CURRENT METHODOLOGICAL APPROACHES IN RESEARCH IN THE FIELD OF GENERAL SURGERY

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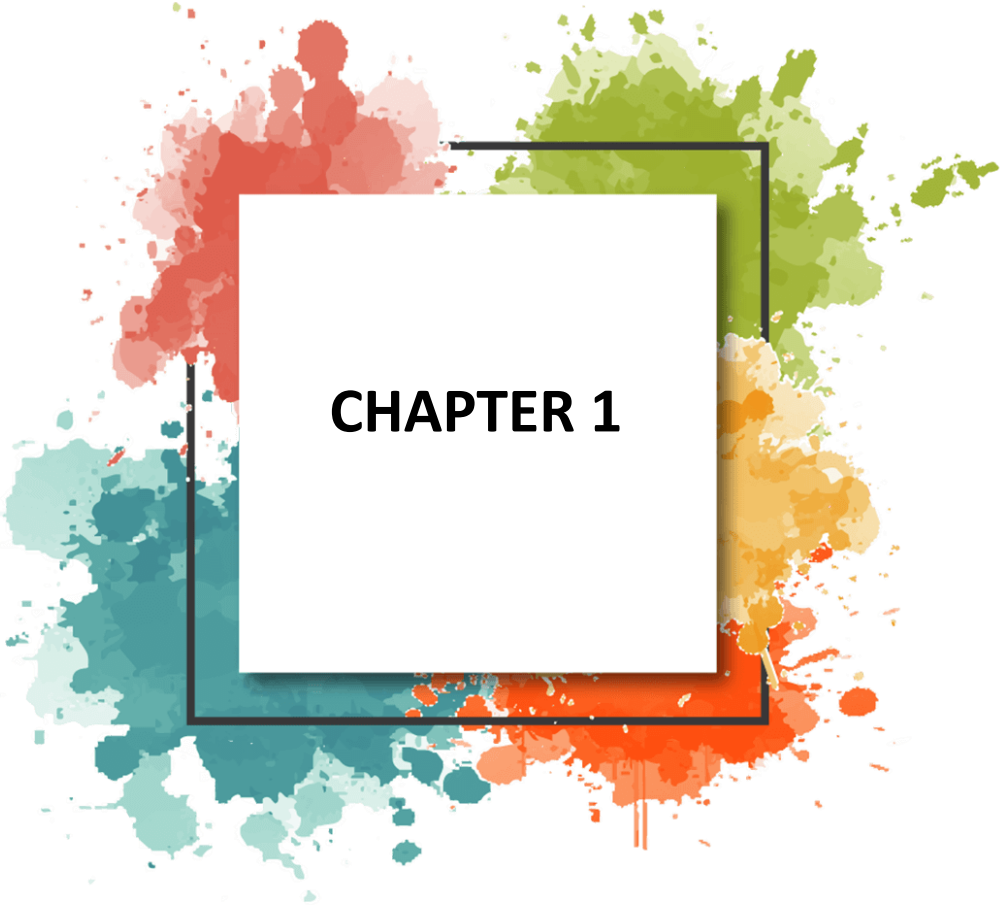
CHAPTER 1

Achalasia

Hikmet Özesmer[1] & Eda Yıldızhan[2]& Burak Veli Ülger[3]

Introduction

Achalasia is a chronic primary esophageal motility disorder characterized by impaired relaxation of the lower esophageal sphincter (LES) and loss of coordinated peristalsis in the esophageal body (1,2). In clinical practice, patients typically present with progressive dysphagia to both solids and liquids, regurgitation of undigested food, chest discomfort, and weight loss (3,4). Although no curative therapy currently exists, modern diagnostic tools and therapeutic interventions allow effective symptom control and substantial improvement in quality of life (1,5).

Pathophysiology

The pathogenesis of achalasia involves degeneration of inhibitory neurons within the myenteric (Auerbach) plexus, leading to defective nitric oxide–mediated LES relaxation and disordered esophageal body motility (2,6). As a result, basal LES pressure remains elevated and coordinated bolus transport is lost. Over time, chronic esophageal stasis may cause progressive dilatation, tortuosity, aspiration-related pulmonary complications, and an increased risk of esophageal squamous cell carcinoma (2,3).

Diagnostic Evaluation

High-Resolution Esophageal Manometry (HRM)

High-resolution manometry is the cornerstone and gold standard for the diagnosis of achalasia (1,7,8). It demonstrates incomplete LES relaxation and absent or abnormal peristalsis. Based on HRM findings, achalasia is classified according to the Chicago Classification (version 4.0) into three clinically meaningful subtypes (7,8):

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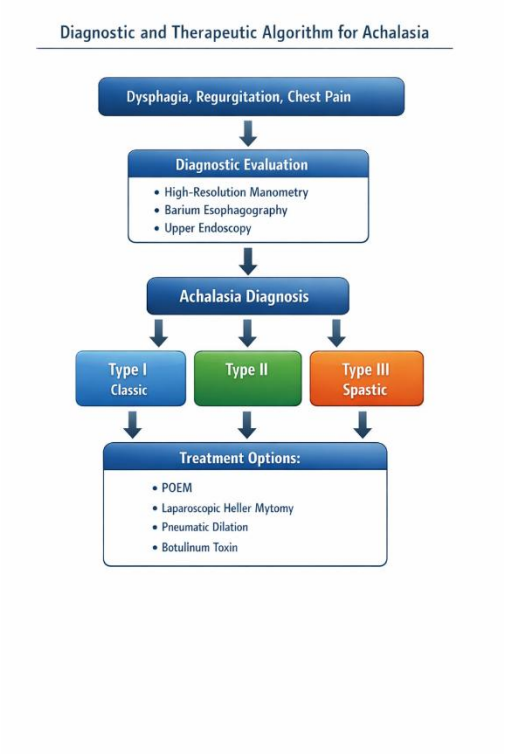
Type I (classic achalasia): Absent peristalsis with minimal pressurization

Type II: Failed peristalsis with panesophageal pressurization

Type III (spastic achalasia): Premature or spastic distal esophageal contractions

This subclassification has major prognostic and therapeutic implications and is now central to modern treatment algorithms (1,7,9).



Barium Esophagography

Timed barium esophagography remains a valuable adjunctive test, providing functional and anatomical information. Typical findings include esophageal dilatation, delayed contrast emptying, and smooth tapering at the gastroesophageal junction, classically described as a “bird-beak” appearance (2,3). It is particularly useful for assessing disease severity and post-treatment response (4).

Upper Gastrointestinal Endoscopy Upper endoscopy is mandatory in all patients to exclude mechanical obstruction, strictures, and malignancy presenting as pseudoachalasia (10,9). Endoscopic features may include retained food, dilated

esophageal lumen, mucosal inflammation, and increased resistance at the LES (10).

Principles of Treatment

The primary objective of achalasia management is not restoration of normal peristalsis, which is currently not feasible, but durable reduction of LES outflow resistance. This approach improves esophageal emptying, relieves symptoms, and supports adequate nutrition (1,3,9). Treatment selection should be individualized based on achalasia subtype, patient characteristics, and local expertise (1,5).

Therapeutic Modalities

1. Pharmacological Therapy

Smooth muscle relaxants such as nitrates and calcium channel blockers can transiently lower LES pressure, but their clinical efficacy is limited and side effects are common (1,6). Consequently, pharmacological therapy is generally reserved for patients who are not candidates for endoscopic or surgical interventions (3).

2. Endoscopic Therapies

Botulinum Toxin Injection

Endoscopic injection of botulinum toxin into the LES inhibits acetylcholine release, resulting in temporary sphincter relaxation. Although short-term symptom relief is common, the effect typically wanes within months, and repeated injections may compromise later definitive therapy (10,6). It is therefore mainly reserved for elderly or high-risk patients (9,10).

Pneumatic Dilation

Pneumatic dilation achieves mechanical disruption of LES muscle fibers using a high-pressure balloon. Randomized trials and long-term studies have demonstrated its effectiveness, particularly in Type I and Type II achalasia (11,12). However, repeated dilations are often required, and esophageal perforation remains the most serious complication (11,3).

Peroral Endoscopic Myotomy (POEM)

First described by Inoue in 2010, POEM has fundamentally reshaped achalasia therapy (13). By creating a submucosal tunnel, POEM allows tailored myotomy extending proximally as needed. This flexibility accounts for its excellent outcomes across all achalasia subtypes and its particular advantage in Type III disease (14,5,15). Randomized trials and meta-analyses confirm clinical

success rates exceeding 90%, though post-procedural gastroesophageal reflux is common and must be actively monitored (5,12,15).

3. Surgical Therapy

Laparoscopic Heller Myotomy (LHM)

LHM, usually combined with partial fundoplication, remains a cornerstone of achalasia management. Long-term follow-up studies confirm its durable efficacy and acceptable safety profile (11,15). It is particularly suitable for patients in whom reflux control is a priority or where advanced endoscopic expertise is unavailable (1,9).

Subtype-Oriented Treatment Strategy

Current evidence strongly supports a subtype-based approach (1,7,9):

Type I and II achalasia: Pneumatic dilation, POEM, and LHM are all effective options (1,5,11,12).

Type II achalasia: Demonstrates the most favorable and consistent response across all modalities (1,3,12). (Figure 1)

Type III achalasia: POEM is generally preferred due to its ability to provide extended myotomy of spastic segments that are difficult to treat with dilation or standard surgery (5,13,14).

Complications and Follow-Up

Gastroesophageal reflux disease is a frequent consequence of effective LES disruption, particularly following POEM and surgical myotomy (5,15). Long-term follow-up should include symptom assessment, nutritional evaluation, and endoscopic surveillance for reflux esophagitis, stricture formation, and late complications including malignancy (2,4,9).

Conclusion

Achalasia is a lifelong esophageal motility disorder requiring a physiology-based, individualized management strategy. High-resolution manometry is essential for diagnosis and subtype classification (7,8). Contemporary interventions—including POEM, laparoscopic Heller myotomy, and pneumatic dilation—offer effective and durable symptom relief (1,11,15). Among these, POEM has expanded therapeutic possibilities, particularly for spastic achalasia, underscoring the importance of subtype-directed therapy and multidisciplinary expertise (5,13,9).

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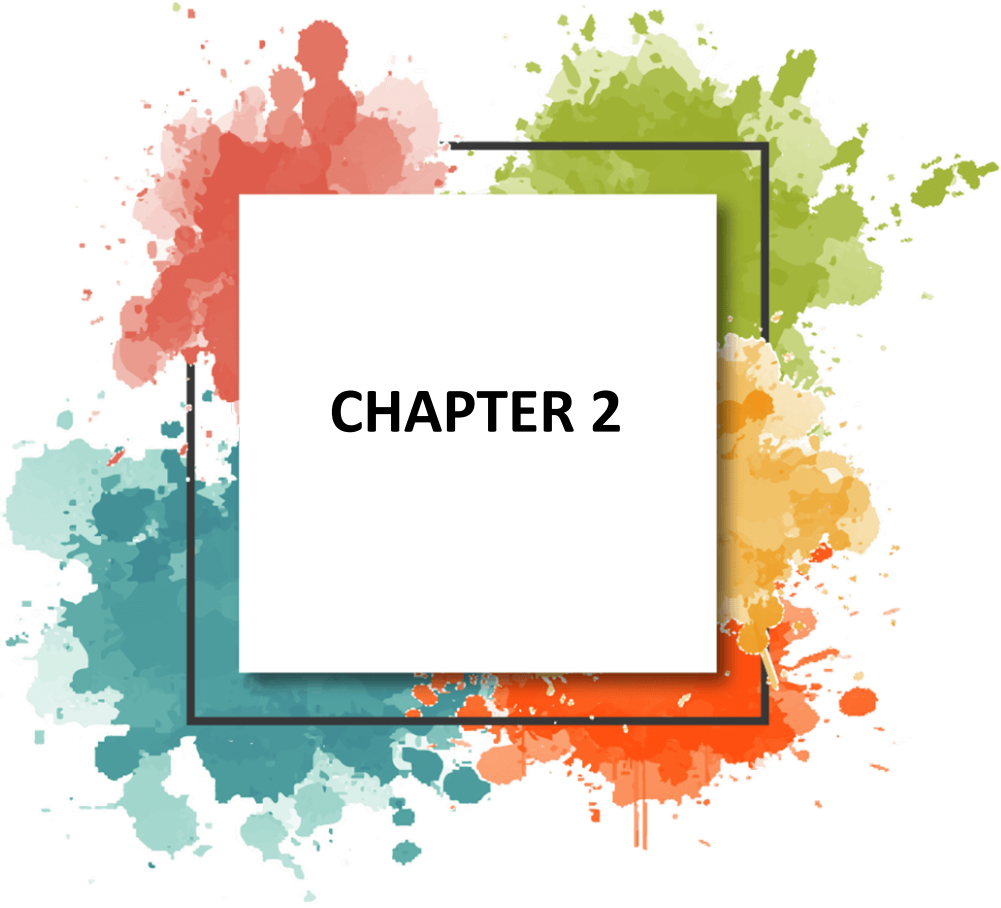
CHAPTER 2

Complications of Acute Appendicitis: Pathophysiology, Clinical Manifestations, and Management

Mehmet Şükrü Kara[1]

1. Introduction

Acute appendicitis is an inflammatory condition of the vermiform appendix and remains one of the leading causes of acute abdomen requiring surgical intervention. The lifetime risk of developing appendicitis is approximately 7–8%, with a peak incidence in the second and third decades of life. Although appendectomy is considered a definitive and relatively safe procedure, complications still occur, particularly in cases of delayed diagnosis or atypical presentation.

The pathogenesis of acute appendicitis is primarily related to obstruction of the appendiceal lumen. Common causes include fecaliths, lymphoid hyperplasia, parasitic infections, foreign bodies, and rarely neoplasms. Luminal obstruction leads to increased intraluminal pressure, impaired venous drainage, ischemia of the appendiceal wall, and subsequent bacterial proliferation. If untreated, this process progresses to necrosis, perforation, and dissemination of infection [1].

While early diagnosis and prompt surgical management significantly reduce complication rates, delays beyond 24–48 hours markedly increase the likelihood of disease progression. Reported complication rates range between 15% and 35%, particularly in elderly patients, children, pregnant women, and immunocompromised individuals [2,4]. These complications prolong hospital stay, increase healthcare costs, and worsen overall prognosis.

2. Pathophysiology and Ischemic Progression

The pathological evolution of acute appendicitis follows a predictable sequence from inflammation to ischemia, necrosis, and perforation.

2.1 Gangrenous Appendicitis

Gangrenous appendicitis represents an advanced stage characterized by transmural ischemia and necrosis of the appendiceal wall. As intraluminal pressure exceeds capillary perfusion pressure, arterial inflow becomes

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compromised. This ischemic injury disrupts mucosal integrity, facilitating bacterial translocation and endotoxin release.

Histopathologically, gangrenous appendicitis is marked by extensive neutrophilic infiltration, hemorrhage, thrombosis of mural vessels, and full-thickness necrosis. Clinically, patients may present with severe abdominal pain, systemic inflammatory response, and signs of sepsis [2]. Without timely intervention, gangrenous appendicitis almost invariably progresses to perforation.

2.2 Appendiceal Perforation

Appendiceal perforation is the most common complication of acute appendicitis and typically occurs within 36–72 hours of symptom onset. Perforation results in spillage of enteric contents into the peritoneal cavity, triggering localized or generalized infection.

Elderly patients often exhibit atypical symptoms such as mild pain or absence of fever, leading to delayed diagnosis. Consequently, perforation rates in patients over 65 years may exceed 50% [4]. Perforated appendicitis is associated with higher rates of postoperative infection, intra-abdominal abscess formation, and mortality.

3. Localized Complications: Phlegmon and Abscess Formation

In some cases, the inflammatory process is partially contained by host defense mechanisms.

3.1 Appendiceal Phlegmon (Plastron)

An appendiceal phlegmon is a localized inflammatory mass consisting of the inflamed appendix, omentum, and adjacent bowel loops. This represents an attempt by the body to limit the spread of infection.

Clinically, patients present with a palpable right lower quadrant mass, prolonged fever, and elevated inflammatory markers. Immediate surgical intervention in this setting carries an increased risk of bowel injury, fistula formation, and bleeding [1].

Current evidence supports initial non-operative management with intravenous broad-spectrum antibiotics, bowel rest, and close clinical monitoring. Interval appendectomy, typically performed 6–8 weeks later, remains controversial but may be considered in selected patients [3].

3.2 Periappendiceal Abscess

A periappendiceal abscess develops when purulent material accumulates within the localized inflammatory mass.

Diagnosis: Contrast-enhanced computed tomography (CT) is the diagnostic modality of choice, allowing precise localization, size assessment, and evaluation of surrounding structures [3].

Management: Abscesses larger than 3 cm generally require image-guided percutaneous drainage in addition to intravenous antibiotics. This approach reduces systemic infection, avoids emergency surgery, and improves outcomes, especially in high-risk patients [2].

4. Generalized Peritonitis

Generalized peritonitis occurs when infection spreads freely throughout the peritoneal cavity, usually following free perforation. Patients present with diffuse abdominal pain, rebound tenderness, guarding, fever, tachycardia, and signs of systemic sepsis. Physical examination often reveals a rigid, “board-like” abdomen.

This condition represents a surgical emergency. Delayed intervention may result in septic shock, disseminated intravascular coagulation, and multi-organ failure [1,5].

Treatment includes urgent surgical exploration, appendectomy, extensive peritoneal lavage, and broad-spectrum intravenous antibiotics tailored to cover aerobic and anaerobic organisms.

5. Pylephlebitis: A Rare but Fatal Complication

Pylephlebitis is septic thrombophlebitis of the portal venous system, most commonly involving the superior mesenteric vein. It arises from the hematogenous spread of infection via the appendiceal veins.

Although rare in the modern antibiotic era, pylephlebitis remains associated with mortality rates approaching 30% [4]. Clinical manifestations include high-grade fever, abdominal pain, jaundice, hepatomegaly, and abnormal liver function tests.

Diagnosis: relies on contrast-enhanced CT or Doppler ultrasonography. **Management:** consists of prolonged intravenous antibiotics and, in selected cases, anticoagulation therapy [2].

6. Postoperative Complications

Postoperative complications remain a significant source of morbidity following appendectomy, particularly in cases of complicated acute appendicitis.

The incidence and severity of these complications are closely related to the stage of disease at presentation, presence of perforation, degree of peritoneal contamination, and patient-related factors such as age, comorbidities, and immune status. Despite advances in laparoscopic techniques and perioperative care, postoperative adverse events continue to challenge surgeons worldwide.

6.1 Intra-abdominal Abscess Formation

Intra-abdominal abscess is one of the most frequent postoperative complications, especially following perforated or gangrenous appendicitis. Abscess formation typically occurs between postoperative days 5 and 10 and is associated with persistent fever, abdominal pain, leukocytosis, and elevated inflammatory markers.

The pathogenesis involves residual bacterial contamination, inadequate peritoneal lavage, or failure of localized inflammatory control. Laparoscopic appendectomy, although associated with lower wound infection rates, has been reported to carry a slightly higher risk of postoperative intra-abdominal abscess in perforated cases due to pneumoperitoneum-related bacterial dissemination [3].

Diagnosis is best achieved with contrast-enhanced CT, which allows precise localization and differentiation from postoperative ileus or hematoma. Management includes intravenous broad-spectrum antibiotics and, when feasible, image-guided percutaneous drainage. Surgical re-exploration is reserved for refractory or multiloculated abscesses.

6.2 Surgical Site Infection (SSI)

Surgical site infection remains a common postoperative complication, particularly after open appendectomy and in patients with perforated appendicitis. SSIs are classified into superficial, deep incisional, and organ-space infections.

Risk factors include delayed surgery, gross peritoneal contamination, diabetes mellitus, obesity, and inadequate perioperative antibiotic prophylaxis. Laparoscopic appendectomy has been shown to significantly reduce the incidence of superficial and deep SSIs compared to open techniques [4].

Preventive strategies include appropriate antibiotic timing, meticulous surgical technique, minimization of tissue trauma, and adequate wound care. Most superficial infections respond well to local wound management and antibiotics, while deep infections may require surgical drainage.

6.3 Postoperative Ileus

Postoperative ileus is a transient impairment of gastrointestinal motility that may complicate appendectomy, particularly in cases of generalized peritonitis.

Clinically, patients present with abdominal distension, nausea, vomiting, delayed passage of flatus, and intolerance to oral intake.

The condition is multifactorial, involving inflammatory mediators, electrolyte imbalance, opioid analgesia, and extensive bowel manipulation during surgery. Although usually self-limiting, prolonged ileus may increase hospital stay and healthcare costs.

Management is primarily conservative and includes bowel rest, correction of metabolic abnormalities, minimization of opioid use, and early mobilization.

6.4 Adhesive Small Bowel Obstruction

Adhesive small bowel obstruction (ASBO) represents a long-term complication that may occur months or even years after appendectomy. The risk is significantly higher following complicated appendicitis due to extensive peritoneal inflammation and adhesion formation.

Patients typically present with colicky abdominal pain, vomiting, abdominal distension, and absence of bowel movements. While many cases resolve with conservative management, recurrent or complete obstruction may necessitate surgical intervention [5].

Preventive measures include gentle tissue handling, minimizing peritoneal trauma, and the use of minimally invasive surgical techniques.

6.5 Enterocutaneous Fistula and Cecal Injury

Although rare, enterocutaneous fistula formation and unrecognized cecal injury represent severe postoperative complications, most often associated with difficult dissections in the presence of dense inflammatory adhesions or phlegmon.

These complications result in prolonged hospitalization, nutritional deficiencies, and significant morbidity. Early recognition and multidisciplinary management involving surgical, nutritional, and infectious disease teams are essential for optimal outcomes.

6.6 Systemic Complications and Sepsis

Patients with perforated appendicitis remain at risk for postoperative sepsis, septic shock, and multi-organ dysfunction syndrome. Persistent tachycardia, hypotension, altered mental status, and rising inflammatory markers should prompt immediate evaluation for ongoing infection or source control failure.

Early goal-directed therapy, aggressive fluid resuscitation, appropriate antimicrobial coverage, and timely re-intervention are critical in reducing mortality.

6.7 Impact on Length of Hospital Stay and Quality of Life

Postoperative complications significantly prolong hospital stay and negatively affect patient quality of life. Recurrent infections, readmissions, and long-term bowel dysfunction contribute to increased healthcare utilization and economic burden.

Therefore, early diagnosis of complicated appendicitis, appropriate surgical timing, and meticulous postoperative monitoring are crucial for minimizing adverse outcomes

7. Conclusion

Complicated acute appendicitis continues to represent a significant clinical challenge despite substantial advances in diagnostic imaging, antimicrobial therapy, and surgical techniques. While uncomplicated appendicitis is generally associated with excellent outcomes, delayed diagnosis and disease progression markedly increase morbidity, mortality, and healthcare burden. The transition from simple inflammation to gangrene, perforation, and systemic infection underscores the dynamic and time-dependent nature of appendiceal disease.

This review highlights that the development of complications is closely linked to pathophysiological mechanisms such as luminal obstruction, ischemia, bacterial translocation, and host inflammatory response. These processes not only determine the severity of local tissue damage but also influence systemic involvement and postoperative outcomes. Early recognition of disease severity, therefore, remains the cornerstone of effective management.

Advances in cross-sectional imaging—particularly contrast-enhanced computed tomography—have significantly improved diagnostic accuracy and enabled more precise stratification between uncomplicated and complicated appendicitis. This distinction is critical in guiding therapeutic decisions, including the selection of non-operative management, timing of surgery, and extent of postoperative surveillance. Evidence-based guidelines increasingly support individualized treatment strategies rather than a uniform surgical approach for all patients.

The management of complicated appendicitis requires a multidisciplinary and patient-centered approach. Optimal outcomes depend on timely surgical source control, appropriate antimicrobial therapy, and meticulous postoperative care. In selected cases, non-operative strategies such as antibiotic therapy and image-guided percutaneous drainage play an essential role in reducing surgical morbidity, particularly in high-risk patient populations.

Postoperative complications remain a major determinant of prognosis and quality of life. Intra-abdominal abscess formation, surgical site infections,

adhesive bowel obstruction, and systemic sepsis contribute to prolonged hospitalization, readmissions, and long-term functional impairment. Preventive strategies, including minimally invasive surgical techniques, careful tissue handling, and enhanced recovery protocols, are crucial in minimizing these adverse events.

Looking forward, future research should focus on improving early risk stratification, identifying reliable biomarkers of disease progression, and refining non-operative treatment protocols. Standardization of clinical pathways and broader implementation of guideline-based care may further reduce variability in outcomes. Ultimately, a comprehensive understanding of the clinical and pathological spectrum of complicated acute appendicitis is essential for improving patient outcomes and optimizing emergency surgical practice.

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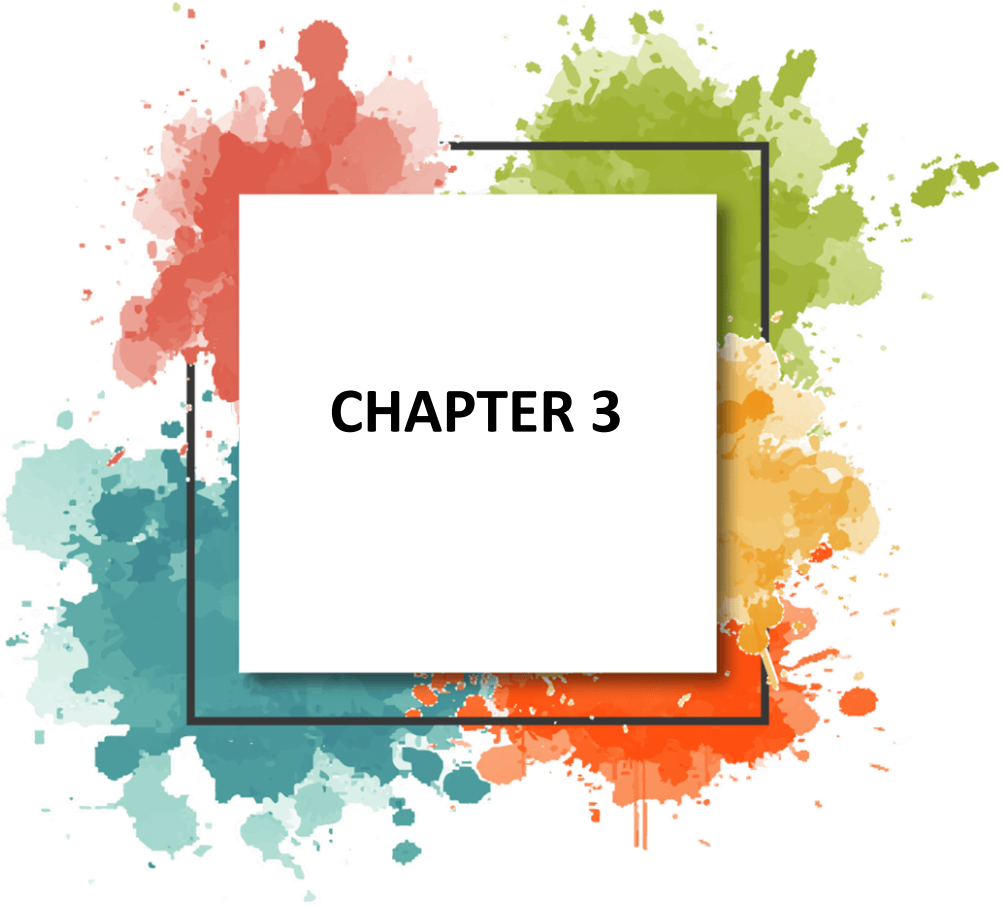
CHAPTER 3

Paradigm Shifts in Breast Cancer Surgery: An Evidence-Based Journey from Radical Surgery to De-escalation

Ferdi Bolat[1]

1. Introduction: Historical Perspective and Paradigm Shifts

The history of breast cancer surgery represents one of the most striking examples of paradigm shifts in medical thinking. Viewed through Thomas Kuhn's model of scientific revolutions, this field has undergone at least three major paradigm ruptures over the past 130 years:

- The emergence of radical surgery
- The acceptance of the biological model
- The era of de-escalation

Each rupture represents not merely a change in surgical technique, but a fundamental transformation in the underlying assumptions about the nature of the disease.

1.1. The Halsted Paradigm: "More is Better"

William Stewart Halsted systematically established the foundations of breast cancer surgery in 1882 by describing the radical mastectomy (RM) (1). Halsted's mechanistic model of tumor spread postulated that cancer disseminates sequentially from the primary focus to regional lymph nodes, and that the disease could therefore be cured at its root through sufficiently wide en bloc resection. This assumption justified a procedure in which the entire breast tissue, the pectoralis major and minor muscles, and the axillary lymph nodes were removed together.

The Halsted paradigm went unquestioned for nearly a century, as it was consistent with the clinical observations of the era and reduced local recurrence rates. However, this approach harbored a critical methodological weakness: the relationship between surgical extent and survival was evaluated not through comparative, controlled studies but through single-arm case series. Consequently,

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the relationship between the breadth of surgery and survival remained, for a long time, not a proven fact but merely an assumption.

1.2. The Biological Model: Fisher's Conceptual Revolution

In the 1960s and 1970s, Bernard Fisher proposed that breast cancer is a systemic disease from its inception, and that the extent of local treatment does not determine the development of distant metastasis. This hypothesis stood in direct opposition to Halsted's model of sequential spread. According to Fisher, micrometastatic disease may already be present at the time of diagnosis; under these circumstances, it would be the addition of systemic therapy - not the widening of surgical resection - that would determine prognosis.

The first major test of this hypothesis was the NSABP B-04 (National Surgical Adjuvant Breast and Bowel Project Protocol B-04) trial. A total of 1,079 patients randomized between 1971 and 1974 were assigned to radical mastectomy, total mastectomy, or total mastectomy + RT (radiotherapy). The 25-year follow-up results revealed no statistically significant difference among the three arms in overall survival (OS) or disease-free survival (DFS) (2). The significance of NSABP B-04 lies not only in its clinical results but in its methodological courage and conceptual transformation: for the first time, it was demonstrated that surgical practice should be grounded not in dogmatic acceptance but in randomized controlled evidence.

1.3. The Birth of Breast-Conserving Surgery: NSABP B-06 and Milan I

The next logical step following the biological model was to question whether removal of the entire breast was necessary. The NSABP B-06 trial (1976–1984) randomized 1,851 patients with stage I–II invasive breast cancer to total mastectomy, lumpectomy, or lumpectomy + RT. Twenty-year follow-up results demonstrated that lumpectomy + RT was non-inferior to mastectomy in overall survival; only the lumpectomy-alone arm showed significantly higher local recurrence rates (3). This finding established that breast-conserving surgery, when combined with RT, is a safe alternative to mastectomy.

Concurrently, the Milan I trial (1973–1980), conducted under the leadership of Umberto Veronesi, compared radical mastectomy with quadrantectomy + RT in 701 patients. Twenty-year follow-up data confirmed no survival difference between the two arms (4). The same conclusion reached on two different continents, by different surgical teams, using different techniques (lumpectomy vs. quadrantectomy), reinforced the external validity of the findings and established breast-conserving surgery as a global standard of care.

1.4. From "Maximum Tolerable" to "Minimum Effective"

The message shared by these three landmark trials - B-04, B-06, and Milan I - constitutes the conceptual foundation of today's de-escalation philosophy: the extent of surgery is not the primary determinant of survival; tumor biology and response to systemic therapy shape prognosis far more powerfully. Morrow (2022) summarized this transformation as "the shift from maximum tolerable treatment to minimum effective treatment" (5). Loibl, Poortmans, Morrow, Denkert, and Curigliano (2021) emphasized in their contemporary Lancet review that pathologic complete response (pCR) rates to neoadjuvant systemic therapy - particularly in HER2 (human epidermal growth factor receptor 2)-positive and triple-negative breast cancer (TNBC) - now exceed 50–60%, raising the possibility of further narrowing the surgical scope, or even omitting surgery altogether in selected patients (6).

However, a careful epistemological distinction must be made here. The concept of de-escalation does not, despite its everyday connotations, simply mean reducing or lightening treatment. In oncologic surgery de-escalation refers to the elimination of unnecessary surgical morbidity without compromising oncologic safety, by individualizing the intensity of treatment according to tumor biological behavior, patient risk profile, and evidence-based data. In other words, de-escalation means not "less treatment" but "smarter treatment." It aims to reduce the physical and psychological burden of overtreatment - lymphedema, chronic pain, restricted range of motion, body image disturbance - while not accepting the oncologic risks of undertreatment. Achieving this balance depends on accurate characterization of tumor biology, reliability of imaging and pathologic assessment, and multidisciplinary decision-making. This principle forms the shared conceptual foundation of all the developments discussed in subsequent sections of this chapter: the evolution of primary breast surgery, shifts in axillary management, surgical planning following neoadjuvant therapy, and research into non-surgical approaches.

2. Evolution of Primary Breast Surgery

The conceptual transformation discussed in the preceding section laid the groundwork for a series of concrete clinical changes in primary breast surgery. This section addresses the transition from radical mastectomy to modified radical mastectomy, the standardization of breast-conserving surgery and the evolution of the surgical margin concept, the rise of oncoplastic approaches, and modern mastectomy options - skin-sparing mastectomy (SSM), nipple-sparing mastectomy (NSM), and robotic applications - together with their evidence base.

2.1. From Radical Mastectomy to Modified Radical Mastectomy

The serious functional impairment caused by Halsted's radical mastectomy - upper extremity weakness due to pectoral muscle resection, chest wall deformity, and significant cosmetic disfigurement - was long accepted in clinical practice as "the price to be paid for cure." The first to challenge this dogma was David Patey. Patey and Dyson (1948) described the modified radical mastectomy (MRM), which preserved the pectoralis major muscle while removing the minor, demonstrating that axillary lymph node dissection (ALND) could be performed adequately without muscle resection (7). John Madden subsequently proposed a further modification preserving the pectoralis minor as well. Both approaches significantly improved functional outcomes while maintaining oncologic safety.

However, the evidence base supporting this transition rested on retrospective comparisons and case series; large-scale randomized controlled trials directly comparing MRM with radical mastectomy were limited. The true paradigm shift was delivered by the NSABP B-04 trial discussed in the preceding section (2). By demonstrating no survival difference between radical mastectomy and total mastectomy, NSABP B-04 definitively established that pectoral muscle resection was rooted not in oncologic necessity but in historical habit. By the late 1980s, MRM had become the standard surgical approach for invasive breast cancer, and radical mastectomy took its place in history.

2.2. Breast-Conserving Surgery: Standardization and the Evolution of the Surgical Margin Concept

Following the demonstration by NSABP B-06 (3) and Milan I (4) that breast-conserving surgery (BCS) was a safe option, a new problem emerged in clinical practice: what constitutes a negative surgical margin, and how wide should it be? This question, despite its apparent simplicity, became one of the most contentious issues in breast surgery and led to significant inter-institutional variation in practice for decades.

The root of the problem lies in the multifocal nature of breast cancer. Holland et al. (1985) demonstrated that residual foci located more than 2 cm from the primary tumor could be identified in up to 40% of mastectomy specimens (8). This finding fueled the pursuit of wider margins by reinforcing the notion that "the more we remove, the safer we are." However, this approach gave rise to clinical problems including increased re-excision rates, compromised cosmetic outcomes, and unnecessary conversion to mastectomy. Morrow et al. (2017) reported, in a population-based US sample, that 38% of patients undergoing initial lumpectomy were subjected to additional surgery 26% re-excision and

12% conversion to mastectomy (9). These data exposed the tangible clinical burden of the lack of standardization in surgical margin management.

In response to this problem, the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) published an evidence-based consensus guideline for invasive breast cancer in 2014. Based on a meta-analysis encompassing 33 studies, the guideline led by Moran, Schnitt, Giuliano et al. (2014) defined "no ink on tumor" - the absence of tumor cells at the inked surgical margin - as a sufficient negative margin (10). The guideline emphasized that wider margins did not meaningfully reduce local recurrence, and that tumor biology and systemic therapy were far more determinative of local control than the width of the surgical margin. This consensus brought about a marked standardization in clinical practice.

For ductal carcinoma in situ (DCIS), the margin definition was more complex. The tendency of DCIS to spread segmentally along the ductal system required a different margin approach than invasive cancer. Morrow, Van Zee et al. (2016), in the joint SSO–ASTRO–ASCO guideline, determined that a 2 mm negative margin was adequate for DCIS cases planned for whole-breast radiotherapy (11). While this guideline was also based on a comprehensive meta-analysis, it emphasized that clinical decisions for margins below the 2 mm threshold should be individualized according to the radiotherapy plan and patient risk profile. The shared message of both consensus documents is clear: surgical margin management should be evaluated within the context of tumor biology and multimodal therapy, rather than a preoccupation with millimetric width.

2.3. Oncoplastic Surgery

The widespread adoption of BCS revealed a new clinical tension: the balance between oncologic adequacy and cosmetic outcome. In cases with a large tumor-to-breast ratio in particular, wide resection could lead to breast deformity and patient dissatisfaction. In response to this problem, oncoplastic breast surgery - developing from the 1990s onward - combines oncologic resection principles with plastic surgical techniques, aiming to achieve both negative surgical margins and acceptable cosmetic outcomes.

Clough, Kaufman et al. (2010) developed a classification system dividing oncoplastic techniques into two levels according to the extent of volume loss (12):

- Level I techniques encompass simple glandular rearrangement and cavity closure methods for volume loss of up to 20% of breast volume.

- Level II techniques include mammoplasty patterns, local dermoglandular flaps, and volume displacement methods for volume loss of 20–50%.

This classification has been widely adopted in clinical practice as a guide for selecting the most appropriate technique based on the volume of resection.

Silverstein, Savalia et al. (2015) introduced the concept of "extreme oncoplasty," demonstrating that breast conservation may be achievable through advanced oncoplastic techniques even in cases with large tumors or multifocal disease that would classically be considered mastectomy indications (13). This approach has substantially expanded the indication boundaries of BCS.

However, an important methodological limitation regarding the evidence base of oncoplastic surgery must be emphasized. The majority of data in this field derives from retrospective case series and cohort studies; no randomized controlled trial directly comparing oncoplastic techniques with standard BCS exists. While oncologic safety data are promising, the extent to which these outcomes are influenced by selection bias remains unclear. Furthermore, the lack of standardized criteria for cosmetic outcome assessment makes cross-study comparisons difficult. Oncoplastic surgery, therefore, despite its broad acceptance in clinical practice, has yet to attain a gold standard supported by randomized data in terms of evidence level.

2.4. Mastectomy Options: SSM, NSM and Robotic Applications

In cases where BCS is not appropriate - multicentric disease, extensive DCIS, risk-reducing surgery in BRCA mutation carriers, or patient preference - mastectomy may be unavoidable. However, the de-escalation principle manifests here as well: removal of the entire breast need not entail sacrifice of the breast skin envelope or the nipple-areola complex.

Skin-sparing mastectomy (SSM) is an approach that preserves the majority of the breast skin, enabling immediate reconstruction. Toth and Lappert (1991) laid the conceptual foundation for SSM by emphasizing that mastectomy incisions should be designed in integrated fashion with the reconstruction plan (14). Subsequently accumulated data have demonstrated that SSM, in appropriately selected patients - particularly those without skin involvement - does not increase local recurrence rates compared with conventional mastectomy.

Nipple-sparing mastectomy (NSM) goes one step beyond SSM by leaving the nipple-areola complex in place. The early series of Sacchini, Pinotti et al. (2006) provided the first systematic data on the oncologic safety of NSM (15). The feasibility of NSM depends on patient selection criteria including tumor distance

from the nipple, absence of nipple involvement, breast size and ptosis, smoking history, diabetes, prior RT, and skin flap quality. Careful evaluation of these criteria is of critical importance in minimizing complications such as flap necrosis and nipple loss.

In recent years, endoscopic and robotic NSM applications have attracted increasing interest. The robotic approach enables removal of breast tissue through an axillary or lateral incision, leaving no visible scar on the breast. Ryu, Paik et al. (2025) published a consensus statement on robotic mastectomy through an international modified Delphi process (16). This statement emphasizes that robotic NSM is feasible in appropriate centers and selected patients, but that long-term prospective data on oncologic safety and cost-effectiveness are needed. The current evidence base for robotic surgery relies predominantly on single-center case series, and no randomized controlled trial data comparing it with conventional NSM are yet available. This situation constitutes a methodological limitation analogous to that of oncoplastic surgery, reflecting a landscape in which clinical adoption has outpaced evidence generation.

2.5. Section Summary

The evolution of primary breast surgery has followed a consistent de-escalation trajectory: from radical mastectomy to MRM, from MRM to BCS, from BCS to oncoplastic approaches, and from there to SSM/NSM. At each stage, the surgical scope has narrowed while oncologic safety has been maintained or improved. The supporting evidence for this progression has been derived largely from randomized controlled trials; however, in emerging fields such as oncoplastic surgery and robotic applications, the evidence level has yet to reach the same maturity.

The impact of neoadjuvant therapy on surgery - to be addressed in the next section - carries this de-escalation trajectory a step further, with the potential to render mastectomy candidates suitable for BCS and even to call into question the necessity of surgery altogether in selected patients.

3. Neoadjuvant Therapy and its Impact on Surgery

Neoadjuvant systemic therapy (NST) was initially introduced to render inoperable tumors resectable in locally advanced breast cancer. Over the past two decades, however, this approach has become a strategic tool in early-stage breast cancer as well to narrow the surgical scope, assess treatment response in vivo, and individualize adjuvant therapy decisions.

This section addresses tumor downstaging and conversion from mastectomy to breast-conserving surgery through neoadjuvant therapy, tumor bed marking and localization methods, and current research into the complete omission of surgery following pathologic complete response.

3.1. Downstaging and Conversion from Mastectomy to BCS

The first large-scale randomized data evaluating the impact of neoadjuvant chemotherapy (NACT) on surgery were obtained from the NSABP B-18 and B-27 trials. Rastogi, Anderson et al. (2008), in the combined update of these two trials, demonstrated that clinical response rates reached 80% in patients receiving NACT, and that a significant proportion of patients initially planned for mastectomy became eligible for BCS (17). However, a critical finding also emerged from these trials: NACT did not improve survival compared with adjuvant chemotherapy; it only altered the timing and scope of surgery. This distinction is conceptually important neoadjuvant therapy should be positioned not as a survival strategy but as a tool for surgical de-escalation.

Today, the downstaging efficacy of NACT is strongly linked to the biological subtype of the tumor. In HER2-positive disease, the combination of dual anti-HER2 therapy (trastuzumab + pertuzumab) with chemotherapy has elevated pCR rates to 50–70%. In TNBC, the addition of immunotherapy (pembrolizumab) has pushed pCR rates beyond 60% (6). In contrast, response rates to NACT in the hormone receptor (HR)-positive/HER2-negative subtype are markedly lower, with pCR rates remaining around 10–20%. In this subtype, neoadjuvant endocrine therapy (NET) - particularly with aromatase inhibitors in postmenopausal patients - is considered an alternative for narrowing the surgical scope; however, the evidence base for the downstaging efficacy of NET is not as mature as that for NACT.

As emphasized in the comprehensive Lancet review by Loibl, Poortmans, Morrow et al. (2021), the decision for neoadjuvant therapy is now made not solely on the basis of tumor size, but through a multidisciplinary process that takes into account tumor biology, imaging response, patient preference, and planned surgical type (6). This approach represents an extension of the individualization principle into the preoperative period.

3.2. Tumor Bed Marking and Localization Methods

Tumor shrinkage or complete disappearance with neoadjuvant therapy creates a new technical challenge for the surgeon: reliable intraoperative identification of the pretreatment tumor bed. In cases showing clinical and radiologic complete

response, the absence of knowledge regarding the pretreatment tumor location may lead to inadequate resection or unnecessarily wide excision.

To address this problem, clipping of the tumor bed prior to treatment has become standard practice. Metallic clips placed under ultrasound or stereotactic guidance at the time of diagnosis or before initiation of NACT enable identification of the tumor bed on post-treatment imaging. Dubsky, Pinker et al. (2021) emphasized, in the "Lucerne Toolbox" approach systematizing surgical planning following neoadjuvant therapy, that clipping should be considered a mandatory step (18).

Intraoperative localization of the clipped tumor bed was traditionally performed using wire-guided methods. However, wire-guided localization carries well-known limitations: the necessity of wire placement on the morning of surgery, patient discomfort, risk of wire migration, and constraints on surgical workflow. In recent years, wireless localization systems have been developed to overcome these limitations. Hayes (2017), in a comparative review of available localization methods, reported that systems such as radar reflectors (SAVI SCOUT), magnetic seeds (Magseed), radioactive seeds (I-125 seed), and radiofrequency tags (LOCalizer) improve patient comfort, enhance surgical planning flexibility, and carry the potential to reduce re-excision rates compared with wire-guided methods (19). These systems, by virtue of being placeable days or weeks before surgery, eliminate dependence on radiology on the day of the operation.

However, cost-effectiveness analyses of wireless localization systems and randomized controlled trial data comparing different systems remain limited. The majority of available evidence consists of prospective cohort studies and retrospective comparisons. The question of which system is superior in which clinical scenario has not yet been definitively answered, and preference largely depends on institutional experience and accessibility.

3.3. Non-Surgical Approach Following Pathologic Complete Response

The most radical extension of the de-escalation philosophy is the question of whether surgery can be omitted entirely in patients who achieve a complete response to neoadjuvant therapy. This is not merely a technical matter but an existential interrogation of breast cancer surgery itself: if the tumor has been completely eradicated by systemic therapy, what is the therapeutic contribution of surgical resection?

The fundamental obstacle to answering this question is the difficulty of reliably confirming pCR without a surgical specimen. Imaging modalities - mammography, ultrasound, and magnetic resonance imaging (MRI) - have limited sensitivity in detecting residual disease, and false-negative rates may remain at clinically unacceptable levels.

To overcome this obstacle, Kuerer et al. from MD Anderson Cancer Center conducted a series of prospective studies investigating the accuracy of image-guided vacuum-assisted core biopsy (VACB) in confirming pCR prior to surgery. In the initial feasibility study (2018), it was demonstrated that VACB performed after NACT in patients with T1-3N0-3 TNBC or HER2-positive disease could achieve an accuracy rate approaching 98% when approximately 12 tissue samples were obtained (20). This biopsy protocol, unlike standard core biopsy, requires systematic and comprehensive sampling of the tumor bed, thereby minimizing the risk of false negativity due to inadequate sampling.

The 5-year results of the phase II prospective multicenter trial (NCT02945579) designed on the basis of these feasibility data were published in JAMA Oncology in 2025 by Kuerer, Valero, Smith et al. (21). In this study, patients with early-stage TNBC or HER2-positive breast cancer who demonstrated clinical complete response following NACT and in whom pCR was confirmed by VACB underwent RT alone, with surgery omitted. At a median follow-up of 55.4 months, the ipsilateral breast tumor recurrence rate was 0% and ipsilateral breast tumor control was 100%. These results provide a strong signal that surgery can be safely omitted in carefully selected patients.

In parallel, the results of the multicenter cooperative group trial NRG-BR005 were also published in 2025 by Basik et al. in JAMA Surgery (22). This phase II trial investigated whether core biopsy of the tumor bed following trimodal imaging (mammography, ultrasound, MRI) confirming clinical complete response after NACT could predict pCR with an accuracy of 90% or above. NRG-BR005 complements Kuerer's single-center data by evaluating the feasibility of the non-surgical approach in a broader population.

However, several critical limitations must be considered when interpreting the evidence in this field. First, the available trials are phase II in design and non-randomized; phase III randomized controlled trial data directly comparing the non-surgical approach with surgery are not yet available. Second, study populations are predominantly limited to TNBC and HER2-positive subtypes; the applicability of this approach in HR-positive/HER2-negative disease, where pCR rates are low, remains uncertain. Third, while the negative predictive value (NPV)

of VACB is promising, meta-analytic data indicate that the NPV of VACB alone (7–10 gauge) remains approximately 80% meaning that one in five negative biopsies may be false negative (21). The substantially lower rate achieved in Kuerer's study is attributable to strict patient selection criteria, advanced imaging interpretation, and comprehensive tissue sampling; the generalizability of these conditions to routine clinical practice is debatable. Finally, the limited duration of long-term follow-up data warrants caution, particularly in HR-positive disease where late recurrence risk is a concern.

3.4. Section Summary

Neoadjuvant therapy has established itself as one of the most powerful catalysts of de-escalation in breast cancer surgery. Its capacity to convert mastectomy candidates to BCS through tumor downstaging is a well-established practice in routine clinical care. Tumor bed marking and wireless localization systems strengthen the technical infrastructure of this conversion. The non-surgical approach, while still at an experimental stage, yields data from early-phase trials suggesting that this strategy may enter standard practice in the future for appropriate subtypes under strict selection criteria. The next section addresses axillary management - another critical front of de-escalation - and its evolution.

4. Evidence-Based Evolution of Axillary Management

Axillary lymph node status occupies a central role in breast cancer for both staging and treatment planning. However, the surgical approach to the axilla has undergone perhaps the most radical transformation of any area in breast surgery over the past three decades. The progression from routine axillary lymph node dissection (ALND) to sentinel lymph node biopsy (SLNB), from SLNB to omission of dissection in limited nodal disease, and ultimately to the questioning of SLNB itself, represents the field in which de-escalation possesses the most mature chain of evidence. At each stage, a randomized controlled trial has dismantled the preceding standard and ceded its place to a less invasive approach.

4.1. From ALND to SLNB: NSABP B-32

From the Halsted era onward, ALND was accepted as an inseparable component of breast cancer surgery. The rationale was straightforward: removal of axillary lymph nodes provided both staging information and aimed at regional disease control. However, the cost of ALND was substantial. According to the prospective data of Lucci et al. (2007), lymphedema developed in 20-30%, chronic pain or sensory disturbance in 30–40%, and shoulder range-of-motion restriction in 15–20% of patients following ALND (23). These morbidity rates -

particularly in clinically node-negative (cN0) patients, in whom the probability of axillary metastasis is below 30% - raised the question of whether the harm of treatment might outweigh its benefit.

The sentinel lymph node concept is based on the idea that one or a few lymph nodes representing the first site of lymphatic drainage from the tumor can be identified, and that axillary status can be assessed by removing only these nodes. This concept was introduced in breast cancer in the 1990s and rapidly entered clinical practice; however, the definitive evidence demonstrating non-inferiority of SLNB to ALND came from the NSABP B-32 trial. Krag, Anderson et al. (2010) randomized 5,611 clinically node-negative patients to SLNB + ALND or SLNB alone. The results revealed no significant difference between the two arms in overall survival, disease-free survival, or regional recurrence rates (24). NSABP B-32 established SLNB as the new standard for axillary staging in cN0 breast cancer and proved that ALND should no longer be performed routinely in this patient group.

4.2. Questioning ALND in the Presence of a Positive Sentinel Node: Z0011 and AMAROS

Following the standardization of SLNB, a further step was taken: whether completion ALND was truly necessary in patients with sentinel node metastasis was called into question. This was an intuitively unsettling proposition - leaving a known metastatic lymph node in situ appeared contrary to oncologic principles. Yet Fisher's biological model implied that the answer to this question might not be as straightforward as expected.

The trial that answered this question was ACOSOG Z0011 - one of the most influential and most debated randomized controlled trials in the history of breast surgery. Giuliano, Ballman et al. (2017) randomized 891 patients with T1–T2 tumors, clinical N0 status, planned BCS + whole-breast RT, and 1–2 positive sentinel nodes on SLNB to completion ALND or observation. The 10-year results demonstrated no statistical difference between the two arms in overall survival (83.6% vs. 86.3%), disease-free survival, or locoregional recurrence rates (25).

The clinical impact of Z0011 was enormous: as the first randomized controlled trial evidence demonstrating that ALND can be omitted in the presence of limited axillary metastasis, it directly changed surgical practice worldwide. However, the methodological limitations of the trial have also been extensively discussed. First, the study was closed early with 891 patients instead of the planned 1,900, reducing statistical power. Second, approximately 20% of patients in the ALND arm did not receive ALND per protocol (crossover). Third, RT

quality assurance data were not prospectively collected; a retrospective analysis by Jagsi et al. revealed that approximately 50% of patients received high tangent fields and approximately 20% received direct regional nodal RT suggesting that the low regional recurrence rates in the observation arm may have been partly attributable to RT coverage of the axilla. Despite these limitations, the consistent 10-year results of Z0011 and subsequent confirmatory data have ensured that the core message of the trial remains valid.

The EORTC 10981-22023 AMAROS trial, conducted in parallel with Z0011, approached the question from a different angle: whether axillary RT (ART) could be applied instead of ALND in the presence of a positive sentinel node. Donker, van Tienhoven et al. (2014) randomized 1,425 patients to ALND or ART, demonstrating that 5-year axillary recurrence rates remained below 1% in both arms (26). AMAROS established ART as an oncologically safe alternative to ALND, while once again highlighting the distinctive morbidity of ALND most notably the marked difference in lymphedema rates (23% vs. 11%).

4.3. Questioning SLNB Itself: SOUND and INSEMA

Z0011 and AMAROS questioned ALND in the presence of a positive sentinel node. The next step posed an even bolder question: in clinically node-negative patients, is SLNB itself truly necessary? Although SLNB carries far lower morbidity than ALND, it can still give rise to complications such as lymphedema (5–8%), chronic pain, and sensory disturbance. If the staging information obtained from SLNB does not alter treatment decisions, the necessity of the procedure becomes open to question.

The first randomized controlled trial to address this question was the Italian SOUND trial. Gentilini, Botteri et al. (2023) compared SLNB with observation (no axillary surgery) in patients with tumors up to 2 cm (cT1) and negative axillary ultrasonography. The 5-year results of the trial encompassing 1,405 patients demonstrated no significant difference in distant disease-free survival (97.7% vs. 98.0%) or overall survival (98.0% vs. 98.2%) between the two arms (27). The axillary recurrence rate remained below 1% in both arms. SOUND provided the first randomized evidence that SLNB can be safely omitted in low-risk early-stage breast cancer, inaugurating a new era in the de-escalation of axillary surgery.

The primary results of the INSEMA trial - confirming these findings in a substantially larger population - were presented at the San Antonio Breast Cancer Symposium in late 2024 and simultaneously published in the New England Journal of Medicine. Reimer, Stachs et al. (2025) randomized 5,502 clinically

node-negative patients with T1–T2 invasive breast cancer to SLNB or no axillary surgery in a 4:1 ratio. At a median follow-up of 73.6 months, in the per-protocol population (4,858 patients), 5-year invasive disease-free survival (iDFS) rates were 91.7% in the SLNB arm and 91.9% in the no-axillary-surgery arm, with non-inferiority demonstrated (HR 0.91; 95% CI 0.73–1.14) (28). Distant recurrence rates were identical at 2.7% in both arms. The axillary recurrence rate was higher, as expected, in the no-surgery arm (1.0% vs. 0.3%); however, this absolute difference was considered clinically insignificant. Conversely, the lymphedema rate was significantly lower in the no-surgery arm (1.8% vs. 5.9%).

Several methodological limitations of INSEMA merit notation. The trial initially planned an event-driven analysis with 851 events projected for non-inferiority; however, only 525 events occurred, leaving statistical power lower than planned. Furthermore, 90% of the study population comprised clinical T1 tumors, and confidence intervals widen substantially in the T2 subgroup. The large majority of participants had HR-positive/HER2-negative disease, and the safety of SLNB omission in tumors with aggressive biology and in T2 disease has not yet been sufficiently validated.

Morrow (2024), in an editorial written on the occasion of the simultaneous publication of SOUND and INSEMA results, emphasized that these two trials represent a turning point in the evolution of axillary surgery (29). Morrow argued that the limited therapeutic contribution of SLNB must now be acknowledged, while also noting that nodal information can still influence systemic therapy decisions - particularly in contexts where genomic testing is limited - and that SLNB omission should therefore remain an individualized decision.

4.4. The Axilla Following Neoadjuvant Therapy: Z1071, SENTINA, and Targeted Axillary Dissection (TAD)

Axillary management following neoadjuvant therapy harbors distinctive challenges in patients who were initially node-positive (cN+) and demonstrated nodal response to treatment. In this patient group, the reliability of SLNB - in particular the false-negative rate (FNR) - has emerged as a critical concern.

Two large prospective trials defined this problem. In the ACOSOG Z1071 trial, Boughey, Suman et al. (2013) reported a false-negative result in 12.6% of cN+ patients undergoing SLNB following NACT meaning that SLNB missed residual axillary disease (30). Similarly, in the SENTINA trial, Kuehn, Bauerfeind et al. (2013) reported an FNR of 14.2% for SLNB in patients who were cN+ before NACT and became clinically node-negative after treatment

(31). The FNR exceeding 10% in both trials was considered above the clinically acceptable threshold.

Strategies proposed to reduce this high FNR include dual-agent mapping (radiocolloid + blue dye), removal of three or more sentinel nodes, and targeted removal of the metastatic node by clipping it prior to treatment and retrieving it during surgery. This last strategy has been systematized under the concept of targeted axillary dissection (TAD). Caudle, Yang et al. (2016) defined TAD in a prospective study conducted at MD Anderson Cancer Center: applied as a combination of SLNB and retrieval of the clipped node, TAD reduced the FNR to 2.0% (32). A noteworthy finding was that the clipped node was not identified as a sentinel node in 23% of patients meaning that had SLNB alone been performed, the known metastatic node would have been left unevaluated entirely. This data strongly supports the superiority of TAD over SLNB in post-neoadjuvant axillary assessment.

TAD has now been adopted at many centers as the standard axillary staging method for cN+ patients following NACT. In a European-wide survey conducted in 2022, TAD was reported as the most frequently applied axillary procedure (54.2%) in patients converting from cN1 to ycN0 following NACT. However, long-term data on the oncologic safety of TAD remain limited, and prospective randomized trials comparing the procedure with ALND are ongoing.

4.5. Ongoing Trials: TAXIS, AXSANA, and POSNOC

Several important trials that will define the boundaries of de-escalation in axillary surgery are still ongoing.

The TAXIS trial is investigating whether TAD + axillary RT is non-inferior to ALND in the presence of residual axillary disease following NACT. AXSANA is a European prospective registry study comparing the oncologic outcomes of different axillary surgical approaches following NACT (SLNB, TAD, ALND) with real-world data. POSNOC is a non-inferiority trial evaluating the safety of omitting axillary treatment (ALND or ART) in a population similar to Z0011 BCS or mastectomy with a positive sentinel node.

The primary results of these trials will clarify the boundaries of individualized de-escalation in axillary management and seek answers to the question of how far surgery can be reduced in the presence of residual disease.

4.6. Section Summary

The evolution of axillary management represents the field in which evidence-based de-escalation has been most systematically realized in breast cancer

surgery. NSABP B-32 enabled ALND to cede its place to SLNB. Z0011 and AMAROS demonstrated that ALND can be omitted or replaced by ART in limited nodal disease. SOUND and INSEMA established that even SLNB may be unnecessary in low-risk patients. TAD has minimized false negativity in post-neoadjuvant axillary assessment, enabling targeted surgical intervention. Each step has been built upon the preceding one and advanced forward in the evidence hierarchy. However, the safety boundaries of de-escalation in tumors with aggressive biology, in T2 disease, and in residual nodal disease following neoadjuvant therapy have not yet been fully delineated, and ongoing trials aim to fill these gaps.

5. Reconstruction, Patient-Centered Outcomes, and Quality of Life

The evolution of breast cancer surgery cannot be measured by oncologic outcomes alone. The fundamental promise of de-escalation - eliminating unnecessary morbidity while preserving oncologic safety - inherently places quality of life at the center of outcome assessment. This section addresses the evolution of breast reconstruction, the growing importance of patient-reported outcome measures (PROMs), and the progression toward legitimizing the option of forgoing reconstruction altogether.

5.1. The Evolution of Breast Reconstruction: From Timing to Technique

Postmastectomy breast reconstruction was historically performed as delayed reconstruction. The rationale rested on concerns that reconstruction might delay oncologic treatment or complicate recurrence surveillance. From the 1990s onward, however, accumulating evidence consistently demonstrated that immediate reconstruction does not adversely affect oncologic outcomes. In the systematic review by Alderman, Gutowski et al. (2009), immediate reconstruction was reported not to increase local recurrence rates, to improve cosmetic outcomes compared with delayed reconstruction, and to enhance overall patient satisfaction (33). Immediate reconstruction is today accepted as the standard approach in patients requiring mastectomy, while delayed reconstruction is applied in cases planned for postmastectomy radiotherapy (PMRT) or according to patient preference.

Reconstruction methods are broadly divided into implant-based (prosthetic) and autologous tissue-based approaches. Implant-based reconstruction is the most frequently preferred method due to its shorter operative time and absence of donor site morbidity; according to US data, approximately 80% of all reconstructions are implant-based. Autologous reconstruction - most notably the deep inferior epigastric perforator (DIEP) flap - offers the advantages of a natural

tissue feel, long-term durability, and resistance to radiotherapy; however, its applicability is limited by the requirement for microsurgery, donor site morbidity, and prolonged operative time.

5.2. Paradigm Shift in Implant-Based Reconstruction: From Subpectoral to Prepectoral

The most prominent evolution within implant-based reconstruction is the change in implant placement plane. Traditionally, implants have been placed beneath the pectoralis major muscle (subpectoral/submuscular plane). The rationale for this approach was to provide adequate soft tissue coverage over the implant, thereby reducing implant palpability, capsular contracture, and skin necrosis. However, subpectoral placement carries its own distinctive morbidities: animation deformity (displacement of the implant with pectoral muscle contraction), chronic chest pain, and functional loss attributable to muscle dissection.

With the introduction of acellular dermal matrix (ADM) and synthetic mesh, placement of the implant anterior to the muscle (prepectoral) has become feasible. In prepectoral reconstruction, the implant is placed directly beneath the skin flaps, wrapped with ADM or mesh, while the integrity of the pectoral muscle is preserved. Sbitany et al. (2020), in their multicenter prospective study encompassing 818 prepectoral reconstruction cases, reported that complication rates were comparable to subpectoral cohorts, animation deformity was eliminated, and patient satisfaction scores were high (34). Prepectoral reconstruction has attracted particular attention for its capacity to recreate a natural breast appearance, especially when performed in conjunction with SSM and NSM.

Nevertheless, randomized data demonstrating the superiority of prepectoral over subpectoral reconstruction are limited. The OPBC-02/PREPEC trial, designed as the first randomized controlled trial directly comparing these two approaches, has not yet yielded mature results. The current evidence base consists largely of retrospective comparisons and prospective cohort studies. Furthermore, the success of the prepectoral approach is critically dependent on adequate mastectomy flap thickness and skin vascularity; in patients with thin flaps or prior radiotherapy, complication risk is increased.

5.3. The Interaction Between Radiotherapy and Reconstruction

The timing and method of reconstruction in patients requiring PMRT remains one of the most contentious issues in clinical practice. The adverse effects of

radiotherapy on implant-based reconstruction - capsular contracture, infection, implant loss, and deterioration of cosmetic outcomes - are well documented. The meta-analysis by Ho, Bovill et al. (2012) demonstrated that complication rates in implant-based reconstruction in patients receiving PMRT were up to twofold higher than in those not receiving PMRT (35).

Various strategies have been developed to address this problem. In the delayed-immediate approach, a tissue expander is placed at the time of mastectomy, and transition to definitive reconstruction proceeds once pathology and adjuvant therapy planning are clarified. Autologous reconstruction, by virtue of its greater resistance to the postradiation environment and its ability to better tolerate the effects of radiation damage compared with implant-based reconstruction, is generally recommended as the preferred method in patients planned for PMRT.

5.4. Patient-Reported Outcome Measures and BREAST-Q

The centrality of quality of life within the de-escalation philosophy has also transformed how surgical outcomes are measured. Traditionally, surgical success was assessed through recurrence rates, survival, and complication incidence. However, these metrics do not adequately reflect the patient's own experience body image, sexual well-being, psychosocial adjustment, and daily functional capacity.

BREAST-Q is a psychometrically validated patient-reported outcome measure (PROM) instrument developed specifically for breast surgery. Developed by Pusic, Klassen et al. (2009), this scale evaluates domains including breast satisfaction, psychosocial well-being, physical well-being, and sexual well-being separately (36). BREAST-Q is today recognized as a standard outcome measure in breast surgery research and is used as a primary or secondary outcome variable in numerous randomized controlled trials.

One of the most important contributions of BREAST-Q data to clinical practice is the comparative demonstration of the impact of different surgical approaches on patient experience. In studies comparing BCS + RT with mastectomy + reconstruction, BCS has been consistently reported to yield higher scores in psychosocial well-being and breast satisfaction evidence that de-escalation not only reduces morbidity but improves patient experience. Conversely, patients undergoing reconstruction following mastectomy have been shown to have markedly higher body image and psychosocial adjustment scores compared with those who do not undergo reconstruction.

5.5. The Option of Forgoing Reconstruction: "Going Flat"

While the legitimization and widespread adoption of reconstruction represents an important achievement, this process has paradoxically created a normative expectation: the perception that reconstruction is the "expected" or "standard" step following mastectomy. This norm may indirectly exert pressure on patients who do not wish to undergo reconstruction. The option referred to as "going flat" - mastectomy without reconstruction - has in recent years entered the agenda of both patient advocacy groups and the surgical literature.

Rosenberg, Dominici et al. (2020), in a study investigating the experiences of patients who chose to go flat, reported that 25% of patients felt directed toward reconstruction by their surgeons, and that 14% reported that their request for a flat closure - rather than an aesthetically revised closure with residual tissue - was not honored (37). These findings demonstrate that the preservation of patient autonomy in surgical decision-making - as a dimension of de-escalation - is concerned not only with what is done, but with respectful acknowledgment of what is chosen not to be done.

From an oncologic standpoint, going flat carries equivalent safety to reconstruction; it additionally offers the advantages of facilitating recurrence surveillance and avoiding additional surgical morbidity. BREAST-Q data have demonstrated that patients who choose to go flat and do so as an informed decision may achieve psychosocial well-being scores comparable to those of patients who undergo reconstruction. This supports the principle that a "good outcome" is the outcome aligned with the patient's own values and preferences.

5.6. Section Summary

The evolution of breast reconstruction is an inseparable component of the de-escalation paradigm. Immediate reconstruction alleviates the cosmetic and psychosocial burden of mastectomy, while the prepectoral approach reduces morbidity within implant-based reconstruction itself. PROMs such as BREAST-Q have broadened the definition of surgical success by placing the patient perspective at the center. The legitimization of the going flat option represents the most nuanced dimension of de-escalation: the patient's right to be protected from the pressure of "more surgery." However, the evidence base in reconstruction is not as mature as that in axillary or primary breast surgery. Randomized controlled trials comparing prepectoral with subpectoral placement, optimal reconstruction methods in the PMRT setting, and long-term psychosocial outcomes of going flat remain limited.

6. Synthesis and Future Perspectives

The trajectory traced throughout this chapter reveals a recurring pattern in the history of breast cancer surgery spanning more than a century and a half: the "standard" surgery of each era has become the "overtreatment" of the next. Halsted's radical mastectomy was questioned by Fisher's biological model. ALND was replaced by SLNB. SLNB itself was found unnecessary by SOUND and INSEMA. This pattern is not coincidental; it is the inevitable consequence of surgical practice being reshaped by the disciplined interrogation of evidence-based medicine.

6.1. The Epistemological Structure of De-escalation

A common epistemological structure is observable at each stage of the de-escalation process. First, clinical observation or retrospective data questions the necessity of the prevailing standard. This questioning is then tested through a prospective - preferably randomized - trial. When the trial demonstrates that the less invasive approach is non-inferior from an oncologic standpoint, the new standard is established. This cyclical process requires surgery to continuously redefine itself and demands intellectual humility: the acknowledgment that the approach defended today will be questioned tomorrow.

However, this structure also has its limitations. Non-inferiority trials, by definition, prove that the new approach is "not worse" - not that it is "better." The determination of the non-inferiority margin - what level of oncologic difference is considered "acceptable"- is fundamentally a value judgment, and this judgment may vary from patient to patient. A 1% absolute survival difference may be inconsequential for one patient yet unacceptable for another. The ethical legitimacy of de-escalation is strengthened by incorporating these individual value differences into the decision-making process.

6.2. Heterogeneity and Critique of the Evidence Base

The methodological quality of the evidence discussed throughout this chapter is not homogeneous. Some areas of surgical de-escalation are supported by robust randomized controlled trial data, while others remain at a weaker level of evidence.

Areas with strong randomized controlled trial support include the equivalence of BCS to mastectomy (NSABP B-06, Milan I), the non-inferiority of SLNB to ALND (NSABP B-32), omission of ALND in limited nodal disease (Z0011, AMAROS), and omission of SLNB in clinically node-negative disease (SOUND,

INSEMA). The common features of these areas are a clearly defined research question, adequate sample size, and mature follow-up duration.

Areas remaining at a weaker level of evidence also exist. Oncoplastic surgery, prepectoral reconstruction, robotic mastectomy, and the non-surgical approach following neoadjuvant therapy are supported predominantly by retrospective series, prospective cohort studies, and early-phase trials. This does not mean that these approaches are invalid; however, it indicates that their integration into practice should be more cautious compared with areas supported by robust randomized controlled trial data. The legitimacy of surgical de-escalation derives from the strength of its evidence, not its popularity this distinction must always be preserved in clinical practice.

6.3. Biological Subtype and Individualization: One Size Does Not Fit All

The most defining characteristic of modern breast cancer surgery is the transition from a "one disease - one surgery" approach to "biologically subtype-guided individualized surgical strategy." This transition reveals that de-escalation is not a policy applicable homogeneously to all patients, but a principle requiring titration according to biological context.

In HER2-positive and triple-negative subtypes, high pCR rates render surgical de-escalation - and even omission of surgery - following neoadjuvant therapy the strongest candidates. In the HR-positive/HER2-negative subtype, low pCR rates limit the efficacy of neoadjuvant chemotherapy as a surgical de-escalation tool; neoadjuvant endocrine therapy represents an alternative in this group, though its evidence base has not yet matured. Genomic tests - particularly Oncotype DX and MammaPrint - individualize systemic therapy decisions, while the direct integration of these tests into surgical decision-making remains an evolving area.

6.4. Technology and the Future of Surgery

Technological advances carry the potential to expand the boundaries of de-escalation. Artificial intelligence (AI)-assisted imaging may enable more accurate non-invasive assessment of neoadjuvant therapy response and improve patient selection for the non-surgical approach. Liquid biopsy - analysis of circulating tumor DNA (ctDNA) - is emerging as a promising biomarker for the detection of minimal residual disease (MRD). Studies pioneered by Coombes, Page et al. (2019) have demonstrated that ctDNA may be used to individualize adjuvant therapy decisions and to detect recurrence risk at an early stage (38). ctDNA negativity may in the future be positioned as a biomarker supporting

decisions to narrow the surgical scope or omit surgery altogether - however, the prospective validation of this application has not yet been completed.

Robotic surgery, as discussed in Section 2, is being applied with increasing frequency in breast surgery; however, its cost-effectiveness and genuine clinical superiority remain debated. The contribution of robotic approaches to de-escalation lies in offering a less invasive surgical access; however, the concepts of "smaller incision" and "less surgery" must not be conflated. Minimally invasive access does not alter the scope of surgery - it only changes the manner of its execution.

6.5. Shared Decision-Making and Patient Autonomy

The ultimate goal of de-escalation is not to apply "the least surgery" to every patient, but to apply "the most appropriate surgery" to every patient. This distinction positions shared decision-making as the ethical foundation of the de-escalation paradigm. The patient must understand the oncologic risks, surgical options, expected cosmetic outcomes, and quality of life implications, and arrive at a decision aligned with their own values.

Morrow and Katz (2015), in their study analyzing the breast cancer surgical decision-making process, demonstrated that patients' surgical preferences are influenced more by fear, anxiety, and information deficits than by clinical factors (39). The increasing use of contralateral prophylactic mastectomy (CPM) in particular - even in patients without genetic predisposition - represents an "escalation" tendency at the opposite pole of de-escalation. It is true that CPM reduces the risk of contralateral breast cancer; however, in sporadic breast cancer the absolute magnitude of this risk is small, and there is no evidence that CPM confers a survival advantage. This paradox - evidence-based de-escalation on one side, fear-driven escalation on the other - underscores how critical informed consent and psychological support are in the surgical decision-making process.

6.6. Conclusion

Breast cancer surgery has undergone one of medicine's most remarkable paradigm transformations, on a journey from Halsted's radical mastectomy to the debate over non-surgical approaches. The driving force of this transformation is the tradition of evidence-based inquiry initiated by Fisher's biological model and consolidated through successive randomized controlled trials.

At the point reached today, several foundational principles have crystallized. First, more surgery does not mean better oncologic outcomes this is now an empirically established fact. Second, de-escalation is not a policy but a principle,

and must be individualized on the basis of biological subtype, treatment response, and patient preference. Third, the measure of surgical success is not survival alone, but patient experience and quality of life. Fourth, respect for the evidence hierarchy is the foundation of de-escalation's legitimacy popularity or technological novelty cannot substitute for randomized controlled trial evidence.

The future likely points toward an era in which surgery is further individualized, can be entirely omitted in certain patient groups, and surgical decisions are shaped by genomic, biomarker, and AI-assisted data. However, the path to this future passes through not forgetting the lessons of the past: no new approach, however compelling, can become standard until confirmed by prospective evidence. De-escalation, ultimately, represents the triumph not of the surgeon's hand, but of the surgeon's mind and of science itself.

7. Kaynakça

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