THE PROGNOSIS AND PREDICTION OF BREAST CANCER: OPPORTUNITIES FOR IMPROVEMENT

DROZGYIK ANDRÁS DR

Thesis of Ph.D. dissertation

University of Pécs
Medical School

2024

Consultant
Prof. Dr. Molnár, F. Tamás
Department of Operational Medicine

University of Pécs Medical School – Clinical Medical Sciences Doctoral School (D94)
Leader of the Doctoral School: Dr. Bogár, Lajos
B-2/2013 Acute and chronic injuries of parenchymal organs and the consequences: diagnostics and therapy

Program leader: Prof. Dr. Molnár, F. Tamás 2022-2023, Dr. habil. Szántó, Zalán (2023-)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS 3

1. INTRODUCTION 4
2. AIMS 4
3. BACKGROUND 5
4. CHALLENGES IN LOCALIZING NON-PALPABLE BREAST CANCER – A COMPARISON OF ROLL AND WIRE-GUIDED LOCALIZATION TECHNIQUES 6
5. NEW APPROACH TO BREAST SPECIMEN ORIENTATION: THE SPECIMEN PLATE CONCEPT 11
6. MALIGNANT PLEURAL EFFUSION ASSOCIATED WITH ADVANCED BREAST CANCER 14
7. FINDINGS 16
8. LIST OF PUBLICATIONS RELATED TO THE DISSERTATION 17
9. OTHER PUBLICATIONS 18

LIST OF ABBREVIATIONS

ALND	Axillary Lymph Node Dissection
ABD	Axillary Block Dissection
BI-RADS:	Breast Imaging Reporting and Data System
BRCA	BReast CAncer gene
CRP	C-Reactive Protein
CT	Computed Tomography
DIEP:	Deep Inferior Epigastric Perforators (flap)
ER	Estrogen Receptor
HER2:	Human Epidermal Growth Factor Receptor 2
HITHOC	Hyperthermic Intrathoracic Chemotherapy
ILC	Invasive Lobular Carcinoma
NST	No Special Type
PR	Progesterone Receptor
ROLL:	Radio-guided Occult Lesion Localization
SLN	Sentinel Lymph Node
SLNB	Sentinel Lymph Node Biopsy
TNM:	Tumor Node Metastasis
TRAM:	Transverse Rectus Abdominis Myocutaneous (flap)
US	Ultrasound
VAS	Visual Analogue Scale
WGL	Wire-guided Localization

1. INTRODUCTION

Breast cancer accounts for 11.7% of all malignancies and became the most commonly diagnosed cancer by 2020, with 2.3 million new cases globally. Although its incidence has risen, mortality rates have decreased, with five-year survival reaching up to 90%. The history of breast cancer treatment spans from mastectomy to advancements in tumor biology, radiology, and pharmacology. In the 20th century, surgical practices became more radical, transitioning to minimally invasive techniques by the millennium, with the adoption of a comprehensive oncological approach.

Advances in imaging, pathology, and immunohistology have transformed breast cancer management. The frequency of non-palpable tumors has risen due to screening and neoadjuvant therapies, posing challenges for preoperative localization. Wire-guided localization (WGL), introduced in the 1960s, was the standard for decades, but issues like wire displacement led to the development of radio-guided occult lesion localization (ROLL). Comparative studies confirm the effectiveness of both, but optimal indications remain unclear.

Accurate pathological diagnosis in breast cancer surgery requires proper orientation of the resected specimen. In Hungary, localization techniques vary, and while the Breast Cancer Consensus Conferences have formalized protocols, further improvement is needed.

This dissertation addresses three topics: the localization of non-palpable tumors, specimen orientation errors, and malignant pleural effusion in advanced breast cancer. Our goal is to enhance diagnostic accuracy, surgical efficiency, and patient quality of life through novel methodologies.

2. AIMS

In this doctoral dissertation, I sought to address the following questions:

1. Which clinical and surgical conditions make one localization technique (ROLL or WGL) preferable over the other in the management of non-palpable breast cancers, and under what circumstances is each technique recommended?

2. How does the peritumoral isotope injection in ROLL compare to the peri-areolar isotope injection used in wire-guided localization (WGL) in terms of effectiveness for axillary sentinel lymph node marking, considering tumor location, breast size, and density?

3. What potential errors are associated with tumor orientation techniques used during intraoperative specimen mammography and pathological evaluation of non-palpable breast cancers??

4. What methodologies or techniques can enhance the accuracy and clarity of breast specimen orientation to improve surgical and diagnostic precision and ensure patient safety?

5. What prognostic significance does malignant pleural effusion associated with advanced breast cancer hold?

3. BACKGROUND

The evolution of breast cancer diagnosis and treatment from ancient Egypt to the present has been complex. Surgical treatment, the only potential cure, was historically limited to mastectomies. Progress during the Renaissance focused on anatomical descriptions. With anesthesia and asepsis, surgery dominated until the mid-20th century, becoming increasingly radical. Radiotherapy, initially standalone, later became integral to neoadjuvant and adjuvant therapies. Understanding breast cancer pathology and the role of adjuvant radiotherapy transformed surgical practices, reducing the need for extensive procedures. Today, minimally invasive techniques emphasize precision, aesthetics, and reconstruction as part of multimodal care by oncology teams.

Technological advancements enable earlier detection of non-palpable tumors, increasing the need for precise localization. Techniques like wire-guided localization (WGL) by Kopans and DeLuca and radio-guided occult lesion localization (ROLL) by Zurrida are essential for successful removal. Emerging methods, including magnetic, radar, and radiofrequency technologies, continue to improve surgical outcomes.

4. CHALLENGES IN LOCALIZING NON-PALPABLE BREAST CANCER – A COMPARISON OF ROLL AND WIRE-GUIDED LOCALIZATION TECHNIQUES

4.1 INTRODUCTION

Breast cancer screening and neoadjuvant therapies have increased the number of early-stage or clinically regressed tumors undergoing surgery. Accurate preoperative localization is essential for the safe excision of non-palpable lesions.

Wire-guided localization (WGL) is a standard method but has limitations, including technical challenges with wire placement and excessive removal of healthy tissue. It is primarily used when sentinel lymph node (SLN) marking is unnecessary or alternative techniques are unavailable. The ROLL technique, introduced in 1998, uses radioactive colloids for simultaneous tumor and SLN marking, reducing excised tissue volume and improving cosmetic outcomes. There is no significant difference between ROLL and WGL in localization success.

A randomized prospective comparison of these techniques has not yet been conducted.

4.2 AIMS

- The primary objective was to compare the effectiveness of the ROLL and WGL techniques in the isotopic marking of axillary sentinel lymph nodes.
- The secondary objective was to evaluate the accuracy, efficiency, and ergonomics of the radiological and pathological outcomes of the ROLL and WGL techniques. Additionally, patient-reported pain levels were assessed through questionnaires, along with the preferences of surgeons and radiologists.

4.3 PATIENTS AND METHODS

4.3.1 Study Design and Patient Selection

A single-center, prospective, randomized, comparative study was conducted at the Petz Aladár University Teaching Hospital in Győr, Hungary, a high-volume breast oncology center. The study enrolled 110 women aged 36 to 80 years with non-palpable breast lesions. Participants were randomly assigned to either the ROLL group (n=56) or the WGL group (n=54) using a random number generator. No significant differences were observed between the two groups regarding age or BMI distribution.

4.3.2 Proportion of Neoadjuvant Therapy Among Study Participants

In the ROLL group, 43 patients (77%) and in the WGL group, 44 patients (79%) were diagnosed with non-palpable tumors due to early detection through breast cancer screening. Complete clinical regression following neoadjuvant therapy was observed in 13 patients (23%) in the ROLL group and 10 patients (18%) in the WGL group. There was no significant difference between the two groups in terms of the rates of screening-detected tumors or neoadjuvant therapy ($p=0.5449$).

4.3.3 Breast Sizes, Types, and Tumor Locations

Breast size and type were categorized as small (A), medium (B, C), and large (D or larger), and tissue types were classified as glandular, fatty involution, retro-mammillary fibrosis, adenotic, and fibrotic. Tumor locations were determined based on anatomical reference points (nipple, skin surface, pectoralis fascia) and breast quadrants. The distribution of breast types and tumor locations was similar between the two groups. However, larger breasts were more common in the ROLL group, while medium-sized breasts were more frequently observed in the WGL group.

4.3.4 Localization Techniques and Outcomes

Tumor localization was performed under ultrasound guidance in both the ROLL (93%) and WGL (93%) groups. In four cases (7%), stereotactic guidance was used in both groups. For the ROLL technique, the time between isotope injection and surgery ranged from 16 to 32 hours, whereas in the WGL group, the surgery was performed on the same day.

Radiologists evaluated the duration and difficulty of the localization procedures using a Visual Analog Scale (VAS) ranging from 1 to 5.

4.3.5 Sentinel Lymph Node Marking

All patients underwent dual lymphatic marking: an isotope injection was administered 16–32 hours prior to surgery, followed by the injection of patent blue dye approximately 10 minutes before sentinel lymph node excision.

4.3.6 Evaluation and Statistical Analysis

The ROLL and WGL techniques were evaluated based on feedback from surgeons, radiologists, and patients. Surgeons also documented the duration and difficulty of the localization procedures using questionnaires, with difficulty rated on a VAS from 1 to 5. Following preoperative localization, the primary tumor and axillary sentinel lymph node were removed in all patients. The use of the Specimen Plate system ensured precise orientation for pathological processing. Data on specimen weight and histopathological outcomes, including the success of R0 resections, were systematically recorded.

Statistical analyses were performed using Python tools, with differences between techniques evaluated using the Mann-Whitney test (significance threshold: $p < 0.05$).

4.4 RESULTS

4.4.1 Difficulty of Preoperative Localization – Radiological Evaluation

Radiologists rated the ROLL technique as significantly easier compared to the WGL technique. The mean difficulty score in the ROLL group was 1.75 (±0.96) versus 2.31 (±0.97) in the WGL group, with the difference being statistically significant ($p = 0.00022$).

4.4.2 Duration of Preoperative Localization

The average time required for preoperative tumor localization was significantly shorter in the ROLL group (2.93 ± 3.71 minutes) compared to the WGL group (3.92 ± 3.16 minutes) ($p = 0.001$).

4.4.3 Pain Caused by Preoperative Tumor Localization

Patients reported significantly lower subjective pain scores (VAS scale: 0–10) during localization with the ROLL technique (1.41 ± 1.42) compared to the WGL technique (3.78 ± 2.03) ($p = 0.0000000007$).

4.4.4 Surgical Evaluation of Intraoperative Tumor Localization

Surgeons assessed the difficulty of intraoperative tumor localization using a Visual Analog Scale (VAS) ranging from 0 to 5. The ROLL technique demonstrated a significant advantage, with lower difficulty scores (1.91 ± 0.96) compared to the WGL technique (2.29 ± 1.04; $p = 0.0197$).

4.4.5 Duration of Surgery in Both Groups

There was no significant difference in surgical duration between the two groups (ROLL: 71.05 ± 18.92 minutes; WGL: 69.26 ± 14.51 minutes; $p = 0.9593$).

4.4.6 Comparison of Resected Breast Specimen Weights

The average weight of specimens resected using the ROLL technique was 88.48 g (±45.25), compared to 72.43 g (±33.55) for the WGL technique. While not all statistical tests demonstrated significant differences, the Mann-Whitney test indicated a significant difference ($p = 0.019$).

All 110 patients underwent successful surgeries with precise tumor localization, achieving tumor-free resection margins regardless of whether the ROLL or WGL technique was used. The distribution of tumor sizes was similar between the two groups.

4.5 RESULTS OF AXILLARY SENTINEL LYMPH NODE MARKING

The isotopic sentinel lymph node (SLN) marking failure rates were analyzed across various tumor quadrants for both the ROLL and WGL techniques. Higher failure rates were observed with the ROLL technique, particularly in the lower-inner quadrant (ROLL: 67%, WGL: 14%; $p = 0.0265$) and the upper-inner quadrant (ROLL: 40%, WGL: 10%; $p = 0.0607$).

The WGL technique, with peri-areolar isotope injection, resulted in lower failure rates across various breast quadrants, even in unfavorable anatomical conditions. Statistical analyses revealed significant differences (e.g., $p < 0.05$ in the lower-inner quadrant), consistently favoring the WGL technique.

Confidence intervals and additional statistical evaluations further confirmed that the WGL technique generally provided more stable results for SLN marking. A limitation of the study was the small sample size, which may have impacted the statistical significance of certain differences.

4.5.1 DISCUSSION

The management of non-palpable breast tumors poses significant challenges, particularly in preoperative localization and the identification of axillary sentinel lymph nodes (SLN). While the ROLL technique offers advantages such as simplicity, reduced pain, and better cosmetic outcomes, the WGL technique with peri-areolar isotope injection provides more reliable SLN detection, especially in large breasts or those with fatty involution.

The ROLL technique allows for a faster and simpler procedure, requiring only a single isotope injection for both tumor and axillary lymph node marking, making it a less painful alternative for

patients. However, the WGL technique demonstrated greater accuracy in SLN detection with peri-areolar isotope injection, particularly in tumors rendered non-palpable after neoadjuvant therapy. Furthermore, WGL is recommended for cases with extensive microcalcifications, radial scars, or complex sclerosing lesions, where the use of isotopes may be unnecessary.

The combination of peri-areolar and peritumoral isotope injection, as well as emerging technologies like superparamagnetic iron oxide nanoparticles and indocyanine green, presents promising alternatives for improving SLN identification. These approaches have the potential to reduce radiation exposure and enhance SLN visualization.

4.6 CONCLUSION

Our findings indicate that the ROLL technique offers advantages for patients in terms of comfort and simpler surgical ergonomics. However, the WGL technique, with peri-areolar isotope injection, demonstrated higher efficiency in SLN marking, particularly in cases involving large breasts and tumors located in the inner quadrants. A personalized approach is recommended for the localization of non-palpable breast tumors to achieve optimal outcomes.

4.7 PROPOSED PROTOCOL FOR LOCALIZING NON-PALPABLE BREAST TUMORS

A Based on the effectiveness of the ROLL and WGL techniques, a personalized approach is recommended to ensure successful SLN marking and to avoid unnecessary axillary surgeries.

- **Patient Assessment**: The tumor location, breast size, and density should be evaluated. For tumors located in the inner quadrants, WGL or peri-areolar radiocolloid injection should be prioritized.
- **Preferred Technique**:
  ROLL is the primary choice due to its simplicity and better patient comfort.
  WGL is more effective for tumors in the inner quadrants, particularly following neoadjuvant therapy.
- **Intraoperative Contingency**: In cases of unsuccessful ROLL, blue dye should be utilized, or axillary lymph node dissection should be performed if necessary

5. NEW APPROACH TO BREAST SPECIMEN ORIENTATION: THE SPECIMEN PLATE CONCEPT

5.1 INTRODUCTION

The primary goal of breast-conserving surgery is the complete removal of the tumor with tumor-free resection margins (R0) while achieving satisfactory cosmetic outcomes. The increasing prevalence of non-palpable tumors highlights the importance of accurate preoperative localization and precise orientation of the resected specimen for radiological and pathological evaluation. Incorrectly oriented specimens can lead to inaccurate diagnoses and inadequate re-excision, thereby increasing the risk of tumor recurrence. Clear communication between surgeons, pathologists, and radiologists, as well as standardized marking of resection margins, is essential for oncological safety. The aim of our study was to evaluate the specimen orientation techniques used in Hungarian breast cancer treatment centers. Based on our findings, we developed a new tool to accurately and unequivocally reconstruct the in vivo position of the tumor.

5.2 MATERIALS AND METHODS

The aim of the survey was to assess and understand the surgical specimen orientation techniques used in Hungarian breast cancer centers and to gather insights from surgeons, radiologists, and pathologists. Twelve institutions were selected based on their annual surgical volume and their role in national breast cancer care.

An online questionnaire was used to evaluate orientation protocols, their clarity, and their effectiveness in guiding re-excision directions for non-palpable tumors. Questions covered topics such as marking methods, intraoperative imaging, the consistency of orientation practices, and the perceived need for a national standard.

Based on the responses, the causes of orientation errors and deficiencies in current practices were analyzed. The data from each center were provided anonymously by one breast surgeon, one radiologist, and one pathologist from each center. The goal was to identify opportunities for improving orientation techniques, with a focus on addressing ambiguous practices.

5.3 RESULTS

Suture marking based on anatomical directions (cranial, caudal, lateral, medial) was the most commonly used method for orienting breast tissue. The length and number of sutures determined

the marked directions. Three-quarters of the respondent centers used a consistent system within their institution, marking three or four directions. Some institutions also created orientation diagrams to assist with pathological evaluation.

Specimen mammograms were found to cause confusion for over half of the surgeons, although they were clear to radiologists. None of the centers produced mammographic images in coronal plane. According to 70% of pathology departments, orientation issues occurred in 5–10% of cases, with half of these errors attributed to ambiguous markings, such as suture length or direction, loss of orienting suture, or specimen distortion during mammography or transport.

Seventy-five percent of respondents believed that coronal mammographic images would be particularly useful for the removal of non-palpable tumors. Two-thirds of surgeons felt that intraoperative photographs would aid in orienting the surgical cavity and specimen for re-excision. Frequent sources of error included the displacement of three-directional sutures or clips and unclear orientation on mammographic images.

Based on the survey findings, the fundamental requirements for a breast specimen presentation device were defined: stable fixation, accurate reproduction of the in vivo position, reproducibility, and no obstructive X-ray shadows. A device suitable for sterile, intraoperative use was developed in the form of a 3D-printed plastic specimen plate. This tool ensures precise anatomical positioning of the breast tissue and facilitates both surgical and pathological processing.

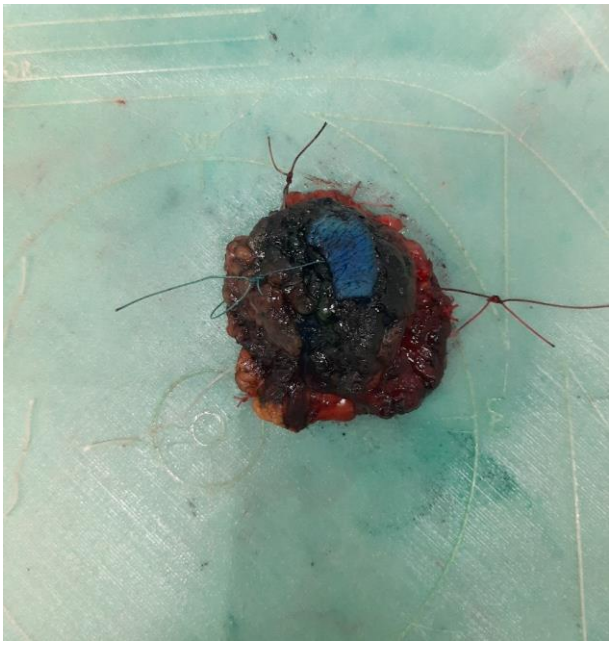

Figure 1. Properly oriented breast specimen on the specimen plate (the tumor was marked using the ROLL technique)

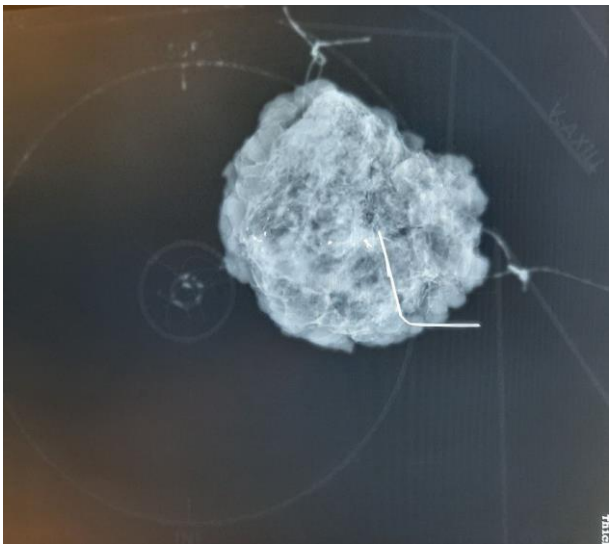

Figure 2. Mammographic image of an oriented breast specimen, localized using the wire-guided technique, positioned on the specimen plate. Traditional suture marking was also applied (long suture = lateral, short suture = superior) using thick sutures that create clearly visible X-ray shadows.

The breast scheme is clearly visible on the mammographic images, while the plastic plate does not produce any disturbing radiopaque shadows (Figures 1 and 2). The plate provides mammograms of the breast specimens in coronal plane, making them easier to interpret and more reliable for surgeons and pathologists.

5.4 DISCUSSION

The rate of re-excisions following breast-conserving surgery is uncertain, ranges from 4% to 30% according to the literature. The adoption of oncoplastic techniques has reduced the frequency of re-excisions. In nearly half of reoperations, the resected specimen margins are tumor-free, indicating that margin assessment is influenced by various factors, such as the number of histological sections and the techniques used to prepare them. Specimen orientation errors often arise from ambiguous markings or distortion during transportation and mammography. Despite the "no tumor on ink" criterion for clear margins, re-excisions are frequently performed even in cases with R0 status. Local recurrence is influenced not only by resection margins but also by the biological characteristics of the tumor (e.g., tumor stage, receptor status).

The lack of standardized orientation protocols and challenges in multidisciplinary communication pose significant problems. The survey highlighted the need for a device that

ensures clear orientation of resected tissues, aligns with anatomical relationships, and does not interfere with mammography. Coronal plane specimen mammography provides substantial assistance for pathological and surgical orientation.

The newly developed 3D-printed specimen orientation plate securely stabilizes breast specimens while representing their anatomical position, thereby improving surgical and pathological accuracy. The aim of the specimen plate is to minimize information loss and enhance patient safety, while facilitating collaboration between surgeons, pathologists, and oncologists.

5.5 CONCLUSION

Based on the national survey and our own experience, it has become evident that specimen orientation techniques in breast cancer surgery need to be improved to enhance patient safety and treatment quality. The developed specimen plate with the breast scheme, combined with coronal plane specimen mammography, provides pathologists with more accurate interpretations and offers surgeons a clear orientation tool.

6. MALIGNANT PLEURAL EFFUSION ASSOCIATED WITH ADVANCED BREAST CANCER

6.1 INTRODUCTION

Malignant pleural effusion (MPE) associated with advanced breast cancer occurs in 10–30% of breast cancer cases and accounts for 20–25% of MPE cases. MPE is an indicator of poor prognosis in late-stage cancers, with cytological sensitivity ranging from 40% to 87%. Its management is palliative, includes options such as closed drainage to pleurodesis, and rarely involves VATS (Video-Assisted Thoracic Surgery) or RATS (Robotic-Assisted Thoracic Surgery) techniques. The aim of our study was to refine prognostic assessments and analyze survival patterns in MPE originating from breast cancer.

6.2 PATIENTS AND METHODS

We retrospectively analyzed data from female patients diagnosed with breast cancer-associated malignant pleural effusion (MPE) treated at the Petz Aladár University Teaching Hospital between September 1, 2012, and December 31, 2023. The mean age at the time of breast cancer diagnosis was 58 years (SD: 9.89 years). The analysis included demographic data,

laterality of breast cancer, TNM stage, hormone receptor status, and HER2 status. Univariate and multivariate statistical methods were used for evaluation.

Of the 142 cases of malignant pleural effusion identified during the study period, 53 (37%) were of breast cancer origin. In 19% (10 cases) of breast cancer-associated MPE, synchronous bilateral breast cancer was present, which far exceeds the general occurrence rate of synchronous bilateral breast cancer (1–2%).

In 19% of breast cancer-related MPF cases (10 cases), synchronous bilateral breast cancer was identified, significantly exceeding the general prevalence of synchronous bilateral breast cancer (1–2%). Among the 53 cases, 43 were invasive NST (No Special Type), 5 were lobular carcinoma, and 2 were medullary breast cancer. Molecular subtypes were distributed as follows: hormone receptor-positive, HER2-negative (34 cases), triple-positive (6 cases), triple-negative (8 cases), and HER2-positive, hormone receptor-negative (5 cases). The T-stage distribution at diagnosis was: T1 (12 cases), T2 (12 cases), T3 (5 cases), and T4 (6 cases).

6.3 RESULTS

We examined the time between breast cancer diagnosis and the onset of MPE, as well as the time from MPE diagnosis to death. In cases of breast cancer-associated MPE (n=53), the average time from diagnosis to the development of MPE was 116 months. No significant differences were observed in the time to MPE onset across molecular subtypes of breast cancer.

The 5-year survival rate was 18.7%, with an average time to death of 114.5 months (range: 68–181 months).

Overall survival patterns aligned with the prognostic characteristics of breast cancer molecular subtypes. The overall survival for hormone receptor-positive, HER2-negative tumors was 125 months, while HER2-positive, hormone receptor-negative subtypes showed a longer survival of 141 months. Triple-negative tumors had significantly poorer overall survival, averaging only 75 months. The therapeutic significance of HER2-positive status was highlighted, as adequate treatment demonstrated improved prognosis even in the absence of hormone sensitivity.

Survival after the onset of MPE also varied by molecular subtype: triple-negative cases had an average survival of 6 months, while hormone receptor-negative, HER2-positive subtypes showed an average survival of 46 months, and hormone receptor-positive, HER2-negative tumors demonstrated an average survival of 36 months. Median survival for invasive NST-type tumors was 33 months, whereas invasive lobular carcinomas had a significantly shorter median survival of only 8 months. Following drainage and pleurodesis (D&PD), 50% of patients

survived beyond one year, 25% beyond three years, and 19% lived more than five years after MPE diagnosis, with an average survival of 114.5 months. The complication rate of D&PD was low (7.1%), and no mortality was observed within 30 days of the procedure.

6.4 DISCUSSION

Compared to literature data, 25% of the patients in our cohort survived beyond three years, and nearly 20% lived more than five years, challenging the classical definition of "palliation." While pleural drainage is primarily aimed at improving quality of life and mitigating acute pulmonary risks, it may have supportive or minimal adjuvant effects. Despite the small sample size, clear clinical patterns emerged that align with the known prognostic characteristics of breast cancer molecular subtypes. Triple-negative and invasive lobular carcinomas (ILC) were associated with the poorest prognoses. In ILC, the lack of cellular cohesion and frequent multifocal presentation promote the development of MPE, especially in advanced stages. Its diagnostic challenges present difficulties, but understanding its characteristics allows for more accurate diagnosis and effective therapy. The prognosis of MPE patients is heterogeneous, but our data suggest that active treatment strategies, such as drainage, pleurodesis, or VATS, may offer survival benefits if tailored to the patient’s overall condition and tolerance. Emerging therapies, such as hyperthermic intrathoracic chemotherapy (HITHOC), present a promising alternative, particularly when combined with targeted therapies or immunotherapies. This multimodal approach aims to improve both quality of life and symptom-free survival.

6.5 CONCLUSION

Our findings challenge the traditional approach of treating MPE solely as a palliative condition. Prolonged survival justifies proactive interventions, such as early pleural pressure relief and surgical procedures. Histological and receptor status are critical determinants of prognosis, providing opportunities for personalized therapies. Advancing targeted treatments and diagnostic innovations is essential for optimizing the management of MPE.

7. FINDINGS

The following answers to the five research questions outlined in Chapter 2 are supported by our findings and peer-reviewed publications:

ad 1. The ROLL technique is recommended as the primary localization method for non-palpable breast cancers due to its simplicity, reduced pain, and cosmetic advantages, particularly

for smaller, non-fatty breasts. The WGL technique is more suitable for large, fatty breasts and tumors in the inner quadrants, as well as after neoadjuvant chemotherapy, where sentinel lymph node marking is critical.

ad 2. The efficiency of sentinel lymph node marking with the ROLL technique decreases for tumors in the inner quadrants and breasts with fatty involution, where marking errors are four times more frequent than with the WGL technique (67% vs. 14%). Combining peri-areolar isotope injection with localization techniques can improve the accuracy of axillary sentinel lymph node marking.

ad 3. The inaccuracies and displacements of traditional suture marking, the inadequacy of two-view mammographic imaging, and deficiencies in multidisciplinary communication often increase the need for re-excisions. The specimen plate device provides a solution by ensuring stable fixation and clear orientation of the specimen, minimizing diagnostic and surgical errors.

ad 4. The 3D-printed, radiolucent specimen plate enables precise fixation of the resected specimen and coronal-plane mammographic imaging, thereby improving the accuracy of surgical and pathological processing. The device facilitates accurate margin assessment.

ad 5. Our findings challenge treating MPE solely as a palliative condition, highlighting the value of proactive interventions, such as early pleural pressure relief and surgery. Histological and receptor status guide prognosis and enable personalized therapies. Emerging modalities like HITHOC offer promising survival benefits, emphasizing the need for advanced targeted treatments and diagnostics.

8. LIST OF PUBLICATIONS RELATED TO THE DISSERTATION

1. **Complex oncological treatment for patients with locoregionally advanced breast cancer in the presence of prolonged SARS-CoV-2 PCR positivity**
   Journal: Orvosi Hetilap, 2021; 162(16): 611-614. (IF: 0.707)
   Authors: *Drozgyik A., Kollár D., Knausz M., Sipőcz I., Molnár FT., Kullmann T.*
2. **Abdominal metastases of breast cancer – an unusual entity: case report**
   Journal: Magyar Sebészet, 2022; 75(4): 265-269.
   Authors: *Drozgyik A., Molnár FT., Tokodi Zs.*
3. **A New Approach to Breast Specimen Orientation: Avoiding Pitfalls with the Specimen Plate Concept**

Journal: Current Oncology, 2024 Aug 10; 31(8): 4589-4598. (IF: 2.8)

Authors: *Drozgyik A., Szabó T., Kovács G., Kollár D., Molnár TF.*

4. **Non-Palpable Breast Cancer: A Targeting Challenge - Comparison of Radio-Guided vs. Wire-Guided Localization Techniques**

   Journal: Biomedicines, 2024 Oct 27; 12(11):2466. (IF: 3.9)

   Authors: *Drozgyik A., Kollár D., Dankházi L., Harmati I., Szalay K., Molnár TF.*

5. **Narrative Review of Theoretical Considerations Regarding HITHOC Between Past and Future**

   Journal: Annals of Translational Medicine, 2021 Jun; 9(11): 954. (IF: 3.932)

   Authors: *Molnár TF., Drozgyik A.*

9. OTHER PUBLICATIONS

6. **Cardiac SERCA2A Function Is Impaired in Type 2 Diabetes**

   Journal: Acta Physiologica Hungarica, 2010; 97(1): 99. **(IF: 0.453**)

   Authors: *Drozgyik A., Benis É., Kemecsei P., Miklós Zs., Ivanics T.*

7. **SERCA2A Dysfunction Enhances the Susceptibility of the Diabetic Heart to Hypoxia**

   Journal: Acta Physiologica Hungarica, 2010; 97(4): 436. **(IF: 0.453)**

   Authors: *Drozgyik A., Benis É., Kemecsei P., Ivanics T., Miklós Zs.*

8. **Early Cardiac Dysfunction is Rescued by Upregulation of SERCA2A Pump Activity in a Rat Model of Metabolic Syndrome**

   Journal: Acta Physiol (Oxf), 2012 Jul; 205(3): 381-93. **(IF: 5.97)**

   Authors: *Miklós Z., Kemecsei P., Bíró T., Marincsák R., Tóth BI., Op den Buijs J., Benis É., Drozgyik A., Ivanics T.*

9. **Perioperative nutritional state as a surgical risk in oncologic patients**

   Journal: Orvosi Hetilap, 2021; 162(13): 504-513**. (IF: 0.497)**

   Authors: *Kollár D., Benedek-Tóth Z., Drozgyik A., Molnár FT., Oláh A.*

10. **To Feed or Not to Feed - Nutritional Risk Assessment and Support in Elective Colorectal Surgery. A Prospective Study on the Effect of Screening**

    Journal: Nutrition and Cancer, 2022 May 18: 1-9. **(IF: 2.364)**

    Authors: *Kollár D., Benedek-Tóth Z., Drozgyik A., Molnár TF., Oláh A.*