mobilization and tailored physical therapy programs, have been shown to enhance recovery times and functional outcomes. These techniques are designed to minimize complications and promote healing, allowing patients to regain strength and mobility effectively.[51]

8.4.2 Programs and Support

Structured rehabilitation programs, often supported by healthcare teams, play a vital role in patient recovery. These programs may include physical therapy, occupational therapy, and psychological support, tailored to the individual needs of patients. Support groups and educational resources also contribute to enhanced recovery experiences, helping patients navigate the challenges of post-surgical life and fostering a sense of community.In summary, patient outcomes and quality of life are significantly influenced by survival rates, aesthetic and functional outcomes, and effective recovery and rehabilitation strategies. Advances in surgical techniques and supportive care continue to enhance these aspects, leading to improved overall patient experiences.[52,53]

9. Future Directions

It is anticipated that the treatment of breast cancer will undergo revolutionary changes shortly, particularly as a result of the development of new methods, customized medicine, and evolving administrative structures. With current research and clinical trials exploring revolutionary surgical approaches, such as intraoperative radiation treatment and targeted medication delivery systems, emerging techniques are at the forefront of this transformation. This progress is being driven by ongoing research and clinical trials. The purpose of these procedures is to improve precision, shorten the time of treatment, and lessen the severity of adverse effects. It is anticipated that the treatment of breast cancer would undergo a revolution as a result of potential innovations. These innovations include the utilization of nanotechnology for the administration of drugs in a targeted manner and the creation of smart implants that monitor for recurrence. [54]

A further important path is personalized medicine, which focuses on developing treatment strategies that are specific to individual patients by taking into account the genetic and molecular profiles that are unique to them. Clinicians can select the most effective therapy, decrease unpleasant effects, and enhance overall results when they have a thorough grasp of the precise genetic alterations and molecular characteristics of a patient's breast cancer. The advancements that have been made in genetic testing and the development of targeted treatments that selectively target specific genetic mutations are making this strategy easier to implement. [55]

In the end, policies and rules are being revised in order to stay up with the improvements that have been made. The goal of the updates and recommendations made by health authorities, such as the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO), is to establish best practices that include new technology and treatment modalities while simultaneously assuring the safety and effectiveness of patients. Furthermore, it is vital to have a global perspective in order to enhance breast cancer outcomes on a worldwide scale. This is because healthcare systems all over the world are adapting to these changes and sharing their ideas and tactics. These potential future avenues hold the possibility of considerably improving the entire patient experience as well as the quality of care that is provided to people who are afflicted with breast cancer and are now receiving treatment. [56]

10. Conclusion

A major increase in patient outcomes and quality of life has been brought about as a result of the advancements that have been made in breast cancer treatment and surgery. One of the most important aspects is the proliferation of minimally invasive methods, such as oncoplastic surgery, which combines the removal of cancer with the preservation of the patient's appearance. This results in high levels of patient satisfaction and survival rates that are comparable to those of classical mastectomy. Personalized medicine is increasingly gaining popularity, and genetic and molecular profiling are making it possible to create individualized therapy programs that improve

treatment efficacy while simultaneously minimizing adverse effects. In addition, the incorporation of these advances into clinical practice is dependent on the development of regulations and guidelines, which are essential to guarantee that patients receive the most efficient and secure care that is now available. As we look to the future, we can see that the future of breast cancer surgery is bright. The current research and clinical trials are anticipated to result in the development of new techniques and technologies that will further improve surgical precision and the outcomes for patients. Technology advancements such as intraoperative imaging and robotic-assisted operations have the potential to improve the capabilities of surgeons, making it possible for them to do procedures that are even more polished and less intrusive. The landscape of breast cancer treatment is continuously evolving, driven by technical improvements and a deeper understanding of the illness. In conclusion, this describes the current state of the field. They have the potential to revolutionize the patient experience, bringing hope for better survival rates, improved cosmetic outcomes, and enhanced quality of life for people who are affected by breast cancer. These advancements are still in the process of unfolding.

11. Conflict of interest

The authors have no conflict of interest.

12. Acknowledgement

Authors are highly thankful to their Universities/Colleges for providing library facilities for the literature survey.

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