

# From the treatment of breast cancer to the treatment of the woman with cancer: History of breast surgery and its prejudices

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**Abstract.** *Background and aim:* The article offers a comprehensive analysis of the historical evolution in breast cancer treatment since antiquity and provides a comprehensive overview of the evolution of medical practice over time and highlighting the studies and researches that have led us to current surgical approaches. *Methods:* analysis of literature and historical studies. *Results:* Following the technique described by Halsted in 1894, which involved an extremely invasive procedure, advancements in scientific knowledge gradually allowed for more advanced surgical techniques that are respectful of bodily integrity. As treatments have evolved, the focus has been on increasing overall and disease-free survival. The increased understanding of tumor characteristics, adoption of multidisciplinary approaches, and societal shifts towards health have led to a significant evolution in breast cancer diagnosis and treatment. *Conclusions:* This transition from aggressive to more tailored therapies, including localized and systemic treatments, has improved survival rates and patient quality of life. Current research is exploring the possibility that future breast cancer therapies may even eliminate the need for breast and axillary surgeries, thus revolutionizing the therapeutic approach. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** breast cancer history, breast surgery, mastectomy, breast-conserving therapy, sentinel node biopsy

## Introduction

Surgical oncology is one of the cornerstones in the management of breast cancer, a disease known and described since antiquity. Since the first description of breast cancer treatment over 3,000 years ago, the growth of anatomical and scientific knowledge has greatly impacted surgical techniques. The historical course of surgical methodology has been marked by several pivotal phases, each coinciding with significant advances in medical knowledge and noteworthy discoveries in the field of breast oncological surgery. These discoveries have enabled the abandonment of extremely invasive approaches involving extensive mutilation of the chest wall, allowing the evolution

towards more conservative and targeted procedures, reducing complications and psychological impact of these treatments.

This evolution especially in recent decades reflects not only technological progress but also a greater understanding of breast cancer and an increasing focus on the physical integrity and on patients' quality of life.

This historical perspective provides an illuminating view of the evolution of the breast cancer surgery over time, highlighting the path that has led us to the actual medical practice. It also emphasises the importance of close collaboration and integration between surgical and medical treatment modalities, in a multidisciplinary approach that can guarantee optimal results and a tailored approach.

In the following analysis, we will explore in detail the historical pathway of oncological surgery, highlighting key milestones and illustrating the current scientific evidence in the surgical management of breast cancer.

### **Evolution of surgical practice: from antiquity to Halsted's surgery**

Breast cancer has been known since ancient times (1-3). Cotlar indicates the presence of a description of 8 distinguishable tumor cases from breast infections in Smith's Egyptian papyrus, as they were cold to the touch and not fluctuant (4). One case was treated by cauterization with a fire drill. However, according to this document, such a condition could not be cured. According to Nunn, on the other hand, evidence of tumors in the Egyptian papyri is still uncertain. Nevertheless, the presence of the word "weshau" (to eat) could at least in some cases be interpreted as indicative of malignancy, suggesting that such a condition could be recognized (3).

From the Greek historian Herodotus (484 BCE - 430 BCE), we have the story of Princess Atossa, the second wife of Persian King Darius I and daughter of Cyrus the Great, and mother of Xerxes. She suffered from a breast nodule but, out of modesty, did not seek examination by any physician. When the swelling increased in size, the renowned court physician from Croton, Democedes, was consulted. He managed the lesion, presumed to be either a breast abscess or a benign tumor, although the specific method used is not documented (5, 6).

Hippocrates (around 460 BCE - 380 BCE), the most renowned physician of ancient Greek times, mentions breast tumors only sparingly: the short lifespan of women, typically less than 20 years at that time, contributed to their low incidence.

The "corpus hippocraticum" reports the case of a woman from Abdera diagnosed with a *karkinôm* (Latin: *cancrum*, *carcinoma*) in her breast, associated with bleeding from the nipple. What began as a small lesion had grown and ultimately led to her death (7). In Hippocratic philosophy, which endured for a long time, tumor formation was seen as part of

an inflammatory process involving a "flow of tumors," where an excess of black bile was the reason. However, the Hippocratic text does not indicate a proposed treatment. Particularly, although surgery was a significant and well-developed aspect of the *Corpus*, there are no specific references to breast surgery (8). The recommendation for small tumors was to leave them be to avoid potentially shortening the patient's life through treatment (9).

After Hippocrates, in the centuries that followed, many remedies of animal, vegetable, and mineral origin, including cabbage specifically mentioned by Cato in his "De Agricultura" as a panacea for various ailments including tumors, were used as anti-tumor therapies. Gradually, elements of surgery and cauterization began to be introduced for more advanced tumors (10).

In the Roman period, Celsus (14 BCE - 37 CE), who practiced during the time of Augustus, in the second volume of "De Medicina," first outlined different stages of breast cancer, specifying that only the initial stage (*cacoethes*) was curable (11). He suggested that due to the difficulty in accurately distinguishing between early and advanced stages, caustic medications should be applied. He also, for the first time, recommended that tumors should be completely removed down to healthy tissue.

The thesis of Galen, who lived in the 2nd century, largely supported the theories of Hippocrates and other subsequent authors that attributed breast tumors to an excess of black bile. Galen emphasized that certain benign lesions, which he termed "*karkinoi genomenoi*" found in the breast, could develop into tumors. He regarded breast cancer as the most prevalent, noting its tendency to often develop after menopause (12, 13).

Galen revitalized the concept of surgical treatments for the breast, facilitated by the availability of fairly adequate surgical instruments, as evidenced by findings in Pompeii. In the initial phase, the tumor could be treated by inducing bleeding to rid the body of excess black bile, along with topical remedies applied to the breast (1). While upholding Hippocratic advice to avoid deeply rooted tumor treatment, he thought that if breast tumors did not respond to conservative approaches, they should be surgically removed. He was the first to recommend clear margins and the removal

of tumor extensions “shaped like a crab,” discouraging the use of cautery due to potential damage to surrounding structures (9). He described the practice of mastectomy as creating a circle in the area where tissues remained healthy. He also associated scar treatment with packs made of licorice, sulfur, and opium.

In Galen’s view, tumors could be treated in their initial stages by removing the nodule (what is now termed as lumpectomy). In cases of more advanced tumors, he recommended an extended mastectomy, which involved the removal of the pectoral muscle, if necessary, although he considered advanced tumors incurable.

Surgical therapy, aimed at eradicating the disease, was later abandoned. This decision was influenced by several factors, including the high incidence of post-operative septic complications and the lack of adequate anesthetics to mitigate surgical procedures. Moreover, as early as the 2nd century, the idea spread that breast carcinoma was a systemic pathology that derived only temporary benefits from surgery, without guaranteeing definitive healing. This belief contributed to the use of topical treatments based on herbal extracts and the emergence of figures such as charlatans and itinerant vendors selling purportedly curative mixtures.

The first comprehensive technical description of surgical removal of tumors comes from Aetius of Amida, the imperial physician of the Byzantine Emperor Justinian (527-565). Aetius based his authoritative writings on breast cancer on the opinions of Greek physicians like Archigenes of Apamea (late 1st century), often cited by Galen, and Leonidas of Alexandria (1).

After relocating to Rome, Aetius performed “radical” surgery on breast tumors: “usque ad sanam partem”, echoing Celsus (1, 14). The Byzantine physician stressed the need for preparatory interventions to optimize the patient’s overall health before surgery, including proper nutrition, selected medications, and establishing correct bowel movements. He was likely the first person to describe Paget’s disease of the nipple (1).

Paulus Aegineta, a 7th-century surgeon who compiled a comprehensive history of breast surgery up to his time, referenced surgeons who cautioned against prioritizing technique over reason and warned against

operating on extensive tumors so as not to hasten the patient’s death (15).

In the Middle Ages, the Arabs made significant contributions by preserving crucial Greek and Roman medical works and laying the groundwork for new sciences such as astrology, the occult, and alchemy.

Avicenna (980-1037) stands out as the most representative physician of the Arab scientific world, characterized by the fusion of Hellenistic scientific principles with marvelous and fantastic elements. Arab surgical innovations involved using cauterization even as a cutting tool to adhere to the Islamic commandment against “cutting flesh.” Avicenna was among the first to introduce the concept of metastatic breast tumors, recommending treatment in the early clinical stage due to his belief that tumors generate immediate metastases (16).

Albucasis, an Arab surgeon operating in the 10th century, also utilized cauterization in surgically treat breast cancer, albeit expressing doubts about its efficacy for this disease (17).

Despite most surgeons belonging to the disparaged category of wandering quacks practicing an art passed down from father to son, this period witnessed the establishment of the first true surgical schools and universities in Italy. Both Arab surgery and the School of Salerno represented a bridge to the surgery of the later Middle Ages, known as “university surgery”, as it was studied and applied within universities.

During the Renaissance, Vesalius’s detailed anatomical descriptions in his anatomy treatise “*De Humani Corporis Fabrica*” enabled surgeons to ligate vessels to manage bleeding and improve precision during breast dissections (18).

Paré was among the first to recognize the role of axillary lymph nodes in the spread of breast cancer (19). He treated large ulcerous tumors with ointments but preferred the surgical removal of small breast tumors, ensuring well-defined margins (17).

By the late 1500s, a systematic surgical approach emerged. Neapolitan surgeon Marco Aurelio Severino, from the Hospital degli Incurabili in Naples, performed mastectomies and axillary lymph node removal when the disease presented itself. However, during that century, the prevailing belief persisted that surgery, despite being the only available option, did not cure cancer.

Swiss physician-chemist Paracelsus (Philippus Theophrastus Bombastus von Hohenheim, 1493–1541) challenged the theories of his predecessors (15). He proposed that diseases stemmed from an individual's internal struggle against their weaknesses, attributing them to spiritual disharmony, overturning established concepts. His therapeutic approach revolved around seeking remedies for illnesses, crafted in laboratories using mineral substances, leading to the emergence of a new discipline, iatrochemistry. Paracelsus was among the pioneers advocating the use of chemical products to treat diseases. While this era introduced numerous remedies, effective cures for cancer remained elusive.

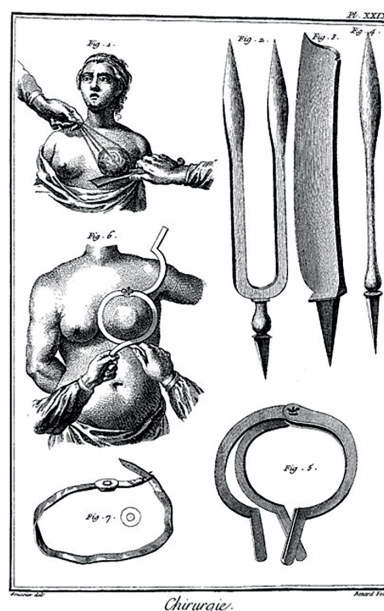
During the 16th and 17th centuries, surgeons, lacking the availability of anesthesia introduced only in the mid-19th century, developed instruments to facilitate rapid breast amputation (Figures 1 and 2).

Gerard Tabor's mastectomy instrument, resembling a small guillotine and illustrated in 1721, enabled swift breast extraction.

During darker periods, the Catholic Church slowed the progress of medicine and surgery, believing in healing through faith in divine intervention. The Council of Tours in 1162 condemned breast surgery (2).



**Figure 1.** Johannes Schultes / Scultetus *Armamentarium Chirurgicum*, Ulm 1655, Tabula XXXVI: instruments for a mastectomy.



**Figure 2.** Breast surgery. A print from the *Encyclopédie, ou Raisonner des Sciences, des Arts et des Metiers* by Diderot & d'Alembert, 1751–1777. From a private collection.

Italian surgeon Angelo Nannoni (1715–1790) was among the first to grasp the real possibility of tumor spreading through vessels, reaching distant parts of the body.

In the 18th century, the connection between breast carcinoma and axillary lymph nodes was established. Petit (1674–1750) and Bell (1749–1806) advocated for procedures involving the removal of breast tissue, chest wall, and lymph nodes based on the concept that breast carcinoma initiated as a local disease, and if diagnosed early, could be treated with appropriate surgical therapy (20). Also in the 1700s, a French physician, Henri Francois Le Dran, sensed that breast tumors initially manifested as a local ailment before becoming a systemic condition. He believed that early surgical intervention could ensure a cure, marking the onset of an oncological approach to breast cancer.

Lorensius Heister (1683–1758), a renowned German professor whose famous book on surgery was translated into English around 1748, supported the surgical approach advocated by Petit. In some cases, he even proceeded to remove a portion of the ribcage if it was affected by the tumor (21).

The surgical technique, now refined, lacked anesthesia, sepsis control, and pain management, essential milestones that were later developed (22).

Reflecting on the evolution of breast surgery, it's crucial to note that many surgeons were disheartened by the high recurrence rate and the tragic mortality within two years post-surgery.

London anatomist Matthew Baillie, in "The morbid anatomy of some of the most important parts of the human body" (1793) unequivocally disproved Galen's theory on humors, marking the abandonment of that theory forever.

Paget (1814-1899), based on an experience of 235 cases, recorded a concerning 10% mortality rate during surgery and, even worse, a complete recurrence within eight years. His conclusion was stark: it was preferable to avoid surgical risks for patients. However, this period of disillusionment took a turn with the emergence of Halsted. Following the new approach advocated by Petit and Bell, W. S. Halsted from Baltimore (1825-1925) became the advocate for the "radical mastectomy" procedure from 1882, which was already being performed by surgeons worldwide. This type of procedure (later modified by Patey, Auchincloss, Madden, Handley, Jeis, Jesnick) remained a worldwide treatment dogma for almost eighty years, until the late 1960s (23).

#### *From Halsted to 'Gentle' surgery: a new vision of care*

In the second half of the 19th century, radical mastectomy had become extremely invasive, involving the removal of breasts, pectoral muscles, axillary lymph nodes, and in some cases, parts of ribs, sternum, clavicle, and internal mammary lymph nodes, resulting in a significant alteration of physical appearance. This approach stemmed from the belief that cancer was an intense threat, requiring an extreme response from surgeons who had to operate up to the anatomical limits allowed.

Meanwhile, Halsted emerged as an undisputed figure in oncologic surgery (24, 25). He introduced the centrifugal theory, conceptualizing cancer as a kind of malignant whirlwind spreading from the chest to the axillary lymph nodes and, via the bloodstream, involving various organs. According to the American

surgeon, to halt this centrifugal expansion, every fragment of the tumor had to be removed from the body, following the principle that the more you remove, the better (26).

Halsted's theory succeeded in convincing most physicians in America, but moving away from Baltimore, its influence seemed to gradually wane.

In 1924, English surgeon Geoffrey Langdon Keynes (1887-1982), at St Bartholomew's Hospital in London, encountered a young woman suffering from an ulcerated breast cancer in a debilitated state.

Keynes, concerned about the patient's particular physical frailty, opted for a more conservative strategy rather than a risky surgical procedure that could have endangered her. Drawing from the insights gained by radiologists like Emil Grubbe who had already demonstrated the effectiveness of X-rays in treating breast cancer, Keynes chose to directly introduce 50 mg of radium into the patient's chest to irradiate the tumor, closely monitoring its effects. Unexpectedly, the tumor mass began to rapidly shrink, prompting Keynes to consider the possibility of a conservative surgical intervention.

Encouraged by subsequent results, Keynes and his colleagues explored various strategies, among which the most effective seemed to be removing the nodule without the lymph nodes, followed by moderate-dose radiotherapy. These approaches showed recurrence rates at least comparable to those observed in New York or Baltimore.

Keynes' approach faced strong resistance within the scientific community that remained loyal to Halsted's school of thought. However, studies conducted on mice had revealed that tumors implanted in animals did not behave as envisioned by Halsted. When a large tumor grew in one place, small metastatic masses often bypassed local lymph nodes and developed in distant organs such as the liver and spleen. This demonstrated that cancer did not spread like a centrifuge, but its spread was discontinuous and unpredictable.

This finding led Crile to advocate for a preference, in the case of early-stage tumors, for targeted surgical removal combined with radiotherapy, over overly invasive surgery involving half of the chest. On the other hand, if breast cancer had already spread as a systemic

disease from the beginning, then any type of surgery would have been futile, and highly destructive intervention would have been considered cruel (27).

Crile began to practice according to a method very similar to Keynes, adopting a less invasive approach he called “simple mastectomy”. He observed comparable survival outcomes to Keynes, who, however, solely performed nodulectomy combined with radiotherapy. Nonetheless, Keynes did not have the opportunity to experiment with this method.

In 1928, four years after Keynes’ nodulectomies began in London, there was a strong desire to demonstrate that radical and less radical surgical strategies were comparable in terms of survival. However, starting a clinical trial faced strong disinterest from the medical community.

Four decades after Keynes’ innovation, Crile faced resistance to change within the hierarchical structure of medicine. This resistance hindered his efforts to organize a study challenging Halsted’s established theory.

Surgical tradition was challenged thanks to the intervention of Bernard Fisher, a surgeon from Pennsylvania. Trained in Pittsburgh, where Halsted’s theory was entrenched, Fisher began to question this theory by comparing it with the ideas of Crile and Keynes. He realized that organizing a comparative study among different procedures would be impossible in the academic and surgical environment of that time. So, Fisher had an innovative idea: directly involve the patient.

In the 1960s, the feminist movement was also influencing the medical field, while some medical principles were in crisis, and the relationship between doctor and patient was slowly changing.

The fact that one of the most invasive procedures on women’s bodies had never been put to the test appeared shocking and cruel to the new generation of women. Considering the voices of patients in these debates was becoming increasingly relevant.

In 1967, Bernard Fisher took over the leadership of the “National Surgical Adjuvant Breast and Bowel Project”, a university hospital consortium aimed at developing an extensive study on breast cancer. Convincing American surgeons to participate was a challenging task, so involving Canadian colleagues was crucial to complete the study. Ten long years were needed to gather the essential data.

In 34 hospital centers spread across the United States and Canada, 1665 patients with clinically negative lymph nodes were divided into three treatment groups. One underwent radical mastectomy, the second underwent simple mastectomy and removal of lymph nodes only in case of subsequent development of lymph node metastasis, and the third underwent simple mastectomy followed by regional radiotherapy (involving the breast and armpit). The result of the NSABP-04 Trial was published in 1977 (28).

What emerged was a surprising picture: no significant difference among the three groups in terms of mortality, recurrence, and distant metastases. Furthermore, patients with lymph node metastases achieved the same results both with armpit radiotherapy after mastectomy and with radical mastectomy. Fischer also highlighted that metastatic lymph nodes were not precursors of metastatic disease but a manifestation of an already widespread disease (29).

From that moment, Halsted’s theory lost its foundation, revolutionizing the very concept of radical surgery in breast cancer treatment. Over the years, the revolution in breast carcinoma treatment saw a significant leap forward due to the association with radiotherapy and chemotherapy, as well as tumor typing (ER, PR, HER-2), leading to targeted therapies like Tamoxifen and Herceptin. This change led to a considerable increase in the survival of women with cancer (30).

Based on this revolution and the achieved results, along with the widespread use of mammography allowing for the detection of increasingly smaller tumors, Italian oncologist Umberto Veronesi adhered to a therapeutic strategy of removing axillary lymph nodes but only partially removing the breast, followed by preventive radiotherapy. This practice not only marked a significant shift in the philosophy of breast surgery but also presented a new ethical approach to breast cancer treatment, respecting and preserving patients’ self-image and perception through the so-called “gentle surgery”.

Veronesi maintained confidence in the emerging conservative approach, even though the first comparative trial, conducted by Hatkins at Guy’s Hospital in London in 1972, showed lower survival rates and more local recurrences in conservative surgery followed by

radiotherapy, compared to radical mastectomy and axillary lymph node dissection (ALND). Later, it was discovered that these results were mainly due to under-dosage of the radiotherapy used in Hatkins' trial.

At the Istituto dei Tumori in Milan, between 1973 and 1989, Veronesi conducted the Milano I, Milano II, and Milano III studies, demonstrating that in the initial phase of the tumor, conservative surgery combined with radiotherapy provided the same overall survival and disease-free survival results as demolitive surgery (31).

Other studies conducted by various groups (NSABP 1976-1982, EORTC 1980-1985, Hadley 2003, Scottish Trial, Manchester Trial, West Ireland Trial, Uppsala Orebro) confirmed that radiotherapy reduces the percentage of local recurrences, although it does not affect long-term survival. Conservative surgery was now becoming the standard in breast cancer treatment, provided the tumor and breast sizes allowed it (32).

These findings urged the question of whether systematic removal of axillary lymph nodes, often found to be negative on histologic examination (about 80%), was always necessary. It was recognized that the main cause of morbidity in patients with early-stage disease (T1-2 N0 M0) paradoxically came from ALND complications (such as lymphedema, axillary vein thrombosis, nerve and lymphatic injuries) rather than the consequences of primary tumor treatment.

Regarding regional disease control related to ALND, the B-04 study conducted by Fisher et al. (28) effectively excluded any survival advantage associated with ALND principle, even with a prolonged follow-up of up to 25 years. A similar conclusion was found in Greco et al.'s clinical experience (33). Only in a meta-analysis conducted by Orr (34), evaluating the results of four studies (B-04, Guy's Hospital, Southeast Scotland, Institute Curie), was a modest survival advantage (4.7%; 95% CI = 1.9-7.5%,  $P < 0.01$ ) observed in patients undergoing ALND principle compared to those undergoing selective dissection.

However, knowing the lymph node stage remained crucial for choosing adjuvant therapy. Until then, there was no precise method to assess the lymph node stage without performing ALND. Clinical assessments were unreliable, with a false-negative rate

between 21% and 38%, directly related to tumor size, while imaging techniques provided limited accuracy.

### **Staging of axillary lymphnode: from ALND to sentinel lymph node biopsy**

The response to the challenge of assessing lymph node status, without resorting to invasive intervention, was provided by the research of Morton (35) in 1992, which demonstrated that the lymphatic drainage of the skin is not erratic but that the first draining lymph node of the examined area, the so-called "Sentinel Lymph Node" (SLN), previously identified by urologist Ramon Cabañas who was the first to describe the SLN concept for patients with penile cancer in 1977 (36).

Morton applied this method to melanoma, showing that if the sentinel lymph node is negative, then other regional lymph nodes are also clear. Giuliano (37) in 1994 applied the SLN method to breast carcinoma, demonstrating that false negatives are less than 2%. The SLN is identified by the injection of vital dyes (Patent-Blue Violet) with an accuracy ranging from 60% to 90%, or by using a radioisotope tracer (approximately 100% accuracy) (38). From the initial experiences in 1993-94, limited to a few dozen cases, there has been a progression to increasingly substantial case studies, involving several hundred patients, and the commencement of numerous clinical trials.

The trend toward elective localization of metastases in the SLN, compared to other lymph nodes of the axillary cavity (non-sentinel, non-SLN lymph nodes), was confirmed by the high frequency (40-50%) of metastases found exclusively in the SLN. The histopathological validation of the SLN theory as an elective site for metastasis among all other lymph nodes of the axillary cavity was subsequently provided by Turner in 1997 (39). Additionally, with the development of SLN biopsy, new methods for treating the SLN have been introduced to ensure that the presence of disease in this lymph node is not overlooked. This type of evaluation has led to an increasingly frequent identification of micrometastases ( $\leq 2$  mm in diameter) and isolated tumor cells (ITCs), the prognostic significance of which was later defined.

All studies conducted from 1994 onwards consistently demonstrated the accurate staging capability of the SLN in the axilla, indicating that ALND could be avoided in most cases. Notably, Veronesi and Giuliano published studies in 1999 and 2000 that underscored the SLN assessment's precision. Moreover, in 2001, Giuliano's study involving 101 women even revealed that patients with micrometastases in the SLN had minimal chances of further metastasis in other lymph nodes, suggesting the potential avoidance of completion lymph node dissection.

Various influential scientific societies, including the American Society of Breast Surgeons, Institute for Clinical Systemic Improvement, Canadian Steering Committee, Consensus Conference Committee Philadelphia, and German Society of Senology, contributed to consensus statements on this matter.

In 2001, the Philadelphia Consensus Conference, drawing on expert opinions and a thorough literature review by scientific societies, concluded that a negative SLN could replace routine ALND without the need for additional axillary treatment. Rarely has a procedure been adopted without substantive clinical trials validating its feasibility. Four years later, the American Society of Clinical Oncology (ASCO) released SLN recommendations, effectively affirming the 2001 Consensus Conference conclusions.

The ASCO recommendations were derived from the analysis of 69 clinical studies (highlighting the low number) conducted from 1994 to 2004, of which only a few were controlled trials.

However, SLN biopsy had become standard practice in almost all centers, spanning from the United States to Europe and Australia, rapidly becoming an integral part of conservative breast cancer treatment. The development and widespread acceptance of this technique have profoundly transformed the management and treatment of this disease. Throughout 5,000 years of history, never before have we witnessed such a rapid conceptual evolution as in the last 60 years.

Regarding micrometastatic lymph nodes, the available data strongly support conclusions for patients eligible for conservative surgery and complementary radiotherapy. Despite only a small percentage of patients (9%) undergoing mastectomy in the IBCGS 23-01 Trial, it is currently believed that

Completion ALND can be omitted even in mastectomy cases (40).

As for macrometastatic lymph nodes, controversies remain largely unresolved. Giuliano et al. (41) demonstrated in the American College of Surgeons Oncology Group (ACOSOG) Z0011 Trial that even in patients with macrometastases in 1-2 SLNs, SLN biopsy alone did not significantly worsen disease-free survival in the locoregional area (83.9% vs. 82.2%) or overall survival (92.5% vs. 91.8%) compared to Completion ALND. However, these conclusions apply only to patients undergoing breast-conserving surgery followed by complementary breast RT.

Despite these criticisms, American authors have fully embraced the conclusions of Giuliano's study.

Hence, in patients undergoing conservative surgery and planned adjuvant RT, Completion ALND is almost systematically omitted even in patients with 1-2 macrometastatic SLNs (NCCN, ASCO). The preliminary results of the multicentre randomized trial SINODAR ONE have shown that, in patients with T1-2 breast cancer and one or two sentinel lymph nodes macro metastases treated with breast conserving surgery or mastectomy, overall survival and disease-free survival rates were comparable in the two analysis arms. To confirm these results the study was reopened considering only patients who underwent mastectomy (42).

Protocols are currently being evaluated which, for early-stage tumors and in the absence of ultrasound-detectable lymphadenopathy, omit SLN biopsy altogether in selected subgroups of patients (Sound Trial) (43).

### **De-escalation surgery after primary systemic therapies**

Current therapies are tailored to each patient through the biological characterization of each tumor. Systemic treatments (chemotherapy, targeted therapies, hormonal therapy), increasingly effective and personalized, allow for a reduction in the aggressiveness of locoregional therapies (surgery and radiotherapy), outlining a perspective of de-escalation of aggressive surgery.



A good response to primary systemic therapies allows the implementation of conservative surgery in patients who would otherwise face the physical and psychological consequences of mastectomy. Beyond mitigating the surgical aggressiveness of the mammary gland, an effective response to therapies can also lead to the omission of ALND, reducing the risk of upper -limb complications, such as lymphedema and paresthesias, while allowing SLN biopsy also in patients that showed extensive involvement of axillary lymph nodes before neoadjuvant therapy.

Neoadjuvant systemic therapies can now be considered the first real weapon in the hands of the surgeon in an attempt to limit surgical aggression.

Currently, several ongoing trials might lead to the conclusion, in selected cases, of even omitting the surgical treatment itself.

## Conclusion

The study of breast cancer and its treatment dates back to an extremely remote past, but only in last decades has it undergone exponential development.

The gradual but growing knowledge of the characteristics of tumors, the development of a multidisciplinary approach, together with significant cultural and social changes concerning the conception of health and well-being have, in fact, enabled a major evolution in both the diagnostic and therapeutic approach to this pathology (44, 45).

The shift from extremely aggressive and mutilating practices, which imposed radical excisions, to 'gentle' surgery and targeted and personalised treatment strategies both local (radiotherapy and systemic) have increased survival and significantly affected patients' quality of life (46).

This approach aligns with the current philosophy that promotes the principle of 'minimum effective treatment' (according to the ethical principle of non-maleficence) versus 'maximum tolerable treatment'. It also reflects the ethical commitment to provide optimal, personalized care while respecting patients' values and well-being (according to the ethical principle of beneficence).

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