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# Advances In Detection And Clinical Use Of Circulating Tumor Cells In Breast Cancer Management

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## ABSTRACT

***Background**: Breast cancer is the most common cancer in women, and its mortality is largely attributed to distant metastases. Distant metastasis typically begins with the spread of a small group of cells from the primary tumour to regional and remote sites.*

***Objectives**: This study aims to review the molecular mechanisms underlying the metastatic process in breast cancer. Additionally, it will assess the available techniques for the enrichment, identification, and molecular characterization of circulating tumour cells (CTCs), as well as evaluate their clinical application, particularly concerning perioperative management during breast cancer surgery.*

***Methods**: A review of the literature was conducted, focusing on techniques used for the enrichment and detection of CTCs. Molecular characterization methods were also analyzed for their effectiveness in identifying metastasis precursors in breast cancer patients.*

***Results**: CTCs are present in the bloodstream of cancer patients, making them valuable markers for detecting and monitoring metastasis. Various techniques for the enrichment and identification of CTCs have demonstrated clinical utility, particularly in managing perioperative conditions during breast cancer surgeries.*

***Conclusions***: *CTCs play a crucial role in the metastatic process of breast cancer, and their detection and molecular characterization can provide important insights into disease progression. Clinical applications of CTC analysis, particularly during the perioperative phase, offer significant potential for improving patient outcomes. Further research is needed to refine these techniques and expand their application in breast cancer treatment.*

***KEYWORDS***: *Breast Neoplasms; Neoplastic Cells, Circulating; Neoplasm Metastasis; Biomarkers*

## INTRODUCTION

The panorama of breast cancer can be presented from three facts: it is the first cause of death due to neoplasms in women, surgery is the most frequently applied treatment, and recurrence due to metastasis continues to be a cause of death. You put it This disease begins from a small group of cells that spread in a region distant from the site of the primary origin of the cancer. Circulating tumour cells (CTCs) detach from the primary tumour or tumour (Sayed et al., 2024)

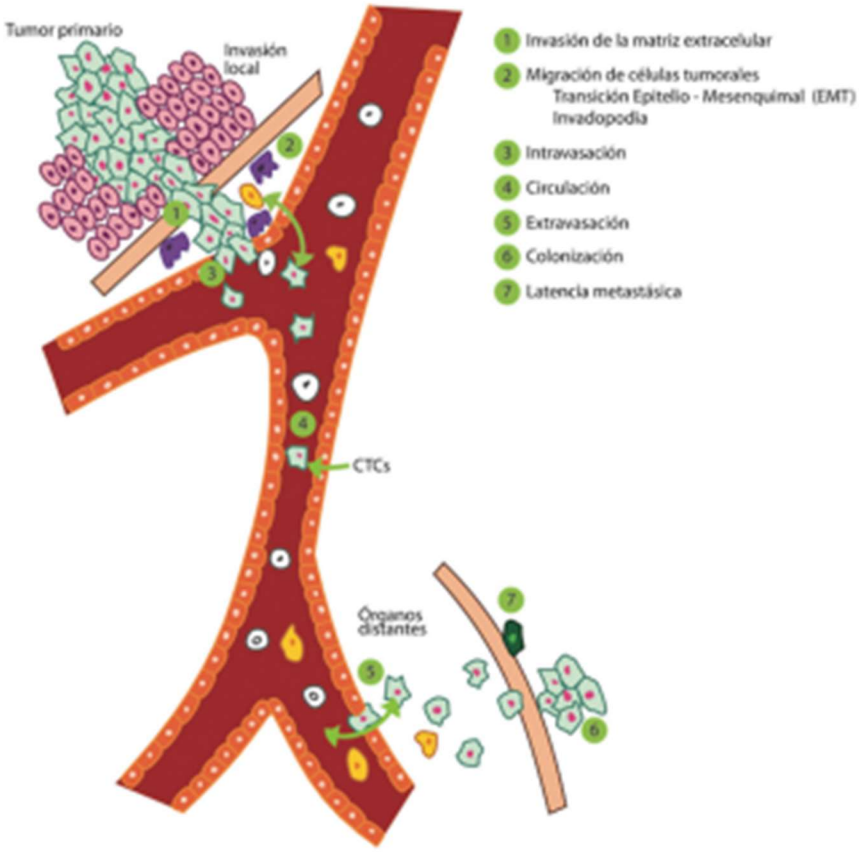


Figure 1. Phases of the metastatic process.

The objective of this review is to describe the participation of CTCs in the metastatic process, the main techniques available for their detection (Henri question and analysis), and the potential clinical applications for treatment, therapeutic monitoring, and prognosis in patients with breast cancer.

## Importance of CTCs in the metastatic process in patients with breast cancer

The majority of cancer cells in the primary breast tumour have a metastatic phenotype, which involves the dissemination of tumour cells early in the carcinogenesis process. For the metastasis to spread, a group of tumour cells must be able to invade the host tissue. Fart, survive and proliferate. This process requires the entry of breast tumour cells into the circulation, their permanence in the distal vascular bed, their extravasation into the interstitium and parenchyma of the distant organ, and proliferation as a secondary colony (Fig. 1) (Cani & Hayes, 2024).

The factors that determine the lymphatic or hematogenous route for the dissemination of tumour cells and whether they are independent of each other are not known exactly. Hartkopf showed that the dissemination of tumour cells through the hematogenous route seems to be independent of lymphatic dissemination and that the differences in the cellular phenotype allow the discrimination of cell populations with high and low metastatic potential, as well as determining the preferential direction of cellular tumour dissemination. In addition to the dissemination route, various molecular mechanisms necessary for tumour cells to complete the metastatic process have been proposed (Fig. 1) (Fehm et al., 2024).

**Local invasion of the extracellular matrix:**

Mutations in genes that encode matrix-cell and cell-cell adhesion proteins, as well as changes in the extracellular matrix and tumour microenvironment, allow local invasion. In the Local invasion: Breast cancer cells spread to the storma and surrounding normal tissue of the primary tumour, inducing thinning and linearization or even rupture of the basement membrane (Bardol et al., 2024).

**Migration of tumour cells:**

It can be carried out by multicellular migration or invasion of single cells. The occurrence and frequency of breast tumour cell migration processes depend on the histological type and the factors. Tors of the underlying microenvironment. Some of the processes necessary for migration to occur are chemotaxis, degradation or proteolysis of the extracellular matrix, and biomechanical modifications, which occur in response to changes in the microenvironment and regulatory factors, such as miRNAs (Alkhafaji et al., 2024).

**Epithelial-mesenchymal transition (EMT):**

It is a process in which cells lose their epithelial characteristics, including cell-cell adhesion, apical-basal polarity, and loss of motility, to acquire mesenchymal properties such as invasiveness, resistance to apoptosis, and motility. EMT facilitates the migration of breast tumour cells and the invasion of the surrounding microenvironment by weakening cell-cell cohesion, in addition to increasing the degradation capacity of the extracellular matrix and modifying the cell cytoskeleton. EMT promotes the resistance of tumour cells to apoptotic signals, contributing to the survival of CTCs in the bloodstream, and is transient, since CTCs recover their epithelial characteristics in the distant organ through the mesenchymal-epithelial transition (Bidard et al., 2024).

**Invadopodia:**

It is described as the sites of cellular adhesion in the form of rosettes that degrade the extracellular

matrix, allowing invasiveness and metastasis. The formation of invadopodia by metastatic breast tumour cells during intravasation has been reported. In cells deficient in Tsk5 (a marker of invadopodia) in cells that fail to carry out breast cancer metastasis to the lungs and with altered N-WASP function (involved in invadopodia) that is associated with decreased invasion and intravasation of breast tumour cells (Park et al., 2024).

**Intravasation:**

Breast tumour cells can cross the barrier of endothelial cells and pericytes that make up the walls of microvessels. Transforming growth factor beta (TGF-b) and tumour-associated macrophages (TAM) perivascular promote the intravasation of breast tumour cells. Furthermore, through vascular endothelial growth factors (VEGF), cyclo-oxygenase 2 (COX-2), epiregulin (EREG), and matrix metalloproteinases 1 and 2 (MMP-1 and MMP-2), tumour cells stimulate the form tion of new blood vessels, which are tortuous, with greater permeability and in constant remodelling, facilitating intravasation (Deutsch et al., 2024).

**Circulation:**

CTCs modify the pentose phosphate signaling pathway and glucose reuptake, anoikis(apoptosis induced by the loss of anchorage of the cell to the extracellular matrix or because matrix-cell interactions are insufficient or inappropriate), They acquire a greater capacity for deformation than normal epithelial cells, evade the hemodynamic force and the immunological response by forming relatively large emboli when they come into contact with platelets through the expression of tissue factor, L- and P-selectins, as well as such as the involvement of micro tentacles. CTCs and platelets form a microembolus that, in turn, increases the time they persist in circulation until they are sequestered in distant tissues (Grigoryeva et al., 2024).

**Sequestration in distant organs:**

CTCs are sequestered (with a predilection for certain specific tissues) in a passive manner due to vasculature size restrictions in the capillaries of distant organs. Some tumoural cells form adhesive interactions at particular sites, sharing and cooperating with target tissue through cytokine signaling networks, to determine the organotropism of metastasis.[18] Sequestration of metastatic breast cells at a distance is facilitated by platelets and leukocytes, which form L- and P-selectin complexes with tumour cells (Verschoor et al., 2024).

**Extravasation:**

CTCs can initiate intraluminal growth and form microcolonies that break the walls of the surrounding blood vessels to be released into the target tissue or organ or penetrate the layer of endothelial cells and pericytes, by increasing the expression of genes. That favours the remodelling of the vasculature to increase its permeability (Y. Chen et al., 2024).

**Colonization:**

Once in the target tissue or organ, breast tumour cells establish a bidirectional relationship with the microenvironment, suppress the immune response, promote angiogenesis, and release factors that promote growth, cell survival, and motility. In response, the recipient tissue alters its gene expression to provide a favourable environment for tumour cells. Breast cancer cells can colonize specific organs

(lung, spinal column, and brain) as a consequence of modifications in the genes involved in metastasis and that have been categorized as initiation, progression, and virulence, the latter being the ones that allow colonization of secondary organs (Lin et al., 2024).

**Metastatic latency:**

Tumour cells can remain silent and viable for a long period since they progressively acquire genetic and epigenetic modifications that allow them to maintain a reduced proliferative and metabolic state (preventing adjuvant therapy from eradicating them, given that it is directed at cells with an active proliferative and metabolic state) (Gerratana et al., 2024).

## Techniques for the enrichment and detection of CTCs

CTCs are scarce, so tests with high degrees of sensitivity are required to detect them, and specificity to reduce the probability of selection of false positives that give an unsafe result in estimating the prognosis of the disease and response to treatment. Enrichment methods have been developed to increase the isolation rate, taking into account biophysical differences (size, weight, density, flow, elasticity, and charge of the cell surface) and immunoaffinity (positive selection: based on the molecule of epithelial adhesion, EpCAM, and negative selection: based on CD45, CD15 and CD66b) (Jia et al., 2024).

To date, numerous enrichment methods have been developed, including size separation of epithelial cells withISET(Rarecells Diagnosis) y ScreenCell (Sarcelles, France); by size and inertia with CTC iChip(CytoFluidix); size, deformability and inertia withClearCell FX1 System (Genomax Technologies); by density gradient withFicoll Hypachus(GE Healthcare) u Oncoquick (Greiner Bio-One); immunomagnetic separation through positive, negative or both selection, using microbeadsMACS Magnetic Activated Cell Sorting System (Militenyi, Biotec), perlasDynabeads (Dynak), monoclonal antibodies directed against specific cell surface markersEasySep (Stem Cell Technology) y CellSearch (Veridex), and for the combination of density gradient and negative selectionRosetteSep (Stem Cell Technology), entre otros (Hwang et al., 2024).

However, even though there are multiple and diverse CTC enrichment methods, it is important to take into account the analysis or research that will be carried out later on the isolated cells (for example: quantification, cytometric analysis, gene expression analysis, sequencing, etc. .), to select find the most appropriate method. It is worth mentioning thatCellSearch is the first and only system approved for clinical use by the United States Food and Drug Administration, (Food and Drug Administration, FDA), for the detection of CTC and evaluate the disease-free period and overall survival in patients with breast, prostate and colorectal cancer (Nanou et al., 2024).

Once the CTCs are enriched and collected, the identification process is carried out to know their origin and genetic or protein profile. Current CTC analysis techniques are based on quantification (immunofluorescence), genomic analysis (targeted DNA sequencing), transcriptomic analysis (hydride on-site RNA, single-cell RNA sequencing, polymerase chain reaction [PCR]), epigenetic analysis (targeted visual phyto sequencing), proteomic analysis (ELISA, mass cytometry, western blot, single cell mass spectroscopy) and multimodal analysis (glucose recapture, protein analysis, mutational analysis and high-resolution image analysis of unpurified cell preparations) (Topa et al., 2024). PCR-based methods are the most used for the detection of CTCs since they can achieve

sensitivity to detect one cell in every 10-10 normal cells. Currently, real-time retrotranscription-PCR (RT-qPCR) techniques allow the detection of CTCs through the precise quantification of the expression of epithelial cell or breast cancer-specific biomarkers (Gao et al., 2024). Epithelial markers are typically expressed by all tumour cells of epithelial origin and include EpCAM, various cytokeratins (CK6, CK7, CK8, CK18, CK19, and CK20), surface markers (CD45, CD15, and CD66b), and epithelial antigen. Meme dam (EMA). Regarding specific breast cancer markers, the following have been proposed: HER2/Neu, mammoglobin, mucin, and maspin, among others. However, the markers considered tumour-specific are not only expressed in tumour cells but also some normal cells, including leukocytes, although at a lower level, so

There may be the possibility of false-positive signals. For this reason, genetic and epigenetic alterations have been proposed as specific markers, which are found exclusively in breast tumour cells. Furthermore, the use of a multimarker panel increases the sensitivity and specificity for the detection of CTCs with potential clinical use for the diagnosis and monitoring of response to treatment in patients with breast cancer (Smit et al., 2024).

## Clinical applications of CTCs in breast cancer

The presence of occult tumour cells at the time of diagnosis in patients with early-stage breast cancer is the major cause of recurrent metastatic disease in patients with resection of the primary tumour. Recudetection Early recognition allows the initiation of treatment to increase survival and improve quality of life, Therefore, CTC quantification has been proposed as a non-invasive test for diagnosis, estimation of prognosis, monitoring of disease recurrence, and response to anticancer therapy (Cortés-Hernández et al., 2024).

It has been shown that the prognostic value of CTC detection may be superior to known prognostic factors (site of metastasis and hormone receptor status) and that it may provide greater information than conventional imaging methods for the evaluation. Response to treatment. Below we review some of the studies in which the potential clinical use of CTC detection in early and metastatic breast cancer (Smit & Pantel, 2024).

–Early breast cancer:

The presence of CTCs in peripheral blood before chemotherapy is an adverse prognostic factor for the disease-free period and overall survival, both in patients with negative nodes and in patients with positive nodes; A cut-off point of five or more CTC has even been proposed for greater risk of recurrence. CTC quantification is also a tool to monitor response to treatment since the presence of CTCs after two years of chemotherapy in clinically disease-free patients has been associated with poor prognosis. Stathopoulouet al (Riazi & Fathi, 2024).

Demonstrated that in patients with early breast cancer, in stages I and II before adjuvant chemotherapy, the presence of cells with positive expression to CK19 mRNA level is an independent prognostic factor for the disease-free period and overall survival, both in patients with negative nodes and in patients with positive nodes. Cells with positive expression of CK19 mRNA were detected in 29.7% of the patients and there was a reduction in the disease-free period ($p = 0.0007$) and overall survival ($p = 0.01$) (Sinha et al., 2024).

The same characteristics were confirmed by Xenidiset al. who reported that positive expression of

CK19 mRNA in CTCs constituted a prognostic factor for an adverse clinical outcome. Later, this same group demonstrated, in a cohort of 444 patients, the presence of detectable CTCs in 40.8% of cases; however, an adverse impact on prognosis was observed in triple-negative and HER2/Neu-negative tumours, but not in estrogen receptor (ER)-positive and HER2/Neu-negative tumours. Apostolakiet al. demonstrated the expression of HER2/Neu mRNA in CTCs in 21% of patients with stage I and II breast cancer, after completing their treatment with adjuvant chemotherapy (Vardas, 2024).

On the other hand, Xenidiset al. demonstrated that cells with positive expression of CK19 mRNA were found in 32.7% of patients at the end of adjuvant chemotherapy, and their detection was significantly associated with an increased risk of recurrence and death. Ignatidiset al. evaluated the expression and prognostic value of mammoglobin, HER2/Neu, and CK19 in 175 patients with breast cancer in stages I, II, and III before starting adjuvant therapy, finding cells with positive expression of CK19, mammoglobin, and HER2 mRNA. /Neu in 41.1%, 8%, and 28.6% of patients, respectively. Positive expression of CK19 and mammoglobin mRNA was associated with a short disease-free period ($p < 0.001$ and $= 0.001$) and lower overall survival ($p = 0.044$ and 0.034), while positive HER2/Neu mRNA expression was associated with a short disease-free period ($p < 0.001$), but not with overall survival (Kulus et al., 2024).

– Metastatic breast cancer:

The detection of CTCs in peripheral blood is an independent predictor of the effectiveness of systemic therapy and a prognostic marker. In patients who persist with a high level of CTC (including a level higher than that detected before treatment), resistance to chemotherapy is suggested, so they should be changed to a new line of treatment. Patients with metastatic breast cancer with more than (Ren et al., 2024)

| | |
|---|---|
| Surgery invasive (mayor risk than surgery minimally invasive) | Perioperative blood transfusion |
| | Hypothermia |
| | Inadequate pain control and nociceptive stimulation |
| | psychological stress |
| | General anaesthesia (higher risk than with the use of regional analgesia and local anaesthetics) |
| | Use of NSAIDs (lower risk when using them) |
| | Beta-adrenergic blockade (lower risk when using them, preferably in combination with COX-2 inhibitors) |
| NSAIDs: non-steroidal anti-inflammatory drugs; COX-2: cyclo-oxygenase 2 | |

Table I.Factors associated with immunosuppression and CTC disseminationAfter the initiation of systemic therapy, they have short progression-free survival and a high incidence of radiographic progression of the disease, Furthermore, the presence of CTC has been associated with a greater number of recurrences and disease-related deaths. Cristofanilli et al. showed that a higher number of CTCs in the peripheral blood of patients with metastatic breast cancer is associated with poor prognosis, regardless of the number of previous treatments, the site of metastasis, the type of therapy, and the time of recurrence after the initial surgery. The CTC positivity rate was similar in patients with a recent diagnosis of metastatic breast cancer (52%) than in those already receiving treatment (48%) (D. Chen et al., 2024).

Another study demonstrated the significant association of positive CK19 mRNA expression with clinical decline ($p < 0.001$) and disease-related death ($p < 0.001$). CTC patients with positive CK19 mRNA expression after chemotherapy have shorter disease-free periods ($p < 0.001$) and lower overall survival ($p = 0.001$). Liu et al. reported that the presence of more than five CTCs detected at the initial time, three to five weeks, and seven to nine weeks after the start of adjuvant systemic therapy in patients with metastatic breast cancer, was associated with a shorter cancer-free period. Progression and high incidence of radiographic disease progression compared to those who had fewer than five CTCs (Ali et al.).

## Importance of CTCs in the surgical, anaesthetic, and perioperative management of breast cancer

Surgical treatment is capable of completely removing the primary tumour, and metastatic lymph nodes and achieving complete macroscopic cytoreduction; however, 90% of deaths related to breast cancer are due to metastasis and not the primary tumour. Paradoxically, curative oncological surgery can contribute to metastatic dissemination due to the tumour surgical manipulation itself and due to perioperative immunosuppression induced by anaesthesia. Surgery triggers a neuroendocrine response due to the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, with the release of catecholamines (D. Chen et al., 2024), adrenocorticotropic hormone, cortisol, and prostaglandin $AND_2$, a situation that suppresses cellular immunity and increases the secretion of immunosuppressive cytokines and proinflammatory cytokines, substances that promote angiogenesis

and tumour metastasis (Ali et al.).

Even when macrophages, monocytes, neutrophils, and natural killer (NK) cells keep CTCs under pressure, they are capable of developing immune defence and evasion mechanisms. Furthermore, CTCs overexpress proteins that inhibit the phagocytic activity of immune cells and downregulate the expression of major histocompatibility antigen class I. Through the expression of vascular signalling proteins, CTCs can attract hematopoietic stem cells that express the vascular endothelial growth factor receptor (VEGFR), which influences fibroblasts at the potentially metastatic site, creating a favourable microenvironment (Wishart et al., 2024).

Perioperative management during oncological surgery is important, given that during tumour resection there are potentially modifiable factors that can contribute to improving the immune response, reducing or preventing the dissemination of CTCs, and reducing the probability of recurrence (Table I). During the intraoperative period, the drugs used in the anaesthetic process produce multiple effects on the immune system (Table II). General anaesthesia consists of the administration of intravenous anaesthetics (for example, thiopental or propofol) for induction, followed by relaxants (Hassan et al., 2024)Table II.Anaesthetic drugs and their relationship with the immune response,

| | Count | Activity | |
|---|---|---|---|
| Ketamine | ↓ | ↓ | ↑ Apoptosis |
| Thiopental | ↓ | ↓ | ↓ Apoptosis |
| Propofol | → | → | ↑ TBI activity |
| Midazolam | | | → Activity<br>by LCT |
| Hello | ↓ | ↓ | |
| Isofluorano | ↓ | ↓ | ↑ Apoptosis |
| Sevofluorano | ↓ | ↓ | ↑ Apoptosis |

| | | | |
|---|---|---|---|
| Morphine | ↓ | ↓ | ↓ Differentiation of Th |
| Fentanyl | ↓ | ↓ | ↑ Tregs |
| Sufentanil | ↓ | ↓ | ↑ Tregs |
| Alfentanil | ↓ | ↓ | ↓ Proliferation |
| Remifentanil | ↓ | ↓ | |
| Tramadol | ↑ | ↑ | |
| COX-2 inhibitors | ↓ | ↓ | ↑ TBI activity |
| Beta Blockers adrenergic | ↓ | ↓ | ↓ number and function suppressor MDSC |
| Lidocaine | ↑ | ↑ | |
| NK: Natural killers; Th: T helper cells; Tregs: CD4+, CD25+, and Foxp3+ regulatory T cells; LCT: Cytotoxic lymphocytes; MDSC: Myeloid-derived suppressor cells. | | | |

Muscle and endotracheal intubation, administration of volatile anaesthetics (e.g., sevoflurane) and opioids for maintenance and pain control; while in regional anaesthesia local anaesthetics (for example, lidocaine or bupivacaine) are used to block peripheral or spinal nerve transmission and produce a paravertebral or epidural block.[8] It has been observed that local anesthetics prevent surgical pain and reduce neuroendocrine stress, by suppressing neural afferent transmission to the central

nervous system, avoiding the response of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, and therefore reducing immunosuppression during surgery (Xie et al., 2024).

Table III.Mechanisms of Regional analgesia and local anaesthetics on tumour dissemination

| | |
|---|---|
| ↓ Answer neuroendócrina | ↓ Stress response |
| Preserves immune function (including the NK cell cytotoxicity) | ↓ Effect of EGFR<br>↓ Cell proliferation<br>↓ Differentiation<br>↓ Tumour progression<br>↓ Cellular invasion and metastasis |
| ↓ Use of opioid analgesics | ↓ Activation of sodium channels<br>↑ Activation of calcium and potassium channels<br>↓ Metastatic invasion |
| ↓ Liberation of endogenous opioids | ↓ Signage of<br>↓ Cell-cell adhesion<br>↓ cell division in fibroblasts<br>↓ Tumour progression<br>↓ Cellular invasion and metastasis |

| | |
|---|---|
| Preserves apoptosis of tumour cells | ↑ Tumour cell demethylation<br>↑ Gene activation<br>tumour suppressors<br>↓ Tumour progression |
| NK: Natural killers; EGFR: Epidermal growth factor receptor. SRC: SRC proto-oncogene non-receptor tyrosine kinase. | |

In general, anaesthetic management not only has short-term immunological repercussions but also on recurrence and long-term prognosis as it is related to the dissemination of CTC. (Fig. 2). The use of regional anaesthesia avoids much of the neuroendocrine stress response produced by surgery, preserves NK cell function virtually intact, achieves significantly greater pain relief (compared to opioids), decreases the release of endogenous opioids, and reduces the consumption of volatile anaesthetics (Table III) (Salu & Reindl, 2024).

In addition to the anaesthetic technique, inadequate pain control, the use of opioids, the indiscriminate use of blood transfusion, hypothermia, and psychological stress are factors that contribute to immunosuppression and, therefore, to the spread of CTCs. Pain itself produces a suppression of NK cells; However, its control with opioids is one of the most effective strategies for treating severe pain in patients with cancer, so its use in this group of patients is still controversial. Morphine has shown effects on both (Akkiprik et al.).

## Conclusion

The CTC study offers the advantages of a peripheral blood test, including easy access and monitoring. Taking into account the metastatic process, the quantification and analysis of CTCs have important implications for prognosis, response to treatment, and the identification of new therapeutic targets in patients with breast cancer. Currently, oncological management is based on the characteristics of the primary tumour, however, tumour cells themselves are heterogeneous and frequently experience They indicate changes related to selective and immune pressure, so the study of CTCs can provide useful information to adjust treatment.

Given the intimate relationship that exists between the immune response and the dissemination of CTCs, the establishment of strategies that reduce the immunosuppression associated with the disease, surgical treatment, and anaesthetic management, can have important implications in the short and long prognosis. Term in patients with breast cancer.

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