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Ciclo XXXV

Upper-limb lymphedema after axillary node dissection in patients with breast cancer: risk-reduction strategies.

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TABLE OF CONTENTS

ABSTRACT

BACKGROUND: In recent years, the paradigm of completion ALND (axillary lymph node dissection) after a positive SLNB (sentinel lymph node biopsy) has been questioned, and several studies have led to revolutionary changes in clinical practice. Many clinical trials compared the difference in morbidity of the upper limb after SLNB versus ALND and concluded for a reduced prevalence of arm morbidity in case of ALND omission. During the last decade, a number of randomize trials (among the others ACOSOG Z0011 and SINODAR-ONE) have shown that not all patients with positive axillary lymph nodes benefit from axillary node dissection. Despite accurate surgical technique, there is no evidence that post-ALND complications could be efficaciously spared by adopting technical tips intraoperatively. The only consistent results in reducing arm morbidity after axillary surgery are linked to the important difference between SLNB and complete ALND. In this context, application of surgical de-escalation that is nowadays widely supported and validated can be the key element to bring to a substantial reduction in long-term arm morbidity for breast cancer survivors. The principal aim of our research was to investigate whether the onset of arm complications (notably arm lymphedema) could be significantly influenced by a correct and thorough adhesion to ACOSOG Z0011 and/or SINODAR criteria. *PATIENTS AND METHODS:* We performed a retrospective cross-sectional monocentric study. All patients who underwent axillary node dissection following breast cancer diagnosis in the years 2019-2022 in the Breast Unit of Modena University Hospital

were enrolled. For each patient the presence/absence of post-ALND upper-limb complications was recorded. In particular we considered: chronic pain, chronic Axillary Web Syndrome, lymphedema of any grade. Each record was then checked to verify if all the criteria of ACOSOG Z0011 trial and SINODAR-ONE were retrospectively present. We also considered the concomitant presence of the two studies by defining two categories: possible/not possible enrollement in at least one of the two studies. *RESULTS:* Overall 366 patients underwent ALND in the Breast Unit of Modena University Hospital form January 2019 to December 2022.

Upper-limb complications, notably arm lymphedema of any grade, chronic pain and chronic axillary web syndrome, were described in 102 patients (27,9%). Arm lymphedema accounted for the 79,4% of complications. 83/366 (22,7%) patients fulfilled the ACOSOG Z0011 criteria to avoid ALND. Taking SINODAR trial into account, 100/366 patients (27,3%) could have been enrolled and randomized to standard treatment (ALND) or experimental treatment (ALND omission). If considering possible inclusion in at least one trial, 114/366 patients resulted suitable (31,1%). We then applied the enrollment criteria to the population of patients that developed an upper-limb complication and hypothesize an ideal cohort obtained in case of optimal surgical de-escalation. Significant difference in arm complications presence, was found in the scenario of ideal application of ACOSOG Z0011 trial (p=0,04) and in the scenario of ideal application of both studies together (p=0,009). The impact of SINODAR-ONE trial alone did not result

significant (p=0,18), probably because we considered a randomization of 50% of patients to standard arm (ALND).

CONCLUSIONS: Overall, our study showed a statistically significant inferior risk of developing arm complications in case of optimal de-escalation (application of ACOSOG Z001 and SINODAR-ONE criteria). Previous studies confirmed and validated the results of ACOSOG Z011 and SINODAR-ONE trials in terms of OS, DFS and recurrence-rate, but our study directly highlights how surgical de-escalation have a direct impact on upper-limb complications reduction, in particular concerning breast cancer-related lymphedema.

RIASSUNTO

BACKGROUND: Il paradigma della dissezione ascellare completa (ALND) dopo riscontro di una biopsia del linfonodo sentinella positiva è stato recentemente messo in discussione e numerosi studi hanno portato a cambiamenti rivoluzionari nella pratica clinica. Molti Clinical Trials hanno paragonato la differenza di morbidità dell'arto superiore dopo biopsia del linfonodo sentinella e dopo dissezione ascellare completa e hanno dimostrato una ridotta prevalenza di problematiche dell'arto superiore in caso di omissione dello svuotamento ascellare. Nell'ultimo decennio, alcuni trial clinici randomizzati (tra cui l'ACOSOG Z0011 e il SINODAR-ONE) hanno mostrato che non tutti i pazienti con linfonodo sentinella positivo beneficiano del successivo svuotamento ascellare. Anche in caso di tecnica chirurgica ottimale, non ci sono evidenze che esistano accortezze tecniche applicabili in sede intraoperatoria che contribuiscano a ridurre il rischio di complicanze post-linfadenectomia ascellare. Gli unici risultati significativi in tema di riduzione della morbidità dell'arto superiore dopo chirurgia ascellare, sono legati all'importante differenza tra la biopsia del linfonodo sentinella e la dissezione completa. In questo contesto, uno ruolo chiave nella riduzione delle complicanze a lungo termine dell'arto superiore potrebbe appartenere all'applicazione dei criteri di de-escalation chirurgica dell'ascella, che sono oramai ampiamente validati e supportati da evidenze scientifiche. Lo scopo principale del nostro studio è stato quello di verificare se l'insorgenza di complicanze del braccio dopo chirurgia ascellare (in particolare del

linfedema dell'arto superiore) potesse essere influenzata in maniera statisticamente significativa da una corretta e capillare adesione ai criteri di ACOSOG Z0011 e/o del SINODAR-ONE. *PAZIENTI E METODI:* Abbiamo eseguito uno studio osservazionale retrospettivo monocentrico. Sono state arruolate tutte le pazienti sottoposte a dissezione ascellare in seguito a diagnosi di tumore della mammella negli anni 2019-2022 nella Breast Unit dell'Azienda Ospedaliero-Universitaria Policlinico di Modena. Per ogni paziente è stata indagata la presenza o assenza di una complicanza dell'arto superiore dopo dissezione ascellare. In particolare abbiamo considerato: dolore cronico, Axillary Web Syndrome cronica e linfedema di ogni grado. Per ogni soggetto inserito abbiamo quindi verificato retrospettivamente che i criteri di inclusione dell'ACOSOG Z0011 e del SINODAR-ONE fossero applicabili. Abbiamo anche preso in considerazione la contemporanea applicabilità di entrambi gli studi definendo due categorie: possibile/non possibile inclusione in almeno uno dei due studi. *RISULTATI:* Complessivamente 366 pazienti sono state sottoposte a dissezione ascellare nella Breast Unit del Policlinico di Modena da Gennaio 2019 a Dicembre 2022. La presenza di complicanze dell'arto superiore, in particolare linfedema di ogni grado, dolore cronico e Axillary Web Syndrome cronica, sono state riscontrate in 102 pazienti (27,9%). Il linfedema dell'arto superiore è risultato responsabile del 79,4% di tutte le complicanze. 83/366 (22,7%) pazienti soddisfavano tutti i criteri per l'omissione della dissezione ascellare secondo ACOSOG Z0011. Considerando invece il SINODAR, 100/366 pazienti (27,3%) sarebbero

stati arruolabili e randomizzabili nel braccio standard (dissezione ascellare) o nel braccio sperimentale (no dissezione ascellare).

Analizzando la possibile inclusione in almeno uno dei due trial, 114/366 pazienti sarebbero risultati idonei (31,1%). Abbiamo quindi applicato i criteri di arruolamento al sottogruppo di pazienti che ha sviluppato una complicanza dell'arto superiore e abbiamo ipotizzato una coorte di studio ideale ottenuta in caso di adesione ottimale alla de-escalation chirurgica. Una differenza significativa nella presenza di complicanze dell'arto superiore è stata osservata nell'ipotesi di applicazione ottimale dei criteri Z0011 (p=0,04) e nell'ipotesi di considerare l'arruolamento in almeno uno dei due trial disponibili (p=0,009). L'impatto dell'adesione ottimale al SINODAR-ONE non è invece risultato statisticamente significativo (p=0,18), probabilmente in conseguenza della randomizzazione del 50% dei pazienti arruolabili nel braccio standard (svuotamento ascellare). *CONCLUSIONI:* Complessivamente il nostro studio dimostra un rischio significativamente inferiore di sviluppare una complicanza dell'arto superiore in caso di de-escalation chirurgica ottimale (applicazione sia dei criteri ACOSOG Z0011 sia dell'arruolamento al SINODAR-ONE). I risultati di questi trial in termini di sopravvivenza globale, sopravvivenza libera da malattia e tasso di recidiva, sono stati ampiamente confermati e validati nella letteratura ma la nostra ricerca evidenzia direttamente come la de-escalation chirurgica abbia un impatto diretto sulla riduzione delle complicanze dell'arto superiore, con particolare interesse al linfedema.

1. INTRODUCTION

1.1 Surgical Axillary Staging in Breast Cancer

Axillary lymph nodes status is the most important prognostic indicator in overall survival (OS) and disease-free survival (DFS) in the management of early stage breast cancer. It is fundamental to estimate the prognosis and plan adequate adjuvant treatments.

In the last decades, axillary surgery has evolved, aiming to offer the best oncologic treatment and improve the quality of life of women.

Axillary lymph node dissection (ALND) has been an integral part of the surgical management of breast cancer since Halsted described the radical mastectomy in 1894 (1). Although controversial in specific situations, ALND remains an integral part of surgical treatments in patients with invasive breast cancer and axillary lymph node metastases.

Traditional level I and level II ALNDs require that at least 10 lymph nodes be provided for pathologic evaluation to accurately stage the axilla (2)(3). ALND should be extended to include level III nodes only if gross disease is apparent in the level II and I nodes. In the absence of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle (level I and II).

The management of the axilla, however, changed radically with the introduction of the sentinel lymph node biopsy (SLNB) in the early 1990s (4).

Two randomized trials compared SLNB alone versus ALND. The Milan trial (1998–1999) randomized 516 patients treated with BCS with tumors up to 2 cm to two arms, one receiving immediate axillary dissection and the other receiving the dissection only if the sentinel node was involved (5). After 79 months follow-up, there was no difference in OS and DFS (6).

Another similar study, (NSABP) B-32, conducted between 1999 and 2004, randomized 5611 patients with invasive breast cancer up to 2 cm to either ALND or SLNB alone with ALND performed only if the SLN was positive (7). After 95.6 months of follow-up, OS and DFS were similar in the two groups. Results of a subgroup analysis of this study showed patients with ALND had significantly higher arm morbidity and significantly more restricted work and social activity and impaired QoL (8) (9).

On these basis, Axillary lymph-node dissection (ALND) has been replaced by sentinel lymph-node biopsy (SLNB) in women with early clinically node-negative breast cancer, providing adequate axillary nodal staging information with minimal morbidity, and becoming the standard of care in the management of breast cancer (10).

Optimal axillary surgical staging in patients who underwent preoperative chemotherapy is still subject of research and debate. The question that is being explored is whether ALND may be omitted in patients with complete pathologic response after preoperative therapy. Several prospective studies have evaluated patients with positive lymph-nodes before preoperative systemic therapy who had clinical complete response to preoperative therapy and underwent SLNB and ALND.

1.2 Complications after axillary surgery

Any surgical procedure on axillary lymph nodes may lead to the development of immediate or delayed complications. In most cases, they can be mitigated with rehabilitation but when conservative treatment fails, women experience functional discomfort and a dramatic worsening in quality of life.

Many clinical trials compared the difference in morbidity of the upper limb after SLNB versus ALND.

The results of the NSABP B-32 study indicate the superiority of the SLNB compared to the ALND treatment approach relative to post-surgical morbidity outcomes over a 3-year follow-up period (9).

Other clinical trials explored the difference between SLNB and ALND procedures in terms of arm swelling, reduced range of motion, shoulder abduction, sensory loss, pain and paresthesia, patient reported arm symptoms and quality of life in general (11-15)(6)**.** All the results led to the conclusion that SLNB resulted in less morbidity compared to ALND although the study morbidity effect sizes appeared to vary due to differing samples sizes and follow-up durations.

1.2.1 Persistent Post-Surgical Pain (PPSP)

Breast cancer patients with musculoskeletal pain demonstrate significantly lower health-related quality of life including physical and mental functioning (16)**.**

A meta-analysis suggests that almost half of all the women undergoing breast cancer surgery develop persistent post-surgical pain, and about one in four develop moderate-to-severe persistent post-surgical pain(17).

Some evidence suggests that education(18), exercise therapy(19), psychological or behavioural interventions(20), and paravertebral blocks in addition to general anaesthesia(21) or ketamine infusion perioperatively(22)(23), may reduce the rate of persistent pain after breast cancer surgery.

Higher prevalence of persistent pain is associated with ALND, likely because of sacrifice of the intercostobrachial nerve(17).

1.2.2 Axillary Web Syndrome (AWS)

Axillary web syndrome (also known as cording) is a common condition after breast and axillary surgery wherein subcutaneous cord-like scarring develops in the axilla and may extend down the arm and chest wall. The cause of these cords, which can be painful and limit shoulder movement, is thought to be related to lymphatic injury(24). It most commonly occurs in patients following breast cancer surgery with axillary lymph node dissection (ALND)(24)(25).

It usually presents within 2–8 weeks of surgery but can develop or recur months to years later. It can be associated with later lymphedema in a minority of patients. Physical therapy and exercise can reduce pain and increase range of motion (24).

Early literature described AWS as a self-limited condition, which resolved within 3 months of onset (25)(26). More recent research has

demonstrated that AWS does not resolve in all patients, can persist for years after surgery, and may reoccur after resolution (27-29), chronically worsening the QoL of patients.

1.2.3 Breast Cancer Related Lymphedema (BCRL)

Lymphedema is perhaps the most dreaded long term complication related to axillary lymph node surgery. Once present it implies a lifelong problem. In addition to functional impairment, lymphedema may result in a daily reminder of breast cancer and be an added psychological burden (9).

Lymphedema is defined as the interstitial collection of protein-rich fluid due to disruption of lymphatic flow. Lymphedema occurs when the lymphatic load exceeds the transport capacity of the lymphatic system, which causes filtered fluid to accumulate. Lymphedema that occurs as the result of disease or treatments is called secondary lymphedema.

Treatment of breast cancer (eg, surgery, radiation therapy) is one of the most common causes of secondary peripheral upper-limb lymphedema. In particular, ALND is the primary cause of breast and upper extremity lymphedema in patients with breast cancer (30). Indeed, lymphedema is significantly more liely to occurr following ALND than after SLNB alone(31)(32).

According to reports, the incidence of BCRL varies and is approximately 20% at one year and increases to 40% at ten years after breast cancer treatment with a cumulative incidence of 28% (33)(34).

Cardinal principles of lymphedema treatment are conservative (patient education, control of concomitant disease that may worsen swelling , decongestive therapy such as manual lymphaticadrainage, bandages, compression garments and individualized excersises)(35).

Surgical techniques for treatment of upper limb lymphedema should be taken into consideration in case of failure of conservative approaches. However, determining the best treatment for each patient remains challenging (35). Pappalardo et al(35). proposed a classifcation of surgical procedures into two classes: (1) physiologic procedures (lymphaticovenous anastomosis, vascularized lymph node transfer) and (2) excisional procedures (reduction or liposuction). This classification, with advantages and disadvantages of each procedure has been summarized in Figure 1. Lymphedema grade is classified following Cheng's Lymphedema Grading(36).

Treatment	Indication	Advantages	Disadvantages
Complex Decongestive Therapy	• CLG 0-I	• Reduction lymphedema volume, pain and arm heaviness • Improvement lymphatic function • Acceptable quality of life • Reduction episodes of cellulitis	• It is a purely symptomatic treatment • Needs patient compliance • Life-long compression garments.
Lymphovenous anastomosis	• CLG I- early II	• Safe • Reduces of Circumference • Reduces callulitis	• Technically difficult • Needs supermicrosurgery instruments • Needs high resolution microscope • Needs ICG lymphography • Difficult to monitor the anastomoses patency
Vascularized Lymph Node Transfer	• CLG late II-III-IV	• Improvements in circumferential measurements, episodes of cellulitis, and quality of life	• Requires intraoperative techniques of greater complexity • Higher risk for postoperative re-exploration and the flap inset • Risk of donor-site lymphedema
Liposuction	• CLG III-IV	• Decrease limb size • Reduces episodes of cellulitis • Improve quality of life	• Risks of swelling recurrence • Life-long compression garments

CLG: Cheng's Lymphedema Grading.

Fig 1. Surgical available treatments for patients with Breast Cancer-Related Lymphedema(35)

2. BACKGROUND

2.1 De-escalation of axillary surgery

In recent years, the paradigm of completion ALND after a positive SLNB has been questioned, and several studies have led to revolutionary changes in clinical practice(10).

The finding that axillary lymph nodes with metastases do not require resection is disturbing to surgeons. However, the history of breast cancer management has revealed that our preconceptions concerning the extent of operation necessary to achieve cure for patients with early breast cancer have often been excessive. During the last decade, a number of randomize trials have shown that not all patients with positive axillary lymph nodes benefit from axillary node dissection. Now it appears that even with long-term follow-up, selected patients with early SLN metastases do not require ALND when treated with optimal contemporary management. Locoregional control can be achieved with excellent long-term results with SLNB alone, whole breast irradiation, and adjuvant systemic therapy(37).

2.2 The ACOSOG Z0011 trial

The American College of Surgeons Oncology Group Z0011 trial is a milestone in the de-escalation process of axillary surgery for women affected by breast cancer. It has been a practice-changing study, after which many Breast Centers ceased to perform ALND in patients with 1 to 2 metastatic sentinel lymph-nodes and specific tumor features.

In this trial 856 patients were enrolled with cT1-2 tumors and 1-2 macrometastatic sentinel lymph nodes at the histology. Inclusion criteria are shown in *Table 1.* Randomization took place in 11 Breast centers in the USA. Patients were randomized between group (ALND) and experimental group (no further axillary surgery despite positive sentinel lymph node). After a median follow up of 9.3 years, data showed no significant difference between the two groups in terms of overall survial (OS), disease-free survival (DFS) and rate of local recurrence(38)(37). The results of the ACOSOG Z0011 trial demonstrate that there is no benefit to ALND in patients with early-stage breast cancer who have only one or two SLN metastases (minimal nodal burden) on SLNB after receiving WBRT as part of breast cancer treatments. Mastectomy patients were not enrolled in the ACOSOG Z0011 trial since these patients do not routinely receive radiation.

The results of ACOSOG Z0011 trial have been extensively debated by breast cancer experts during the years. The first observation was that all the patients underwent conservative surgery and breast radiation therapy, probably influencing the outcomes of the population. Moreover 96-97% of patients received adjuvant treatments. Further criticism raised from the fact that enrollment in the study closed ahead of time, including only 40% of patients compared to the initial sample calculation (37). Authors replied that the study was closed because the event rate was much lower than anticipated for both arms(39). Moreover 80% of enrolled patients were considered "low risk" (T1, post-menopausal, hormone receptor positive)(37)**.** It is true that breast cancer tends to

occur in postmenopausal women and tends to be hormone receptor-positive. However, the question of whether these results are applicable to women who are premenopausal and those with hormone receptor-negative tumors is valid. Only 16 % of patients in each arm of the study were hormone receptor-negative. Patients with hormone receptor-negative tumors, however, are not more likely to develop nodal recurrences (39).

Despite harsh criticism, ACOSOG Z0011 signed a sharp break in breast cancer treatment. The observed results in this trial with SLNB alone were excellent and most Breast Cancer centers worldwide altered axillary treatment paradigm since its publication. The latest versions of NCCN guidelines recommend no further axillary surgery in patients with 1-2 macrometastatic sentinel lymph nodes, who meet all the eligibility criteria of ACOSOG Z0011 trial.

Eligibility
Adult women
Histologically confirmed invasive breast carcinoma
Clinical T1-T2 breast carcinoma
No palpable axillary adenopathy
1 to 2 sentinel lymph nodes containing metastases (detected without immunohistochemical stains)
Patients treated with lumpectomy with negative margins (no tumor at ink)
Planned tangential whole-breast irradiation and adjuvant systemic therapy
Written Informed Consent
Exclusion
Metastasis in axillary lymph nodes identified initially
Metastasis in the sentinel lymh nodes identified solely with immunohistichemical staining

3 or more positive sentinel lymph nodes
Matted nodes
Gross extranodal disease
Neoadjuvant hormonal or chemotherapy

Table 1. Eligibility criteria for ACOSOG Z0011 trial(40)

2.3 The SINODAR-ONE trial

The SINODAR-ONE trial is an Italian multicentric randomized trial, designed with the aim to confirm and validate ACOSOG Z0011 results and to extend surgical de-escalation to patients who underwent mastectomy. 889 women with T1-T2 unilateral breast cancer who underwent all types of breast surgery (both conservative and mastectomies), were enrolled from 52 different Italina Breast Centers. After diagnosis of 1-2 macrometastatic sentinel lymph-nodes, patients were randomized in the standard treatment arm (ALND) versus experimental treatment arm (no further axillary surgery)(41). The 3-year survival, regional, and distant relapse rates of patients with T1–2 BC and one or two macrometastatic SLNs treated with BCS, SLNB only, and adjuvant therapy were not inferior to those of patients treated with ALND. These results do not support the use of routine ALND in this category of patients(41). Only 24.8% of enrolled patients were treated with mastectomy, leading to the necessity of further investigations. The enrollment was thus reopened to increase the data and to extend the results to this category of patients.

By the way, a meta-analysis that incorporates data from the subgroup analysis of the randomized controlled trial (SINODAR-ONE)(42), demonstrates that there is no survival advantage for complete ALND over

SLNB in patients with T1–T2 breast cancer and 1–3 positive sentinel lymph nodes (pN1) undergoing mastectomy. This suggests that, following thorough multidisciplinary evaluation, complete ALND can be safely omitted in these patients.

SINODAR-ONE eligibility criteria are resumed in *Table 2.*

Eligibility
Age ≥ 40 and ≤ 75 years
Invasive BC (cytology/core biopsy assessment)
Unilateral lesion
Tumor size ≤ 5 cm (cT1–2) (ultrasound/mammography assessment)
Clinically negative axillary nodes (N0) (ultrasound assessment)
No more than two SLNs proven metastatic (histological assessment)
Involved SLNs with macrometastasis (≥ 2 mm)
No distant metastasis (M0)
No neoadjuvant therapy
No previous invasive BC
Signed and dated written informed consent
Exclusion
Ongoing pregnancy or breast-feeding
Inflammatory BC
In situ BC
Synchronous contralateral BC
Comorbidity possibly preventing adjuvant therapy
Disease, comorbidity, or psychological conditions preventing compliance to regular follow-up
Previous neoplasm within the 3 years preceding randomization (with the exception of in situ carcinoma of the cervix, basalioma, and spinocellular carcinoma of the skin)

Table 2. Eligibility and Exclusion criteria for SINODAR-ONE trial(41)

3. RATIONALE AND AIMS

Although post-ALND complications are often minor, in some cases they can persist for a long time following surgery, thereby affecting the quality of life of breast cancer survivors(43).

The most disabling side effects of axillary surgery are chronic pain, chronic Axillary Web Syndrome inducing motion impairment and above all upper-limb lymphedema.

Despite accurate surgical technique, there is no evidence that post- ALND complications could be efficaciously spared by adopting technical tips intraoperatively.

Furthermore most of the features that are known to contribute to complications development (namely age, type of tumor resections surgery, cN staging at the time of diagnosis and indication for adjuvant treatments such as radiation therapy or taxane-based chemotherapy), are not-modifiable.

The only consistent results in reducing arm morbidity after axillary surgery are linked to the important difference between SLNB and complete ALND.

In this context, application of surgical de-escalation that is nowadays widely supported and validated can be the key element to bring to a substantial reduction in long-term arm morbidity for breast cancer survivors.

The results of the ACOSOG Z0011 trial brought to deep changing in clinical practice, corroborated by data on 10 years follow-up. The latest versions of NCCN Breast Cancer Guidelines recommend not to proceed to

ALND in patients with 1-2 macrometastatic sentinel lymph nodes that fulfill all the criteria of Z0011 trial enrollment and most professionals working in Breast Units worldwide apply this results in daily practice.

The opening of SINODAR trial (an Italian multicentric randomized trial) brought new attention to surgical de-escalation, with the intent to confirm ACOSOG Z0011 results and to extend them to patients who underwent mastectomy.

Despite the strong evidence given by these trials in favor of ALND omission in selected categories of patients, this practice is still not completely accepted in some Breast Units. The resistance to apply surgical de-escalation may be given in part by the fact that ALND allows for a qualitative and quantitative evaluation of the extent of disease and may aid in the selection for and intensity of adjuvant chemotherapy and radiotherapy. Moreover, the notion of the role of axillary dissection as a staging procedure rather than a therapeutic intervention is not always accepted from Breast Cancer Specialists.

The purpose of our research raised from the aim to establish and efficiently dedicate the resources for a "Lymphedema Program" inside the Breast Unit of University Hospital in Modena, where around 750 patients per year are treated for a new diagnosis of breast cancer. The Breast Oncological Surgery Unit together with Plastic and Reconstructive Surgery Unit and Physical Rehabilitation Unit worked during the years to create a defined and dedicated program for patients who undergo axillary surgery for breast cancer and develop upper-limb complications, such as secondary lymphedema.

Considering the role that Oncological Breast Surgeons have in the lymphedema onset, we realized that application of surgical de-escalation in axillary surgery was not optimal in our Breast Center. Actually we sometimes continue to perform complete Axillary Lymph Node Dissection in patients that could fulfill the eligibility criteria of ACOSOG Z0011 or had all the features to be enrolled in the SINODAR-ONE trial.

The aim of our research was to study the prevalence and features of upper-limb complications in patients who underwent complete axillary lymph node dissection in the Breast Unit of Modena University Hospital and to investigate whether the onset of arm complications (notably arm lymphedema) could be significantly influenced by a correct and thorough adhesion to ACOSOG Z0011 and/or SINODAR criteria.

4. PATIENTS AND METHODS

Study population and Clinical Data

We performed a retrospective cross-sectional monocentric study.

All patients who underwent axillary node dissection following breast cancer diagnosis in the years 2019-2022 in the Breast Unit of Modena University Hospital were enrolled. Patients who underwent axillary dissection for local recurrence of a previous breast cancer were excluded.

All clinical data were extracted from patients computerized medical records and institutional programs and stored in a prepared database. After data collection the records were anonymized and a numeric ID was assigned to each record.

For each patient, the following information was collected:

- Date of birth
- Age at the time of Axillary Lymph Nodes Dissection
- Tumor Side (right/left)
- Primary tumor quadrant location (upper-outer, lower-outer, lower-inner, upper-inner, central, multicentric)
- cT staging after core-biopsy at the time of diagnosis measured with ultrasound or x-ray mammogram (cT1, cT2, cT3, cT4, cTis)(44)
- cN staging at the time of diagnosis (cN0, cN1, cN2, cN3)(44)
- Distant metastases at the time of diagnosis (present/absent)
- Tumor histotype on core-biopsy (ductal carcinoma/lobular carcinoma/others)

- Tumor grading on core-biopsy (g1-low, g2-moderate, g3-high)
- Estrogen Receptors Status on core-biopsy (positive/negative and percentage of expression)
- Progesteron Receptors Status on core-biopsy (positive/negative and percentage of expression)
- Ki67 (%) on core-biopsy
- HER2 Status on core-biopsy (negative for 0, 1+ or 2+ with non-amplified FISH and positive for 2+ with amplified FISH or 3+)
- Lymphovascular Invasion either on core-biopsy or on final histology (present/absent)
- Neoadjuvant treatments, both hormonal treatments and chemotherapy (performed/not performed)

Data regarding surgical intervention were also collected, notably:

- Sentinel Lymph Node Biopsy before Axillary Lymph Node Dissection (performed/not performed) and date of surgery
- Surgical timing of Sentinel Node Biopsy when performed (during main first surgical procedure/during second surgical procedure/during third or subsequent surgical procedures)
- Number of excised Sentinel Lymph Nodes when SLNB performed
- pN (SLN) staging according to Sentinel Lymph Node Biopsy when performed (44)
- Surgical timing of Axillary Lymph Node Dissection (during main first surgical procedure/during second surgical procedure/during third or subsequent surgical procedures) and date of surgery

- pN staging according to complete Axillary Lymph Node Dissection(44)
- Number of excised lymph nodes during ALND
- Number of macrometastatic Non Sentinel Lymph Nodes (NSLN)
- Type of primary tumor surgery (lumpectomy or quadrantectomy/mastectomy without reconstruction/mastectomy with reconstruction) and date of surgery

Study Evaluation Criteria

Each ID record was then checked to verify if all the criteria of ACOSOG Z0011 trial were retrospectively present and each ID record was classified in two categories: ALND not recommended/ALND recommended according to Z001.

The same procedure was conducted for SINODAR eligibility and exclusion criteria and each ID record was classified in two categories: possible/not possible enrollement in the SINODAR trial.

We also considered the concomitant presence of the two studies by defining two categories: possible/not possible enrollement in at least one of the two studies.

For each patient the presence/absence of post-ALND upper-limb complications was recorded. In particular we considered:

- Chronic pain (persisting after 1 year from surgery or requesting stable treatment with analgesic drugs)
- Chronic Axillary Web Syndrome (conditioning reduced range of motion and persisting after more than 5 physical therapy sessions)

- Lymphedema of any grade

Statistical Analysis

Descriptive statistical reports were generated to summarize the patient cohort, tumor characteristics and surgical data. Nominal and categorical variables were reported as frequencies and proportions; continuous variables were reported as means, standard deviations and range when appropriate.

Cross-tabulation was employed to examine the relationships between variables. Chi-square analysis (for nominal, ordinal categories) or Welch's *t*-Test (for continuous categories) were used to compare groups. A p-value of ≤ 0.005 was considered statistically significant.

Ethical Statements

Data were collected anonymously and for the retrospective nature of the study, the analysis did not affect the standard type of treatment proposed to patients.

5. RESULTS

Overall, 366 patients underwent Axillary Lymph Node Dissection in the Breast Unit of University Hospital in Modena between January 2019 and December 2022 and were enrolled.

Sample characteristics are summarized in *Table 3.*

Mean age of the sample was 58.5 (SD±13.0) years, range between 30-89.

In 177 patients (48,4%) the primary tumor was on the right side, in the remaining 189 patients (51,6%) it was on the left side.

Primary tumor quadrant location was distributed as follows: 183 patients upper-outer quadrant (50,0%); 67 patients lower-outer quadrant (18,3%); 32 patients lower-inner quadrant (8,7%); 32 patients upper-inner quadrant (8,7%); 30 patients central quadrant (8,2%) and 22 patients ha a multicentric distribution of the primary tumor (6,0%).

The majority of patients had tumor stage cT1 (40,4%) or cT2 (45,9%) at the time of diagnosis. Only 6,3% had cT3 primary tumor and 6,8% underwent axillary lymph node dissection for cT4 diagnosis. We recorded only one patient who underwent axillary dissections for a primary in situ tumor and one patient who underwent axillary dissection with an unknown primary carcinoma.

Nodal status at the time of diagnosis was negative (cN0) in most patients (52,2%). 147 patient had cN1 status (40,2%) and only a minority of the population presented with worse axillary involvement (cN2 in 6,3% and cN3 in 1,4% of the sample).

Only 3 patients had distant metastasis at the time of diagnosis (0,8%). The remaining 363 patients were M0.

The histotype of primary tumor was ductal in 81,2% of patients, lobular in 16,1% and we recorded different histotypes only in 2,7% of the entire sample.

The vast majority of patient had a moderate grade-g2 tumor (69,4%), 27% had high grade-g3 tumor and 2,5% had low grade-g1 carcinoma. Data on grading were not available in 4 patients.

Estrogen Receptor Status was positive in 297 patients (81,1%) and negative in 69 patients (18,9%). Progesterone Receptor Status was positive in 259 patients (70,8%) and negative in 107 patients (29,2%).

The average value of Ki67 was 25 (SD±18).

In the majority of patients HER2 status was negative (80,9%) while only in 70 patients (19,1%) it was positive.

Thus, tumor biological profiles were distributed as follows: most patients (247) had an ER-positive/HER2-negative tumor (67,5%), 70 patients (19,1%) had a HER2-positive carcinoma and only 49 patients (13,4%) presented with triple negative breast cancer.

Lymphovascular invasion was a missing data in 23,2% of cases. It was detected either on the core-biopsy or at the final histology in 31,4% of patients while it was negative in the remaining 45,4%.

As regards neoadjuvant treatments, we considered both hormonal and chemotherapy. 149 patients (40,7%) underwent some kind of neoadjuvant therapies while 217 (59,3%) did not.

SAMPLE CHARACTERISTICS (n=366)			
	Average	***St.Dev.***	***Range***

Age	58,5	13,0	30-89
		n	***n (%)***
Side	Right	177	48,4%
	Left	189	51,6%
		n	***n (%)***
Tumor quadrant	UOQ	183	50,0%
	LOQ	67	18,3%
	LIQ	32	8,7%
	UIQ	32	8,7%
	Central	30	8,2%
	Multicentric	22	6,0%
		n	***n (%)***
cT	1	148	40,4%
	2	168	45,9%
	3	23	6,3%
	4	25	6,8%
	IS	1	0,3%
	X	1	0,3%
		n	***n (%)***
cN	0	191	52,2%
	1	147	40,2%
	2	23	6,3%
	3	5	1,4%
		n	***n (%)***
Distant Metastasis	Absent	363	99,2%
	Present	3	0,8%
		n	***n (%)***
Type	Ductal	297	81,2%
	Lobular	59	16,1%

	Other	10	2,7%
		n	***n (%)***
Grading	Low (g1)	9	2,5%
	Moderate (g2)	254	69,4%
	High (g3)	99	27,0%
	NA	4	1,1%
		n	***n (%)***
ER	Negative	69	18,9%
	Positive	297	81,1%
		n	***n (%)***
PgR	Negative	107	29,2%
	Positive	259	70,8%
	Average	***St.Dev.***	
Ki67 (%)	25	18	
		n	***n (%)***
HER2	Negative	296	80,9%
	Positive	70	19,1%
		n	***n (%)***
	TRIPLE NEGATIVE	49	13,4%
	ESTROGEN RECEPTOR POSITIVE/HER2-NEGATIVE	247	67,5%
	HER2-POSITIVE	70	19,1%
		n	***n (%)***
Lypmhovascular invasion	Absent	166	45,4%
	Present	115	31,4%
	NA	85	23,2%
		n	***n (%)***
Neoadjuvant treatments	Not performed	217	59,3%

	Performed	149	40,7%

Table 3. Sample characteristics – descriptive analysis

Records concerning surgical procedures are displayed in *Table 4.*

Among the 366 patients enrolled, 198 (54,1%) underwent sentinel lymph node biopsy prior to axillary node dissection. The remaining 168 patients (45,9%) underwent direct axillary lymph node dissection.

Of the 198 patients that underwent SLNB, the vast majority (99%) did it during the first surgical intervention. The average number of excised SLN was 1,8 (SD±0,8). 193 patients had positive sentinel lymph nodes while 5 patients underwent subsequent ALND despite a negative sentinel lymph node biopsy.

Most of the ALND procedures were performed during the first surgical intervention (86,3%), while only 13,7% of patients was treated with a second or subsequent surgical procedure. pN staging after ALND was distributed as follows: 13,9% of patients were pN0, 60,4% were pN1, 19,1% were pN2 and 6,6% were pN3. An average number of 16,2 lymph nodes were removed (SD±7,2) with an average number of 2,5 (SD±4) macrometastatic Non Sentinel Lymph Nodes.

As regards the type of primary tumor surgery, 51,9% of patients underwent conservative procedures (lumpectomy/quadrantectomy), while the remaining patients were treated with mastectomy. Among them, 28,1% received reconstructive surgery.

SURGICAL DATA			
		n	***n (%)***
Sentinel Lymph Node Biopsy (SLNB) (n=366)	Not performed	168	45,9%
	Performed	198	54,1%
		n	***n (%)***
Surgical Timing of SLNB (n=198)	First Surgery	196	99,0%
	Second Surgery	2	1,0%
	Average	***St.Dev.***	
Excised SLN (n=198)	1,8	0,8	
		n	***n (%)***
pN (SLN) (n=198)	0	5	2,5%
	1	193	97,5%
		n	***n (%)***
Surgical Timing of ALND (n=366)	First Surgery	316	86,3%
	Second Surgery	49	13,4%
	Other	1	0,3%
		n	***n (%)***
pN (ALND) (n=366)	0	51	13,9%
	1	221	60,4%
	2	70	19,1%
	3	24	6,6%
	Average	***St.Dev.***	***Range***
Excised lymph nodes during ALND (n=366)	16,2	7,2	0-49

		Average	*St.Dev.*	*Range*
Macrometastatic NSLN (n=366)		2,5	4,0	0-24
			n	***n (%)***
Type of primary tumor surgery (n=366)	Lumpectomy/Quadrantectomy		190	51,9%
	Mastectomy without reconstruction		73	19,9%
	Mastectomy with reconstruction		103	28,1%

Table 4. Surgical Data

The presence of upper-limb complications, notably arm lymphedema of any grade, chronic pain and chronic axillary web syndrome, was searched in the entire sample. Complications were described in 102 patients (27,9%) and were represented as follows: 3 patients developed chronic pain (2,9%); 18 patients developed chronic axillary web syndrome (17,6%) and 81 patients developed arm lymphedema (79,4%). Results are pointed out in *Table 5.*

UPPER LIMB COMPLICATIONS (n=366)		
	n	***n (%)***
Absent	264	72,1%
	n	***n (%)***
Present	102	27,9%
CHRONIC PAIN	3	2,9%
AWS	18	17,6%
LYMPHEDEMA	81	79,4%

Table 5. Upper-limb complications

Patient, tumor and surgical characteristics were taken into account to explore the possible role on upper-limb complications in the entire sample.

Tumor side, affected quadrant and cT did not show any significant association. Neither nodal status at the time of diagnosis (cN) did. We considered all cN stages and we also divided patients in node-negative (cN0) and node-positive (all positive cN stages) but p-values did not show any assocication with complications onset in both configurations. Likewise, no statistically significant correlation was found for tumor grading, Ki67 levels, lymphovascular invasion and neoadjuvant treatments.

We mention two features that resulted close to statistical significance and in particular age *(p-value=0.08)* and tumor biological profile *(p-value=0.08)* with a trend of less complications in HER2-positive patients.

As regards for surgical aspects (Table 4), pN status after ALND *(p=0.002)* and the total number of excised lymph nodes *(p=0.02)* showed a significant association with the development of arm impairment. No statistically significant correlation was observed for other surgical variables.

Considering the study evaluation criteria retrospectively analyzed, 83/366 (22,7%) patients fulfilled the ACOSOG Z0011 criteria to avoid ALND. On the contrary, 283/366 (77,3%) patients were confirmed eligible for ALND to a retrospective evaluation.

Taking SINODAR trial into account, 100/366 patients (27,3%) could have been enrolled and randomized to standard treatment (ALND) or experimental treatment (ALND omission). The remaining 266 patients (72,7%) had at least one exclusion criteria and resulted retrospectively not eligible. If considering possible inclusion in at least one trial, 114/366 patients resulted suitable (31,1%) while 252 were not (68,9%).

We then applied the enrollment criteria to the population of patients that developed an upper-limb complication.

We used these proportions to hypothesize an ideal condition of axillary surgical de-escalation. We considered three different scenarios:

1. First scenario: optimal adhesion to ACOSOG Z0011 criteria *(*as shown in *Table 6).* Out of the 102 patients that developed upper limb complications, 24 resulted eligible for ALND omission. The ideal cohort would thus be represented by 78 patients who developed upper-limb complications (21,3%) and 288 patients who did not (78,7%). The difference between the two cohorts resulted statistically significant *(p=0,04).*

	STUDY COHORT n=366		***IDEAL COHORT IN CASE OF OPTIMAL DE-ESCALATION (ONLY ACOSOG Z0011) n=366***
UPPER-LIMB COMPLICATION	n=102 (27,9%)	Eligible for ALND omission n=24 Not eligible for ALND omission n=78	n=78 (21,3%)
NO UPPER-LIMB COMPLICATION	n=264 (72,1%)		n=288 (78,7%)

Table 6. Difference between the real cohort and the ideal cohort in case of optimal application of ACOSOG Z0011 criteria

2. Second scenario: optimal enrollment in the SINODAR trial (as shown in *Table 7*). Out of the 102 patients that developed upper limb complications, 32 patients fulfilled the criteria to be included in the SINODAR trial. We hypothesized an ideal randomization of 50% of patient in the standard arm (ALND) and 50% in the experimental arm (ALND omission). The ideal cohort would thus be represented by 86 patients with arm impairment (23,5%) and 280 patients without (76,5%). The difference between the two cohorts did not show any statistical significance *(p=0,18).*

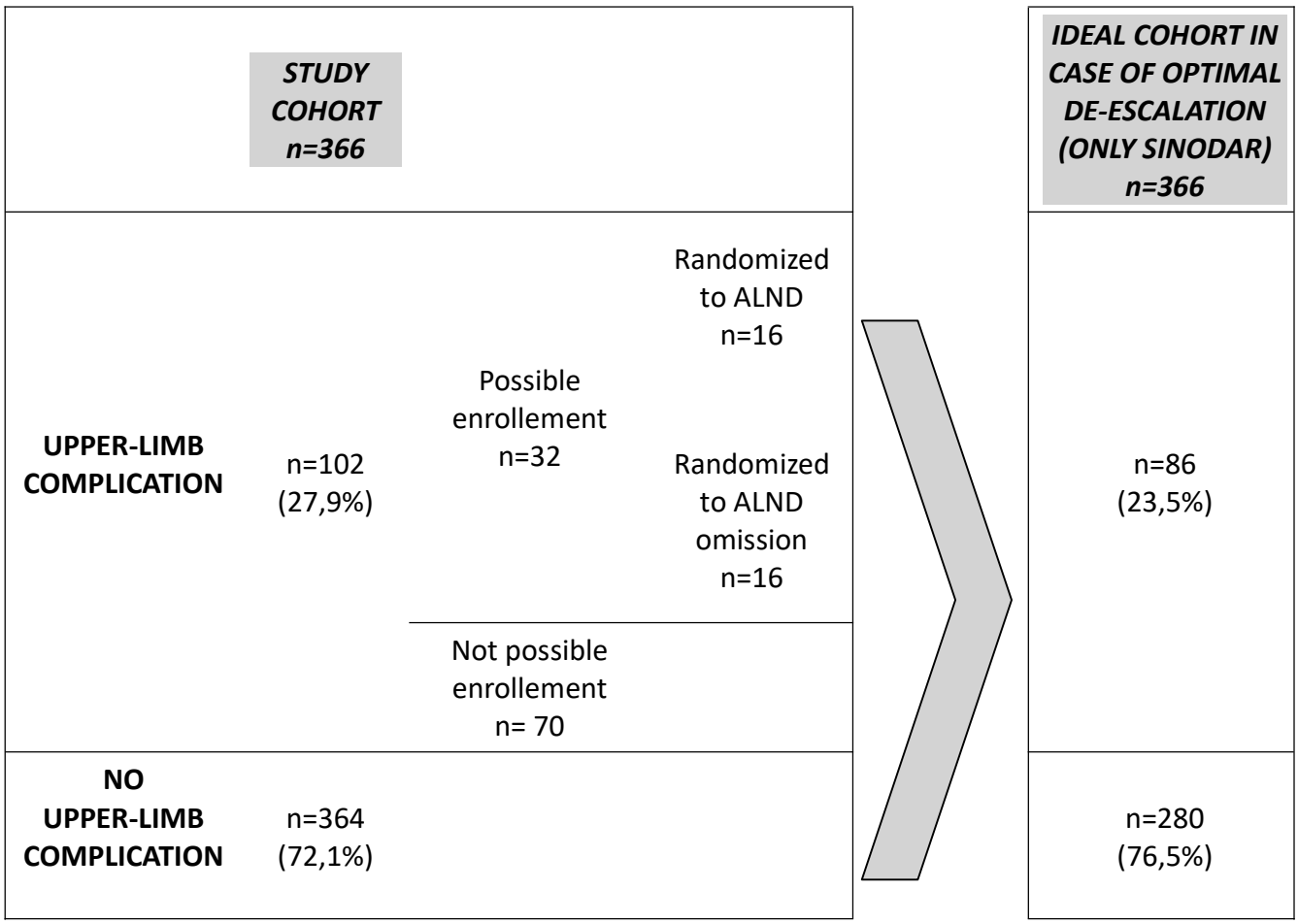

Table 7. Difference between the real cohort and the ideal cohort in case of optimal enrollment in the SINODAR-ONE trial

3. Third scenario: optimal de-escalation of axillary surgery taken into account the simultaneous application of both trials (ACOSOG Z0011 criteria for ALND omission and SINODAR trial enrollment) (as displayed in *Table 8)*. Since the two studies slightly differ in some of the eligibility criteria, we considered the possible inclusion in at least one of the two studies. Of the 102 patients that developed upper-limb complications, 4 patients resulted eligible to ALND omission for ACOSOG Z0011 criteria, 12 patients fulfilled only the SINODAR-ONE inclusion criteria (as in the previous scenario we hypothesized an ideal randomization 50% for ALND and 50% for ALND omission) and 20 patients coverd both trials conditions. The ideal cohort in case of optimal de-escalation would thus

be represented by 72 patients with complications (19,7%) and 294 patients who did not develop any arm impairment (80,3%). The difference between the two cohorts (actual sample and ideal sample) resulted significant *(p=0,009)*.

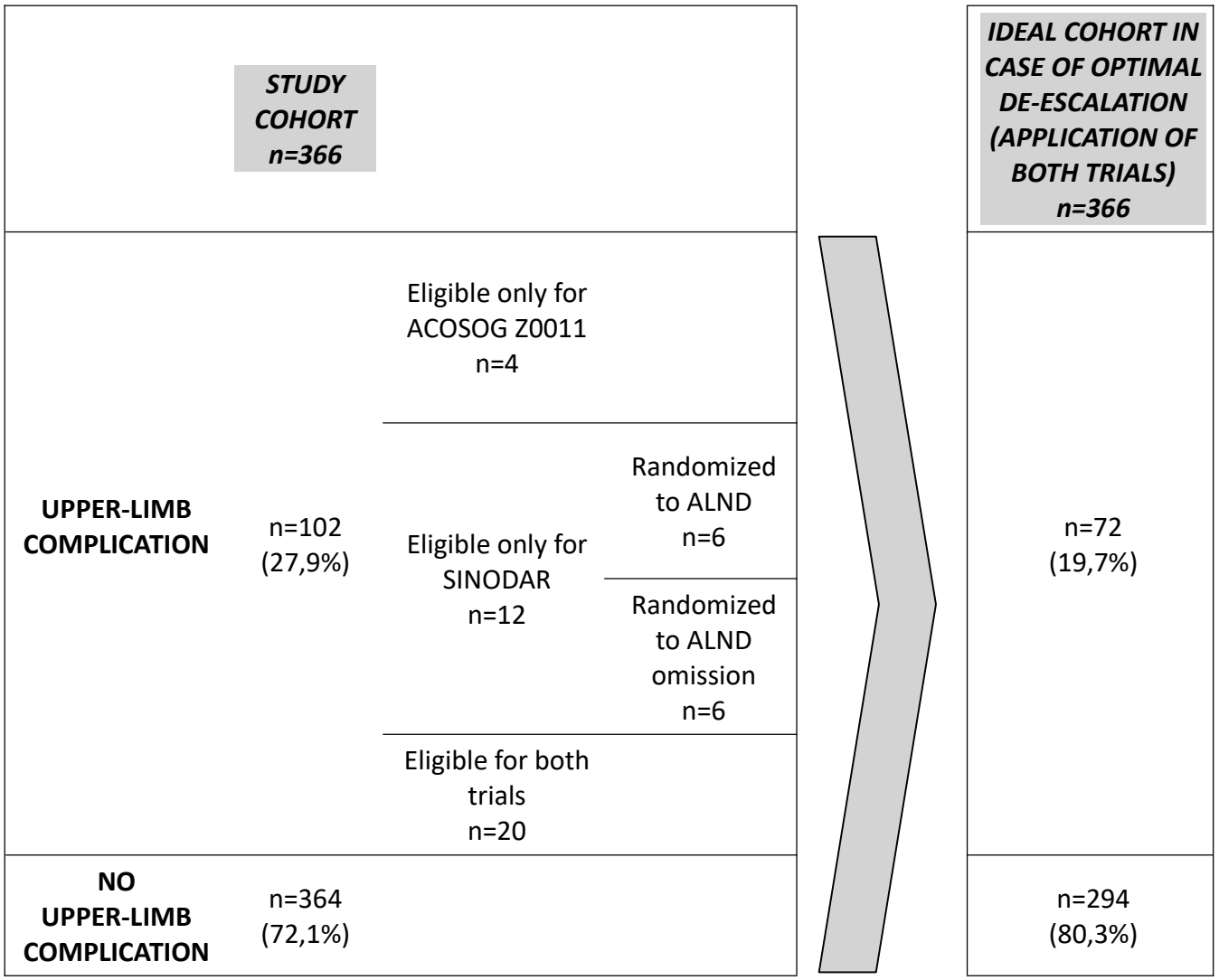

Table 8. Difference between the real cohort and the ideal cohort in case of optimal de-escalation (application of both ACOSOG Z0011 and SINODAR trial

Finally, we verified if the inclusion in either Z0011 or SINODAR-ONE criteria, could led to a significant reduction of a second surgical procedure in patients who underwent complete Axillary Lymph Node Dissection

after Sentinel Lymph Node Biopsy. The difference did not result significant neither for the two trials separately applied nor for the two trials together.

5. DISCUSSION

Breast cancer represents the most common cancer among women worldwide. In the last decades progress in prevention, diagnosis and treatment of BC was massive. This translates to many more breast cancer survivors experiencing long-term adverse consequences of therapy. Axillary surgery remains a milestone in Breast Cancer treatment and axillary lymph nodes status is the most important factor in defining OS and DFS (39). Post-surgical complications of axillary surgery (above all Breast Cancer Related Lymphedema) are often mild and can be mitigated with rehabilitation but when conservative treatment fails, women experience functional discomfort and a dramatic worsening in quality of life. A recent systematic review(45) confirmed that ALND patients were observed to have higher rates of lymphedema, pain, reduced strength and ROM compared with SLNB.

Koelmeyer et al.(46) analyzed the risk factors related to breast cancer-related lymphedema and observed that the percentage of patients who had ALND was significantly lower in the group of patients who did not develop lymphedema. A meta-analysis on the incidence of unilateral arm-lymphedema confirmed the results(34). This is an additional proof of correlation between the type of axillary surgery and the development of complications. Other factors such as type of primary tumor surgery or age did not show a statistically significant association, as it was in our sample. In addition, our results show that upper-limb complications are significantly associated with pN status on final histology after ALND and with the total number of retrieved lymph nodes. This trend confirms the

findings of previous research (34)(47) and contributes to outline the features of patients that underwent ALND and have a higher risk of developing long-term arm complications. We believe that this knowledge can lead to an early detection and treatment of the complications immediately after the onset, thus ameliorating the post-surgical experience of patients with breast cancer.

As regards the frequency of lymphedema, various results are reported in literature, ranging from around 13%(48)(40) up to 40%(33)(34) depending on which grade is considered and on the duration of follow-up. *Koelmeyer et al.*(46) stratify the grade of upper-limb swelling in sublinical (19,5% of patients), progressed to chronic lymphedema despite conservative intervention (3,2%) and chronic lymphedema without conservative intervention (4,2%), with a cumulative percentage of 26,9%. This data is consistent with our sample, since 27,9% of our patients developed an upper-limb impairment considering lymphedema of any grade, chronic pain and chronic axillary web syndrome together.

Axillary de-escalation is driven by both a desire to minimize injury and a growing awarness of oncological safety of axillary conservation(49).

Following the publication of ACOSOG Z0011 trial results in 2011, some teams (mainly in the Unites States), quickly changed their clinical practices and decided to no longer perform complete ALND in patients who fulfilled the Z0011 criteria(50). On the other hand, the same results were received with some more reluctance from some other centers, especially in Europe(51) and Eastern countries(52). *Pop et al.*(51)

performed a retrospective study in patients treated from 2102 to 2015 to evaluate the possible modifications in the surgical attitude of the axilla by retrospective application of the ACOSOG Z0011 trial criteria. They conclude that 40,2% of the patients in their cohort could have been spared more aggressive axillary surgery (ALND) if the patient selection criteria of the ACOSOG Z0011 study were applied. *Peng et al.*(52) applied the ACOSOG Z0011 criteria to a Chinese population and concluded that ALND could be avoided in a large majority of patients with positive SLNs (73,25%). Instead, our data show that only 22,7% of the entire sample (83/366 patients in the years 2019-2022) could have been spared ALND with optimal application of Z0011 criteria. This suggests that attention to de-escalation indications is raising and improving during the years in European Breast Centers like ours and that, even if the application of de-escalation is not already at its best, our cohort is aligned with other European Centers.

By observing patients who underwent Breast Surgery in our Breast Unit in Modena and developed upper-limb complications, we worked to find a possible role for Oncological Breast Surgeons in reducing the risk and improving daily practice. We observed that some patients were treated with axillary node dissection even if they could avoid it according to ACOSOG Z001 criteria or they could be enrolled and randomized in the SINODAR trial (opening a possibility to avoid ALND also for patients that are candidate to mastectomy).

Since the validity of ACOSOG Z0011 and SINODAR trials concerning OS, DFS and recurrence rate has been widely explored and confirmed in

literature, taking into account all the collateral indirect implications that this trials have in various clinical fields, may be a source of new knowledge.

On this basis, collateral advantages derived from an optimal application of ACOSOG Z0011 criteria are highlighted by *Nguyen et al.*(53)*:* a retrospective evaluation of nearly 14000 patients with ACOSOG Z0011 criteria from 179 German breast cancer units, showed that the implementation of ACOSOG Z0011, resulted in gain of 335 quality-adjusted life-years and substantial cost savings for the society (1924 EUR per patient).

Instead, our research focused on the impact that ACOSOG Z0011 and SINODAR-ONE trial might have on upper-limb complications and notably arm-lymphedema. While a great amount of literature production retrospectively applied the ACOSOG Z0011 criteria to selected populations to assess validity and clinical impact, the SINODAR-ONE trial is more recent and, to our knowledge, our study is the first to explore the potential impacts that an optimal enrollment in SINODAR-ONE trial could have retrospectively produced. We showed how an ideal application of ACOSOG Z0011 criteria for ALND omission and a precise enrollment in SINODAR-ONE trial, could have significantly reduced the onset of upper-limb complications in our sample. We analyzed actual condition of the population of patients who underwent axillary lymph node dissection in the years 2019-2022 and then we focused on patients who developed upper-limb complications. Among them we hypothesized to retrospectively apply ACOSOG Z0011 criteria and/or enroll them in

SINODAR-ONE trial if feasible. Thus, we outlined an ideal cohort of patients that reflects the optimal application of axillary de-escalation. Significant difference in arm complications presence, was found in the scenario of ideal application of ACOSOG Z0011 trial (p=0,04) and in the scenario of ideal application of both studies together (p=0,009). The impact of SINODAR-ONE trial alone did not result statistically significant (p=0,18), probably because we considered a randomization of 50% of patients to standard arm (ALND). Overall, the comparison of the two groups (real cohort and ideal cohort), showed a statistically significant inferior risk of developing arm complications in case of optimal de-escalation.

As regards the limitations of our analysis, we assumed that patients who did not undergo ALND did not develop any upper-limb complication. Actually, some complications are described also after SLNB, even if they lead to fewer side effects than ALND. Some Authors calculate an overall complication rate of 3% after SLNB compared to 35% after ALND (15)(54). Nevertheless, we must say that it is the type and duration of complications that is deeply different between the two groups. In fact, *Giuliano at al*.(54) describe the post-surgical conditions of a cohort of patients treated with SLNB, in which only short-term wound complications, cellulitis and seroma were experienced. No patients undergoing SLNB without ALND, experienced numbness or paresthesia of skin over the intercostobrachial nerve distribution and chronic lymphedema, the most debilitating sequela of ALND, has not been observed after SLNB alone and is unlikely to occur in such patients(54).

Likewise another limitation of our research is that when we analyzed the SINODAR-ONE trial potential enrollement, we assumed that 50% of patients were allocated in the standard treatment arm (ALND) and the other 50% of patients in the experimental treatment arm (ALND omission). Actually the exact ideal 50/50 proportion in randomized trial is hardly reached even with much more numerous samples.

In our opinion, two aspects of the impact of surgical de-escalation must be further explored. First, the comprehensive study of population, surgery, radiation therapy and adjuvant treatments risk factors for the development of chronic pain, AWS and BCRL should be extended in order to better define which patients have a higher risk. This might lead to better tailored treatments with early taking charge and rehabilitation. Second, our research group believes that all the collateral implications of surgical de-escalation should be explored, not only to confirm its oncological safety but also to ameliorate the awareness on multiple aspects (Quality of Life, Socioeconomic Benefits, better allocation of public resources, psychological impact) that can have a role in life of breast cancer patients.

6. CONCLUSIONS

This research raised inside a multidisciplinary group, from the necessity to contribute to the creation of a "Lymphedema Program" in the Breast Unit of University Hospital in Modena for Breast Cancer Patients who undergo axillary nodes surgery. It is well-known that conservative treatments and physical therapy have a crucial role in the management of patients who develop upper-limb complications (i.e. Chronic Pain, Chronic Axillary Web Syndrome and Breast Cancer-related Lymphedema). Where rehabilitation fails, modern microsurgical procedures can contribute to mitigate the symptoms for selected patients.

The potential role of Oncological Breast Surgeon in upper-limb complications was explored through this study.

Robust results on safety and feasibility of surgical de-escalation (ALND omission in patients with macrometastatic SLNB) were produced in literature and well outlined which patients could be candidate for ALND omission. Notably, ACOSOG Z011 study and the Italian SINODAR-ONE trial stood out as milestones in clinical practice changing for axillary surgery.

Nonetheless, the application of the criteria of de-escalation is not always optimal and might be improved. We hypothesized that this may play a significant role in upper-limb complications onset (in particular arm lymphedema).

In this study we showed how a better and optimal adhesion to surgical de-escalation criteria may reduce the onset of upper-limb complications in patients that undergo breast surgery for cancer.

Previous studies confirmed and validated the results of ACOSOG Z011 and SINODAR-ONE trials in terms of OS, DFS and recurrence-rate, but our study directly highlights how surgical de-escalation have a direct impact on upper-limb complications reduction, in particular concerning breast cancer-related lymphedema.

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ABBREVIATIONS

ALND: Axillary Lypmh Node Dissection

AWS: Axillary Web Syndrome

BC: Breast Cancer

BCRL: Breast Cancer Related Lymphedema

BCS: Breast Conserving Surgery

CLG: Cheng's Lymphedema Grading

DFS: Disease-free Survival

ER: Estrogen Receptors

FNAC: Fine Needle Aspiration Citology

ICG: Indocyanine Green

NSLN: Non Sentinel Lymph Nodes

OS: Overall Survival

PGR: Progesterone Receptors

PPSP: Persistent Post-Surgical Pain

QoL: Quality of life

ROM: Range of Motion

SLN: Sentinel Lymph Node

SLNB: Sentinel Lymph Node Biopsy

WBRT: Whole Breast Radiation Therapy

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