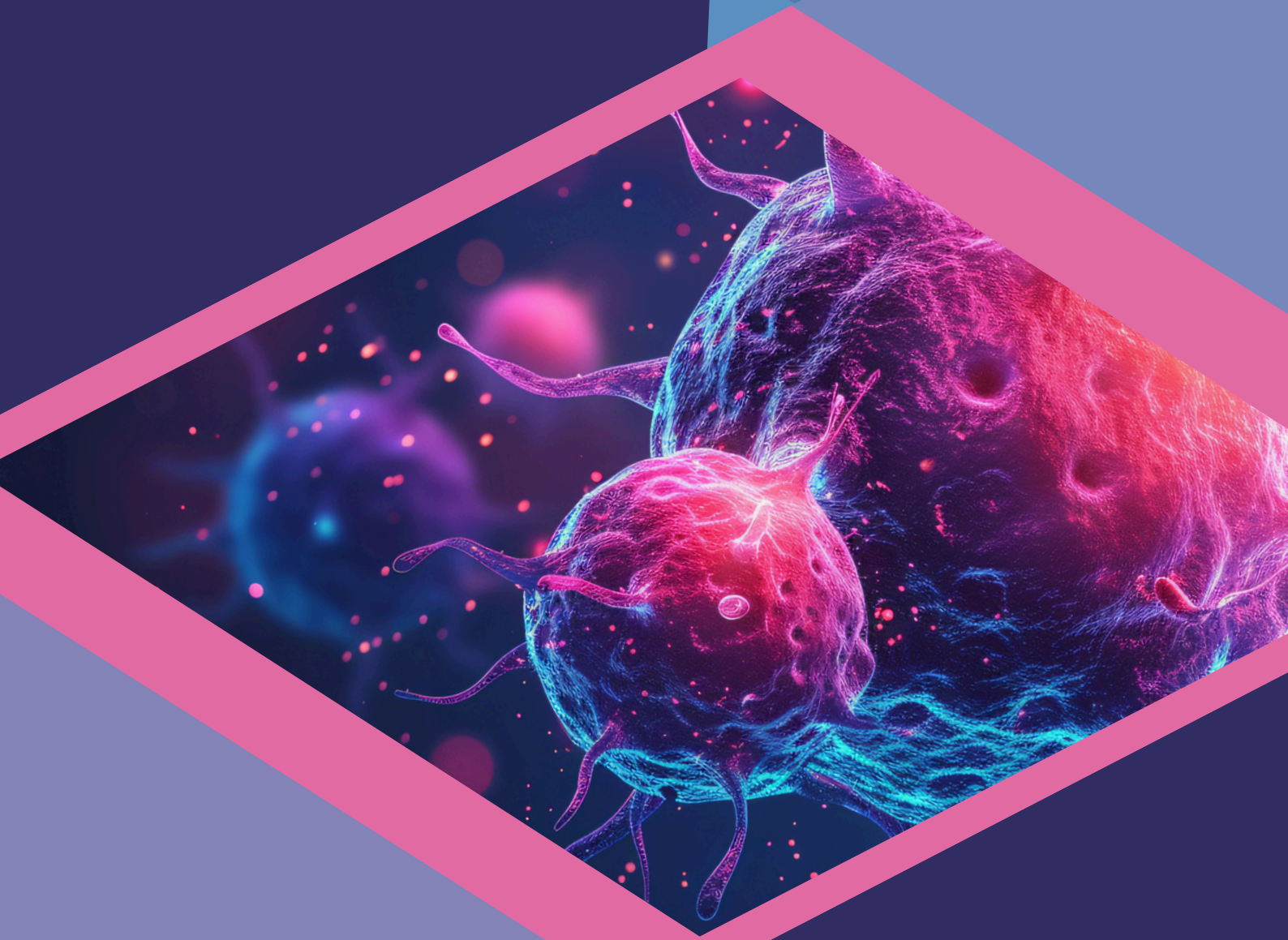
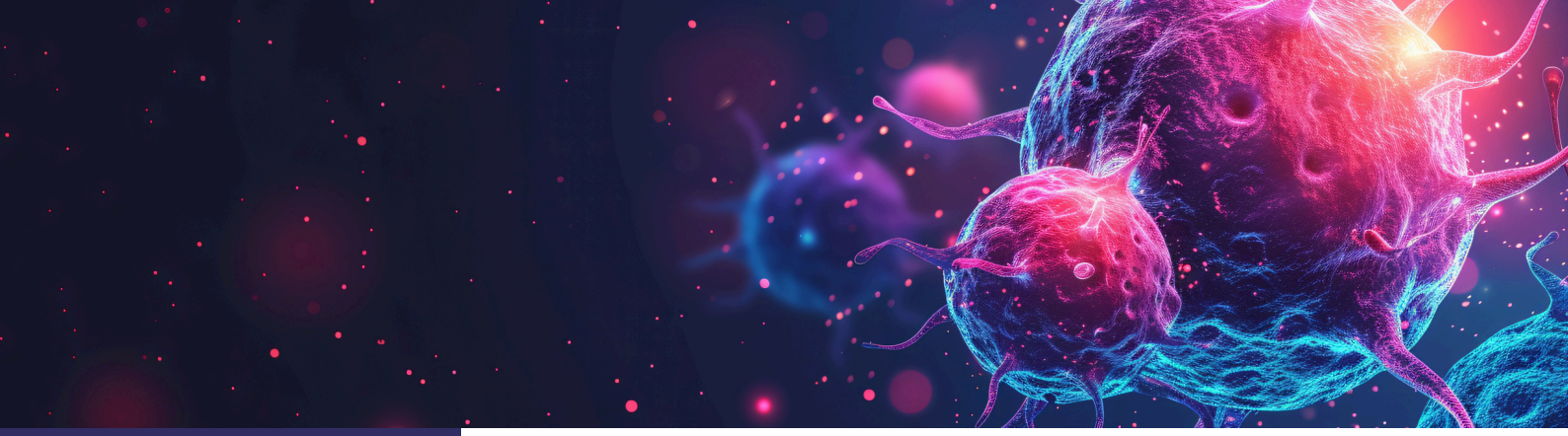
Oncology Central



Beyond remission: understanding breast cancer dormancy

Taylor & Francis



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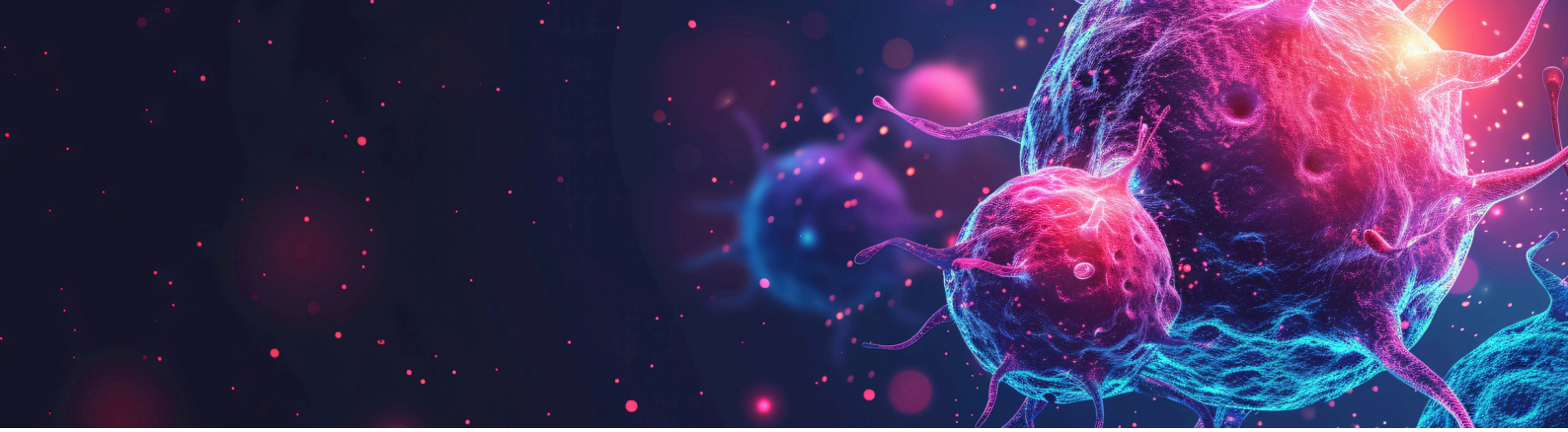

Foreword

The phenomenon of breast cancer dormancy, where cancer cells remain quiescent for extended periods before reactivating, represents one of the most complex aspects of breast cancer care.

Its direct impact on long-term patient outcomes and survivorship creates both challenges and opportunities for clinicians and researchers working to improve quality of life outcomes.

In this modern era of precision oncology, understanding the cellular and molecular mechanisms of breast cancer dormancy has become essential for developing targeted interventions that can prevent or delay disease recurrence. Current research exploring the role of immune cells, alongside investigations into gene therapy approaches represent the cutting edge of translational breast cancer research.

In this eBook, we explore the multifaceted nature of breast cancer recurrence and dormancy, by examining how clinical factors guide post-neoadjuvant treatment strategies, reviewing innovative approaches to locoregional recurrence management and investigating the biological mechanisms that govern tumor dormancy.

We hope this eBook serves as a valuable resource for understanding one of the most challenging aspects in breast cancer care and inspires continued innovation in this critical area.

Jade Parker
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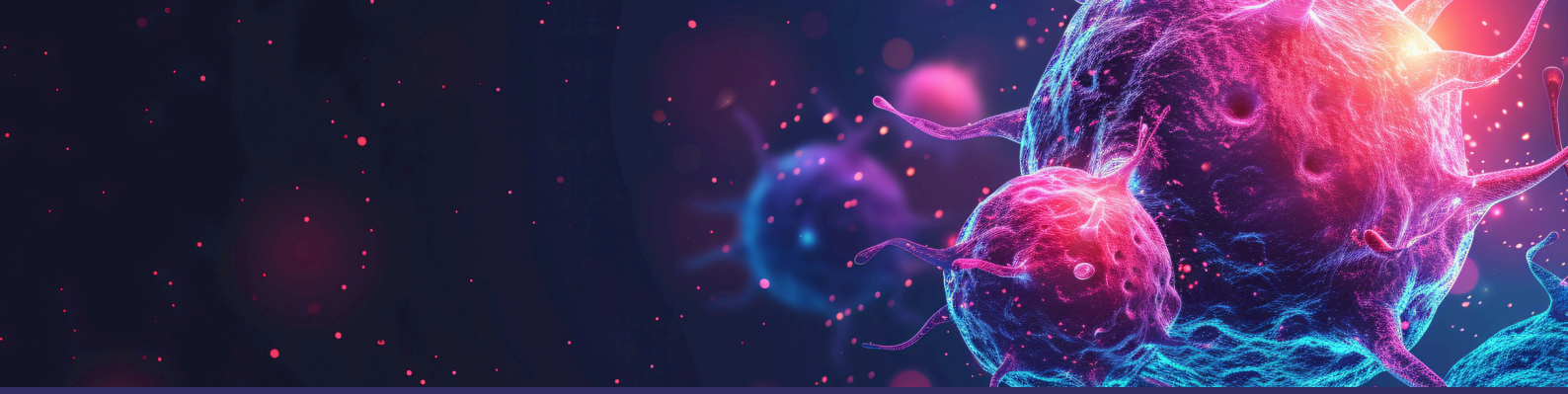


Ask the Experts: Breast cancer dormancy and late recurrence

Dormancy is one of the greatest unknowns and challenges in breast cancer care. In this Ask the Experts feature, we dive into the complexities of studying dormant cancer cells and reveal promising developments in gene therapy and immune-based approaches. The experts also discuss the potential implications of groundbreaking research in working towards breast cancer patients and survivors being able to live happy, healthy lives without fear of the disease coming back.

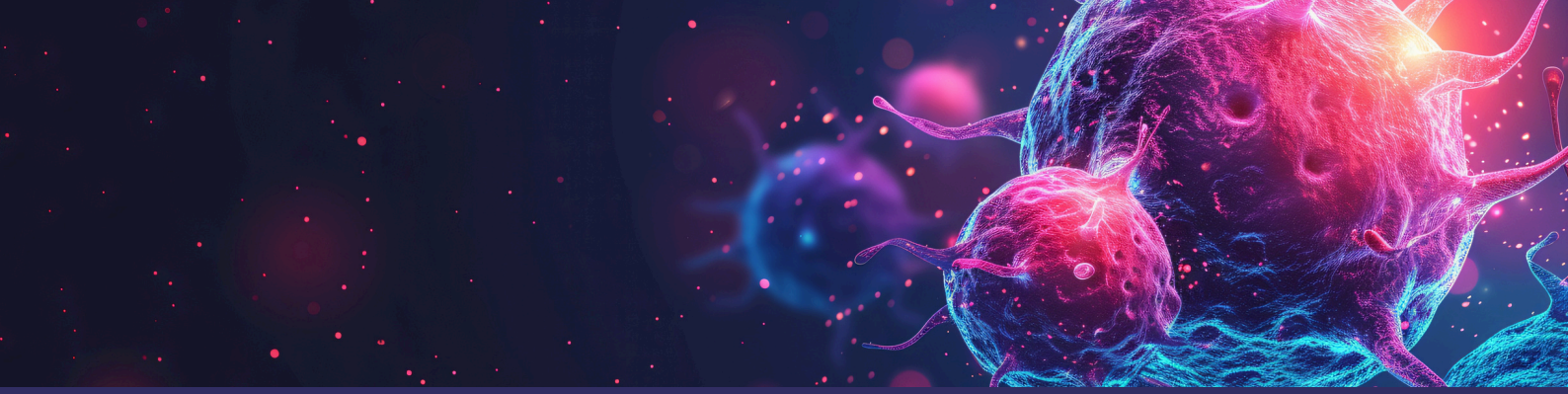
Discover more about this topic from our experts: Penelope Ottewell (University of Sheffield, UK), Simon Vincent (Breast Cancer Now, UK), and Frances Turrell (University of Manchester, UK) and major supporter and campaigner Robert Swannell (Breast Cancer Now, UK). Meet the experts here.

Could you outline the concept of breast cancer dormancy and the impact it has on patients throughout their survivorship journey?

Simon Vincent: Dormancy is one of the hardest challenges we must solve if everyone diagnosed with breast cancer is to live and live well. It is where tumor cells are present after treatment of primary breast cancer, but they are in a prolonged inactive state. Most breast cancers don't return after treatment. However, breast cancer is known for asymptomatic periods of up to 25 years, with no evidence of the disease, followed by a relapse.

If the breast cancer cells have spread to a different part of the body and the cancer recurs, it will be classified as a secondary cancer (also known as metastatic or Stage 4 breast cancer), which is treatable, but not yet curable. Around 61,000 people are thought to be living with secondary breast cancer in the UK, and 31 women die of the disease every day. Thanks to breakthroughs in the treatment of primary breast cancer, people are living longer than ever. However, this progress means dormancy is becoming a more pressing issue and we need new treatment options to prevent breast cancer from recurring years after initial treatment.

At Breast Cancer Now, we've had the privilege of working with the late Patricia Swannell and her husband Robert, who launched the 'Patricia Swannell Appeal for Secondary Breast Cancer' in 2022 to raise funding for critical research into secondary breast cancer, dormancy and late recurrence.



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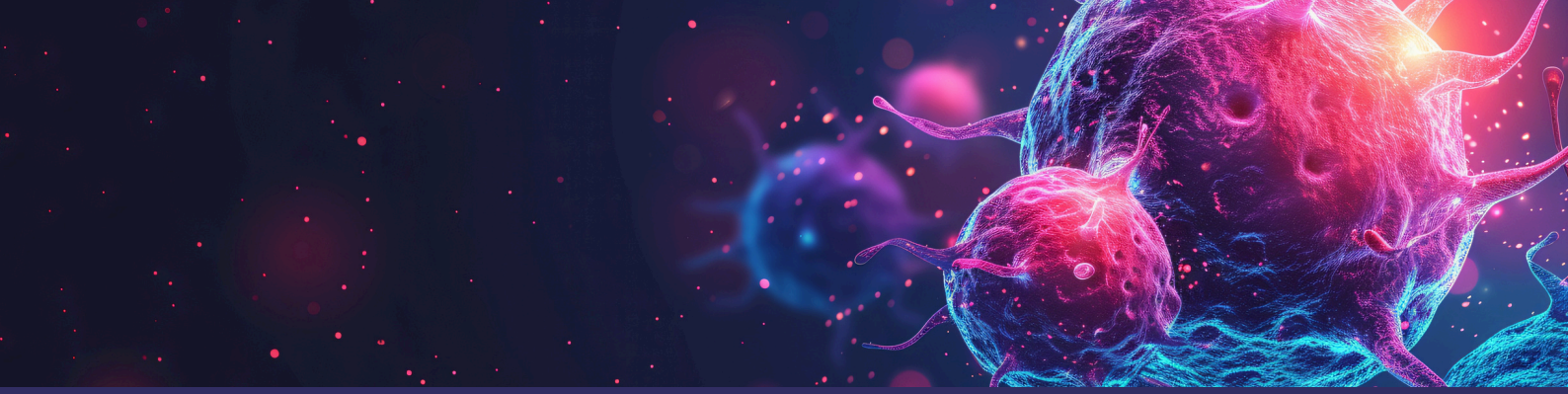
The appeal has raised over £1.4 million to date, and we are now funding two major research projects in this area. And one of the key commitments from our new organizational strategy, Change Happens Now, is that we'll double what we spend on research over the next 5 years, with a focus on the challenges of dormancy and late recurrence.

Patricia and Robert Swannell

Robert Swannell: When my wife, Patricia, was diagnosed with secondary breast cancer we were astonished to find two realities. First was how badly women and clinicians were educated about secondary breast cancer, leading to frequent late diagnosis. Second was how little was known about the science behind dormancy and late recurrence. As a result, although women were living longer after a primary breast cancer diagnosis, the number dying from secondary breast cancer remained much the same as it had decades earlier. Patricia died 2 years after her diagnosis with secondaries.

Dormancy is described as "one of the greatest unknowns of breast cancer." What makes this area particularly challenging to study compared to other aspects of cancer research?

Frances Turrell: A key challenge is that it is difficult to identify and isolate dormant cancer cells from patients to study. We have samples of primary and secondary cancer once it has grown but we need to study the dormant state to understand the biology behind dormancy and reawakening. We have different ways of modelling dormancy in the lab, but they typically fail to faithfully mimic the long periods of hibernation observed in breast cancer patients. It is also very challenging to mimic the complex changes occurring in individuals, which can impact cancer dormancy and reawakening. These include lifestyle and hormonal changes, changes that occur with age, as well as changes that impact the effectiveness of the immune system to keep cancer cells in check.



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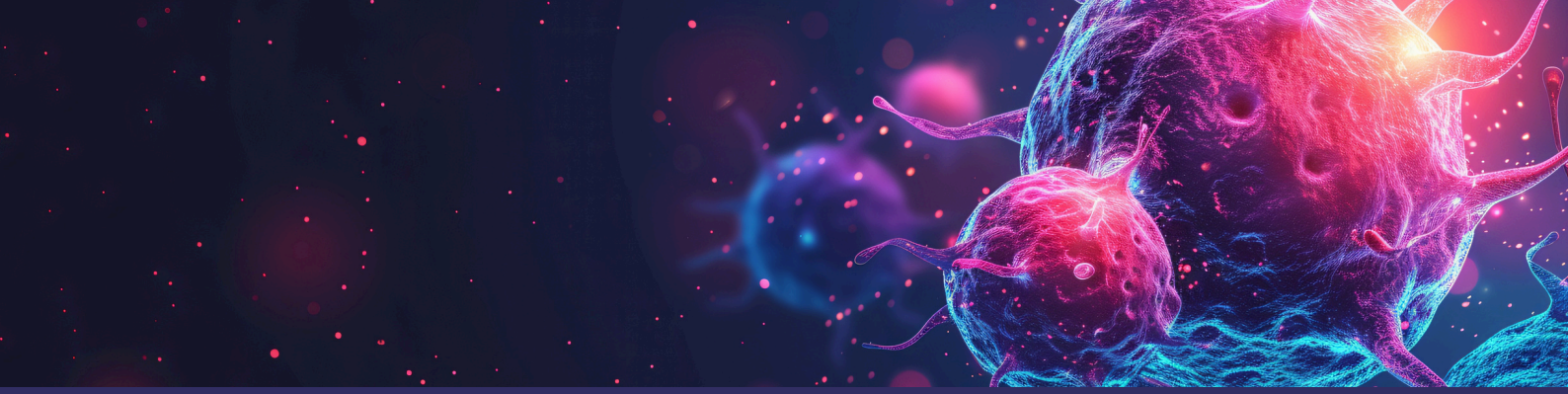
In breast cancer, these long dormancy periods are typically observed in patients with estrogen-receptor-positive (ER+) breast cancer, the most common type of breast cancer. However, we have even fewer ways of studying dormancy in ER+ breast cancer, particularly how the immune system influences dormancy and reawakening. Finally, we don't have enough data from the dormancy period in patients. If more information was collected from patients following the end of their treatment, via patient follow-up, we could establish whether there are links between certain events or lifestyle changes and recurrence of the disease. This could help us to determine which individuals may be at higher risk of future recurrence.

> *There needs to be research on what happens to women at the end of their primary treatment… to identify those who would benefit from further or a different treatment.*

Simon Vincent: Little is known about what causes dormancy, and – despite the clinical importance of tumor dormancy – the biology of dormant cells is poorly understood. We need to improve our understanding of dormancy, the role of the tumor microenvironment in maintaining dormancy and in triggering the reawakening of tumor cells as well as the genetic and molecular mechanisms underlying recurrence. We also need to find out at a cellular level what happens to breast cancer cells that become dormant during initial treatment and when it ends.

There needs to be research on what happens to women at the end of their primary treatment, particularly those ending hormone therapy, because we want to identify those who would benefit from further or a different treatment. One area of research could be to establish a cohort of such women who are at high risk of recurrence and work with them to investigate the causes of dormancy and late recurrence.

We also need better biomarkers for dormancy and late recurrence as well as improved laboratory models for studying this stage of the disease.



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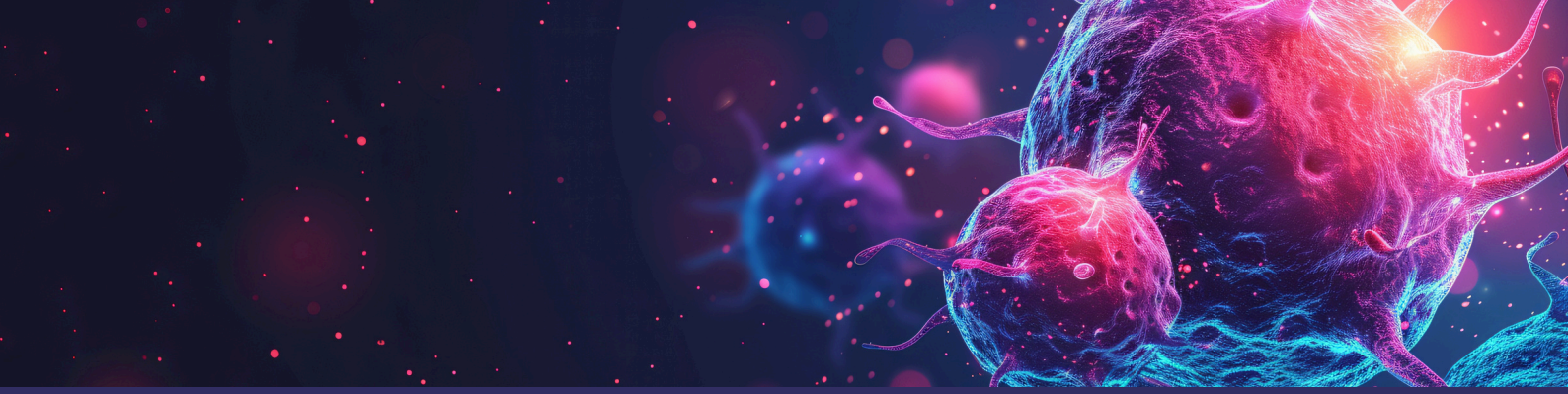
Penelope Ottewell: Breast cancer dormancy is particularly challenging to study because it's almost impossible to isolate dormant cancer cells from humans. We know which organs are likely to be populated by dormant cancer cells. However, very few cancer cells that leave the primary site survive and seed secondary organs. This means that dormant cancer cells are rare. We therefore need to rely on model systems to work out how dormant cancer cells seed other organs, why cancer cells "sleep" when they arrive in distant organs and what causes them to reawaken.

What do you believe are the most promising developments in breast cancer dormancy research from the past 5 years?

Simon Vincent: One current line of research is looking at keeping cells in a dormant state so that they can't reawaken. Regulating the tumor microenvironment with drugs may prevent dormant cancer cells from waking up. For example, Clare Isacke and her team at Breast Cancer Now's (UK) Toby Robins Research Centre at the Institute of Cancer Research (all London, UK) showed that if the level of a protein called PDGF-C increases, which is more likely in an aging lung or when its tissue becomes damaged or scarred, it can cause dormant cancer cells to grow and develop into secondary breast cancer. They targeted the PDGF-C protein with an existing cancer growth blocker, termed imatinib, which is currently used to treat patients with chronic myeloid leukemia. They showed that mice with ER+ tumors treated with the drug both before and after tumor development had significantly reduced cancer cell growth within their lungs.

Frances Turrell: There has been considerable development in our understanding of how different immune populations can control breast cancer dormancy and reawakening. While further work is needed, I believe these represent the most promising developments. Immunotherapy has revolutionized the treatment of many types of cancer in recent years. These therapies work by harnessing our immune system to fight cancer. If we can understand 1) how dormant cancer cells evade detection and attack by the immune system and 2) how, conversely, specific cancer–promoting immune populations may support their reawakening, we can design new immunotherapy approaches to target cancer cells.



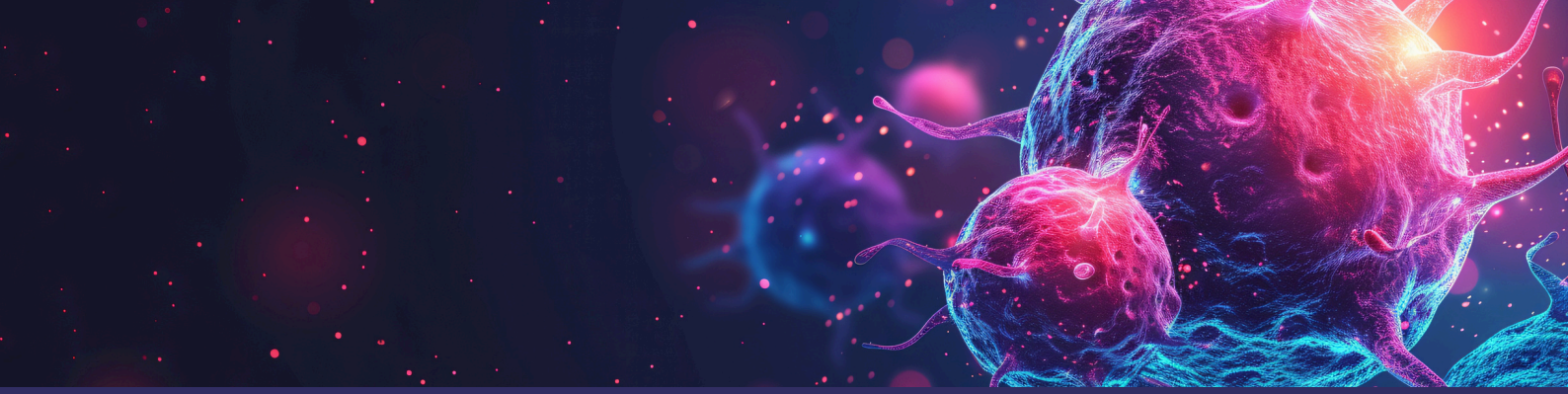
Ask the Experts: Breast cancer dormancy and late recurrence

Dormant cancer cells are essentially hibernating and therefore resistant to standard anti–cancer therapies designed to target rapidly dividing cells. Immunotherapy approaches represent promising alternative strategies for eliminating or suppressing dormant cancer cells in patients and thus preventing the development of secondary cancer.

Penelope Ottewell: We now understand that dormancy is influenced by the tumor microenvironment. Over the last 5 years, research has shown us that dormancy is regulated by interactions with specific cells known as “niche cells” and that maintaining the stability of this niche is important to prevent re-awakening of dormant cells. Two main regulators of the “niche” are IL-1β and macrophages. Targeting these factors could prevent dormant cells from waking up.

Can you provide further details on research investigating the role of macrophages in breast cancer dormancy and those evaluating gene therapy–based approaches?

Penelope Ottewell: Current strategies to prevent dormant cancer cells from reawakening include a gene therapy approach. This approach involves introducing a small piece of DNA into “niche” cells. This DNA causes the “niche” cells to produce a naturally occurring substance that “switches off” IL-1β. Strong evidence suggests that “switching off” IL-1β prevents re-awakening of dormant cells, eliminating growth of secondary cancers in bone. We will genetically alter human breast cancer cells to make them produce high or low amounts of proteins involved in IL-1β activity. We’ll then observe which bone cells breast cancer cells interact with when they first grow, and how these are affected by IL-1β in human bone tested in the lab. After this, we’ll genetically target relevant bone cells, enabling them to produce IL1Ra.



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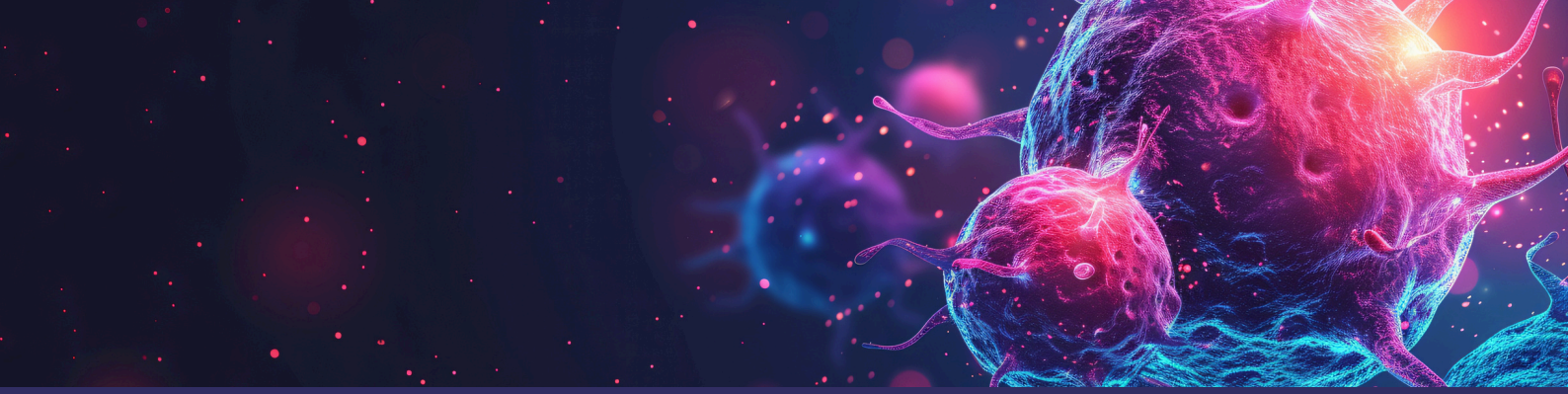
This project will lay the groundwork for gene therapy–based treatments that can prevent dormant breast cancer cells in the bone from reactivating. Since bone can act as a “reservoir” for these cells, keeping them dormant could also reduce recurrence in organs like the lungs, liver and brain. The team will wish to find the ways in which IL-1β controls dormancy, and we’ll explore if drug s targeting IL-1β should be further developed.

> *This project will lay the groundwork for gene therapy–based treatments that can prevent dormant breast cancer cells in the bone from reactivating.*

Frances Turrell: Macrophages are a type of immune cell. However, they are not just one uniform population – they are incredibly diverse, have high plasticity and perform many different functions. In the context of cancer, some macrophages have cancer-suppressing functions and some have cancer-promoting effects, including at secondary sites. Studies have demonstrated that macrophages have a role in maintaining breast cancer dormancy in the lung. It’s when communication between cancer cells and macrophages is disrupted that cancer cells can grow rapidly into a secondary cancer.

One reason for a potential communication disruption is that macrophages change function. My lab is exploring how macrophage populations change with age and whether age-associated changes in these cells contribute to the dormant cancer cells reawakening in secondary sites. The diversity and plasticity of macrophages make them a unique treatment target and work is now underway to develop therapeutic strategies, to shift macrophages from cancer–promoting to cancer–suppressing.

These strategies are promising, although there are challenges to navigate. These include ensuring specific macrophage subsets are targeted and accounting for the impact of the dynamic and complex microenvironment on macrophage function, which may reverse the treatment–induced functional changes in the macrophages. Cell therapy approaches, where macrophages are engineered so that they always produce molecules involved in cancer-suppressive functions, are also being considered.



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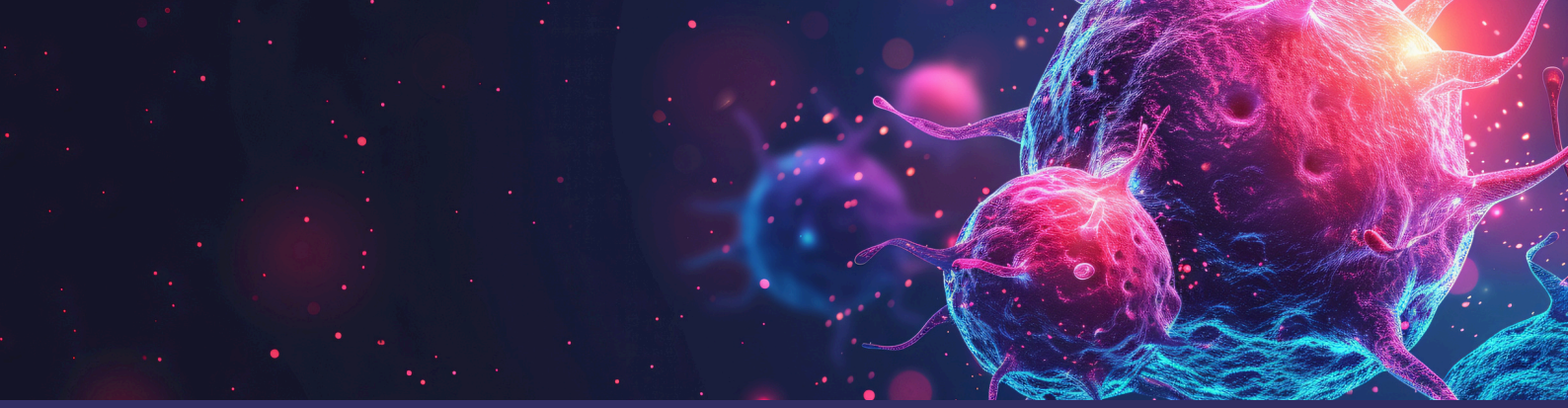
How would you like to see this research impact clinical practice?

Penelope Ottewell: The majority of secondary breast cancers occur in bone. If successful, administration of a niche–based gene therapy would prevent reawakening of cancer cells in bone, saving thousands of lives a year. The benefit of the gene therapy approach discussed is that the gene is only switched on if a dormant cancer cell starts to wake up, so it's unlikely to result in adverse effects.

Simon Vincent: This research could lead to new diagnostics that identify women with dormant cancer cells or who are at higher risk of recurrence. We want to go further and use this information to develop preventative treatments, including drugs or gene therapies, to either eliminate dormant cells or keep them permanently inactive. The follow-up that breast cancer patients receive would become more personalized, helping patients and clinicians make better decisions about long-term treatment plans. Most importantly, this research gives hope that we can intervene earlier, before recurrence begins – offering women the possibility of a life free from the fear of secondary breast cancer.

Robert Swannell: There is still a very long way to go to solve the mysteries of dormancy and late recurrence. We need to tackle this now if tens of thousands of women are to be saved from dying of secondary breast cancer each year in the UK. My hope is that the research we helped fund through Breast Cancer Now will be the catalyst to real breakthroughs in early detection, treatment and, ultimately, cure secondary breast cancer.

Frances Turrell: We can group strategies for targeting dormant cancer cells into two main approaches: eliminating dormant cancer cells or preventing them from ever reawakening. Either approach, if successful, would suppress the development of secondary cancer, extending the lives of breast cancer patients. Through elucidation of the mechanisms by which different macrophage populations control cancer dormancy and reawakening, this research could uncover novel immunotherapy approaches to harness immune cells to kill dormant cancer cells or maintain cancer cells in their dormant state. Further work will be required to establish whether the mechanisms identified are tissue-specific or are relevant across different sites of secondary disease (for example, the lungs, liver or bone), and how existing treatments could be optimally combined.



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The long-term objective will be to translate the findings from the preclinical setting to patients. Here, the first approach – eradication of the dormant cancer cells – would be the preferred strategy. The second approach would likely involve a long-term maintenance therapy, which increases the likelihood of side effects from the treatment. We would also need ways of identifying who is at risk of developing secondary cancers that arise after extended dormancy periods and, therefore, who would benefit from additional therapeutic interventions.

In future research, it will be important to determine whether we can track dormancy–regulating immune changes occurring in the secondary sites in the patients' blood. This would be a relatively easy way of monitoring and identifying patients who are at increased risk of their dormant cancer cells reawakening.

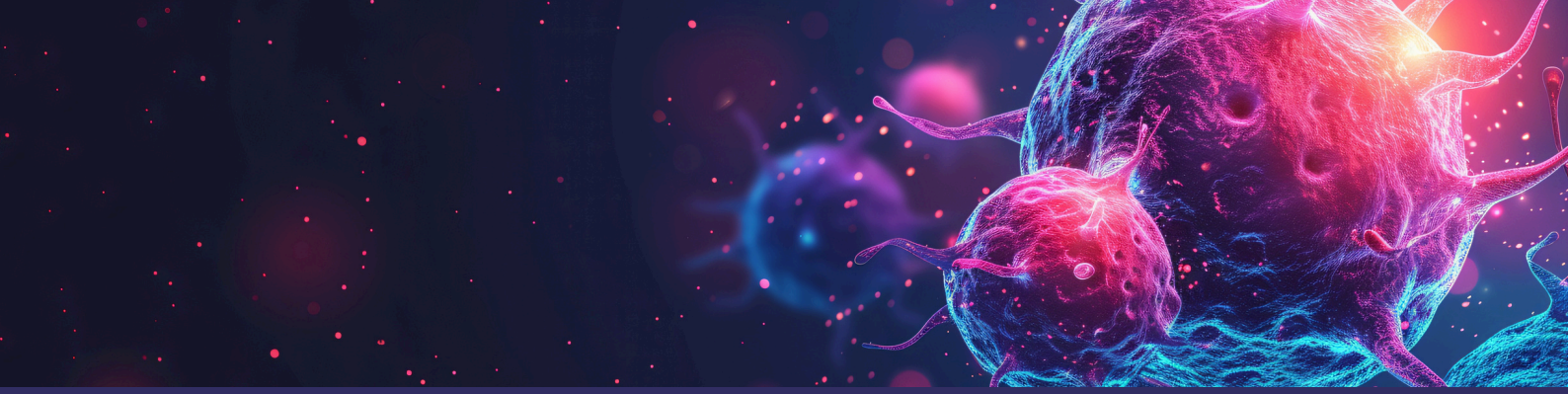
What are the implications of this work on the wider breast cancer field?

Simon Vincent: Dormancy is not well understood; we need to understand some of the fundamental biology of dormant cells, what causes them and how we can stop them from reawakening years after initial treatment. By focusing on discovering how dormant breast cancer cells behave in the lung and bone, we will deepen our understanding of dormancy and recurrence, which will lay the foundations for future research.

These projects could also lead to future treatments to prevent dormant cells from waking up and causing late recurrence of secondary breast cancer. More research will be needed to develop treatments for treating breast cancer in women, our funded research could be the start.

We hope that the findings from this research will help ensure people who have been treated for breast cancer are able to live happy, healthy lives without fear of the disease coming back.

Our ambition is that by 2050, anyone diagnosed with breast cancer lives and is supported to live well. This is just 25 years away, so we have no time to waste in gaining an understanding of dormancy and late recurrence so we can solve the challenge of breast cancer.



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Frances Turrell: The principal goal is to identify ways of targeting cancer dormancy, which underpins a critical problem in breast cancer treatment and management, particularly in ER+ cancers. However, immune cells, such as macrophages, have important roles throughout the development and progression of both primary and secondary breast cancers. Delineating the macrophage–mediated mechanisms of dormancy and reawakening will also provide insights into how macrophage populations and functions shift when secondary cancer has escaped dormancy and is actively growing. Therefore, mechanisms uncovered by research in this area will likely inform new treatment approaches for targeting both growing and established secondary cancers, as well as those targeting dormancy. This will have important implications for the treatment of patients who develop secondary breast cancer quickly or already have secondary cancer at diagnosis and potentially broaden the implications of this work to other breast cancer subtypes.

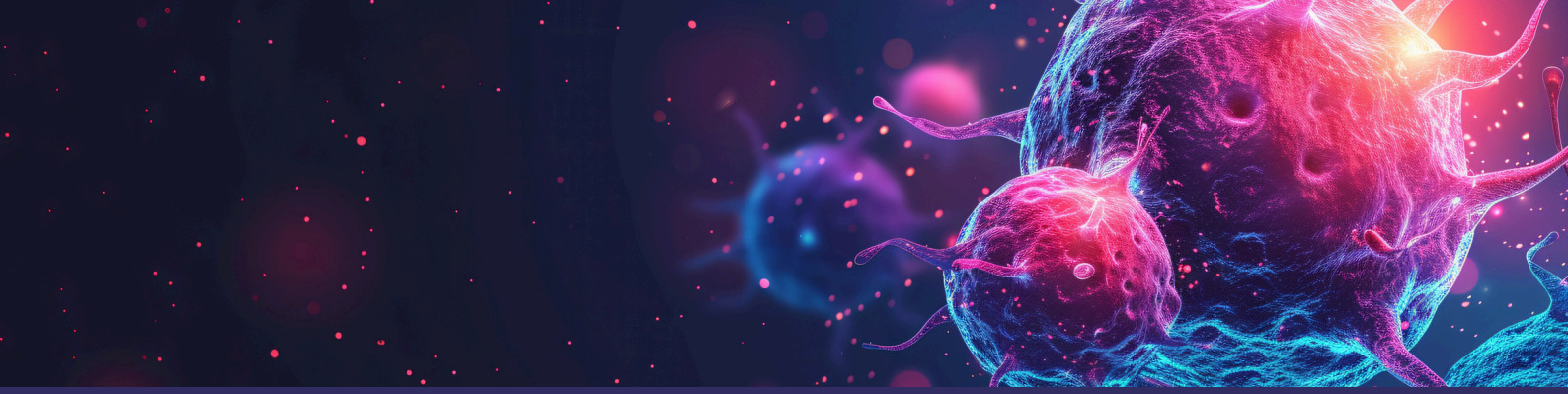
Furthermore, there is evidence that dormant cancer cells can exist alongside established secondary cancer. Treatments targeting dormant cancer cells could be combined with anti-cancer treatments targeting the established, clinically detectable secondary cancer to prevent additional recurrences that may arise from dormant cancer cells in the future.

Robert Swannell: My hope is that this work will not only be valuable for its own sake but will also open up further areas for research

Penelope Ottewell: Gene therapies have successfully been used to treat many conditions. Successful generation of gene therapies that target cancer-causing or dormancy-regulating genes could provide new, non-toxic treatment avenues.

BREAST CANCER NOW The research & support charity

For more information about The Patricia Swannell dormancy and late recurrence research programme visit: [The Patricia Swannell dormancy and late recurrence research funding programme | Breast Cancer Now]



Ask the Experts: Breast cancer dormancy and late recurrence

Meet the Experts

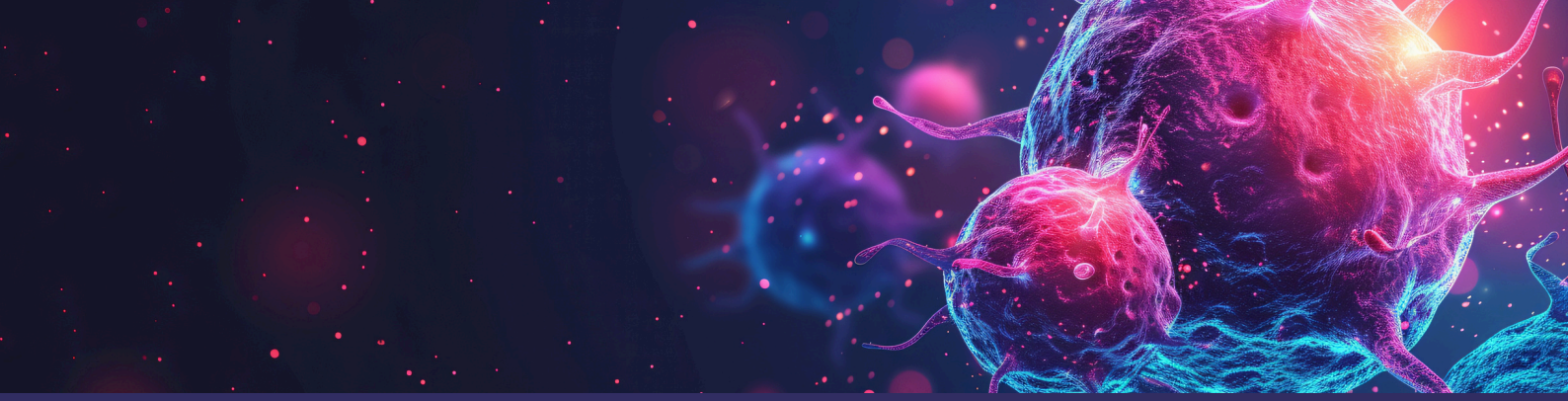
Simon Vincent

Simon Vincent has a PhD in genetics from the University of Nottingham (UK) and has been working with major UK medical charities for over 20 years. He joined Cancer Research Campaign in 2000, which would go on to become Cancer Research UK (UK). He spent most of 2013 on secondment at the Academy of Medical Sciences (UK), supporting early-career biomedical researchers. This involved mentoring, career support and policy development and awarding grants. He came to Breast Cancer Now in 2014, originally leading just the research team. Then in 2020, he became Director of research, support and influencing. He became Chief Scientific Officer at Breast Cancer Now in 2025.

Penelope Ottewell

Penelope (Penny) Ottewell completed her PhD at the University of Liverpool (UK), before joining the University of Sheffield as a Research Associate. Whilst based in Sheffield, Penny has carried out international collaborative work spending time at INSERM (France) and at TUFTS Medical School (MA, USA). She has been awarded a total of 13 national and international prizes for her research, including the nternational Bone and Mineral Society Mundy Research Fellowship. In 2022 Penny was awarded her personal chair as Professor of Cancer Biology in the Mellanby Centre for Musculoskeletal Research (University of Sheffield).

Penny's work is focused on cancer metastasis with a particular emphasis on breast cancer dormancy and immune cell regulation and the bone microenvironment. Her work in this field is currently funded by AstraZeneca (UK), Bayer (Germany), Medical Research Council (MRC; UK), Yorkshire Cancer Research (UK) and Breast Cancer Now, including the Patricia Swannell Dormancy and Late Recurrence Programme. Penny works on the editorial board for multiple peer reviewed journals, sits on the former NCRI Bone metastasis strategy working group and is a member of the Cancer and Bone Society Executive Committee. She is also a member of the grant review committees for Breast Cancer Now and The National Science Centre (Poland).



Ask the Experts: Breast cancer dormancy and late recurrence

Frances Turrell

Frances Turrell is a Principal Investigator at the University of Manchester and Manchester Breast Centre (UK). Her research focuses on the role of the microenvironment in breast cancer dormancy and metastasis. Prior to starting her own research group, Frances completed her PhD at the MRC Cancer Unit, University of Cambridge (UK) with Carla Martins before moving to the Institute of cancer Research for her postdoctoral training in Clare Isacke's group.

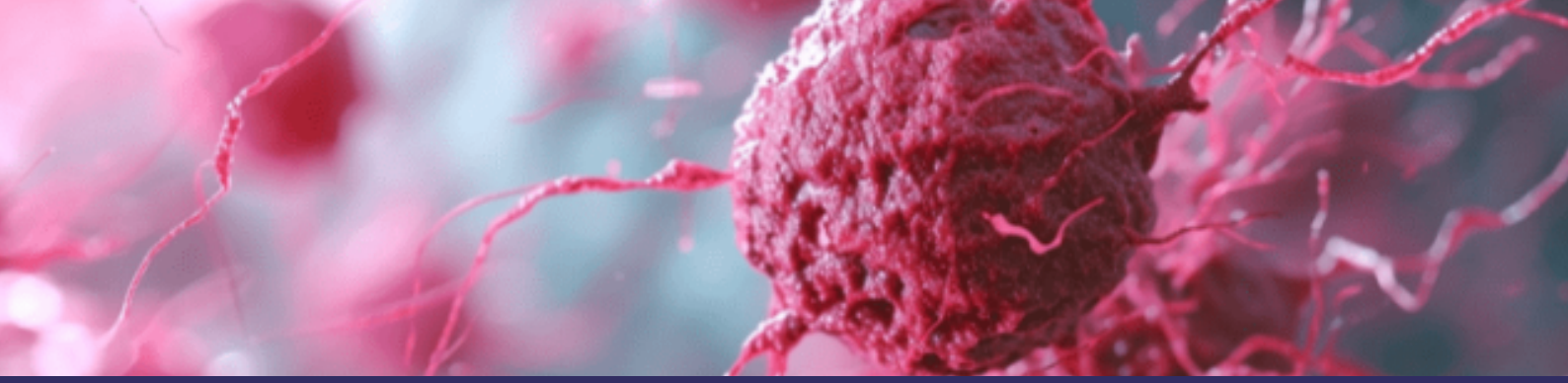
Frances and her team are particularly interested in understanding how the microenvironment at secondary sites changes with age and whether these age-associated changes impact the behavior of disseminated cancer cells in hormone receptor-positive breast cancer. Frances's vision is to understand the crosstalk between cancer cells and immune cells in secondary niches to identify novel therapeutic approaches to target the dormant cancer cells. This year, Frances was awarded funding from the Breast Cancer Now Patricia Swannell Dormancy and Late Recurrence Programme to study age–associated changes in macrophages and their role in breast cancer dormancy and reawakening.

Robert Swannell

With his late wife, Robert established the Patricia Swannell Appeal for Secondary Breast Cancer. He is a British businessman and former chairman of Marks and Spencer (UK).

Robert and his wife Patricia Swannell launched the appeal with Breast Cancer Now in 2022. The appeal was set up to fund critical work in raising awareness of the signs and symptoms of secondary breast cancer, supporting healthcare professionals with education and training; and developing better testing, diagnosis and treatment through funding research tackling the challenge of dormancy.

Patricia was diagnosed with primary breast cancer in 2007 and, after a mastectomy, chemotherapy and radiotherapy, went on to celebrate 5 years all clear. She continued medication for a further 9 years. In 2019, Patricia began to experience pain in her hips and joints and, in 2021, was eventually diagnosed with secondary breast cancer, which had spread to her bones, liver, and abdomen. She passed away in 2023. Patricia devoted the last 18 months of her life to driving change for people affected by secondary breast cancer and fundraised over £1 million for Breast Cancer Now. To date, the fund has raised over £1.4m.



Tackling TNBC recurrence with gdT cell immunotherapies

Triple negative breast cancer (TNBC) accounts for approximately 15% of all breast cancer diagnoses. This aggressive subtype demonstrates a distinct clinical behavior, being more likely than other breast cancers to spread to other organs, particularly the lungs, within 5 years of diagnosis. Limited targeted treatment options underscore the urgent need for novel therapeutic approaches for TNBC patients.
Now, research led by Professor Seth Coffelt at the University of Glasgow (UK) is illuminating a potential new path through immunotherapy, by harnessing the power of immune cells that appear naturally equipped to combat this aggressive disease.

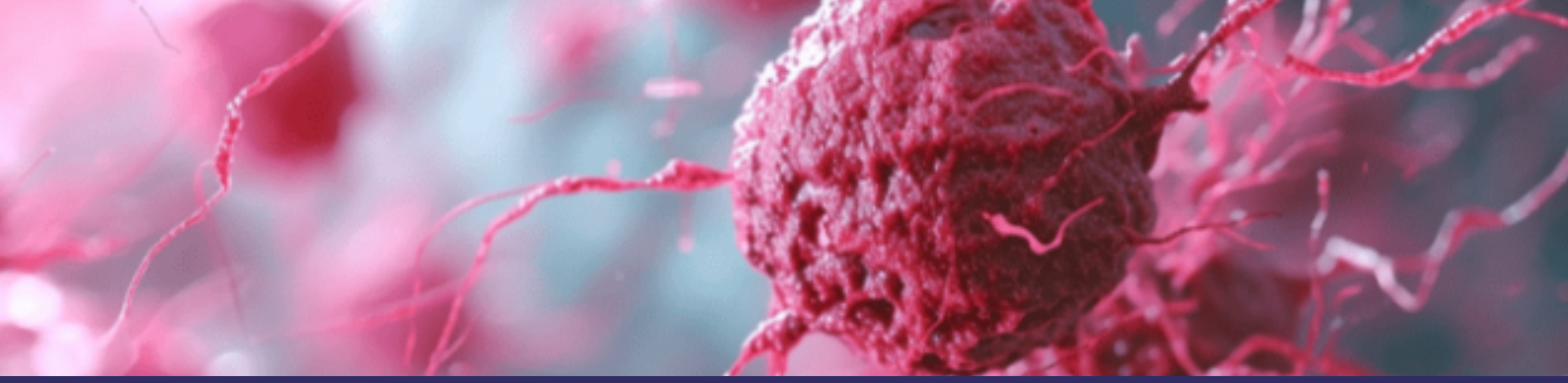
The breakthrough: Nature's cancer killers

The £399,670 research project, funded by Breast Cancer Now and Secondary1st, builds upon Coffelt's previous discovery of CD27 Ly6C gamma delta T cells (gdT cells), immune cells with a unique ability to target TNBC.

What makes these cells noteworthy in their ability to target TNBC cells? According to Coffelt: "Unlike conventional T cells, which rely on presentation of peptides by cancer cells, gdT cells can use a variety of different receptors to recognize TNBC cells." This versatility in recognition mechanisms gives them a significant advantage in identifying and attacking cancer cells that might otherwise evade the immune system.

One of the most intriguing aspects is that these cells are particularly effective in lung tissue, precisely where TNBC often spreads. "gdT cells are naturally enriched in the lung because their normal role is to patrol mucosal tissue and prevent invasion by microorganisms," explains Coffelt. "Because these cells are found at increased numbers in the lung, any cancer cell arriving in the lung will be up against these cells."

This natural positioning could explain why the team's previous research showed these cells can slow the growth of cancer and prevent secondary tumors from developing in the lungs of mice, a finding with potentially profound implications for preventing metastasis.



Tackling TNBC recurrence with gdT cell immunotherapies

The challenge: Finding a needle in a haystack

The research now faces a formidable technical challenge: tracking individual cancer cells as they spread. “Essentially, we need to find a needle in a haystack,” Coffelt notes. “We want to image breast cancer cells as soon as they arrive in the lung after spreading from the primary breast tumor. This spread normally occurs with single cancer cells, so we need to be able to find 1 cancer cell amongst millions of cells in the lung.”

To accomplish this, the team will employ cutting-edge microscopy techniques that enable them to visualize how the location of gdT cells allows them to find breast cancer cells entering the lung.

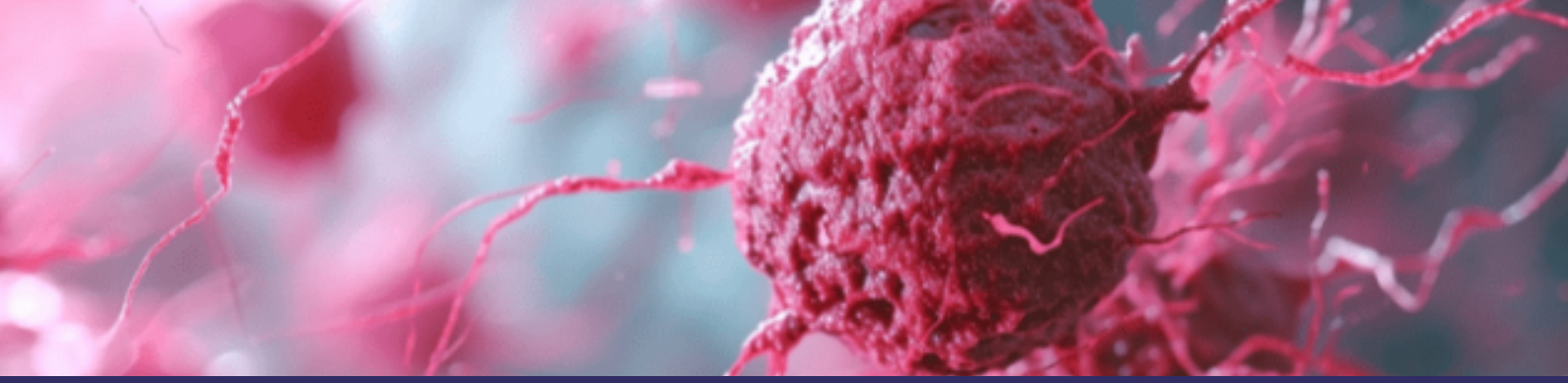
From laboratory to clinic: The path forward

In terms of next steps, the team is focusing on determining the precise mechanisms through which these immune cells combat cancer. “We want to know whether gdT cells can kill breast cancer cells directly or whether they activate other immune cells to prevent metastasis,” says Coffelt.

“For this, we will use mouse models of breast cancer combined with advanced imaging techniques to visualize interactions between breast cancer cells and gdT cells as well as co-culture assays in vitro.”

Speaking on the potential clinical translation, Coffelt noted that gdT immunotherapies are in development, but it’s too early to know how they will work in people and that further research is needed to better understand their mechanisms of action to ensure that they’re as safe and effective as possible.

Coffelt’s vision is clear: “My overall goal is to determine how, when, and where gdT cells kill breast cancer cells, specifically in the metastatic setting. With this information, hopefully gdT cell-based immunotherapies can be used for people with secondary breast cancer.” The road from laboratory discovery to clinical application remains challenging but Coffelt’s research illuminates a path forward that could move us closer to developing therapies that prevent metastasis before it begins.



Tackling TNBC recurrence with gdT cell immunotherapies

Breast Cancer Now is the research and support charity here for anyone affected by breast cancer. Call their free confidential helpline on 0808 800 6000 to speak to their expert nurses or find out more and donate at breastcancernow.org
The mission of Secondary1st is to raise awareness of and raise funds for research into secondary breast cancer. Find out more about Secondary1st at www.secondary1st.org.uk

BREAST CANCER NOW The research & support charity

Interviewee profile:

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During this time, Seth discovered how immune cells cooperate with each other to promote metastasis through the suppression of other immune cells. Seth moved to Scotland in the summer of 2016 to focus on the molecular mechanisms that regulate gd T cell function during the evolution of metastasis and cancer progression. Seth was awarded the British Association for Cancer Research AstraZeneca Young Scientist Frank Rose Award in 2018 and a Career Establishment Award from Cancer Research UK in 2021. Seth became full Professor in 2023.

The opinions expressed in this interview are those of the author and do not necessarily reflect the views of Oncology Central or Taylor & Francis Group.

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RESEARCH ARTICLE

Predictive risk factors of recurrence in breast cancer after neoadjuvant treatment: the NEORISK study

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ABSTRACT

Background: Neoadjuvant chemotherapy (NACT) improves oncologic and cosmetic outcomes in breast cancer (BC), yet recurrence remains a concern. This study identifies factors associated with recurrence at 3 and 5 years in BC patients receiving NACT.

Methods: A retrospective analysis of 933 stage I – III BC patients (2014–2021) evaluated event-free survival (EFS) predictors using multivariate analyses.

Results: Lower 5-year EFS was linked to axillary staging (cN, $p < 0.001$), molecular subtype ($p < 0.001$), surgery type ($p = 0.030$), and post-surgical nodal status (ypN, $p = 0.005$). High recurrence risk was observed with aggressive tumor biology, advanced disease, and residual nodal burden, while favorable responses correlated with better outcomes.

Conclusion: Biological and clinical factors guide post-NACT strategies to reduce recurrence in high-risk BC patients.

PLAIN LANGUAGE SUMMARY

What is this paper about?

In breast cancer, chemotherapy performed before surgery (neoadjuvant chemotherapy) has revolutionized strategies of treatment. It allows cancer size reduction with easier surgery (fewer side effects), choosing the best therapy after operation, and increases lifespan. Despite these advantages, some patients continue to have cancer coming back in the breast, axilla or other parts of the body. Why do these recurrences occur despite those benefits? Our study aims to identify what characteristics may predict the development of recurrence. What is our goal? The purpose is to achieve an early discovery of cancer reactivation in order to use more effective therapies and reduce mortality.

What were the results?

We showed that patients with: 1. cancer with more aggressive attitude (faster growth, lack of target for drugs, faster release of cells to reach other organs); 2. a high cancer size before chemotherapy (in breast or the axillary lymph nodes); and 3. residual cancer during surgery have a high risk of having a new cancer episode. In contrast, patients with tumors that decrease or disappear during chemotherapy have a lower risk of developing recurrence during follow-up.

What do the results mean?

This finding may allow us to identify patients at higher risk of having disease reactivation and modify diagnostic exams with aims to implement earlier diagnosis of this event and improve survival.

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Article highlights

New paradigm of neoadjuvant chemotherapy in the treatment of breast cancer

- The introduction of neoadjuvant chemotherapy in breast cancer treatment has determined improved cosmetic and oncologic outcomes. Despite these benefits, many patients continue to have cancer recurrences.

Knowledge of factors that increased the risk of recurrence could help early diagnosis and improve treatment

- Many studies were largely focused on the evaluation of predictive factors of complete pathologic response. Few data were available regarding predictive factors for risk of recurrence in case of early progression. Identification of clinical and biological predictive and prognostic factors could lead to selecting classes of patients at very high risk of recurrence who could benefit from different follow-up programs aimed at early detection of recurrence. Our single-center analysis showed several variables associated with this increased risk and we have defined them in three groups: pre-chemotherapy, post-chemotherapy, and surgical/pathological response

A high extent of disease at diagnosis, aggressive biology, poor radiological response and high residual disease after surgery were predictive factors of high recurrence.

- Histologic subtype, most prevalent in ductal invasive carcinoma, a high extent of disease on both T and N, aggressive biological subtypes with triple-negative and HER2-positive tumor, poor radiological response to chemotherapy assessed by RECIST criteria and large residual disease on breast and axilla after surgery were factors associated with worse event-free survival.

An initial diagnosis of recurrence improves local and systemic treatment and reduce mortality

- Identification of short- (within 3 years from diagnosis) and long-term (after 5 years from diagnosis) risk factors can promote the development of early diagnostic programs of recurrence in order to improve the treatment of those high-risk patients and reduce mortality.

1. Introduction

Breast cancer (BC) is the most common malignancy globally and a leading cause of cancer mortality in women [1]. Survival improvements are attributed to screening, early diagnosis, a better understanding of tumor biology, and advances in treatments, including biologic and targeted therapies. From a molecular perspective, BC is composed of at least four main so-called intrinsic subtypes, namely luminal A, luminal B, HER2-enriched and basal-like (BL) or triple-negative breast cancer (TNBC), with different clinical behavior, prognosis, and response to different treatments [2]. A significant advancement is the use of neoadjuvant chemotherapy (NACT), which has enhanced treatment options for locally advanced and chemotherapy-responsive tumors, such as TNBC [3,4] and HER2-positive subtypes [5,6].

NACT facilitates tumor downstaging, lowering locoregional recurrence and morbidity, enhancing cosmetic outcomes, enabling personalized adjuvant treatments, and potentially improving survival [7–17]. Studies show that a pathologic complete response (pCR) – the absence of invasive cancer on final histology – is predictive of better survival; however, the correlation between pCR and long-term outcomes remains uncertain [18–22]. Recently, the advent of new neoadjuvant therapeutic regimens, immunotherapy plus CT in TNBC tumors and double-block anti-HER2, pertuzumab/trastuzumab in HER2-positive tumors, increased the pCR and benefit in terms of outcome disease.

Research has explored clinical, pathological and radiological predictors of pCR [21], but fewer studies have investigated factors predicting recurrence, particularly very early recurrence.

This study aims to identify factors associated with a worst event-free survival (EFS; risk of developing loco-regional and/or distant recurrence and death for any causes) in BC patients treated with NACT. Additionally, we analyze factors associated with very early recurrence and death for any causes, defined as the onset of recurrence within 3 years post-CT initiation. We decided to evaluate the risk factors associated with a very-early EFS (within 36 months) to highlight a cohort of patients who could benefit from different follow-up programs of new diagnostic methodologies for even earlier diagnosis of recurrence in order to start early any kind of treatment.

2. Patients and methods

This retrospective, single-center study was conducted at Fondazione Policlinico Universitario Agostino Gemelli IRCCS (FPG), Rome, evaluating BC patients who underwent NACT between January 2014 and June 2021, with follow-up until December 2022. The study included patients with histologically confirmed invasive BC (stages I – III), encompassing all BC subtypes and available clinical follow-up data. Exclusion criteria were prior or concurrent systemic malignancies, history of ipsilateral or contralateral BC, evidence of metastatic disease (stage IV), and receipt of neoadjuvant endocrine therapy.

Data were prospectively collected and updated in a database of FPG that give permission to use them and categorized into three groups: pre-NACT factors, post-NACT factors, and surgical/pathological results (detailed in the Supplementary Materials). Ethical approval was obtained from the Central Ethics Committee (ID 6081; NCT06441240), and the study complied with the Declaration of Helsinki.

2.1. Treatments

NACT was recommended by a multidisciplinary team (MDT), including breast and plastic surgeons, oncologists, radiotherapists, radiologists, pathologists, geriatricians, psychologists, geneticists, and case managers. Treatment decisions were shared according to guidelines [23], and specific systemic regimens are detailed in Supplementary Table S1. Surgical planning followed MDT evaluation based on pre- and post-NACT imaging and genetic assessments. All patients underwent post-NACT locoregional staging using clinical assessment, breast and axillary ultrasound, mammography, and MRI, with radiologic responses evaluated per RECIST 1.1 criteria. Types of breast surgeries included quadrantectomy (Q), level II oncoplastic surgery (OPS), conservative mastectomy with immediate reconstruction (CMiR), and modified radical mastectomy (MRM). Axillary surgery depended on the clinical response to NACT, with methods described in Supplementary Materials.

During surgery, cavity shavings were routinely performed to assess any tumor presence near surgical margins [24]. Definitive histological evaluation was conducted to detect residual invasive tumor, ductal carcinoma in situ (DCIS) and to assess biological features. This evaluation also aims to assess the direct

involvement or distance of the residual tumor from surgical margins. In case of *ink on tumor* for invasive cancer and close margins for in situ neoplasm, patients underwent a new surgery aimed at enlarging those margins. Complete pCR was defined as the absence of invasive carcinoma on the surgical specimen, regardless of DCIS presence [25].

Adjuvant therapy was determined by the MDT based on pre-NACT staging, surgical type, tumor biology, and pathological stage. Patients with TN tumors achieving pCR received no additional treatment, while those with residual invasive disease were treated with capecitabine as previously suggested [3,26]. HER2-positive patients with pCR continued with trastuzumab every 3 weeks up to 18 doses. From 2018, patients with residual HER2-positive disease received trastuzumab – emtansine (TDM-1) for up to 1 year [11]. Hormone receptor-positive patients were given adjuvant hormonal therapy based on menopausal status, and radiotherapy was administered per international recommendations [27,28].

2.2. Follow-up

Follow-up assessments included outpatient visits or telephone interviews (primarily during the COVID-19 pandemic), occurring every 6 months for the first 5 years, then annually for up to 10 years, especially for patients on prolonged hormonal therapy. Evaluations followed the guideline recommendations [23].

2.3. Statistical analysis

Data analysis was performed using SPSS, version 26. Continuous variables were summarized as mean ± standard deviation (median; interquartile range) and compared using ANOVA, while categorical variables were summarized by count and percentage and compared via chi-square tests. Survival curves were generated using the Kaplan – Meier method and compared with the log-rank test, with statistical significance set at $p < 0.05$. Univariate and multivariate analyses for EFS were conducted with Cox regression to evaluate predictive factors. EFS was defined as the period from the start of NACT to locoregional or distant recurrence or death from any cause [29]. Predictive factors for recurrence were assessed at 36 and 60 months, with the 3-year EFS analysis limited to patients followed for over 36 months. Five-year EFS consists in all the events occurred from NACT start to month 60 and 3-year EFS (early-EFS) consists of events occurring from NACT start to month 36. Overall survival (OS) was defined as the time from BC diagnosis to death from any cause, loco-regional recurrence was defined as time between the start of NACT and any recurrence in omo- or contra-lateral breast or homolateral axilla; distant recurrence was defined as time between the start of NACT and recurrence in any of distant organs.

3. Results

From January 2014 to March 2021, 1,054 patients underwent NACT. A total of 121 patients were excluded due to metastatic disease at diagnosis or neoadjuvant hormone therapy. The analysis included 933 patients (see CONSORT diagram in Figure 1).

3.1. Demographic and biological characteristics

Pre-NACT characteristics are summarized in Supplementary Table S2. The median age was 48.8 years (range: 42.1–57.5), with 51.4% of patients of childbearing age and a median BMI of 24.0 kg/m^2 (21.7–27.3). Most cases were invasive ductal carcinoma (64.6%) with high-grade tumors (62.4%). Luminal B tumors were the most prevalent subtype (43.4%), followed by HER2+ (32.4%) and triple-negative (20.3%) tumors. Clinical T2 stage (57.9%) and N1 stage (43.3%) were the most common. Two patients (0.2%) had unknown breast primaries with axillary involvement, and 311 patients (35.5%) had no axillary involvement (cN0).

3.2. Systemic treatment and response to NACT

NACT regimens varied by subtype (Suplementary Table 3). Sequential anthracyclines and taxanes were the most common for luminal tumors (44.9%) and triple-negative tumors (69.8%). HER2+ patients primarily received anthracyclines and taxanes plus trastuzumab (67.7%) or docetaxel, cyclophosphamide and

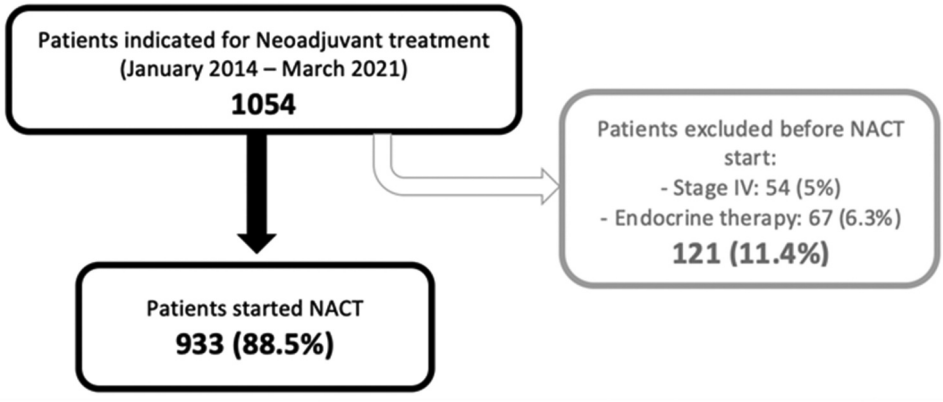

Figure 1. Consort diagram. Patients with breast cancer and indication to NACT between January 2014 and March 2021. The first box shows the total number of patients undergoing NACT in the selected period, the second box shows the excluded patients with their cause, and the last box shows the patients enrolled for the final analysis.

Table 1. Post-NACT assessment of radiological response in T and N by breast MRI for biological subtypes.

Response*	Luminal A ($n = 36$)	Luminal B ($n = 406$)	HER2+ ($n = 302$)	Triple-negative ($n = 189$)	Total ($n = 933$)
Breast (ycT)					
• Complete response	4 (11.1)	111 (27.3)	142 (47.0)	77 (40.7)	334 (35.8)
• Partial response	18 (50.0)	184 (45.3)	117 (38.7)	72 (38.1)	391 (41.9)
• Stable disease	12 (33.3)	97 (23.9)	40 (13.2)	32 (16.9)	181 (19.4)
• Progression disease	2 (5.6)	14 (3.4)	3 (1.0)	8 (4.2)	27 (2.9)
Overall response rate	22 (61.1)	295 (72.6)	259 (85.7)	149 (78.7)	725 (77.7)
Lymph node (ycN)					
• N0	20 (55.6)	279 (68.7)	241 (79.8)	153 (81.0)	693 (74.3)
• N+	16 (44.4)	127 (31.3)	61 (20.2)	36 (19.0)	240 (25.7)

All values represent the number of patients (%). **Evaluation based on RECIST criteria.*

trastuzumab (28.6%). Fewer patients received taxane-free (2.7%) or carboplatin-inclusive regimens (6.4%). Table 1 displays the Post-NACT assessment of radiological response in T and N by breast MRI for biological subtypes.

3.3. Response to NACT

Radiological response to NACT was mostly partial (41.9%) or complete (35.8%) for breast tumors. Complete response rates were similarly high in the axilla (74.3%), with 320 patients (34.3%) showing ycN0 at baseline and an additional 373 patients (39.9%) achieving ycN0 post-NACT. HER2+ and TN tumors showed higher complete response rates than luminal tumors (40.7% and 40.7% in TN and HER2+ vs. 27.3% in Luminal B and 11.1% in Luminal A, $p < 0.0001$). Overall response rates (ORR) were higher in TN and HER2+ tumors than in luminal subtypes (85.7% and 78.7% vs. 61.1% and 72.6%, respectively; $p < 0.0001$). Higher rates of ycN0 were also observed in HER2+ (79.8%) and TN (81.0%) patients compared to luminal subtypes (55.6% in Luminal A and 68.7% in Luminal B; $p < 0.0001$).

3.4. Surgical and pathological outcomes

After NACT, 424 patients (45.4%) underwent quadrantectomy, 106 (11.5%) had oncoplastic surgery, 299 (32.0%) underwent conservative mastectomy with immediate reconstruction, and 104 (11.1%) had modified radical mastectomy (Supplementary Table 4). Pathologic response rates did not differ significantly among the surgical groups ($p = 0.345$).

Pathological evaluation showed that 309 patients (33.1%) achieved a breast pCR. In contrast, 29 patients (3.1%) had residual tumors >50 mm, and 20 (2.1%) had skin, muscle or inflammatory carcinoma involvement, leading to a modified radical mastectomy in 57.1% of these cases. Sentinel lymph node biopsy (SLNB) was performed on 383 patients (41.1%), with a mean of seven nodes excised, and no cancer cells were found in 77.5% (ypT0) (Supplementary Table 5). In the remaining cases, axillary dissection (AD) was performed on patients with lymph node involvement (58.9%), with ypN0 achieved in 158 cases. AD was guided by preoperative lymph node status and clinical palpation when nodes were enlarged. A mean of 4.3 nodes were excised in SLNB cases and 14.6 in AD. Post-NACT, 153 patients (16.4%) had ≥4 lymph nodes involved (ypN2–3).

3.5. Disease outcomes and predictive factors

At a median follow-up of 45.8 months (27.4–62.9), 182 patients (19.5%) experienced cancer recurrence or death: 70 (7.5%) had locoregional recurrence, 108 (11.6%) systemic recurrence and 4 (0.4%) died. The remaining 751 patients (80.5%) were recurrence-free. The 5-year EFS was 78.5%, and the 3-year EFS was 82.8%.

The median OS was not reached; 113 deaths (12.1%) were reported, with 109 (11.7%) due to systemic disease progression. OS rates at 5 and 3 years were 81.6% and 90.7%, respectively.

Factors associated with recurrence included molecular subtype, initial T and N stages, type of surgery, and pathologic response (Figure 2). TN patients had the lowest 5-year EFS (74.0%), followed by Luminal A (77.1%), Luminal B (76.3%), and HER2+ (82.9%) subtypes ($p = 0.007$). EFS was also lower with more advanced T stage (T1: 85.6%; T2: 80.7%; T3: 73.6%; T4: 52.5%; $p < 0.0001$) and higher N stage (cN0: 85.4%; cN1: 79.1%; cN2–3: 65.5%; $p < 0.0001$). Quadrantectomy showed the highest 5-year EFS (84.5%), while modified radical mastectomy had the lowest (54.1%; $p < 0.0001$). Patients with ypT0 showed higher 5-year EFS (89.4%) compared to those with ypT3 (53.7%) and ypT4 (21.2%; $p < 0.0001$). ypN0 patients also had better 5-year EFS (85.6%) compared to ypN2–3 patients (51.0%; $p < 0.0001$).

In HER2+ patients, pCR was associated with higher EFS (93.3% vs. 79.2%, $p = 0.021$), and in TN patients, pCR was also predictive of better outcomes (86.9% vs. 70.7%, $p = 0.046$) (Supplementary Figure S1).

3.6. Univariate and multivariate analyses

Supplementary Table 6 summarizes the results of univariate and multivariate analyses for EFS. Univariate analysis identified significant recurrence predictors, including histologic subtype ($p = 0.027$), clinical T and N stages ($p < 0.001$), molecular subtype ($p = 0.008$), radiologic response ($p < 0.001$), surgery type ($p < 0.001$), pCR ($p = 0.001$), and final tumor (ypT, $p < 0.001$) and nodal status (ypN, $p < 0.001$). In multivariate analysis, four independent predictors of recurrence were confirmed: clinical N stage ($p < 0.001$), molecular subtype ($p < 0.001$), type of surgery ($p = 0.030$), and ypN status ($p = 0.005$).

3.7. Very early progression outcomes

After excluding patients with a follow-up of <36 months, this analysis included 638 patients, with 126 (19.7%) experiencing

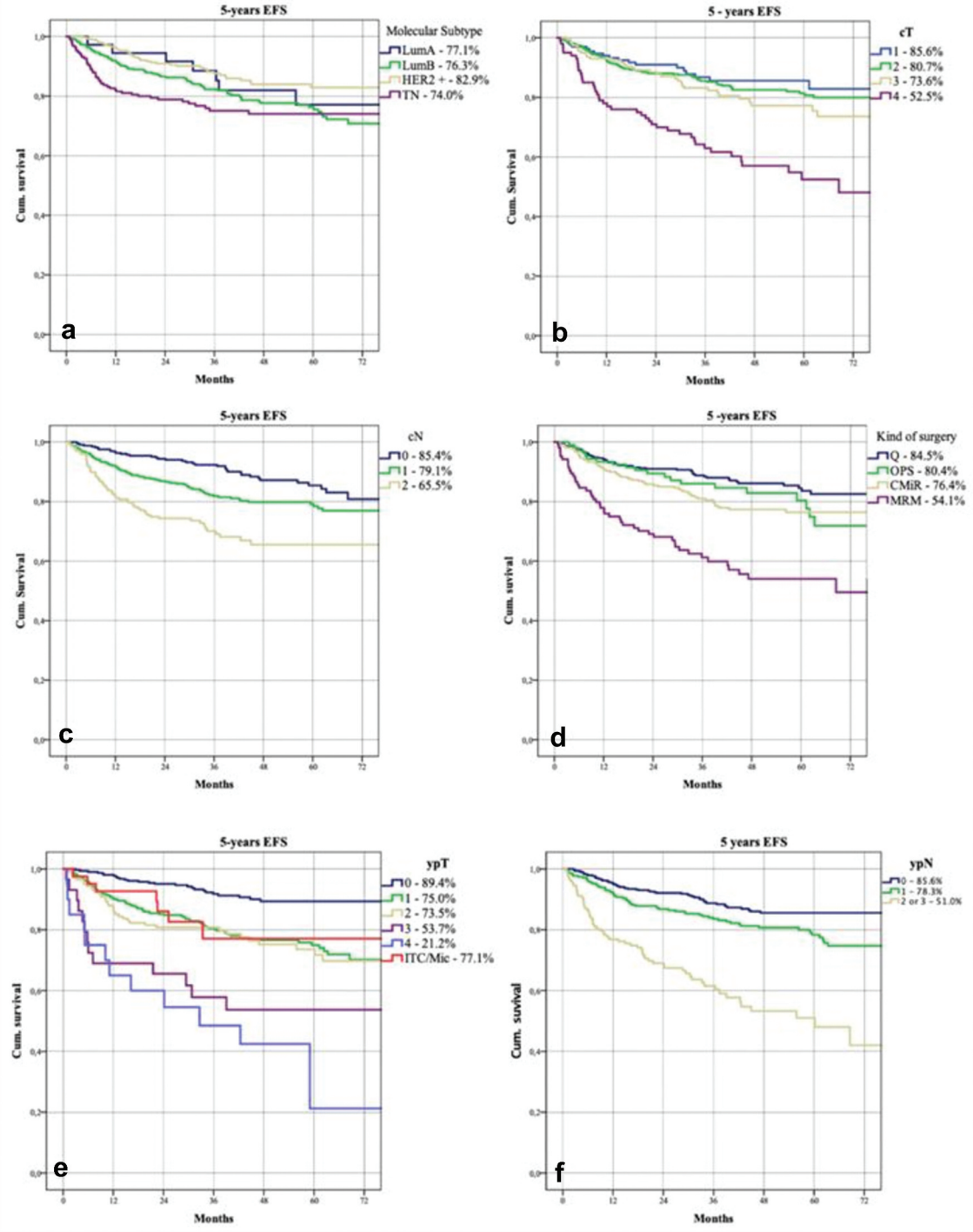

Figure 2. Evaluation of 5-year event free survival. (a) molecular subtype. (b) Baseline clinical tumor stage. (c) Baseline clinical node stage. (d) Kind of surgery. (e) Breast pathological response. (f) Axillary pathological response to NACT.

CMiR, conservative mastectomy with immediate reconstruction; MRM, modified radical mastectomy; OPS, oncoplastic surgery; Q, quadrantectomy.

events (72 distant, 52 locoregional recurrences, and two deaths). Predictive factors for 3-year EFS included tumor size (cT, $p < 0.001$), axillary staging (cN, $p < 0.001$), molecular subtype ($p = 0.042$), radiologic response to NACT ($p < 0.001$), surgery type ($p < 0.001$), and histologic response on ypT ($p < 0.001$) and ypN ($p < 0.001$). Multivariate analysis confirmed cN stage ($p < 0.001$), molecular subtype ($p = 0.007$), surgery type ($p = 0.009$), and ypN ($p = 0.003$) as 3-year EFS predictors (Table 2). Supplementary Table 7 summarizes the results of univariate and multivariable analysis for predictive factors of 3-year EFS. Age, menopausal status and pathological variants of *BRCA* genes were not found to be predictive of recurrence at both 3 years and 5 years.

4. Discussion

The introduction of NACT has transformed the treatment approach for BC, particularly for patients with locally advanced

Table 2. Significative predictive factors for event-free survival.

	Univariate analysis			Multivariable analysis		
Characteristics	*OR*	*p-value*	*95% CI*	*OR*	*p-value*	*95% CI*
cN		**<0.0001**			**<0.0001**	
• 0	Ref.			Ref.		
• 1	3.046	**<0.0001**	1.783–5.205	3.135	**<0.0001**	1.777–5.532
• 2 or 3	5.947	**<0.0001**	3.390–10.430	5.426	**<0.0001**	2.878–10.230
Molecular subtype		**0.042**			**0.007**	
• Luminal A	Ref.			Ref.		
• Luminal B	2.243	0.172	0.704–7.152	2.761	0.093	0.844–9.027
• TN	1.610	0.431	0.492–5.268	2.692	0.113	0.791–9.158
• HER2	3.030	0.066	0.928–9.984	5.312	**0.008**	1.544–18.278
Kind of surgery		**<0.0001**			**0.009**	
• Q	0.271	**<0.0001**	0.166–0.440	0.604	0.114	0.324–1.129
• OPS	0.319	**0.001**	0.164–0.619	0.754	0.484	0.355–1.605
• CMiR	0.501	**0.002**	0.321–0.783	1.302	0.379	0.723–2.345
• MRM	Ref.			Ref.		
ypN		**<0.0001**			**0.003**	
• 0	Ref.			Ref.		
• 1	1.448	0.096	0.937–2.239	0.768	0.317	0.457–1.289
• 2 or 3	4.682	**<0.0001**	3.048–7.194	1.768	0.056	0.933–3.148

tumors or chemoresponsive biological profiles, such as HER2-positive and TN cancers [10–17,30]. Clinical and pathologic responses to NACT have been associated with favorable prognosis, including reduced risk of locoregional and systemic recurrence. The analysis by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed a local recurrence of 21.4%, a distant recurrence of 38.2% and a death for any causes of 0.9% after 15 years of follow-up [9]. On the other hand, in the analysis recently reported by Falo et al. in 482 patients, the 10-year estimated disease-free survival was 77.3% (95% CI 73.3–81.4%) and the BC-specific survival was 83.7% (95% CI 80.3–87.2%) [31].

The results of our analysis report a cumulative risk of recurrence after 5 years of 21.5% (EFS of 78.5%) and a risk of death of 18.4% (OS 81.6%). The worse OS and recurrence risk could be explained by the characteristics of the patients included in our study. Compared with the patients enrolled in the previous reported studies, our patients presented worst clinical and biological characteristics (cT4: 11%, cN2–3: 21%; TNBC: 20%; HER2 enriched; 32%). This mainly explains the high number of systemic recurrences and mortality.

Numerous studies have sought to identify predictors of NACT response; however, despite the prognostic significance of pCR, it remains an imperfect surrogate for EFS and OS [32].

Although survival outcomes have improved, some patients continue to face risks of locoregional recurrence and distant metastases, sometimes very early (within 36 months). While many studies focus on pCR as a predictor of OS, few have assessed factors specifically predictive of EFS, particularly early EFS [33–35]. We also decided to evaluate the risk factors associated with very-early recurrence (within 36 months) to possibly highlight a cohort of patients who deserve more attention during the follow-up with the purpose of catching relapses earlier.

Our study analyzed a cohort of BC patients (stage I – III) who underwent NACT, finding a 19.5% recurrence rate over a median follow-up of 46 months. This study aimed to examine factors predictive of both long-term and early EFS, dividing the predictors into three categories: pre-NACT factors, post-NACT factors, and surgical/pathological response.

Among pre-NACT factors, histological subtype (ductal invasive, lobular invasive, and no special type) was associated with recurrence risk ($p = 0.027$). Molecular subtype also emerged as an independent prognostic factor ($p = 0.008$), consistent with literature indicating higher recurrence risk in TN and HER2-positive cancers [36,37]. Thus, the molecular subtype influences the risk of recurrence. Particularly luminal subtypes seemed to have much more delayed recurrence than TNBC and HER2-positive cancers. Probably this difference is associated not only to the intrinsic genomic profile of estrogen-positive tumors, but also to the endocrine adjuvant therapy, that is precluded in TNBC patients and in HER2-positive BC patients without hormonal receptors.

Clinical T and N stages at diagnosis were both confirmed as independent predictors of recurrence ($p < 0.001$), suggesting that initial tumor extent and nodal involvement are important in recurrence risk assessment.

Our findings align with previous studies, such as Simons et al., which showed clinical T4 stage was associated with a significantly higher risk of distant disease-free survival (HR 3.336, 95% CI 1.214–9.165, $p = 0.019$) in a cohort of 561 patients [38]. In multivariate analysis, clinical N stage (cN) and molecular subtype remained independently predictive of EFS, with HER2+ cancer showing the strongest association with recurrence risk (HR 4.151, $p = 0.002$).

Factors identified here align with those predictive of pCR reported in the literature [33,35–37,39]. Specifically, a recent meta-analysis by Mittal et al. demonstrated that tumor size and nodal positivity at diagnosis correlated with worse 3-year disease-free survival [40]. Age at diagnosis does not affect 3- and 5-year EFS.

In our cohort, these pre-NACT factors were also predictive of recurrence beyond the 3-year mark. Multivariate analysis of

3-year EFS showed clinical N stage ($p < 0.001$) and molecular subtype ($p < 0.0001$) were particularly influential, with HER2+ status linked to higher recurrence risk (HR 5.312, $p = 0.008$).

Regarding post-NACT predictors, radiological response assessed at treatment completion by RECIST criteria emerged as a significant predictor of EFS and 3-year EFS ($p < 0.001$), although it did not retain significance in multivariate analysis.

Surgical approach and final histopathological evaluation were both significant predictors of recurrence risk. Among surgical approaches, quadrantectomy was associated with the most favorable EFS ($p = 0.030$) and may indicate a protective effect. This association could reflect a selection bias, as patients with complete radiologic response may have been more likely to receive breast-conserving surgery than those requiring modified radical mastectomy (MRM) due to disease progression during NACT [41].

Histopathologic residual burden in the breast (ypT) and nodes (ypN) were strong predictors of EFS. For instance, patients achieving ypT0 exhibited the best 5-year EFS (89.4%), with progressively lower EFS as residual tumor size increased (ypT3: 53.7%; ypT4: 21.2%, $p < 0.0001$). Lymph node involvement after NACT (ypN) also significantly influenced EFS, with patients having ypN0 faring better than those with ypN2–3 (5-year EFS 85.6% vs. 51.0%, $p < 0.0001$). This aligns with findings from our group, where positive sentinel lymph node findings correlated with distant metastasis risk after 24 months of follow-up [36].

Simons et al. also demonstrated that pCR in both breast and axilla correlated positively with disease-free survival (HR 0.467, 95% CI 0.238–0.918, $p = 0.027$ for breast; HR 0.332, 95% CI 0.193–0.572, $p = 0.001$ for axilla) [38]. Thus, tumors with a more aggressive biological profile (e.g., HER2+), greater initial disease burden (cT4, cN2–3), and significant post-surgical residual disease (ypN2–3) are associated with higher recurrence risk, while tumors responding well to NACT and treated with breast-conserving surgery demonstrate lower recurrence rates. Direct margin assessment regarding the risk of local recurrence was not included in this work. Anyway, in the multidisciplinary team, all patients were evaluated after surgery and in case of tumor infiltrated margins or close for tumors in situ, decision for surgery for widening the margins was performed.

Adjuvant treatments also influenced the EFS. The recent introduction of T-DM1 in HER2-positive patients with residual tumor after neoadjuvant therapy in according to the Katherine study [9] resulted in a better EFS when compared with trastuzumab alone (90.7% vs 68.8%, respectively; $p < 0.0001$ – data not shown). A better EFS without statistical significance was present in TNBC patients treated with capecitabine (77.8% vs 67.5%; $p = 0.124$), in according to standard of care as resulted by Masuda et al. [10].

This study's strengths include a large single-center sample size, enabling analysis of a broad spectrum of BC biology. Our examination of long-term and early-term (36-month) predictors also adds value for patient monitoring and follow-up.

However, the single-center design may limit generalizability due to clinical and pathological biases. Moreover, this study's retrospective nature lacks the genomic analysis that might provide additional insight into recurrence risk. The absence of centralized radiological review presents a potential limitation. Another weakness is the lack of assessment of genomic and molecule profiling that may influence the risk of recurrence. The introduction of the new vision to capture minimal residual disease after surgery by liquid biopsy could be open personalized approaches in the adjuvant setting. Overall, even if previous studies investigated potential clinical and pathological factors associated with recurrence risk in patients with BC patients underwent NACT according to our knowledge, no prior analyses included clinical, surgical, anatomopathological, radiological and biological factors in the same study.

5. Conclusion

This study highlights predictive factors for long-term and short-term outcomes in BC patients undergoing NACT. Our findings support more detailed assessments for patients being considered for NACT, although further multicenter studies with centralized imaging and genomic analyses are required to confirm these observations.

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Author contribution

Antonio Franco contributed to Conceptualization, Methodology, Investigation, Data curation, Formal Analysis; Writing-Original Draft; Luisa Carbognin contributed to Conceptualization, Methodology, Investigation, Writing-Original Draft; Ida Paris contributed to Conceptualization, Investigation, Supervision, Writing – Original Draft; Alba Di Leone contributed to Conceptualization, Investigation, Supervision, Writing – Original Draft; Armando Orlandi contributed to Investigations, Supervision, Writing-Original Draft; Fabio Marazzi contributed to Investigations, Supervision, Writing-Original Draft; Antonino Mule contributed to Investigations, Supervision, Writing-Original Draft; Paolo Belli contributed to Conceptualization; Methodology, Supervision, Writing-Original Draft; Alessandro Rossi contributed to Investigation; Data curation; Formal Analysis; Writing-Original Draft; Stefano Magno contributed to Supervision; Investigation; Antonella Palazzo contributed to Conceptualization; Data Curation; Writing-Original Draft; Valeria Masiello contributed to Conceptualization; Data Curation; Writing-Original Draft; Santoro Angela contributed to Data Curation; Formal analysis; Writing-Original Draft; Paola Fuso contributed to Investigation, Data curation; Sabatino D'Archi contributed to Investigation, Data curation; Lorenzo Scardina contributed to Investigation, Data curation; Diana Giannarelli contributed to Conceptualization, Data curation, Formal analysis, Writing – Review & Editing; Riccardo Masetti contributed to Conceptualization, Supervision, Writing – Review & Editing, Gianluca Franceschini contributed to Conceptualization, Supervision, Writing – Review & Editing; Alessandra Fabi contributed to Conceptualization, Investigation; Methodology; Supervision, Writing – Review & Editing.

Disclosure statement

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Ethical Declaration

The study was conducted in accordance with the ethical standards of Declaration of Helsinki and the protocol was approved by Central Ethics Committee (ID 6081; NCT06441240).

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Data availability statement

The data underlying this article are available in the article and in its online supplementary material. All data are available from the Corresponding Author upon reasonable request.

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REVIEW

Locoregional recurrence in triple negative breast cancer: past, present, and future

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ABSTRACT

Introduction: Triple negative breast cancer (TNBC) is a rare but aggressive biological subtype of breast cancer associated with higher locoregional and distant recurrence rates and lower overall survival despite advancements in diagnostic and treatment strategies.

Areas covered: This review explores the evolving landscape of locoregional recurrence (LRR) in TNBC with improved surgical and radiation therapy delivery techniques including salvage breast conserving surgery (SBCS), re-irradiation, and thermo-radiation. We review current retrospective and prospective, albeit limited, clinical data highlighting the optimal management of locoregionally recurrent TNBC. We also discuss tumor genomic profiling and transcriptome analysis and review potential investigational directions.

Expert opinion: Significant progress has been made in the prevention of LRR but rates remain suboptimal, particularly in the TNBC population, and outcomes following LRR are poor. Further prospective studies are needed to identify the most effective and safest systemic therapy regimens and to whom it should be offered. There has been growing interest in the role of molecular markers, genomic signatures, and tumor microenvironment in predicting outcomes and guiding LRR treatment. Transcriptome analyses and biomarker-driven investigations are currently being studied and represent a promising era of development in the management of LRR.

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Local recurrence; locoregional recurrence; regional recurrence; triple negative breast cancer; transcriptome analysis

1. Introduction

Patients with curable breast cancer (BC) unfortunately remain at risk of local or distant recurrence. BC is a heterogeneous disease with variable biomarker expression, pattern of disease spread, and response to treatment, and there are four major molecular subtypes of BC: luminal-A, luminal-B, human epidermal growth factor receptor-2 (HER2), and basal subtypes [1]. Basal molecular subtype largely represents triple negative breast cancer (TNBC) which tends to have a higher risk of local or distant recurrence. Breast or chest wall have been the common sites of LRR in luminal-A, luminal-B or HER2 subtypes, whereas regional lymph nodes or chest wall are the more common in TNBC [1].

TNBCs account for approximately 15–20% of all BCs. A rising body of literature has suggested a strong association of molecular subtype and risk of LRR of BC, with highest risk of LRR with TNBC and HER2-expressing tumors in absence of HER2-directed treatments [2]. This risk of recurrence remains high despite mastectomy and even in the setting of postmastectomy radiation, again highlighting the intrinsic aggressive nature of this TNBC subtype. Multiple reviews have estimated a 8–10% 5-year risk of LRR in setting of BCS, and almost 20% 5-year risk of LRR after mastectomy for basal subtype, 7–10% 5-year risk of LRR in setting of BCS, 13% 5-year LRR risk for mastectomy for HER2-enriched subtype, and up to 4% 5-year LRR risk in setting of BCS and up to 3% 5-year LRR risk after mastectomy for luminal A and B subtypes combined [2].

In terms of local recurrence, it is important to differentiate between locoregional recurrence (LRR), which may present as an ipsilateral breast tumor relapse (IBTR), and development of a new primary tumor. LRR occurs when the initial tumor reappears in the ipsilateral breast, chest wall, or lymph nodes. All patients with LRR should get repeat biopsy with evaluation of breast biomarkers of recurrent disease, as well as systemic staging studies to rule out distant metastases [3]. Patients with synchronous metastatic disease should be treated as stage IV disease with systemic therapies, although select patients may be offered local therapies for palliative disease control [3]. Alternatively, the IBTR may represent a new primary tumor altogether. A new primary tumor is defined as one with different histological properties, located in a different region of the same breast, or with different flow cytometry findings, compared to the original primary tumor [4]. Smith et al. reviewed 1152 patients treated for BC with breast conservation surgery (BCS) and radiation therapy (RT), 136 of which were identified as IBTR as their primary site of failure. Of those 136, 70 were classified as new primaries, and 60 were classified as true relapses, while 6 unclassified [4]. New primaries were defined as such if the relapse changed in one or more of the following: histology, location, DNA flow cytometry. Interestingly, the nodal status, estrogen and progesterone positivity and adjuvant therapy did not vary between those who were classified as new primaries or true recurrences. Tumors classified as new primaries had a better

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Article highlights

- Distinct molecular mutations and gene expression patterns have been associated including LRR risk and may provide insight into treatment response and clinical outcomes.
- Repeat biopsy and breast cancer markers should be repeated to distinguish between LRR and new breast cancer primary.
- Salvage mastectomy is historically considered standard of care treatment in LRR although SBCS can be considered in select patients.
- Repeat radiation therapy can be offered to select patients in conjunction with surgery or systemic therapy to achieve better outcomes.
- Chemotherapy is likely to be beneficial for TNBC LRR based on the findings of the prospective CALOR trial, though it must be noted CALOR trial only included patients with optimal resection of local recurrence.

overall survival (OS) at 10 years, 75% versus 55% noted for true relapses ($p < 0.001$) [4,5].

Whether effective definitive therapies are available for LRR is a major determinant of long-term prognosis as recurrences that are deemed resectable or amenable to definitive radiation or systemic therapy generally portend a favorable prognosis [5]. In this review, we will revisit risk factors and prognosis of LRR, discuss role of [repeat] surgery or radiation, summarize role of systemic therapy, and share molecular determinants of prediction and response of treatment in TNBC LRR.

2. Risk factors for TNBC LRR

Disease-free interval (DFI) following treatment for the initial BC is a well-established prognostic factor for LRR, with longer DFI strongly independently associated with improved survival (long DFI versus short DFI: HR 0.65, 95% CI 0.48–0.88; medium DFI versus short DFI: HR 0.81, 95% CI 0.65–1.01) [6]. Other negative prognostic factors include: age (greater than or equal to 60 years old), number of positive lymph nodes on initial treatment (4 or more), primary tumor size (≥2 cm), and histology (invasive disease associated with worse outcomes) [7]. LRR is significantly more common in Black non-Hispanic patients (40%) and in Hispanic patients (18%), compared to White non-Hispanics with a rate of 11% [8]. Additional risk factors associated with a high probability of LRR for all molecular subtypes include: younger age, positive surgical margin, lymphovascular invasion presence, and omission of adjuvant radiation therapy [9].

3. Prognosis

Patients with LRRs are at an unequivocally higher risk of distant metastases and poor clinical outcomes [10,11]. Halverson et al. reported a 5-year and 10-year survival rate of 43% and 26% in 224 postmastectomy patients with LRR and subsequent treatment with RT, respectively [12]. Similarly, in trials led by the Danish Breast Cancer Group, up to 50% of postmastectomy patients who experienced LRR developed distant metastases within 2 years [13]. Compared to patients with other BC subtypes, patients with TNBC LRR have poorer clinical short and long-term outcomes, including worse OS [14].

The DFI prior to an LRR has been associated with survival after LRR, with longer DFI predicting a longer survival [6]. In addition, age and surgical removal of recurrence have been associated with survival outcomes following LRR management. Interestingly, chemotherapy or hormone therapy (for all molecular subtypes) did not suggest a strong association with survival after an LRR event in after analyzed with covariates. As expected, recurrence during adjuvant therapy likely suggests treatment resistance [6].

Recurrence location and nodal involvement have been shown to be prognostic factors as well. Pooled analyses of the National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials showed a much inferior 5-year distant-disease free survival (DDFS) in IBTR in node positive (51.4%) versus node negative patients (67%) [10,11]. Among nodal recurrences, the 5-year DDFS rates were 31.5% for axillary recurrences and 12.1% for supraclavicular events [10,11].

Second LRRs and distance metastases are common following treatment of an LRR and these patients have a particularly poor prognosis. In the CALOR trial with a median follow-up after subsequent BC recurrence of 3.67 years, 47% of patients with second LRRs and 51% with a distant recurrence had died [15]. Although hormone receptor positivity data were available, HER2 status was not reported so exactly how these results apply to TNBCs remains to be determined.

Early recurrence, defined as LRR within two years of initial BC diagnosis, is widely associated with poor survival. One study found that the 5-year OS after LRR occurring within the 2-year interval was only 19.5% [11]. Other predictors of mortality include: older age, nodal involvement, large tumor size (≥2.0 cm), multiple LRR, ER positivity, Black race, and higher body mass index (BMI) [10,11,13].

It has also been noted that TNBC has a distinct pattern of LRR and has a high risk of recurrence in the first 2 years after diagnosis, peak at 2–3 years followed by a decline in recurrence risk over the next 5 years, with a low risk thereafter [16]. In contrast to other BC subtypes, TNBC distant recurrences have been rarely shown to be preceded by a LRR event, and LRR alone may not be a predictor of distant recurrence [16].

4. Management of LRR

4.1. Role of surgery

Among patients with IBTR who had previously received BCS, salvage mastectomy (SM) is historically considered standard of care treatment. However, studies indicate that salvage breast conservation surgery (SBCS) can be considered for patients who have undergone previous BCS [17]. A study [18] that followed 146 patients with IBTR who previously underwent BCS found that there was no significant difference in 10-year survival between patients who received SM and SBCS. RT following SBCS yields improved local control in patients who have not previously received RT. A review of 355 patients who were initially treated with BCS showed that those treated with SBCS and RT had a 5-year actuarial local control rate of 82% [19]. This approach is typically reserved for patients with small tumors (≤2 cm) whose relapse occurs >48 months after diagnosis [19]. Those that undergo completion mastectomies,

many groups have reported favorable outcomes with skin sparing and even with nipple-sparing mastectomy with history of whole-breast irradiation, but skin and nipple necrosis rates were higher compared to those without history of radiation [20].

For patients with IBTR who have previously undergone mastectomy, the role of further surgery has not been clearly established. For chest wall lesions that are resectable, chest wall resection (CWR) followed by RT is generally recommended [21]. In this setting, CWR has been shown to improve OS as demonstrated by a retrospective study that studied 44 patients. The median overall survival (mOS) was 4.8 years and 5-year survival was 45% [22]. If resection is not feasible, treatment with RT and systemic chemotherapy is considered [21].

If axillary recurrence is suspected, suspicious lymph nodes should undergo fine needle biopsy (FNA). In patients who have undergone sentinel lymph node biopsy (SLNB) previously, stage I and II axillary lymph node dissection (ALND) should be performed. If ALND has been performed previously, axillary exploration and resection is recommended [17]. A recent study that retrospectively reviewed 2141 patients with IBTR after lumpectomy demonstrated survival benefit for patients who undergo surgical axillary staging (SAS) [23]. 524 patients did not receive SAS and 1617 received SAS either in form of repeat SNLB or ALND. 10-year OS was 61.9% in the non-surgical group and 73.8% in the SAS group ($p = 0.001$). This study also demonstrated similar 10-year OS benefit among patients treated with repeat SNLB and ALND [23]. A unique challenge for patients with IBTR is that repeat SNLB can be difficult, and often unsuccessful, and the role of ALND after repeat SNLB is unclear. The Sentinel Node and Recurrent Breast Cancer (SNARB) study explored this issue and identified 60 patients among 239 who underwent repeat SNLB which was unsuccessful and underwent subsequent ALND. This study demonstrated that risk of regional recurrence in patients with IBTR after unsuccessful repeat SNLB was very low [24]. The 5-year regional recurrence rate was 0% in the patients who underwent ALND and 3.7% in the patients who did not undergo ALND ($p = 0.113$). Among the 179 patients who did not undergo ALND, after median follow up time of 5.1 years, only 7 developed regional recurrence and none of those cases occurred in the ipsilateral axilla. This study demonstrates that additional surgical intervention, such as ALND, is not always indicated in patients who had unsuccessful repeat SNLB [24].

For patients choosing to undergo mastectomy, breast reconstruction can be offered and is typically considered safe. Guidelines have not been established for reconstruction in the setting of LRR, and requires discussion and shared decision making between the medical team and the patient regarding timing and reconstruction approach [17]. For those undergoing completion mastectomy for IBTR with or without reconstruction, historically autologous tissue reconstruction was preferred because radiated tissue may not allow further tissue expansion to accommodate implant-based reconstruction [3]. With the availability of acellular dermal matrices to fully cover the implant, implant-based reconstruction may be considered though complication rate may be higher compared to autologous tissue-based reconstruction [3]. Several studies have explored success and failure rates of reconstruction and radiation which have yielded similar outcomes for patients who were treated with radiation before or after reconstruction [25,26]. Conversely, a study evaluating 4781 patients who previously underwent radiation found that amongst patients who have underwent radiation, method of reconstruction impacted outcomes [27]. Eighty percent of the studied patients underwent implant reconstruction. A larger percentage of patients who underwent implant reconstruction (45.3%) experienced overall complications compared to those that underwent autologous reconstruction (30.8%). The implant reconstruction cohort also had higher reconstruction failure rate (29.4%) in comparison to the autologous reconstruction cohort (4.3%) [27]. Concerns have also been raised about reconstruction outcomes and complication rates for patients who require systemic chemotherapy. The potential delay for chemotherapy initiation due to reconstruction is a worry shared by patients and clinicians. However, a systematic review evaluated 14 studies comprising 5270 patients total who had received adjuvant chemotherapy found that breast reconstruction did not necessarily delay start of chemotherapy after surgery [28]. Additionally, studies have shown comparable complication rates among patients who underwent reconstruction and did or did not receive neoadjuvant chemotherapy [29].

When determining whether patients with BC and subsequent LRR are suitable for surgery, surgical candidacy is determined by several patient characteristics. Important factors to consider include: prior history of RT, presence of metastatic disease, and performance status. Patients with inoperable metastatic, regional nodal, or extensive local recurrent disease may not benefit from revision [17]. To date, there are no specific recommendations pertaining to surgical management of LRR in TNBC and current strategies are extrapolated from general LRR guidelines across subtypes.

4.2. Role of radiation/reirradiation

RT is widely used in the adjuvant setting to prevent LRR in patients with BC [30,31]. The role of RT in the treatment of LRR remains a therapeutic challenge as several factors must be considered including patient characteristics, tumor biology, and prior therapies used for the initial BC [32]. Generally, it is given in conjunction with surgical intervention and/or systemic therapies in a multi-modality approach. Nevertheless, RT (and reirradiation) remains a component of definitive locoregional therapy and is often employed for palliative purposes [33].

As previously discussed, SM or SBCS remain the standard of care for IBTR in patients who have undergone BCS and whole-breast adjuvant RT for the initial BC [3]. RT is often considered in the salvage setting to improve locoregional control. Reirradiation is potentially feasible because most of the previously irradiated tissue is removed during a SM although multidisciplinary consensus is recommended [34]. The emergence of partial breast irradiation (PBI) has allowed for the use of reirradiation in cases where a second breast conservation surgery is pursued. In the NRG Oncology/RTOG 1014 phase II clinical trial [35], both distant metastasis free survival (DMFS)

and OS rates at 5 years were 95% (95% CI, 85%-98%) in patients receiving PBI following second lumpectomy for LRR. The safety profile with this approach was promising with only 7% of patients reporting a grade 3 treatment-related adverse event and no documented grade 4 events. The data supporting the addition of RT after SBCS was strengthened by a systematic review that showed improved local control in the BCS and reirradiation group over the BCS alone group [36]. Other novel radiation delivery techniques include modified radiation fields, electrons, twice-daily radiation, pulse-dose-rate brachytherapy, hyperthermia, and concurrent systemic therapy [33,37–48]. Reirradation with the addition of local hyperthermia therapy (thermoradiation) has been compared to reirradiation alone in several small trials and these data were aggregated in a systematic review and meta-analysis [49]. Findings showed the thermoradiation cohort achieved a complete response rate of 60.2% compared to 38.1% in the radiation alone group (OR 2.64, 95% CI1.66–4.18; $p < 0.0001$) with minimal toxicities. Notably, over half of the 1,483 patients had prior history of RT, suggesting that thermoradiation is a viable option in this subset of patients.

In patients who did not originally receive RT as part of their treatment plan, mainly those who underwent mastectomy for the initial BC, comprehensive locoregional radiation should be offered in the event of LRR. In the absence of intact breast tissue, these recurrences tend to occur in the chest wall and regional nodal basin. One study found that the ability to use RT to treat chest wall recurrences in postmastectomy patients was an independent predictor of improved outcomes [50]. It should be mentioned that this study predated advancements in modern systemic therapies so the initial management of patients in this study does not reflect the current BC treatment landscape. Combining RT with another treatment modality to eliminate gross disease, whether it be with surgical resection of the LRR or with neoadjuvant chemotherapy, resulted in improved local control and OS compared to RT alone [51,52].

However, selection of patients for reirradiation is complex, as the risk for treatment-related toxicity increases with repeat RT [48]. Evaluation of any previous RT history is of utmost importance as it informs future clinical decisions pertaining to dosage and radiation fields. The most common side effects of radiation therapy include skin erythema, fatigue, and edema. Long-term complications may include fibrosis, telangiectasia, lymphedema, and a small increased risk of secondary malignancies [53,54]. There are ongoing efforts to continue improving RT methods, particularly in the setting of reirradiation to mitigate these toxicities.

It is important to note that RT recommendations presented here are obtained from the literature supporting practices for LRR BC of all subtypes necessitating further inquiry on whether such findings can be widely applied to patients with TNBC LRR.

4.3. Role of systemic therapy

The role of chemotherapy or additional systemic therapy in LRR of TNBC has not been firmly established after local therapies [55,56]. Management of LRR must account for clinical presentation, tumor biology including prognostic factors for metastatic disease development, previous therapies received, and patient's preference [57]. In patients with LRR without distant metastasis, experts recommend aggressive multimodality therapy with curative intent [5,55]. Patients with TNBC and axillary recurrences should be treated with optimal systemic therapy. Local salvage therapy depends on prior axilla management (if they underwent axillary LN dissection ± RT or not) [55]. In cases of isolated supraclavicular nodal recurrences, they should be treated with systemic chemotherapy and RT, as better outcomes have been demonstrated [55].

A study by Lee et al. assessed 4-year disease free survival (DFS) and OS in patients with TNBC who received salvage adjuvant chemotherapy for LRR. Chemotherapy regimen was determined by the treating physician and based on prior chemotherapy agents, particularly anthracyclines or taxane use [44]. In patients with TNBC, there was a trend of both DFS and OS extension among those who received chemotherapy: 4-year DFS: 61.9 vs 42.8% (HR = 0.49, 95% CI 0.24–1.02, log rank $p = 0.056$) and 4-year OS: 80.5 vs 62.6% (HR = 0.40, 95% CI 0.16–1.01, log-rank $p = 0.0536$) [56]. Of note, patients with a small tumor size (<10 mm) or patients who refused did not receive chemotherapy.

The MARECA (national study of MAnagement of breast cancer locoregional REcurrence and oncologiCAl outcomes) study, based in the UK, is a prospective, observational multicenter longitudinal cohort study aimed to establish the practice of breast multidisciplinary teams (MDTs) regarding management of LRR [57]. It is a national practice questionnaire provided through standardized patient vignettes. In this study, 90% of MDT members would always (64.3%) and usually (26.2%) offer chemotherapy in TNBC with LRR [15]. However, how these management decisions influence patient outcomes still remains to be determined.

Unfortunately, there are few prospective trails to provide high-quality evidence to provide guidance on optimal systemic treatment of LRR, and prospective trials from various cooperative groups investigating the benefit of adjuvant systemic therapy in this setting have been unsuccessful and unreported [58]. The Chemotherapy as Adjuvant for LOcally Recurrent breast cancer (CALOR) trial is a randomized prospective trial designed to determine impact of chemotherapy on outcomes in cases of optimally resected isolated LRR [58,15]. The primary endpoint was DFS and all analyses were by intention-to-treat. In the ER-negative cohort, the median time to recurrence from primary BC to ILRR was 3.6 years [58]. 5-year DFS in patients with ER-negative LRR was 67% (95% CI 44–82) in the chemotherapy group vs 35% (95% CI 18–53) in the no chemotherapy group. OS in this same group was 79% (95% CI 55–91) vs 69% (95% CI 47–83), respectively. In the ER-negative group with LRR, at 9 years of median follow up, chemotherapy improved DFS substantially. 10-year DFS and Breast Cancer Free Interval was 70% in patients who received chemotherapy, and 34% in patients without chemotherapy (HR 0.29, 95% CI 0.13 to 0.67) [15]. The CALOR trial demonstrated that adjuvant chemotherapy in patients with LRR of BC led to significantly increased OS and DFS, particularly in patients with ER-negative ILRR. In addition, chemotherapy reduced the relative risk of further relapses by about two-thirds [15]. It was also shown that no benefit could

be ascertained in the ER-positive cohort (10-year DFS rate, 50% vs 59%, respectively; HR, 1.07; 95% CI, 0.57–2.00). Multivariable analysis identified hormone receptor status of the recurrence was the best predictor of a chemotherapy benefit, further underscoring the importance of determining receptor status to inform the recommendation for systemic therapy [58].

Based on the results of CALOR trial, adjuvant chemotherapy may be reasonable after complete resection of isolated recurrences in ER-negative LRR. Standard chemotherapy regimens are usually recommended, but choice of drugs, modalities, and duration remain unclear, and are dependent on previous agents received, and timing of relapse from initial cancer diagnosis [55]. CALOR was a pragmatic trial where the participating physicians' choice of therapy was allowed to focus on the question on hand, i.e. the benefit of systemic chemotherapy in the setting of LRR. Available/allowable regimens included: single agents (docetaxel, paclitaxel, capecitabine) or combinational agents, such as cyclophosphamide, methotrexate, fluorouracil (CMF), gemcitabine, navelbine, combinations including anthracycline chemotherapy, taxanes, or anthracycline plus taxane combination [58]. However, findings from the CALOR trial should be interpreted with caution, as they do not constitute definitive conclusions.

Newer systemic therapy options, possibly targeting molecular pathways, are needed to improve outcomes in this difficult to treat subgroup. Molecular pathways that have been targeted in TNBC include PARP inhibitors, epidermal growth factor (EGFR), mammalian target of rapamycin (mTOR), vascular endothelial growth factor (VEGF), and targeting high-proliferation gene pathways [16]. PARP inhibitors have demonstrated a benefit in patients with germline BRCA mutation in the OlympiAD trial [59], and sacituzumab govitecan has meaningful clinical efficacy in second lines and beyond settings [60,61]. Furthermore, fam-trastuzumab deruxtecan (T-DXd) has clinical activity in ER-negative HER2-low patients as shown in subgroup analysis of DESTINY-Breast04 where an improvement of median progression free survival (PFS) of 8.5 months was noted in the T-DXd group compared to a mean PFS of 2.9 months in the physician's choice group (HR0.46, 95% CI: 0.24–0.89) [62]. It must be noted that these treatment indications are currently for metastatic disease and it remains how those agents can be utilized in a setting of a TNBC LRR particularly those that are optimally resectable.

5. Molecular determinants and predictors

Evidence suggests that recurrence patterns observed in TNBC reflect the inherent molecular heterogeneity of the disease. Several molecular determinants of LRR risk in TNBC have been identified including genetic mutations, gene expression profiles, and tumor microenvironment factors. Gaining a better understanding of the TNBC molecular landscape may help improve LRR risk stratification and guide treatment strategies.

Ongoing translational research aims to evaluate molecular alterations associated with recurrence. Identifying high risk patients who would derive benefit from more aggressive approaches such as intensive radiation regimens or additional targeted systemic therapies would spare low risk patients of potentially unnecessary intervention. A retrospective Translational Breast Cancer Research Consortium study performed DNA analysis of 57 primary tumors, 15 of which were TNBC and evenly distributed between groups [58]. There was a significantly higher proportion of NF1 mutations and MAPK pathway mutations among patients who developed LRR compared to patients who did not relapse, (24% vs 0%; $p = 0.0213$) and (47% vs 0%; $p < 0.0001$), respectively [63]. Of the NF1 mutations, some were deleterious, truncating of frameshift, while others were variants of unknown significance [63]. There was not enough tissue to analyze if the NF1 mutation was subclonal in the primary tumor. In 1 patient with a gain of function NF1 mutation, when the primary tumor was reviewed, there was an indication that this mutation may have been present in the primary tissue and got enriched in the LRR sample [63]. Other molecular entities potentially driving LRR in TNBC include somatic alterations of TP53/MYC and TGFß signaling which has been shown to predict inferior time-to-recurrence [63,64].

Genomic signatures like the 70-gene signature and 21-gene recurrence score assay (Oncotype Dx) have been associated with LRR in a subset of patients [63]. Distinct gene expression patterns have also been associated with variation in responses to treatment and clinical outcomes, including LRR risk. This has been captured in different classification systems that distinguish TNBCs by molecular subtypes. Lehmann/Pietenpol classification [65–67] initially described six molecular subtypes, which was later revised to four subtypes, that displayed unique clinicopathological properties and differential response to conventional chemotherapy: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), and luminal androgen receptor (LAR). In the original study that characterized six subtypes, patient recurrence-free survival (RFS) and distant-metastasis – free survival (DMFS) differed among TNBC subtypes. Notably, RFS was significantly decreased in the LAR subtype compared with the BL1 (hazard ratio [HR] = 2.9), immunomodulatory (IM) (HR = 3.2), and mesenchymal stem – like (MSL) (HR = 10.5) subtypes ($p < 0.05$) without a statistically significant difference in DMFS (log-rank test; $p = 0.2176$) [66]. Inferior RFS for patients in the LAR subtype in the absence of DMFS variability suggests that recurrence was due to local relapse. The authors postulate that increased age at diagnosis in the LAR group may be a contributing factor along with performance status, advanced disease, and age-related comorbidities potentially influencing the delivery of standard-of-care treatments [66]. Several gene expression profiling indices have been developed and studied in the postmastectomy RT space to identify subgroups of patients at increased risk of developing a LRR after BCS [68,69]. A key limitation to the gene expression work has been the primary use of RNA sequencing as a preclinical investigative modality, which has its own set of challenges. For instance, RNA sequencing analyses can be affected due to suboptimal RNA preservation due to variation in fixation methods or aged blocks, and general RNA sequencing quality [63].

The role of tumor microenvironment, in particular tumor-infiltrating lymphocytes (TILs), in BC prognostication is under investigation. TILs are most frequently found in highly proliferative tumors, such as TNBCs, and their presence at diagnosis

increased the likelihood of pCR attainment following NACT and improved survival in these patients [70–72]. Several studies have shown that the degree of stromal lymphocytic infiltration is predictive of distant recurrence risk but the prognostic impact of TILs in LRR has yet to be studied [73–75].

5.1. Transcriptome analysis

Transcriptome analysis serves as an extension to gene expression profiling by utilizing molecular signatures and has been used in the study of TNBC and LRR to improve risk stratification and optimize therapeutic pathways. Jiang et al evaluated and validated an integrated mRNA-lncRNA signature based on the following species: FCGR1A, RSAD2, CHRDL1, HIF1A-AS2, and AK124454 [69]. 138 TNBC patients were assigned to high versus low-risk group for recurrence according to the integrated mRNA-lncRNA. The high-risk group was more likely to experience a recurrence event than patients in the low-risk group (hazard ratio (HR) 11.02; 95% CI, 2.89–41.97; $p < 0.001$) and similar results were obtained in the validation set [76]. It is important to note in this study, a recurrence event was defined as recurrence of invasive disease (LRR or distant), contralateral BC, and death from any cause. These findings suggest that transcriptome analysis may represent a reliable predictive tool for tumor recurrence in TNBC but more focused studies are needed to understand its role in LRR. Despite the progress made in transcriptome analysis of TNBC, there remain challenges translating these findings into clinical practice including validation and reproducibility of gene signatures across different patient cohorts, the integration of transcriptomic data with other clinicopathologic factors, and the development of cost-effective and clinically applicable assays.

6. Conclusion

Patients with TNBC who develop LRR have poorer short- and long-term outcomes, including worse OS. Gaining a better understanding of the TNBC molecular and genomic landscape in conjunction with the incorporation of predictive biomarkers to clinical features may help improve LRR risk stratification and guide treatment strategies. Yet currently, there is no standardized treatment paradigm, and the complexity of these cases requires multimodality therapy directed by multidisciplinary team, which includes surgery, re-irradiation when appropriate, and systemic or targeted therapies.

7. Expert opinion

TNBC is associated with early recurrence and lower survival rates of all the subtypes in BC [77]. TNBC status has been identified as a risk factor of LRR, and of all the LRRs in BC, about 18% of those tend to be TNBC [14]. LRR of BC represents a heterogeneous entity and requires a multidisciplinary assessment and integration of treatment of modalities. For all LRR, a repeat biopsy should be obtained and BC markers should be repeated and clinicopathological information should be used to ascertain an LRR from a new primary [3]. In general, LRR has become less common due to improvements in upfront management of primary disease with improvement of local and systemic therapies with incidence of LRR as 0.5% per year [3]. Factors contributing to this include improved diagnostic workup, attention to surgical margins, improved radiation localization, and lastly improvement of neoadjuvant therapies with incorporation of immune therapy that has provided with a significant improvement in pathological complete response rate [3,78]. Patients with BCS and isolated LRR are commonly offered completion mastectomy, though select patients can be treated with repeat BCS especially in a setting of favorable breast to tumor ratio. Re-irradiation in select situations with or without hyperthermia can be considered in those undergoing BCS [49].

There are no robust prospective data suggesting optimal systemic therapy in patients with isolated LRR. All patients must be screened for metastatic disease, and those with synchronous metastatic disease should be treated as such [3]. CALOR is the only prospective trial investigating the efficacy of systemic therapy in patients with resected LRR. The investigators showed that patients with ER-negative disease benefitted from chemotherapy (whereas those with ER-positive did not) and chemotherapy allowed was chemotherapy of physicians' choice [58]. It must be noted that this was a multi-center trial that did not meet its accrual goal, partly due to an overall low incidence of isolated LRR, which restricted the pool of eligible patients. Secondly, investigators felt that treating physicians likely favored extrapolating data from other randomized or non-randomized data from other clinical settings to apply to patients, particularly in the case of HR-positive disease [57]. As we know from treatment of early TNBC that residual cancer burden after neoadjuvant treatment is predictive of outcomes [79], a preoperative approach in a multi-center clinical trial setting may provide a better estimation of response of LRR to systemic treatment. We await findings from the MARECA study which continues to recruit patients diagnosed with BC LRR with or without distant metastasis across the UK [57]. The study aims to provide insights into current treatment strategies and associated patient outcomes to better inform best practice guidelines, particularly pertaining to systemic therapies and LRR of TNBC.

There is growing interest in the study of predictive markers to guide therapeutic disease in optimal treatment of LRR. Identification of a unique molecular profile would allow oncologists to avoid aggressive therapies in those that are low risk for recurrence, and would allow for appropriate intensification of therapies in the treatment of primary tumor in those that are high risk. Preclinical work to better understand tumor microenvironment has primarily used RNA-based sequencing and due to logistical limitations of using RNA as an analysis modality, has not been widely reproducible. Therefore, more reliable and precise techniques with digital spatial profiling may be needed to better understand genomic signatures in LRR. Given the rapidly evolving pace of drug development, biomarker-driven investigations and even incorporation of this information in clinical practice are ultimately needed to better understand the optimal treatment of LRR.

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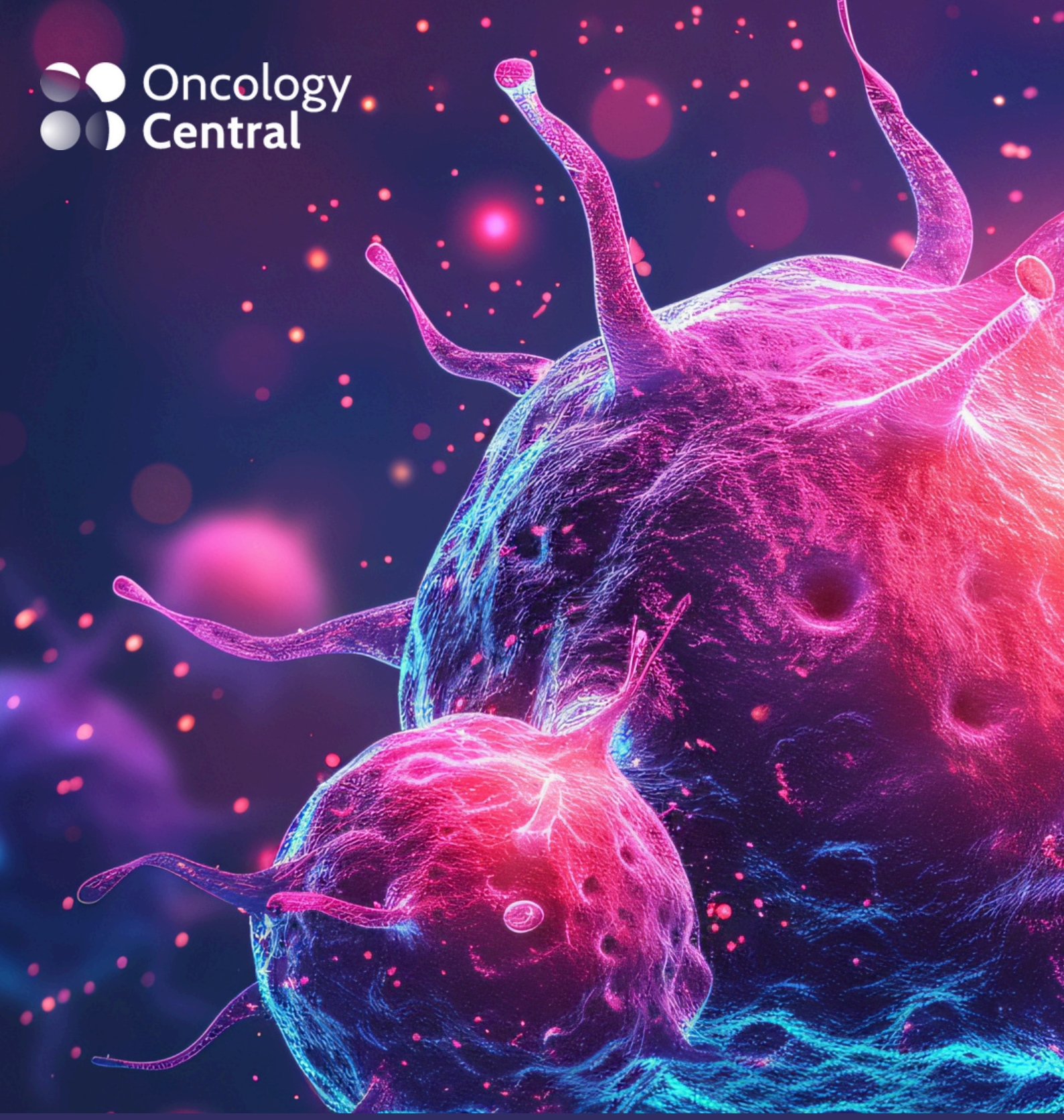

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